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Paediatric Volume II

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10.1 | Developmental neurobiology of pain

The majority of information on this topic to date is experimental (mostly rodent) data, which presents translational challenges to the interpretation of developmental changes in the neurodevelopmental pathways of the human embryo-foetus-infant. The combination of basic science, fetal surgery and neonatal imaging studies is enhancing our understanding of pain pathway development and the influence of pacemakers and various receptors. In embryonic life, nociceptive pathways develop under the influence of (generally non-noxious) afferent input (Skaper 2018 **NR BS**; Li 2011a **BS**) and several trophic signalling pathways eg nerve growth factor and tropomyosin receptor kinase (NGF-TrK). Growth factor signalling systems are extremely important in the developing cytoarchitecture of nociceptor pathways and remain well conserved across species (Wheeler 2014 **BS**). Interspecies differences appear to stem from divergent roles played by (downstream) transcription factors (Guo 2011 **BS**). The expression of a number of molecules and channels involved in nociception are developmentally regulated. During early life, there are changes in the distribution and density of many important receptors and the levels and effects of several neurotransmitters alter significantly (Verriotis 2016a **NR**; Fitzgerald 2005 **NR**).

Animal studies confirm that activity-dependent maturation is a cornerstone of development and, in early gestation, intrinsically active neurons (endogenous pacemaker cells) contribute significantly to this (Li 2011b **BS**). Within lamina I of the spinal cord, pacemakers are positioned to regulate both the level of activity in developing motor circuits and the ascending flow of nociceptive information suggesting a role in the maturation of pain and sensorimotor networks (Li 2015 **BS**). Postnatal tuning of these pathways requires continued somatosensory (again non-noxious) input at a spinal level. The development of inhibitory pathways within nociceptor systems appears somewhat later and involves a developmentally regulated alteration in the synaptic effects of glycine and GABA (Hathway 2012 **BS**; Rajalu 2009 **BS**). Little is known about the trophic factors and essential synaptic inputs that guide the development of these pathways. Neuropeptides, receptors and ion channels implicated in the development of (and activity within) these pathways include sodium leak channels (spinoparabrachial tracts: Ford 2018 **BS**), metabotropic GABA-B receptors (Brewer 2018 **BS**) and atypical cadherins (Wang 2017 **BS**). Important signalling systems in early development include the ephrin-receptor tyrosine kinase system which influences cell movements (Wilkinson 2001 **NR**) and extracellular signal receptor kinases (O'Brien 2015 **BS**). Modulation of activity within these spinal pathways by tissue injury and inflammation appears to be mediated through glutaminergic signalling in an age-dependent fashion (Baccei 2010 **BS**). As a result, cortical coding of 'injury-induced pain states' also appears to be developmentally regulated (Chang 2016 **BS**).

Rodent studies confirm that C-fibre polymodal nociceptors are mature in their pattern of firing at stages equivalent to term gestation in humans. They are capable of being activated in the periphery by exogenous stimuli, although their central synaptic connections in the dorsal horn are initially immature. However, "wind-up" can be produced by relatively low-intensity A-fibre (rather than C-fibre) stimulation. A-beta fibres initially extend up into the spinal cord's laminae I and II and only withdraw once C fibres have matured. This overlap means there is less discrimination between noxious and non-noxious stimuli and, as the receptive fields of dorsal horn neurons are large, peripheral stimuli can excite a greater number of central neurons in early development. In addition, descending inhibitory pathways and inhibitory networks in the dorsal horn are not fully mature in early development (Schwaller 2017 **BS**). While activity of the rostroventral medial medulla (RVM) can facilitate or inhibit dorsal horn

neuron inputs in the mature animal, in young animals descending facilitation dominates and is likely generated by spontaneous brainstem activity (Hathway 2012 **BS**). Only later in postnatal life does this descending activity become modulated by ascending nociceptive inputs in a functional spinal-bulbo-spinal loop (Schwaller 2016 **BS**).

By 7 wk gestation, human primary afferent nerve fibres that innervate skin and projection neurons from the dorsal horn of the spinal cord reach the thalamus. Ascending pathways are present and functional by 25 wk gestation. Central neural projections and synaptic connections continue to mature and, from 26 wk gestation, peripheral noxious stimuli can elicit responses in the increasingly layered thalamic and cortical neurons (Verriotis 2016a **NR**).

Anatomical and electrophysiological evidence confirms that biological systems necessary for nociception are intact and functional from 26 wk gestation (Verriotis 2016a **NR**). This is clearly confirmed during fetoscopy and medical interventions in utero (Bellieni 2018 **NR**). Despite this, inferences regarding fetal pain are limited. Our understanding of the conscious, cognitive, affective and evaluative experience of pain during fetal and late gestational life remains conjectural (Derbyshire 2006 **NR**). In contrast to the protected environment *in utero* (in which the fetus is buffered from environmental stimuli and continuously exposed to the anaesthetic effects of endocrine neuroinhibitors), postnatal life brings intense afferent stimulation and wakefulness (Lagercrantz 2009 **Level IV**). With this, comes the possibility of psychological processes involving content derived from the environment (objects, people and symbols) (Derbyshire 2006 **NR**). Following birth, the neural pathways required for nociception are functional and cortical responses to noxious stimuli such as skin lancing can be demonstrated in even the most preterm neonate (Verriotis 2016a **NR**; Slater 2006 **Level IV**). However, as significant functional and structural changes occur in nociceptive pathways during the postnatal period (Hirschfeld 2012 **Level IV**), the pattern of activity evoked by tissue trauma also changes (Fitzgerald 2009 **Level IV**).

Although the underlying mechanisms may differ from adults, nociceptive pathways can be sensitised by painful stimuli in early life, as demonstrated by a reduction in reflex thresholds in neonates following repeated heel lance (Fitzgerald 1988 **Level IV**) and infants following abdominal surgery (Andrews 2002 **Level IV**). Both animal and human studies suggest that there is a relative excess of excitatory mechanisms and delayed maturation of inhibitory mechanisms in early life (Fitzgerald 2005 **NR**). Hence, neonates once thought to be less sensitive to painful stimuli in fact, produce more generalised and exaggerated reflex responses to lower intensity stimuli.

The disposition and clinical effects of drugs administered in early life are subject to many factors including changes in body composition, protein binding and membrane permeability as well as maturation of major organ systems and receptor signalling systems. Each of these may in turn be affected by disease-related alterations (van den Anker 2011 **NR**). Factors affecting the pharmacokinetic (PK) profile of analgesic drugs (body water and fat composition, plasma protein binding, hepatic metabolism and renal function) change rapidly during the first weeks of life (Funk 2012 **NR**). Postnatal changes in the PK profile of a number of analgesic drugs (eg morphine and paracetamol [acetaminophen]) result in significant age-related changes in dose requirements during infancy and childhood (Allegaert 2014 **NR**; Palmer 2008 **PK**; Prins 2008 **PK**; Bouwmeester 2004 **NR**). In addition, changes in nociceptive processing may have significant effects on the pharmacodynamic response to analgesics in early life (Walker 2008 **NR**). Therefore, developmental age and not just weight should be considered when calculating analgesic dosing (Allegaert 2014 **NR**) (see also Section 10.4 for PKs of the various analgesic drugs). Laboratory studies have demonstrated postnatal changes in the mechanism of action, analgesic efficacy and adverse-effect profile of analgesics that can inform subsequent clinical trials (Nandi 2005 **NR**; Walker 2008 **NR**; Fitzgerald 2009 **NR**).

Prolonged reductions in synaptic activity by general anaesthetics and analgesics can produce unexpected neurotoxic effects, such as accelerated apoptosis, in the developing nervous system. The clinical significance of these laboratory findings remains uncertain (Mellon 2007 **NR BS**). Researchers are now assessing long term outcomes of repeated or extended exposure but the assessment of the impact of analgesic and general anaesthetic administration upon the infant's developing brain and pain pathways will always remain confounded by the underlying pathology, concomitant surgical intervention and comorbidities present (Davidson 2018 **NR**).

KEY MESSAGES

1. Following birth, even the most preterm neonate responds to nociceptive stimuli (**U**) (**Level IV**).
2. In early development, more generalised reflex nociceptive responses occur in response to lower intensity stimuli (**U**) (**Level IV**).

10.2 | Consequences of early pain and injury

10.2.1 | Early neurodevelopmental consequences

Significant reorganisation of synaptic connections occurs in the postnatal period. Activity within sensory pathways is required for normal development but abnormal or excessive activity related to pain and injury during the neonatal period may alter normal development and produce persistent changes in sensitivity that outlast the injury (Walker 2013 **NR**; Fitzgerald 2009 **NR**; Walker 2009 **Level III-2**).

However, the effect of pain in the neonatal period on neurodevelopment and the child or adult's later pain experience is difficult to quantify. In researching this, there are many factors that may confound the determination of the contribution of early pain to altered neurodevelopment and the extent to which this can be modulated by interventions. The likely patient confounders include sex, birth weight, gestational age at birth and at the time of insult, intercurrent illness type and severity (including hypotension), the extent of tissue damage (Brummelte 2012 **Level IV**), as well as genetic and epigenetic factors (Provenzi 2018 **Level IV SR** [PRISMA], 9 studies, n=1,516). While the treatment confounders that may influence neurodevelopment include type, dose and duration of analgesia (including opioids and benzodiazepines), other drugs administered (such as dexamethasone [for chronic lung disease] and anaesthetic agents (Davidson 2013 **NR**), as well as the neonatal unit's practices (which vary) and the quality of neonatal intensive care (see below: Montirosso 2012 **Level IV**). An additional confounder is the limited ability to quantify the neonate's pain experience in the intensive care setting; some studies have used the number of skin-breaking procedures (including blood tests, heel lances, vascular access and surgery) received by the neonate as a surrogate measure to then investigate impact on adverse outcomes. Nociceptive related reflex withdrawal activity and activation of higher cortical areas do not correspond well to observational pain assessment (or outward phenotype) of the neonate when compared to the adult (Fitzgerald 2015 **NR**). This means that behavioural pain assessment may not reflect physiological responses to pain. Importantly, our understanding is expanding regarding the interplay of stress exposure vs developmentally targeted care (eg in the NICU) and the influence upon epigenetics and resultant phenotypic trajectory (in terms of brain maturation, neurobehaviour, the child's current and later capacity to regulate stress, behaviour or emotions and social functioning) (Provenzi 2018 **Level IV SR** [PRISMA], 9 studies, n=1,516).

In clinical studies of ex-preterm neonates, neuroimaging studies done at the equivalent of term age showed greater pain exposure was associated with structural changes. White matter and subcortical grey matter maturation was reduced in infants born at 24–32 wk (related to the number of heel lances and single but not multiple surgical interventions), as assessed by diffusion tension and magnetic resonance spectroscopy (Brummelte 2012 **Level IV**). In a group of similarly premature infants, both neonatal pain and greater early illness severity (measured by the Score for Acute Neonatal Physiology–II) were associated with delayed microstructural development of the corticospinal tract (Zwicker 2013 **Level IV**). In MRI imaging of ex-extreme and very preterm (24–32 wk) neonates at a median of 32 and 40 wk post menstrual age (PMA), early exposure to repetitive procedural pain was associated with volume loss in the lateral thalamic (somatosensory) region with abnormal thalamocortical pathway development (Duerden 2018 **Level IV**, n=155). These changes were more pronounced in the extreme preterm infants. Neurodevelopmental outcome assessments (Bayley-III scores) showed that increased volumetric thalamic growth predicted higher cognitive and motor scores at 3 y corrected age.

Among extremely preterm infants (born at <30 wk gestation), those exposed to surgery (and anaesthesia) had greater white matter injury and smaller total brain volumes, particularly

smaller deep nuclear grey matter volume (Filan 2012 **Level III-3**). In those born at <29 wk gestation, clinical outcomes associated with greater pain exposure were delayed growth with lower body weight at 32 wk (Vinall 2012 **Level IV**) and poorer cognitive and motor function at 8 and 18 mth (Grunau 2009 **Level III-2**). No difference was seen in mental development scores at 2 y in ex-extreme preterm patients (<30 wk) who had surgery vs no surgery, following adjustment for confounders (Filan 2012 **Level III-3**).

Preterm behavioural epigenetics (PBE) is the study of the role of environmental factors such as pain-related stress, which may influence epigenetic modifications in the preterm infant and thus development and behavioural phenotype (Provenzi 2018 **Level IV SR** [PRISMA] 9 studies, n=1,516). In very preterm neonates exposed to high levels of pain-related stress, serotonin transporter gene SLC6A4 methylation in peripheral blood samples increased from birth to NICU discharge at CpG sites 5 and 6 vs neonates exposed to low pain-related stress (Provenzi 2015 **Level III-2**, n=88).

10.2.2 | Longer term consequences of early pain and injury

Longer-term consequences of early pain and injury have been well described, particularly in rodent models and ex-neonatal intensive care unit (NICU) populations. In laboratory studies, the degree of long term change varies with the type and severity of injury (Fitzgerald 2009 **NR**). Inflammation, full thickness skin wounds and skin incision produce prolonged alterations in sensitivity and the response to future injury, in the absence of any visible persistent peripheral injury. By contrast, allodynia following nerve injury is less apparent in early life (Moss 2007 **BS**; Howard 2005 **BS**). These findings are of considerable importance, as pain and injury in neonates may have effects on nociceptive processing that differ in mechanism and duration from those experienced by older children and adults. There is accumulating evidence in neonatal animal models that there are complex interactions between increased excitatory and decreased inhibitory synaptic signalling within the spinal cord in addition to changes in descending inhibitory control from the brainstem in response to tissue injury during the neonatal period (see 10.1 above and Beggs 2015 **NR**).

Neonatal pain results in an increased response to future painful stimuli months to years after the initial insult. Surgery (neonatal circumcision) without anaesthesia or analgesia is associated with an increased behavioural response during immunisation at 4–6 mth when vs uncircumcised infants (Taddio 1995 **Level III-2**). Increased perioperative analgesia requirements and pain scores occurred when subsequent surgery was performed months later in the same dermatome, vs children who had no previous surgery (Peters 2005 **Level IV**). Early pain-related stress was associated with greater SLC6A4 methylation and greater behavioural problems as assessed by the Child Behaviour Checklist in ex-extreme to very preterm children at age 7 y vs full term controls, but only in individuals with the *COMT* 158 Met/Met genotype (Chau 2014 **Level III-2**, n=111).

Ex-preterm preschool children show alterations in pain-related behaviour such as increased somatisation (Grunau 1994 **Level IV**) and ex-NICU school-aged children had higher levels of pain-related catastrophisation (Hohmeister 2009 **Level III-2**). In ex-NICU preterm children and adolescents, thermal pain thresholds were reduced at age 9–14 y (Hermann 2006 **Level III-2**), and at 11 y in ex-extreme preterm children born at <26 wk gestation (along with reduced thermal and mechanical sensitivity around their neonatal thoracotomy scars) (Walker 2009 **Level III-2**). Increased gain in pain pathway signalling was seen at 11–16 y on functional magnetic resonance imaging (fMRI) in response to painful heat stimulus (Hohmeister 2010 **Level III-2**) and responses were enhanced to noxious stimuli (dolorimetry and number of tender points) vs term peers

at age 12–18 y, more so in girls (Buskila 2003 **Level III-2**). The clinical significance of these findings is uncertain.

A prospective cohort study of children born in 1958 investigated the association of chronic widespread pain in adulthood with "early trauma" (Jones 2009 **Level III-2**, n=7,571). It found no association between surgery in childhood before the age of 7 y (RR 1.0; 95%CI 0.9 to 1.1) but positive association for hospitalisation following a road traffic accident (RR 1.5; 95%CI 1.1 to 3.0). A later survey of this British cohort showed no increased risk of chronic widespread pain at 45 y in ex-premature adults (RR 1.26; 95%CI 0.95 to 1.67) (Littlejohn 2012 **Level III-2**, n=8,572).

10.2.3 | Modification by pain management intervention

Importantly, analgesia at the time of the initial painful stimulus may modulate long term adverse effects. The behavioural response to immunisation of male infants was reduced in those who had neonatal circumcision with local anaesthetic applied prior to surgery, vs neonates who had no local anaesthetic (Taddio 1995 **Level III-2**). Infants undergoing surgery in the neonatal period who received morphine did not show any increase in response to later immunisation vs infants without significant previous pain experience (Peters 2003 **Level III-2**). The quality of pain management in the NICU setting may also be important. Very preterm infants cared for in NICUs with high-quality infant pain management (ie use of pharmacological and nonpharmacological treatments for procedural pain, use of pain assessment tools and guidelines for preventing and treating pain) had better neurobehavioural outcomes vs low-quality scoring NICUs (Montirosso 2012 **Level IV**).

Further research is required to determine the most developmentally appropriate and effective analgesia regimens for modulating the effects of early pain and injury. This research will be challenged in its capacity to identify the impact of a single analgesic intervention as in- and out-patient 'care packages' have evolved including nonpharmacological intervention to support preterm and term neonates in intensive care (Provenzi 2018 **Level IV SR** [PRISMA], 9 studies, n=1,516; Valeri 2015 **Level IV SR** [PRISMA,] 13 studies, n unspecified) and procedural interventions in infants and younger children (see procedural Section 10.7).

KEY MESSAGES

1. Pain and injury in early life cause structural changes in cortical and subcortical pathways and are associated with alteration in somatosensory thresholds in later life (**U**) (**Level III-2**).
2. Analgesia may modulate the long term effects of pain and injury in early life but more information is required to determine the optimal dosing and type of agents to avoid negative impact of the pharmacological intervention itself (**U**) (**Level III-2**).
3. Improving quality of infant pain management delivery in neonatal intensive care (including pharmacological and nonpharmacological interventions) may result in improved neurodevelopmental outcomes (**U**) (**Level III-2**).
4. Understanding of the epigenetic factors that contribute to the behavioural pain trajectory is evolving; this may lead to enhanced developmentally targeted care to reduce stress exposure and long term impacts for infants (**N**) (**Level IV SR** [PRISMA]).

10.3 | Paediatric pain assessment

Pain assessment is a complex social interaction, with multiple factors contributing to the child's pain experience, its expression, subsequent interpretation and response (Voepel-Lewis 2012 **NR**). Assessment is a prerequisite to optimal pain management; it should involve a clinical interview with the child and/or their parent/carer, physical assessment and use of an age and context-appropriate pain intensity measurement tool (Howard 2008a **NR**). However, pain in hospitalised children remains common and is often under assessed and inadequately managed (Walther-Larsen 2017 **Level IV**, n=570 [4 hospitals]; Friedrichsdorf 2015a **Level IV**, n=178). Improvements in pain management and in patient, parent and staff satisfaction have been associated with regular assessment and measurement of pain (Deindl 2013 **Level IV**). Uniformity within an institution lends to staff familiarity. This and ease of use are major factors in the successful implementation of a pain management strategy. Adoption of written guidelines or pain management algorithms improved both assessment and management of pain in neonates and children (Williams 2019 **Level IV SR** 20 studies, n=6,390; Stevens 2014b **Level III-2**, n=3,822; Gharavi 2007 **Level IV**, n=225 neonatal units; Falanga 2006 **Level IV**, n=56). Clinical interventions have focussed usually on assessment of pain intensity (and rescue analgesic use). As in adults, domains of pain other than intensity (eg location, quality), the multidimensional nature of the pain experience (eg concomitant emotional distress, coping style of the child, previous pain experience) and parental expectations should be incorporated into overall assessment (Pillai Riddell 2013 **Level IV**, n=458 to 574; Liossi 2007 **Level IV**, n=45).

Verbal self-report is considered to be the best measure of pain in adults. Child self-report is desirable but not always possible, as a child's understanding of pain and their ability to describe it changes with age; while cognitive impairment alters a child's capacity to contribute to an assessment of their pain experience. Therefore, the measurement tools employed must be appropriate to the developmental stage. A range of alternative assessment methods have been established as surrogates for/or adjuncts to self-report. These include assessment scales incorporating observable behaviours, physiological markers and brain imaging techniques. Over 65 paediatric pain scales are published (Andersen 2017 **Level I** [PRISMA], 12 SRs [number of studies & n unspecified]), examples of which are listed in Tables 10.1 to 10.4. These scales can be unidimensional (behavioural indicators only) or multidimensional (combining behavioural, physiological or contextual factors). Assessment should be expanded to evaluate aspects that are relevant to the patient and their family and the clinician, and include tools measuring global satisfaction, adverse effects, assessment of the emotional and financial impact, and physical recovery following paediatric acute pain (Walco 2018 **GL**; Berde 2012 **NR**; McGrath 2008 **GL**).

10.3.1 | Pain assessment in neonates

Noxious stimuli have deleterious short and long term effects on the developing neonate (Valeri 2015 **Level IV SR** [PRISMA], 13 studies, n unspecified) making recognition and management of pain crucial in this age group (see also Sections 10.1 and 10.2).

10.3.1.1 | Uni- and multi-dimensional neonatal pain scales

Over 40 scales have been developed for neonates and infants (Lee 2014 **NR**). These scales are comprised of overlapping combinations of surrogate measures (eg physiological signs such as increased heart rate) or behavioural responses (eg facial characteristics and cry). Choice of the most appropriate tool depends on contextual factors (the infant's age, health status), the stimulus (eg procedural or postoperative pain and whether repeated acute episodes – also

termed recurrent or "persistent" pain) and the purpose of the measurement (eg clinical care or research).

Table 10.1 lists examples of uni- and multi-dimensional scales used in neonates.

10.3.1.2 | Physiological measures used in neonatal pain assessment

Changes in physiological parameters associated with procedural interventions are assumed to indicate the presence of pain, including increases in heart rate (HR), respiratory rate, blood pressure, intracranial pressure, cerebral blood flow and palmar sweating; and decreases in oxygen saturation, transcutaneous CO_2 tension and vagal tone (Cong 2013b **NR**). As these changes are reduced by analgesia, they have been considered useful surrogate outcome measures of pain. Researchers have pursued the use of physiological parameters as objective measures of pain, particularly for preterm neonates (born at 24 to <36 wk). However, as their sensitivity and specificity are influenced by concurrent clinical conditions (eg HR increase with sepsis, illness severity, prematurity) and other factors (eg distress, environment, movement), they are predominantly experimental, have limited clinical utility and should be used in conjunction with behavioural measures.

Heart rate variability

Heart rate variability (HRV) analyses the R-R interval as a noninvasive marker of autonomic sinoatrial node input. It decreased during procedures (Padhye 2009 **Level IV**) and with postoperative pain (Faye 2010 **Level IV**). This contrasts with changes seen in adults with experimentally induced pain where HRV generally increases (Koenig 2014 **Level IV SR** [PRISMA], 20 studies, n=642).

Skin conductance

Skin conductance measures palmar/plantar stress-induced sweating electrically. In a review, skin conductance correlates with 3 unidimensional pain scales (ABC Pain Scale, 1 study; Neonatal Facial Coding System (NFCS), 1 of 2 studies; Comfortneo, 1 of 2 studies), crying time (1 study) and with one of two arousal/movement scales (Prechtl Scale: 8 studies). It has low positive predictive value for moderate pain (NFCS>4/10) and does not correlate with HR (in 6 of 8 studies), O_2sat (6 studies), respiratory rate (2 studies), or multidimensional pain scales (8 studies) (Hu 2019 **Level IV SR** [PRISMA], 28 studies, n=1,061). Study results assessing the impact of gestational (10 studies) and postnatal (9 studies) age are conflicting. Counterintuitively, skin conductance can be increased following oral (PO) glucose (Solana 2015 **Level IV**; Munsters 2012 **Level IV**). Due to the inconsistent results, skin conductance cannot be recommended for pain assessment in neonates (Hu 2019 **Level IV SR** [PRISMA], 28 studies, n=1,061).

Near infrared spectroscopy

Near infrared spectroscopy (NIRS) measures changes in haemoglobin oxygenation to calculate cerebral blood flow as a proxy for neuronal activity. Regional cerebral blood flow increases in the somatosensory cortex, contralateral to the side receiving a painful stimulus. Two systematic reviews have assessed NIRS correlations with other pain assessment scales (Relland 2019 **Level IV SR** [PRISMA], 8 studies [NIRS], n=237; Benoit 2017b **Level IV SR** [PRISMA], 9 studies [NIRS], n=272) (7 study overlap). NIRS correlated with Premature Infant Pain Profile (PIPP) particularly for the facial expression component (r 0.53 for the right prefrontal area: Ozawa 2011 **Level III-2**, n=80) (r 0.57: Slater 2008 **Level IV**, n=12 [33 tests]) and Neonatal Facial Coding System (NFCS) scores (r 0.27–0.41: Roue 2018 **Level IV**, n=133) but not with Faces Legs Arms Cry Consolability (FLACC) scores (Ranger 2013a **Level IV**, n=42) or Neonatal Infant Pain Scale (NIPS) (Bembich 2015 **Level IV**, n=16). Confounders include gestational age, activation of nearby motor cortex, sleep-wake cycle and previous pain exposure (Bembich 2016 **Level IV**, n=16; Ozawa 2011 **Level III-2**, n=80). Of note, one

third of infants showed NIRS responses without facial changes during some procedures (Slater 2008 **Level IV**, n=33 tests). Similarly NIRS and electroencephalography (EEG) changes do not consistently co-occur in neonates following innocuous cutaneous stimulation (Verriotis 2016b **Level III-2**, n=36). Use of NIRS for pain assessment requires further research.

Neurophysiological monitoring

Using scalp EEG, a pain-specific response that correlates with the spinal withdrawal reflex (1 RCT), and is reproducible, dependent on stimulus intensity and independent of sleep state is demonstrated in preterm and term neonates and infants (Relland 2019 **Level IV SR** [PRISMA], 7 studies [EEG], n=265; Benoit 2017b **Level IV SR** [PRISMA], 8 EEG, n=298) (4 study overlap). A template of brain activity that is sensitive to analgesic administration and quantifies procedural pain in neonates has been identified (Hartley 2017 **Level IV**, n=18). Data has also demonstrated temporal, topographic and amplitude patterns in EEG potentials evolving with neonate and infant neural maturation: from 28 wk gestation nonspecific neural bursts transition to specific somatosensory tactile and nociceptive potentials at 35–37 wk (Green 2019a **Level IV**, n=122; Fabrizi 2016 **Level IV**, n=18 infants & 21 adults; Fabrizi 2011 **Level IV**, n=30 term & 30 preterm). The EEG evolution correlates with development of discriminative facial expression from 33 wk gestational age (Green 2019a **Level IV**, n=122). Additionally, sex-related differences in cortical pain responses in females were consistent with those of adult females (Verriotis 2018 **Level III-2**, n=81), with individual differences in neonates in simultaneously recorded EEG and NIRS data (Verriotis 2016b **Level III-2**, n=36). Researchers reported that PO sucrose reduced PIPP score but did not alter cortical nociceptive activity to heel lance (Slater 2010 **Level II**, n=59, JS 5), and controversially concluded that sucrose may not be an effective analgesic. Scalp EEG measurement has shown promise as a surrogate measure of neonatal pain.

Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) to study brain responses to pain in neonates has gained attention (Benoit 2017b **Level IV SR** [PRISMA], 2 studies [fMRI]: details below). Some similarities are seen in the unique patterns of activity between the neonatal and adult brain in response to painful stimuli (Goksan 2015 **Level IV,** n=10 infants & 10 adults), including when sedated with chloral hydrate (Williams 2015 **Level IV,** n=19 infants). However, the role that this modality may play in pain assessment is still unclear.

Stress markers

Markers of stress have been measured in infant pain studies. In critically ill neonates postcardiac surgery, plasma but not urinary cortisol rose (Franck 2011 **Level IV**, n=81). In healthy newborns, salivary chromogranin and amylase did not change peri-heel lance (Shibata 2013 **Level IV**, n=47), while salivary cortisol rose after venipuncture and correlated with NFCS scores (r 0.42: Roue 2018 **Level IV**). In expreterm neonates in NICU, salivary cortisol was measured in patients receiving painful stimuli (8 studies: 5 heel lance), physical examination and heel lance (2 studies), and standard (2 studies nappy change; 1 study prone positioning) vs pleasant handling (3 studies) (Morelius 2016 **Level IV SR** [PRISMA], 16 studies, n=1,027). Plasma and salivary (but not urinary) cortisol rises with painful procedures, is modified by intervention (cocaine, prone positioning and music), while salivary cortisol does not change with non-painful handling eg nappy change. The review suggests future study designed to address the gaps in our understanding of cortisol regulation in neonates.

Integrated multimodal measurement

An integrated system (NIRS, EEG, electrocardiograph [ECG], electromyelograph [EMG], combined with physiological and behavioural indices) is likely to provide the most reliable and reproducible measurements of noxious stimulation (Roue 2018 **Level IV**, n=113; Worley 2012

Level IV, n=6). This expensive system may feasibly assist bedside tool validation but is unlikely to play a direct role in pain assessment.

10.3.1.3 | Behavioural measures used in neonatal pain assessment

Noxious stimuli produce a series of behavioural responses in neonates and infants that can be used as surrogate measures of pain including crying, changes in facial activity, torso and limb movement, consolability and sleep state (Chorney 2014 **NR**).

Crying

Crying is described in terms of presence or absence, duration, amplitude or pitch. Up to 20% of preterm and some acutely ill infants do not cry or cry inaudibly during heel stick (Johnston 1999 **Level IV**). Amplitude or audible cry occurrence did not correlate with nociceptive brain activity measured with NIRS (Bucher 1995 **Level IV**) and EEG (Relland 2019 **Level IV SR** [PRISMA], 1 study [cry response]: Maitre 2017 **Level IV**, n=54).

Facial expression

Facial expression in response to pain is widely studied and forms part of a number of pain scales, for preterm neonates up to school-aged children (Schiavenato 2012 **Level IV**, n=63) (see Tables 10.1 to 10.3). In neonatal intensive care, facial actions were more reliable than physiological measures for evaluating pain responses (Stevens 2007 **Level IV**) but may be dampened in preterm neonates (Green 2019a **Level IV**, n=122; Slater 2008 **Level IV**, n=12 [33 tests]; Holsti 2007 **Level IV**, n=92) and, like cry, may be absent (Hartley 2017 **Level IV**, n=18; Slater 2008 **Level IV**, n=33 tests), not linked to nociceptive brain responses (Hartley 2017 **Level IV**, n=18) or be present only if previous noxious stimulus has been experienced (Ozawa 2011 **Level III-2**, n=80). The use of video recordings for translation to pain scales' graphics (Schiavenato 2012 **Level IV**, n=63) has been superseded by facial recognition software. The latter has been validated with various neonatal and infant observer pain scales and provides automated identification of the expression of pain (Sakulchit 2019 **Level IV**, n=77; ; Xu 2018b **Level IV**, n=143; Zhi 2018 **Level IV**, n=26 [204 images]; Zamzmi 2018 **Level IV**, n=8 [15 videos]; Heiderich 2015 **Level IV**, n=30 [360 images]) and may overcome clinician bias when assessing facial expression (Blais 2019 **Level IV**, n=20 [adults]).

Contextual influences

Contextual factors include physical, psychological and social elements. A number of contextual factors influence the specificity and sensitivity of behavioural responses in ex-preterm neonates (Sellam 2011 **Level IV SR** [PRISMA], 23 studies, n=1,649). Pain can be affected by behavioural state (awake, asleep, activity prior to a stimulus), distress for other reasons (eg hunger and fatigue), age (postmenstrual and postnatal) and neuromuscular developmental status. Previous pain exposure and handling (Ozawa 2011 **Level III-2**, n=80; Holsti 2006 **Level IV**, n=43) altered both behavioural and physiological responses, eg infants experiencing higher numbers of procedures have reduced facial expression in response to pain, reduced nociceptive brain activity (Ozawa 2011 **Level III-2**, n=80), reduced brain maturation (Ranger 2013b **Level IV**, n=42; Brummelte 2012 **Level IV**, n=86) and long term alteration of their pain pathway processing on MRI (Hohmeister 2010 **Level III-3**, n=27). Sex differences are inconsistent: female vs male neonates, both preterm and term, have more facial actions (Verriotis 2018 **Level III-2**, n=81; Guinsburg 2000 **Level III-2**, n=65) but no difference in PIPP scores or cortical activity (Ozawa 2011 **Level III-2**, n=80) and, in preterm infants only, no difference in NFCS scores (Valeri 2014 **Level III-2**, n=53). In most studies, severity of illness or neurological impairment was not associated with altered behavioural pain responses. However, data in term infant NICU patients suggested that stress and illness impacts on cortical activity in the absence of behavioural changes (Jones 2017 **Level IV**, n=56). Surveyed health providers' knowledge gaps and attitude affect scoring and provision of pain relief (Cong 2013a **NR**).

Observational scales

The reliability and validity of behavioural measures is best established for procedural interventions such as heel lance but many observational scales have not been rigorously evaluated (Meesters 2019 **Level IV SR**, 9 studies, n=645). The PIPP (Stevens 2010 **Level IV SR**, 62 studies, n=3,158) and COMFORT scales (Maaskant 2016 **Level IV SR** [PRISMA], 30 studies, n=2,593) are the best validated and most widely used (McGrath 2008 **GL**). The PIPP-revised (PIPP-R) has had validation initially (Stevens 2014a **Level IV**, n=137) and after translation into 6 other languages (Bueno 2019 **Level IV**, n=187; Olsson 2018 **Level IV**, n=37; Taplak 2019 **Level IV**, n=200). The FLACC scale, developed for infants >2 mth old, was used in hospitalised neonates with simultaneous assessment with PIPP in a skin conductance study (Ahmed 2015 **Level IV**, n=85 [measurements]).

The following scales are recommended in reviews spanning a decade (Eriksson 2019 **NR**; Hatfield 2015 **Level IV SR,** 10 studies n=742; Lee 2014 **NR**; Cong 2013b **NR**; Howard 2008a **NR**). They are supported by current data (see Tables 10.1 and 10.2 with relevant references) acknowledging that the evidence supporting the psychometrics of recommended scales is usually Level III or IV (Andersen 2017 **Level I** [PRISMA], 12 SRs (number of studies & n unspecified):

- Acute procedural pain — PIPP; Neonatal Facial Coding Scale (NFCS); Neonatal Pain, Agitation and Sedation Scale (N-PASS);
- Postoperative pain — PIPP; N-PASS;
- Intensive care — COMFORT; COMFORTneo; COMFORT B (for repeated acute pain exposures termed "persistent" pain in intensive care patients); Faceless Acute Neonatal Pain Scale (FANS) (when facial expression is concealed eg with nasal continuous positive airway pressure) (Milesi 2010 **Level IV**, n=53).

10.3.2 | Pain assessment in infants and children

Observational and behavioural scales

Assessment for infants and young children is largely achieved using observational assessment scales. Many scales incorporate both physiological and behavioural parameters to determine an overall pain score and may result in more comprehensive measurement (Lee 2014 **NR**; Chorney 2014 **NR**). Some examples are included in Table 10.2 but a wider range of measures, their strengths and limitations and issues of testing reliability and validity have been reviewed (Chorney 2014 **NR**; Lee 2014 **NR**; van Dijk 2012 **NR**; McGrath 2008 **GL**; von Baeyer 2007 **Level IV SR**, 129 studies, n unspecified; Johnston 2003 **NR**). In infants and young children, behavioural items that predicted analgesic demand in the postoperative period were crying, facial expression, trunk and leg posture and motor restlessness, but physiological variables were unreliable (Buttner 2000 **Level III-2**).

There is still no single gold standard for pain assessment as requirements vary with the age and developmental stage of the child, the type of pain (eg procedural vs postoperative), and the context (eg clinical utility vs research reliability). Based on reviews summarising the wide data on this topic, the following observational/behavioural measurement tools are recommended for pain measurement in infants ≥1 y (McGrath 2008 **GL**), children and adolescents (Crellin 2018 **Level IV**, n=100; Crellin 2015 **Level IV SR** [PRISMA], 52 RCTs & 26 psychometric studies, n unspecified; Chorney 2014 **NR**; von Baeyer 2007 **Level IV SR**, 129 studies, n unspecified) (see Table 10.2):

- Acute procedural and postoperative pain — FLACC
- Postoperative pain managed by parents at home — Parents Postoperative Pain Measure (PPPM); and
- Intensive care — COMFORT & COMFORT B scales.

10.3.3 | Self-report in children and adolescents

10.3.3.1 | The change in capacity of children to self-report with age

Self-report of pain is preferred when feasible, and is possible to an extent from 4 y of age, dependent upon the child's cognitive and emotional maturity. Scales for self-report need to consider the child's age, their ability to differentiate intensity levels, and their ability to separate the emotional from the physical components of pain (von Baeyer 2014 **NR**) (see Table 10.3). It is important that a measurement tool be used regularly and uniformly within each centre as staff familiarity and ease of use are major factors in the successful implementation of a pain management strategy. Children aged 3 y cannot provide valid graded self-report of pain intensity, and the evidence is weak for the capacity of those aged 4 y with published scales (Birnie 2019 **Level IV SR** [PRISMA], 80 studies, n unspecified; von Baeyer 2017 **Level IV SR** [PRISMA], 14 studies n=766) (8 study overlap). For 4 y olds and some 3 y olds, performance can improve by confirming pain is present, then providing an explanation of the scale with a reduced number of choices (eg 3 choices with the Simplified Faces Pain Scale or Pieces of Hurt: low, medium, high hurt). From 5 y, the standard 6 choice Faces Pain Scale-revised (FPS-R) (Figure 10.1) can be used and provides extra data (Emmott 2017 **Level II**, n=180, JS 3). At around 5 y, children have some capacity to appraise current pain and match it to previous experience, but they are more likely to choose the extremes of the scale (von Baeyer 2009b **NR**). In scales anchored with smiling or tearful faces, pain may be confused with other emotional states such as happiness, sadness or anxiety (Tomlinson 2010 **Level IV SR**, 127 studies, n=17,372).

Between ages 7–10 y, children develop numerical competency skills with measurement, classification and seriation (ie placing things in ascending or descending order). The upper end of the scale is less static than in adults changing with the individual child's ability to objectify, label and remember previous pain experiences (von Baeyer 2014 **NR**). Literacy is also important regarding the wording associated with the scales' upper anchor (such as most pain or worst pain imaginable vs very much hurt); this is also relevant for between study consistency (Castarlenas 2017 **Level IV SR** [PRISMA], 15 studies n=2,174; von Baeyer 2009a **NR**).

It is not until 10–12 y that children can clearly discriminate the sensory intensity and the affective emotional components of pain and report them independently (McGrath 1996 **Level III-2**). Verbally competent children aged ≥12 y can understand multidimensional tools designed for adults such as the McGill Pain questionnaire (MPQ) (see below).

10.3.3.2 | Unidimensional pain intensity paediatric self-report scales

Of sixty self-report scales, only eight have well established reliability and validity for acute pain assessment in children and adolescents (aged 3–18 y): Pieces of Hurt tool (scored 0–4); Faces Pain Scale-Revised (FPS-R) (0–10); Oucher pain scale photographic and numeric scales (0–10); Wong-Baker FACES Pain Rating Scale (WBFPRS) (0–10); Visual Analogue Scale (VAS) (0–100 mm), Colour Analogue Scale (CAS) (0–10) and Numeric Rating Scale NRS-11 (0–10) (Birnie 2019 **Level IV SR** [PRISMA], 80 studies, n unspecified).

Numeric Rating Scale (NRS)-11

The NRS-11 has the greatest number of studies assessing its measurement properties (Birnie 2019 **Level IV SR** [PRISMA], 24 NRS-11 studies [7 postoperative], n unspecified) including correlation between PACU scores by children aged 4–16 y with the nurse and parent (Brahmbhatt 2012 **Level IV**, n=33). This scale has been validated across a variety of paediatric settings and is available in a number of formats (verbal/printed/electronic) (Castarlenas 2017 **Level IV SR** [PRISMA], 15 studies n=2,174) (14 study overlap with Birnie 2019). Children <8 y may require screening tasks to assess numerical competency to then use the NRS-11 effectively.

Faces pain scales (FPS)

Of the fourteen FPSs, four have undergone extensive psychometric testing: FPS, FPS-R, Oucher and WBFPRS (Tomlinson 2010 **Level IV SR** [PRISMA], 127 studies, n=13,388). When given the choice, children prefer faces scales in general. The WBFPRS is most preferred but its smiling and crying anchor faces may lead to confounding with affect and it has weak recommendation for use (Birnie 2019 **Level IV SR** [PRISMA], 16 WBFPRS studies [1 postoperative], n unspecified). While the FPS-R (second to NRS-11 in the number of studies assessing measurement properties) is strongly recommended for research purposes (Birnie 2019 **Level IV SR** [PRISMA], 21 FPS-R studies [8 postoperative], n unspecified). In the ED setting, FPS-R (Tsze 2013 **Level IV**, n=620) and WBFPRS (Garra 2013 **Level IV**, n=197) have been validated. An electronic version FPS-Re has also been validated and is preferred by children (Birnie 2019 **Level IV SR** [PRISMA], 4 FPS-Re studies, n unspecified).

Coloured analogue scale (CAS)

The CAS has been assessed in the same review as the above 2 scales, mostly in English (and 4 other languages) and is strongly recommended for ≥8 y (Birnie 2019 **Level IV SR** PRISMA, 19 CAS studies [5 postoperative], n unspecified). It is coloured from small white gradations widening up to deep red, with a slider form with a 0–10 back measure or a pocket sized scale with variations in the upper anchor's wording.

Visual analogue scale (VAS)

The VAS form in children is the same as that used for adults with either a line or rule and 100mm scale, with numerical values of 0–10 or 0–100 mm. It has been assessed in children mainly in acute pain conditions with a weak recommendation for use ≥ 8 y (Birnie 2019 **Level IV SR** [PRISMA], 15 VAS studies [4 postoperative], n unspecified).

10.3.3.3 | Recommended scales according to age

Using chronological age as a guide of developmental stage, the below scales are recommended for acute pain assessment (with weaker recommendations for postoperative and chronic pain assessment) (Birnie 2019 **Level IV SR** [PRISMA], 80 studies n unspecified; von Baeyer 2017 **Level IV SR** [PRISMA], 14 studies, n=766; Tomlinson 2010 **Level IV SR** [PRISMA], 127 studies, n=13,388; Emmott 2017 **Level II**, n=180, JS 3):

- <4 y —self-report unreliable
- 4–5 y —Simplified-FPS or Pieces of Hurt
- Some 5y and ≥6y —NRS-11 (which requires numerical competency) & FPS-R
- ≥8 y —CAS & VAS

The validity of the gold standard of asking for and documenting pain scores is being questioned, due to the inherent subjective nature of self-report (von Baeyer 2014 **NR**; Berde 2012 **NR**). As is occurring in paediatric chronic pain assessment (Varni 2010 **Level IV**, n=3,048), acute paediatric pain measurement may warrant inclusion of measures of self and observed functional impairment (eg post laparotomy the child is remaining in bed vs able to sit out in chair vs attend ward play room or in-hospital school) combined with rescue analgesic use. This is particularly relevant when self-reported pain scores are either high or low and conflict with the clinical context and the paediatric clinicians' observations (von Baeyer 2014 **NR**).

Paediatric pain scale investigators argue that self-report scales of pain intensity are more valuable on a population or research level than for effective pain management for an individual child (Twycross 2015 **NR**). They suggest pain scores are best considered a primary source of information rather than a gold standard. Particularly in younger children, assessment should combine self-report with observations of activity, parental report and consideration given to psychosocial influences.

10.3.3.4 | Concordance between pain scales and subdivisions within scales

Debate continues as to concordance between the various scales (Le May 2018 **NR**; Sanchez-Rodriguez 2012 **NR**). NRS-11 correlates with FPS-R, VAS and CAS but this does not reflect agreement or interchangeability.

The minimum clinically significant difference (MCSD) for the NRS-11 is 1/10 (Castarlenas 2017 **Level IV SR** [PRISMA], 4 studies [MCSD], n=496). In the ED triage setting, for the Verbal V-NRS, MCSD and Perceived Patient Adequate Analgesia (PPAA) were both 2/10 and for the FPS-R was 2/10 and 4/10 respectively (Tsze 2019a **Level IV**, n=431 [344 VNRS and 415 FPS-R analysed]); the same group assessed FPS-R with MCSD of 2/10 vs CAS which was 1/10 (Tsze 2015 **Level IV**, n=314).

Suggested subdivisions for no, mild, moderate and severe pain are respectively: 0 to 2, 4, 6, and 8 to 10 for FPS-R vs 0 to 1, 1.25 to 2.75, 3 to 5.75 and 6 to 10 for CAS (Tsze 2018 **Level IV**, n=620).

Suggested VAS cut-offs for children and adolescents are 35 mm for mild pain and 60 mm for severe pain (in contrast to adult cut-offs of 30 mm and 70 mm respectively) (Hirschfeld 2013 **Level IV**, n=5,258). Pain intensity measurements within 12 mm on the paper VAS may be considered the same (Bailey 2012 **Level IV**, n=151).

Of importance, pain scale subdivisions or cut-offs and pain scores, as a uni-dimensional assessment, should not be used solely to guide the administration of analgesia.

10.3.3.5 | Facial recognition software applications

Types of facial recognition software applications (relevant to infants, children and adults) presented in computing conference abstracts over the last decade have been summarised (Subramaniam 2018 **NR**).

Digital burst photographs taken by iPhone® of young children during venipuncture were imported into an Emotion Application Programming Interface (Sakulchit 2019 **Level IV**, n=77). A subsequent 8 face pain scale was developed which correlated with FLACC scores (positively for 'sadness' and negatively for neutral expression) and was sensitive to EMLA use.

Facial videos of older children aged 5–18 y were taken post-laparoscopic appendicectomy at rest (ongoing pain) and with abdominal palpation (transient pain) at three time points (postoperatively, 20 h post and POD 21) to assess pain trajectory (Sikka 2015 **Level IV**, n=50). These were analysed with a computer expression recognition toolbox. The facial action units were compared to blinded self, parental and nursing report using NRS-11. A binary pain (4/10) vs no pain (0/10) and continuous model were developed. The computer version machine learning (CVML) system was accurate for binary classification and correlated with self and parental report (including over time). As nurses under reported pain vs child and parents, the CVML detected pain more accurately than nurses (particularly for ongoing pain). A similar CVML process was conducted in primarily Hispanic teenagers also at three time points post-laparoscopic appendicectomy (within 24 h, subsequent day, and POD 25) (Xu 2018b **Level IV,** n=143). With transfer learning, the ROC curve improved to better detect true positives and was consistent when tested on a new pain data set.

10.3.3.6 | Observer-rated or composite scales used prehospital and in EDs

The French Evaluation ENfant DOuLeur (EVENDOL) scale (0–15) for children aged 0–7 y was developed as a single observer-rated scale for pain assessment prehospital (Beltramini 2019 **Level IV**, n=422 [144 in pain]) and in EDs (Fournier-Charriere 2012 **Level IV**, n=291). It has been translated into English but not reviewed systematically.

The UK Royal College of Emergency Medicine launched the Composite Pain Scale; this combines a modified WBFPRS (4 faces) (observer-rated <8 y and self-reported ≥8 y) with an observer-rated behaviour scale, injury example prompts and NRS-11 self-report for older children (James 2017 **Level III-2**, n=117). Pain scores were then categorised as absent, mild, moderate or severe. Doctors and nurses correlated well including with the older child's face scale report, but not with the V-NRS-11 component.

10.3.3.7 | Function scales: observed vs self-report

As in paediatric chronic pain assessment (Varni 2010 **Level IV**, n=3,048), acute paediatric pain measurement may warrant inclusion of measures of self and observed functional impairment (eg post laparotomy the child remaining in bed vs able to sit out in chair vs attend ward play room or in-hospital school) and rescue analgesic use.

An in-hospital Youth Acute Pain Functional Ability Questionnaire has been developed in children admitted with sickle cell crises and subsequently validated in children post-surgery (Rabbitts 2017 **Level IV**, n=564). A 3 item short form with 5 point Likert rating of capacity to dress, wash and go outside the room was developed (assuming normal baseline capacity). Functional capacity is particularly relevant when self-reported pain scores are either high or low and conflict with the clinical context and the paediatric clinicians' observations (von Baeyer 2014 **NR**).

10.3.3.8 | Multidimensional pain intensity self-report scales for adolescents

One tool modelled after the MPQ, the Adolescent Pediatric Pain Tool assesses pain with a body diagram, word intensity scale and multiple quality descriptors (Fernandes 2014 **Level IV SR**, 23 studies, n=1,750 children & adults). It has been validated in multiple settings: acute and chronic pain, hospital, home, and in English and Spanish (pending further validation in Portuguese and Chinese). The extra dimensions are useful to examine effectiveness of pain management but pen/paper and 3–6 min time is required to complete it, and further validation in interventional studies and consistency scoring across studies is needed.

10.3.4 | Children with cognitive impairment or intellectual disability

Most children with intellectual disability (ID) or severe cognitive impairment (CI) experience pain proportional to their degree of neurological impairment (Hauer 2017 **NR**) and probably in a similar way to their peers. However, there are some examples of disorder-specific alterations in pain perception eg the higher pain and temperature threshold seen in patients with Prader-Willi syndrome (de Knegt 2011 **NR**). In addition, children with ID/CI or communication difficulties (including neonates at risk of neurological impairment in intensive care) may experience more pain episodes than other children because of their associated complex medical disorders/neurological impairment, physical comorbidities and increased need for procedures (Hauer 2017 **NR**; Breau 2009 **NR**; Stevens 2003 **Level III-2**, n=194). Both neonates (who were perceived in the past as being less responsive to painful stimuli) (Breau 2006 **Level III-2**, n=99 [clinicians]; Stevens 2007 **Level IV**, n=149) and older children with CI (Valkenburg 2012 **Level III-3**, n=45 [15 Downs syndrome]) have received less analgesia vs peers. Assessment of pain is difficult in ID/CI, particularly in the severe neurological impairment cohort, and can contribute to inadequate analgesia (Hauer 2017 **NR**). Older children with CI received less analgesia during surgery but comparable amounts and types of analgesics as cognitively intact children postoperatively (Valkenburg 2012 **Level III-3**, n=45; Long 2009 **Level III-3**, n=148; Koh 2004 **Level III-2**, n=290) contrasting with the findings in an earlier series (Malviya 2001 **Level III-3**, n=42).

10.3.4.1 | Pain assessment scales for children with neurodevelopmental disorders and severe cognitive impairment (CI)

Observer-rated scales

Specific observer-rated behavioural tools have been developed for children with neurodevelopmental disorders and severe CI (Crosta 2014 **Level IV SR**, 7 studies [4 tools], n≈270; Valkenburg 2010 **NR**) (see Table 10.4). Behaviours reported by carers to be associated with potentially painful stimuli, and that discriminate these from distressful or calm events, have been compiled in the revised Non-Communicating Children's Pain Checklist (NCCPC-R) for home (Breau 2002a **Level IV**) and postoperative use (NCCPC-PV) (Crosta 2014 **Level IV SR** 1 study: Breau 2002b **Level IV**, n=24). Cut-off scores for NCCPC-PV were developed against VAS scores, with good inter-observer reliability between primary carer and the researcher who had not met the child. It has been translated and validated in French, Swedish and German. NCCPC does not need to be individualised for the patient, it discriminates distress from pain but was rated least desirable by clinicians based on complexity and length (2 h observation) vs other scales (Quinn 2015 **NR**). The NCCPC scales have formed the basis of validated adult scales – Chronic Pain Scale for Non-verbal Adults with Intellectual Disabilities (CPS-NAID) (24 items for persistent pain) and Non-Communicating Adult Pain Checklist (NCAPC) (18 items for acute/procedural pain) (Breau 2009 **NR**).

The Paediatric Pain Profile (PPP) rates 20 behaviours to assess pain in children with neurodevelopmental disorders and severe CI (Crosta 2014 **Level IV SR,** 1 study: Hunt 2004 **Level IV**, n=140). It includes the child's pain history, baseline and ongoing pain assessments, interventions and discussion with clinicians about the child's pain but does not require knowing the individual behaviours. This scale had demonstrated potential for children with recurrent acute (persistent) pain at home but was less sensitive perioperatively. Its usability is limited by its teaching requirements and length (Crosta 2014 **Level IV SR**). The PPP is validated and used across all Gross Motor Function Classification System (GMFCS) levels of cerebral palsy (CP) (Kingsnorth 2015 **Level IV SR**, 240 studies, [54 chronic pain assessment tools screened]). It is more accurate but takes longer (5 min vs 1) and is less preferred than revised (r)FLACC (see below). Of note (as with neonates), salivary cortisol measurement in children with severe neurological disability was not found a useful marker for pain assessment (Hunt 2007 **Level IV**, n=29).

An Individualised Numeric Rating Scale (INRS), where carer proposed pain indicators are ranked on a 0–10 NRS scale, has been validated for pain assessment in children with severe CI (Crosta 2014 **Level IV SR**, 1 study: Solodiuk 2010 **Level IV**, n=50). The bedside nurse INRS scores correlated with but were lower than the carer's assessment, with only modest correlation with NCCPC-PV. INRS use fosters carer and nurse collaboration. As it is developed with input from carers and educators, it may be the best option for school nurses (Quinn 2015 **NR**).

The rFLACC scale (0–10), incorporating specific descriptors and parent-identified behaviours for individual children, has also been developed for children with severe CI (Crosta 2014 **Level IV SR**, 1 study: Malviya 2006a **Level IV**, n=52). It remains the easiest, preferred and most flexible tool to use in the acute hospital setting (Crosta 2014 **Level IV SR**, 7 studies, n≈270). Compared to VAS-observer (0–10), rFLACC (Danish) was valid and reliable for pain assessment post-orthopaedic surgery in children with CP GMFCS II–V; 2 nurse observers experienced in nursing children with CP scored video-recordings and had high intra-rater reliability (Pedersen 2015 **Level IV**, n=27). When assessing videotapes without audio of children with CP (all GMFCS grades I to V) having physiotherapy, the Child Facial Coding System (which codes 13 facial actions; 10 of which indicate pain not present) correlated with observer-rated NRS-6 (Hadden 2016 **Level IV**, n=85). Future work using pain expression facial coding combined with facial recognition software and computer

learning algorithms may be useful in children who cannot self-report, as is being explored for adults with dementia (eg PainChek®) (Atee 2018 **NR**).

Self-report scales in children with neuromuscular disorders and lower degrees of cognitive impairment

Self-report scales may not be reliable even in those with mild to moderate CI (Quinn 2015 **NR**). For physically disabled children aged 8–20 y with various neuromuscular disorders and no CI, self-report with NRS outperformed the WBFPRS (4 faces) and 6 point Verbal rating scale (Miro 2016 **Level IV**, n=113). A study assessed self-report NRS-6 (0–5) vs observer-rated NCCPC-PV in children with CP of varying severity (diplegic 32% to quadriplegic 54 %) having physiotherapy (Hadden 2015 **Level III-2**, n=63). The children had their hearing, vocabulary and receptive knowledge assessed and 52% were able to self-report. Carer ratings were lower than ratings by researcher, physiotherapist and the child capable of self-report.

10.3.4.1 | Children with Autism Spectrum Disorder (ASD)

ASD is a developmental disorder affecting communication, socialisation and sensory processing to varying degrees, which may influence the reliability of the pain assessment scales (Allely 2013 **Level IV SR** [PRISMA], 10 studies & 5 case reports, n=1,137). Assessment is further complicated by the frequent comorbidities of altered perception (hypo and hypersensitivity), anxiety, attentional deficient disorder and ID. Typical pain behaviours (pain expression) may be absent in some patients, which does not reflect an absence of pain perception and can lead to underappreciation, even by carers. In fact, individuals with ASD who self-injure may have pain insensitivity (Allely 2013 **Level IV SR** [PRISMA] , 10 studies & 5 case reports, n=1,137) or enhanced pain expressions (Courtemanche 2016 **Level III-3**, n=51). For children with limited understanding of graded response, carers should be asked to complete individualised pain behaviours on the rFLACC scale. For children with ASD who are verbal and can grade response, a qualitative perioperative study recommends the following (Ely 2016 **Level IV**, n=40):

- Individualise care by using words familiar to each child;
- Describing pain is possible and often preferred to using a numerical scale – extremes are selected when using self-report scales;
- Locating pain is a favoured technique to start with – most can describe but some find this anxiety provoking;
- Children frequently rely on their parents to confirm or validate their report or to interpret behaviours/social cues;
- Facial expressions and body language often do not match pain scores or descriptors of pain intensity.

For pain assessment in less acute daily living, NCCPC (French) with some modifications for ASD behaviours was useful (Dubois 2017 **Level IV**, n=35).

KEY MESSAGES

1. Pain measurement tools are available for children of all ages (**S**) (**Level IV SR**).
2. Paediatric pain measurement tools must be matched to the age and development of the child (**U**) (**Level IV SR**).
3. Adoption of written guidelines or pain management algorithms improves both assessment and management of pain in neonates and children (**N**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Pain assessment and measurement are important components of paediatric pain management (**U**).

☑ Pain scores generated from different pain scales may not be congruent and this should be considered when used clinically and in research (**N**).

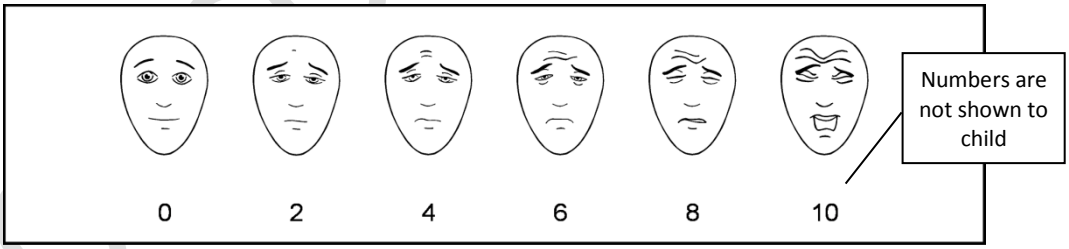
☑ Pain scores and pain score subdivisions (cut-offs) should not be used as a sole guide to administration of analgesia (**N**).

☑ Children with neurodevelopmental disorders (with and without cognitive impairment and varying levels of physical disability) may be more susceptible to pain and communicate it in different ways (**N**).

☑ Pain measurement tools must be appropriate for the clinical context, be explained and used consistently (**U**) and be validated when translated into other languages (**Q**).

☑ Facial recognition software applications may reduce clinician bias and become useful bedside tools in neonates and children with and without cognitive impairment (**N**).

Figure 10.1 | Faces Pain Scale — Revised



Note: *The full-size version of the FPS-R, together with instructions for administration (available in many languages), are freely available for non-commercial clinical and research use from www.iasp-pain.org/FPSR.*

Source: *FPS-R; (Hicks 2001); adapted from (Bieri 1990).*
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Table 10.1 | Acute pain intensity measurement tools — neonates

Scale	Indicators	Score	Utility
Unidimensional			
NFCS Grunau 1987 Johnston 1993	Brow bulge Deep nasolabial fold Eyes squeezed shut Open mouth Taut tongue Horizontal mouth stretch Vertical mouth stretch Pursing of lips Chin quiver Tongue protrusion	Presence or absence of action during discrete time intervals scored	Preterm to 4 mth Procedural pain
Multidimensional			
PIPP Stevens 1996 PIPP-Revised (PIPP-R) Stevens 2014a	Postmenstrual age Behavioural state Heart rate Oxygen saturation Brow bulge Eye squeeze Nasolabial furrow	Each scored on 4-point scale (0,1,2,3) ≤6 = minimal pain; >12 = moderate to severe pain In the revised form postmenstrual age and behavioural state points are only applied if other variables indicate pain.	Procedural pain in preterm and term neonates; Postoperative pain in term neonates
Neonatal Infant Pain Scale (NIPS) Lawrence 1993	Facial expression Cry Breathing patterns Arms Legs State of arousal	Each scored on 2 (0,1) or 3-point (0,1,2) scale; total score: 0–7	Preterm and term neonates; Procedural pain
CRIES Krechel 1995	Crying Requires oxygen for SaO_2 >95% Increased vital signs (heart rate/blood pressure) Expression Sleeplessness	Each scored on 3-point scale (0,1,2); total score: 0–15	32–60 wk Postoperative pain

Scale	Indicators	Score	Utility
N-PASS Hummel 2008	Crying/irritability Behavioural state Facial expression Extremities tone Vital signs (heart rate/blood pressure/SaO_2)	Each scored on 5-point scale (-2,-1,0,1,2); Total score: -10 to +10 with minus scores reflecting responses if sedated Extra point added for prematurity <30 wk Score >3 indication for treatment	23–40 wk Postoperative pain; Procedural pain; Persistent pain; Sedation level
COMFORTneo Modified from COMFORT B van Dijk 2009	Alertness Calmness/agitation Respiratory response (ventilated) or crying (spontaneous ventilation) Body movement Facial tension Muscle tone	Each scored on 5-point scale (1–6); total score: 6–30 Score >14 indicating moderate-severe pain/distress	24–42 wk Prolonged pain; Sedation
FANS Milesi 2010	Acute discomfort Limb movements Vocal expression Heart rate variation	Each scored differently; total score: 0–10 Nonintubated but face not visible	30–35 wk Procedural Pain

Note: Further details available in Lee 2014; Cong 2013b; Howard 2008a; Bandstra 2008;.

Table 10.2 | Composite scales for infants and children

Scale	Indicators	Score	Utility
CHEOPS Chorney 2014	Cry Facial expression Verbal expression Torso position Touch Leg position	Each scored as 0, 1, 2 or 3; total score 4–18	1–7 y Postoperative pain; Procedural pain
FLACC Merkel 1997 Crellin 2015	Face Legs Activity Cry Consolability	Each scored on 3-point scale (0,1,2); total score 0–10	Young children Postoperative pain
COMFORT scale Ambuel 1992	Alertness Calmness/agitation Respiratory response Physical movement	Total score 8–40	Newborn to adolescent Distress in paediatric intensive care unit;

Scale	Indicators	Score	Utility
COMFORT B scale (behavioural elements) van Dijk 2000	Muscle tone Facial expression Mean arterial pressure Heart rate		Postoperative pain 0–3 y (van Dijk 2000); Downs Syndrome 0–3 y (Valkenburg 2011); Burns 0– 5 y (de Jong 2010); Post-cardiac surgery in term infants (Franck 2011)

Further details available in Chorney 2014 and Howard 2008a.

Table 10.3 | Self-report tools for children

Scale	Components	Anchors	Utility
Poker Chip Tool Hester 1979	4 chips=pieces of "hurt"	± white "no pain" chip; 1 chip="a little hurt"; 4 chips="most hurt you could ever have"	4–6 y Procedural; Acute and Postoperative pain
FPS-R Hicks 2001	6 graphically depicted faces Simplified version for 4 y electronic versions available	Neutral anchors Verbal anchors: No pain to Very much pain	>5/ 6 y Acute pain; Postoperative pain; Chronic pain
WBFPRS Wong 1988	6 cartoon faces (and 4 cartoon faces) culturally adapted versions	Faces graded from smiling to tears with verbal anchors from "no hurt" to "as much as you can imagine"	6 y Acute pain; Procedural pain
Coloured Analogue Scale McGrath 1996	Modification of 10 cm horizontal VAS; scored 0–10 in 0.25 increments ruler or flat Electronic version	Gradations in colour (white to deep red) and area (progressively wider tetragon); verbal labels "no pain" to "most pain"	>6 y Acute pain; Postoperative pain
Numeric Verbal Scale (NRS-11) Miro 2009	Pain intensity from 0–10 Electronic version	0=No pain or hurt 10 worst pain or hurt you can imagine/possible	>6 y Acute pain; Postoperative pain; Chronic Pain

Further details available in Birnie 2019 and von Baeyer 2014.

Table 10.4 | Sample of observational pain assessment scales for intellectually disabled children

Scale	Components	Score	Utility
NCCPC-PV Breau 2002b NCCPC-R for home setting Breau 2002a	Facial Vocal Social Activity Body and limbs Physiological (Eating/sleeping in NCCPC-R)	27 items over 6 domains, rated 0–3 based on frequency of behaviour over a 10 min observation period; total score 0–81 score 6–10 mild pain >11/81 mod pain (≥3 on VAS) (NCCPC-R 30 items scored over a 2 h period: >7/90 indicates pain)	Nonverbal/ID 3–18 y Postoperative pain Familiarity with child not necessary Other languages Requires 2 h observation
PPP Hunt 2004	20 typical pain behaviours selected based on interview and questionnaire	20 items scored 0–3 based on frequency of behaviour; total score 0–60 14/60 moderate pain	1–18 y Pain Takes 5 min
Revised (r)FLACC Malviya 2006a	Face Legs Activity Cry Consolability	5 items each scored on 3-point scale (0,1,2); total score 0–10 4/10 Moderate Pain Can individualise	4–19 y ID Postoperative pain Takes 1 min
INRS Solodiuk 2010	Individual Pain indicators proposed by carers	0–10 NRS scale with pain indicators superimposed Needs to be collaboratively individualised	6–18 y Nonverbal ID Postoperative pain Needs time to design

Further details available in Chorney 2014, Crosta 2014 and Valkenburg 2010.

10.4 | Analgesic agents

The following section describes the evidence supporting the use of various medications as analgesics in children. Most medications listed (beyond paracetamol, ibuprofen and morphine) are not licensed for paediatric use. Consequently, they are often used off-label (Kimland 2012 **Level IV SR**, 18 international hospital & primary care studies) for acute (and also chronic) pain management, or are used below licensed age cut-offs (such as 6 or 12 mth or 12, 16 and 18 y) or by non-licensed novel routes, with both being accepted practice (which then varies locally and regionally). Commonly doses for 'routine and non-routine off-label' use (TGA 2013 **GL**) are extrapolated from adult dosing and this is frequently unsupported by either paediatric pharmacokinetic (PK) data (in particular) or pharmacodynamic (PD) study. Considerations pertinent to paediatrics are that countries differ in their licensing for single agents including nonuniformity of age cut-offs and in the formulation types and strengths available. Further to this, when a suspension is not available, adult tablets and capsules require cutting/crushing/dispersing and often disguising (eg in food to improve palatability), which has implications for compliance and dose administration error.

10.4.1 | Paracetamol (acetaminophen)

Paracetamol is effective for mild to moderate pain in children (Allegaert 2017 **NR**; Marzuillo 2014 **NR**). The dose required for analgesia is greater than for antipyretic effect. The proposed mechanism of analgesic action includes inhibition of prostaglandin synthesis and central cannabinoid/TRPV1 receptor (Allegaert 2017 **NR**; de Martino 2015 **NR**; Graham 2013 **NR**) and indirect serotonergic effects (see also adult Section 4.1.1). The serotonergic mechanism has been investigated in adults, and subsequently in children undergoing tonsillectomy (Ramirez 2015 **Level II**, n=69, JS 4). Children received paracetamol, corticosteroid, fixed dose morphine/ nonselective non-steroidal anti-inflammatory drugs (nsNSAIDs) and ondansetron vs droperidol intraoperatively. More ondansetron vs droperidol recipients required rescue morphine in PACU (57 vs 21%), suggesting ondansetron suppressed paracetamol's analgesic effect.

10.4.1.1 | Efficacy

Paracetamol has similar efficacy to nsNSAIDs depending on the surgery type assessed. Paracetamol is a useful adjunctive treatment as part of multimodal analgesia for more severe pain. A systematic review of paracetamol has defined the NNT for different doses in adults, with no evidence of dose-dependent effect (see Section 4.1.2 and in Chapter 5 Table 5.1); this has not been defined for children. Paracetamol is established as opioid-sparing in adults (see Section 4.1.2). In children, opioid-sparing efficacy is variably demonstrated and dependent upon the route of administration, the duration of therapy and follow-up, and dose size used. The RCTs and subsequent systematic reviews are challenged by variable timing of administration and various outcomes. Interpretation is complicated by study heterogeneity and inclusion of surgical procedures with low postoperative analgesic requirements, as well as the lack of data regarding equipotent dosing between the different comparators (Marzuillo 2014 **NR**). In many instances, paracetamol is considered the standard of care in various RCTs where additional medication intervention is then assessed. It has been recommended as part of routine multimodal therapy for post tonsillectomy analgesic protocols by various bodies (Mitchell 2019 **GL**). The RCTs where paracetamol is one of the treatment arms are presented below.

Paracetamol use in neonates and infants

A review has been performed of use in neonates and infants in heterogeneous painful conditions (Ohlsson 2016 **Level I** [Cochrane], 9 RCTs, n=728):

- Post major thoracic (noncardiac) or abdominal surgery, IV paracetamol 30 mg/kg/d reduced cumulative morphine dose in the first 48 h postoperatively (MD -157 mcg/kg; 95%CI -27 to -288) but did not reduce pain scores or opioid-related adverse effects (Ohlsson 2016 **Level I** [Cochrane], 1 RCT: Ceelie 2013 **Level II,** n=71, JS 5). While in a similar patient group, PR paracetamol was not morphine-sparing (Wong 2013b **Level I** [PRISMA], 1 RCT: van der Marel 2007 **Level II**, n=71 [57 analysed], JS 5).
- Following heel lance, PO paracetamol given 60–90 min prior did not reduce pain vs placebo (water or cherry elixir) or EMLA cream applied at 60 min (3 RCTs, n=346); PO glucose-treated infants had lower pain scores 3 min after heel lance vs those paracetamol-treated (MD 2.21/21; 95% CI 0.72 to 3.7) (1 RCT, n=38) (Ohlsson 2016 **Level I** [Cochrane], 9 RCTs, n=728).
- For eye examinations, RCT results conflicted for PO paracetamol 15–20 mg/kg 30 to 60 min prior vs water or sucrose 24% 0.2 mL: in two RCTs, no difference was found in pain scores taken in the first 45 s, last 45 s and 5 min after the examination, whilst the third and largest RCT reported lower pain scores vs water during the examination (Ohlsson 2016 **Level I** [Cochrane], 3 RCTs [eye], n=213).

For PICC placement in very preterm neonates <32 wk, paracetamol vs PO sucrose 24% 0.5–1 mL had similar median pain scores: 8/21 (IQR 6–10.5) for 10 mg/kg, 7 (IQR 6–9) for 15 mg/kg and 8 (IQR 6–10) for both 20 mg/kg paracetamol group and 24% sucrose (Roofthooft 2017 **Level II**, n=80, JS 5).

For pain management in very preterm neonates <32 wk, IV paracetamol 20 mg/kg load then multidosing with 7.5 mg/kg 6 hly (mean dose number 17 [SD 11.7]) decreased cumulative morphine requirements from median 0.37 mg/kg (SD 0.96) (prior to its introduction) to 0.17 mg/kg (SD 0.45) (Harma 2016 **Level III-2**, n=218). For postoperative pain management in term neonates, IV paracetamol 20 mg/kg initial dose then dosed according to age below or above 30 d of 10 or 15 mg/kg 6 hly was administered first line in preference to IV morphine infusion, with 99% adherence to the protocol (Baarslag 2018 **Level IV**, n=75).

Perioperative Analgesia

In a systematic review of paediatric use comparing paracetamol (IV, PO and PR routes) to placebo or nsNSAIDs or in combination, 7 of 13 RCTs are positive with an opioid-sparing effect in cleft palate repair (1 RCT), inguinal surgery (2 RCTs), ureteroneocystostomy (1 RCT), adenoidectomy and tonsillectomy (3 RCTs) (Wong 2013b **Level I** [PRISMA], 31 RCTs, n=2,624). A further systematic review of multiple opioid-sparing adjuvant medications lists outcomes for the paracetamol trials individually (Zhu 2017 **Level I**, 11 RCTs [paracetamol], n=1,011) (3 RCT overlap). While a subsequent systematic review of systematic reviews does not include these two systematic reviews but includes the other reviews (including the Cochrane reviews) discussed later in this chapter (Radman 2019 **Level I** [PRISMA], 17 SRs: 72 RCTs [42 both agents, 17 paracetamol], n unspecified). This systematic review assesses paracetamol and ibuprofen in combination or each agent alone concluding that the evidence is disappointingly limited considering these two medications listings as WHO essential medicines.

In young children following ureteroneocystostomy, IV paracetamol (15 mg/kg initial bolus and subsequent infusion with bolus prn) vs placebo added to IV fentanyl (infusion with bolus prn) had similar pain scores, with reduced fentanyl requirements (POD 1 and 2), reduced vomiting (16% vs 56) and sedation (10% vs 47) (Zhu 2017 **Level I**, 1 RCT: Hong 2010 **Level II**, n=63, JS 5).

Following scoliosis surgery, IV paracetamol 90 mg/kg/d for 24 h reduced pain scores vs placebo, but not opioid use or PONV (Zhu 2017 **Level I**, 1 RCT: Hiller 2012 **Level II**, n=36, JS 5).

Post cleft palate repair, paracetamol 12.5 mg/kg IV and 15 mg/kg PO (given every 6 h for 24 h) reduced postoperative morphine requirements vs placebo (Nour 2014 **Level II**, n=48, JS 5).

Post paediatric dental restorations, patients who received IV paracetamol 15 mg/kg vs IM pethidine 1 mg/kg had modestly higher pain scores but with less sedation and 10 min earlier discharge from PACU (Zhu 2017 **Level I**, 1 RCT: Alhashemi 2007 **Level II**, n=40, JS 5). Preemptive administration of very low dose paracetamol prior to dental treatment under local anaesthesia did not have benefit over placebo (2 RCTs, n=120) (Ashley 2016 **Level I** [Cochrane], 3 RCTs [paracetamol], n=165).

For inguinal herniorrhaphy in young children, both PR and IV paracetamol 15 mg/kg reduced pain scores (0–2 h) and vomiting postoperatively vs placebo (Khalili 2016 **Level II**, n=120, JS 3). For the same procedure, addition of PR paracetamol 30 mg/kg to caudal block had similar time to first rescue analgesia vs caudal block alone (while PR diclofenac 1 mg/kg with caudal block was superior to both) (Nnaji 2017 **Level II**, n=90, JS 4).

Post paediatric (adeno)tonsillectomy, paracetamol by different routes has had varying analgesic benefits:

- PO vs PR 40 mg/kg reduced opioid requirements (Anderson 1996 **Level II**, n=100, JS 5);
- PR 40 mg/kg vs IV 15 mg/kg resulted in a longer time to first rescue analgesic request (median 10 h vs 7) (Capici 2008 **Level II**, n=50, JS 5);
- PR 15 mg/kg vs IV 10 mg/kg had slightly lower pain scores at 4 and 6 h, with more patients pain free (44% vs 10) and a longer time to analgesic rescue (5 h vs 3.8) (Haddadi 2014 **Level III-1**, n=96);
- PO 15 mg/kg, as a single preoperative dose, resulted in lower early pain scores vs ibuprofen 10 mg/kg and placebo (Mahgoobifard 2014 **Level II**, n=60, JS 5);
- PO 12 mg/kg and 6 mg/kg ibuprofen, alone and in combination, were similarly effective over 48 h, with similar area under the curve for pain scores at rest and on swallowing (Merry 2013 **Level II**, n=152, JS 5);
- IV 15 mg/kg provided similar analgesic effects to IV tramadol 1 mg/kg in the early postoperative period (Uysal 2011 **Level II**, n=64, JS 5) and was similarly effective vs IM pethidine 1 mg/kg with similar pain scores, slightly less sedation and 10 min earlier discharge from PACU. However, 17 vs 0% of patients required morphine rescue (Alhashemi 2006 **Level II**, n=80, JS 4); and
- There were no differences in pain intensity between patients administered PO paracetamol (alone or in combination with codeine or hydrocodone) as required vs fixed schedule for 3 d despite the 33 to 68% lower dose/volume of analgesia used in the prn groups (Erskine 2015 **Level I** [Cochrane], 3 RCTs, n=207).

PO paracetamol 15 mg/kg with PO diclofenac 1 mg/kg provides equivalent analgesia to PO paracetamol 30 mg/kg (Hannam 2014 **Level I PK**, pooled data from 3 RCTs, n=466).

A subsequent PK-PD study has determined analgesic plasma concentrations for ibuprofen and paracetamol (Hannam 2018 **PK**, n=251 [1,168 paracetamol and ibuprofen samples]). The simulated time concentration effect profiles for varying doses demonstrate that ibuprofen alone decreased pain scores further and for longer than paracetamol alone. In combination, the simulated effect was additive: clinically used doses of paracetamol 15 mg/kg combined with ibuprofen 4.5 mg/kg decreased the pain score by 65%. Adding tramadol 0.5–1 mg/kg to this combination model maintained the pain score <6/10 for a further 7 h.

Paracetamol use in other painful conditions (non-surgical)

For acute otitis media [AOM], monotherapy with either PO paracetamol 15 mg/kg or PO ibuprofen 10 mg/kg had more children pain free at 48 h (90 and 93%) vs placebo (75%) (1 RCT n=148) (RR [paracetamol] 0.38, 95%CI 0.17 to 0.85; NNT 7) with no difference at 24 h, 48 to 72 h or 4–7 d (Sjoukes 2016 **Level I** [Cochrane], 3 RCTs, n=327 [AOM]).

For musculoskeletal injuries in children presenting to the ED, PO paracetamol 15 mg/kg vs codeine 1 mg/kg were both inferior to ibuprofen 10 mg/kg analgesia 1 h post dose (Clark 2007 **Level II**, n=300, JS 5), and paracetamol combined with codeine was equivalent to ibuprofen (Friday 2009 **Level II**, n=68, JS 4) (both RCTs in Le May 2016 **Level I** [PRISMA], 8 RCTs, n=1,169).

10.4.1.2 | Pharmacokinetics and pharmacodynamics

Paracetamol's bioavailability is dependent on the route of administration. Oral bioavailability is high (hepatic extraction 0.11–0.37) (Anderson 2014a **PK**) and peak plasma concentrations are reached in 30 min with the liquid and effervescent formulations (longer with tablet and capsule) (Marzuillo 2014 **NR**; Gibb 2008 **NR**); the equilibration halftime ($t_{1/2keo}$) between plasma and effect compartment is 53 min (Anderson 2001 **PK**). Rectal administration is associated with slower and less predictable absorption and PR loading doses of 30–40 mg/kg paracetamol may be required to achieve therapeutic plasma concentrations associated with analgesia (eg 10 mg/L which correlates with VAS reduction of 2.6/10) (Howell 2003 **Level II**, n=24, JS 2; Anderson 1996 **Level II**, n=100, JS 5). Neonates generally have delayed oral absorption, attributed to slower gastric emptying which reaches adult rates at 6–8 mth of age (Gibb 2008 **NR**; Marzuillo 2014 **NR**). An IV formulation of paracetamol achieves more predictable concentrations, because PK variability attributable to absorption is avoided, but also has more rapid offset than a PR formulation that has slow delayed absorption (Capici 2008 **Level II**, n=50, JS 5) as explored with simulation (Anderson 2014a **PK**).

Clearance is reduced in neonates and increases with age to reach adult rates during infancy (using allometric scaling expressed as L/h/kg). The volume of distribution (Vd: L/kg) is increased in neonates and rapidly reduces in the first year of life (Wang 2014 **PK**; Allegaert 2013 **NR**; Mohammed 2012 **PK**; Allegaert 2011a **PK**). Dose regimens that target a steady state plasma concentration of 10–20 mg/L have been determined. There is some evidence for analgesic efficacy at this concentration in children and neonates (Allegaert 2013 **NR**; Anderson 2001 **Level III-1 PK**). A PK model based on data from 220 subjects (neonatal up to adult) proposes dosing to achieve a concentration of 9 mg/L, chosen as this concentration is predicted with the clinically used schedule of 15 mg/kg every 6 h (for patients weighing 10–50 kg) (Wang 2014 **PK**). For paracetamol dosing see Table 10.5 where expert opinion is combined with supportive PK data, where available.

Table 10.5 | Suggested paracetamol dosing for infants and children

Postmenstrual age or weight	Oral (PO)/ Rectal (PR) dose	IV dose	Maximum daily dose	References
Infants 28–29 wk	Nil data	10 mg/kg 12 hly proposed	20 mg/kg/d proposed	Caution against use: van den Anker 2011 Note: Limited data in extreme premature Allegaert 2011a **PK**; Allegaert 2013 **NR**; Veyckemans 2014

Postmenstrual age or weight	Oral (PO)/ Rectal (PR) dose	IV dose	Maximum daily dose	References
Infants 30–31 wk	Nil data	10 mg/kg 8–12 hly	25–30 mg/kg/d	
(Weight 0.5–2 kg)		Initial bolus 12 mg/kg; 6–7 mg/kg 6 hly		Wang 2014 **PK**
Infants 32–44 wk (Weight 3–5 kg)	15 mg/kg 8 hly	Initial bolus 0–20 mg/kg; 10 mg/kg 6 hly	IV: 40 mg/kg/d PO: 45 mg/kg/d	Palmer 2008 **Level IV PK**; Allegaert 2011a **PK**; Allegaert 2013 **NR**; Wang 2014 **PK**; Veyckemans 2014.
Infants >45 wk		15 mg/kg 6 hly	IV/PO: 60 mg/kg/d	Veyckemans 2014; Palmer 2007 **Level IV**; Howard 2008b **NR**; Wang 2014 **PK**
Older children 6 mth–12 y	15–20 mg/kg 4–6 hly	15 mg/kg 6 hly	IV: 60 mg/kg/d PO: 90 mg/kg/d suitable for acute administration for 2–3 d	Anderson 2002 **PK**; Wang 2014 **PK**

10.4.1.3 | Adverse effects and safety

Overall safety

Paracetamol use at therapeutic doses can generally be considered safe. Dosing recommendations have been revised and capped at 75–80 mg/kg/day for PO and IV acute use (Ajjan 2016 **Level IV**, n=72) and 60 mg/kg/day for short term use (eg in the British National Formulary or Australian Medicines Handbook), but the margin for safety particularly in ill children and adults weighing less than 50 kg is unclear (Caparrotta 2018 **NR**). A review assessing a range of adverse effects (including abdominal, hepatic, skin, respiratory and neurological effects) suggests paracetamol and ibuprofen have similar safety and tolerability profiles vs placebo if prescribed and administered at recommended doses in children (Southey 2009 **Level IV SR**, 24 RCTs, n=119,166 & 12 studies, n=221,459).

Safety in neonates and preterm infants

Data regarding safety of paracetamol (all routes) in neonates is scant and cautious dosing and monitoring of hepatic function is recommended (Anderson 2009 **NR**). There is minimal safety data in preterm <32 wk (Allegaert 2011a **PK**). Dosing practices in NICUs vary (with decreasing dose and or frequency) and are not informed by pharmacodynamic data (Allegaert 2017 **NR**).

Limited data on liver function during repeated IV (Palmer 2008 **Level IV**, n=50) and PR dosing for pain or fever (Chen 2018 **Level IV**, n=25) suggest alteration was contributed to by factors other than paracetamol.

Use of paracetamol for patent ductus arteriosus (PDA) closure also provides some limited safety data in preterm neonates ≤34 wk (Ohlsson 2018a **Level I** [Cochrane], 8 RCTs, n=916). Paracetamol has equivalent efficacy for this indication to NSAIDs, with reduced gastrointestinal bleeding vs ibuprofen (RR 0.28; 95%CI 0.12 to 0.69) (4 RCTs, n=537), higher platelet counts (2 RCTs [ibuprofen], n=287; 1 RCT [indomethacin], n=200), lower bilirubin (2 RCTs [ibuprofen], n=290) and less renal impact with lower creatinine (4 RCTs [ibuprofen], n=537; 1 RCT [indomethacin], n=200), less oliguria (3 RCTs [ibuprofen] ,n=337) and greater daily urine output (1 RCT [ibuprofen], n=200; 1 RCT [indomethacin], n=200).

In extreme preterm neonates ≤28 wk, PO paracetamol 15 mg/kg 6 hly for 3 d vs ibuprofen 10 mg/kg d 1, 5 mg/kg d 2 and 3 was as effective for PDA closure 89 vs 84%, with similar side effect profile in terms of intestinal, liver and renal function (Karabulut 2019 **Level III-2**, n=87).

Hepatotoxicity

Paracetamol is metabolised in the liver, predominantly via glucuronidation and sulphation. Increased production of a reactive oxidative product, N-acetyl-p-benzoquinone imine (NAPQI), occurs if the usual metabolic enzyme systems become saturated (eg acute overdose) or if glutathione is depleted (eg with prolonged fasting). An increased contribution of sulphation to metabolism and reduced production of oxidative metabolites may reduce the risk of toxicity in neonates, particularly in the presence of unconjugated hyperbilirubinaemia (Palmer 2008 **Level IV**, n=50) but, as overall clearance is reduced, a lower dose is appropriate. Hepatotoxicity has been reported in infants aged 3–7 wk having received PO dosing of 60 mg/kg/d for 3 and 6 d and 100 mg/kg/d for 2 d (Bucaretchi 2014 **Level IV**, n=3).

Risk factors for paracetamol hepatotoxicity may include fasting (malnourished state), vomiting, dehydration, systemic sepsis, pre-existing liver disease and prior paracetamol intake, however the situation remains unclear (Caparrotta 2018 **NR**; Kaplowitz 2004 **NR**) (see also 4.2.3). Hepatic injury results from the NAPQI metabolite. Single overdoses in children of 120 to 150 mg/kg have caused hepatic injury (AAP 2001 **NR**). Notably, acute liver failure has occurred with 3–4 d dosing of 68–82 mg/kg/d in 4 young children in an Australian and New Zealand cohort (Rajanayagam 2015 **Level IV**, n=14 [paracetamol]). Hepatic failure in this paediatric series (age range 0.7–13 y) was mostly associated with medication error involving higher multiday (median 4 d, range 2 to 24) dosing: 7/14 (50%) received >120 mg/kg/d and the remainder had double doses or excessive frequency, were coadministered other medications containing paracetamol or received regular dosing. Ten survived without requiring transplant, 2 survived post-transplant; while 2 died (1 without and 1 post-transplant). A Spanish series documents similar reported acute and chronic dosing with accidental overdose in younger children (n=38) and attempted suicide in teenagers (n=43) with 50% receiving N-acetylcysteine (NAC), 4 patients developing acute liver failure with none requiring transplant or dying (Tong 2017 **Level IV**, n=90). In adolescent overdose, early predictors of severity of paracetamol hepatotoxicity included the initial INR elevation, presence of hyperbilirubinaemia and hypophosphataemia, the number of prehospital vomiting episodes (≥3) and time to NAC administration (Hedeland 2014 **Level IV**, n=25). In contrast to adults, no relationship was found for the severity of hepatoxicity and the amount ingested (either as overall dose [mean 16.4 g, range 6.5–60 g] or when weight adjusted). All patients received NAC and recovered; none required transplant.

Repeated paracetamol ingestion (dose known for 78 patients as >76 mg/kg/d [median 120] for median 3 d [IQR 2–5]) resulted in severe hepatic damage (ALT/AST ≥1000 IU/L) (93%), liver failure (69%) and death (39%) (Acheampong 2016 **Level IV SR**, n=199 [78 children ≤6 y]).

The commonest prescribing error in paediatrics is a ten-fold dosing error. This has significant impact when involving paracetamol, as occurred for an infant where 2 doses of 150 mg/kg were given (detected after the 2nd dose) with hepatotoxicity; successfully treated with NAC (Aslan 2019 **CR**).

A review of therapeutic dosing of paracetamol beyond 24 h in children assessed hepatic adverse effects (Lavonas 2010 **Level IV SR**, 62 studies, n=32,414). It reports no cases of liver disease, need for antidote or transplantation or death (0.0%; 95%CI 0.000 to 0.009) and only 10 children experienced major or minor hepatic adverse effects (0.031%; 95%CI 0.015 to 0.057). This review identified 22 case reports of hepatotoxicity associated with therapeutic doses of paracetamol; in 9 cases, Naranjo scoring suggested probable causation.

Of note, the guidelines for the management of paracetamol poisoning have been revised (Chiew 2020 **GL**). Specifically for younger children <6 y who have ingested an excessive dose of the more rapidly absorbed liquid preparation, an earlier measurement of plasma concentration from at least 2 h is recommended (rather than at ≥4 h for tablet ingestion) and intervention tailored to whether this is >150 mg/L. The guideline also incorporates response to modified release paracetamol overdoses, large or massive overdose and repeated supratherapeutic ingestions. The three infusion NAC dosing schedule has been revised to two (Chiew 2018 **Level I** [Cochrane], 4 RCTs [NAC route and dose regimens in adults], n=518), with the recommendation to double the 2nd infusion if the plasma concentration is greater than twice the height of the paracetamol toxicity nomogram line.

Cardiovascular effects of paracetamol

Paracetamol has poorly understood vasoactive effects. It is as effective as ibuprofen for closure of a PDA in preterm neonates (Ohlsson 2018a **Level I** [Cochrane], 8 RCTs, n=916). There is also a potential association between constriction and premature ductus arteriosus closure and maternal paracetamol use in pregnancy (see below: Allegaert 2019 **Level IV**, n=25).

The overall effect of paracetamol on blood pressure in adults and children remains unclear (see also adult Section 4.1.3.3). Observational studies show a variable association between PO paracetamol use and hypertension, but RCTs are inconsistent (Turtle 2013 **Level III-3 SR**, 6 RCTs, n=152 & 4 studies n=155,910). While use of IV propacetamol and IV paracetamol and hypotension has been reported (with variable definitions: systolic vs MAP change as absolute value or 15–20% decrease) in mostly critically ill (often cardiac) patients (14/19 studies) (Maxwell 2019 **Level IV SR**, 19 studies (5 RCTs, 6 open label trials & 8 retrospective reviews), n=3,470 [2 paediatric, n=680]). Clinically significant hypotension appears to be an issue when patients have cardiovascular compromise prior to administration; importantly regular four times daily dosing with IV paracetamol where mannitol is the stabilising agent exposes the patient to 0.23 mg/kg/d mannitol (with its diuretic and secondary hypotensive effect) (Chiam 2015 **NR**). Within the above systematic review, IV paracetamol (with mannitol excipient) vs mannitol vs placebo reduced MAP by only 1.8 mmHg in healthy adult volunteers (Chiam 2016 **Level II**, n=24, JS 5). Of the two paediatric studies, the first included neonates receiving IV propacetamol where a minor decrease in MAP (-3 mmHg) occurred 60 min post dose (Allegaert 2010, **Level IV**, n=72). This may reflect analgesic effect, although the 8 neonates who developed hypotension all had lower baseline MAP prior to administration. Further to this, 5% of young children in a cardiac PICU (mostly postsurgical), whose MAP had started to decline prior to IV paracetamol administration, progressed to clinically significant hypotension (≥15% decrease in MAP from baseline) within 30–75 min of IV paracetamol, and 20% experienced a 10–14% decrease (Achuff 2019 **Level IV**, n=608 [777 doses]). This series excluded patients who had a vasoactive medication within 1 h before or after paracetamol. Severe hypotension and cardiac arrest is also described in a toddler with febrile neutropenia occurring 5 min into the infusion (Yaman 2016 **CR**).

Paracetamol hypersensitivity

Hypersensitivity to paracetamol is uncommon (Gabrielli 2018 **Level IV SR** [PRISMA], 85 studies, n=1,030). The classification of reaction types and mechanisms of immune reaction in children are summarised (Kidon 2018 **GL)** (and discussed further below in nsNSAID hypersensitivity Section 10.4.2.3).

Most reported cases of hypersensitivity to paracetamol involve the skin, including nonimmediate cutaneous eruptions, fixed drug eruptions, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and urticarial/angioedema/anaphylaxis. Reactions to paracetamol have been reported usually in association with suspected nsNSAIDs reactions; with its proposed weak cyclooxygenase (COX) effect, paracetamol was presumably included to explore cross sensitivity with nsNSAIDs. Three such paediatric series have focussed on nsNSAIDs hypersensitivity, skin and oral drug provocation testing and explored associations eg with atopy (Arikoglu 2017 **Level IV**, n=106; Topal 2016 **Level IV**, n=64; Cousin 2016 **Level IV**, n=107). Paracetamol was either implicated directly or was coadministered with nsNSAIDs at the time of reaction; as with nsNSAIDs most reactions were cutaneous or urticarial/angioedema. No anaphylaxis to paracetamol was reported in these series. One confirmed two patients with positive skin testing to paracetamol and two further (aged 6 and 15 y) skin test positive to a nsNSAID then reacting to 'high-dose oral provocation' with 90–120 mg paracetamol (Topal 2016 **Level IV**, n=18 confirmed [2 paracetamol] of 64 evaluated). The second explored applicability of the European Network of Drug Allergy (ENDA) classification to children and association of allergy with urticaria and atopy; it confirmed 7 reactions to paracetamol with 'urticaria/angioedema or anaphylaxis' (defined as 'single agent reaction' as the patients tested negative with at least one other nsNSAID; where paracetamol was not implicated in the patient subgroup with cross-intolerant hypersensitivity) (Cousin 2016 **Level IV**, n=107). While the third also explored the ENDA concepts of selective responders vs cross intolerant and confirmed patients with nsNSAID allergy (with skin and/or drug provocation testing) (Arikoglu 2017 **Level IV**, n=33 confirmed of 106 evaluated [6 paracetamol; 27 nsNSAIDs]). Paracetamol was frequently implicated on history (59%) but oral provocation was only positive for 6 patients (two of whom tested negative on skin prick testing). The majority of patients with confirmed nsNSAID allergy in this series subsequently had oral drug provocation with paracetamol establishing its use as a safe alternative for the nsNSAID allergic children (see also Section 10.4.2.3). A subsequent meta-analysis (including the first of these series) established a pooled estimate for paracetamol hypersensitivity prevalence in children who reported a previous reaction to paracetamol and underwent an oral challenge of 10.1% (95% CI 4.5–15.6) (Gabrielli 2018 **Level IV SR** [PRISMA], 10 studies [meta-analysed] [5 mixed/ 5 paediatric], n=259]. Skin testing has not been developed as a diagnostic tool for paracetamol (and other nsNSAIDs beyond aspirin).

In 2013, the USA's Food and Drug Administration (FDA) investigated paracetamol as a rare cause of SJS/TEN syndrome (FDA 2013a **Level IV**, n=91, 6 [probable]; 85 [possible]). While, a French pharmacovigilance study reported 112 cases involving 574 suspected drugs (5.1 per case) (Lebrun-Vignes 2018 **Level IV**, n=23 [children])). In 80 cases, drugs other than paracetamol had a higher suspicion for causality; in a further 12 paracetamol was unlikely to be involved. In the remaining 20 cases, paracetamol was possibly or probably involved, but in 14 there was protopathic confounding bias (where the drug is taken for a symptom or illness).

Anaphylactic reactions to paracetamol have been reported rarely, mostly following PO administration and one following IV (Sørensen 2014 **Level IV**, n=12). Six (50%) of these children notably had negative skin tests with initial or subsequent reactions to low dose, high dose provocation or therapeutic dosing.

Pregnancy and early childhood exposure and association with various childhood issues

Paracetamol is a Category A medicine and is regarded as the analgesic of choice during pregnancy and infancy in Australia and New Zealand (currently unassigned in the USA). There are numbers of observational cohort studies in the literature claiming modest associations between paracetamol exposure in utero and various early infancy and childhood issues (as presented below). Caution should be used with interpretation of these retrospective analyses because of the possible effect of unknown or unmeasured confounding factors; the relevance of these reports to limited acute use remains unclear.

Childhood asthma

The scientific literature has debated whether paracetamol can precipitate asthma (by increased *de novo* myeloperoxidase production) or causes a shorter less severe asthmatic episode in aspirin-sensitive people with asthma (Graham 2013 **NR**). An important potential confounder of the below epidemiological study is protopathic: where the indication for paracetamol is fever due to viral upper respiratory tract illness (in mother and or the child), which in itself precipitates asthma.

Two systematic reviews, with no overlap of included studies, report an association between paracetamol use in pregnancy and subsequent childhood wheezing (OR 1.5; 95%CI 1.1 to 2.1) (Etminan 2009 **Level III-3 SR**, 5 studies [wheezing], n unspecified) and asthma (OR 1.28; 95%CI 1.13 to 1.39) (Etminan 2009 **Level III-3 SR**, 4 studies [asthma], n unspecified) (OR 1.21; 95%CI 1.02 to 1.44) (Eyers 2011 **Level III-2 SR**, 6 studies, n=28,038). A subsequent systematic review of heterogeneous studies (with 2 study overlap with each of the above SRs) revealed any paracetamol use was associated with increased childhood asthma risk: during the first trimester (pooled OR 1.39; 95%CI 1.01 to 1.91) (5 studies, n unspecified) and during the second and third trimesters (OR 1.49; 95%CI 1.37 to 1.63) (3 studies, n unspecified) (Cheelo 2015 **Level III-2 SR** (PRISMA), 11 studies, n=910,054: 4 pregnancy studies n=896,313; 2 pregnancy and infant studies n=9,527; 4 infant-toddler studies n=4,241]). Importantly, only one study adjusted for maternal respiratory tract infections.

The epidemiological literature has also reported an association between childhood asthma and paracetamol exposure in children in the year prior to diagnosis (pooled OR 1.60; 95%CI 1.48 to 1.74) (3 studies, n unspecified) and in the first year of life (pooled OR 1.47, 95%CI 1.36 to 1.56) (3 studies, n unspecified), with one study reporting an association with high doses (Etminan 2009 **Level III-3 SR**, 19 studies, n=425,140 [15 paediatric, n=361,018]). However, when adjusted for respiratory tract infections in the child, increasing frequency of use (defined as doubling of dose) of paracetamol during infancy (up to 6, 12 and 24 mth) was no longer associated with increased odds of childhood asthma (OR 1.06; 95% CI 0.92 to 1.22) (Cheelo 2015 **Level III-2 SR** (PRISMA), 3 studies [infant & toddler use], n=3,327).

A subsequent RCT in children with mild persistent asthma (on glucocorticoid and leukotriene receptor antagonist inhaler treatment) assessed acute use of paracetamol vs ibuprofen for pain or fever and frequency of asthma exacerbations (over a 48 wk period) (Sheehan 2016 **Level II**, n=300, JS 5). Participants received a median of 5.5 doses (IQR 1 to 15) with no difference in the number of asthma exacerbations (RR 0.94, 95%CI 0.69 to 1.28), asthma-control days (85.8 and 86.8%), albuterol rescue inhaler use (2.8 vs 3.0 inhalations per week) or unscheduled health care utilisation for asthma (0.75 and 0.76 episodes per participant).

Childhood atopy

Paracetamol exposure during pregnancy has been implicated in childhood atopy (nutritional, eczema, wheezing) in early infancy (Allegaert 2017 **NR**). Certain maternal antioxidant gene polymorphisms may modify this relationship, as is also relevant to asthma above (Shaheen 2010 **Level IV**, n=4,000 [mothers]). At present, the association may be explained by confounders.

Cryptorchidism

Association between paracetamol exposure in utero and cryptorchidism has been of interest due to paracetamol's potential to act as an endocrine disrupter. For the association between 'ever' use of paracetamol and cryptorchidism in highly heterogeneous studies, the pooled crude OR was 1.11 (95%CI 1.00 to 1.23), and when separately analysed as study type no association was shown for case-control studies (OR 1.23; 95%CI 0.85 to 1.78) or cohort studies (OR 1.09; 95%CI 0.97 to 1.22) (Gurney 2017 **Level III-2 SR** [PRISMA], 10 Studies, n=501,456).

Premature closure of the ductus arteriosus

Maternal paracetamol use in pregnancy has been proposed as causal in premature constriction or closure of the ductus arteriosus: 4 certain and 11/25 probable (Allegaert 2019 **Level IV**, n=25).

Childhood neurobehavioural outcomes

The relationship of paracetamol exposure in utero and early childhood to neurobehavioural outcomes has been explored. Suggested mechanisms for an effect of paracetamol include impact on cerebral inflammation and metabolite production eg cannabinoids or again this may reflect a protopathic bias. Three overlapping reviews have included birth cohort studies with follow-up at various ages (18 mth vs 3, 5, 7 and 11 y) including different assessments for several neurobehavioural outcomes eg attention deficit hyperactivity disorder (ADHD) (4 studies, n=75,633), conduct and emotional problems (1 study, n=7,796), attention/executive function (1 study, n=1,491), and autistic spectrum disorder (ASD) with hyperkinetic disorder (HR 1.51; 95%CI 1.19 to 1.92) (1 study, n=1,491) (Bauer 2018 **Level III-2 SR,** 9 studies, n=176,955; Masarwa 2018 **Level III-2 SR** [PRISMA], 7 studies, n=132,738; Allegaert 2017 **Level III-2 SR,** 7 studies, n=174,732) (6 to 7 study overlap). Lower IQ (by 3.4 points; 95%CI 0.3 to 6.6) was reported (1 study, n=1,491); where an earlier study (included in the 1st and 3rd review) had found no effect (Streissguth 1987 **Level III-2**, n=421). Duration of exposure (<28 vs >28 d) was assessed in 2 studies and was associated with reduced communication/motor attainment and greater hyperactivity (Bauer 2018 **Level III-2 SR**, 1 study: Brandlistuen 2013 **Level III-2**, n=48,631 [2,919 same sex sibling matching]); when adjusted for confounders, delayed motor milestone attainment remained an association (OR 1.35, 95%CI 1.07–1.70), but not communication issues (OR 1.38, 95%CI 0.98 to 1.95) (Bauer 2018 **Level III-2 SR**, 1 study: Vlenterie 2016 **Level III-2**, n=51,200). In the largest study (in all 3 reviews), the use of paracetamol in pregnancy was associated with child hyperkinetic disorder (HR 1.37; 95%CI 1.19 to 1.59), use of ADHD medications (HR 1.29; 95%CI 1.15 to 1.44) and ADHD-like behaviours at age 7 y (RR 1.13; 95%CI 1.01 to 1.27) (Liew 2014 **Level III-2**, n=64,322). The third review determined mean duration of use as 4-7 d and range 4 to more than 28 d (Masarwa 2018 **Level III-2 SR** [PRISMA], 7 studies, n=132,738). It calculated increased risk for ADHD (RR 1.34; 95%CI 1.21 to 1.47) (6 studies, n=118,085), hyperactivity symptoms (RR 1.24; 95%CI 1.04 to 1.43) (5 studies, n=124,264) and ASD (RR 1.19; 95%CI 1.14 to 1.25) (5 studies, n=117,214). A subsequent study analysed the number of days of use of paracetamol in pregnancy and after adjustment for family history also revealed association with childhood ADHD for longer >29 d (HR 2.2; 95%CI 1.5 to 3.2) but not short term <8 d use (HR 0.9; 95%CI 0.8 to 1.0) (Ystrom 2017 **Level III-3**, n=112,973 [2,246 ADHD]).

In addition, a birth cohort study subsequently linked to administrative data, paracetamol was used in 49% of pregnancies and was associated with a modest increase in numbers of cerebral palsy (CP) affected children (OR 1.3; 95%CI 1.0 to 1.7) and unilateral spastic CP (OR 1.5; 95%CI 1.0 to 2.2), where confounders (use for fever and viral illness) are again likely relevant (Petersen 2018 **Level III-2**, n=185,617).

KEY MESSAGES

1. Post tonsillectomy in children, paracetamol (alone or combined with opioids) administered as required compared to fixed schedule achieved similar pain scores over 3 days; with lower dosing administered in the as required groups (**N**) (**Level I** [Cochrane Review]).
2. For pain of acute otitis media in children, paracetamol is similar to ibuprofen and both are superior to placebo in achieving pain freedom at 48 hours, but not other time points (**N**) (**Level I** [Cochrane Review]).
3. Paracetamol is effective for moderately severe pain and decreases opioid requirements after major and minor surgery in children (**U**) (**Level I** [PRISMA]).
4. Paracetamol has a similar safety and tolerability profile compared with ibuprofen and placebo if prescribed and administered at recommended doses in children (**U**) (**Level IV SR**).
5. Retrospective epidemiological studies linking paracetamol use in pregnancy or infancy to later development of childhood asthma are inherently confounded (**U**); when adjusted for respiratory tract infections in the child the association is lost (**Q**) (**Level III-2 SR** [PRISMA]).
6. Retrospective epidemiological studies report modest association of paracetamol use in pregnancy with childhood neurodevelopmental disorders such as attention deficit and hyperkinetic disorders; this is strengthened when adjusted for longer term use (>28 days) and disappears for short term use (<8 days) (**Q**) (**Level III-2 SR** [PRISMA]).
7. Paracetamol has unclear vasoactive effects; in critically ill children, hypotension is reported with both IV formulations (**N**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Safe dosing of paracetamol requires consideration of the age and body weight of the child and the duration of therapy (**U**).

☑ Paracetamol related hepatotoxicity generally occurs in children who have received doses greater than 120 mg/kg, as single or repeated daily dosing; with contributions from rounding up or 10-fold dosing error and formulation substitution or confusion by prescribers and parents (**N**).

☑ Paracetamol is recommended routinely following tonsillectomy and pharmacokinetic/pharmacodynamic simulation is exploring the optimal combinations of multimodal analgesia in this surgical model (**N**).

☑ There is insufficient pharmacokinetic/pharmacodynamic and safety data of use of paracetamol in preterm and term neonates; use for patent ductus arteriosus closure in preterm neonates provides limited data in this age group of an improved safety profile compared with nsNSAIDs (**N**).

☑ Emerging evidence suggests that maternal paracetamol use may influence premature closure of the fetal ductus arteriosus (**N**); use in pregnancy should be limited to the minimum dose and duration that is clinically necessary.

☑ Intravenous paracetamol in haemodynamically unstable patients has been associated with hypotension (**N**).

10.4.2 | Nonselective NSAIDs

For mild to moderate pain, nonselective non-steroidal anti-inflammatory drug (nsNSAIDs) are effective analgesic agents. The product information states that safety in children <2 y is unestablished, while the lower age limit for licensing varies by country and by NSAID agent. Despite this, nsNSAIDs have been studied and used in all age groups including infants, as reported by surveyed anaesthetists (Eustace 2007 **Level IV**, n=314) and German anaesthetic departments (Emons 2016 **Level IV**, n=342 [hospitals treating children]). Use of nsNSAIDs for analgesia is generally not approved for infants aged <3 mth; some authors suggest caution under 6 mth of age due to a paucity of data (Tobias 2014 **NR**). There is off-label use in neonates postoperatively (Moffett 2006 **Level IV**; Papacci 2004 **Level IV**) and in patent ductus arteriosus [PDA] closure and intraventricular haemorrhage prevention providing limited safety data (Aranda 2017 **NR**). The choice between ibuprofen, diclofenac, ketorolac, naproxen, ketoprofen and others mainly depends on available formulations and convenience of administration.

10.4.2.1 | Pharmacokinetics and pharmacodynamics

Data on pharmacokinetics (PKs) for the commonly used NSAIDs are available for children but pharmacodynamic (PD) studies are few. The clearance (CL) of diclofenac (Litalien 2001 **NR**), ketorolac (Lynn 2007 **PK**) and ibuprofen (Kyllonen 2005 **PK**) is immature in neonates and matures within the first year of life. Equilibration half times of drug concentration with clinical effect ($t_{1/2\,keo}$) are 14 min for diclofenac (Hannam 2014 **Level II**, n=151, JS 3), 24 min for ketorolac (Mandema 1996 **PK**) and 28 min for ibuprofen (vs 53 min for paracetamol) (Li 2012a **PK**). Studies of analgesic effects are frequently flawed by failing to account for the variations in time to onset when assessing outcomes. A paediatric pain consortium has determined acute pain clinical trial models to improve study design for analgesic trials in children (Walco 2018 **GL**).

Rectal bioavailability of diclofenac is high in children (van der Marel 2004 **PK**). A population PK study estimated diclofenac CL as 16.5 L/h/70 kg and bioavailability as 35% for dispersible tablet or suspension and 63% for suppository (Standing 2011 **PK**). Dosing for children aged 1–12 y was predicted as IV 0.3 mg/kg, PR 0.5 mg/kg and PO 1 mg/kg. A PK-PD study revealed the maximum effect of both paracetamol and diclofenac (VAS reduction 4.9/10; 95%CI 4.7 to 5.2) (Hannam 2014 **Level II**, n=151, JS 3) as similar to that described for ibuprofen in adults (Li 2012a **PK**). Combination therapy of PO diclofenac 1 mg/kg with PO paracetamol 15 mg/kg is predicted to achieve equivalent analgesia to PO paracetamol 30 mg/kg. Synergistic interaction is complex as the drugs have different onset and half-lives. Studies must take this into account to determine the optimum combination-dosing schedule to improve or extend duration of analgesia.

Plasma and cerebrospinal fluid (CSF) concentrations after PO naproxen have been studied in children (mean age 5–6 y, range 0.25–12 y), establishing that CL and Vd <5 y of age are similar to values for adults and children >5 y (Valitalo 2012 **PK**). High unbound naproxen concentrations in CSF suggest an active uptake mechanism. Ketoprofen PKs are summarised in a narrative review (Kokki 2010 **NR**). PKs in children (aged 0.25–13 y) after PO and IV flurbiprofen have been reported, with increased concentrations in CSF vs plasma (Kumpulainen 2010 **PK**).

Adult data suggest ketorolac has a half maximal effective concentration (EC_{50}) of 0.37 mg/L (Mandema 1996 **PK**). PK modelling demonstrates that current IV dosing regimens of 0.5 mg/kg every 6 h maintain a trough concentration above this EC_{50} in children (aged 0.75–16 y) (McLay 2018 **PK**). In adolescents, the PKs of IN ketorolac 15–30 mg (via metred aerosol device) has good bioavailability (81%) and similar time to maximum plasma concentration (T_{max}) and clearance to adults. A 30 mg dose reached a predicted effect compartment concentration of 0.37 mg/L at 30 min and remained above this target for 10 h (Drover 2012 **PK**).

For ibuprofen, analgesic plasma concentrations of 10–25 mg/L have been suggested post paediatric inguinal hernia repair (Kokki 2007 **NR**). Target analgesic concentrations (ideally surgery-specific) for other NSAIDs, developmental changes in PDs, and the impact of different stereoisomer forms and the influences of various covariates (including weight, postmenstrual and postnatal age, renal function, obesity, enzyme maturation and influence of ethnicity/pharmacogenomics and comedications) on the differential PK, efficacy and adverse-effect profile require further evaluation (Admiraal 2014 **NR**; Anderson 2011 **NR**).

10.4.2.2 | Efficacy

Clinical studies of nsNSAIDs and paracetamol suggest similar (Shepherd 2009 **Level II**, n=72, JS 3; Riad 2007 **Level II**, n=108, JS 3; Hiller 2006 **Level II**, n=120, JS 5; Tay 2002 **Level II**, n=63, JS 2) or superior efficacy of nsNSAIDs (Wong 2013b **Level I** [PRISMA], 4 RCTs (nsNSAIDs vs paracetamol), n=330). Benefit is dependent on dose and route (absorption PKs eg via PR vs IV routes), timing (preop/intra/postoperative), intermittent vs regular and duration of administration, and type of surgery (eg cleft palate, hernia repair vs laparotomy).

Three systematic reviews on use of NSAIDs in paediatrics are published, reporting results differently. The 2017 review does not perform meta-analysis and references the earliest meta-analysis and 2 further tonsillectomy trials detailed below (Zhu 2017 **Level I**, 1 meta-analysis [27 RCTs, n=978] and 2 RCTs, n=443). The earliest meta-analysis includes two RCTs using coxibs and finds NSAIDs, alone or as a component of multimodal analgesia, decrease opioid consumption in PACU and at 24 h (Michelet 2012 **Level I** [QUOROM], 27 RCTs, n=985). NSAIDs also reduce pain intensity in PACU but not in the first postoperative 24 h. The second meta-analysis overlaps by 24 RCTs, including 1 coxib RCT, but also incorporates outcomes for paracetamol (13 RCTs) (Wong 2013b **Level I** [PRISMA], 31 RCTs, n=2,624). NSAIDs (and/or paracetamol) reduce opioid consumption in 38 of 48 treatment arms (21 of 31 RCTs), with a higher proportion positive in NSAID-only trials and with this being more apparent in moderate to major surgery. Where systemic opioids were available via patient-controlled or nurse-controlled analgesia (PCA/NCA) (ie after major surgery), mean opioid consumption was reduced by 32% (95%CI 17 to 47) (7 RCTs) when studied for >24 h and not reduced when studied for ≤6 h (24%; 95%CI -1.7 to 50) (3 RCTs). Where systemic opioids were available by intermittent bolus (21 RCTs, usually short or day-stay surgery), opioid consumption was decreased by 24% (95%CI 6.3 to 43). Pain scores, reported in various ways, were reduced in 16 of 29 RCTs. The impact on adverse effects is difficult to interpret due to study heterogeneity and small study size.

In a review of diclofenac studies only, diclofenac reduces the need for postoperative rescue analgesia vs placebo (5 RCTs) and paracetamol (NNT 3.6; 95%CI 2.5 to 6.3, 2 RCTs) (Standing 2009b **Level I** [Cochrane], 7 RCTs [analgesic rescue], n=404) (1 & 2 RCT overlap with above meta-analyses).

In a review of low quality ketorolac only studies with 3 and 4 RCT overlap with the above 2 reviews there was no difference in PACU rescue (4 RCTs) or PACU opioid requirement (3 RCTs), with a small reduction in postoperative morphine requirement (1.58 mg; 95%CI -2.58 to -0.57 mg, 2 RCTs) in the 4 postoperative h only vs placebo (McNicol 2018 **Level I** [Cochrane], 13 RCTs, n=920).

Additional trials have found NSAIDs effective with reduced pain scores and rescue morphine use post inguinal hernia repair (Riad 2007 **Level II**, n=108, JS 5), reduced need for early rescue analgesia post tonsillectomy (Pickering 2002 **Level II,** n=103, JS 5), reduced pain scores post multiple dental extractions (Gazal 2007 **Level II,** n=201, JS 5) and reduced pain scores and need for rescue opioid 0–48 h post cleft palate repair (more so when combined with paracetamol) (Mireskandari 2011 **Level II**, n=120, JS 5). A ketorolac infusion was more effective than fentanyl infusion following ureteric-bladder surgery with less bladder spasm (4% vs 30) and less rescue analgesic

administration over 48 h (21% vs 65) (Jo 2011 **Level II**, n=52, JS 5). SL ketorolac was equianalgesic vs SL tramadol for moderate and severe pain post fracture or dislocation (Neri 2013 **Level II**, n=131, JS 5). Intraoperative IV ibuprofen resulted in a small reduction in early postoperative fentanyl rescue administration after adenotonsillectomy surgery vs placebo (Moss 2014 **Level II**, n=161, JS 4). A combination of individually titrated intraoperative opioids and regularly administered perioperative nonopioid analgesics (NSAID and/or paracetamol) is recommended for pain management following paediatric tonsillectomy (Hamunen 2005 **Level I**, 36 RCTs, n=2,309). The combination of paracetamol (48 mg/kg/d) and ibuprofen (24 mg/kg/d) was not superior to either agent alone following tonsillectomy (Merry 2013 **Level II**, n=152, JS 5). Ketoprofen has been studied using IV, PO and PR route (Kokki 2010 **NR**). It is not currently used in children in Australia and New Zealand, where it is available as CR and topical forms only.

A Cochrane review of nsNSAIDs (and paracetamol) found ibuprofen use for acute otitis media reduces the number of patients in pain at 48 h vs placebo (7 vs 25%) (RR 0.28; 95%CI 0.11 to 0.70: NNT=6) (3 RCTs, n=146) with similar efficacy to paracetamol (Sjoukes 2016 **Level I** [Cochrane], 3 RCTS, n=327).

A Cochrane review of efficacy of NSAIDs in paediatric cancer found no RCTs (Cooper 2017b **Level I** [Cochrane], 0 RCTs).

Nonselective NSAIDS and reduction of postoperative nausea and vomiting

Diclofenac use in acute pain is associated with reduced nausea and vomiting (or both) vs placebo, paracetamol and opioids (OR 0.58; 95%CI 0.47 to 0.73: NNT 7.7; 95%CI 5.3 to 14.3) (Standing 2009b **Level I** [Cochrane], 13 RCTs, n=775). NSAIDs do not affect vomiting in PACU but reduce vomiting over 24 h (OR 0.75; 95%CI 0.57 to 0.99) (Michelet 2012 **Level I** [QUOROM], 17 RCTs, n=1,302 [events analysed]). Less vomiting occurs following tonsillectomy when nsNSAIDs are part of the analgesic regimen (RR 0.72; 95%CI 0.61 to 0.85) (Lewis 2013 **Level I** [Cochrane], 13 RCTs, n=1,021). The suggested mechanism is through improved pain relief, rather than reduced opioid rescue requirement. A fourth meta-analysis, of heterogeneous surgery types, found no association (with confidence interval overlap) between opioid-sparing effect and PONV reduction; 47% (95%CI 22 to 72) for those reporting PONV reduction vs 26% (95%CI 20 to 31) for those reporting equivalent PONV rates (Wong 2013b **Level I** [PRISMA], 31 RCTs, n=2,624).

10.4.2.3 | Adverse effects of nsNSAIDs in children

Overall safety

In large series of children with febrile illnesses (n=55,785), the risk of serious adverse effects following short term use of ibuprofen was low, and similar to that following the use of paracetamol (Lesko 1995 **Level II**, n=84,192, JS 4) including in the subgroup of children aged <2 y (Lesko 1999 **Level II**, n=27,065, JS 4). Diclofenac use for postoperative pain is also safe, with an overall serious adverse effect rate (including bleeding) of 8 in 10,000 (95%CI 2 to 24) (Standing 2009b **Level IV SR** [Cochrane], 18 RCTs and 54 studies [diclofenac], n=3,611). See also Section 4.2.1.2.
Ketorolac has been used as an analgesic in preterm and term neonates with no reported adverse effects (Gupta 2004 **Level III-1,** n=70; Moffett 2006 **Level IV,** n=53; Papacci 2004 **Level IV,** n=18). In children (<19 y) admitted to hospital with community acquired pneumonia, pre-hospital exposure to NSAIDs is associated with empyema in 4 of 5 studies, but use at home may reflect illness, pain and fever severity rather than causation (Voiriot 2019 **Level III-3 SR**, 5 paediatric studies, n=1,753).

Nonselective NSAID hypersensitivity

NsNSAID hypersensitivity reactions may be immune or non-immune mediated. Immune mediated include immediate reactions (IgE mediated, onset <1 h), which may be single or

multiple nsNSAID induced, and delayed reactions (T cell mediated, onset >24 h) (Kidon 2018 **GL;** Blanca-Lopez 2015 **NR**). Non-immune nsNSAID hypersensitivity includes NSAID-exacerbated respiratory disease (NSAID-ERD) (see below), NSAID exacerbated cutaneous disease and NSAID induced urticaria/angioedema; a mixed phenotype is common in children (Cousin 2016 **Level IV**, n=107). These reactions are COX-1 mediated with consequent excessive release of leukotrienes, and present within several hours of nsNSAID exposure (Cavkaytar 2019 **NR**). Also called cross-intolerance hypersensitivity, these accounted for most of the reaction types (67-85%) in a group of drug provocation test positive children (Arikoglu 2017 **Level IV**, n=106; Cousin 2016 **Level IV**, n=107).

Cutaneous symptoms of NSAID hypersensitivity reactions vary from urticaria/angioedema to more rare severe cutaneous reactions (Stevens-Johnson Syndrome [SJS] and toxic epidermal necrolysis [TEN]). The skin reactions are confounded by the use of the nsNSAID for the possible underlying viral or bacterial infection (Blanca-Lopez 2015 **NR**). Chronic urticaria (OR 7.74; 95%CI 3.38 to 18.30), atopic status (OR 2.51; 95%CI 1.50 to 4.36) and allergic rhino-conjunctivitis (1.80; 95%CI 1.14 to 2.84) are risk factors for nsNSAID hypersensitivity (Cousin 2016 **Level IV**, n=107).

Life-threatening NSAID-exacerbated respiratory disease (ERD) (see section below) and anaphylaxis are rare events. Anaphylaxis rates to nsNSAIDs are very low (0/100,000 hospitalisations; 95%CI 0 to 5.4) (Lesko 1995 **Level II**, n=84,192, JS 4). Allergic reactions are infrequently reported with diclofenac: one fatality from study data (Standing 2009b **Level IV SR** [Cochrane], 18 RCTs and 54 studies [diclofenac], n=3,611) and nine nonfatal from case reports (Standing 2009a **Level IV**). The frequency of implication of a particular nsNSAID in published series of children with allergic reactions likely reflects local prescribing and parental administration practices and has included all subclasses of nsNSAIDs (and also paracetamol) (Arikoglu 2017 **Level IV**, n=106; Topal 2016 **Level IV**, n=64). These children have been admitted for skin testing and/or oral provocation tests with either the drug implicated or aspirin. Predictors include:

- Onset of the reaction within 1 h of administration - OR 3.0; 95%CI 1.2 to 7.7 (Arikoglu 2017 **Level IV,** n=33 confirmed of 106 evaluated [6 paracetamol, 27 nsNSAIDs]) and OR 26.4; 95%CI 1.7 to 403 (Topal 2016 **Level IV**, n=18 confirmed of 64 evaluated [2 paracetamol, 16 nsNSAIDs]);
- Reported history of multiple nsNSAID-hypersensitivity (OR 27; 95%CI 1.5 to 482) (Topal 2016 **Level IV**) and (OR 2.9; 95%CI 1.2 to 7.6) (Arikoglu 2017 **Level IV**); and
- Family history of atopy (OR 4.0; 95%CI 1.50 to 10.82) (Arikoglu 2017 **Level IV**).

In these two series, the proven allergic children were subsequently tested to find a safe alternative. This is a better approach than telling the families to avoid all nsNSAIDs in their child as recommended by a prior paediatric series (Quiralte 2007 **Level IV**, n=223) referenced in this book's previous edition. Cross sensitivity may be limited to those in the same chemical group eg arylpropionic agents (ibuprofen and ketoprofen), arylacetic derivatives (diclofenac and aceclofenac) and pyrazolones (propyphenazone and dipyrone) (Blanca-Lopez 2015 **NR**).

Aspirin or NSAID-exacerbated respiratory disease (NSAID-ERD)

NSAID-ERD prevalence is reported at 1.8-44%; the variability is influenced by whether the population is from the community self-reporting sensitivity or a patient cohort with known sub-classified severity of their asthma and nasal disease, assessed with spirometry or provocation tests vs admitted to intensive care units (Kowalski 2019 **NR**). Age is relevant: younger children are stated to have reduced prevalence vs adults, with case series mostly of older children with moderate to severe asthma (usually with coexistent nasal disease/polyps) developing NSAID-ERD (Kanabar 2017 **NR;** Tuttle 2016 **Level IV**, n=3; Karagol 2015 **Level IV**, n=10; Cavkaytar 2015 **Level IV**, n=161**;** Palmer 2005 **CR**). Old series (referenced in the two narrative reviews) report prevalence of 5% in children, but a lower value of 2% (95% CI 0.2 to 7.0) in older asthmatic children reporting sensitivity (n=100) assessed with spirometry post ibuprofen provocation. In most children with mild asthma, nsNSAIDS are likely to be safe. Single-dose diclofenac had no significant effect on

respiratory function tests (spirometry) in children with asthma (Short 2000 **Level III-3**) and short term use of ibuprofen (vs paracetamol) reduced the risk of outpatient visits for asthma (RR 0.56; 95%CI 0.34 to 0.95) (Lesko 2002 **Level II**, n=1,879, JS 4). In toddlers with mild persistent asthma, no difference in asthma control or the exacerbation frequency was found between as-needed use of paracetamol and ibuprofen over 48 wk (Sheehan 2016 **Level II**, n=300, JS 4).

Reye's syndrome

Aspirin should be avoided in children with a febrile illness, as it has been associated with Reye's syndrome (encephalopathy and liver dysfunction) (Schror 2007 **NR**). The Therapeutic Goods Administration (TGA 2004 **GL**), Medsafe (Medsafe 2015 **GL**), the FDA (FDA 2003 **GL**) and the Medicines and Healthcare Products Regulatory Agency (MHRA 2003 **GL**) all recommend against aspirin under the ages of 12, 12, 12 and 16 y respectively.

Platelet effects and bleeding

The issue of nsNSAIDs and postoperative bleeding risk remains controversial.

Diclofenac use for various surgery types was not associated with increased bleeding risk requiring reoperation (OR 1.25; 95%CI 0.31 to 5) (Standing 2009b **Level I** [Cochrane], 7 RCTs, n=463).

In children (median 5 y, IQR 0.7-12) having neurosurgery (mostly major cranial and spinal interventions), perioperative ketorolac (dose unspecified) was not associated with an increase in clinically significant bleeding events (OR 0.69; 95% CI 0.15 to 3.1) or radiographic haemorrhage (OR 0.81; 95% CI 0.43 to 1.51) (Richardson 2016 **Level III-2**, n=1,451 [955 ketorolac]). In three small trials, ketorolac did not increase the risk of bleeding complications in infants after congenital cardiac (Gupta 2004 **Level III-1**, n=70; Moffett 2006 **Level IV**, n=53) or general surgery (Papacci 2004 **Level IV**, n=18).

Bleeding after tonsillectomy is of clinical significance but occurs infrequently: 1–5% in children depending on how bleeding is defined – any bleeding (which can have rates up to 10%), postoperative primary or secondary (>24 h) vs those requiring admission/transfusion/surgical intervention. Past studies have been small with contradictory results. Bleeding risk has been the subject of several meta-analyses with varying conclusions (6–7 RCT overlap). Ketorolac use is associated with increased post tonsillectomy bleeding in adults (RR 5.64; 95%CI 2.08 to 15.27) (n=246) but not children (RR 1.39; 95%CI 0.84 to 2.30) (n=1,111) (Chan 2014 **Level III-2 SR** [PRISMA], 10 studies [7 paediatric], n=1,357). An earlier review of only paediatric tonsillectomy trials (with 7 ketorolac RCT overlap) demonstrates no increased bleeding requiring either nonsurgical or surgical intervention (Lewis 2013 **Level I** [Cochrane], 15 RCTS, n=1,101). A larger tonsillectomy review also found no increased bleeding risk (surgical or nonsurgical) for all NSAIDs in adults and children, children only or for specific NSAIDs (Riggin 2013 **Level I**, 36 RCTs, n=3,193 [1,747 children]). Importantly, to definitively answer the question of whether NSAIDs increase bleeding post tonsillectomy, a study size of 2,400 is required (Lewis 2013 **Level I** [Cochrane], 15 RCTS, n=1,101).

Of note, the majority of studies in these meta-analyses have used a single dose of NSAID vs placebo. A multicentre RCT in children (median 5 y, range 2 to 18) comparing ibuprofen and paracetamol (with an overall rate of any bleeding of 9.4%) was unable to show non-inferiority for returns to theatre for bleeding post tonsillectomy (1.2 vs 2.9%: difference of 1.7% where non-inferiority margin was set at 3%) (Diercks 2019 **Level II**, n=741, JS 5). Multiple postoperative dosing for some days is routine clinical practice and has not been prospectively studied, with regard to the issue of bleeding, and surgical techniques are evolving. In a single institution with low return to theatre for post-tonsillectomy bleeding (3.3% in 3.5 years), postoperative ibuprofen exposure (n=2,122 of 6,710) did not increase post-tonsillectomy haemorrhage requiring surgical intervention (OR 0.90; 95%CI 0.68 to 1.19), but of those returning to theatre, ibuprofen users had a 3-fold greater transfusion rate than non-users (OR 3.2; 95%CI 1.0 to 9.9) (Mudd 2017 **Level III-3**, n=6710 [222 return to theatre: 15 transfusion requiring]). Predictors for post-tonsillectomy

haemorrhage requiring surgical intervention included age ≥12 y (OR 2.74; 95% CI 1.99 to 3.76) and preoperative diagnosis of recurrent tonsillitis (OR 1.52; 95% CI 1.12 to 2.06) but not obstructive indications. Cumulative dose data per patient was not reported.

Gastrointestinal effects

Epigastric discomfort, gastric or duodenal inflammation, oesophageal and peptic ulceration has occurred in association with nsNSAID use for fever and pain in children (Kanabar 2017 **NR**; Cardile 2016 **Level IV**, n=51). Following ibuprofen use for fever management, the incidence of hospital admission for gastrointestinal bleeding was low at 7.2 per 100,000 (95%CI 2 to 18) and similar to those treated with paracetamol (Lesko 1995 **Level II**, n=84,192, JS 4). A prospective series of young children admitted with gastroduodenal symptoms, haematemesis or melaena after mostly short term use had increased upper gastrointestinal complications with ibuprofen (OR 2.9; 95% CI 2.1 to 4.0), PO steroids (OR 2.9; 95% CI 1.7 to 4.8) and paracetamol (OR 2.0; 95% CI 1.5 to 2.6) vs non-use (Bianciotto 2013 **Level III-2**, n=486).

Although NSAIDs are used infrequently for analgesia in young infants, limited data on adverse gastrointestinal effects is available following PO, IV, bolus and infusion for PDA closure. Ibuprofen is as effective as indomethacin (indometacin) for PDA closure (PO or IV; 32 RCTs, n=1,862) with reduced risk of necrotising enterocolitis (18 RCTs, n=1,292) (Ohlsson 2018b **Level I** [Cochrane], 39 RCTs, n=2,843) – of relevance recent trials comparing NSAID with paracetamol for this indication suggest equivalent efficacy for paracetamol with reduced gastrointestinal bleeding (4 RCTs, n=537) and lower creatinine (4 RCTs) and bilirubin (2 RCTs) (Ohlsson 2018b **Level I** [Cochrane], 8 RCTs, n=916).

Renal effects

Renal blood flow, glomerular filtration and renal drug clearance are affected by nsNSAIDs (Allegaert 2005a **PK**). Acute kidney injury and renal failure (due to acute tubular necrosis or interstitial nephritis) in association with nsNSAID use is a serious but rare complication. It has occurred in all age groups (de Martino 2017 **NR;** Musu 2011 **NR** with reviewed case series overlap; Misurac 2013 **Level IV**) from newborns (after maternal use), neonates (Andreoli 2004 **NR**), and infants to older children (Taber 2006 **NR**). A review has shown the risk in children is lower than in adults but paediatric fatalities have occurred (Musu 2011 **NR**). No renal impairment with ibuprofen exposure was observed in a large fever trial including the subgroup of patients admitted to hospital (risk 0/100,000; 95%CI 0 to 5.4) (Lesko 1995 **Level II**, n=84,192 [n=55,785 ibuprofen], JS 4). NSAID induced acute renal failure is usually reversible with cessation of the drug (Musu 2011 **NR**). Children susceptible to dehydration (eg with high fever, vomiting and diarrhoea) may be at increased risk of nephrotoxicity.

Retrospective analysis of the FDA's spontaneous reporting system suggests increased risk of acute kidney injury with ibuprofen alone, which is higher when paracetamol was coprescribed (Yue 2014 **Level IV**). However, no data on illness type, severity, comorbidity or suspected causation (determined by expert panel review) was provided.

Vascular effects

Neonatal bolus and short term use for PDA closure can alter pulmonary (although no pulmonary hypertensive events were reported in Ohlsson 2018b **Level I** [Cochrane], 3 RCTs [pulmonary hypertension], n=255), cerebral (Naulaers 2005 **NR**), gastrointestinal and renal blood flow (Aranda 2006 **NR;** Allegaert 2005b **PK**) with oliguria (Ohlsson 2018b **Level I** [Cochrane], 6 RCTs [oliguria], n=576; Musu 2011 **NR**). Ibuprofen for PDA closure is associated with reduced risk of transient renal insufficiency vs indomethacin (Ohlsson 2018b **Level I** [Cochrane], 6 RCTs [oliguria], n=576 and 11 RCTs [creatinine levels], n=918). Subsequent to findings in non-RCT data (Musu 2011 **NR;** Ment 2004 **Level III-2,** n=431 [65 events]), the relative effects of indomethacin on the risk of intraventricular

haemorrhage (IVH) continue to be debated: of relevance, RCTs do not have a placebo arm, they differ in their report of outcomes eg severity grade of the bleed including all IVH grades (83 events/524 [7 RCTs]) vs severe grades (71/798 [10 RCTs]) or the consequence of cystic periventricular leukomalacia 37/573 [6 RCTs]) and duration of follow-up (Ohlsson 2018b **Level I** [Cochrane], 39 RCTs, n=2,843).

Bone healing effects

NSAID use following orthopaedic injury and surgery remains controversial. NSAIDs do improve analgesia, increase mobility and reduce opioid consumption following orthopaedic (including spinal) surgery, but they are also used to suppress and treat heterotopic bone ossification. The paediatric data is limited and we still do not have an understanding of the effects on bone healing and, more specifically, the impact of dosing schedules, timing and duration of exposure and whether they only delay union or contribute to non-union (Borgeat 2018 **Level III-2 SR** [PRISMA], 5 studies [paediatric], n=1,602) (see also Section 4.2.1.2). In this review, the three small retrospective reports of paediatric spinal fusion patients did not find adverse effects from <14 d of ketorolac use (total n=415) (Horn 2010 **Level III-3**; Sucato 2005 **Level III-3**; Vitale 2003 **Level III-3**). Specifically the incidence of pseudoarthrosis and revision surgery was not increased. Two retrospective series of fracture and osteotomy surgery (with one surgeon) report no delayed or non-union with perioperative ketorolac (0.5 mg/kg every 6 h) (n=468 ketorolac treated vs n=80 not) (Kay 2011 **Level III-3** in neither above nor below review; Kay 2010 **Level III-3** in both reviews). Ibuprofen exposure in children presenting to ED with a fracture (tibia, femur, humerus, scaphoid, or fifth metatarsal) and followed in orthopaedic clinic did not increase bone healing complications (OR 0.8; 95% CI 0.4 to 1.8) (DePeter 2017 **Level III-2**, n=808). The cohort were initially managed conservatively or by closed reduction or surgery. Data on ibuprofen dosing and duration was not reported.

A meta-analysis of 4 of the above studies concludes that NSAID exposure did not increase delayed or non-union risk (OR 0.58; 95%CI 0.27 to 1.21) (Wheatley 2019 **Level III-3 SR** [PRISMA], 4 studies [paediatric], n=2,017 [analysed as broken bones]) (4 study overlap with Borgeat).

The balance of low-level evidence suggests that a short-duration NSAID regimen is safe for post fracture or osteotomy pain control and for postoperative use in spinal fusion surgery.

Local necrosis following intramuscular injection

Serious local necrosis following IM injection of diclofenac is reported in six patients (Standing 2009a **Level IV**).

Table 10.6 | Common nsNSAIDs and dosing recommendations in children

nsNSAID	Suggested age cut-off	Recommended Dose	Suggested dosing frequency	References
Ibuprofen (PO)[#]	>3 mth (>5 kg) Some suggest >6 mth	5–10 mg/kg (max 400-800 mg)	6–8 hly (max 30-40 mg/kg/d)	Ziesenitz 2017 **NR PK**
Diclofenac (PO/PR)	1–12 y	1-2 mg/kg (max 50 mg)	PO: 6–8 hly PR: 12 hly	Hannam 2014 **PK**

Ketorolac* (parenteral) Australia	>16 y	0.2–0.25mg/kg (max 10 mg)	6 hly	Marzuillo 2018 **NR**; McLay 2018 **PK**
Ketorolac (parenteral) USA	>3 mth–2 y 2–16 y >16 y	0.5 mg/kg (USA: <50 kg max 15 mg; ≥50 kg max 30 mg)	6 hly	

 # IV formulation of ibuprofen is minimally used clinically to date as it is more costly than ketorolac

** These dosing recommendations are based upon study data: ketorolac does not have regulatory approval in Australia for use under 16 y (and is not available in New Zealand).*

KEY MESSAGES

1. Nonselective NSAIDs do not increase the risk of either surgical or nonsurgical intervention for bleeding after paediatric tonsillectomy (**U**) (**Level I** [Cochrane Review]); however this was not supported by a large non-inferiority RCT where surgical intervention was increased with ibuprofen versus paracetamol (**Q**) (**Level II**).
2. Nonselective NSAID (ibuprofen) use for acute otitis media reduces pain (at 48 hours) vs placebo, with similar efficacy to paracetamol (**N**) (**Level I** [Cochrane Review]).
3. Nonselective NSAIDs are effective for moderately severe pain and decrease opioid requirements after major paediatric surgery (**U**) (**Level I** [PRISMA]) and postoperative nausea and vomiting (**U**) (**Level I** [QUOROM]).
4. Serious adverse effects after nonselective NSAIDs are rare in children over 6 months of age (**U**) (**Level II**).
5. Ibuprofen may increase severity of haemorrhage post tonsillectomy in patients returning to theatre (**N**) (**Level III-3**).
6. Short term use of ketorolac or ibuprofen do not increase bone healing complications in children undergoing posterior spinal fusion, osteotomy, or fractures managed surgically (**S**) (**Level III-3**) or conservatively (**N**) (**Level III-3**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Aspirin should be avoided in children (**U**).

☑ Combined population pharmacokinetic-pharmacodynamic modelling is required to inform targeted dosing recommendations of analgesics in children (**U**).

10.4.3 | Coxibs

Paediatric trial data is limited and thus the understanding of the degree of COX-2 selectivity, the pharmacokinetic-pharmacodynamic (PK-PD) relationship and adverse effects of these agents in children remains poor and paediatric use is again off-licence.

10.4.3.1 | Pharmacokinetics

The PKs of a celecoxib suspension, capsule sprinkles and the commercial capsule have been compared (Krishnaswami 2012 **PK**). The different formulations achieve similar areas under the curve post ingestion. For pain relief in juvenile idiopathic arthritis (JIA), a suggested dosing regimen is 2–4 mg/kg bd. Although metabolism and excretion processes are typically fully functional by age 2 y, absolute oral clearance (L/h) of celecoxib is reduced in younger patients; by 40% in infants weighing 10 kg and by 24% in children weighing 25 kg vs a 70 kg adult. The major clearance pathway for celecoxib is via CYP2C9 (Murto 2015 **Level II**, n=195, JS 5). Other drugs cleared by this pathway (eg ibuprofen) have increased clearance (L/kg/h) in childhood. It is reported that clearance may be further increased in children with oncological disease (Stempak 2002 **PK**).

Parecoxib is a prodrug metabolised to the active valdecoxib, which reaches peak serum concentration at 27 min (Tan 2016 **PK**). A pooled PK analysis of parecoxib demonstrates no change in clearance with age for children over 1 y (Tan 2016 **PK**, n=112). The first year of life is when the major clearance pathways for parecoxib mature. Parecoxib dose-response relationship modelling suggest a ceiling analgesic effect at doses of less than 1 mg/kg (Tan 2016 **Level II**, n=59, JS 5). Allometric dosing of parecoxib IV (0.9 mg/kg for 2 y, 0.75 mg/kg for 7 y and 0.65 mg/kg 12 y: 40 mg max) is suggested to maintain the concentration of valdecoxib above the *in vitro* 50% inhibitory concentration for cyclooxygenase for >12 h. This achieves dose equivalence of 40 mg in a 70 kg adult, where 12 h dosing may be appropriate for both adult and paediatric age groups (Tan 2016 **PK** incorporated data from Hullett 2012 **PK**). A dose reduction or increased dosing interval is suggested for children aged <2 y. In practice for older children, paediatric centres are using 1 mg/kg (max 40 mg).

10.4.3.2 | Efficacy

Celecoxib (6mg/kg pre-induction then 3 mg/kg 12 h for 3 days) reduced early pain (POD 0-2) and co-analgesic use following adenotonsillectomy (Murto 2015 **Level II**, n=195, JS 5). Carriers of the *CYP2C9*3* allele are slow celecoxib metabolisers and demonstrate less pain and improved functional recovery. This suggests dosing may need to be more frequent than 12 h for normal metabolisers. Celecoxib use has previously been reported in children with chronically painful medical conditions. Celecoxib (3–6 mg/kg twice/d) was as effective as naproxen (7.5 mg/kg twice/d) in children with JIA (Foeldvari 2009 **Level II**, n=242, JS 5). Celecoxib use was reported in a series of JIA patients (n=68; 68 person-years) vs nsNSAID treatment (mostly naproxen, meloxicam, and nabumetone) (Sobel 2014 **Level III-2**, n=268 [person-years]) and in a small series of haemophiliac patients (Rattray 2006 **Level IV**).

Parecoxib 0.5–1.5 mg/kg for various surgery types reduces pain scores at 2 h (MD -1.9/10; 95%CI -3.0 to -0.8) and 12 h (MD -2.0; 95CI -2.3 to – 1.8) (Bu 2015 **Level I** [PRISMA], 6 RCTs [pain scores], n=350). Its use reduces PONV (4 RCTs) vs fentanyl and tramadol and postoperative opioid consumption (2 RCTs) (Bu 2015 **Level I** [PRISMA], 12 RCTs, n=994). Parecoxib 1mg/kg for post tonsillectomy pain was modestly effective in the immediate postoperative period (Li 2016 **Level II**, n=60, JS 5; Tan 2016 **Level II**, n=59, JS 5). IV parecoxib 20–40 mg (alone and combined with topical local anaesthetic) was superior to IV fentanyl 2 mcg/kg for pain after repair of corneal

perforation, with reduced rescue analgesic requirements and PONV (Subramaniam 2007 **Level II**, n=90, JS 3).

10.4.3.3 | Adverse effects of Coxibs in children

Overall safety

Prospective data from 3–12 mth use in JIA patients had similar incidence of treatment related adverse events to nsNSAIDs (Sobel 2014 **Level III-2**; Krishnaswami 2012 **PK**). None were serious which is reassuring but sample size was limited (overall n=220) (See Section 4.2.2.2 for discussion of safety and adverse effects in adults).

Safety in overdose

Paediatric overdose of celecoxib was reported in children aged 0–5 y (Forrester 2009 **Level IV**, n=177). For 92 patients, the dose was known and was large; mean 506 mg (range 10–2,300 mg) equating to mean ingested amounts of 22–39 mg/kg (for the half with documented weight) across the age groups. This resulted in no adverse effects in 96%, and minor adverse effects (rash, abdominal pain, vomiting, agitation or drowsiness) in only 4%.

NSAID hypersensitivity including NSAID-exacerbated respiratory disease (ERD)

Based upon adult data (see Section 4.2.2), coxibs are generally considered safe for use in paediatric patients with asthma and aspirin- or NSAID-exacerbated respiratory disease. In 223 patients (aged 5–78 y) with various levels of allergic reaction to nsNSAIDs or paracetamol (cutaneous/angioedema/urticaria/rash [61%], naso-ocular/cutaneous/asthma [15%], respiratory alone [9%] and anaphylaxis [16%]) having placebo-controlled multidrug oral challenges (n=697), celecoxib precipitated no events and meloxicam one event (Quiralte 2007 **Level IV**). Other smaller series have reported cross-sensitivity for coxibs in patients with cutaneous or naso-ocular reactions. In 28 nsNSAID-sensitive patients (aged 10–61 y), use of rofecoxib and valdecoxib produced urticaria or angioedema in 3 (10%) (Sanchez-Borges 2005b **Level IV**). Of 58 similarly aged patients, 5 (9%) had reactions to celecoxib and 3 (5%) had reactions to etoricoxib (Sanchez-Borges 2005a **Level IV**). As a small percentage of patients have reactions suggesting cross-sensitivity, oral challenge under medical supervision for 2 h is advisable (see Section 10.4.2.3 regarding detail of Anaphylaxis and allergy, and of NSAID-ERD with nsNSAIDs in children).

Platelets effects and bleeding

In adolescent haemophiliac patients, etoricoxib and rofecoxib treated patients had similar numbers of presentations for bleeding vs placebo (Tsoukas 2006 **Level II**, n=102, JS 5). Bleeding following paediatric tonsillectomy has been assessed (Lewis 2013 **Level I** [Cochrane], 15 RCTS, n=1,101) (see Section 10.6.5.1). This meta-analysis includes only one small coxib trial, with no differences in bleeding rates of rofecoxib vs ibuprofen vs placebo (added to paracetamol) (Pickering 2002 **Level II**, n=98, JS 5). A subsequent still relatively small trial found no difference in post tonsillectomy bleeding rates for celecoxib vs placebo (Murto 2015 **Level II**, n=195, JS 5).

Gastrointestinal effects

In children with JIA treated chronically (where 68–71% were receiving disease-modifying agents, with the number on corticosteroids unspecified), rates of abdominal pain were similar between those treated with nsNSAIDs (15/100 patient-years; 95%CI 10 to 19 [n=225 patient-years]) and celecoxib (18/100 patient-years; 95%CI 8 to 28 [68 patient-years]) and not statistically different from patients in "off-NSAID" periods (8/100 patient-years, 95%CI 2 to 15 [n=75 patient-years]) (Sobel 2014 **Level III-2**). One patient experienced gastrointestinal ulceration in an off-NSAID period. Nausea and vomiting rates were similar in the three groups.

Renal effects

Two unspecified renal disorders (not categorised as serious) occurred in chronically celecoxib-treated children with JIA during 68 patient-years of therapy (Sobel 2014 **Level III-2**). Celecoxib's safety profile for acute kidney injury in adults is specified in Section 4.2.2.2.

Table 10.7 | Coxib dosing recommendations in children

Coxib Drug	Age	Recommended Dose	Dosing frequency	References
Celecoxib (PO)*		3-6 mg/kg (max 200mg)	12 h (2-4 mg/kg repeat dosing)	Murto 2015 **Level II**
Parecoxib (IV)*	>2 y	1 mg/kg (max 40 mg) was studied: to derive allometric dose scaling see doses in text.	Single intraop. dose, >12 h before next NSAID dose	Tan 2016 **PK** Hullett 2012 **PK**

** These dosing recommendations are based upon study data; at the time of writing neither coxib is licensed for acute postoperative pain indication under 18 y.*

KEY MESSAGES

1. Parecoxib use in children reduces early postoperative pain scores, PONV (compared to tramadol and fentanyl) and postoperative opioid consumption (**N**) (**Level I** [PRISMA]).
2. Parecoxib may have a ceiling analgesic effect in children in doses less than 1 mg/kg (**N**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ The safety profile of coxibs in the setting of allergy or contraindication to nonselective NSAID in adults and children is encouraging; but safety data specific to short term use in the perioperative period is limited (**Q**).

☑ Celecoxib for 3 days reduces pain and additional analgesic requirement post-tonsillectomy in children (**N**).

☑ Some paediatric centres retain the 1 mg/kg 40 mg max daily dosing schedule for Parecoxib for off license use (**N**).

10.4.4 | Conventional and atypical opioids

There are significant developmental changes in the pharmacokinetic (PK) handling and pharmacodynamic (PD) response to opioids (Allegaert 2014 **NR**; Anderson 2014b **NR**; Holford 2012 **PK**). Doses must therefore be adjusted according to age, body weight, coexistent liver or renal impairment, and individual response. Routine and regular assessment of pain severity, the analgesic response, and the incidence of adverse effects (particularly nausea, vomiting, sedation and opioid induced ventilatory impairment [OIVI]) is essential, with titration of opioid treatment according to individual needs. As with adult patients, appropriate dose regimens, guidelines for monitoring, documentation, management of adverse effects, and education of staff and carers are required (Ellis 2011 **Level IV**; Wrona 2007 **Level IV**) (see Section 4.3.1 and subsection 4.3.1.5).

The issue of sleep-disordered breathing (SDB) is discussed here under the individual opioid adverse events subheadings and not as a subsection (See also the adult Section 9.4 on sleep-disordered breathing and subsection 9.4.1 Opioids and obstructive sleep apnoea). The issue of opioid-related tolerance and withdrawal in children and adolescents is discussed in Section 10.4.6.

10.4.4.1 | Pharmacogenomics

The evidence for the effect of pharmacogenetics on opioid responses is accumulating. Examples of relevant polymorphisms include: the liver enzyme cytochrome-P450 CYP2D6 (Balyan 2017a **PK**, n=30; Yee 2013 **Level IV**; Friedrichsdorf 2013 **Level IV;** Soderberg Lofdal 2013 **NR**; Kelly 2012 **Level IV**); enzymes involved in glucuronidation (UGT1A1) (Toce 2019 **CR)**; liver cell transporter proteins (OCT1) (Fukuda 2013 **Level IV**), ATP-binding cassette (ABC) subfamily member *B1* (or MDR1) (Horvat 2017 **Level III-3**, n=63; Sadhasivam 2015b **NR**) and ABCC3 (Chidambaran 2017c **Level III-3**, n=316; Venkatasubramanian 2014 **Level III-3**); opioid receptor subtypes (Anderson 2014a **NR**), including OPRM1 genes involved in pain perception (Sadhasivam 2015c **Level III-3**, n=259; Lee 2016 **Level III-3**, n=88) and COMT, a regulating enzyme involved in pain pathways (Elens 2016 **Level III-3**, n=34; Sadhasivam 2014 **Level IV**). Genome wide association studies have also identified single nucleotide polymorphisms associated with opioid effects in children (Cook-Sather 2014 **Level IV**). Further considerations are the differential risk with genetic differences and varying prevalence of racial/ethnic phenotypes (Anderson 2014a **NR**) and consequent variability in sensitivity to adverse effects (Balyan 2017b **Level III-3**, n=30; Chidambaran 2017a **Level III-3**, n=101; Sadhasivam 2015c **Level III-3**, n=259; Fukuda 2013 **Level IV**; Jimenez 2012 **Level III-3**) (see also Sections 1.7.2 and 1.7.3). Despite a growing understanding of the genetic factors determining drug effects, the link between genetic polymorphisms and the relevance to the observed clinical outcome is not always clear (Balyan 2017b **PK**). For some of the best understood polymorphisms, genetic screening to support clinical decision making is being explored (Gammal 2016 **Level IV**, n=2,468 [621 sickle cell disease])**.**

10.4.4.2 | Medication prescribing errors

Medication errors continue to be problematic, particularly in children. Ten-fold dose errors in prescribing made up a small proportion of hospital prescribing errors (3.8%) but were associated with significant morbidity when involving opioids (Doherty 2012 **Level IV**, n=6,643). In a single paediatric centre 5 y audit (≈1,320 medication error reports per year), the most frequently implicated drug class was opioids (8.5%) (Doherty 2012 **Level IV**) and drug was morphine (3.2%) (Mc Donnell 2011 **Level IV**). This is concerning due to the frequency of prescription within hospitals and the community and the adverse effect profile of opioids.

Conventional opioids

10.4.4.3 | Morphine

Morphine has a long history of use in paediatric acute pain management as either the gold standard comparator or rescue agent in analgesic trials.

Pharmacokinetics and pharmacodynamics

Morphine clearance is influenced by postmenstrual/postnatal age and weight (Holford 2012 **PK**; Krekels 2011 **PK**). Morphine clearance is reduced and half-life prolonged in neonates and infants, achieving adult values from age 2 y, related to the maturation of glucuronidation. Within age groups, individual variability in kinetics results in large interindividual variation in clearance, from

2 to 20 fold (Altamimi 2015 **NR**), with subsequent variability in observed maximum plasma concentration, including after PO administration (Dawes 2017 **PK**, n=34). In neonates, infants and children to 3 y, age is the most important factor affecting morphine requirements and plasma morphine concentrations (Bouwmeester 2003b **Level II**, n=68, JS 2). Mechanical ventilation reduces hepatic blood flow (up to 45%) and is associated with reduced clearance, as is renal failure (Anderson 2014b **NR**). Post cardiac surgery, there was no difference in morphine PKs seen between patients with Down syndrome vs without (Goot 2018, Valkenburg 2016 **Level III-2 PK**, n=38; Goot 2018 **Level III-2 PK**, n=42). Pharmacodynamics also change with age eg the change seen in older children for average patient-controlled morphine requirements (Hansen 1996 **Level IV**) with contribution, as outlined above, from genetics with resultant racial differences (Anderson 2014b **NR**).

The risk of respiratory depression is reduced when infusions are targeted to plasma morphine concentrations <20 mcg/L. However, no minimum effective concentration for analgesia has been determined (Anderson 2014b **NR**). No clear relationship between plasma concentration and analgesia has been identified due to variability in individual requirements, clinical state of the child, type of surgery, assessment measure used and small sample size in many studies.

Efficacy

Morphine (administered via IV, epidural, IM and IT routes) has analgesic efficacy in comparison with inactive controls, but with significantly increased vomiting and sedation (Duedahl 2007 **Level I**, 36 RCTs, n=1,908). The majority of studies analysed compared single perioperative doses and only one study evaluated a postoperative infusion of morphine. A further trial in bilateral myringotomy demonstrated equivalence of IN fentanyl, IV and IM morphine (Hippard 2012 **Level II**, n=171, JS 5). In children with SDB post tonsillectomy, more desaturation events per h occurred with PO morphine vs ibuprofen, leading to early RCT termination (Kelly 2015 **Level II**, n=91, JS 3).

In children having minor day-stay orthopaedic surgery with low pain scores, multidosing with prn PO morphine 0.5 mg/kg (max 20mg) was not more effective than ibuprofen 10 mg/kg (max 600mg) and, similar to above, was associated with more adverse effects (Poonai 2017 **Level II**, n=154, JS 5). While in a systematic review of single and repeat dosing, IV morphine 50–150 mcg/kg is inferior to IV buprenorphine 1.5–6mcg/kg in time to rescue analgesia in a range of paediatric surgeries (MD: 115 min; 95% CI 43 to 186) (Murray 2018 **Level I**, 4 RCTs, n=137).

10.4.4.4 | Fentanyl

Fentanyl is a highly lipophilic and potent mu-opioid agonist and is used in paediatric acute pain management.

Pharmacokinetics

Fentanyl's rapid redistribution contributed to its relatively rapid offset of action following single IV bolus doses (Tibboel 2005 **NR**). Fentanyl is metabolised by CYP3A4 to inactive metabolites and clearance is only 70–80% of adult levels in neonates but rapidly matures within the first 2 weeks of life, when standardised using allometric scaling. Clearance is greater per kg than adults in older infants and children 3 mth and 6 mth to 6 y (Ziesenitz 2018 **Level IV SR PK**, 24 studies [IV fentanyl], n=777).

After transbuccal administration, when children retained the lozenge in the cheek, the bioavailability was 50% vs other studies of lozenge (2 studies) vs solution (1 study), where swallowing likely contributed to the lower bioavailabilities of 33 to 36% (Lotsch 2013 **NR PK**; Ziesenitz 2018 **Level IV SR PK**, 3 studies [oral transmucosal fentanyl citrate], n=67) (1 study overlap).

Intranasal (IN) fentanyl PKs have been assessed in adults demonstrating high bioavailability (and rapid onset of effect), but not in children to date. Small volumes are necessary to reduce delivery to the posterior pharynx (where it is swallowed).

TD fentanyl has high bioavailability. In children vs adults, the time to reach steady state serum drug concentrations following TD application is longer, and the elimination half-life is shorter as clearance is enhanced (Ziesenitz 2018 **Level IV SR PK**, 1 study [TD fentanyl]: Paut 2000 **PK**, n=8).

Efficacy

Fentanyl has been administered for perioperative pain management in neonates and children (APAGBI 2012 **GL**) and also in the intensive care setting (Anand 2013a **Level III-2**) by multiple routes, including IV bolus (He 2013 **Level I,** 3 RCTs, n=283; Elshammaa 2011 **Level II**, n=60, JS 4), infusion (Jo 2011 **Level II**, n=52, JS 5), patient-controlled analgesia (PCA) (Antila 2006 **Level II** n=45, JS 4) (see Section 10.5.2), IT injection (Duman 2010 **Level II**, n=50, JS 5; Batra 2008 **Level II**, n=56, JS 5) and as an additive to peripheral nerve and epidural infusions and patient-controlled epidural analgesia (PCEA) (Saudan 2008 **Level III-3**) (see Section 10.6.3.3).

Due to its rapid onset and short duration of action, fentanyl can be used alone or in combination with sedatives to control procedural pain (see Section 10.7.2 and APAGBI 2012 **GL**; Tibboel 2005 **NR**).

Due to its high lipophilicity, fentanyl can also be administered via transmucosal (transbuccal, IN, nebulised) and TD routes. Transmucosal fentanyl is attractive when IV access is challenging or unavailable. Transbuccal fentanyl has been used for children having burns dressing changes and lumbar punctures (see Section 10.7.2).

In the prehospital or ED setting for orthopaedic trauma, 10–15 mcg/kg by transbuccal route (Davis 2011 **Level IV SR**, 1 RCT [paediatric]: Mahar 2007 **Level II**, n=87, JS 3) and 1–4 mcg/kg IN have been used effectively (Karlsen 2014 **Level IV**, n=903; O'Donnell 2013 **Level III-3**, n=946). It has also been used to manage pain from abdominal, back and other conditions (Bendall 2011a **Level III-2**, n=3,312). In paediatric EDs, IN fentanyl (INF) 1.5–2 mcg/kg was used for pain from injured extremities (Schoolman-Anderson 2018 **Level IV**, n=132; Setlur 2018 **Level IV SR** [PRISMA], 4 RCTs, n=281 and 2 studies (fracture) n=1800), burns, the abdomen and other sources (Hansen 2012 **Level IV SR**, 7 studies [paediatric], n=878 analysed). A second systematic review describes efficacy of similar dosing in three ED studies (one of fractures, one mixed pain types and one in burns [see Section 10.9.1 and 10.9.2]) and four perioperative myringotomy studies (Mudd 2011 **Level IV SR**, 12 studies, n=1,743) (5 study overlap). Further myringotomy studies have also been published (Dewhirst 2014 **Level II**, n=100, JS 5; Karlsen 2014 **Level IV**, n=903; Hippard 2012 **Level II,** n=171, JS 5). A Cochrane review did not perform meta-analysis due to the 3 different active comparator arms studied (Murphy 2014b **Level I** [Cochrane], 3 RCTs, n=313) (1 & 2 RCT overlap with above & below). In a fourth systematic review (1 & 3 study overlap: 2 RCTs and the largest prehospital study above), INF 1.5–2 mcg/kg in a variety of settings was superior to placebo and IM morphine and similar to IN and IV ketamine and IV morphine in reducing pain scores (Setlur 2018 **Level IV SR** [PRISMA], 6 RCTs, n=350; 4 retrospective studies n=5,595). In acute care settings, use of INF vs IV morphine achieved earlier time to analgesic administration in 2 cohorts by 24 and 29 mins (Borland 2008 **Level III-3**, n=617); and in a further study by 8.5 min (Schoolman-Anderson 2018 **Level III-3**, n=132). A subsequent RCT in procedural pain showed INF added to nitrous oxide (N_2O) did not improve analgesia over N_2O alone in children with low preprocedural pain scores and short procedure duration (Seiler 2019 **Level II**, n=402, JS 5). No serious adverse effects of INF were reported in the above studies with a total of >6,000 patients.

Data on nebulised fentanyl in children is limited showing similar reduction in pain scores vs IV fentanyl and IV morphine (Thompson 2016 **Level I** [PRISMA], 2 RCTs (paediatric), n=118). There have been no randomised trials of efficacy of the TD route.

Adverse effects to morphine and fentanyl in children

Side effects

Mild to moderate but not life threatening opioid-related adverse effects that greatly disturb children, and their parents, include nausea, vomiting, constipation, dizziness, sedation, dysphoria, nightmares, itch/skin rash and urinary retention. They occur commonly; no large scale comparative data is available. See data for other opioids in Table 10.8.

Major adverse events

Respiratory complications, coma and death have occurred with these two opioids. Younger aged children may have increased risk postoperatively (Tait 2016 **Level III-2**, n=678; Chidambaran 2014 **Level IV**, n=38), including post tonsillectomy (Sadhasivam 2015a **Level IV**, n=275). Comorbidities are likely to contribute (see below) but the degree of interplay of other factors such as variation in opioid potency, prescriber error (dosing or with change of opioid) and severity of pathology is unknown. National outpatient 'weak and strong opioid' prescription data has been published for New Zealand (HQSC 2019 **Level IV**, n=58,272), Australia (Bell 2019a **Level IV**, n=78,320) and USA (Chung 2018a **Level IV**, n=1,362,503), with low level (0 to 3.5%) oral morphine prescription in children.

Certain groups of paediatric patients are at higher risk of opioid induced ventilatory impairment (OIVI). Children with neurodevelopmental disabilities (eg cerebral palsy, Down's syndrome and encephalopathy) experienced more OIVI than children without (1.1 vs 0.6%; OR 1.8) with similar median dosing of morphine infusions POD 0-2 (Jay 2017 **Level III-3**, n=12,904). Children with SDB receiving postoperative opioids following various surgery types (frequently tonsillectomy in the SDB group) triggered oxygen desaturation alarms, required escalation of care and treatment with naloxone more than children without SDB (53 vs 27%: OR 2.0; 95%CI 1.6 to 2.5) (Tait 2016 **Level III-2**, n=678). Additionally, children with SDB who have worse night time oxygen desaturation (<85% nadir) required half the morphine dose to achieve the same analgesic effect (Brown 2006 **Level III-2**, n=22). Amongst hospital inpatients (n=60,467), 38 (0.06%) opioid-induced respiratory events requiring naloxone occurred, with higher incidence in those patients who were under pain service care (0.23%) (Chidambaran 2014 **Level IV**, n=38). Most patients were postoperative (71%) and were more likely to have had recent airway surgery, be underweight or obese, age <1 y and ex-premature vs pain service patients who did not receive naloxone. See also the adult Section 9.4 on sleep-disordered breathing and subsection 9.4.1 Opioids and obstructive sleep apnoea. Of three patients with renal failure who received morphine, two experienced OIVI and one died, with likely contribution of metabolite accumulation (Niesters 2013 **Level IV**, n=27).

Fentanyl-related deaths are described in children unrelated to therapeutic use. Illicitly manufactured fentanyl has caused death in a teenager and two toddlers (related to parental administration) (DeRienz 2018 **Level IV**, n=3). The transdermal patch formulation has resulted in poisonings in young children (mostly in boys with 48% mortality: Stoecker 2016 **Level IV**, n=25) and has been deliberately misused in an adolescent suicide attempt (five 100 mcg/h patches applied) (Lyttle 2012 **CR**). Partial occlusion of fentanyl patches does not reduce the dose received (Nelson 2009 **NR**). Thus the practice of applying an occlusive dressing to the skin surface of a transdermal fentanyl delivery system to limit drug delivery is not supported; some authors have inappropriately suggested this practice (Mitchell 2010 **NR**).

10.4.4.5 | Codeine

Codeine has been used for decades in paediatric acute pain. Multiple factors have led to reduced prescription of this opioid prodrug. These include the publications of codeine-related deaths, increased understanding of the relevant pharmacogenomics (see below), upscheduling (eg in Australia) and removal by the World Health Organisation (WHO) of codeine from its tiered analgesic ladder for treatment of (persistent) pain in children (WHO

2012 **GL**) in response to the blacklabelling by the USA's Food and Drug Administration (FDA) (2012 statement archived: FDA 2013b **GL**) and European Medicines Agency (EMA) (EMA 2013 **GL**). National USA data is available for 1996 to 2013 with opioid use in trauma, dental pain, outpatient procedures, postsurgery and for infections, where codeine comprised 27-40% of prescriptions (Chung 2018a **Level IV**, n=547,726 [codeine]; Livingstone 2017 **Level IV**, n=1.03 million [codeine in 2013]; Groenewald 2016 **Level IV**, n=917,700 [codeine in 2012]). Comparison of USA adenotonsillectomy claim data pre and post FDA investigation assessed children who received opioid prescriptions (Chua 2017b **Level III-3**, n=362,992 [246,459 prescriptions]). In Jan 2010 vs Dec 2015, codeine decreased from 46.8% to 9.1% of prescriptions (while hydrocodone increased from 48.4 to 72.7%). In Dec 2015, off label prescription of codeine occurred for 5.1% of all children and 3% of children with OSA. While still in 2017, codeine made up the majority of community opioid prescriptions in Australia for children <17 y (50.5%: AIHW 2019 **Level IV**) and in New Zealand for <24 y (54.3%: HQSC 2019 **Level IV**).

Pharmacokinetics

PO codeine has a similar time to peak effect but decreased total absorption vs PR and IM delivery (McEwan 2000 **PK**). Administration IV should be avoided as severe hypotension may result (Shanahan 1983 **Level IV**).

Pharmacogenomics and adverse effects

Relevant to codeine as a prodrug, the numerous CYP2D6 enzyme's polymorphisms result in four phenotypes, which demonstrate an overlapping spectrum of activity (Chidambaran 2017b **NR**) (see also Sections 1.7.3 and 4.3.1.2). The phenotypes are variably represented in populations of different ethnicities. The most common (>70% of Caucasians to 92% of Asians) "normal" phenotype, termed extensive metabolisers, has 1–2 x CYP2D6 activity and analgesic effect with codeine. Intermediate metabolisers have reduced (0.5 x CYP2D6 activity) and poor metabolisers no effect (nil CYP2D6 activity) from codeine: affecting 46% of a group of UK children having tonsillectomy (Williams 2002 **Level II PK**, n=96, JS 4) and 49% (intermediate 44% and poor 5.3%) of children with sickle-cell disease (Yee 2013 **Level IV**, n=75); while ultra metabolisers (>2 x activity) attain high peak morphine levels and are at risk of sedation and respiratory depression (Chidambaran 2017b **NR**; Yee 2013 **Level IV**, n=75; Racoosin 2013 **Level IV**, n=7) (case report overlap). Somnolence, lethargy and respiratory depression have been reported with antitussive use of codeine (Paul 2018 **Level IV**, n=98 [38 codeine related]). Several paediatric deaths associated with codeine administration have been reported, some with confirmed ultra and extensive metaboliser phenotype. Subgroups at particular risk included breastfeeding neonates (whose ultra/extensive metaboliser mothers were taking codeine in the puerperium) (Madadi 2007 **CR**), toddlers (Racoosin 2013 **Level IV**, n=7; Kelly 2012 **Level IV**, n=3 [2 deaths]) and obese older children following adenotonsillectomy (Chidambaran 2017b **NR**, case report summary including Friedrichsdorf 2013 **Level IV**, n=3 [obese]).

The USA's FDA has subsequent to 2013 contraindicated against codeine use in all children under 12 y and in adolescents who are obese or having adenotonsillectomy (with a recommendation against use by breastfeeding mothers) (FDA 2017 **GL**). The EMA has extended their 2013 contraindication to also exclude use as an antitussive (EMA 2015 **GL**). Australia's Therapeutic Goods Administration (TGA) applied the same warnings as the FDA in 2017 (TGA 2017 **GL**) and further limited access with upscheduling of combination codeine containing products in 2018 (TGA 2019 **GL**). New Zealand applied the same warnings in children and breastfeeding mothers in mid 2018 (Medsafe 2018 **GL**) and plans scheduling changes in 2020. Several paediatric hospitals have removed codeine from their drug formularies (Tremlett 2013 **NR**).

Efficacy

Codeine efficacy data has been published in a few RCTs prior to 2009. In the majority of studies with a codeine treatment arm (see below), CYP2D6 activity is not accounted for and is a significant confounder contributing to conflicting reports of efficacy for postoperative pain. Early perceived advantages of codeine include less respiratory depression in neonates and reduced nausea and vomiting vs morphine (at one only of four time points) (Williams 2002 **Level II**, n=96, JS 4). These conclusions are probably compromised by low levels of active metabolites and resultant reduced efficacy (Williams 2001 **NR**). Comparison of codeine and morphine for tonsillectomy has shown either no difference (Semple 1999 **Level II**, n=40, JS 4) vs an increased requirement for rescue analgesia following codeine (Williams 2002 **Level II**, n=96, JS 4). Codeine was less effective than ibuprofen for acute musculoskeletal pain in children (Clark 2007 **Level II**, n=336, JS 5). Addition of codeine to paracetamol has been reported to improve analgesia (Pappas 2003 **Level II**, n=120, JS 5) or have no effect (Moir 2000 **Level II**, n=79, JS 5) and was as effective as ibuprofen for fracture pain but ibuprofen-treated patients had fewer adverse effects and better functional outcomes (Drendel 2009 **Level II**, n=336, JS 5). Use of codeine in paediatric neurosurgical case series has been published (Bronco 2014 **Level IV**; Teo 2011 **Level IV**).

10.4.4.6 | Oxycodone

Oxycodone is increasingly used in paediatric acute pain management. USA prescription data for children is available. One tertiary USA centre has documented oxycodone as the most commonly prescribed opioid (72.5%) by mostly surgical services, with decreased annual codeine prescription over 7 y from 377 to only 3 prescriptions (George 2016 **Level IV**, n=34,218). The USA's national community opioid prescription data has not yet reflected this change with only 4.6% and 15.5% being for oxycodone vs the more commonly prescribed codeine and hydrocodone (Chung 2018a **Level IV**, n=62,675 [oxycodone]; Groenewald 2016 **Level IV**, n=314,650 [oxycodone]; see Table 10.8 for data detail). In the USA's adenotonsillectomy claim analysis pre and post FDA investigation, oxycodone prescription increased from 3.8% in 2010 to 17.4% in 2015, outranked by increased hydrocodone (Chua 2017b **Level III-3**, n=362,992 [246,459 prescriptions]). Community prescription of oxycodone for children in 2017 was low in New Zealand at 1.3% of all opioid prescriptions (HQSC 2019 **Level IV**), while in Australia oxycodone was commonly prescribed comprising 36.5% of opioid prescriptions for children (AIHW 2019 **Level IV**).

Pharmacokinetics and pharmacogenomics

In children aged >6 mth, the PK profile of oxycodone is similar to adults and dosing can be based on weight (El-Tahtawy 2006 **PK**). Similar absorption is seen following buccal and SL administration (Kokki 2006 **PK**). PK variability remains large, exacerbated by CYP2D6 polymorphism, as is the case with other opioids (Soderberg Lofdal 2013 **NR**). In expreterm to term neonates and infants, the half-life is prolonged with an inverse relationship to age (reflecting the lower body weight adjusted clearance and higher apparent Vd) and increased variability in kinetics is seen even following IV administration (Valitalo 2017 **PK**, 3 Studies, n=119). The body weight adjusted clearance is lowest and the apparent Vd is highest in preterm babies, which results in elimination half lives typically around 8 h in extremely preterm neonates. The parent compound contributes the majority of drug effect but the impact of polymorphisms and cotherapies that influence CYP2D6 and CYP3A4 enzymes, and thus metabolite (eg oxymorphone, noroxymorphone and noroxycodone) concentration, has been debated (Kokki 2012a **NR**) (see Section 1.7.3). In children, a difference in the plasma concentrations of oxycodone metabolites relating to CYP2D6 genotypes was found, but the clinical significance has not yet been explored (Balyan 2017a **PK**, n=30). See adult Section 1.7.3.4.

Efficacy

Oxycodone's efficacy has been shown in various paediatric settings: PO use of 0.1–0.2 mg/kg in the ED for children with orthopaedic injuries (Charney 2008 **Level II**, n=107, JS 5; Koller 2007 **Level II**, n=66, JS 5), use of a PO controlled-release (CR) preparation as a step-down following PCA in adolescents after spinal fusion (Czarnecki 2004 **Level IV**), IV bolus dose administration for postoperative rescue analgesia (Kokki 2006 **Level IV**) and IV PCA in adolescents and adults (Silvasti 1999 **Level II**, n=52, JS 4). Oxycodone CR (OxyContin®) has been approved in the USA for use in children >11 y who are 'opioid-tolerant' defined as minimum 5 d prior oxycodone therapy of >20 mg/d (Product information: FDA 2018b), but use is off-label elsewhere. There has been no study reporting paediatric use of the CR oxycodone/naloxone combination (eg Targin®) to date.

Adverse effects

Like for the other commonly used opioids, large scale data on mild to moderate adverse effects is not available for oxycodone specifically. USA data following outpatient opioid prescription and subsequent ED presentation with an adverse event likely related to the prescribed opioid is summarised in Table 10.8 below. See also 10.4.5 Issues with discharge opioid prescriptions for children.

Literature search reveals no data specific to oxycodone and QT prolongation in children, however this is different for adults. See adult Section 4.3.1.5 Adverse effects of opioids where the issue of cardiac effects of opioids and also nausea and vomiting and QT prolongation related to antiemetics is discussed.

Table 10.8 | Opioid prescription data (USA) for children and adolescents including subtypes of opioids and adverse events

Author Year	**Groenewald 2016**	**Chua 2017b**	**George 2016**	**Chung 2019**	**Chung 2018a**
Data type	**National**	**National**	**One hospital**	**One state#**	**National**
Prescriptions, n	2,030,000 in 2012	246,459	34,218	529,731 prescriptions for 201,940 adolescents	1,362,503
Years	1996-2012	2010-2015	2007-2014	1999-2011	1999-2014
Prescribed opioids* (%)					
Hydrocodone	42.1	72.7	2	59	42.1
Codeine	39.9	9.1	7.3	27	40.2
Oxycodone	15.5	17.4	73	8.6	4.6
Hydromorphone	NS	--	3.7	NS	NS
Morphine	NS	NS	1.1	NS	NS
Tramadol	NS	--	NS	5.5	2.9
Other	--	0.8	--	--	5.2 (meperidine)
Adverse events related to opioids, n (per prescription)			25 (7/1 million)	275 (5/1 million)	437 (3/1 million)

Author Year	Groenewald 2016	Chua 2017b	George 2016	Chung 2019	Chung 2018a
Adverse event subtype n (%)					
Death			NS	1 (0.36%)	3 (0.7%)
Resp. depression				10 (3.3%)	12 (2.8%)
CNS depression				71 (25.8%)	97 (22.2%)
Neuro-psychiatric				83 (30.2%)	83 (30.2%)
Gastrointestinal				57 (20.7%)	134 (30.7%)
Dermatological				51 (18.5%)	102 (23.3%)
Allergic				35 (12.7%)	77 (17.6%)
Other				4 (1.5%)	15 (3.4%)
Prescriber error			25 total 16 patients with weight entry error: 14 with <10% error; two with >15% error -one under and one over		

 # Tennessee **(alone or as combined products)* *NS= not specified* *Resp.=respiratory*

Other conventional opioids

A large number of opioid preparations have been used in children (see below), but availability varies by country and many have not been investigated in controlled trials. For additional details see (APAGBI 2012 **GL**).

10.4.4.7 | Hydromorphone

Hydromorphone has no advantage over other opioids in terms of analgesic efficacy or adverse-effect profile, administered by PO, IV, caudal or epidural route (Quigley 2002 **Level I** [Cochrane], 4 RCTs [paediatric], n=122). Oral hydromorphone prescriptions were uncommonly dispensed from a single USA paediatric institution over 8 years (George 2016 **Level IV** n=1,266 prescriptions). IV Hydromorphone has been used in the PICU setting usually as second or third line opioid therapy for analgesia and sedation for malignancy and following trauma with a median dose 10 mcg/kg/h (Reiter 2012 **Level IV**). IN Hydromorphone was titrated in children presenting to the ED with various painful conditions (such as fracture or abdominal pain); 30–60 mcg/kg over 30 min total achieved ≥3/10 pain reduction (Tsze 2019b **Level IV**, n=35).

See Section 10.6.3.3 and 10.6.6 for neuraxial use and Section 10.8.1 and 10.8.3 for use in paediatric cancer.

10.4.4.8 | Hydrocodone

Hydrocodone is not available for analgesic use in Australia or New Zealand. In other countries, it is generally used in combination with paracetamol (Sutters 2010 **Level II**, n=123, JS 3; Rees 2019 **Level IV**, n=1,246). In the USA in 2014, hydrocodone (combination product with paracetamol) was upscheduled. As documented in Table 10.8, it has been the most commonly prescribed opioid for children in the USA over a 16 year period, with no evidence base.

Oral clearance is higher in children (weight adjusted) vs adults; weight-based dosing in children thus leads to reduced exposure which is overcome if body surface area adjusted dosing is used for children aged 6–17 y (Liu 2015 **PK**, n=17). Hydrocodone is metabolised by CYP2D6 to

hydromorphone and CYP3A4 to norhydrocodone. Inhibition of these enzymes by coadministered antibiotics and anticonvulsants resulted in a child's death where hydrocodone was being used for antitussive effect (Madadi 2010 **CR**). Three further fatalities have been reported in children <12 y associated with antitussive use of hydrocodone combined with antihistamine and a further 57 patients had respiratory depression, somnolence and/or lethargy (Paul 2018 **Level IV**, n=98). The FDA has limited hydrocodone (along with codeine) containing cough and cold products to adults ≥18 y (FDA 2018a **GL**).

10.4.4.9 | Methadone

Methadone is used in children for persistent pain, for opioid weaning (Dervan 2017 **Level IV SR** [PRISMA], 12 studies, n=459; Johnson 2012 **Level IV**, n=96) and as part of a multimodal approach to complex surgeries. In adolescent posterior spinal fusion patients receiving intraoperative remifentanil infusion up to 0.3 mcg/kg/min, the addition of IV methadone 0.1 mg/kg reduced intraoperative hydromorphone administration with resultant lower overall 0–24 h requirement of 0.26 ± 0.10 mg/kg vs magnesium (50 mg/kg bolus then intraoperative infusion 10 mg/kg/h) 0.38 ± 0.10 mg/kg vs remifentanil alone 0.34 ± 0.11 mg/kg, with no difference in pain scores (Martin 2018 **Level II**, n=60, JS 4). Methadone has also been used for the Nuss procedure (Singhal 2016 **Level III-2**, n=125) and as a third line intervention for acute neuropathic pain in children post limb salvage surgery (Anghelescu 2011a **Level IV**, n=6/150). The more extensive published use in children is in oncology and palliative care (Habashy 2018 **NR**; Mott 2018 **Level IV**, n=16) and in neonatal abstinence syndrome.

There is limited PK information in children, but the available data show similar parameters in neonates, infants and children to adults (Ward 2014 **PK**). The conversion to methadone from other opioids is complex and dependent on recent opioid exposure. Patients with higher opioid exposure require relatively lower methadone conversion ratios (Mott 2018 **Level IV**, n=16).

In children receiving methadone for cancer pain, some QT prolongation was seen in patients taking a median dose of 0.37 mg/kg/day (most of whom were on other QT prolonging agents), but there have been no published reports of severe dysrhythmias in children receiving methadone for pain (Habashy 2018 **NR**).

See adult sections 4.3.1.2 Methadone and 4.3.1.5 Cardiac effects of opioids for discussion of QT prolongation.

10.4.4.10 | Sufentanil, Alfentanil and Remifentanil

Sufentanil

Sufentanil PKs have been assessed after IV use, and clearance maturation is the same as for other drugs metabolised by CYP3A4 eg fentanyl (Ziesenitz 2018 **Level IV SR PK**, 8 studies [sufentanil], n=129). After IN sufentanil 2 mcg/kg, maximum concentration (Cmax) occurred at 15-30 min with syringe dropper technique (Ziesenitz 2018 **Level IV SR PK**, 1 study [IN sufentanil]: Haynes 1993 **PK**, n=15).

IN sufentanil 0.5 mcg/kg combined with IN ketamine via actuating device spray was effective for various procedures (n=50) with respective bioavailabilities of 25 and 36% and a Cmax at 13.8 min (Nielsen 2014 **Level IV**). IV sufentanil infusion was used to manage post-thoracotomy pain in intubated preterm neonates at 0.1–0.2 mcg/kg/h initially and subsequently reduced to 0.03–0.04 mcg/kg/h, with no difference in time to extubation (Soreze 2017 **Level III-3**, n=109).

Epidural sufentanil use alone and with local anaesthetic is described in Section 10.6.3.

There is no current data on SL sufentanil use in children.

Alfentanil

Alfentanil PKs have been reviewed (Ziesenitz 2018 **Level IV SR PK**, 15 studies [alfentanil], n=244). Use of IN alfentanil 10 mcg/kg (in low volume solution 0.2 mL) is described in the ED for analgesic management of mostly orthopaedic injuries (Brenchley 2006 **Level IV**, n=36). Only intraoperative and not postoperative use of alfentanil in children has been described. Caudal epidural administration with local anaesthetic is described in Section 10.6.3.

Remifentanil

Remifentanil PKs have been reviewed (Ziesenitz 2018 **Level IV SR PK**, 7 studies [remifentanil], n=118). Mostly intraoperative use of remifentanil in children has been described. Extension of use into PACU has been reported for modification of emergence agitation (and is not presented here). Use in neonates having non cardiac surgery and while in NICU to facilitate endotracheal tube tolerance and sedation has been described (Kamata 2016 **NR;** Allegaert 2016 **NR**), as well as in PICU for sedation without documenting pain scores (Hungerford 2019 **Level IV**, n=38).

See Sections 10.7.2.2 for use in procedural intervention in children with cancer and 10.7.2.9 for use of remifentanil in combination with propofol for procedural intervention in burns.

See Section 10.4.7 and adult Sections 4.6.1.1 and 4.6.1.3 for data on the adjuvant use of ketamine and magnesium to reduce remifentanil induced tolerance.

10.4.4.11 | Diamorphine (diacetylmorphine, heroin)

This opioid is not available for analgesic use in Australia and New Zealand. In the UK, it is used IN in paediatric EDs (by 118 of 205 surveyed paediatric EDs) (Hadley 2010 **Level IV**) for trauma pain management eg alone post fracture (Kendall 2001 **Level II**, n=404, JS 3; Kidd 2009 **Level III-2**; Regan 2013 **Level III-3**; Kendall 2015 **Level IV**, n=226) or for fracture reduction with N_2O (Kurien 2016 **Level IV**, n=100), and for sickle cell crises (Telfer 2009 **Level IV**) (see Section 8.6.4.1). The bioavailability following IN drop installation is 33%, with T_{max} of 10 min (Kidd 2009 **Level III-2**).

Atypical opioids: Tramadol, Buprenorphine and Tapentadol

10.4.4.12 | Tramadol

Tramadol, first launched as an opioid, is now recognised as an atypical opioid with its multimodal antinociceptive and antineuropathic effects. Its two enantiomers act via noradrenaline and serotonin reuptake inhibition and mu-receptor agonistic effect, where for the latter the metabolite O-desmethyl-tramadol (or M1) has greater efficacy than the parent compound (Anderson 2017b **NR**). Evidence for tramadol use in paediatric acute pain is still limited by studies of small sample size and difficulty determining comparative analgesic doses. With the 2012 FDA black box warning for young children and tonsillectomy, codeine prescription has decreased post-tonsillectomy (Van Cleve 2017 **Level IV,** n=230 [477 tonsillectomies]). Meanwhile from 2012 to 2015, tramadol use has increased in the USA by 23% from 170 to 209 per 1,000 population (Bigal 2019 **Level IV**, n=18.8 million [12 to 64 y olds]); but it is not known how many prescriptions are paediatric or post-tonsillectomy. Interestingly codeine prescription over the same period, after an initial decrease, has also increased. Subsequent to codeine's relabeling, the FDA has applied the same warning against tramadol use in paediatric acute pain (FDA 2017 **GL**). Frequent off label use occurs in young children with variable paediatric licensing internationally: over 1–3 y in Europe (country-dependent) (Rodieux 2018 **NR**) vs ≥12 y previously in Australia (with June 2019 revised Consumer medicine information leaflets for the oral capsule stating 'should not be used in children') (NPS Medicinewise 2019a **GL**) with New Zealand changing its licensing from ≥2 y

(Medsafe 2017 **GL**) to follow the USA FDA with contraindication <12 y and <18 y following tonsillectomy/adenoidectomy (Medsafe 2020 **GL**).

Pharmacokinetics and pharmacogenomics

Oral bioavailability is 68–75% post single dose in adults (See section 4.3.1.3) and is likely similar in children. Due to extensive first-pass hepatic metabolism and higher hepatic blood flow in children and infants, plasma concentrations are lower (Vandenbossche 2015 **PK**; Allegaert 2011b **PK**). Rectal bioavailability is good with low interindividual variability (Zwaveling 2004 **PK**, n=12 in Bozkurt 2005). Maximum plasma concentrations post IV, PO and PR dosing are achieved between 0.3–2.4 h (Bozkurt 2005 **Level III-3 SR PK**, 3 studies, n=164), with peaks post PO at 1–2 h for tramadol and 3 h for M1 (Vandenbossche 2015 **PK**, 3 studies, n=97). Analgesic efficacy is associated with a plasma concentration of tramadol of 100 ng/mL in adults and children and M1 of 15 ng/mL (Garrido 2006 **PK**).

Tramadol is transported to the liver via the organic cation transporter-1 (OCT1). Reduced OCT-1 function resulted in lower tramadol requirements in adults (Stamer 2016 **PK**, n=205). It is metabolised primarily to M1 by the hepatic enzyme CYP2D6 (Anderson 2017b **NR**) (see also Sections 1.7.3 and 4.3.1.3). CYP2D6 activity matures with age increasing rapidly from 25 wk postmenstrual age to 50% of the adult value by 44 wk postmenstrual age and to 90% by 1 y of age (Allegaert 2011b **PK**). M1 is primarily inactivated via glucuronidation, most extensively by UGT2B7 and UGT1A8 (with the glucuronide forms then renally excreted) (Lehtonen 2010 **BS**). The relevance of the UGT enzymes is now being explored. In addition to this, M1 is eliminated renally but preterm neonates, because of their reduced renal function, have relatively higher plasma M1 concentrations (Allegaert 2008 **PK**). While, infant size and postmenstrual age constitute the greater contribution (53%) to inter-individual variability in tramadol and M1 metabolism and clearance, significantly more so than CYP2D6 activity score in the very young (Allegaert 2008 **PK**). In older children, tramadol clearance is linked to weight (Bressolle 2009 **PK**). OCT1 expression and function is highly genetically variable and may be a further consideration, alongside CYP2D6 phenotype, in at risk groups (Tzvetkov 2017 **NR BS**) (see also Section 10.4.4.5).

The poor, normal, extensive or ultra metaboliser CYP2D6 phenotype has been the reason for codeine's black box warning, but the clinical significance in terms of tramadol/M1's analgesic efficacy and adverse effect profile is still unknown.

Dose and efficacy

Systemic administration

In children IV dosing is the same as in adults (1–2 mg/kg every 6 h), with an initial IV dose 2 mg/kg recommended, followed by IV infusion rates of 0.25–0.41 mg/kg/h (6–10 mg/kg/24 h) (Allegaert 2011b **PK**; Bressolle 2009 **PK**). Lower infusion rates have been reported (Alencar 2012 **Level II**, n=160, JS 5; Moyao-Garcia 2009 **Level II**, n=24, JS 5).

A meta-analysis has graded the existing heterogeneous RCTs as low in quality with methodological problems (Schnabel 2015 **Level I** [Cochrane], 20 RCTs, n=1,170). It finds single doses of IV tramadol 0.5–3 mg/kg for postoperative pain relief in children is superior to placebo reducing the number of patients in moderate to severe pain (2 RCTs, n=94), need for rescue analgesia in PACU (RR 0.4; 95%CI 0.2 to 0.8) (5 RCTs, n=189), with similar efficacy in terms of rescue use (0–24 h) to morphine (3 RCTs, n=127), fentanyl (1 RCT, n=42), pethidine 1 mg/kg (2 RCTs, n=120) and nalbuphine (2 RCTs , n=110).

For tonsillectomy, PO tramadol 2.5 mg/kg was more effective than low-dose PR paracetamol (Pendeville 2000 **Level II**, n=50, JS 5), IV 1 mg/kg had similar efficacy to IV paracetamol 15 mg/kg (Uysal 2011 **Level II,** n=64, JS 5), IV 1–2 mg/kg had similar efficacy to IV morphine 0.1 mg/kg (Engelhardt 2003 **Level II**, n=60, JS 5) as did PCA IV tramadol bolus of 0.2mg/kg vs 0.02 mg/kg morphine for 24 h postoperatively (Ozalevli 2005 **Level III-1**). Conversely IV 1 mg/kg was less effective than IV pethidine

1 mg/kg (Ozer 2003 **Level II**, n=50, JS 3), PO dextromethorphan 1 mg/kg (Ali 2008 **Level II**, n=90, JS 1), ketoprofen (IV initial bolus 2 mg/kg and 6 h infusion of same dose) (Antila 2006 **Level II**, n=45, JS 4) and ropivacaine infiltration, while being similarly effective to placebo (Cocelli 2012 **Level II**, n=90, JS 3) (all 4 RCTs in Schnabel 2015 **Level I** [Cochrane]). Multidosing post tonsillectomy in 4–15 y olds for 5–10 d of PO tramadol 1.05 mg/kg (max 52.5 mg) alone 6 hly provided comparable analgesia to combination paracetamol 7.2 mg/kg with codeine 0.72 mg/kg (max 36 mg) (Friedrichsdorf 2015b **Level II**, n=84, JS 2). More paracetamol-codeine treated patients were sedated only on POD 1 (21 vs 3%), while the tramadol-treated experienced more itch in the 10 d (33 vs 13%).

Post abdominal surgery, IV tramadol 2 mg/kg was similarly effective to IV pethidine 1 mg/kg (Ekemen 2008 **Level II**, n=110, JS 3). In postoperative ventilated neonates, multidosing of IV tramadol 2 mg/kg 6 hly vs placebo in addition to IV paracetamol and morphine infusion did not offer clinical benefit in pain scores, morphine requirements or time to extubation (Olischar 2014 **Level II**, n=71, JS 5). In ventilated neonates following major abdominal and minor surgery, IV tramadol infusion (0.1–0.2 mg/kg/h) was similar to fentanyl infusion (1–2 mcg/kg/h) in terms of pain scores over 72 h, time to extubation and to full enteral feeding (Alencar 2012 **Level II**, n=160, JS 5). In children having various surgery types, IV tramadol infusion 0.12 mg/kg/h for 72 h was trialled against nalbuphine infusion (Schnabel 2015 **Level I** [Cochrane], 1 RCT [nalbuphine]: Moyao-Garcia 2009 **Level II**, n=24, JS 5).

For further data on IV tramadol administration to children: see Section 10.5.2 for PCA and 10.5.3 for NCA.

Sublingual administration

SL tramadol 2 mg/kg use in paediatric fracture pain was effective and comparable to SL ketorolac 0.5 mg/kg at 100 min (Neri 2013 **Level II**, n=131, JS 5), but PK data to support this route is not available.

Neuraxial administration

After neuraxial administration, efficacy has generally not been compared to systemic administration; the safety of this route remains uncertain (Walker 2012c **NR**; Engelman 2012 **Level I** [PRISMA], 9 RCTs [tramadol], n=258). Caudal tramadol 1–2 mg/kg added to caudal local anaesthetic prolongs the time to first rescue analgesic (4.5 h; 95%CI 2.8 to 6.1) at the expense of increased vomiting (OR 2.5; 95%CI 1.3 to 4.6), with no IV comparator.

For inguinoscrotal surgery, caudal tramadol 2 mg/kg added to bupivacaine and levobupivacaine was similarly effective (Sezen 2014 **Level II**, n=68, JS 5). Post abdominal surgery, epidural tramadol 2 mg/kg added to epidural ropivacaine 0.2% was superior to ropivacaine alone, with lower pain scores, reduced rescue requirement and longer time to first analgesic request (14.5 h vs 5) (Inanoglu 2010 **Level II**, n=44, JS 5). For lower abdominal, urological and lower extremity surgery in young children, caudal tramadol 1 mg/kg added to caudal bupivacaine 0.25% 1 mL/kg increased time to first analgesia vs local anaesthetic alone (7.8 h vs 4) (Regmi 2017 **Level II**, n=60, JS 5). As a sole agent for urological surgery (without a systemic arm or epidural local anaesthetic comparator), epidural tramadol 2 mg/kg vs morphine 0.1 mg/kg had similar pain scores and time to first rescue analgesic, but with reduced adverse effects (Demiraran 2005 **Level II**, n=80, JS 3) (see also Section 10.6.3.1 and 10.6.3.3).

Infiltration and topical administration

Whether tramadol has clinically useful local anaesthetic effects has been debated. Peritonsillar infiltration of tramadol 2 mg/kg has been studied in several small RCTs and was effective for control of early (0–8 h) postoperative pain following adenotonsillectomy. Its benefits were similar to lidocaine (Heiba 2012 **Level II**, n=60, JS 4), similar (Ugur 2013 **Level II**, n=75, JS 5) and superior to ketamine infiltration (Ayatollahi 2012 **Level II**, n=126, JS 4), superior to placebo (Atef 2008 **Level II**,

n=40, JS 5) and, when combined with IV ketamine, superior to either agent alone and placebo (Honarmand 2013 **Level II**, n=75, JS 5). Only one small systemic comparator trial is available, which found infiltration of tramadol 2 mg/kg to be superior to IM administration and placebo (Ugur 2008 **Level II**, n=45, JS 5).

For inguinal herniorrhaphy in young children, preincisional infiltration of tramadol 2 mg/kg was as effective as bupivacaine 0.25% with regard to pain scores and time to first analgesic use (Numanoglu 2014 **Level II**, n=52, JS 4). While infiltration post hernia repair of SC tramadol 2 mg/kg resulted in higher initial pain scores but similar time to first rescue analgesic request vs bupivacaine infiltration, with both having a longer effect than IM tramadol (6.7 h vs 6 vs 4.5) (Demiraran 2006 **Level II**, n=75, JS 5).

For awake circumcision, ring block combined with pudendal nerve block with tramadol 5%/adrenaline was effective and superior to prilocaine/adrenaline with reduced rescue requirements (Kargi 2010 **Level II**, n=40, JS 4), but was ineffective vs lidocaine/adrenaline (Polat 2013 **Level II**, n=47, JS 4).

A small tonsillectomy study showed no benefit on POD 0 following single topical application of tramadol 5%, but pain scores were reduced on POD 6 (Akbay 2010 **Level II**, n=40, JS 5). Tonsillar application of tramadol 40 mg/ketamine 20 mg was superior to placebo, with similar pain scores and rescue analgesic requirements on POD 0 (Tekelioglu 2013 **Level II**, n=60, JS 5).

Adverse effects

Tramadol has similar or reduced rates of nausea and vomiting (10–40%), sedation and fatigue to those found with conventional opioid use, generally with lower rates of constipation and pruritus (Bozkurt 2005 **Level III-3 SR**, 20 studies, n unspecified). Following a large tramadol overdose with plasma level >1 mg/mL, a seizure and cardiogenic shock have been reported in a child; cardiac function normalised within 48 h (Perdreau 2015 **CR**). Anaphylaxis (Mori 2015 **CR**) and deaths have been reported (see below).

Nausea and vomiting

In mixed surgery types, PONV is not reduced in tramadol vs placebo recipients in PACU (RR 0.84; 95%CI 0.28 to 2.52) (3 RCTs, n=215) or to 24 h (RR 0.78; 95%CI 0.54 to 1.12) (4 RCTs, n=150) (Schnabel 2015 **Level I** [Cochrane], 20 RCTs, n=1,170). In accidental and intentional overdose, nausea and vomiting rates were 16 to 25% (Stassinos 2019 **Level IV** n=1,115; Hassanian-Moghaddam 2015 **Level IV**, n=20; Tsutaoka 2015 **Level IV**, n=3,051 [tramadol exposures in children under 19y]; Marquardt 2005 **Level IV**, n=190).

Sedation and ventilatory impairment

Lower sedation rates with tramadol vs conventional opioids have been described (Schnabel 2015 **Level I** [Cochrane], 7 RCTs, n=526); the heterogeneity of the included RCTs documenting sedation scores did not permit subanalysis. Drowsiness is common post overdose with rates in adults of 27% (Marquardt 2005 **Level IV**, n=190) and 55–100% in children (mean dose of 13.1 mg/kg) (Stassinos 2019 **Level IV**, n=1,115 [symptomatic children] of 7,334 exposures; Tanne 2016 **Level IV**, n=7; Hassanian-Moghaddam 2015 **Level IV**, n=20; Marquardt 2005 **Level IV**, n=8 [<5 y]) and may or may not be associated with miosis.

In the Cochrane review, no tramadol-treated child had ventilatory impairment, but sample sizes were small. Subanalysis of tramadol vs placebo (3RCTs, n=165) and multiple opioid comparator arms (8 RCTs, n=532) revealed non-estimable or minimal effect sizes (Schnabel 2015 **Level I** [Cochrane], 20 RCTs, n=1,170). In an RCT included in the Cochrane involving tonsillectomy in children with OSA, fewer desaturation events were reported with tramadol 2 mg/kg than with morphine 0.1 mg/kg, significant only between 1–2 h postoperatively (Schnabel 2015 **Level I** [Cochrane], 1 RCT: Hullett 2006 **Level II**, n=66, JS 4). Three ex-premature infants given tramadol

2 mg/kg (with local anaesthetic drops: for outpatient eye examination) experienced prolonged sedation, returned and were admitted (Bilgili 2012 **Level IV**, n=20). One experienced frequent apnoea required continuous positive airway pressure (CPAP) and transfusion, one required supplemental oxygen and one was observed only.

Following mostly supratherapeutic doses or accidental/intentional overdose, ventilatory impairment is reported in both adults (following a high mean dose of 2,125 mg, range 200-4,600) (Hassanian-Moghaddam 2013 **Level IV**, n=19 [1 death] in 114 hospital presentations post-tramadol) (see Section 4.3.1.3) and children (following high doses of ≥7–10 mg/kg) (Stassinos 2019 **Level IV**, n=37 [36 ventilatory impairment, 1 death]; Moulis 2018 **Level IV**, n=5 [4 life threatening, 1 death]; Rodieux 2018 **Level IV**, n=18 [15 ventilatory impairment, 3 deaths] and a further 14 deaths [tramadol implicated but not as sole agent]; Tanne 2016 **Level IV**, n=7 [6 ventilatory impairment, 1 death]; Hassanian-Moghaddam 2015 **Level IV**, n=3 [ventilatory impairment]). The FDA investigation identified nine cases of ventilatory impairment following tramadol over 1969–2016 (overlapping with the above series; including three deaths of children under 6 y) (FDA 2017 **GL**). This is in the context of a single year's USA dispensing data for 167,000 prescriptions for children (<18 y) for 2014.

In the event of excess sedation or ventilatory impairment, naloxone has been used as a reversal agent (Tanne 2016 **Level IV**, n=3/7; Hassanian-Moghaddam 2015 **Level IV**, n=16/19 [apnoeic patients]; Tsutaoka 2015 **Level IV**, n=540 [naloxone use age unspecified]; Hassanian-Moghaddam 2013 **Level IV**, n=3/19 [apnoeic adult patients]; Marquardt 2005, **Level IV** n=2/51 young children; Grosek 2009 **CR**).

Seizures

Lowering of the seizure threshold and seizures are reported in adults (46.1% of adult presentations: Tsutaoka 2015 **Level IV**, n=5,491 [tramadol exposures >19 y]; Hassanian-Moghaddam 2013 **Level IV**, n=525; see also Section 4.3.1.3) and children with therapeutic and supratherapeutic dosing (Li 2012b **Level IV**, n=2) vs overdose >4.8 mg/kg with variable incidences of: nil (Hassanian-Moghaddam 2015 **Level IV**, n=20), 2.2% (Stassinos 2019 **Level IV**, n=24/1,115), 13.7 % (Marquardt 2005 **Level IV**, n=26/190; but 0/51 under 5y), 20% (Moulis 2018 **Level IV**, n=1/5 seizures), 71% (Tanne 2016 **Level IV**, n=7) and case series (Tsutaoka 2015 **Level IV**, n=3,051 [tramadol exposures <19 y; higher RR vs tapentadol]; Mazor 2008 **Level IV**, n=2), including in association with hypoglycaemia (Aliyu 2016 **CR**). In one report, naloxone administration is suggested to have terminated a recurrent seizure in a single toddler with tramadol overdose (Tanne 2016 **Level IV**, n=7).

Agitation and serotonin syndrome

Agitation occurs with therapeutic dosing and in adult and paediatric overdose in 0.7–14% of patients (Stassinos 2019 **Level IV**, n=51/7,334; Moulis 2018 **Level IV**, n=1/7; Marquardt 2005 **Level IV**, n=1/8 [children]). Drug-drug interactions are an important consideration. In adults, serotonin syndrome has been reported; it occurs more frequently with SSRIs sometimes in combination with tramadol. It has occurred with tramadol in isolation and has been reported in an infant following 28 mg/kg ingestion, but not older children (Marechal 2011 **CR**).

Fetal, neonatal and infant exposure with maternal use

Neonatal abstinence syndrome is described after chronic (maternal) exposure (Hartenstein 2010 **CR**; Willaschek 2009 **CR**). Infant exposure through breastmilk has been a literature focus subsequent to the FDA adding warning against tramadol by breastfeeding mothers (FDA 2017 **GL**). Exposure of infants was very low relative to maternal exposure and well below therapeutic dosing used in this age group (LactMed Database 2019 **NR**; Palmer 2018 **NR**).

Formulation issues and adverse outcome

A concentrated drop formulation (100 mg/mL) is available in many countries, licensed for adult palliative care (eg in Australia) but also in children (eg in France). Dosing error confusing the

number of drops with the number of mL is a concern in paediatrics (10 drops=25 mg=0.25 mL). Two children dosed at home with the concentrated oral tramadol drops post adenotonsillectomy had adverse outcomes. One aged 5 y with ultrarapid genotype experienced significant respiratory depression (Orliaguet 2015 **CR**). The single urine sample of M1 reported for this case was not accompanied by plasma concentrations of tramadol or M1. Thus, the accuracy of the stated single analgesic dose administered cannot be determined and dosing confusion was likely. The second child aged 2 y died due to tramadol toxicity with concentrated oral drops treatment. The TGA subsequently does not support the use of this concentrated oral formulation in children aged <12 y (TGA 2015 **GL**). New Zealand (NZ)'s Medicines and Medical Devices Safety Authority (Medsafe) has delisted the concentrated formulation (for all ages) and compounding pharmacists in NZ make a 10 mg/mL formulation (Medsafe 2017 **GL**; Pharmac 2016 **GL**). An Australian centre has described dispersing 50 mg in 5 mL (10 mg/mL) for administration to smaller children (Kluger 2016 **Level IV**, n=20 [dose preparations]). In France, following a further death with the concentrated formulation of a 3 y old boy of normal CYP2D6 metaboliser phenotype, the formulation has been retained with a revised dosing leaflet instruction (Moulis 2018 **CR**).

Impact of the FDA Announcement for Tramadol

Particularly following the FDA's contraindications for use of codeine and tramadol (in children and warning against use in breastfeeding mothers), further data is required to determine the role, optimum dose and safety of tramadol in children and the monitoring level required. Inadvertent overdose and formulation issues are likely of greater risk than CYP phenotypes resulting in variable drug metabolism; evidence for harm from this second mechanism is lacking (Anderson 2017b **NR**). Restriction of use of an effective analgesic and replacement with full agonist conventional opioids presents a similar or greater hazard in the at-risk population with SDB/OSA and post adenotonsillectomy.

10.4.4.13 | Tapentadol

Tapentadol is available in tablet IR and ER forms in Australia, but as of 2020 not in New Zealand. Both formulations are only indicated for adult use: IR for acute pain and ER for chronic pain. Evidence for tapentadol use in acute paediatric pain is limited in terms of number of studies and their sample size. There is drug company sponsored data for use of an oral solution in children postoperatively (studied for regulatory application in Europe: see below). See also Section 4.3.1.3 for summary of tapentadol in adults.

Pharmacokinetics and efficacy

Non-obese children received tapentadol 1 mg/kg oral solution postoperatively following dental or adenotonsillectomy (aged 2–18 y: Muse 2019 **Level IV PK**, n=66) and mixed surgery types (aged 6–18 y Finkel 2019 **Level IV PK**, n=44). Plasma concentrations of tapentadol were similar to adult data (following 50–100 mg) peaking at 1–1.5h (while the non-active metabolite tapentadol-O-glucuronide concentrations were lower or the same) (Muse 2019 **Level IV PK**). Pain scores decreased over 15 to 120 min post-dose in 2–18 y olds using developmentally-appropriate pain scales (Muse 2019 **Level IV**). Median times to rescue analgesia intake were 5 h (Finkel 2019 **Level IV**) and 6.3 h (Muse 2019 **Level IV**).

Adverse effects

Adverse events in the above studies included PON, POV, dizziness and headache (without placebo comparator nor provision of anaesthetic details including antiemetic prophylaxis).

USA toxicity data is available for single agent (mostly accidental) ingestion by children where 61% were aged ≤2 y (Borys 2015 **Level IV**, n=104). Most had no (59.6%) or minor (32.7%) ill effect;

5.8% had moderate and 2% major effects. Most common was drowsiness (29%), with other neurocognitive effects (in 6%) and nausea/vomiting, tachycardia and dizziness (each in 2 to 4%). The two patients with major effects were an infant who experienced coma with respiratory depression requiring naloxone (and was discharged) and a toddler with drowsiness and dyspnoea requiring oxygen and critical care monitoring. There were no deaths. No detail of formulation, dose or mg/kg was provided.

A further USA study analysed single agent exposures of tapentadol (n=217) vs tramadol (n=8,566) (Tsutaoka 2015 **Level IV**). The analysis included 31 tapentadol vs 1,785 tramadol accidental ingestions by children <6 y vs 9 and 1,266 accidental and intentional ingestions in older children (6–19 y). The children <6 y had greater risk of severe outcome from tapentadol exposure vs tramadol (formulation/ dose detail not provided). Neurological sequelae occurred in both groups: the tapentadol vs tramadol exposed more commonly experienced hallucinations, coma (RR 4.2; 95% CI 2.3-7.4), drowsiness, slurred speech, confusion and respiratory depression (RR 5.6; 95% CI 3.5 to 8.8), and use of naloxone (RR 3.8; 95% CI 3.0-4.9). Tramadol exposed more commonly experienced seizures (RR 7.9; 95% CI 3.0 to 21) and vomiting (RR 2.0; 95% CI 1.1 to 3.6). A cohort study assessing trends in selfpoisoning in children aged 5–19 y reported no adverse events related to tapentadol (2006–2016: Cairns 2019 **Level IV**, n=33,501).

See adult Section 4.3.1.3 for post-marketing surveillance ADR data, reports of serotonergic syndrome and mortality where tapentadol has been implicated (rarely as a single agent).

Potential for abuse

Intentional ingestions have been reported by adolescents (3 abuse, 3 suicide attempts and 2 other: Borys 2015 **Level IV**, n=104 [8 intentional]). There is no further data on abuse potential of tapentadol in adolescents. Reported nonmedical use in USA college students was low in comparison to conventional opioids and has decreased post initial launch (Dart 2014 **Level IV**); diversion rates and black market cost are low (Dart 2016 **Level IV**).

10.4.4.14 | Buprenorphine

Buprenorphine is used off-label in children for the treatment of acute pain including in cancer pain, palliative care (Vicencio-Rosas 2018 **NR**; Michel 2011 **Level IV SR**, 8 studies & 3 RCTs, n=274), opioid misuse disorders in teenagers (Borodovsky 2018 **NR**) and neonatal abstinence syndrome (NAS) (Kraft 2018 **NR**), with low level evidence support.

Pharmacokinetics and pharmacodynamics

With IV bolus 3 mcg/kg and infusion of 0.72 mcg/kg/hr, ex-preterm neonates have reduced clearance consistent with their immature CYP450 and glucuronidation (*UGTB27*) pathways and a prolonged half-life of 20–26 h. Following a single IV 3 mcg/kg dose, allometric scaling suggested clearance is higher in children (Michel 2011 **Level IV SR**, 8 studies & 3 RCTs, n=274). Combined PK-pharmacodynamic study is required to explore a possible paradoxical prolongation of effect.

See adult Sections 4.3.1.3 and 5.4.1.2, 5.5.2.2 and 5.5.3.1 for discussion of buprenorphine's PKs and PDs in adults (Butler 2013 **NR**).

A liquid formulation has been made for SL administration for NAS (Anagnostis 2011).

Efficacy

Buprenorphine via various routes (IV, SL, caudal usually 2.5–5 mcg/kg and transdermal [TD]) has been used in a few small studies of children having thoracotomy, orthopaedic, abdominal, hernia and genitourinary surgery (Michel 2011 **Level IV SR**, 8 studies & 3 RCTs, n=274):

Following inguinal herniorrhaphy or orchidopexy surgery,

- Caudal and IV buprenorphine 2.5 mcg/kg was added to and compared with caudal bupivacaine 0.5% 1 mL/kg alone with no difference in pain outcomes. The RCT ceased

recruitment with higher vomiting in both buprenorphine arms (80% caudal vs 50% IV vs 20% caudal bupivacaine alone) (Khan 2002 **Level II**, n=30, JS 5);
- Caudal buprenorphine 4 mcg/kg vs caudal bupivacaine 0.25% 0.5 mL/kg was equieffective on a 3 point Lickert scale, with longer duration following buprenorphine (Girotra 1990 **Level III-1**, n=40);
- Caudal buprenorphine 4 mcg/kg vs caudal morphine 50 mcg/kg was equieffective with longer duration (Girotra 1993b **Level II**, n=65, JS 5).

In orthopaedic surgery,
- IV buprenorphine 3 mcg/kg vs IV morphine 100 mcg/kg was transitioned to ward treatment with SL buprenorphine 6 mcg/kg vs IM morphine 150 mcg/kg with equianalegsic effect with self-report on a 4 point scale, similar side effect profile (for nausea and vomiting and urinary retention) and longer duration in the buprenorphine group (Maunuksela 1988a **Level II**, n=60, JS 4).
- Caudal buprenorphine 4 mcg/kg had a longer time to rescue analgesic request vs IM route (Girotra 1993a **Level III-1**, n=44).

Following thoracotomy, IV buprenorphine 1.5 or 3 mcg/kg vs IV morphine 50 or 100 mcg/kg was similarly effective (Sum of Pain Intensity Difference scores) (Maunuksela 1988b **Level II**, n=57, JS 4).

In a later systematic review of single and repeat IV dosing, IV buprenorphine 1.5–6mcg/kg was superior to IV morphine 50–150 mcg/kg in time to rescue analgesia (MD: 115 min; 95% CI 43 to 186) (Murray 2018 **Level I**, 4 RCTs, n=137) (2 RCT overlap with Michel 2011 above).

SL Buprenorphine 50 mcg rescue use has been reported for acute pseudo-obstruction pain crises in children who had chronic abdominal pain managed with TD buprenorphine (Prapaitrakool 2012 **Level IV**, n=3). A small dose finding study (2.5–10 mcg/kg) suggests 5 mcg/kg SL 12 hly is effective in children with cancer pain (Massimo 1985 **Level IV**).

Adverse effects

In the past, it was suggested that buprenorphine had a ceiling effect for ventilatory impairment (Khanna 2015 **NR**); this is now under debate with increasing overdose presentations and reports of death (Butler 2013 **NR**; Michel 2011 **Level IV SR**, 8 studies and 3 RCTs, n=274). It has not been reassessed recently in the paediatric population (Vicencio-Rosas 2018 **NR**). Case series of accidental paediatric overdose (total n=150) document opioid adverse effects including ventilatory impairment requiring hospitalisation for young children (Vicencio-Rosas 2018 **NR**; Toce 2017 **Level IV**, n=88). Children <6 y have accounted for the majority of buprenorphine poisoning exposures in the USA (5,761 of 5,078; 88%) and of these, 51% were admitted to a health care facility (Allen 2017 **Level IV,** n=188,468 [opioid poisonings]). One series found no relationship between ventilatory impairment incidence and estimated ingested dose in the range of 0.03–7.62 mg/kg (Toce 2017 **Level IV**). Naloxone boluses of 0.04–0.2 mg/kg were administered to most paediatric patients in these series and some received continuous infusion. The resistance to naloxone reported in adult volunteer studies (Dahan 2010 **NR**) was not noted in these children.

Plasma vs cord concentrations are low at birth following maternal opioid replacement therapy, with NAS incidence similar to other opioids of 6/10 (60%) (Bartu 2012 **PK Level IV**). In infants born to buprenorphine vs methadone-treated mothers, the NAS incidence was similar between groups with 27/58 (47%) buprenorphine-exposed infants requiring therapy for NAS (Jones 2012 **Level II**, n=175, JS4). In each of two further studies, 4/7 infants had NAS and 1/7 required therapy; breast milk penetration after maternal SL administration was assessed and resulted in a relative infant dose exposure of 0.18 to less than 1% (Ilett 2012 **PK**; Lindemalm 2009 **PK**).

See also subsection 9.1.1.1 opioids use as Medications used in pregnancy and subsection 9.8.9.2 of Pain in pregnant patients with an opioid use disorder.

10.4.4.15 | Nalbuphine

Nalbuphine is a mu antagonist and partial kappa agonist. It has been used in paediatrics and Cochrane reviewed (Schnabel 2014 **Level I** [Cochrane], 10 RCTs, n=658). The trials were old, heterogeneous and determined low quality. Nalbuphine reduces the number of patients in severe pain at 1 and 2 h (1 RCT) and requirement for rescue (1 RCT) vs placebo, was similar to morphine for patients in severe pain at 2 h (2 RCTs), was similar to tramadol at 2 h (1 RCT) and 12 h (1 RCT), and pethidine at 2 h and 24 h (1 RCT). PONV rates in PACU were similar vs placebo and morphine.

KEY MESSAGES

Opioids

1. Young and obese children with history of obstructive sleep apnoea/sleep-disordered breathing are at higher risk of developing serious opioid-induced ventilatory impairment and death (**U**) (**Level IV**).
2. Opioid-induced ventilatory impairment and death occur rarely with therapeutic dosing in children taking opioids at home (**N**) (**Level IV**).
3. Safe dosing of opioids requires consideration of the child's age, body weight, comorbidities and ethnicity (**U**) (**Level IV**).

Fentanyl

4. Intranasal fentanyl is an effective treatment for paediatric acute pain management, with an acceptable adverse effect profile and ease of delivery (**N**) (**Level I**).

Codeine

5. The efficacy of oral codeine in children is unpredictable due to genetic differences in the ability to generate the active metabolite morphine (**U**) (**Level II**), as are adverse effects and serious toxicity (**U**) (**Level IV**).
6. Codeine should not be used in children, especially after adenoidectomy or tonsillectomy, due to an increased risk of opioid-induced ventilatory impairment and death (**S**) (**Level IV**).

Tramadol

7. Tramadol provides superior analgesia to placebo and has similar efficacy to conventional opioids in children of all ages administered by various routes for multiple surgery types (**S**) (**Level I** [Cochrane]).
8. It is unclear if tramadol causes less ventilatory impairment than other opioids in children due to insufficient trial size (**N**) (**Level I** [Cochrane]).

Buprenorphine

9. Buprenorphine administered IV or caudally has similar efficacy to morphine or caudal local anaesthetic in children for different surgery types (**N**) (**Level II**).

Nalbuphine

10. Nalbuphine intravenously is effective for postoperative pain relief in children in several low quality heterogeneous trials (**N**) (**Level I** [Cochrane]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

- ☑ Careful titration of opioids is advised according to the individual child's response (analgesia and adverse effects) (**U**).
- ☑ Despite the regulatory response with boxed warning and upscheduling of codeine, prescription continues in at risk patients (with obstructive sleep apnoea/sleep-disordered breathing or post adenotonsillectomy) or has been replaced by prescription of potent conventional opioids such as oxycodone and hydrocodone which present similar or greater hazard (**N**).
- ☑ The practice of applying an occlusive dressing to the skin surface of a transdermal fentanyl delivery system does not limit dose delivery (**U**).
- ☑ Tramadol shares some adverse effects with the conventional opioid class in children, with similar or reduced rates of nausea and vomiting, sedation and fatigue but less constipation and pruritus (**U**). Sedation (not necessarily associated with miosis), seizures, ventilatory impairment and deaths have occurred (**N**).
- ☑ Naloxone has been used to treat tramadol overdose in children with effect (**N**).
- ☑ CYP2D6 phenotype has been the reason for codeine's black box warning, but the clinical significance in terms of tramadol/M1's analgesic efficacy and adverse-effect profile including safety is still unknown (S). Inadvertent overdose and formulation issues are likely of greater risk than CYP phenotypes resulting in variable drug metabolism; evidence for harm from this second mechanism is lacking (**N**).
- ☑ Tramadol 100mg/mL concentrated drops formulation use is potentially harmful in children with possible dosing confusion (drops with millilitres) and resultant overdose (**U**).
- ☑ In paediatric overdose, buprenorphine causes the spectrum of neurocognitive adverse events as seen with conventional opioids which may be reversible with naloxone (**N**).
- ☑ More studies are required to determine tapentadol's comparative efficacy in paediatric acute pain and if its adverse effect profile in children is improved versus placebo, conventional opioids or tramadol (**N**).
- ☑ In paediatric overdose, tapentadol causes the spectrum of neurocognitive adverse events seen with conventional opioids, which may be reversible with naloxone (**N**).

10.4.5 | Discharge opioid prescribing for children

USA survey data from 1996–2012 indicates that whilst opioid prescriptions for adults have more than doubled in this time, it has not increased for children <18 y (Groenewald 2016 **Level IV**, n=144,918 children). Despite this, the public health concerns surrounding discharge and community opioid prescribing have extended to children; there are relevant implications of current opioid prescribing practices and consumer use patterns in both adults (who are relatives of children and adolescents who may then have access to these medications) and children for postoperative, post-trauma and medical indications. The recent literature focus on community and discharge prescribing for the paediatric age group is presented below; the majority is North American data, with Australia and New Zealand data provided where available.

See also the relevant adult Section 8.13 Discharge opioid medications for acute pain management.

10.4.5.1 | Prescribers of opioids and types of opioid prescribed

A systematic review identifies the paucity in research on opioid prescription and usage in children and adolescents for at home pain management postoperatively or post trauma (Dautremont 2017 **Level IV SR** [PRISMA], 9 studies [5 adolescent], n unspecified). Post hospital discharge, prescribers are generally surgeons. Since the FDA investigation of children after (adeno)tonsillectomy, codeine use has reduced in the USA (Chua 2017b **Level III-2**, n=362,992). However, as of December 2015, 1 in 20 children undergoing these procedures were still prescribed codeine (by ear nose and throat surgeons), with high potency agents such as hydrocodone and oxycodone increasingly prescribed. In two USA audits of paediatric patients (surgical and medical) discharged from hospital, discharge opioids were mostly prescribed postoperatively by surgical teams, most commonly orthopaedic (Monitto 2017 **Level IV**, n=343 families; George 2016 **Level IV**, n=34,218). Long acting preparations were rarely prescribed. Oxycodone was the most frequently prescribed agent at both centres, with the larger audit revealing near cessation of codeine prescribing. In the smaller audit, over 80% of patients also utilised paracetamol and/or ibuprofen (Monitto 2017 **Level IV**, n=343). Nearly half (47%) of patients were discharged with diazepam, having had mostly orthopaedic (70%) or urological surgery (22%). Notably, the Society for Pediatric Anesthesia guidelines recommend that opioids should not be prescribed in combination with benzodiazepines in outpatient management of paediatric patients, adding the proviso 'unless there are specific indications, with parents being warned of the risk of sedation and respiratory depression' (Cravero 2019 **GL**). These guidelines also state there is insufficient evidence to guide whether prn or scheduled opioid dosing strategies are most appropriate for paediatric patients following surgery, with expert consensus tending toward prn dosing (Cravero 2019 **GL**).

10.4.5.2 | Opioid-related poisonings and deaths

In Australia between 2003 and 2013, prescription opioids were the commonest cause of poisoning death (accounting for 24%) in children (of which 59% were adolescents: 12–16 y) (Pilgrim 2017 **Level IV,** n=90 deaths). New Zealand paediatric poisoning data is not available.

From the USA's National Poison Data System review 2000–2015, poisoning exposures to prescription opioids (most often hydrocodone, oxycodone, codeine and tramadol) was common among children <6 y and teenagers (Allen 2017 **Level IV,** n=188,468; Tadros 2016 **Level IV,** n=21,928). Causes of opioid poisoning varied between age groups with unintentional or therapeutic error most common for children <6 y and intentional overdose most common for teenagers. Over 6% of children poisoned with opioids experienced serious medical outcomes (particularly with fentanyl exposure) with overall fatality of 0.1%. In a third USA series, the mortality rate of children and adolescents with opioid poisonings has increased nearly 3-fold over 18 years, where prescription opioids were implicated in over 70% of deaths (Gaither 2018 **Level IV**, n=8,986 deaths). In this latter series, one quarter of deaths in children <5 y were homicide, while most opioid-related deaths were adolescents aged 15–19 y (88%); most (80%) were unintentional (in contrast to the above series). Co-ingestion of one or more prescription or illicit substances was found in 38.5% of adolescent cases; in adolescents, synthetic opioids (eg illicitly manufactured fentanyl) was an increasing cause of death (Gaither 2018 **Level IV**, n=8,986 deaths). For a further USA cohort of opioid-naïve adolescents, prescription opioid overdose rate was 1 in 1,600 (0.06%) (Groenewald 2019b **Level IV**, n=725). In this cohort, a subanalysis revealed the risk for overdose in adolescents increased with increased number of dispensed tablets: ≥30 opioid tablets vs ≤18

tablets (HR 1.35; 95%CI 1.05 to 1.7). Tramadol was also associated with increased risk after controlling for sociodemographic level, pre-existing health conditions, pill quantity and dose (HR 2.7; 95%CI 1.9 to 3.8). Receipt of oxycodone, presence of comorbid mental health conditions or receiving multiple opioid prescriptions did not increase risk. Across the first three series, the majority of opioid-related deaths occurred outside a medical setting. The increase of accidental opioid overdoses in children and adolescents (Burghardt 2013 **Level IV**, n=62,416 [opioid-related overdoses]) and paediatric mortality rates for opioid poisonings follow similar temporal and drug use patterns to adults and the prescribing patterns for prescription opioids (Gaither 2018 **Level IV**, n=8,986 deaths).

From USA's outpatient prescription data, the most commonly prescribed opioids include hydrocodone, oxycodone, codeine, hydromorphone, pethidine (meperidine) and tramadol (included by some authors) (see Table 10.8). One of the series reported combined rates for paediatric opioid-related ED visit, hospitalisation or death of 1 in 2,611 opioid prescriptions for children, with three deaths overall (Chung 2018a **Level III-3**, n=1,362,503 [outpatient prescriptions]) and subsequently published their state's data with one death (Chung 2019 **Level III-3**, n=529,731 [opioid prescriptions]). A further USA series specific to opioid-related deaths demonstrated increase across all age groups between 2001 and 2016: from 0.4 to 1.5% of all-cause mortality (Gomes 2018 **Level III-3**, n=335,123 [opioid-related deaths]). The rates were 1.4 /1 million for children <15 y and higher at 92.3/1 million in 15–24 y olds, without stating if relating to overdose (intentional or accidental). Simultaneously (between 2004 and 2015), the rate of opioid-related paediatric hospitalisations (where 43% required intensive care) increased in the USA (Kane 2018 **Level IV**, n=3,647 [opioid-related] of 4,175,624 admissions [31 hospitals]). The majority were adolescents 12–17 y, but one-third were children <6 y; events were coded as accidental poisoning (1,658: 80% related to opioids other than methadone and heroin) and poisonings (1,989: 61% related to opioids other than opium, methadone and heroin). The number specific to therapeutic prescriptions was not stated in this series.

In a legal settled claims post-tonsillectomy series, opioids (most commonly codeine) were implicated in death (17 of 96 claims), respiratory depression (20 of 137) and hypoxic brain injury (20 of 137) (Subramanyam 2013 **Level IV**, n=233). The ultrarapid metabolism issue for codeine and published cases of serious adverse events (including deaths) led to the 2013 FDA restriction on codeine administration in this paediatric surgical population (see Section 10.4.4.5). Subsequently, a paediatric anaesthetist survey revealed 92 cases and closed claim report analysis a further 19 serious adverse events, including apnoea and subsequent death post tonsillectomy (and adenoidectomy); 57% of patients were determined to be at risk of OSA (Cote 2014 **Level IV**, n=111). Importantly 58% of the postoperative events occurred within 24 h and 48% occurred after hospital discharge.

10.4.5.3 | Opioid-related adverse events: out of hospital

National USA prescription data revealed opioid-related adverse events were increased in adolescents vs young children (12–17 y vs 2–5 y: incidence rate ratio [IRR] 2.22; 95%CI 1.67 to 2.96) and with higher opioid doses (>0.66 mg/kg/d MED vs ≤0.38: IRR 1.86; 95%CI 1.45 to 2.39) (Chung 2018a **Level III-3**, n=1,362,503 [outpatient prescriptions]). The most frequent prescribed opioid-related adverse drug events (ADEs) were gastrointestinal (31%), neuropsychiatric (28%), CNS depression (22%) and dermatological (23%). Respiratory depression was uncommon at 2.8%. Notably most ADEs (72%) were associated with therapeutic use of the prescribed regimen. The same author group published their state's data with the same ADEs and similar incidences (Chung 2019 **Level III-3**, n=529,731 [opioid prescriptions]) (see Table 10.8). In children prescribed opioids upon discharge from hospital, ADEs were also common: 48% of 218 responding parents reported that their child had ≥1 ADE; these were also dose-related (MD 0.05 MED mg/kg/d;

95%CI 0.02 to 0.08) (Voepel-Lewis 2015b **Level IV**, n=514 parents). Concerningly, only 14 of 38 parents who reported their child as experiencing over sedation changed their child's analgesic therapy in response to this ADE. Children who received an opioid prescription post laparoscopic appendicectomy vs those who did not had increased risk of ED presentation in one audit for constipation (overall 1%; with increasing RR related to duration of opioid use) but not for pain (Sonderman 2018 **Level III-2**, n=9,684) and in a second audit for both constipation and abdominal pain (OR 3.3; 95%CI 1.3 to 8.2) (Anderson 2018 **Level III-2**, n=590). Post paediatric tonsillectomy, less severe adverse effects in patients prescribed codeine after discharge included nausea, vomiting and light-headedness; pain scores and time (POD 0) predicted sedation, but not obstructive sleep apnoea or CYP2D6 phenotype (Prows 2014 **Level IV**, n=249).

Prescribing and dispensing error is a recognised source of harm with paediatric opioid prescription. For young children <3 y, excessive dose prescribing errors (>10%) were made in 2.7% of outpatient opioid prescriptions, with higher frequency in infants (8.9% 0–2 mth and 5.7% 2–5 mth) (Basco 2015 **Level IV**, n=59,536). While discharge opioid prescriptions for children written by trainees at one USA paediatric centre had errors in 82% (re weight, dispensing information or date) and 2.9% had the potential for serious harm if dispensed and administered as prescribed (Lee 2009 **Level IV**, n=314 prescriptions). Electronic prescribing, including weight-based dosing logic with alerts, may reduce the rate of errors in paediatric opioid prescribing (George 2016 **Level IV**, n=34,218).

See also Section 8.13.2.4 Impaired driving as relevant to adolescents who drive.

10.4.5.4 | Risk of inducing long term opioid use in adolescents

Unintended prolonged opioid use was identified as a significant concern following acute postoperative opioid prescribing (Harbaugh 2018b **Level III-2**, n=88,637 perioperative opioid prescription fills). Following various surgeries, 3–15% (4.8% overall) of previously opioid naïve adolescents were using opioids at 90–180 d. Factors that increased risk slightly included older age (OR 1.07; 95%CI 1.05 to 1.08), female sex (OR 1.22; 95%CI 1.14 to 1.31), substance use disorder (SUD) (OR 1.41; 95%CI 1.12 to 1.77), chronic pain diagnosis (OR 1.48; 95%CI 1.33 to 1.66), preoperative opioid use (OR 1.26; 95%CI 1.17 to 1.36) and cholecystectomy or colectomy surgeries. Following cleft palate related surgery in children >8 y, persistent opioid use was 4.4% at 90 to 180 d vs 0.1% of non-surgical controls (Bennett 2018 **Level III-2**, n=4,139). Distractor surgery increased risk (OR 5.34; 95%CI 2.00 to 14.24) and older age only slightly (OR 1.11; 95%CI 1.04 to 1.17). Following traumatic injury (46.2% major trauma), 7% of adolescents reported prescription opioid use prior and 12.5% of adolescents continued on opioids at 1 y, with increased risk in those with preinjury mixed substance use and higher baseline pain score, but not older age (Whiteside 2016 **Level IV**, n=120). Of adolescents treated at one USA major paediatric and one adult trauma hospital (where 10 % experienced major trauma), after discharge 20% had filled >2 opioid prescriptions at 1 y, while 13% had filled >8 prescriptions at 4 y (Bell 2019b **Level IV**, n=736). Concurrent mental health diagnoses were relatively uncommon compared with adults: anxiety 11 %, depression 6% and post-traumatic stress disorder (PTSD) 2.1%.

Following each new opioid prescription filled by adolescents in the USA, the incidence of long term opioid therapy (>90 days' supply within 6 mth) was estimated as 3 in 1,000 (95%CI 2.8 to 3.1) within 3 y (Quinn 2018 **Level III-2,** n=1,224,520 prescriptions). Adolescents with mental health conditions were more likely to be prescribed opioids than those without (OR 1.13; 95%CI 1.10 to 1.16). While, the risk of long term opioid therapy was increased with ADHD (HR 1.73; 95%CI 1.54 to 1.95), non-opioid SUD (HR 4.02; 95%CI 3.48 to 4.65) and prior opioid use disorder (OUD) (HR 8.90; 95%CI 5.85 to 13.54); a greater number of co-existing or pre-existing mental health conditions increased risk of long term opioid therapy.

10.4.5.5 | Misuse, abuse, overdose and diversion of prescription opioids in children

North American data

Between 1990 and 2014, the prevalence of past-year prescription opioid misuse in the USA had increased in young people aged 11–30 y by 0.4% each year (Jordan 2017 **Level IV** [PRISMA], 19 studies, n=503,845). The pooled prevalence in high-school/college settings was 7.4% (95%CI 5.8 to 8.9). In 2016, of the USA's 12–17 y olds, 3.6% reported opioid misuse (Groenewald 2019a **NR**). However, medical prescription without nonmedical use of prescribed opioids was not associated with OUD development reported at age 35 (McCabe 2016 **Level IV**, n=4,072). In an adolescent trauma series 5 y post-discharge from two USA centres (one paediatric and one adult), 11% required opioid antagonist injection, 14% had SUD diagnosis and 8% an overdose (Bell 2019b **Level IV**, n=736). Older age (>15 y), male sex, African ethnicity, penetrating injury and treatment at the adult hospital were associated with later overdose and SUD (the latter was also associated with positive alcohol/drug screen and non-blunt/non-penetrating injury). Injury severity score was not an association (where 10% experienced major trauma).

The most common reported motives for adolescents misusing medically prescribed opioids were to get high (sensation seekers) and to relieve pain (self treaters) (McCabe 2013b **Level III-3**, n=393). Medical opioid users are up to 10 times more likely to report lifetime and past-year nonmedical opioid use, however use is usually not consistent (Boyd 2006 **Level IV**, n=1,086). Most paediatric nonmedical opioid users obtain the medications from family or friends (SAMHSA 2019 **Level IV**; McCabe 2013a **Level IV**, n=8,888 [647 nonmedical use]; Brands 2010 **Level IV**, n=2,914; Boyd 2006 **Level IV**, n=1,086).

Opioid use disorder in the past-year is estimated to affect 0.4–0.6 % of adolescents (12–17 y) in the USA in 2015–2018 surveys (SAMHSA 2019 **Level IV**, n=104,000 [2018 data]). In 2018, approximately 310,000 adolescents (850 per day) in the USA misused prescription pain relievers for the first time in the past-year. Nearly all OUD (99%) reported in 2016 by USA adolescents was related to prescription opioids and OUD was a risk factor for opioid overdose (HR 3.1; 95%CI 2.3 to 3.4) (Groenewald 2019b **Level IV**, n=1,146,412 new prescriptions). Rates of opioid prescribing for children and adolescents with common, noncancer pain conditions (eg dental, postoperative and trauma indications) are high (Groenewald 2019b **NR**). Legitimate opioid use prior to high school graduation in the USA is independently associated with a 33% increase (from 1.7–3% to 3–5%) of nonmedical use of prescription opioids by age 23 (Miech 2015 **Level IV**, n=6,220). Importantly, these individuals report little to no history of drug use and have a baseline disapproval of drug use. In USA high school seniors with nonmedical use of prescription opioids, their most common pattern was initial use of medically prescribed opioids followed by subsequent nonmedical use (McCabe 2017 **Level III-3**, 40 cohorts [Monitoring the Future], n=2,181 to 3,791 per cohort).

In Canada, the nonmedical use of prescription opioids by adolescents (at least one occasion) is common (prevalence: 20%; 95%CI 18.9 to 22.3), but behind alcohol and cannabis (Brands 2010 **Level IV**, n=2,914). Of prescription drugs, opioids were the most frequently misused by 5.9% adolescents, particularly females (Currie 2012 **Level IV**, n=44,344 [Youth Smoking Survey]).

Medical use of prescription opioids without any history of nonmedical use in adolescence is not associated with SUD symptoms at age 35 (McCabe 2016 **Level III-3**, n=4,072 surveyed). Adults at age 35, who as adolescents used opioids with high misuse potential or more than one opioid, co-ingested them with other substances or used them nonmedically and/or progressed to later medical use, have increased odds of subsequent SUD symptoms compared with those who used prescription opioids medically or no opioids during adolescence (McCabe 2019 **Level III-2**, n=8,373). Compared to low prevalence of OUD in adolescents, past-year use and misuse of prescription opioids is common, and was highest for those not engaged in schooling (Schepis 2018 **Level IV**, n=13,585 adolescents & 14,553 young adults).

National USA data has shown correlation of increased opioids prescriptions with increased poison centre telephone calls by adolescents who had abused opioids (Sheridan 2016 **Level IV**, n=4,186). For each opioid prescription increase per 100 persons per year, the annual rate of calls increased by 1.8% (95%CI 0.9 to 2.8) or 4–5 calls per 1,000 teens annually.

In one USA state (Ohio), while overall opioid prescriptions for adolescents have decreased (7 per capita annually), adult prescriptions remained unchanged (100 per capita annually) over 2008–2012 (McKnight 2017 **Level IV**, n=50,030,820 doses for 12–20 y & 3,811,288,395 doses for adults >20 y). This provides a potential source for nonmedical access by adolescents.

Low parental monitoring and low adolescent perception of parental warmth predicted pro-substance attitudes and social ties, which in turn predicted higher levels of lifetime nonmedical prescription opioid use (Donaldson 2015 **Level III-3**, n=17,339).

Harm minimisation interventions for young people who use prescription opioids nonmedically, such as provision of and education on the use of naloxone, as well as harm reduction education in schools has been proposed to address the known risks associated with opioid misuse (Marshall 2016 **NR**).

New Zealand and Australian data

In New Zealand in 2017, national opioid prescriptions for children and young adults (0–24 y) remained low: most prescriptions per 1,000 population were for the 'weak opioids' codeine (24.8) and tramadol (18.7), and infrequently the 'strong' opioids: morphine (1.6), oxycodone (0.6) and fentanyl (0) (HQSC 2019 **Level IV**, n=3,327 [dispensed to ≤24 y]). Morphine prescriptions had increased from 0.8 per 1,000 in 2011 to 1.6 per 1,000 in 2017 in this age group. A small percent of morphine (4.1%) and oxycodone (5.9%) were prescribed for more than 6 wk; the division for cancer vs noncancer indications was not specified. The majority of prescriptions in this age group were in association with a hospital event (73%). New Zealand data for nonmedical use is not available.

In Australia between 2012 and 2017, the number of prescriptions of opioids has increased by 11% (AIHW 2019 **Level IV**, n=15,419,793 [dispensed in 2016–17] with n=232,588 to ≤24 y). The extent of pharmaceutical opioid consumption is lower per capita when compared to the USA, however has specifically risen in the population aged >14 y (Chan 2019b **Level IV**, n=23,233). The Australian National Drug Strategy Household Survey 2016 found 3.6% of the population >14 y old used prescription opioids nonmedically, 33% with other illicit substances. The latter were more likely to be younger (and possibly started nonmedical prescription opioid use opportunistically and for recreation). While Australia's Pharmaceutical Benefit Scheme's data, which captures community prescriptions only (and not over the counter, hospital or private purchase), revealed annual opioid dispensing to children decreased slightly by -2.2% (CI -3.5 to -0.8) between 2013–2017 (Bell 2019a **Level IV**, n=78,320 prescriptions to 50,730 children). In 2017, one in 74 Australian children (0–17 y) overall were dispensed an opioid, highest in the adolescent age group at one in 25. Like New Zealand, codeine and tramadol comprised most dispensed prescriptions (51 and 10% respectively); oxycodone was the most frequently dispensed 'strong' opioid (37%), with other opioids dispensed infrequently (4%). Strong opioid dispensing increased in all age groups, with the 1.5 fold increased oxycodone dispensing; codeine dispensing decreased in all age groups, except those <1 y. Long acting opioids were dispensed to 7.5% of children (1–12 y) and 9.5% of adolescents prescribed opioids. Noncancer vs cancer indication information was not provided. The majority of children (80%) were dispensed one prescription only. General practitioners prescribed 48%, medical specialists 28% and other prescribers 22%. General practitioners prescribed mostly codeine and tramadol, while specialists prescribed strong opioids.

The Australian national survey revealed low rates of nonmedical use of opioids (1.1%) and sleeping pills/tranquilisers (2.7%) by adolescents (14–19 y) in the previous 12 mth (AIHW 2019 **Level IV**).

10.4.5.6 | Consequences of excess prescribed opioids

Practice varied widely regarding doses and amount of opioid prescribed for children and adolescents <21 y following various surgery types eg arthrodesis, humeral supracondylar fracture repair and Nuss surgery (Harbaugh 2018b **Level III-3**, n=88,637) and laparoscopic appendicectomy (Anderson 2018 **Level III-2**, n=590). As a consequence, many children are prescribed and dispensed excessive amounts of opioid that remain at large in the community. Several audits have documented a mean or median duration of discharge opioid prescription: 4.8 d (± 2.9) prescribed for 63% post laparoscopic appendicectomy (Anderson 2018 **Level III-2**, n=590), 4 d (IQR 3–5 d) for 68% post laparoscopic appendicectomy (Sonderman 2018 **Level III-2**, n=9,684) and 4 d (IQR 1–8) for 100% post mixed surgery (Monitto 2017 **Level IV**, n=343). In the latter, 36% of patients were still taking opioids 7 d post discharge. Of concern, one prescription at times provided opioid for up to 30 and 65 d (Sonderman 2018 **Level III-2**, n=9,684; Anderson 2018 **Level III-2**, n=590) and in separate series, the number of dispensed opioid doses (median 43, IQR 30–85) (Monitto 2017 **Level IV**, n=343), liquid volumes (mean 106 mL 125) and tablets (mean 51 51) (George 2016 **Level IV** n=34,218) were high. Another centre reported a low median of 10 doses (IQR 6-15) of discharge opioid prescribed for 22%; this audit included the 7 commonest (mostly day-stay) paediatric surgical procedures (Harbaugh 2019 **Level IV**, n=404). Postoperative intake of non-opioids with opioids was high (but could be improved upon): paracetamol 88% and/or ibuprofen 78% were taken for a median of 3 d (IQR 2–5 d), with opioids used for a median of 2 d (IQR 1–3 d) (Harbaugh 2019 **Level IV,** n=404); and both agents by 81% of patients at a second centre (Monitto 2017 **Level IV**, n=343).

Where opioid prescription exceeds use, leftover medications result. Parental surveys have documented high proportions (25–90%) of unused/leftover prescription opioid doses following paediatric surgeries (Groenewald 2019a **NR**; Hunsberger 2019 **Level IV**, n=115 interviewed; Monitto 2017 **Level IV**, n=343), where 14% (Voepel-Lewis 2015a **Level IV,** n=223) to 31% of parents report using none of the prescription and 37% less than half (Harbaugh 2019 **Level IV**, n=404 [78 prescribed opioid]). Various factors contribute to this such as age of the child (younger patients consumed fewer doses than patients >15 y), decrease in daily use with recovery (and appropriate cessation as pain is well controlled) or early cessation due to side effects (as reported by 18% of parents whose children had nausea, vomiting or sedation) (Monitto 2017 **Level IV**, n=343) versus early tapering and discontinuation of opioid medications by parents (Voepel-Lewis 2015a **Level IV**, n=223). However, for some surgery types such as Nuss and major orthopaedic surgery, the mismatch of dispensed vs use was large (Monitto 2017 **Level IV**, n=343). Leftover opioids represent a major source of nonmedical use of prescribed opioids in adolescents (McCabe 2013a **Level III-3**, n=647 [nonmedical use]) and leftover prescription opioids have been implicated in accidental opioid overdoses (Groenewald 2019b **NR**). The strongest predictor of the number of doses remaining was the number of doses dispensed (Monitto 2017 **Level IV**, n=343).

10.4.5.7 | Safe opioid storage and disposal

Opioids were kept in locked storage in the USA by only 28% parents whose children were discharged with opioids (Harbaugh 2019 **Level IV**, n=404) and 29% of adults who had past-year use of opioids and were living in households with children and adolescents (McDonald 2017 **Level IV**, n=681). The lack of childproof packaging for many commonly prescribed opioids has been recognised as an area for concern (Gaither 2018 **Level IV**, n=8,986 deaths). Young children commonly gain access to prescribed medications which are stored incorrectly, in plain sight or accessing

from an adult's purse or bag (Allen 2017 **Level IV,** n=188,468). Disposal of leftover opioids is widely variable: 85% of parents were unaware of how to manage leftover opioids and 33% planned to keep them for future use (Groenewald 2019a **NR**), 19% recalled being advised on how to dispose of opioids (Monitto 2017 **Level IV**, n=343) eg by return to a pharmacy, with only 4% and 11% appropriately disposing of the leftover opioids (Harbaugh 2019 **Level IV**, n=404; Monitto 2017 **Level IV**, n=343). Dual harm potential with unsafe storage and non-disposal of prescription opioids leads to a reservoir for nonmedical use by families and adolescents (including diversion) and accidental ingestion by young children. Parents may also be an important source of prescription opioids that are intentionally shared for medical (and nonmedical) use by children and adolescents.

10.4.5.8 | Education of prescribers, families and patients: pain trajectories and safe practices

Perceptions of the expected duration of pain following common surgical procedures vary significantly (Raney 2018 **NR**), although it is known that postoperative pain is commonly experienced by children at home, lasting for days to weeks. The adult Education Section 3.1 provides an overview of the impact of education on various clinical staff members, patients and carers assessed by different outcomes including postoperative pain, analgesic use and quality of life. The safe and practical prescribing sections in 8.13 Discharge analgesia (sections 8.13.2.5 and 8.13.5) have overlap with this paediatric section, which focuses on staff and family education pertaining to opioid prescription and additional safe practices relevant to children.

Barriers to adequate pain relief include various factors (Walker 2015b **GL**):

- Parental factors, eg tendency to underdose and not optimise therapy;
- Child factors, eg anxiety/distress, difficulty swallowing medication (or formulation) or refusal;
- Medication factors, eg incorrect dosing or lack of palatable paediatric formulation that permits appropriate dosing; and
- System factors, eg knowledge base, training, confidence and seniority of staff prescribing analgesia and provision of adequate information.

As highlighted above by the variability in practice, it is important to optimise discharge opioid prescription in the paediatric population (Monitto 2017 **Level IV**, n=343) and create guidelines for safe and responsible opioid prescribing (Groenewald 2019a **NR**; Cravero 2019 **GL**). Education interventions at a hospital level should focus on hospital prescribers, particularly surgical services who write the majority of postsurgical discharge prescriptions (George 2016 **Level IV**, n=34,218). This needs to be informed by research with focus on understanding the pain trajectories after common surgical procedures, to reduce leftover medications and educate the broader opioid prescribing and dispensing community and then carers (Raney 2018 **NR**). There is growth in web-based delivery of education programs for health professionals focussing on opioid prescribing. Online educational resources improve knowledge and skills, but not confidence and competence (Liossi 2018 **Level IV SR** [PRISMA], 32 studies [6 paediatric], n unspecified). Studies were heterogeneous, including paediatric and adult patients, and acute and chronic pain populations in various clinical settings (one specific to primary care and opioids); relevant health outcomes for patients were not assessed. The interventions were generally 1 h in duration and permitted multiple logins. A subsequent survey of clinicians who had completed an interactive online opioid prescription learning module determined that clinician knowledge, likelihood of adherence to prescription guidelines and perceived competence in opioid prescription improved following participation (Langford 2020 **Level III-3**, n=167 [clinical staff]). Quality improvement initiatives include review of postoperative opioid consumption eg post urological surgery where investigators found the median consumption was 2 (IQR 3–6) of the 10 doses prescribed, with subsequent revision of prescription to 5 dose maximum (Cardona-Grau 2019 **Level IV**, n=98). A rapid cycle audit initiative

in the paediatric palliative care setting (for consideration for postoperative patients) has increased use of a risk stratification tool for opioid misuse when seeing children in the clinic, with implications for ongoing prescribing and managing abuse or opioid diversion (Thienprayoon 2017 **Level IV**, n=17 [positive risk ≤18 y]).

It is important to target education of carers to set expectations and simultaneously address the barriers and concerns highlighted above. Web-based parental education and preoperative child preparation strategies have been recommended (Walker 2015b **GL**). A systematic review evaluating educational websites included only two RCTs with information on acute postoperative pain (Bender 2011 **Level I**, 17 RCTs, n=2,503). One was paediatric and assessed preparation of adolescents prior to tonsillectomy (O'Conner-Von 2008 **Level II**, n=69, JS 3). Improved satisfaction and knowledge were seen with internet (commonly viewed >1 time) vs standard face to face afterhours preparation program vs no treatment, with no difference in pain scores or anxiety (the latter were high normal at 34–37, but below the therapeutic cut off of 39/80). A written oxycodone information sheet supplement to verbal instruction was provided to parents after tonsillectomy in children with information regarding dose and timing vs verbal instruction alone (Bailey 2015 **Level II**, n=60, JS 5). The information sheet recipients had higher parental satisfaction and knowledge and some improvements in pain scores up to POD 7. Parental recall of instruction for "around the clock" opioid administration predicted greater opioid use (Voepel-Lewis 2015a **Level IV**, n=166 [prescribed opioids]). This could be positive or negative depending on the response of parents to subsequent adverse events such as sedation (Voepel-Lewis 2015b **Level IV**, n=514 parents). To reduce harm from opioid medications, interventions should also include education of adolescents, and carers (and adults in the home) on the risk of opioids, the importance of storage in a locked medicine cabinet and safe disposal (Cravero 2019 **GL**; Groenewald 2019a **NR**; Binswanger 2015 **NR**). Initiatives such as the Australian National Prescribing Service Choosing Wisely program permit dialogue between consumers and clinical staff with written take home information that addresses at home pain management and safe practices (NPS Medicinewise 2019b **GL**).

The use of state prescription drug monitoring programs is also recommended (Groenewald 2019a **NR**). Some USA states have seen a reduction in problematic opioid behaviours since the utilisation of prescription drug monitoring programs; however it is difficult to directly attribute this change to the use of these programs versus other social and regulatory changes.

KEY MESSAGES

1. Postoperative opioid therapy in children and adolescents may lead to long term opioid use and misuse in later life (**N**) (**Level III-2**); risk factors include type of surgery, psychological and social factors and other substance use (**N**) (**Level III-2**).
2. Long term opioid use following therapeutic medical prescription is uncommon in children and adolescents (**N**) (**Level IV**). However, prior diagnosis of chronic pain, substance use or mental health conditions are risk factors (**N**) (**Level IV**).
3. Misuse of prescription opioids is common amongst adolescents and young adults either as medical use (self-treatment) or nonmedical use (sensation seeking/recreational) (**N**) (**Level IV**).
4. Leftover prescribed opioids are a common source of nonmedical opioid use in adolescents, with most adolescents gaining access through family or friends (**N**) (**Level IV**).

5. Unsafe storage of prescription opioids in the home and non-disposal of leftover opioids is common (**N**) (**Level IV**).
6. Prescription opioids are a large source of opioid-related poisonings: usually accidental in young children and related to recreational use or with intentional overdose in adolescents (**N**) (**Level IV**).
7. Adverse drug events in children and adolescents sent home with prescription opioids are common (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ As for adults, a sensible approach should be used in the setting of prescribing discharge opioid medications for children and to adults with children at home (**N**).

☑ As for adults, prescribing discharge medications for children should be done with consideration of the child's anticipated opioid requirements. The tablet number and volume of opioid solution prescribed should be judicious and individualised (**N**).

☑ Understanding and education is required to determine procedure specific pain trajectories in children (**N**).

☑ Carer/parental, patient and clinical staff education is necessary about risks of opioids and how to safely dispose of unused medication by return to a pharmacy (**N**).

☑ Carer/parental and patient education in case of ongoing pain and analgesic issues is appropriate with follow-up by general practitioners or pain medicine services as indicated (**N**).

☑ Education and guidelines are desirable for adult and paediatric discharge and community opioid prescribers with focus on information provision for staff delivering the advice (ideally written and verbal combined) to carers and families (**N**).

10.4.6 | Opioid tolerance in children and adolescents

10.4.6.1 | Groups of opioid-tolerant children

Opioid tolerance is discussed in the adult section; for the definitions of tolerance and dependence see adult Section 9.7; see Table 9.8. Opioid-tolerant paediatric patients have been less well studied than opioid-tolerant adults.

Like adults, there are four main groups of opioid-tolerant children and adolescents:

1. *Chronic non-cancer pain (CNCP)*

   The prevalence of moderate to severe CNCP in children is suggested to be 1 in 20 (Brooks 2016 **NR**). An Australian dataset revealed opioid use by 15.7% of children at referral to paediatric chronic pain clinics (Lord 2019, **Level IV**, n=1,100) with data also for paediatric sickle cell patients chronically taking opioids (see 10.9.5), but not for other potentially opioid-tolerant paediatric groups with chronic pain (eg inflammatory bowel disease, inflammatory arthritis or pelvic pain). There is no RCT data available in this patient group (Cooper 2017a **Level I** [Cochrane], 0 RCTs).

2. *Paediatric cancer patients being treated with opioids*

   Many government prescription databases provide data that is not linked to a cancer diagnosis and so the prevalence of chronic opioid use in patients with active disease (undergoing treatment or in the palliative phase), in remission or survivors of childhood cancer is unknown. Prescription analgesic use was reported by 16.7% of survivors 16.5 y (mean) post cancer diagnosis vs 12.6% of their siblings (Lu 2011 **Level IV**, n=10,397). Many adolescents and young adults with cancer have at least one psychosocial risk factor for misuse and some have documented aberrant opioid-related behaviours (Ehrentraut 2014 **Level IV**, n=94 [opioid using]); survivors may be at increased risk of opioid use disorder in later life. This raises the ethical challenge of withholding analgesia on the basis of addiction risk – thus screening and subsequent monitoring and management of those found to have opioid misuse is recommended (Pinkerton 2017 **NR**). An initiative in paediatric palliative care increased use of a risk stratification tool for opioid misuse when seeing children in the clinic, with implications for ongoing prescribing and managing abuse or opioid diversion (Thienprayoon 2017 **Level IV**, n=17 [positive risk ≤18 y]).

3. *Nonmedical prescription opioid use (NMPOU)*

   This group are mostly adolescents. Nonmedical use is either long term prescription opioid use postoperatively (4.8 % of previously opioid naïve adolescents (13–21 y) continued use of opioids at 90–180 d) (Harbaugh 2018b **Level III-2**, n=88,637 perioperative opioid prescription fills) or illicit opioid misuse (non-prescription or prescription): 3.6% of USA adolescents (12–17 y) (Groenewald 2019a **NR**), 5.9% of Canadian high school students (Currie 2012 **Level IV**, n=44,344 [Youth Smoking Survey]) or 7.4% of adolescents/young adults (11–30 y) (Jordan 2017 **Level IV SR** [PRISMA], 19 studies, n=503,845) had addiction or SUD, including those on an opioid treatment program (see also Section 10.4.5.4, 10.4.5.5 and adult Section 9.7).

4. *Acute or subacute tolerance in children*

   Children and adolescents, like adults, are at risk of opioid-tolerance, dependence and withdrawal after opioid therapy during inpatient or paediatric intensive care unit (PICU) stay. Opioid tolerance and/or dependence may occur with 5–10 d of therapy with most opioids, particularly with synthetic opioids and/or at high cumulative doses (Best 2015 **Level IV SR** [PRISMA], 33 studies, n unspecified; Anand 2010 **NR**).

   i. Acute opioid tolerance

   Intraoperative remifentanil was associated with an increase in PCA morphine requirement in the 24 h post scoliosis surgery (Crawford 2006b **Level II**, n=30, JS 5), possibly due to acute opioid tolerance or opioid-induced hyperalgesia. In younger children having surgery of approximately 3h duration, patients who received intraoperative remifentanil 0.6-0.9 mcg/kg/min had higher postoperative fentanyl requirements for 24 h vs those who received 0.3 mcg/kg/min or saline (Kim 2013 **Level II**, n=60, JS 4). Intraoperative weaning strategies for remifentanil in children have not been explored (see adult Section 9.7.2).

   ii. Subacute opioid tolerance

   During and following fentanyl and morphine infusion, children, whilst in (Ibach 2017 **Level IV**, n=21/59) and post discharge from PICU and neonatal intensive care units (NICUs) have exhibited tolerance and experienced withdrawal symptoms (Anand 2013b **Level III-2**, n=419 [7 centres]; Anand 2010 **NR**; Birchley 2009 **NR**). Fentanyl administered as a prolonged IV infusion in the NICU and PICU has been associated with more rapid dose escalation and greater likelihood of doubling the daily dose than when the primary opioid is morphine

(Anand 2013b **Level III-2**, n=419 [7 centres]). This was also true for the subgroup admitted immediately postoperatively.

10.4.6.2 | Perioperative outcomes and management of opioid tolerance in children

There is no data on the influence of opioid-tolerance on paediatric perioperative outcomes. Recommendations for management have been primarily based upon extrapolation from multimodal management of opioid naïve patients with severe pain (see paediatric Sections 10.9.1 Management of pain due to trauma in children and 10.9.2 Management of acute burn injury in children) and the adult literature (See Sections 9.7.4.2 and 9.7.6).

Strategies include perioperative use of multimodal analgesia with adjuvant use of (Brooks 2016 **NR**; Geary 2012 **NR**):

- Ketamine (see paediatric Section NMDA Antagonists 10.4.7)
- Alpha-2 agonists (see paediatric Section 10.4.8)
- Alpha-2-delta ligands (see paediatric Section 10.4.9)
- Local anaesthesia – peripheral nerve blocks (see Section 10.6.1), regional (10.6.2 and 10.6.3) and systemic lidocaine infusion (see Section 10.4.11 and adult Section 4.4.1).

Opioid-related withdrawal syndromes in children and management

Recognition and management of opioid-related withdrawal is important to reduce physiological disturbance. This is particularly relevant for PICU patients receiving opioids for sedation, endotracheal tube tolerance and acute or postoperative pain (eg post cardiac surgery, major burns or trauma), where tolerance (particularly to shorter acting opioids eg fentanyl) is recognised (Anand 2013b **Level III-2**, n=419 [7 centres]; Gish 2011 **Level III-3**, n=31) including polytolerance eg to other sedatives such as benzodiazepines (Best 2015 **Level IV SR** (PRISMA), 33 studies (9 opioid only, 22 opioid/benzodiazepine, 2 benzodiazepine only), n unspecified). These patients may frequently experience withdrawal; reported by 63% of burns centres (Singleton 2015 **Level IV**, n=41 centres).

There are several paediatric withdrawal assessment scales such as the validated withdrawal assessment tool (WAT-1) and others (Fenn 2017 **Level IV SR**, 15 studies, n=567; Best 2015 **Level IV SR** [PRISMA], 33 studies, n unspecified; Whelan 2015 **NR**) (8 study overlap). Some paediatric institutions have weaning and concurrent observation guidelines (SickKids 2018 **GL;** Starship 2017 **GL**). Weaning 10–20% of the total opioid dose every 48 h is generally recommended (Galinkin 2014 **NR**; Anand 2013b **Level III-2**, n=419 [7 centres]). There is little evidence to recommend any particular withdrawal prevention or treatment regimen eg with methadone (Dervan 2017 **Level IV SR** [PRISMA], 12 studies, n=459) (7 and 8 study overlap with above SRs) or alpha-2 adrenergic agonist use including as 'bridging therapy' (Whelan 2015 **NR**). IV Ketamine infusion at anaesthetic doses has been used to facilitate opioid rotation for a median of 3 d in patients (median age 2.5 y) who had received opioid infusions for several days with clonidine/midazolam infusion in PICU (Neunhoeffer 2017 **Level IV**, n=32). Upon cessation, fentanyl requirements were reduced and COMFORT-B scores improved vs prior to commencement (See 10.4.7 ketamine use for opioid-induced hyperalgesia).

KEY MESSAGES

1. Iatrogenic withdrawal syndrome following prolonged inpatient intravenous opioid therapy in critically ill children is common (**N**) (**Level IV SR** [PRISMA]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ There are groups of paediatric patients who are opioid-tolerant, as in adults. They require special consideration for inpatient pain management and perioperative care. In children with opioid tolerance, inadequate pain relief and withdrawal (if opioids are acutely ceased) are specific risks. Acute pain service input can assist with preadmission planning and use of various adjuvants beyond standard multimodal interventions (**N**).

☑ For assessment of withdrawal reactions, the use of a validated withdrawal tool in paediatric opioid-tolerant patients is recommended; management strategies vary and include opioid weaning, rotation and adjuvant use (**N**).

10.4.7 | Systemic NMDA-receptor antagonists

10.4.7.1 | Ketamine

This section covers the use of ketamine for acute pain management in children. Ketamine has been studied at varying doses, via various routes and regimens, for multiple paediatric surgery types, generally in small studies rendering interpretation of its effects challenging.

See also Section 10.7 for use in paediatric procedural sedation, Section 10.8 for use in paediatric cancer pain, and Section 10.6.3 for regional adjuvant use and peritonsillar infiltration in addition to those summarised in the various systematic reviews below. See also Adult ketamine Section 4.6.1.1, where neuraxial, adjuvant peripheral nerve use and topical administration are discussed in the one section.

Pharmacokinetics and pharmacodynamics of ketamine in children

Ketamine has a large volume of distribution at steady state (mean 3.3 L/kg 1.3) and a clearance that approximates liver blood flow in children above 1 y of age (Elkomy 2019 **PK**). Pharmacokinetic (PK) modelling reveals ketamine infusions of 0.2 mg/kg/h for 24 h will achieve a median steady-state plasma concentration of 0.15 mg/L (Herd 2007 **PK**). Median ketamine concentration is maintained >0.1 mg/L (assumed minimum analgesic serum concentration) for 0.5 h post cessation of infusion. The metabolite norketamine is thought to have one third the potency of ketamine. With this assumption, the combined "effective" concentration of ketamine/norketamine is >0.1 mg/L for 1.5 h post infusion cessation. After IV ketamine 2 mg/kg, norketamine plasma concentration peaks within 1 h, and may contribute to analgesia for up to 4 h. In an adult volunteer study an anti-analgesic effect of norketamine has also been proposed (Olofsen 2012 **EH**).

Ketamine is a racemic mixture. The isomeric formulation S(+) ketamine has twice the analgesic potency of the racemate, and is shorter acting with slightly less adverse cognitive effects in adults (Mion 2013 **NR**)**.**

For procedural sedation up to 20 min, PK modelling has suggested doses for IV ketamine of 2 mg/kg and for IM ketamine 6-8 mg/kg (Hornik 2018 **PK**). With IM ketamine, bioavailability was estimated at 41% and desired effect achieved at 10 min. Children on extracorporeal membrane

oxygenation (ECMO) had higher ketamine clearance, with a dose suggestion of >5 mg/kg IV for procedural sedation.

Oral ketamine has a high first-pass clearance (See adult Sections 4.6.1.1 Ketamine and 5.5.3.2 regarding sublingual ketamine). This results in high early norketamine concentrations vs IV administration. The peak ratio of norketamine/ketamine at 1 h is 2.8 after PO administration allowing an analgesic contribution from the metabolite at this time. This property has proved useful when racemic ketamine is given 1 h before burns dressings (Brunette 2011 **Level IV**). The PKs following SL and IN route administration have been studied in adults with respective bioavailabilities of 30 and 45% (Yanagihara 2003 **PK**). In adults, a ketamine lozenge (25 mg) had 24% bioavailability by both SL and PO routes (with peak plasma levels at 30 min and 120 min respectively, and high norketamine concentrations) (Chong 2009 **PK**); a SL wafer presentation (25 mg) had similar SL bioavailability of 29% (Rolan 2014 **PK**). For procedural analgesia, the bioavailability of IN racemic ketamine (0.5 mg/kg combined with sufentanil 0.5 mcg/kg) was 36%, with a T_{max} of 8.9 min in awake children (half the value reported in anaesthetised children) (Nielsen 2014 **Level IV**). The IN spray was acceptable to the majority of patients. IN S-ketamine 2 mg/kg has also been administered to anaesthetised children and its PKs assessed but data quantifying effect are not available (Weber 2004 **PK**).

Efficacy of ketamine

Perioperative use of ketamine

Four meta-analyses have assessed perioperative paediatric ketamine use by various routes for various surgery types (Dahmani 2011 **Level I** [QUORUM], 35 RCTs, n=1,925; Cho 2014 **Level I** [PRISMA], 24 RCTs, n=1,257; Tong 2014a **Level I** (PRISMA), 10 RCTs, n=522; Michelet 2016 **Level I** [PRISMA], 11 RCTs, n=508) (0-10 RCT overlap). Studied systemic dose regimens generally consist of a bolus ranging from 0.1 mg/kg to 0.5 mg/kg mostly, to as high as 6 mg/kg. Some incorporated intraoperative and postoperative ketamine infusions which have generally ranged between 0.08 and 0.25 mg/kg/h, with 2 RCTs using 1–1.4 mg/kg/h. Findings for all administration routes are generally positive, mainly for early analgesic outcomes.

Caudal ketamine for inguinal and urological surgery

Caudal ketamine increases the duration of sensory block (SMD 2.26; 95%CI 1.53 to 2.98) (10 RCTs, n=686) and reduces analgesic requirement in PACU (OR 0.26; 95%CI 0.10 to 0.66) (10 RCTs, n unspecified), but did not reduce pain intensity in PACU or in the first 6 h postoperatively (Dahmani 2011 **Level I** [QUORUM], 13 RCTs [caudal], n unspecified).

Systemic ketamine for various surgery types

In patients having adenotonsillectomy (13 RCTs), inguinal hernia repair and circumcisions (2 RCTs), appendicectomy (1 RCT), scoliosis surgery (1 RCT) and ambulatory surgery (1 RCT) (Dahmani 2011 **Level I** [QUORUM], 18 RCTs [systemic], n=985), systemic ketamine:

- Reduces pain intensity in PACU (SMD -0.45; 95%CI -0.73 to -0.16) (10 RCTs, n=647);
- Reduces analgesic requirement in PACU (OR 0.46; 95%CI 0.29 to 0.72) (7 RCTs, n unspecified);
- But not intensity or analgesic requirement later in the 6–24 h postoperative period; and
- Does not reduce opioid consumption in the first 24 h.

Peritonsillar and topical ketamine for adenotonsillectomy

Peritonsillar (2 RCTs) and topical ketamine (1 RCT):

- Reduces pain intensity in PACU (SMD -1.62; 95%CI -2.83 to -0.41) (3 RCTs, n=190) ;
- Reduces analgesic requirement in PACU (OR 0.09; 95%CI 0.03 to 0.27) (2 RCTS, n=90) (Dahmani 2011 **Level I** [QUORUM] 35 RCTs, n=1,925).

Systemic, peritonsillar and topical ketamine for tonsillectomy
Intraoperative ketamine by all three routes:

- Vs opioid, achieves similar pain scores at five time points over 0–24 h (Cho 2014 **Level I** [PRISMA], 9 RCTs [opioid], n=428);
- Vs placebo, reduces early pain intensity
    - at 0 h (SMD -1.7; 95%CI -3.17 to -0.24) (Cho 2014 **Level I** [PRISMA], 6 RCTs [placebo], n=290);
    - at 0.5–2 h (Tong 2014a **Level I** (PRISMA), 10 RCTs, n=522) (10 RCT overlap with Cho);
    - and 4 h (SMD -0.8; 95%CI -1.2 to -0.4) (Cho 2014 **Level I** [PRISMA], 14 RCTs [placebo], n=718), but not later at 6–24 h;
- Subgroup analysis reveals similar results for IV and peritonsillar administration with a stronger effect size for peritonsillar route, countered by higher heterogeneity of the studies. There is reduced need for (LogOR -1.2) and amount of analgesia required (SMD -1.3) and longer time to first rescue analgesic (SMD 0.96) (Cho 2014 **Level I** [PRISMA], 24 RCTs, n=1,257) (overlapping with the first SR by 8 RCTs [4 IV, 1 topical and 3 peritonsillar infiltration]);
- Adminstered as peritonsillar infiltration 2 mg/kg, PR 2 mg/kg or IV 0.5 mg/kg vs IV tramadol 2 mg/kg reduced pain scores similarly (Yenigun 2015 **Level III-1**, n=120).

Multidose perioperative ketamine:
IN pump-pack administration of ketamine 1.5 mg/kg vs fentanyl 1.5 mcg/kg (at induction and then three times daily) reduced pain scores over 24 h similarly (Yenigun 2018 **Level III-1**, n=63). Both were superior but with more sedation vs IV paracetamol 10 mg/kg, with no difference in other adverse effects.

Systemic perioperative ketamine and postoperative opioid-sparing effect
For various surgeries (Michelet 2016 **Level I** [PRISMA], 11 RCTs, n=508) (with 7, 3 & 0 RCT overlap respectively with the above SRs), systemic ketamine vs placebo does not reduce:

- Opioid consumption in the first 24 h (primary outcome) (6 RCTs, n=278) or in PACU or in the first 48 h;
- Pain intensity (in PACU, or in the first 24 and 48 h);
- PONV or psychotomimetic symptoms in the first 24 h.

There was also no difference in subgroup analysis of postoperative ketamine infusions only (4 RCTs, n=179) and use in scoliosis surgery (3 RCTs, n=128) on opioid consumption to 24 h vs placebo. Overall, the authors calculated a sample size of 445 patients would adequately power an RCT to determine if ketamine is opioid-sparing.

- A single additional scoliosis surgery RCT conflicts with those included in the meta-analysis where IV ketamine (0.5 mg/kg bolus and 0.12 mg/kg/h for 48 h) reduced cumulative morphine consumption at 24 and 48 h vs placebo (Minoshima 2015 **Level II**, n=36, JS 5). There was no difference in pain intensity, sedation score or PONV incidence.
- In a further scoliosis RCT, intraoperative IV infusion of ketamine (0.2 mg/kg bolus and 0.15 mg/kg/h)/remifentanil/magnesium (50 mg/kg bolus and 8 mg/kg/h) vs ketamine/ remifentanil/placebo reduced 0-48 h PCA morphine requirements by 29.5% (Jabbour 2014 **Level II**, n=50, JS 5).

Postoperative combined PCA ketamine/opioid
Adding ketamine to opioid in the PCA pump improves pain at rest at 24 h (WMD -21.1/100 mm; 98%CI 21.8 to 20.4) (9 RCTs, n=595), opioid consumption (by 28%) (7 RCTs, n=495) and PONV (by 44%) (7 RCTs, n=435) (Assouline 2016 **Level I** [PRISMA], 19 RCTs [2 paediatric], n=1,453). Respiratory depression (RR 0.31; 98%CI 0.06 to 1.51) (9 RCTs, n=871) and hallucinations (OR 1.16; 98%CI 0.47

to 2.79) (7 RCTs, n=690) are not increased. Both included paediatric studies involved Nuss surgery. Intraoperative ketamine bolus 0.3 mg/kg followed by PCA IV ketamine added to fentanyl (ratio per mL 0.15 mg/kg: 0.5 mcg/kg) vs fentanyl PCA alone resulted in a small but statistically significant decrease in mean pain scores at 6 h (2.5/10 vs 2.9), 24 h (1.4/10 vs 1.9) and 48 h (1.0/10 vs 1.6) and reduced cumulative fentanyl consumption at 24 and 48 h (Assouline 2016 **Level I** [PRISMA], 1 RCT: Cha 2012 **Level II**, n=60, JS 3). Combining ketamine with hydromorphone/ketorolac in a PCA (ratio per mL 0.15mg/kg: 3 mcg/kg: 0.05 mg/kg) reduced postoperative PCA use (50.8 ± 1.9 mL vs 57.8 mL ± 2.5) with no difference in other outcomes (Assouline 2016 **Level I** [PRISMA], 1 RCT: Min 2012 **Level II**, n=44, JS 4).

S(+) ketamine

The efficacy of S(+) ketamine has been investigated in a limited number of paediatric studies. Following major urological procedures, children treated with intraoperative low-dose IV S(+) ketamine (bolus 0.2 mg/kg and infusion 0.3 mg/kg/h) vs placebo had a longer time to first analgesic request, but similar pain scores and 72 h IV NCA morphine consumption (Becke 2005 **Level II**, n=30, JS 5).

Adjuvant caudal S(+) ketamine 0.5 mg/kg had increased duration of analgesia vs local anaesthetic alone (SMD 2.35; 95%CI 1.02 to 3.67) (4 RCTs) (Dahmani 2011 **Level I** [QUORUM], 35 RCTs, n=1,925). The duration was similar to that for adjuvant caudal racemic ketamine 0.25–0.5 mg/kg (9 RCTs).

Ketamine use by various routes in acute non-surgical pain

Ketamine has been used prehospital and in the ED for analgesia, commonly for severe pain (>6/10) following limb injury/fracture, burns, falls or road traffic accidents. Doses of 0.25–1 mg/kg have been used in children via IV, IM and IN routes (Yeaman 2013 **Level IV;** Bredmose 2009a **Level IV**; Bredmose 2009b **Level IV**; Reid 2011 **CR**), as well as higher doses IM (Svenson 2007 **Level IV**). IN Ketamine 1–1.5 mg/kg was similarly effective vs IN fentanyl 1.5–2 mcg/kg for children presenting to the ED with limb injuries, with reduced pain scores at 20–60 min (Frey 2019 **Level II**, n=90, JS 5; Reynolds 2017 **Level II**, n=87, JS 3; Graudins 2015 **Level II,** n=80, JS 5). (See also adult Sections 5.5.2.3 Ketamine via IN route and 8.6.5.2 for use in acute headaches).

Beneficial use of low-dose 0.1–0.2 mg/kg/h infusion in sickle cell crises is described in children in addition to (n=4) or to replace (n=1) IV opioid PCA (Zempsky 2010 **Level IV**). Bolus IV ketamine 1 mg/kg for sickle cell crisis resulted in similar mean maximum percentage change in pain score during a 2 h period vs bolus IV morphine 0.1 mg/kg (66.4% vs 61.3), but with a higher rate of minor adverse effects (37.5% vs 3.3: mainly nystagmus and dysphoria) (Lubega 2018 **Level II**, n=240, JS 5).

Nebulised ketamine 2 mg/kg vs dexmedetomidine 2 mcg/kg vs combination ketamine 1 mg/kg and dexmedetomidine 1 mcg/kg has been trialled for paediatric pre-medication 30 min prior to dental surgery and may contribute to improved postoperative analgesia (although the data on acceptance of the nebulised technique by the young children is not specified) (Zanaty 2015 **Level II**, n=60, JS 5).

When IV ketamine is used for procedural sedation, there is a steep concentration-response relationship (almost all or no response) with an EC_{50} for arousal of 0.56 mg/L (Herd 2008 **Level IV**). A dose finding study of rectal ketamine 4–8 mg/kg with midazolam 0.5 mg/kg achieved effective sedation and analgesia for burns dressing changes in young children; the higher dose of 8 mg/kg was associated with prolonged recovery time and adverse events (Grossmann 2019 **Level II**, n=90, JS 5). Similar doses were effective for botox injections in children with cerebral palsy (Nilsson 2017 **Level IV,** n=61 [128 procedures]).

Ketamine use in opioid-induced hyperalgesia (OIH)

Three RCTs have assessed the opioid-sparing effect of perioperative ketamine in adolescents receiving remifentanil based anaesthesia for scoliosis surgery (Perello 2017 **Level II**, n=48, JS 5; Pestieau 2014 **Level II**, n=54, JS 5; Engelhardt 2008 **Level II**, n=34, JS 4). They each found no difference in pain scores and opioid consumption up to 72 h. The validity of using opioid consumption as a surrogate for OIH has limitations; the 2017 RCT also assessed peri-incisional hyperalgesia at 72 h (using Von Frey hairs) but found no difference between groups. Additionally, there was no difference in the measured area of peri-incisional hyperalgesia in patients who had any vs no pain 6 mth later.

The paediatric data differs to the positive findings in adults: see the adult Section 4.6.1.1 Ketamine.

See also Section 10.4.6 for discussion of use of ketamine in opioid-tolerant children and adult Sections 9.7.2 and 9.7.6.4 for use in opioid-tolerant adults.

Adverse effects of ketamine

Generally, when analgesic (low dose) ketamine has been used perioperatively in children, increased incidence of adverse effects has not been reported. IV Ketamine (median dose 0.5 mg/kg) is not associated with PONV during the first 24 h, or psychomimetic manifestations such as hallucinations, dysphoria-euphoria and sedation (Dahmani 2011 **Level I** [QUORUM], 18 RCTs [systemic], n=985). Similar results were found in a more recent meta-analysis assessing PONV at 2 time points (7 RCTs) and psychomimetic effects (6 RCTs) (Michelet 2016 **Level I** [PRISMA], 11 RCTs, n=508) (7 RCT overlap). The odds ratios were similar for these outcomes in the topical/peritonsillar (4 RCTs) and caudal (13 RCTs) administration routes (Dahmani 2011 **Level I** [QUORUM], 35 RCTs, n=1,925).

After Nuss surgery, ketamine added to fentanyl PCA reduced nausea and vomiting incidence over 48 h when compared to fentanyl PCA alone (23 vs 53%) (Cha 2012 **Level II**, n=60, JS 3).

However, when used in the ED, minor adverse effects (mostly dizziness, bad taste in mouth and sleepiness) were more common with IN ketamine vs IN fentanyl: RR 2.5 (95%CI 1.5 to 4.0) (Frey 2019 **Level II**, n=90, JS 5); 100 vs 61% (Reynolds 2017 **Level II**, n=87, JS 3); and 78 vs 41% (Graudins 2015 **Level II**, n=80, JS 5).

In patients who received ketamine for procedural sedation in the ED, the following adverse effects were recorded: airway and respiratory events (3.9%), laryngospasm (0.3%), apnoea (0.8%), emesis (8.4%), any recovery agitation (7.6%), and clinically important recovery agitation (1.4%) (n=8,282) (Green 2009b **Level IV**; Green 2009c **Level IV**).

Neurotoxicity and ketamine

The possible neurodegenerative effect of ketamine (and other analgesic/anaesthetic agents) on the developing brain is under discussion (Davidson 2013 **NR**; Walker 2012c **NR**). Racemic ketamine (with its preservative benzethonium chloride) and S(+) ketamine have been associated with neuronal apoptosis in developmentally regulated cortical and subcortical areas in rodents and sensorineural consequence in animal models following high dose and/or long term IV and IT administration (Davidson 2013 **NR;** Walker 2012c **NR;** Walker 2010 **BS;** Green 2009a **NR**). Conversely, ketamine has demonstrated neuroprotective effects in the presence of noxious stimuli in animals (Cheung 2019 **NR**). Proposed mechanisms include inhibition of neuronal excitotoxicity, and anti-inflammatory effects. The translatability of these findings to humans is questioned and the impact of lower subanaesthetic doses (bolus and perioperative infusion) is uncertain.

See adult Section 4.6.2.1 ketamine regional administration and neurotoxicity issues.

Efficacy

Magnesium (Mg) administered by local infiltration or IV (bolus and/or infusion) has been studied in children having tonsillectomy (Cho 2018a **Level I** [PRISMA], 10 RCTs, n=615; Xie 2017a **Level I** [PRISMA], 10 RCTs, n=665) (9 RCT overlap). In the earlier systematic review, Mg sulphate (IV or local infiltration) vs control does not reduce pain scores (8 RCTs, n=555), but does reduce the number of patients receiving rescue analgesia (RR 0.53; 95%CI 0.31 to 0.91) (5 RCTs, n=305), having emergence agitation (OR 0.18; 95%CI 0.07 to 0.48) (2 RCTs, n=105) and laryngospasm (OR 0.36; 95% CI 0.13 to 0.96) (7 RCTs, n=500) (Xie 2017a **Level I** [PRISMA], 10 RCTs, n=665). The subsequent systematic review found overall Mg (IV or local infiltration) does not reduce early pain scores at ≤1 h but does reduce late pain scores at 24 h vs control (SMD -0.39; 95%CI -0.71 to -0.07) (6 RCTs, n=330), with sub-analysis revealing that local infiltration is effective (SMD -0.62; 95%CI -0.89 to -0.36) (4 RCTs, n=230) and IV route is not (2 RCTs, n=100) (Cho 2018a **Level I** [PRISMA], 10 RCTs, n=615). Mg vs control increases time to first analgesia (SMD 0.75; 95%CI 0.20 to 1.31) (3 RCTs), reduces rescue analgesia administration (SMD -0.39; 95%CI -0.71 to -0.07) (5 RCTs), postoperative agitation at 15 min (SMD -0.31) (3 RCTs) and 1 h (SMD -0.67) (2 RCTs), and laryngospasm (SMD -1.09; 95%CI -2.11 to -0.07) (8 RCTs), and did not alter bleeding risk (3 RCTs). The sample sizes for the subanalyses were not provided.

For scoliosis surgery, the addition of intraoperative Mg (50 mg/kg initial bolus and 8 mg/kg/h infusion) to ketamine (0.2 mg/kg initial bolus and 0.15 mg/kg/h infusion)/remifentanil reduced postoperative PCA-morphine requirements by 29.5% (over 0–48 h) (Jabbour 2014 **Level II**, n=50, JS 5). While, adding the same bolus and slightly higher dosing of intraoperative Mg (10 mg/kg/h) to remifentanil did not reduce 0–24 h hydromorphone requirement vs remifentanil alone (0.38 ± 0.10 mg/kg vs 0.34 ± 0.11 mg/kg), where IV methadone 0.1 mg/kg did (0.26 ± 0.10 mg/kg), with no difference in postoperative pain scores in the three groups (Martin 2018 **Level II**, n=60, JS 4).

For severe migraine, IV Mg bolus (max dose 1–2 g over 15–30 min) in the ED substantially reduced pain severity in 35-48% of paediatric patients (Orr 2018a **Level IV SR**, 21 studies [2 IV Mg], n [IV Mg]=57 [65 migraines]).

For tonsillectomy, the addition of peritonsillar Mg 2-5 mg/kg to local anaesthetic reduced pain scores (4 RCTs) and the number of analgesic requests (WMD -0.68; 95% CI -1.17 to -0.18) (3 RCTs, n=180) (Vlok 2017 **Level I**, 4 RCTs [Mg], n=230).

See also adult NMDA antagonists discussion of magnesium Section 4.6.1.3 and specific to adult Headache 8.6.5.1 , Migraine 8.6.5.2 and Paediatric Migraine 10.9.3.

KEY MESSAGES

Ketamine

1. Perioperative low-dose intravenous ketamine bolus is similarly effective to opioids and superior to placebo in reducing early pain scores and analgesic requirements in children (**U**) (**Level I** [PRISMA]).
2. Perioperative low-dose intravenous ketamine bolus does not increase the postoperative incidence of nausea and vomiting, sedation, agitation, dreams or hallucinations in children (**S**) (**Level I** [PRISMA]).
3. Peritonsillar infiltration and topical application of ketamine for paediatric tonsillectomy reduces early pain scores and analgesic requirements versus placebo (**S**) (**Level I** [PRISMA]).
4. When added to multimodal analgesia, perioperative ketamine (bolus with or without intra/postoperative infusion) in children is not opioid-sparing vs placebo (**S**), although low postoperative pain scores and small sample sizes mean the meta-analysis is underpowered (**Q**) (**Level I** [PRISMA]).
5. There is low level evidence that combination ketamine and opioid PCA improved pain scores and PCA use post Nuss surgery (**N**) (**Level II).**

Magnesium

6. Magnesium (intravenous or peritonsillar infiltration) in children for tonsillectomy reduces postoperative rescue medication use, and increases time to first analgesia versus control; magnesium also reduces risk of postoperative emergence agitation and laryngospasm (**N**) (**Level I** [PRISMA]).
7. Magnesium (locally infiltrated) in children reduces late (24 hour) but not early (<1 hour) pain scores post tonsillectomy versus control (**N**) (**Level I** [PRISMA]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ High-dose long term ketamine is neurotoxic in animal models. The neurodevelopmental impact in children of subanaesthetic/analgesic doses of ketamine administered by bolus or postoperative infusion is unclear (**U**).

☑ The benefit of perioperative ketamine in preventing remifentanil induced hyperalgesia has not been adequately assessed in paediatric surgery (**U**).

10.4.8 | Alpha-2 agonists

The alpha-2 agonists, clonidine and dexmedetomidine, are attractive for paediatric use with their analgesic, sympatholytic (anxiolytic, haemodynamic modulation), antinausea/antiemetic and behavioural modification/sedative effects (Sottas 2017 NR). Administered as bolus and/or infusion via various routes, both agents have been used in various paediatric settings.

Perioperative use

- Preoperatively as premedication;
- Intraoperatively for controlled hypotension and to modify anaesthetic/perioperative opioid requirements; postoperative nausea and vomiting, shivering and emergence agitation; and
- As local anaesthetic adjuvants (see Section 10.6 and 10.6.3.3).

Use in PICUs and NICUs

Particularly in ventilated patients (Piotrowski 2015 **Level IV**, n=33 [12 postoperative]; Nemergut 2013 **NR**; Gupta 2012 **Level III-2**; Playfor 2006 **GL**):

- For sedation and analgesia;
- To modify distress or hypertensive response and escalating opioid requirements; and
- To prevent and treat opioid withdrawal symptoms (Honey 2009 **Level IV SR**, 9 studies, n=44; Oschman 2011 **NR**;) and facilitate opioid weaning.

Use in other settings

For similar indications, these agents are used in paediatric ward settings and also for procedural sedation and analgesia in the outpatient, ED and radiology settings (Ter Bruggen 2017 **Level I**, 5 RCTs [paediatric], n=372; Jooste 2017 **Level IV**, n=90; McMorrow 2012 **NR**).

See also the adult Section 4.9 Alpha-2 agonists.

10.4.8.1 | Clonidine

Pharmacokinetics

Bioavailability of clonidine after rectal and epidural administration is high (100%) (Potts 2007 **PK**), but is erratic after nasal drop administration in supine anaesthetised children (Almenrader 2009 **PK**, n=11). Oral bioavailability is lower in children than in adults at 55% when mixed with apple juice (which may influence intestinal transport); thus PO doses greater than 4 mcg/kg should be considered (Larsson 2011 **PK**, n=8); nasal administration has higher bioavailability than oral and Tmax occurs later (Blackburn 2014 **PK**, n=66). Clearance at birth is reduced and matures to achieve 82% of the adult rate at 1 y (Potts 2007 **PK**, n=72 [380 samples]).

The PKs of clonidine have also been assessed during sedation as an adjuvant to morphine and midazolam infusion during ECMO in children, with simulation aiming for a target concentration of 2 ng/mL, suggesting 3 boluses of 5 mcg/kg at 20 min intervals and infusion of 1 mcg/kg/h in children >12 y (Kleiber 2017 **PK**, n=22 [375 samples]). For mechanically ventilated patients, PK simulation suggested optimal clonidine dosing for a target of 2 ng/mL was 2 mcg/kg bolus and infusions up to 2 mcg/kg/h; this regimen should be halved in neonates (Hayden 2019 **PK**).

Efficacy

Clonidine has been used for the above indications for decades by various routes (Basker 2009 **NR;** Nishina 2002 **NR;** Eisenach 1996 **NR**).

Preoperative clonidine 2-4 mcg/kg administration (PO in 10 RCTs, rectal in 1 RCT) reduces postoperative pain scores, analgesic requirement and PONV vs midazolam and placebo, but not fentanyl (Lambert 2014 **Level I** [Cochrane], 11 RCTs [comparators: 6 midazolam, 4 placebo and 1 fentanyl], n=748). An earlier review draws similar conclusions (Dahmani 2010 **Level I**, 10 RCTs, n unspecified) (4 RCT overlap). It additionally reports superiority of clonidine vs midazolam for sedation at induction (OR 0.49; 95%CI 0.27 to 0.89) (2 RCTs) and superiority vs diazepam for PONV (OR 0.34; 95%CI 0.13 to 0.94) (2 RCTs). The same review reports reduced emergence agitation incidence (OR 0.25; 95%CI 0.11 to 0.58) (3 RCTs). This is also confirmed for intraoperative IV clonidine administration vs placebo (OR 0.5; 95%CI 0.26 to 0.95) (Pickard 2014 **Level I,** 2 RCTs [clonidine], n=170; Ydemann 2018 **Level II**, n=379, JS 5).

Typical bolus clonidine doses are 1–3 mcg/kg: IV, regionally, for nerve blocks and for infiltration (see Section 9.6).

Clonidine has been infused in cardiac surgery and intensive care at widely ranging rates: 0.18 to 1–3 mcg/kg/h (Lambert 2014 **Level I** [Cochrane], 1 RCT: Hunseler 2014 **Level II**, n=213, JS 5; Basker 2009 **NR**).

Aerosolised IN clonidine 3–8 mcg/kg has unreliable sedative efficacy and time to onset of effect (Larsson 2012 **Level II**, n=60, JS 5). This route has not been used for analgesic indications.

10.4.8.2 | Dexmedetomidine

Dexmedetomidine is more alpha-2 selective than clonidine. Its off licence use has increased in various paediatric settings (Sottas 2017 **NR**) (see below).

Pharmacokinetics

Dexmedetomidine PKs have been studied extensively in children. Population parameter estimates [and between subject variability] for a 2-compartment model were: clearance (CL) 42.1 L/h/70kg [31%], central volume of distribution (V1) 56.3 L/70kg [61%], inter-compartment clearance (Q) 78.3 L/h/70kg [37%] and peripheral volume of distribution (V2) 69.0 L/70kg [47%] (Potts 2009 **PK**, n=95 [730 observations]). Clearance matures with age and increases from 18.2 L/h/70kg at birth in a term neonate to reach 84.5% of the mature value by 1 y of age. Simulation of published infusion rates that provide adequate sedation for PICU patients found a target therapeutic concentration of between 0.4 and 0.8 mcg/L. This estimate has been reviewed and an EC_{50} of 0.9 mcg/L (95%CI 0.45 to 2.34) for sedation proposed by modelling PK-PD data (Li 2018a **Level II PK**, n=8 [3 way cross over study]). The equilibration half time between plasma and the effect compartment was 3.3 min (95%CI 1.8 to 4.7), indicating that slow onset of effect after enteral delivery is mostly due to slow absorption and not a delay between plasma concentration and effect site.

Subsequent IV dexmedetomidine PK studies in children post 1-2 mcg/kg for bronchoscopy, radiological imaging (Vilo 2008 **PK**, n=16), prior to (Liu 2017 **PK**, n=39), and during general surgery, following loading dose and infusion of 0.2–1.4 mcg/kg/h post liver transplantation (Weerink 2017 **NR PK**) are consistent with the earlier study (Potts 2009 **PK**, n=95). Hepatic function, assessed using INR, may alter clearance. Clearance after liver transplantation varied widely and was associated inversely with INR and not weight (Damian 2020 **Level IV PK**, n=20). Titration to clinical effect, rather than weight-based dosing, was suggested for this population, with attention to changes in INR.

Bioavailability in adults is 82% after intranasal and buccal administration (Weerink 2017 **NR PK**) with similar time to onset of 1 mcg/kg by atomiser (47.5 min; 95%CI 25 to 135) and drop administration (60 min; 95%CI 30 to 75) vs IV (15 min; 95%CI 15-20) (Li 2018a **Level II PK**, n=8). In children, after orogastric administration bioavailability was only 16% (Weerink 2017 **NR PK**); while after IN atomiser administration, bioavailability was 84% (95%CI 70 to 98%) (Miller 2018 **Level III-1 PK**, n=18) and lower with intranasal syringe administration (lying supine with head extended, where more pharyngeal run off possibly occurred) (Wang 2019a **PK**, n=13). Absorption half time was 18 to 20 min in both studies.

Efficacy

Several overlapping reviews have been performed with similar findings mostly in favour of dexmedetomidine. Data for emergence agitation is included here as severe pain in PACU may mimic this. Following various paediatric surgery types (mostly tonsillectomy, but also ear, laparoscopic appendectomy and genitourinary surgery), dexmedetomidine:

IV/IN bolus only 0.15–2 mcg/kg intraoperatively vs placebo reduces

- Postoperative pain (RR 0.51; 95%CI 0.32 to 0.81) (2 RCTs, n=138) (Schnabel 2013 **Level I** [PRISMA], 11 RCTs [10 IV, 1 IN], n=874) and pain in PACU (RR 0.41; 95%CI 0.25 to 0.65) (5 RCTs, n=356) (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812) (5 RCT overlap);
- The need for rescue analgesia (OR 0.16; 95%CI 0.05 to 0.48) (3 RCTs, n=168) (Pickard 2014 **Level I**, 10 RCTs [dexmedetomidine], n=669) (7 RCT overlap) and for postoperative opioid rescue (RR 0.4; 95%CI 0.26 to 0.62) (4 RCTs, n=249), but does not reduce overall morphine requirement (2 RCTs, n=98) (Schnabel 2013 **Level I** [PRISMA] [10 IV, 1 IN], n=874);

- Emergence agitation (OR 0.22; 95%CI 0.14 to 0.33) (8 RCTs, n=499) (Pickard 2014 **Level I**, 10 RCTs [dexmedetomidine], n=669) (7 RCT overlap) (RR 0.35; 95%CI 0.26 to 0.45) (12 RCTs, n=812) (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812) (5 RCT overlap).

IV bolus 0.15–2 mcg/kg with short term infusion 0.1–0.7 mcg/kg/h (in 8 RCTs) vs placebo reduces:

- Pain intensity in PACU (MD -1.18; 95%CI -1.88 to -0.48) (13 RCTs, n unspecified) and
- Postoperative opioid consumption in PACU (RR 0.31; 95%CI 0.17 to 0.59) (11 RCTs, n unspecified);
- But does not reduce PONV (RR 0.67; 95%CI 0.41 to 1.08) (3 RCTs, n=290) (Bellon 2016 **Level I** [PRISMA], 14 RCTs, n=1,463) (6 & 7 RCT overlap).

In tonsillectomy only, IV dexmedetomidine 0.15–2 mcg/kg (intraoperative bolus or over 10 min and in 5 RCTs by infusion: pre, during or post surgery) vs mixed comparators (4 opioid, 10 placebo, 1 no therapy) reduces:

- Postoperative pain scores in PACU (MD-1.82; 95%CI -2.5 to -1.13) (5 RCTs, n=480 [3 placebo, 1 opioid, 1 no therapy]);
- Analgesic requirement in PACU (OR -0.59; 95%CI -0.89 to -0.3) (7 RCTs, n=680);
- The need for rescue overall (OR 0.44; 95%CI 0.26 to 0.73) (11 RCTs, n=1,233); and
- Emergence agitation score in PACU (MD -1.4; 95%CI -2.1 to -0.7) and incidence of EA (OR 0.28; 95%CI 0.21 to 0.36) and severe EA (OR 0.22; 95%CI 0.12 to 0.38) (Cho 2018b **Level I**, 15 RCTs, n=1,552) (3 & 4 RCT overlap).

Compared to intraoperative opioids, IV dexmedetomidine 0.75–4 mcg/kg reduces

- Postoperative pain (RR 0.49; 95%CI 0.25 to 0.94) (3 RCTs, n=234);
- But does not reduce the need for postoperative opioids (RR 0.77; 95%CI 0.6 to 1.1) (4 RCTs, n=394) (Schnabel 2013 **Level I** [PRISMA], 11 RCTs [10 IV, 1 IN], n=874).

Subsequent RCTs or ones not included in the above reviews had similar findings. In tonsillectomy, IV dexmedetomidine 0.3 mcg/kg reduced EA vs propofol 1 mg/kg and both were effective given IV 5 min before surgery cessation vs saline placebo (Cho 2018b **Level I**, 1 RCT: Ali 2013 **Level II**, n=120, JS 5). While, IV dexmedetomidine 1 mcg/kg given 10 min preoperatively vs placebo had similar postoperative pain scores, reduced EA, with lower HR and stable mean blood pressure intraoperatively (10 mmHg lower at all time points) (Sharma 2019 **Level II**, n=60, JS 4).

For myringotomy in children (1–8 y), post induction administration of IN dexmedetomidine 1 mcg/kg vs IN fentanyl 2 mcg/kg, with and without midazolam premedication, achieved similar postoperative pain scores (Dewhirst 2014 **Level II**, n=100, JS 5) .

For strabismus surgery, intraoperative IV dexmedetomidine 1 mcg/kg bolus with 1 mcg/kg/h vs IV ketamine 1 mg/kg bolus with 1 mg/kg/h similarly reduced EA and pain scores on the ward (but not in PACU), with both superior to placebo (Chen 2013 **Level II**, n=84, JS 5).

For cardiac surgery, intraoperative dexmedetomidine infusion 0.5 mcg/kg/h reduced postoperative fentanyl and inflammatory markers of the post surgery stress response, with similar pain scores vs placebo (Sun 2017 **Level II**, n=50, JS 4).

Following scoliosis surgery, postoperative IV dexmedetomidine infusion 0.4 mcg/kg/h (for 24 h) in addition to IV morphine PCA had no effect on morphine consumption or adverse effects (Sadhasivam 2009 **Level III-2**). In ventilated scoliosis patients, IV dexmedetomidine 0.4 mcg/kg/h vs IV midazolam 0.1 mg/kg/h reduced pain scores and modestly reduced low 24 h fentanyl consumption (124 mcg 28 vs 165.8 33) (Aydogan 2013 **Level II**, n=32, JS 4).

Postalveolar bone graft surgery in children, dexmedetomidine 0.2–0.4 mcg/kg/h was administered for <24 h as an alternative to opioid infusion (Lopez 2018 **Level III-3**, n=54). Adjuvant

infusion following craniosynostosis repair is also described (Kattail 2018 **Level IV**, n=4). For a 2 y old child with chemotherapy-induced enterocolitis, adjuvant dexmedetomidine 0.05–0.2 mcg/kg/h coadministration for 5 d improved pain control and allowed hydromorphone infusion reduction (Winton 2011 **CR**).

10.4.8.3 | Adverse effects of alpha-2 agonists

Haemodynamic effects

Hypotension and bradycardia are desirable effects with use of these agents for "controlled hypotension" or blunting of pressor response. Alpha-2 agonists have provided cardiac stability in the setting of paediatric cardiac surgery, intensive care patients (Sottas 2017 **NR;** Gupta 2012 **Level III-2;** Basker 2009 **NR**; Phan 2008 **NR**) and in supraventricular tachycardia eg in neonates and children requiring cardiac surgery (Tobias 2013b **NR**). The haemodynamic effects can be undesirable and are variably reported in RCTs and thus the reviews/meta-analyses.

For systemic clonidine:

RCTs with clonidine 2–5 mcg/kg reported no difference overall in hypotension or bradycardia incidence but interpretation was complicated by the use of atropine pretreatment, with no comments made on the use of corrective interventions (Lambert 2014 **Level I** [Cochrane], 4 RCTs, n=279); two included trials of 2 vs 4 mcg/kg clonidine vs placebo were underpowered to detect a difference for hypotension and bradycardia – defined as a 20% decrease from baseline, which occurred in 10 of 60 clonidine-treated vs 0 of 30 placebo-treated (Mikawa 1996 **Level II**, n=90, JS 4) and hypotension defined as <70 mmHg and bradycardia defined as <60 beats/min occurred in 4 of 30 clonidine-treated and 0 of 15 midazolam-treated (Cao 2009 **Level II**, n=45, JS 3).

For dexmedetomidine, significant change that requires medical intervention occurs uncommonly:

- The two largest reviews of IV administration do not comment on bradycardia and hypotension (Cho 2018b **Level I**, 15 RCTs, n=1,552; Bellon 2016 **Level I** [PRISMA], 14 RCTs, n=1,463) (7 RCT overlap). Two earlier reviews stated no haemodynamic events were reported in the included RCTs (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812; Pickard 2014 **Level I,** 10 RCTs [dexmedetomidine], n=669). One series documented bradycardia (>20% decrease from baseline) in 4% of children who received dexmedetomidine 3 mcg/kg for MRI sedation (Mason 2008 **Level III-2**, n=767 referenced in Pickard 2014 **Level I**, 10 RCTs [dexmedetomidine], n=669);
- One review documents 5 RCTs including haemodynamic outcomes (4 RCTs [placebo], n=180 & 1 RCT [opioid], n=60) where 3 dexmedetomidine recipients had >30% change requiring intervention: 1 received atropine for bradycardia and 2 saline bolus and isoflurane decrease for hypotension (1 RCT [placebo], n=26); while no patients needed rescue treatment for bradycardia in the RCT with opioid comparator (Schnabel 2013 **Level I** [PRISMA], 11 RCTs, n=874).

Sedation and delay to discharge

The sedative effect is often useful and therapeutic in children but may be undesirable if delaying discharge. A few small perioperative studies assessed the outcome of time spent in PACU or delay in discharge.

Clonidine RCTs conflict regarding time to discharge:

- With delay (WMD 10.8 min; 95%CI 4.2 to 17.5) and increased sedation frequency post discharge vs placebo (Pickard 2014 **Level I**, 1 RCT: Malviya 2006b **Level II**, n=120, JS 5);
- And slightly earlier discharge vs placebo (1 RCT, n=46), with no difference vs midazolam (2 RCTs, n=194) (Lambert 2014 **Level I** [Cochrane], 11 RCTs, n=748).

While following IV dexmedetomidine, minimal clinical impact is reported on:

- Time to extubation (WMD 0.6 min; 95%CI 0.28 to 0.96) (9 RCTs, n=555) and emergence (WMD 1 min; 95%CI 0.4 to 1.6) vs placebo (8 RCTs, n=548) (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812);
- Duration of PACU stay in 3 reviews (1 and 2 RCTs overlap): WMD 4.6 min (95%CI -0.08 to 9.275) vs placebo (3 RCTs, n=256) (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812), SMD -0.37 (95%CI -1.02 to 0.28) vs placebo or control (5 RCTs, n=792) (Cho 2018b **Level I**, 15 RCTs, n=1,552) and 3 min vs placebo (4 RCTs, n=275) (Pickard 2014 **Level I**, 10 RCTs [dexmedetomidine], n=669);
- Time to discharge (2 RCTs, n=92) (Pickard 2014 **Level I**, 10 RCTs [dexmedetomidine], n=669).

Respiratory events

No oxygen desaturation or postoperative respiratory depression was reported for dexmedetomidine treated patients, while 3 children in the placebo group had bronchospasm (Zhang 2014 **Level I** [PRISMA], 12 RCTs, n=812) and one placebo recipient required oxygen supplementation (5 RCTs, n=295) (Schnabel 2013 **Level I** [PRISMA], 11 RCTs, n=874);

Incidents of desaturation post tonsillectomy occurred less in dexmedetomidine treated vs placebo or control (OR 0.40; 95%CI 0.21 to 0.77) (6 RCTs, n=843) (Cho 2018b **Level I**, 15 RCTs, n=1,552).

Neurotoxicity

In contrast to most anaesthetic agents used, neuraxial clonidine has not been implicated in any reports or studies of neural toxicity/apoptosis and neither has epidural or intraperitoneal dexmedetomidine in animal models (Davidson 2013 **NR;** Walker 2012b **NR**). With dexmedetomidine, some changes are seen with direct neural application of high dose in animal studies. In rats who received a single injection brachial plexus block, the addition of dexmedetomidine 60 mcg/kg to ropivacaine 0.5% reduced inflammatory cytokine (TNF-α and IL-6) amounts in the nerves vs saline (n=15) (Kang 2018 **BS**, n=39). While administration of high dose (60 mcg/kg) alone increased the inflammatory cytokine (including caspase 3, an important apoptosis protease) amounts in the nerves of d 5 rat pups (neonatal equivalent), while moderate dose (20 and 40 mcg/kg) did not in either d 5 or d 14 (child equivalent) rat pups (n=24). In rabbits who received a femoral nerve CPNC infusion (for 72 h), the addition of dexmedetomidine 3 mcg/mL to ropivacaine 0.25% was associated with myelin lamellar structure changes; not seen with 1-2 mcg/mL added to ropivacaine, ropivacaine alone or normal saline (Wang 2019b **BS**, n=30). While, pre-emptive intraperitoneal administration of dexmedetomidine ameliorated the effect of intrathecal administration of toxic doses of 10% lidocaine in rats (an effect that was reversed by intraperitoneal injection of yohimbine or a specific protein kinase C inhibitor) (Xu 2018a **BS**, n=64). The neuroprotective effect of dexmedetomidine in brain injury is not discussed here.

KEY MESSAGES

1. Preoperative oral clonidine reduces postoperative pain scores and analgesic requirement in children compared to placebo or midazolam but not fentanyl (**U**) (**Level I** [Cochrane Review]).
2. Preoperative oral clonidine reduces postoperative nausea and vomiting in children compared to placebo or midazolam (**U**) (**Level I** [Cochrane Review]).
3. Preoperative intranasal dexmedetomidine reduces postoperative pain scores, rescue analgesic requirements and emergence agitation with minimal adverse effects vs placebo (**N**) (**Level I** [PRISMA]) and mixed comparators (**N**) (**Level I**).
4. Intraoperative dexmedetomidine reduces postoperative pain scores (**U**) (**Level I** [PRISMA]) and need for postoperative rescue analgesia (**Q**) (**Level I**) including opioid (**U**) (**Level I** [PRISMA]) in children compared to placebo, with minimal impact on time to discharge (**N**) (**Level I** [PRISMA]) via intravenous (**S**) (**Level I** [PRISMA]) and intranasal routes (**S**) (**Level I**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Alpha-2 agonists offer benefits in addition to analgesia in children in the perioperative, intensive care and procedural settings. These benefits include anxiolysis, sedation (MAC sparing), behavioural modification, prevention or treatment of opioid withdrawal (facilitating opioid weaning) (**U**) and reduction of emergence agitation (**S**).

10.4.9 | Alpha-2-delta ligands (gabapentinoids)

There is increased off licence use of alpha-2-delta ligands in children following the adult experience in various pain states; paediatric data to support this is heterogeneous and limited (Egunsola 2019 **Level III-3 SR** [PRISMA], 7 RCTs, n=379). The meta-analysis includes the small studies quoted below. They demonstrate efficacy for multi-day perioperative but not single preoperative dosing.

Multi-segment scoliosis surgery

A single preoperative dose of gabapentin 600mg (≈11 mg/kg) did not reduce opioid consumption over 24 h vs placebo (Mayell 2014 **Level II**, n=35, JS 5).

Gabapentin over 5 d (15mg/kg preoperatively then 15mg/kg/d) reduced total morphine consumption in PACU, postoperative day (POD) 1 and 2 by 16-23% and pain scores in PACU and the first postoperative morning only, with no differences in other outcomes vs placebo (Rusy 2010 **Level II**, n=59, JS 3).

Gabapentin over 3 d (5–10mg/kg preoperatively then 7.5–22.5mg/kg/d [max 900 mg]/d) reduced:

- POD 1–3 pain scores and opioid use POD 1–2 (Trzcinski 2019 **Level III-2**, n=129);
- The time required to meet physical therapy goals, but not length of stay [LOS] (Thomas 2018b **Level III-3**, n=101); and
- POD 1 (but not day of surgery) PCA opioid consumption by 40%, alone and in combination with transdermal clonidine, with earlier PO intake, ambulation and for the combination slight clinical impact on LOS (Choudhry 2017 **Level III-3**, n=127).

Other surgery types and conditions

For tonsillectomy, preoperative gabapentin (dose 10-20 mg/kg in the 3 paediatric of 6 RCTs) and pregabalin (2 RCTs: 1 mixed, 1 adult) similarly reduce pain in the first 8 h, analgesic requirements in the first 24 h and PONV without increasing adverse effects (Hwang 2016a **Level I** [PRISMA], 8 RCTs [3 adult, 2 mixed, 3 paediatric], n=608).

In laparoscopic appendicectomy, varying doses of pre and postoperative gabapentin for 3 d (range 4.4–30.4 mg/kg/d) alone or with postoperative ketorolac reduced postoperative opioid consumption for simple and complicated appendicitis with no difference in time to pain score ≤3 or LOS (Baxter 2018 **Level III-2**, n=87).

For the Nuss procedure in adolescents, low dose gabapentin 100–200mg three times daily for 72 h has been used in combination with PCA hydromorphone, clonidine patch and local anaesthetic via wound catheter with similar pain scores to those in thoracic epidural recipients (ropivacaine 0.2% with hydromorphone 10 mcg/mL) (Choudhry 2016 **Level III-3**, n=32).

In children with severe cerebral palsy (Gross Motor Function Classification System [GMFCS] IV–V), gabapentin (7–18 mg/kg/dose or 900mg/d) improved pain (and dystonia) frequency and impact (in patients co-receiving baclofen, diazepam and botulinum injections) (Harvey 2018 **Level IV**, n=11 doctors, 57 patients; Liow 2016 **Level IV**, n=82).

In paediatric burns, in addition to or instead of antihistamines (in inpatient and outpatient settings), alpha-2-delta ligands reduced itch and pain: gabapentin 15 mg/kg/d (prescribed for 53% of patients) (Nieuwendijk 2018 **Level IV**, n=413) and 24–34 mg/kg/d (where 23 patients poorly responded to gabapentin had pregabalin 3.7–6.5 mg/kg/d added) (Kaul 2018 **Level IV**, n=136).

In paediatric oncology, preoperative and therapeutic gabapentin use 900 mg/d for 30 d reduced phantom limb pain incidence at 60 d (43 vs 77%) with similar reduction of early perioperative pain scores vs placebo (Wang 2018 **Level II**, n=45, JS5). Gabapentin 20–40mg/kg/d for phantom limb pain is also described in 3 case series (DeMoss 2018 **NR**). Pregabalin 1.25–2.5 mg/kg/d, as part of a multimodal analgesic regimen, has been used in a 4 y old girl with a severe crush injury requiring foot amputation (Wossner 2017 **CR**).

In vincristine induced painful peripheral neuropathy (used for solid tumours and leukaemia), 8 weeks of pregabalin 150-300 mg (4–5.7 mg/kg)/d decreased mean pain score by 59% from baseline with dose dependent effect (Vondracek 2009 **Level IV**, n=30). Gabapentin 15–70 mg/kg/d pre-emptive and therapeutic use is described in a larger series of leukaemic patients (Anghelescu 2011b **Level IV**, n=112 [gabapentin-treated]).

In children with chronic pain from fibromyalgia and CRPS type 1, alpha-2-delta ligands have been used with some benefit (Cooper 2017c **Level I** [Cochrane], 2 RCTs, n=141) as well as in painful restless legs syndrome (Frenette 2011 **NR**).

The use of alpha-2-delta ligands in prevention of chronic postsurgical pain in children has not been studied.

For alpha-2-delta ligands use in adults, see Sections regarding efficacy in acute 4.8.1.1 and chronic pain 4.8.2.1, and Section 1.4.6.3 for prevention of chronic postsurgical pain.

KEY MESSAGES

1. Multi-day perioperative (but not single preoperative) gabapentin dosing reduces postoperative morphine consumption vs placebo following multilevel posterior spinal fusion for adolescents with idiopathic scoliosis (**N**) (**Level II**).
2. Multiday perioperative gabapentin reduces phantom limb pain incidence vs placebo in paediatric oncology amputation surgery (**N**) (**Level II**).
3. Preoperative gabapentin and likely pregabalin improve analgesia after tonsillectomy in children and reduce PONV without increasing adverse effects (**N**) (**Level I** [PRISMA]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Alpha-2-delta ligands use in children for acute (and chronic) pain conditions is expanding based mostly on expert opinion and case series. The pain indications are similar to those for adults with similar benefit and adverse event profiles (**N**).

☑ Gabapentin and pregabalin are used to manage pruritus and neuropathic pain following burn injury in children (**N**).

☑ The use of alpha2 delta ligands for the prevention of chronic postsurgical pain in children has not been studied (**N**).

10.4.10 | Corticosteroids

Systemic corticosteroids

The impact of systemic corticosteroid use on various outcomes in children post-surgery or with acute pharyngitis has been assessed; for data on corticosteroid use in combination with local and regional techniques see paediatric Section 10.6.2.6. See also Section 4.12.1 for use of systemic corticosteroids in adults.

10.4.10.1 | Efficacy in painful medical conditions

Pharyngitis/Sore throat

For pharyngitis (proven bacterial or severe symptoms) presenting in the primary care or emergency department setting, PO dexamethasone 0.6 mg/kg (max 10 mg) achieved onset of analgesia 5–24 h earlier than placebo (measured with three different scoring systems), with a single dose as effective as a 3 d course (Sadeghirad 2017 **Level I**, 3 RCTs [paediatric], n=393) (see Section 8.6.7.5 for adult data which includes information on steroid, as well as antibiotic and topical treatments). Data is not available for systemic corticosteroid administration for post extubation sore throat in children.

Septic arthritis

In low quality RCTs, 4 d of dexamethasone 0.15–0.2mg/kg 6–8 h reduces the number of days of IV antibiotic treatment (MD -2.77; 95%CI -4.16 to -1.39) (Delgado-Noguera 2018 **Level I** [Cochrane], 2 RCTs, n=149). At 12 mth follow-up, dexamethasone may increase the proportion of patients without pain (RR 1.33; 95% CI 1.03 to 1.72) (1 RCT, n=49) and with normal function of the affected joint (RR 1.32; 95% CI 1.12 to 1.57) (1 RCT, n=100). Small study numbers limit the capacity to assess serious adverse effects.

Henoch-Schonlein Purpura and abdominal pain

In case series and retrospective analyses only of patients with Henoch-Schonlein Purpura [HSP] and abdominal pain, corticosteroids reduced pain, usually within 24 h (Haroon 2005 **NR**). In HSP associated pancreatitis, corticosteroid use (pulsed 2nd daily IV methylprednisolone 10–15 mg/kg/d, followed by PO prednisolone 1 mg/kg/d) for 2–3 wk reduced abdominal symptoms including pain (Zhang 2018 **Level IV**, n=13).

10.4.10.2 | Efficacy in postoperative pain

Dental surgery

Following paediatric dental surgery under general anaesthesia, single-dose IV dexamethasone 0.3 mg/kg (max 8 mg) did not improve pain scores or oral intake but reduced postoperative vomiting (McIntyre 2012 **Level II**, n=200, JS 5).

Strabismus surgery

The combination of single dose IV dexamethasone 0.15 mg/kg and intraoperative superhydration (30 mL/kg/h until oral intake) vs single therapy reduced PONV, pain scores and paracetamol use with increased time to first analgesic request (Sayed 2016 **Level II**, n=120, JS 5).

Knee arthroscopy

In teenagers receiving femoral nerve block, neither adjuvant IM or perineural dexamethasone further improved analgesia (Veneziano 2018 **Level II**, n=77, JS 5).

Adenotonsillectomy

Beneficial effects upon multiple outcomes are reported for single-dose dexamethasone in children 1 d following tonsillectomy (Steward 2011 **Level I** [Cochrane], 19 RCTs, n=1,756). Compared to placebo, IV dexamethasone 0.15–1.0 mg/kg (max 8–25 mg) improved postoperative pain scores (MD -1.1/10; 95%CI -1.7 to -0.4) (8 RCTs, n=652), reduced postoperative vomiting (RR 0.49; 95%CI 0.41 to 0.58) (15 RCTs, n=1,273) and resulted in an earlier return to soft diet (RR 1.45; 95%CI 1.15 to 1.83) (5 RCTs, n=452). A subanalysis to assess dose-dependent effect was not performed. A subsequent systematic review of adult and paediatric RCTs includes RCTs with lower dosing to 0.05 mg/kg and PO and local infiltration routes (see below) (Titirungruang 2019 **Level I**, 64 RCTs [42 paediatric], n=6,327) (16 RCT overlap). This meta-analysis has further comparisons of IV route with comparator arms. There were consistent findings with IV administration preoperatively or at time of induction (in mostly paediatric RCTs, some including adults) reducing pain scores across four time periods of <24 h (22 RCTs, n=1,868), 1 d (19 RCTs, n=1,520), 3 d (6 RCTs, n=346) and 7 d (5 RCTs, n=266) and PONV (OR 0.24; 95%CI 0.18 to 0.33) (35 RCTs, n=3,415).

An RCT, excluded from the 2011 Cochrane review (due to early termination), compared dexamethasone 0.05, 0.15 and 0.5 mg/kg (max 20 mg) and demonstrated a dose-dependent effect for PONV (Czarnetzki 2008 **Level II**, n=215, JS 5). The reason for termination was a dose-dependent increase in bleeding in dexamethasone-treated patients (above those ibuprofen-treated) - see bleeding risk discussion below.

IV dexamethasone 0.5 mg/kg with IV ketamine 0.5 mg/kg reduced pain scores, analgesic requirement and vomiting vs single agent therapy and placebo (Safavi 2012 **Level II**, n=120, JS 4).

IV dexamethasone 0.5 mg/kg (max 16 mg) was compared with infiltration with 2–4 mL LIA (2% lidocaine with 1:400, 000 adrenaline [6 mL], 0.5% bupivacaine [3 mL], 25 mcg fentanyl, 50 mcg clonidine). The LIA group had a lower incidence of PONV, pain on jaw opening and swallowing and reduced analgesic use POD 1–5 (Naja 2017 **Level II**, n=129, JS 5).

Following paediatric tonsillectomy, multiday PO prednisolone 0.25–0.5mg/kg (max 10-20 mg/d) for 5–7 d did not reduce PONV, or pain at POD 3 or 7 (3 RCTs, n=441) (Titirungruang 2019 **Level I**, 3 RCTs [prednisolone], n=441).

In comparison with ibuprofen for 4 d (where patients co-received paracetamol for 7 d), adjunctive PO prednisolone for 7d was inferior in pain relief, rescue analgesic use, PONV, sleep and oral intake (Aveline 2015 **Level III-3**, n=1,231). Alternate day therapy with PO dexamethasone in addition to ibuprofen and paracetamol reduced phone calls regarding pain and haemorrhage (Redmann 2018 **Level III-3**, n=1,200).

10.4.10.3 | Bleeding risk post-tonsillectomy

Five systematic reviews of dexamethasone have included the above early terminated RCT and have qualified the issue of bleeding (Titirungruang 2019 **Level I**, 64 RCTs [42 paediatric], n=6,327; Plante 2012 **Level I**, 29 RCTs [19 paediatric], n=2,674; Shargorodsky 2012 **Level I**, 12 RCTs [paediatric], n=1,180; Geva 2011 **Level I**, 14 RCTs [11 paediatric], n=1,429; Bellis 2014 **Level III-1 SR**, 15 RCTs, n=1,693 and 3 studies, n=2,088) (4 to 14 RCTs overlap). The included studies assess haemorrhage as primary or secondary, requiring readmission, transfusion or reoperation and with 6 h to 14 d follow-up. The largest review of RCTs reports an overall bleeding rate of 4.4% (Plante 2012 **Level I**, 29 RCTs [19 paediatric], n=2,674). Dexamethasone does not increase the overall risk of bleeding post tonsillectomy (OR 0.96; 95%CI 0.66 to 1.40 for pooled adult and paediatric data, results comparable regardless of age). However, reoperation for bleeding is increased in children (OR 3.43; 95%CI 1.29 to 9.13) (8 RCTs, n=679), but not in adults (4 RCTs, n=499). The most recent meta-analysis reports no increased odds for either primary (15 RCTs, n=1,740) or secondary haemorrhage (23 RCTs, n=2, 440) (Titirungruang 2019 **Level I**, 64 RCTs [42 paediatric], n=6,327). A retrospective US paediatric cohort study found statistical, but minimal clinical difference in revisits for bleeding in 30 d postoperatively in dexamethasone vs non-dexamethasone treated (3.1 % vs 2.7, difference 0.4 %; 95% CI 0.13 to 0.67) with a small increase risk seen across three age strata (Mahant 2014 **Level III-2**, n=139,715 [97,242 dexamethasone treated]). A subsequent retrospective review with a prevalence of 2.8% secondary haemorrhage did not find a relationship of haemorrhage to dexamethasone (assessed with linear and quintile dose models) (Yiu 2017 **Level IV**, n=9,843). Older age (OR 1.08) and a primary haemorrhage (OR 2.89) were predictors (See Section 10.4.2 Nonselective NSAIDs where age and chronic tonsillitis as the indication for surgery are predictors).

10.4.10.4 | Non-systemic corticosteroids

See Sections 10.6.2.6 for adjuvant use including infiltration, 10.6.5 for topical application and 10.6.6 for comparator use in nerve blocks for tonsillectomy.

KEY MESSAGES

1. Single dose intravenous dexamethasone reduces pain post tonsillectomy, postoperative vomiting and time to soft diet commencement in children (**U**) (**Level I** [Cochrane Review]).
2. Intavenous dexamethasone does not increase the overall risk of bleeding post tonsillectomy but increases the risk of reoperation for bleeding in children (S) (**Level I**).
3. Oral dexamethasone (given in addition to antibiotics) shortens the time to onset of pain relief in pharyngitis in children (**U**) (**Level I**).
4. Oral prednisolone multiday course post tonsillectomy does not reduce pain outcomes at day 3 or day 7 or postoperative nausea and vomiting (**N**) (**Level I**).

10.4.11 | Systemic lidocaine infusions

Systemic lidocaine infusions are used in the paediatric setting for patients experiencing severe refractory pain. As per many analgesic interventions, this has been extrapolated from practice in adults (See Section 4.4.1.1). Paediatric hospital guidelines have been created based upon adult dosing (RCH 2017 **GL**)

In young children <6 y having laparoscopic inguinal hernia repair, intraoperative IV lidocaine 1.5mg/kg and 1 mg/kg/h (17 mcg/kg/min) reduced PACU pain scores vs placebo (Lee 2019 **Level II**, n=66, JS 5).

In young children <6 y having abdominal surgery, IV lidocaine (initial 1.5mg/kg and infusion 1.5mg/kg/h (25mcg/kg/min) for <6 h) vs placebo reduced postoperative fentanyl requirement on POD 1 and 2, time to return of bowel function 19 vs 23 h and hospital stay by 2 d (El-Deeb 2013 **Level II**, n=80, JS 5). Plasma concentrations at 0.5 and 4 h were ≈3 mcg/mL.

For various surgeries (including spinal fusion, Nuss surgery and nephrectomy) in older children (median age 14 y), perioperative IV lidocaine infusion ≈0.86 mg/kg/h (14.4 mcg/kg/min) for 31 22 h has been used (Lemming 2019 **Level IV**, n=50). This study did not provide detail of the patients' multimodal analgesic therapy; adverse events were experienced by 22% of patients (at various rates of 0.53−1.26 mg/kg/h (8.8−21 mcg/kg/min)), with discontinuation in 9% and dose reduction in 4%.

See also Sections 10.8.1, 10.9.3 and 10.9.5 where similar and higher dosing have been used in paediatric cancer pain, migraine and sickle cell disease respectively.

KEY MESSAGES

1. Perioperative intravenous lidocaine infusion in abdominal surgery in children improved various pain and non-pain related postoperative outcomes (**N**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Dosing of perioperative lidocaine infusions have been extrapolated from use in adults and pharmacokinetic study is warranted to determine safe dosing practices in children (**N**).

10.5 | Opioid infusions and Patient Controlled Analgesia (PCA) in children

This section incorporates the techniques of parenteral administration of opioids to children via continuous infusion and patient controlled analgesia (PCA) devices, including a subsection on nurse-controlled and parental proxy. As intermittent intramuscular (IM) injections are distressing for children, parenteral administration via the intravenous (IV) route is preferred; if peripheral perfusion is normal, the subcutaneous (SC) route can be used (McNicol 1993 **Level IV**) with similar safety and efficacy to the IV route (Doyle 1994a **Level II**, n=60, JS 3). Procedure-specific dose recommendations and evidence for the use of these parenteral techniques have been published (APAGBI 2012 **GL**). Large-scale audits (of >10,000 children) provide data for serious clinical incidents and adverse effects associated with the use of these parenteral opioid techniques (see individual subsections and Section 10.5.5 Overall safety at the end of this section).

10.5.1 | Opioid infusions

10.5.1.1 | Pharmacokinetics of opioid infusions

Pharmacokinetic data has provided support for age-adjusted weight-based initial dosing recommendations for morphine infusion for postoperative pain: 10 mcg/kg/h in neonates, 15 mcg/kg/h in toddlers and 25 mcg/kg/h in children >5 y (Taylor 2013 **Level IV PK**); 10–40 mcg/kg/h are standard postoperative ward order parameters (APAGBI 2012 **GL**). Titration and observation of effect is the key as there is wide between subject variability with further impact of critical illness (Anderson 2014b **NR PK**). In ventilated children after cardiac surgery, PKs of morphine have been assessed (Valkenburg 2016 **Level III-2 PK**, n=38). Requirements were similar in children with and without Down's syndrome: 32 mcg/kg/h guided by COMFORT B and observer-NRS scoring. Body weight was the most predictive covariate; while Down's syndrome was not.

10.5.1.2 | Efficacy of opioid infusions

Differences between intermittent bolus doses and continuous infusion of opioid relate more to the total dose than to the administration method (Lynn 2000 **Level III-2**). Comparison in neonates and young infants of the same total dose of morphine given via infusion (10 mcg/kg/h) or bolus (30 mcg/kg every 3 h) found no difference in pain scores (COMFORT and observer VAS) (Bouwmeester 2003a **Level II**, n=68, JS 3; van Dijk 2002 **Level II**, n=181, JS 4) or stress response to surgery (Bouwmeester 2001 **Level II**, n=204, JS 4). However, these doses were inadequate in children aged 1–3 y, in whom additional bolus doses were required and the 3 h interval was less effective (possibly due to more rapid clearance) (van Dijk 2002 **Level II**, n=181, JS 4).

In ventilated postsurgical neonates, various morphine infusion regimens have been used ranging from 2.5–5 mcg/kg/h (Ceelie 2013 **Level II**, n=71, JS 5) to 10–30 mcg/kg/h (Olischar 2014 **Level II**, n=71, JS 5; Anand 2008 **Level II**, n=1,773, JS 5). Fentanyl has been increasingly used in PICUs; seven centres varied widely in terms of initial opioid choice (fentanyl 64% vs morphine 36%) and dosing with peak infusion rates of 0.1–16 mcg/kg/h over a 14 d study period (converting morphine rates to fentanyl equivalents using 1:80 dose ratio) (Anand 2013b **Level IV**, n=419 [half postsurgical]). For control of acute procedural pain in ventilated neonates, continuous opioid infusions have limited efficacy (Anand 2008 **Level II**, n=1,773, JS 5). Bolus opioid administration (eg

fentanyl) (Ancora 2013 **Level II**, n=131, JS 5) and other analgesic interventions are recommended (APAGBI 2012 **GL**) (see also Section 10.4.1).

Following ureteroneocystostomy, fentanyl loading of 1 mcg/kg and then infusion 0.17 mcg/kg/h was effective, although patients who received continuous ketorolac infusion experienced less frequent bladder spasms (Jo 2011 **Level II**, n=52, JS 5).

10.5.1.3 | Adverse effects, complications and outcomes of opioid infusions

Major adverse events

A prospective multicentre audit has reported use of opioid infusions in children (Morton 2010 **Level IV**, n=1,955 [infusions]). This audit reports only two cases of respiratory depression in association with continuous opioid infusion, one requiring naloxone. Sedation scores, oxygen saturations and oxygen administration data were not collected. Programming or prescription errors were the most common reported incidents with continuous opioid infusions (n=9), none of which led to patient harm (see also Section 10.5.2.3 for errors with PCAs).

Opioid infusions in neonates and later neurodevelopmental impact

The impact of the routine use of morphine infusion in ventilated neonates on neurodevelopmental and other outcomes has been studied and remains of concern (Anand 2004 **Level II**, n=898, JS 4). A meta-analysis found no differences in mortality, duration of ventilation, or improvements in short or long term neurological outcomes; but the analysed outcomes were assessed by small, heterogeneous and usually single trials of low quality including 3 RCTs that enrolled preterm and term neonates (Bellu 2008 **Level I** [Cochrane], 13 RCTs, n=1,505).

Detrimental effects of prolonged sedation and/or analgesia on preterm neonates have also been a research focus (Anand 2004 **Level II**, n=898, JS 4; Anand 1999 **Level II**, n=67, JS 5). A 5 y follow-up of very preterm neonates found morphine and sedative exposure for >7 d was associated with poor neurodevelopmental outcome; this association was abolished once adjusted for gestational age and propensity scores (Roze 2008 **Level III-2**, n=1,572). A second author group assessed long term outcomes of expreterm infants who were ventilated and participants in a dual centre RCT comparing continuous morphine infusion 10 mg/kg/h for <7 d vs placebo (Simons 2003 **Level II**, n=150, JS 4). At 5 y follow-up, they suggested a negative association with morphine use and the "visual analysis" intelligence quotient subtest, after adjusting for propensity scores (de Graaf 2011 **Level II**, n=90, JS 4). While at 8 y follow-up, no overall harm was found with positive effects of low-dose infusion 10 mcg/kg/h on higher executive function (WISC-III; de Graaf 2013 **Level II**, n=89, JS 4) and no adverse effects on thermal detection or pain thresholds (assessed with quantitative sensory testing (QST); vs 28 contemporary controls), chronic pain incidence or overall neurological functioning (assessed by physical examination) (Valkenburg 2015 **Level II**, n=89 JS 4). At 2 y follow-up, expreterm toddlers, who as neonates were mechanically ventilated (mostly for lung indications) and received fentanyl infusion 1 mcg/kg/h (and boluses), had worse hand eye coordination vs placebo infusion and fentanyl boluses (Ancora 2017 **Level II**, n=78, JS 5).

As studies vary in the degree and manner of correction for confounding factors, follow-up at a later age focusing on higher-order neurocognitive function is necessary, ideally in a larger cohort.

Subacute opioid tolerance

Administration of parenteral opioids for as little as 5–7 d can produce opioid tolerance/dependence. See Section 10.4.6 for discussion of opioid dependence, tolerance and withdrawal in children, Section 10.4.7 for use of ketamine and 10.4.8 for use of alpha-2 agonists for use in withdrawal, as well as the relevant adult Section 9.7.

10.5.2 | Patient-controlled analgesia (PCA)

PCA can provide safe and effective analgesia for children aged as young as 5–6 y and compares favourably with continuous morphine infusion (Morton 2010 **Level IV** n=5,605 [PCA] & 1,955 [infusion]). PCA (and NCA) have been used for 2 decades in children (in 2016 at a single centre: most commonly morphine 72%, hydromorphone 28% and rarely fentanyl 1% postoperatively) (Donado 2019 **Level IV**, n=32,338 [22 y]).

Patient selection is important and depends on the ability of the child and carers to understand the concepts of PCA and the availability of suitable equipment and trained staff.

10.5.2.1 | Efficacy of PCA

Compared with continuous IV opioid infusions, opioid PCA provided greater dosing flexibility, and similar analgesia. PCA has been associated with higher opioid consumption but the incidence of adverse effects has varied, depending on the PCA dosing parameters (Peters 1999 **Level II**, n=47, JS 3; Bray 1996 **Level III-2**). PCA vs non-PCA techniques result in lower pain scores 9–10/100 over 24–48 h, higher opioid consumption (7 mg ME) and pruritus, with similar incidence of other adverse events (McNicol 2015 **Level I** [Cochrane], 49 RCTs [1 paediatric], n=3,412). The only paediatric study compared PCA bolus alone vs PCA bolus with background 15 mcg/kg/h for orthopaedic surgery found equal efficacy but greater acceptability vs IM morphine (McNicol 2015 **Level I** [Cochrane], 1 RCT: Berde 1991 **Level II**, n=99, JS 3).

PCA can be particularly useful in children with altered opioid requirements. In children with sickle cell disease, postoperative PCA morphine requirements were almost double those of non-sickle children (Crawford 2006a **Level III-3**). Morphine PCA with bolus and background (mean rate 20 mcg/kg/h) has been used for paediatric sickle cell patients (Jacob 2008 **Level IV**). Opioid PCAs have been used by children with cancer including during their terminal phase and at home (Anghelescu 2015b **Level IV**, n=45 [69 PCAs]; Anghelescu 2015c **Level IV**, n=28 [44 PCAs]; Mherekumombe 2015 **Level IV**, n=33); see also sections 10.8.1.2 and 10.8.3.1 re pain management in children with cancer.

Following scoliosis surgery, morphine and hydromorphone by PCA have been used (McDonnell 2012 **Level III-3;** Matava 2014 **Level IV;** Milbrandt 2009 **Level III-3**; Ravish 2012 **Level III-3**). A high early PCA demand ratio predicts higher pain scores, 24 h morphine consumption (Matava 2014 **Level IV**) and the need to rotate to hydromorphone (McDonnell 2012 **Level III-3**). Intraoperative remifentanil was associated with an increase in PCA morphine requirement in the 24 h post scoliosis surgery (Crawford 2006b **Level II**, n=30, JS 5), possibly due to acute opioid tolerance or opioid-induced hyperalgesia.

Following pectus excavatum surgery, PCA morphine and hydromorphone have been compared to epidural analgesia with minimal advantage of epidural analgesia with regard to pain scores and no other differences (Stroud 2014 **Level III-3 SR**, 6 studies, n=403) (see also Section 10.6.2). PCA morphine with ketoprofen vs placebo has been trialled (Rugyte 2007 **Level II**, n=31, JS 5) and morphine by PCA was similarly effective to morphine by continuous infusion (Rugyte 2010 **Level III-3**). In addition to thoracic epidural infusion, paracetamol and ibuprofen, PCA (mostly morphine; rotated to fentanyl in 7.4% of patients for side effects of PONV and pruritus) has been used for a mean of 3 d with low POD 1 pain scores at rest (median 2 [IQR 2–3]) (Frawley 2016 **Level IV**, n=217).

Post tonsillectomy, PCA morphine 20 mcg/kg vs tramadol 0.2 mg/kg bolus were similarly effective for 24 h (Ozalevli 2005 **Level III-1**).

For ureteroneocystostomy or pyeloplasty, PCA (and NCA) opioid has been compared with intrathecal (IT) morphine (mean dose 4.4 mcg/kg) bupivacaine (Putnam 2015 **Level III-2**, n=128). Overall pain scores were low; PCA/NCA patients required earlier and more systemic opioids with less pruritus and constipation. In the IT group, the technique failed in 7 patients and 2 patients required naloxone, with one requiring ICU admission.

Post appendicectomy, PCA opioid was used for laparoscopic (49%) and open operations; pain was improved by combination with diclofenac (Ousley 2016 **Level IV**, n=649 [552 PCA]).

Post neurosurgery in children aged 7–12 y, PCA fentanyl, morphine and tramadol were effective with similarly low pain scores and less ibuprofen and morphine rescue vs placebo PCA (Xing 2019 **Level II**, n=320 [195 PCA], JS 5).

Fentanyl is a useful alternative opioid via PCA, particularly for patients with renal impairment or those experiencing morphine-related adverse effects (Tobias 1992a **Level IV**). Fentanyl PCA has been used safely and effectively following neurosurgery (Chiaretti 2008 **Level IV**), pectus excavatum surgery (Butkovic 2007 **Level IV**) and for acute cancer-related pain (Ruggiero 2007 **Level IV**) (see also Section 10.8).

Oxycodone PCA use in children is not reported to date; although paediatric centres are including prescription recommendations in their pain management guidelines (CHW 2019 **GL**; CHI 2019 **GL**).

As in adults, the use of pethidine should be discouraged in the paediatric setting (Benner 2011 **NR**). Pethidine does not have any advantage over other opioids and neurotoxicity from norpethidine (normeperidine) accumulation has been reported in a healthy adolescent (Kussman 1998 **CR**) (see also Section 4.3.1.2).

See also Section 10.4.7.1 for the paediatric literature of ketamine addition to PCA opioid.

10.5.2.2 | PCA prescription

A survey of paediatric anaesthetists in the USA found significant variation in standard prescribing practices for PCA (Nelson 2010 **Level IV**, n=294). Worldwide, morphine is the medicine used most frequently in paediatric PCA. A bolus dose of morphine 20 mcg/kg is a suitable starting dose (APAGBI 2012 **GL**) and is associated with improved pain scores during movement vs 10 mcg/kg (Doyle 1994b **Level II**, n=40, JS 3).

The addition of a background infusion is more common in children than adults, tends to be reserved for more painful surgeries or conditions such as scoliosis and mucositis, and may be time limited postoperatively eg first 12–48 h or to night-time only. Morphine 0–4 mcg/kg/h is recommended (APAGBI 2012 **GL**). Higher background rates are also prescribed (Nelson 2010 **Level IV**, n=294 [surveyed anaesthetists]). Although use of a background infusion was associated with increased sleep disturbance in one audit (calculated from the number of hours PCA presses were required; OR 0.19), numbers were too small to fully investigate the contribution of the kind of surgery (Kelly 2006 **Level IV**, n=126). Background infusions added to PCA of morphine 4–20 mcg/kg/h in children aged 5–20 y showed no difference in pain scores at 12 and 24 h after surgery (5 RCTs, n=203), total opioid consumption (WMD 2.58; 95% CI −2.77 to 7.93) (7 RCTs, n=338) and improved sleep duration (3 RCTs, n=165), with no difference in the number of night-time awakenings (median of 3 per night in both bolus only vs bolus and background 20 mcg/kg/h groups) (1 RCT, n=42) (Hayes 2016 **Level I SR**, 7 RCTs, n=338).

Morphine PCA 20 mcg/kg bolus with 5–20 mcg/kg/h background infusion has been used for children >7 y having laparoscopic appendectomy (Liu 2013 **Level IV**).

Surveyed anaesthetists reported fentanyl bolus prescriptions of 0.2–0.4 mcg/kg and hydromorphone of 1–3 mcg/kg (with similar background infusion rates) (Nelson 2010 **Level IV**, n=294).

Hydromorphone was dosed in a paediatric series as IV PCA 3 mcg/kg boluses and had similar efficacy and adverse effect profile to morphine 15 mcg/kg boluses (Karl 2012 **Level III-1**). IV Hydromorphone PCA 2 mcg/kg bolus with 2 mcg/kg/h background has been compared with PCEA bupivacaine/hydromorphone in scoliosis surgery (Gauger 2009 **Level II**, n=38, JS 3).

10.5.2.3 | Adverse effects, complications and outcomes of PCA

Recognition of potential complications of PCA use was enhanced by providing set instructions for monitoring and by APS support (Wrona 2007 **Level III-2**). Audit and administrative analysis has provided outcome data for this specialised technique (outlined below and also see Section 10.5.5).

PCA preparation, programming errors and device problems

Some adult hospitals have moved to pre-prepared syringe purchase for infusion and PCA administration. While in paediatric centres, clinical staff generally remain responsible for preparation of weight-based dosing in fixed syringe sizes, where 1–2 mL is then the standard bolus size. An evaluation of syringe preparation in a single centre revealed excess syringe volumes and deviations from stated label strength: usually in excess, with 21% of deviations >20% (Rashed 2016 **Level IV**, n=153 [syringe preparations]).

Programming error data (from a referenced tertiary adult centre report) has highlighted the contribution of human factors such as nursing task interruption (Ocay 2018 **NR**). Errors occurred infrequently: human programming 0.74% and device related 0.19%. Pump misprogramming had serious consequences such as respiratory depression, over sedation or poorly treated pain. The above Canadian paediatric centre has moved to staged implementation of standardised morphine PCA (and NCA) concentrations based on weights of 3 mg (≤3.9 kg), 10 mg (4 to 19.9 kg) and 50 mg (≥20–25 kg) in 50 mL and found this has eliminated preparation errors and reduced setup time (preparation and pump programming) and changed the PCA incidents from confusion with or wrong dose to expiry date issues (Rashed 2019 **Level III-2**, n=175 syringes [157 children]).

Impact of background infusion addition to PCA in children

A meta-analysis reports that the addition of a background infusion increases the odds for respiratory depression in adults (see Section 6.4.3), but not in children (George 2010 **Level I**, 14 RCTS, n=796 [3 paediatric, n=122]). A subsequent meta-analysis of low quality RCTs of mostly children (5–20 y) comparing PCA alone vs PCA with background infusion showed no difference in adverse effects of PONV (18.8% vs 27.6: RR 1.2; 95% CI 0.8 to 1.8) (5 RCTs, n=239) or sedation (0 vs 8.5%: RR 3.5; 95% CI 0.4 to 29.3) (2 RCTs, n=81) (Hayes 2016 **Level I**, 7 RCTs, n=338) (3 RCT overlap).

Major adverse events

A large UK audit has included prospective data for PCA (Morton 2010 **Level IV**, n=5,605 [PCA]). No incident of permanent harm occurred, with a very low incidence (approximately 1 in 500) of "harm with full recovery", including respiratory depression requiring naloxone (n=1), urinary retention (n=4), nausea/vomiting (n=5) and itch (n=3). Sedation scores were not collected. These adverse effects were defined by "requiring cessation of or change in technique", which explains why rates were lower than reported in case-control series and RCTs. Seven programming and prescribing errors that did not lead to harm were also reported.

Administrative data analysis of morphine recipients for non-surgical and surgical indications in 42 USA hospitals demonstrated a low incidence of interventions for PCA patients (Faerber 2017 **Level III-2**, n=62,959 [PCA]); see below for detail of matched comparison with IV morphine recipients).

Nausea and vomiting

Nausea and vomiting occurs in 30–45% of children using morphine PCA and can be reduced by prophylactic antiemetics (Carr 2009 **GL**). Adding antiemetics directly to PCA solutions for children was not effective (Munro 2002 **Level II**, n=60, JS 5).

Pruritus

Addition of a low-dose naloxone infusion 0.25 mcg/kg/h did not impair analgesia but decreased pruritus and nausea in postoperative children treated with PCA (Maxwell 2005 **Level II**, n=46, JS 5). Naloxone 1 mcg/kg/h more effectively decreased pruritus than 0.25 mcg/kg/h in children requiring morphine infusions during a sickle cell crisis (Koch 2008 **Level IV**). The suggested optimal dose of IV naloxone by continuous infusion (determined by up titration from 0.05 to 1.65 mcg/kg/h) is ≈1 mcg/kg/h (Monitto 2011 **Level IV**, n=59). Addition of naloxone to morphine PCA with background infusion (ratio 12 mcg: 1 mg) did not reduce pruritus incidence vs morphine PCA alone (22% vs 36: difference -15%; 95% CI -33 to 4) (West 2015 **Level II**, n=92, JS 5).

Escalation of PCA use as a sign of compartment syndrome

Compartment syndrome in children occurs infrequently (1.3–3%), usually diagnosed at a mean of 19 h (range 1.5–65 h) post fracture or surgery of the limb (Ferlic 2012 **Level IV**, n=1,028). Pain as one of the "5 P hallmarks" can be further qualified as pain escalation at rest as well as with passive movement, unrelieved by plaster splitting and with increased analgesic request. Escalation in PCA demands may occur, as reported in two paediatric patients (Yang 2010 **Level IV**). See also later discussion regarding compartment sydrome and regional use in children 10.6.1.3.

10.5.3 | Nurse-controlled analgesia

In younger children and infants, "PCA" devices have been used by nurses to administer intermittent bolus doses (with or without a background infusion), a technique termed "nurse-controlled analgesia" (NCA). This technique may increase ease of administration particularly prior to movement or procedural interventions, increase dose flexibility and improve parent and nurse satisfaction. Dose recommendations for morphine are generally 5–40 mcg/kg/h with 10–20 mcg/kg nurse-initiated boluses (Howard 2010 **Level IV**, n=10,000). NCA has also been used in older children in intensive care who are unable to activate a conventional PCA device.

10.5.3.1 | Efficacy of NCA

Adequate analgesia comparable to PCA was reported but efficacy was dependent on accurate nurse assessment of pain (Weldon 1993 **Level III-2**). The technique has been used in open vs laparoscopic Nissen fundoplication surgery (McHoney 2011 **Level II**, n=39, JS 5) and for fast-track cardiac surgical patients (Iodice 2011 **Level IV**). In intubated patients post cardiac surgery, tramadol NCA in comparison to morphine NCA provided minor improvements in time to extubation (Chu 2006 **Level II**, n=40, JS 4). In intubated children post cardiac surgery, fentanyl NCA and remifentanil NCA (both with background) achieved similar pain and sedation scores, with less side effects but greater bolus requirement in the remifentanil treated (Xiang 2014 **Level III-1**, n=60). Post neurosurgery, NCA fentanyl, morphine and tramadol were effective with similarly low pain scores and less ibuprofen and morphine rescue required vs placebo NCA in children aged 1–6 y (Xing 2019 **Level II**, n=320 [192 NCA], JS 5).

In young children (<2 y) post ureteroneocystostomy, fentanyl NCA with paracetamol (or placebo) has been used (Hong 2010 **Level II**, n=63, JS 5).

10.5.3.2 | Adverse effects, complications and outcomes of NCA

Major adverse events

The incidence of adverse effects was similar in children self-administering conventional PCA and those receiving NCA (Voepel-Lewis 2008 **Level III-2**, n=302; Morton 2010 **Level IV**, n=3,706 [NCA]). Rescue events (requiring naloxone, airway management or admission to high dependency/ICU) were more common in the NCA (and parental proxy) group but this group was also younger and had a higher prevalence of comorbidities (Voepel-Lewis 2008 **Level III-2**). Cognitive impairment and high opioid dose requirements on d 1 were associated with increased adverse effects. Two large prospective audits in institutions with APS oversight affirm NCA use (mostly morphine) as safe and effective for postoperative analgesia in children (Howard 2010 **Level IV**, n=10,000; Morton 2010 **Level IV**, n=3,706 [NCA]). The multicentre 2007–2008 UK audit reports one incident of harm overall, which was with the NCA technique (cardiac arrest in a 2.5 kg neonate), and eleven respiratory depression events (0.3%) with "harm but full recovery", six requiring naloxone (Morton 2010 **Level IV**, n=3,706 [NCA]). The single centre 1996–2008 audit reports no deaths but a similar rate of 0.4% for serious potentially life-threatening events of oversedation or respiratory depression requiring active resuscitation and naloxone (Howard 2010 **Level IV**, n=10,000). This audit provided rates for respiratory depression and sedation at 4.5% (with 91% improving with temporary cessation or adjustment of technique), PONV 25% (severe for 14%) and pruritus 9.4% (severe for 4%). The incidences varied with age, morphine dose and type of surgery. Notably both audits report higher incidences of serious adverse effects with NCA in neonates than children aged >1 mth: 0.8% vs 0.4 (Morton 2010 **Level IV**, n=3,706 [NCA]) and 2.5% vs 0.27% (Howard 2010 **Level IV**, n=10,000).

10.5.4 | PCA by proxy

Administration by a nurse trained in pain assessment, rather than parents, is recommended in most centres (Howard 2010 **Level IV**, n=10,000). Confusingly the term "PCA by proxy" has been used to describe administration by both nurses and/or parents. The Joint Commission on Accreditation of Healthcare Organisations issued a sentinel alert cautioning against the practice of parental proxy in 2004. In response, some US centres ceased using parental proxy technique (reported by 11% of surveyed anaesthetists) (Nelson 2010 **Level IV**, n=294). However, many centres continue this practice and, as for the conventional PCA technique, selection criteria, education and guidelines should be followed (Chidambaran 2012 **NR**). In a prospective series of PCA by proxy (parents or health care providers), effective analgesia was achieved in 81–95% of children <6 y of age; 25% required supplemental oxygen and 4% required naloxone for respiratory depression (Monitto 2000 **Level IV**). In a retrospective series, PCA by proxy resulted in low pain scores, while somnolence or respiratory depression requiring naloxone occurred in 2.8% of children with developmental delay (Czarnecki 2008 **Level IV**) and 1.9% of infants and preschoolers (Czarnecki 2011 **Level IV**). PCA by proxy vs conventional PCA in children with cancer pain was associated with comparable (Anghelescu 2005 **Level III-3**) and lower complication rates in a follow-on series (Anghelescu 2012 **Level IV**). In children with developmental delay, no differences in outcomes were seen when comparing postoperative use of parental/nurse controlled analgesia vs nurse administered IV opioids (Czarnecki 2018 **Level II**, n=81, JS 2).

Comparison of morphine and hydromorphone via PCA, NCA and PCA by proxy (70% with a background infusion) has been described (Voepel-Lewis 2008 **Level III-3**, n=302). Fentanyl PCA was administered by parental proxy (initial settings 0.075 mcg/kg bolus and background 0.3 mcg/kg/h) for toddlers for 48 h post cleft palate repair to establish an $ED_{50–95}$ of 0.63–0.83 mcg/kg/h (Choi 2008 **Level IV**).

10.5.5 | Overall safety of parenteral opioid use in children

Overall, parenteral opioid techniques are safe in children as long as administered in appropriate settings. Of surveyed paediatric anaesthetists (representing 252 USA institutions with 51% having APS oversight), 8 recalled deaths (in the preceding 5 y) in association with these techniques and 42 recalled cardiorespiratory events requiring naloxone (in the year prior; denominator unknown) (Nelson 2010 **Level IV**, n=294). The incidence rates of respiratory depression in the various paediatric studies will vary depending upon how it is defined; degree of desaturation, requirement for supplemental oxygen, suspension/cessation of opioids, requirement for naloxone or respiratory intervention including ventilation. The studies done to date are generally underpowered to detect differences in the incidence of respiratory depression. The large UK prospective audit of parenteral opioids delivered by the above techniques reports an overall 1 in 10,000 incidence of serious harm and 0.13% incidence of respiratory depression (requiring intervention with respiratory support, naloxone or opioid cessation) (Morton 2010 **Level IV**, n=10,726). Importantly, these low rates occurred in UK centres with 100% oversight by a paediatric APS and with institutional guidelines in place. Safety can be improved through avoidance of concurrent sedatives or opioids by other routes, awareness of comorbidities posing extra risk and by careful dosing, with heightened monitoring in infants. Opioid prescription and pump programming errors were an issue (1 in 631 infusions or 0.16%) and can be minimised through adherence to guidelines and careful cross-checking (Morton 2010 **Level IV**, n=10,726).

Administrative data assessment from 42 USA hospitals revealed morphine by PCA vs morphine by IV route was not associated with an increased risk of requirement for CPR or mechanical ventilation (Faerber 2017 **Level III-2**, n=108,956 [PCA surgical n=11,220 & PCA non-surgical n=6,030; each matched with an IV morphine group]); in the matched cohorts on day 1 of IV morphine use, CPR events occurred in 0.89% of non-surgical and 0.45% of surgical patients. PCA exposure had lower risk of requiring CPR in surgical (OR 0.56; 95%CI 0.45 to 0.70) and non-surgical recipients (OR 0.80; 95%CI 0.76 to 0.85).

A single institution reported use of PCA and NCA over 14 y as associated with 146 errors (1%), of which two resulted in severe and preventable adverse events (Donado 2019 **Level IV**, n=16,806 [PCA or NCA administrations with error reporting]).

KEY MESSAGES

1. Addition of a low-dose background infusion to patient controlled analgesia (PCA) bolus results in similar pain scores and total opioid consumption and improves sleep duration in children; numbers are inadequate to assess safety of adding a background (**N**) (**Level I**).
2. In ventilated preterm neonates, routine use of morphine infusions does not affect mortality, duration of ventilation or neurological outcomes (**U**) (**Level I** [Cochrane Review]**)**, including when followed up as older children (**S**) (**Level II**).
3. Postoperative intravenous opioid requirements vary with age in neonates, infants and children (**U**) (**Level II**).
4. Intermittent intramuscular injections are distressing for children and are less effective for pain control than intravenous infusions (**U**) (**Level III-1**).
5. Patient-controlled analgesia (PCA) can provide safe and effective analgesia for children as young as 5 years old (**S**) (**Level III-3**).
6. Intravenous opioids via continuous infusion, nurse-controlled analgesia and parental proxy use of patient controlled analgesia (PCA) devices can be used effectively (**U**) (**Level III-2**) and safely (**N**) (**Level IV**) in children of all ages.
7. Nurse-controlled analgesia (**U**) (**Level III-2**) and parental proxy use of patient controlled analgesia (PCA) devices in children (**U**) (**Level III-3**) may require more rescue interventions (such as naloxone, airway management or intensive care) than PCA, but this may reflect the younger patient population where this technique is offered.
8. Morphine by patient controlled analgesia (PCA) is at least as safe as intermittent nurse administered intravenous morphine (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Initial doses of opioid should be based on the age, weight and clinical status of the child and then titrated against the individual's response (**U**).

☑ Effective patient controlled analgesia (PCA) prescription in children incorporates a bolus that is adequate for control of movement-related pain (**U**).

10.6 | Paediatric Regional Analgesia

Paediatric regional analgesia (PRA) incorporates peripheral nerve or neuraxial blocks and catheter techniques. The efficacy of various PRA techniques for common paediatric surgical conditions is described below. Differences between groups in RCTs can be difficult to detect with small sample sizes or when outcome measures are relatively insensitive (eg supplemental analgesic requirements following procedures with low ongoing pain). This and the heterogeneity of studies and outcomes leads to systematic reviews with conclusions based often on single RCTs (eg Kendall 2018 **Level I** [PRISMA], 40 RCTs, n=2,408). Previous prospective multicentre French and UK audits (Ecoffey 2010 **Level IV**, n=29,870 PRA with GA & 1,262 PRA alone; Llewellyn 2007 **Level IV**, n=10,633 [epidural]) and retrospective single centre Italian audit (Vicchio 2015 **Level IV**, n=18,279 PNBs) have been superseded by larger scale population safety data provided by the USA's Paediatric Regional Anaesthesia Network (PRAN) with more than 20 children's hospitals participating (Walker 2018 **Level IV**, n=104,393 blocks in 91,701 children). Data collection and publication by PRAN is ongoing and informs our practices and information we can provide to families during the consent process.

PRA safety under general anaesthesia, practice advisory and adjuvant use

PRA is typically performed in children under general anaesthesia. The safety of this has been demonstrated in the PRAN audits and is comparable to placing blocks in awake adults (Walker 2018 **Level IV**, n=104,393 [97,825 under GA]; Walker 2018 **Level IV**, n=2,017; Suresh 2018a **Level IV**, n=40,121).

The European Society of Regional Anaesthesia and Pain Therapy (ESRA) and The American Society of Regional Anaesthesia and Pain Medicine (ASRA) joint committee practice advisory group has published recommendations (Ivani 2015 **GL**):

1. Support for the performance of regional nerve blocks under deep sedation or GA;
2. Discretionary use of an adrenaline (epinephrine) containing test dose (as false negatives occur);
3. Detection of epidural space with loss of resistance to either air or normal saline (or both) in small volumes;
4. Regional anaesthesia does not obscure or delay diagnosis of compartment syndrome.

This practice advisory has since been reaffirmed with dosing recommendations for neuraxial blocks (Lonnqvist 2017 **GL**).

The addition of adjuvant medications to local anaesthetic agent can improve block quality and duration (Forestier 2017 **NR**). Adjuvant agent addition to the regional or peripheral nerve injectate should demonstrate a viable local mechanism of action beyond systemic administration, be safe, tolerable and non-toxic via this route. See later sections 10.6.2.6 and 10.6.3.3.

10.6.1 | Peripheral nerve blocks and catheters

10.6.1.1 | Single injection peripheral nerve blocks (PNBs)

Single injection peripheral nerve blocks (PNBs) are effective and safe adjuncts for the management of procedural, perioperative and injury related acute pain (PNBs: Walker 2018 **Level IV**, n=45,324; Ecoffey 2010 **Level IV**, n=20,576; Giaufre 1996 **Level IV**, n=4,090) (See also Section 5.8). The use of US-guidance for PNBs in children has grown significantly over the last decade, including in the ambulatory setting (Walker 2018 **Level IV**, n=45,324; : Suresh 2018a **Level IV**, n=40,121;

Kendall 2018 **Level I** [PRISMA], 40 RCTs, n=2,408; 1 RCT overlap with Lam 2016 **Level IV SR** [PRISMA], 23 studies [PNBs: including 10 RCTs], n=1,280). PRAN data have shown increase in the proportion of PNB relative to neuraxial blocks: from 43.4 to 52.5% (Walker 2018 **Level IV**, n=86,328 [single injection]; Polaner 2012 **Level IV**, n=10,622).

Dosing

PRAN audit reveals PNB dosing practices vary 5−10 fold with volumes of 0.16 to 2.4 mL/kg and doses of bupivacaine (means 0.5−1.25 mg/kg) or ropivacaine (means 0.42−1.42 mg/kg) (where the upper 95%CI limit is less than the per kg max dose recommendations) (Suresh 2018a **Level IV**, n=40,121).

10.6.1.2 | Continuous peripheral nerve catheters

Continuous peripheral nerve catheters (CPNCs) for continuous local anaesthetic infusion have been used in all age groups (CPNCs: Walker 2018 **Level IV**, n=4,945; Walker 2015a **Level IV**, n=2,074; Ecoffey 2010 **Level IV**, n=1,098). Within the PRAN dataset, the numbers of CPNCs inserted increased gradually, and since 2012 have been stable relative to the more commonly inserted neuraxial catheters (Walker 2018 **Level IV**, n=4,945 [CPNCs] vs 13,120 [neuraxial]). The majority of CPNCs were inserted in older children >10 y; with ultrasound for the majority of catheter placements (Walker 2015a **Level IV**, n=2,074).

Efficacy in hospital and post discharge

Case series report CPNC use in hospital and on discharge as an ambulatory option with elastomeric pumps (discharged home on POD 0–3 (Walker 2015a **Level IV**, n=2,074 [n discharged unspecified]; Gurnaney 2014 **Level IV**, n=1,954 CPNCs in 1,700 patients [1,285 discharged]; Visoiu 2014b **Level IV**, n=410 CPNCs in 403 patients [all discharged]; Ganesh 2007 **Level IV**, n=226 CNPCs in 217 patients [108 discharged]). High efficacy (as an adjuvant to oral analgesia including opioids) has been reported in the above case series (balanced with low complication and failure rates per below). Success rates were 93 to 98% when assessed by numerical rating (NRS) of pain control satisfaction (parent, patient and nurse), pain scores in PACU vs at home and analgesic consumption (Visoiu 2014b **Level IV**, n=403 [discharged]; Gurnaney 2014 **Level IV**, n=1,285 [discharged]; Visoiu 2014a **Level IV**, n=5 [paravertebral]). In PACU, 37% of patients with CPNCs in situ required no opioid (Visoiu 2014b **Level IV**, n=403). Most patients required opioid at home: ≥1 dose for 96% (Visoiu 2014b **Level IV**, n=403), as needed by 64% vs regularly by 15% or 8% as needed which then moved to regular (Gurnaney 2014 **Level IV**, n=1,285).

CPNC dosing

Usual reported CPNC dosing were of plain ropivacaine 0.1−0.2% or bupivacaine 0.1−0.125% at rates of 2−10 mL/h for 2 to 10 d (Walker 2015a **Level IV**, n=2,074; Gurnaney 2014 **Level IV**, n=1,954 [CPNCs]; Visoiu 2014b **Level IV**, n=410 [CPNCs]; Ganesh 2007 **Level IV**, n=226 [CPNCs]). The joint practice advisory committees recommend CPNC local anaesthetic dosing based upon the above audit data practices (with no PK-PD study) for peripheral nerve and fascial planes of 0.1−0.3 mg/kg/h for racemic bupivacaine, levobupivacaine or ropivacaine (ESRA-Suresh 2018a **GL**; ASRA-Lonnqvist 2017 **GL**). Lower dosing is suggested for neonates and younger children (with their differing PK profiles to ≈6 y) reflecting greater risk for local anaesthetic systemic toxicity (LAST) with higher free non protein-bound drug fractions and immature CYP3A4/7 enzyme systems (Suresh 2018a **GL**; Johr 2015 **NR**). Some children have received higher than recommended local anaesthetic dosing without adverse events (Walker 2015a **Level IV**, n=2,074; Moriceau 2015 **CR**).

Safety

Safety of PNB (PNBs: Walker 2018 **Level IV**, n=45,324; Ecoffey 2010 **Level IV,** n=20,576; Giaufre 1996 **Level IV,** n=4,090) are described below and in Section 10.6.2.4 under the individual block headings.

In the largest series, a low overall failure rate for PRA (PNB, CPNC and neuraxial single injection and catheters) of 1% was reported (Walker 2018 **Level IV**, n=104,393). For two PNBs (1 penile and 1 superficial cervical plexus block) broken needles required surgical retrieval and one wrong-sided femoral PNB was performed (Walker 2018 **Level IV**, n=45,324). One wrong-sided block has been reported in an Australian paediatric centre's series (Drake-Brockman 2016 **Level IV**, n=148 [PNBs]). Adoption of the 'Stop Before You Block' checklist (Clebone 2017 **GL**; ANZCA 2015) as an anaesthesia time out (pre or post-induction of GA but preblock, ie before surgical time out) practice in paediatric centres world-wide is unknown. Some paediatric institutions have developed additional local procedures to reduce this error (eg scrub nurses hand the anaesthetist the block needle after the anaesthesia time out) with focus on correct patient identification, site marking, patient weight and safe drug dosing.

Safety of CPNC use has been confirmed by retrospective (CPNCs: Gurnaney 2014 **Level IV**, n=1,954; Visoiu 2014b **Level IV**, n=410; Dadure 2009 **Level IV**, n=339; Ganesh 2007 **Level IV**, n=226 CNPCs) and subsequent prospective PRAN audits (Walker 2015a **Level IV**, n=2,074 case overlap with Walker 2018 **Level IV**, n=4,945) and is described further below.

Complications related to CPNC technique

Primary failure rates of CPNC insertion were reported in the earlier audits (generally ≤2%; higher for upper limb 7.6%).

Recognised vascular puncture rates vary between 2−3% (CPNCs: Gurnaney 2014 **Level IV**, n=1,954; Dadure 2009 **Level IV**, n=339; Ganesh 2007 **Level IV**, n=226 CNPCs) and lower in prospective data of 0.9% (95%CI 0.5 to 1.4) (Walker 2015a **Level IV**, n=2,074).

The most common adverse event for CPNC in all series were secondary failures of the catheter (dislodgement, occlusion or disconnection) or of the delivery system.

In the PRAN audit, the secondary failure rate was 1.3% (95%CI 0.8 to 1.7); while catheters were removed because of various complications on POD 0 to 2 in 6.1% patients; overall 7.3% (95%CI 6.2 to 8.5) (Walker 2015a **Level IV**, n=2,074).This was independent of insertion while under GA, sedated vs when awake, insertion site or patient age. An earlier series reported similar rates of secondary failure (1.9%) and excessive catheter leak in 1% (Gurnaney 2014 **Level IV**, n=1,492 CPNCs). Another series reported catheter problems (6.9%) including elastomeric pump delivery failure and leak (Visoiu 2014b **Level IV**, n=410).

Post discharge, CPNC related problems at home include motor block and difficult removal. The families received education in catheter clamping in the event of adverse effects. With low concentration and low infusion rates (see above), reported rates of motor block were 10% (Ganesh 2007 **Level IV**) to 20% (Dadure 2009 **Level IV**), resolving within 3 h of catheter clamping (Gurnaney 2014 **Level IV**, n=1,492). Most series reported difficult removal in a few patients only (Walker 2015a **Level IV**, n=2,074 [2 difficult–1 attended ED]; Gurnaney 2014 **Level IV**, n=1,492 [2 difficult]; Visoiu 2014b **Level IV**, n=410 [1 difficult, 2 refusals by the patient]).

Anticoagulation and PNB/ CPNCs

Children rarely receive thromboprophylaxis after major surgery. There is no paediatric literature pertaining to anticoagulation and PNBs; practice for paediatric patients receiving anticoagulants generally follows adult recommendations. See discussion in adult Section 5.9.2 (and specific to epidural haematoma and epidural catheters in adults in 5.9.1 and in children in 10.6.3.5).

Infection in CPNCs

Local cutaneous infections related to CPNC use was lower (26/10,000; 95%CI 15 to 45) than with neuraxial catheters (60/10, 000; 95%CI 48 to 75) independent of insertion site (Walker 2018 **Level IV**, n=4,945 [CPNCs] vs 13,120 [neuraxial]). An earlier overlapping series of CPNCs documented superficial infection incidence of 0.9% (95%CI 0.5 to 1.4) associated with longer CPNC duration 4.5 d (range 3 to 7) vs 3 (1 to 3); 3 further catheters were removed in patients with fever only (and no superficial infection) and no deep infections, abscesses or sepsis events were documented (Walker 2015a **Level IV**, n=2,074). Retrospective studies report site infection requiring antibiotics of ≤0.5−0.9% (Gurnaney 2014 **Level IV**, n=1,954; Dadure 2009 **Level IV**, n=339; Ganesh 2007 **Level IV**, n=226 CNPCs).

Local Anaesthetic Systemic Toxicity (LAST) with PNBs/CPNCs

The incidence of Local Anaesthetic Systemic toxicity (LAST) with PNBs has not changed over time (OR 1.08; 95%CI 0.21 to 5.43) (Walker 2018 **Level IV**, n=45,324 PNBs). One severe LAST event (seizure) occurred in a teenager who received an infraclavicular PNB and was treated with lipid emulsion with seizure resolution. While in a femoral fracture ED series of fascia iliaca compartment blocks (FICNB) landmark technique with ropivacaine 0.5% 0.5–0.75 mL/kg (max 30 mL), two patients had a seizure, one treated with intralipid and one (with known subarachnoid haemorrhage) with benzodiazepine (Neubrand 2014 **Level IV**, n=158 [FICNB]).

With CPNCs, LAST incidence in the earlier series was ≤0.3 in 10,000 (Gurnaney 2014 **Level IV**, n=1,954; Dadure 2009 **Level IV,** n=339; Ganesh 2007 **Level IV**, n=226 CNPCs) and 4/10,000 (95% CI 0.6 to 30) (Vecchione 2016 **Level IV**, n=625 CPNC [468 patients]). Early symptoms of LAST (ringing in the ears or metallic taste) occurred in 0.5/10,000 (Suresh 2018a **Level IV**, n=40,121 PNBs; Visoiu 2014b **Level IV**, n=410 CPNCs) and 0.2/10,000 which resolved with clamping and CPNC removal (Gurnaney 2014 **Level IV**, n=1,492 children). One infant had LAST with a self-resolving seizure related to paravertebral CPNC and chloroprocaine bolus: 0.8/10,000 (95%CI 0 to 4.8) (Walker 2018 **Level IV**, n=2,074).

Postoperative Neurological Symptoms (PONS) and PNBs/CPNCs

Prospective audit reports the incidence of neurological complication with PNBs has decreased over time (OR 0.60; 95%CI 0.38 to 0.90) (Walker 2018 **Level IV**, n=45,324). No permanent neurological deficits (95%CI 0 to 0.4/10,000) and low risk of transient neurologic deficit of 2.4/10,000 (95%CI 1.6 to 3.6) were reported (Walker 2018 **Level IV**, n=104,393 blocks in 91,701 children). There was no difference in neurologic complication rate when comparing peripheral vs neuraxial blocks, CPNCs vs single injection (OR 0.63; 95%CI 0.21 to 2.74) or local anaesthetic type (bupivacaine vs ropivacaine).

Case reports have described prolonged neurological deficit (Drake-Brockman 2016 **Level IV**, n=148 PNBs) and permanent injury (Walker 2018 **NR**; Ivani 2015 **GL**).

Acute compartment syndrome and PNB or CPNC

Acute compartment syndrome (ACS) associated with PNBs/CPNBs was not specifically reported in the PRAN audit. There are reports where PNBs have masked ACS in adults with others where PNB/CPNC did not, including three adolescents (Klucka 2017 **Level IV** [PRISMA], 15 studies, n=20; Ivani 2015 **GL**; Munk-Andersen 2013 **CR;** Walker 2012a **CR**; Cometa 2011 **CR**). This highlights the need for frequent clinical monitoring and early review following high-risk injury or surgery (eg diaphysis of long bones, particularly tibia, and comminuted fracture) in the event of breakthrough pain (particularly where analgesia including PRA has been previously effective).

In those deemed at risk, the Joint ASRA-ESRA Practice Advisory has suggested limiting the drug dosing regimens to low concentrations/low volumes and avoiding adjuvants in PNBs, neuraxial blocks and CPNCs (Lonnqvist 2017 **GL**).

10.6.1.4 | Ultrasound guidance impact on safety and success of PNBS and CPNCs

PRAN has documented high use of ultrasound (US) guidance for CPNC placement: 78–90% (Walker 2015a **Level IV**, n=2,074) and increased use for PNB placement from ≈30% in 2007 to ≈90% in 2015, with concomitant decrease in peripheral nerve stimulator use as sole assisting device (Walker 2018 **Level IV**, n=45,324 [PNBs]; Suresh 2018a **Level IV**, n=40,121). The joint committee practice advisory groups suggest lower dosing is required when using US-guidance (Suresh 2018b **GL**; Lonnqvist 2017 **GL**). Although neurologic complications with PRA have decreased over time, US-guidance has not impacted this: with 0/10,000 (95%CI 0 to 4.2) events with US use overlapping with 3.6/10,000 (95%CI 2.1 to 6.0) without US (Walker 2018 **Level IV**, n=45,324 [PNBs]). Neither hasUS use affected LAST incidence (95%CI −1.6 to 1.0/10,000), despite use being associated with documented smaller local anaesthetic volumes.

A systematic review has summarised several heterogeneous RCTs without meta-analysis showing similar or greater success rates vs nerve stimulation (1 RCT [axillary], n=40; 1 RCT [infraclavicular], n=50; 1 RCT [femoral], n=60) and landmark technique (2 RCTs [penile block], n=106), with variable effects on speed of block performance (vs landmark: faster (1 RCT [axillary], n=40) and slower (1 RCT [penile], n=40) and postoperative outcomes including pain scores and opioid requirements (equivocal for transversus abdominus plane block (1 RCT [lap. appendicectomy], n=30) and rectus sheath block (1 RCT [umbilical hernia], n=52) vs positive vs wound infiltration for ilioinguinal/iliohypogastric nerve block (2 RCTs [inguinal hernia], n=109)) (Lam 2016 **Level IV SR** [PRISMA], 23 studies [peripheral: including 10 RCTs], n=1,280). The earlier review by the same authors summarised two earlier RCTs with similar findings: where US-guided ilioinguinal/iliohypogastric block reduced the local anaesthetic dose given and PACU rescue paracetamol requirements vs landmark technique (Tsui 2010 **Level IV SR** [PRISMA], 1 RCT: Willschke 2005 Level II n=100 JS 3) and reduced block onset time for infraclavicular block vs nerve stimulator use (Tsui 2010 **Level IV SR** [PRISMA], 1 RCT: Marhofer 2004 **Level II**, n=40, JS 3).

See sections 10.6.2.1 and 10.6.2.2 for discussion of US use in caudal and epidural insertion respectively.

10.6.2 | Specific peripheral nerve blocks and catheters

10.6.2.1 | Lower limb blocks in children

Lumbar plexus (or psoas compartment) block

For lower limb/hip surgery, lumbar plexus (or psoas compartment) single injection block (Gurkan 2017 **Level IV**, n=75; Walker 2011 **Level IV**, n=305) or CPNC (Walker 2018 **Level IV**, n=274 PNBs & 722 CPNCs) may be useful alternatives to neuraxial techniques (Omar 2011 **Level II**, n=40, JS 3; Villalobos 2019 **Level III-2**, n=61).

Lateral femoral cutaneous or femoral PNB or CPNC alone or in PNB combinations

For lateral thigh skin donor sites in burns surgery, an US-guided single injection lateral femoral cutaneous nerve (LFCN) PNB and US-guided fascia iliaca compartment nerve block (FICNB) with CPNC reduced postoperative pain scores vs local anaesthesia infiltration (Shank 2016 **Level II**, n=19, JS 3). For femoral fracture or surgery, FICNB by landmark technique reduced pain scores (Paut 2001 **Level IV**, n=20) and rescue analgesic use vs IV opioid (Suresh 2014 **Level I** [PRISMA], 1 RCT: Kim 2011 **Level II**, n=64, JS 3; Wathen 2007 **Level II**, n=55, JS 3; Neubrand 2014 **Level III-2**, n=259 [158 FICNB]). For knee reconstructive surgery, FICNB vs femoral PNB were equivalent for postoperative analgesia (Suresh 2014 **Level I** [PRISMA], 1 RCT: Farid 2010 **Level II**, n=23, JS 3) and femoral PNB (alone or via CPNC) was effective vs IV opioid (Micalizzi 2014 **Level III-2**, n=93).

For femoral fracture and traction application, landmark and US-guided (Turner 2014 **Level III-2**, n=81) single injection femoral nerve blocks and CPNCs have been used effectively, including in an infant (Frenkel 2012 **CR**) and PICU patients (Tobias 1994 **Level IV**, n=4; Johnson 1994 **Level IV**, n=23). In the latter, plasma concentrations during bupivacaine 0.125% infusion of 0.3 mL/kg/h at 10–92 h were 0.67–0.93 mg/L.

Three-in-one blocks have been used in iliac bone graft harvest in comparison with wound infiltration and a wound catheter (Kumar Raja 2014 **Level II**, n=60, JS 5).

Following knee arthroscopic surgery, US-guided femoral and obturator blocks reduced pain scores and analgesia requirements vs no block (Kendall 2018 **Level I** [PRISMA], 1 RCT: Marinkovic 2016 **Level II**, n=60 JS 2). In adolescents with skeletal dysplasia having arthroscopic knee surgery, femoral, femoral/sciatic or femoral/sciatic/obturator blocks were effective (Eiszner 2016 **Level IV**, n=10 [PNB]).

Popliteal PNB and CPNC

For lower limb contracture surgery in cerebral palsy patients, US-guided popliteal vs sham block reduced pain scores for 0–12 h (Kendall 2018 **Level I SR** [PRISMA], 1 RCT: Ozkan 2017 **Level II**, n=54, JS 5). Following major foot and ankle surgery, popliteal CPNC with ropivacaine 0.2% 0.1 mL/kg/h achieved comparable analgesia with fewer adverse effects (PONV, urinary retention, early discontinuation) vs continuous epidural infusion 0.2% 0.2 mL/kg/h (Dadure 2006 **Level II**, n=52, JS 3).

10.6.2.2 | Upper limb blocks in children

Brachial plexus blocks

Traditionally the axillary approach to the brachial plexus was preferred in paediatric patients with its relative safety when using the landmark technique. US-guidance has led to new approaches in children for brachial plexus regional analgesia (Walker 2018 **Level IV**, n=5,636 [brachial plexus PNBs/CPNCs]; Marhofer 2004 **Level II**, n=36, JS 3; De Jose Maria 2008 **Level III-1**, n=80; Dadure 2009 **Level IV**, n=31 [upper limb CPNCs]); Ergonenc 2017 **CR**).

Supraclavicular approach: single injection and CPNC

PRAN audit has documented increased use of this approach in children (Walker 2018 **Level IV**, n=2,860 PNBs & 93 CPNCs [supraclavicular]). Following a single injection supraclavicular block, one 2 y old developed a pneumothorax which was managed conservatively.

For percutaneous fixation of supracondylar fractures, US-guided supraclavicular block reduced the mean and peak pain score only in PACU vs IV opioids (Glover 2015 **Level III-2**, n=230 [36 PNB]).

Infraclavicular approach: single injection and CPNC

Infraclavicular nerve block (ICNB) has been described in paediatrics with nerve stimulator (NS) (Ponde 2008 **Level IV**) and/or US-guidance (Walker 2018 **Level IV**, n=811 PNBs & 133 CPNCs [infraclavicular]). This approach is as safe as other brachial plexus approaches, with more reliable musculocutaneous nerve block/less tourniquet pain vs the axillary approach (Chin 2013 **Level I** [Cochrane], 3 RCTs [paediatric], n=156). For arm, forearm and hand surgery, US-guided low-volume 0.25 mL/kg vs standard volume 0.5 mL/kg bupivacaine 0.25%/lidocaine 1% infraclavicular block achieved similar sensory with shorter motor block duration (Kendall 2018 **Level I** [PRISMA], 1 RCT: Ince 2017 **Level II**, n=60, JS 5).

Axillary approach: single injection and CPNC

For forearm and hand surgery, axillary brachial plexus block provided satisfactory analgesia in 75−94% of cases (Gurnaney 2014 **Level IV**, n=2 [axillary]; Dadure 2009 **Level IV**, n=15 [axillary]; Fisher 1999 **Level IV**, n=185 [250 procedures]). US has assisted insertion of axillary catheters in children

(Walker 2018 **Level IV**, n=981 PNBs & 9 CPNCs [axillary]) and single injection block for hand surgery in severe epidermolysis bullosa (van den Heuvel 2016 **Level IV**, n=9 [19 procedures]). Two fractionated nerve stimulator-guided axillary brachial plexus injections in children produced similar sensory and motor block quality at 30 min to a single injection (Carre 2000 **Level II**, n=70, JS 2), unlike in adults (Chin 2016 **Level I** [Cochrane], 22 RCTs [adult], n=2,193). Selective block of the musculocutaneous nerve is recommended when a surgical procedure takes place in its territory.

Interscalene approach: single injection and CPNC

Interscalene single injection blocks and CPNCs use in children is documented in the PRAN audit (Walker 2018 **Level IV**, n=984 PNBs & 103 CPNCs). An earlier PRAN series assessed the safety of the technique where 88% were performed in teenagers (10−18 y) and usually under GA (75%) (Taenzer 2014a **Level IV**, n=518 [472 PNB & 46 CPNCs]). US-guidance in 88%, nerve stimulation with US 11%, nerve stimulation alone 2.5% and rarely fluoroscopy assisted placement. One vascular puncture and one superficial infection were documented and no other serious events (LAST, neurological, cardiovascular or dural puncture) (95%CI 0 to 7.7/1,000). For forequarter amputation, direct surgical placement and infusions via epineural CPNCs in the 3 brachial plexus trunks (for 5 to 14 d) as part of a multi-modal regimen has been described (Kaddoum 2013 **Level IV**, n=4).

Wrist blocks

For distal hand surgery in anaesthetised young children, wrist block vs intraoperative alfentanil reduced postoperative pain scores, PONV and recovery time (De Windt 2010 **Level II**, n=60, JS 3). For trigger thumb release, US-guidance increased median nerve block success rates vs landmark technique (100 vs 74%) (Liu 2018 **Level II**, n=100, JS 3).

10.6.2.3 | Truncal blocks in children

Paravertebral block PVB and CPNC

Paravertebral block (PVB) or PV CPNC infusion has been reported in PRAN audit (Walker 2018 **Level IV**, n=535 PVB & 550 PV CPNC). With US uptake and the advent of newer truncal plane blocks, the role and risk profile of the PVB technique is of interest, but the paediatric evidence base lacks comparative trials. Of note, infant cadaveric studies suggested a single US-guided PVB 0.2−0.3 mL/kg at T12/L1 provides dose dependent coverage of T10 to L1 segments (Albokrinov 2014 **Level III-2**, n=20). Dosing in children for single and multi-injection reported in mg/kg ropivacaine equivalents (not in mL/kg) was higher for infants at a mean of 1.47 and 2 respectively vs 1.25 and 1.75 for older children (Vecchione 2016 **Level IV**, n=2,390 in 871 children [1765 PVBs & 625 CPNCs]). No complications were reported with single injection PVBs. While with PVB CPNC, 2 major complications occurred: one was a LAST event in an infant relating to chloroprocaine 3% 1 mL/kg bolus and one teenager with bilateral PV CPNCs developed a large paravertebral haematoma with epidural extension that was conservatively managed (event rate for paravertebral CPNC: 18.2/10,000; 95%CI 0 to 113) (Walker 2018 **Level IV**, n=535 PVB & 550 PV CPNC). Minor complications for PVB CPNCs recipients included: catheter dislodgement 4.9%, occlusion 1.5%, leakage 5.9%, skin irritation 2.9% and minor bleeding in 1% (Vecchione 2016 **Level IV**, n=625).

Paravertebral block: single injection efficacy

Single injection PVB has provided effective analgesia following thoracoabdominal surgery in children.

In a systematic review of heterogeneous paediatric trials, single and multi-injection PVB reduced pain scores at 4−6 h (SMD 0.85; 95%CI 0.12 to 1.58) and 24 h (4 RCTs, n=282) and supplemental analgesia requirement (3 RCTs [inguinal; comparators no block, ilioinguinal block and caudal] n=199) (OR 0.17; 95%CI 0.08 to 0.34) (Page 2017 **Level I** [PRISMA], 6 RCTs [PVB], n=358). PVBs

have also been effective for several hours (median 10 h to mean 22 h) following cardiac surgery for aortic coarctation (Saleh 2018 **Level II**, n=50, JS 4; Turkoz 2013 **Level IV**, n=15) and PDA ligation (Chalam 2015 **Level II**, n=100, JS 4), Nuss procedure (vs no block; Kendall 2018 **Level I** [PRISMA], 1 RCT: Qi 2014 **Level II**, n=30, JS 2), infant pyloromyotomy (Mata-Gomez 2015 **Level IV**, n=3) and renal surgery (vs caudal Narasimhan 2019 **Level II**, n=50, JS 5; vs IV paracetamol Akinci 2019 **Level II**, n=40, JS 4; Berta 2008 **Level IV**, n=24).

Paravertebral CPNC efficacy

Compared with thoracic epidural catheter infusion, PVB CPNC infusion (US-guided; bilateral) provided equivalent analgesia for cardiac surgery via thoracotomy (nerve stimulator guided) with higher insertion success and less adverse events (El-Morsy 2012 **Level II**, n=60, JS 5) and was equivalent for the Nuss procedure (Muhly 2019 **Level III-2**, n=331 [56 paravertebral, 114 epidural]; Hall Burton 2014 **Level III-2**, n=20) or with higher pain scores and opioid use postoperatively (as with intercostal nerve catheters) but shortest LOS (mean 2.0 vs 4.0 d vs 4.9) (Loftus 2016 **Level III-2**, n=137).

Surgically placed paravertebral CPNCs have been effective post-thoracotomy in children for empyema decortication (bupivacaine 0.1% 0.3 mg/kg/h) (Murphy 2016b **Level IV**, n=83), in infants for congenital pulmonary malformations (ropivacaine 0.125% 0.2 mg/kg/h) (Di Pede 2014 **Level III-3**, n=40) and neonates for tracheo-oesophageal fistula (TOF) surgery (levo-/bupivacaine 0.0625% ≈0.25 mg/kg/h for 43 h median) (Palmer 2012 **Level IV**, n=37), including via US-guided anaesthetist placement for TOF repair (ropivacaine 0.08% 0.2 mg/kg/h for 4−5 d) (Thompson 2015 **Level IV**, n=2).

Unilateral PVB CPNC ropivacaine infusion for 2 d provided equivalent analgesia vs single injection caudal ropivacaine/morphine for upper abdominal surgery in infants (Sato 2017 **Level III-2**, n=21). Bilateral and unilateral US-guided PVB CPNCs have been used for various thoracoabdominal procedures for 1−5 d (Boretsky 2013 **Level IV**, n=22). Following iliac crest bone graft harvest, paravertebral L2 CPNCs with elastomeric pump reservoir (ropivacaine 0.2%, 0.06–0.2 mL/kg/h) were effective for outpatient analgesia (Visoiu 2014a **Level IV**, n=5).

Erector spinae plane block (ESPB)

It is debated whether the erector spinae plane block (ESPB) is a paravertebral variant with neuraxial spread (Tsui 2019 **Level IV**, n=242 [23 children]) vs a myofascial plane block: see the discussion in adult Section 5.8.5.3. A median volume of 3.4 mL per dermatomal level is suggested for ESPB dermatomal spread in adults (De Cassai 2018 **NR**); with no paediatric dosing recommendation data specific to this block.

Erector spinae plane block: single injection

US-guided single injection ESPB has been described in various paediatric surgeries in children (6 mth to 16 y): at T1 for posterior chest wall surgery (Hernandez 2018b **CR**), T5−8 for thoracic surgery (Ueshima 2018 **Level IV**, n=2; Adhikary 2018 **CR**; Munoz 2017 **CR**), T7 for laparoscopic cholecystectomy (Aksu 2019b **Level IV**, n=3; Thomas 2018a **CR**), T12 for nephrectomy for Wilm's tumour (Aksu 2018b **Level IV**, n=2), and at L1 for laparoscopic or open lower abdominal surgeries (Aksu 2019a **Level II**, n=60, JS 4; Aksu 2019c **Level IV**, n=2) and inguinal hernia repair (Aksu 2018a **Level IV**, n=10), including in an ex-preterm infant (Hernandez 2018a **CR**). Post inguinal surgery, ESPB at L1 vs quadratus lumborum block (transmuscular approach) reduced pain scores similarly (0−6 h) with similar times to first analgesic rescue (Aksu 2019c **Level II**, n=60, JS 4).

Erector spinae plane block: continuous infusion

ESPB CPNC infusion is reported as used following thoracotomy (De la Cuadra-Fontaine 2018 **CR**), video assisted thoracoscopic surgery (VATS) (Adhikary 2018 **CR)** and pyeloplasty (Munshey 2018 **CR**).

Intercostal nerve block single injection and CPNC

For ear reconstruction cartilage graft site pain, a surgically placed intercostal CPNC was superior to IV analgesia in reducing pain scores at rest and on coughing (Woo 2016 **Level II**, n=66, JS 3). While a single injection intercostal block was inferior to a wound catheter infusion (Niiyama 2016 **Level II**, n=48, JS 2).

Pectoralis nerves and serratus anterior plane PNBs

Ultrasound-guided pectoralis nerve (PECS) blocks and serratus anterior plane (SAP) blocks are regional analgesia techniques of the thorax (for technique description see also adult Section 5.8.5.4). In paediatric patients having cardiac surgery via thoracotomy, PECS II vs SAP blocks had clinically modest 0.5−0.9/10 difference in pain scores from 4−10 h with reduced fentanyl requirement (by 0.5 and 0.6 mcg/kg) vs ICN blocks (Kaushal 2019 **Level II**, n=108, JS 3).

Sternal bed block single injections

In paediatric cardiac surgical patients having a median sternotomy, parasternal 2nd to 6th intercostal space injections of ropivacaine 0.5% 0.5−2 mL per level (total dose <5 mg/kg) reduced pain scores (MD 2.6/10) and postoperative fentanyl requirement (MD 3 mcg/kg) vs placebo (Chaudhary 2012 **Level II**, n=30, JS 4).

Quadratus lumborum block (QLB) single injection and CPNC

US-guided quadratus lumborum block (QLB) is performed by four approaches: Type 1 (lateral), Type 2 (posterior), transmuscular (TM or anterior) (NYSORA 2020 **GL**) and intramuscular. Use has been described for various lower abdominal surgeries in the T12−L1 dermatomal distribution. The PRAN data set provides no specific data for this block (presumed included in 'other truncal') reflecting the low frequency of use in children (Walker 2018 **Level IV**, n=256 [single injection other truncal] & 20 [other truncal CPNCs]).

In children undergoing lower abdominal surgery, TM QLB reduced pain scores (0−24 h) and analgesic requirements vs IM QLB (18.5 vs 48.1%), but with more quadriceps weakness (29.6 vs 3.7%) (Hussein 2018 **Level II**, n=54, JS 3). Post ureteral reimplantation, US-guided Type 2 QLB recipients had similar pain scores and similar vomiting incidence to US-confirmed caudal ropivacaine 0.2% 1 mL/kg/morphine 30 mcg/kg block (Sato 2019 **Level II**, n=47, JS 5). Post inguinal surgery, TM QLB vs ESPB at L1 were similarly effective (0-6h) (Aksu 2019c **Level II**, n=60, JS 4) and type 2 QLB achieved statistically lower but clinically similar pain scores vs transversus abdominis plane block (TAPB) (means <1 vs 2/10 for 0−24h), with reduced rescue requirement (12% vs 40) (Oksuz 2017 **Level II**, n=50, JS 5). TM QLB had utility in young children having day case inguinal surgery (Aksu 2018c **Level IV**, n=10) and was used for congenital hip dislocation surgery (Ahiskalioglu 2018b **Level IV**, n=2).

The use in children of QLB CPNC infusion of levobupivacaine 0.1% 5 mL/h following radical nephrectomy (Chakraborty 2015 **CR**) and ropivacaine 0.2% 5 mL/h following colostomy closure is described (Visoiu 2013 **CR**).

Transversus abdominis plane block (TAPB)

Paediatric RCT data is limited (see below), surpassed by increasing numbers in the PRAN audit, where no complications specific to TAPB were described (Walker 2018 **Level IV**, n=5,630 [TAPB] & n=199 [TAPB CPNCs]). An earlier PRAN TAPB subgroup analysis (95% US-guided) documented a low incidence of complications 0.1% (95%CI 0.02 to 0.3%): including one vascular aspiration and one peritoneal puncture without sequelae (Long 2014 **Level IV**, n=1,994). Notably, bupivacaine dosing varied widely (mean 1 mg/kg; range 0.47 to 2.29) with 7% of patients receiving potentially toxic doses (2 mg/kg) usually younger in age; this highlights the need to dose according to weight. No

LAST events were reported. US-guided TAPB in children provides abdominal wall sensory block below T10 with 0.4 mL/kg local anaesthetic injection (Palmer 2011 **Level IV**, n=27 [38 TAPB]).

Transversus abdominis plane block: single injection

In a systematic review of heterogeneous RCTs, TAPB is superior to wound infiltration for pain scores at rest at 8 h (7 RCTs, n=416) and 24 h (7 RCTs [2 paediatric], n=425) (Guo 2015 **Level I** [PRISMA], 9 RCTs [3 paediatric], n=500 [176 children]). In the paediatric RCTs, TAPBs vs wound infiltration reduced paracetamol rescue use (1 RCT [inguinal], n=57), with no overall difference in morphine requirements following open pyeloplasty (1 RCT [n=32) or laparoscopic appendicectomy where more TAPB recipients had complicated appendicitis (31 vs 11%) (1 RCT, n=87). In contrast, ipsilateral TAPB reduced morphine requirements vs saline block in open appendicectomy, where perforation and positive histopathology rates were similar (Hamill 2016 **Level I** [PRISMA], 1 RCT: Carney 2010 **Level II**, n=40 JS 4). Several subsequent studies are mostly positive:

- Post laparoscopy, TAPB was superior to surgical site infiltration (Karnik 2019 **Level II**, n=92, JS 4);
- Post mixed abdominal surgery, TAPB was effective and more so with higher dose bupivacaine 0.25% vs 0.125% (with adrenaline/epinephrine 5mcg/mL) 1 mL/kg (Suresh 2015b **Level II**, n=36, JS 5);
- Following ureteral reimplantation, TAPB was effective (0.5 mL/kg) vs caudal block with less morphine (although higher initial PACU pain scores) (Baeriswyl 2018 **Level I** [PRISMA], 10 RCTs, n=505 [4 paediatric, n=195], 1 RCT: Bryskin 2015 **Level II**, n=45, JS 3);
- Following colorectal procedures, TAPB was effective where 90% of infants had pain scores of 0/7 for 24 h (Chen 2015 **Level IV**, n=10);
- Following inguinal surgery, US-guided TAPB bupivacaine 0.25% 0.4 mL/kg vs no block attenuated the surgical stress response (Abu Elyazed 2016 **Level II**, n=60, JS 2). TAPB was more effective than surgical site infiltration (Kendigelen 2016 **Level II**, n=40, JS 2), similarly effective vs caudal block (Baeriswyl 2018 **Level I** [PRISMA], 1 RCT: Sethi 2016 **Level II**, n=80, JS 3) and both TAPB and caudal were more effective vs ilioinguinal-iliohypogastric nerve block (II/IHNB) (Sahin 2017 **Level II**, n=90, JS 3). In contrast, low volume US-guided TAPB 0.3 mL/kg was inferior to US-guided ilioinguinal block in early rescue analgesic requirement (Fredrickson 2010 **Level II**, n=41, JS 3); and
- Post robot assisted laparoscopic renal/urological procedures, neither TAPB nor caudal provided additional benefit vs no block (Faasse 2015 **Level III-2**, n=120).

Transversus abdominis plane block CPNCs

US-guidance is used for TAPB CPNC insertion (97% US-guided) (Walker 2015a **Level IV**, n=58 [TAP CPNCs]). TAPB CPNC infusions have been employed in small children (weighing ≤10 kg) where epidural use was contraindicated or refused (Bakshi 2017 **Level IV**, n=2; Visoiu 2012 **Level IV**, n=6).

Rectus sheath block (RSB)

Rectus sheath block (RSB) provides analgesia for midline abdominal procedures with block of the 7th to 11th intercostal nerve terminal branches (Visoiu 2015 **NR**). There has been wide variation in the dose and volume of local anaesthetic used for RSB: mean bupivacaine dose 0.72 mg/kg (95%CI 0.23 to 2.30) and ropivacaine 1.19 mg/kg (95%CI 0.39 to 2.43) (Suresh 2018a **Level IV**, n=2,331 [RSB]).

Compared to systemic analgesia, RSB has longer time to first morphine rescue (19 min; 95%CI 6 to 33) (3 RCTs [RSB], n=222) and reduces early postoperative morphine consumption at 6−8 h (MD -20 mcg/kg; 95%CI -30 to -10) (4 RCTs [RSB], n=235) (Hamill 2016 **Level I** [PRISMA], 5 RCTs [RSB 4 umbilical and 1 laparoscopic appendicectomy], n=287; Suresh 2014 **Level I** [PRISMA]: 2 RCTs [RSB], n=65) (2 RCT overlap).

Subsequent RCTs show US-guided RSB is similarly effective vs surgical site infiltration for laparoscopic assisted inguinal hernia repair (Uchinami 2017 **Level II**, n=34, JS 3) and for umbilical surgery vs both caudal and pre-incision surgical site infiltration (Relland 2017 **Level II**, n=39, JS 5), independent of whether surgically or US-placed (Litz 2017 **Level II**, n=58, JS 3).

Ilioinguinal/iliohypogastric nerve block (II/IHNB)

The ilioinguinal/iliohypogastric nerve block (II/IHNB) is used for pain relief following inguinal surgery in children. Dosing is variable per PRAN audit data where mean dose for bupivacaine was 0.68 mg/kg (95%CI 0.23 to 1.66) and for ropivacaine 0.95 mg/kg (95%CI 0.29 to 2.48) (Suresh 2018a **Level IV**, n=3,892 [II/IHNB]). Of note, after II/IHNB landmark technique, weak hip flexion (inadvertent FNB) occurred in 8.8% (95%CI 5.1-13.9%) (Lipp 2004 **Level IV**, n=182). Bowel puncture has been described with resultant subserosal haematoma noted during appendicectomy without consequence (Frigon 2006 **CR**), persistent superficial infection with skin flora (Johr 1999 **CR**) and development of intestinal obstruction resulting in laparotomy and bowel resection (Amory 2003 **CR**).

Single vs double injection II/IHNB landmark techniques have similar success rates of 72% (1 RCT, n=87), with similar efficacy of different needle insertion sites (1 cm inferomedial to ASIS; 1 to 2 cm medial to ASIS; 2 cm superomedial to ASIS) (1 RCT, n=132) (Suresh 2014 **Level I** [PRISMA], 15 RCTs [II/IHNB], n=1,046). US-guidance improves the success rate of II/IHNB to 94% with smaller volumes of local anaesthetic administered (2 RCTs, n=166). With US study post landmark technique demonstrating intramuscular injection was common (82%: iliac 18%, transversus 26%, internal oblique 29% or external oblique 9%) and intraperitoneal uncommon (2%) (Weintraud 2008 **Level III-2**, n=62). The overall block success rate was 61%: of those where injectate was deposited in the correct plane, 100% were successful vs when injected into surrounding tissues, 45% failed clinically.

For II/IHNB, the same dose at two concentrations/volumes was similarly effective (1 RCT, n=72) and higher doses were effective for longer (1 RCT, n=60) (Suresh 2014 **Level I**, [PRISMA], 2 RCTs [II/IHNB dose], n=132). Similar analgesic efficacy following inguinal hernia repair has been found with wound infiltration, II/IHNB or caudal analgesia (Baird 2013 **Level III-1 SR,** 1 RCT: Machotta 2003 **Level II**, n=58, JS 4; Splinter 1995 **Level II**, n=200, JS 5).

After US-guided II/IHNB, plasma ropivacaine concentrations were higher and peaked earlier by ≈5 min at 1.78 mcg/mL (range 0.56-2.97) vs 1.23 mcg/mL with landmark technique (Suresh 2014 **Level I SR**, [PRISMA], 1 RCT: Weintraud 2009 **Level II**, n=66, JS 3).

10.6.2.4 | Superficial head and neck blocks

Scalp blocks

Blocks of scalp branches of the frontal (supraorbital, supratrochlear), maxillary (zygomaticotemporal) and auriculotemporal nerves as well as branches of the superficial cervical plexus (greater auricular and occipital nerves) have been used in a small number of children, as an adjunct to postoperative opioids, following craniosynostosis repair (Rothera 2014 **Level III-2**, n=78; Pardey Bracho 2014 **Level IV**, n=32) and neurosurgery (Pardey 2008 **Level IV**, n=3) including in a 700 gm neonate (Suresh 2004b **CR**). See also Section 8.1.8.

Infraorbital nerve block

In addition to use in cleft lip repair (Suresh 2012 **NR**) (see Section 10.6.6 below), infraorbital block has described applications for endoscopic maxillary sinus surgery (Higashizawa 2001 **Level II**, n=50, JS 3) and trans-sphenoidal hypophysectomy (McAdam 2005 **Level IV**). Use of bilateral infraorbital blocks with block of the external nasal branch of the anterior ethmoidal nerve has been used as an alternative option for intra and postoperative pain management of nasal fracture repair (Cok 2015 **CR**).

Superficial cervical plexus block

Superficial cervical plexus block has provided relief in paediatric patients for internal jugular haemodialysis catheter insertion (Ciftci 2014 **Level IV**), thyroplasty in an awake patient (Suresh 2004c **CR**) and cochlear implant (Merdad 2012 **Level III-3**, n=91), though there was association with postoperative fever in the latter.

Blocks for ear surgery

Greater auricular nerve block (GANB) provided near equivalent analgesia with reduced PONV vs IV morphine following tympanomastoid surgery (Suresh 2002 **Level II**, n=40, JS 4). Pre-incision GANB vs placebo in addition to GANB performed at surgery completion did not affect postoperative pain scores, analgesia requirements, time to rescue analgesia or PONV (Suresh 2004a **Level II**, n=40, JS 4). For otoplasty, GANB with lesser occipital nerve block provided equivalent analgesia to surgical site infiltration (Cregg 1996 **Level II**, n=43, JS 2) and local anaesthetic infiltration alone had reduced PONV vs in local/general anaesthesia recipients (Lancaster 2003 **Level III-3**, n=85).

Following bilateral myringotomy and tube insertion, postoperative pain scores or PONV did not differ with auricular (vagal nerve branch) block vs IN fentanyl (Voronov 2008 **Level II**, n=200, JS 4).

10.6.2.5 | Continuous local anaesthetic wound catheter infusions

The evidence for use of wound catheter infusions in children is limited. One RCT was negative where, in children undergoing median sternotomy for ASD closure (with mediastinal drain), wound catheter ropivacaine 0.2% infusion ≈0.35 mg/kg/h vs placebo infusion did not benefit pain scores, opioid consumption (0-72 h), PONV nor time to mobilisation (Mattila 2016 **Level II**, n=49, JS 5). The remaining RCTs have been positive:

- Continuous wound catheter recipients had lower postoperative pain scores (2.5/10 vs 3.5) (with 4-fold lower morphine use) after open appendicectomy vs systemic analgesia and after laparotomy vs epidural analgesia (2.5/10 vs 3.0) (and 1.75 fold lower morphine use) (Machoki 2015 **Level II**, n=71, JS 5). Wound catheter recipients mobilised earlier with no difference in surgical site complications.
- For ear reconstruction cartilage graft site pain, a surgically placed para-rectus 72 h wound catheter infusion ropivacaine 0.2% 2−4 mL/h had extended analgesic benefits vs single injection ICNB ropivacaine 0.75% (Niiyama 2016 **Level II**, n=48, JS 2). Mean plasma concentrations of ropivacaine were low at 0.9 mg/L at 2 and 24 h and 0.7 at 48 h.
- In children with spina bifida undergoing open urinary tract surgery, a wound catheter infusion vs an opioid infusion or PCA (in conjunction with multimodal analgesia) achieved similar pain scores with reduced morphine equivalent use by two thirds and reduced antiemetic requirement (Chalmers 2015 **Level III-2**, n=36).
- For Nuss surgery, wound catheter recipients (who also received hydromorphone PCA, low dose gabapentin 100-200 mg three times daily and clonidine patch 50 mcg/d) had similar pain scores to thoracic epidural infusion recipients (ropivacaine 0.2%/hydromorphone 10 mcg/mL) (Choudhry 2016 **Level III-3**, n=32). While in a study exploring the addition of preoperative self-hypnosis training, wound catheter recipients had higher pain scores but lower PCA opioid requirement vs thoracic epidural recipients (Manworren 2018 **Level III-3**, n=53). In a further study, wound catheter (ropivacaine 0.2%) recipients also had higher mean postoperative pain scores vs thoracic epidural (bupivacaine 0.1%) recipients (3.8/10 vs 2.9) (Thaker 2019 **Level III-3**, n=124). In all three studies, wound catheter recipients had shorter mean LOS: 2.9 d vs 4.1 (Choudhry 2016 **Level III-3**, n=32), 4.4 d vs 5.1 (Manworren 2018 **Level III-3**, n=53) and 4.9 d vs 5.6 (Thaker 2019 **Level III-3**, n=124).

- In neonates following major thoraco-abdominal surgery, wound catheters infusing levobupivacaine 0.125% 0.16mL/kg/h (0.2 mg/kg/h) were used in addition to paracetamol and IV clonidine (Krylborn 2015 **Level IV**, n=20). Median plasma levobupivacaine concentrations over 12−72 h were low [free 0.018 mg/L; total 1.305 mg/L], with 90% of infants' free concentrations remaining below 0.05 mg/L for the duration of the infusion.

10.6.2.6 | Adjuvants in PNBs

Multiple studies have been performed assessing the addition of various adjuvants in PNBs, usually without systemic comparator, and are summarised below.

Alpha-2 agonist adjuvant use in PNBs

Results of RCTs for adjuvant use of alpha-2 agonists are contradictory with small sample sizes, variation in dosing and operation type (major vs minor). To date they have lacked a systemic comparator arm.

Two overlapping SRs are contradictory. The first concludes alpha-2 agonists increase single injection PNB duration with longer time to first rescue analgesic administration based on predetermined pain score change (Lundblad 2016 **Level I**, 3 RCTs & 2 unpublished RCTs' abstracts [4 clonidine, 1 dexmedetomidine], n=283). The time until 25% of patients needed rescue analgesia was ≈6 h longer with alpha-2 agonist/local anaesthetic vs local anaesthetic alone (HR 1.7; 95%CI 1.1 to 2.4) with no complications reported. The prolongation occurred across all the heterogeneous PNBs assessed (Lundblad 2016 **Level I**, 3 RCTs & 2 unpublished RCTs' abstracts, n=283). This finding was also reported in an earlier study (Cucchiaro 2007 **Level III-2**, n=435) where motor block duration was shorter for blocks without adjuvant clonidine (OR 0.33; 95%CI 0.16–0.69).

The second systematic review was negative: concluding clonidine 1−2 mcg/kg added to local anaesthetic does not confer any additional benefit in postoperative pain outcomes for caudal or II/IHNB for inguinal surgery or axillary block for arm surgery (Suresh 2014 **Level I** [PRISMA], 2 RCTs [inguinal], n=160 & 1 RCT [axillary]: Trifa 2012 **Level II**, n=60, JS 5) (2 RCT overlap). A third non-overlapping systematic review of paediatric tonsillectomy concludes no benefit with fixed dose clonidine 25mcg added to peritonsillar local anaesthetic infiltration (Vlok 2017 **Level I**, 2 RCTs [clonidine], n=123).

Subsequent studies are positive with increased duration of analgesia with adjuvant clonidine 1 mcg/kg added to:

- Local anaesthetic DPNB (Anouar 2016 **Level II**, n=40 JS 3) and to nerve stimulator-guided pudendal nerve block for penile surgery (Naja 2013 **Level II**, n=80, JS 5); and
- Bilateral infraorbital nerve blocks for cleft lip surgery (Feriani 2016 **Level I** [Cochrane], 1 RCT: Jindal 2011 **Level II**, n=50, JS 5);

And adjuvant dexmedetomidine 1-2 mcg/kg added to:

- Greater palatine nerve blocks for cleft palate repair (time to first analgesia mean 22h vs 14.2) with no side effects (Obayah 2010 **Level II**, n=30, JS 3);
- II/IH block where the addition doubled the time to first analgesic request following inguinal surgery (Arirachakaran 2018 **Level II**, n=60 JS 5);
- TAPB reduced postoperative morphine requirements and reduced the ED_{min} for bupivacaine from 0.08% to 0.06% (assessed by haemodynamic changes to skin incision at 15 min) for inguinal surgery (Raof 2017 **Level II**, n=60 JS 5).

Adrenaline

Adrenaline as an additive has been used in various PNBs as described in this section; but has not been analysed as an adjuvant comparator in PNBs.

Opioids

Opioids are used frequently as part of multimodal analgesia and rescue therapy in patients receiving PNBs. There are 2 RCTs where the addition of opioids to infraorbital nerve block have been assessed as an adjuvant, without systemic route comparator (see cleft lip Section 10.6.6).

Systemic and perineural steroids – dexamethasone

For tonsillectomy, a Cochrane review is positive for multiple outcomes (see Section 10.4.10 for systemically administered dexamethasone). The below RCTs assess dexamethasone of varying doses 0.1−0.5 mg/kg as an adjuvant to local anaesthesia in PVBs, by perineural and systemic routes.

The adjuvant use of dexamethasone:

- IV 0.5 mg/kg (max unspecified) vs placebo added to DPNB reduced pain scores with longer time to rescue following hypospadias repair, (Shirazi 2016 **Level II**, n=42, JS 3);
- IV 0.15 mg/kg (max 8mg) added to glossopharyngeal nerve block provided superior postoperative analgesia to either in isolation (Mohamed 2009 **Level II**, n=150, JS 3). However, glossopharyngeal nerve block in 2 children has been associated with postoperative airway obstruction (Bean-Lijewski 1997 **Level III-3**, n=8);
- Peritonsillar infiltration added to local anaesthetic reduced analgesic use and PONV incidence (RR 0.56; 95% CI 0.35 to 0.89) following tonsillectomy (2 RCTs, n=299) (Vlok 2017 **Level I**, 3 RCTs [dexamethasone: 2 paediatric], n=361 [309 children]). Infiltration of 0.5 mg/kg (max 8 mg) added to local anaesthetic reduced early and later (>12 h) pain scores vs bupivacaine alone and placebo, where all patients received IV dexamethasone 0.5mg/kg (max 16 mg) (Kilinc 2019 **Level II**, n=120, JS 5);
- In US-guided PVB, expedited extubation by ≈5 h and reduced pain scores at 12 and 24 h following coarctation repair in infants (Saleh 2018 **Level II**, n=50, JS 4);
- While adding perineural or IM dexamethasone to FNB did not further improve analgesia following knee arthroscopy in teenagers (Martin 2018 **Level II**, n=77, JS 5).

Ketamine

Adding IV ketamine 0.5mg/kg to peritonsillar bupivacaine 0.25% was more effective than IV placebo/peritonsillar bupivacaine infiltration, and IV placebo/placebo infiltration with lower pain scores (1−24 h) and longer time to first analgesia (Inanoglu 2009 **Level II**, n=90, JS 5).

See Section 10.4.7.1 for summary of 3 overlapping systematic reviews assessing peritonsillar ketamine administration as a comparator vs placebo and one RCT of peritonsillar administration vs other systemic routes.

Magnesium

The addition of peritonsillar magnesium 2-5 mg/kg (max unspecified) to local anaesthetic reduced pain scores (4 RCTs, n=230) and the number of analgesic requests (WMD −0.68; 95% CI −1.17 to −0.18) (3 RCTs, n=180) (Vlok 2017 **Level I**, 4 RCTs [Mg], n=230).

Tramadol

Tramadol has been assessed as a comparator arm in various RCTs by systemic administration and infiltration and nerve block summarised in Section 10.4.4.12. See also below 10.6.6 for an RCT of peritonsillar infiltration of tramadol as an adjuvant.

Midazolam

Midazolam has not been assessed as an adjuvant for PNBs.

10.6.3 | Neuraxial blocks

Central neuraxial block is used in paediatric patients to provide postoperative analgesia and to supplement intraoperative anaesthesia. Patient selection, technique, choice of medicines, availability of experienced staff for performing blocks, an APS or outpatient resources and adequacy of follow-up vary between centres (Williams 2003 **NR**).

10.6.3.1 | Epidural analgesia

As the epidural space is relatively large with loosely packed fat in neonates, catheters can be threaded from the sacral hiatus to lumbar and thoracic levels (Tsui 2004 **Level IV**). Accuracy of caudal-epidural catheter placement in young infants (2 d to 5 mth) to the desired vertebral level was improved with US-guidance vs external measurement in one study (Ponde 2017 **Level IV**, n=25). In older infants, various techniques have been suggested to improve correct placement including US, nerve stimulation and ECG guidance (Willschke 2006 **Level IV**, n=64; Tsui 2004 **Level IV**, n=10; Tsui 2002 **Level IV**). US provides visibility of the dura mater and ligamentum flavum, especially in infants and younger children.

Insertion of epidural catheters at the segmental level required for surgery was more reliable in older children and has been shown to be safe in experienced hands with appropriately sized equipment (Walker 2018 **Level IV**, n=13,120 [epidural catheters] & 854 single injection epidurals (not including caudal); Llewellyn 2007 **Level IV**, n=10,633 [epidural]; Giaufre 1996 **Level IV**, n=2,396 [epidural]). Cephalad or caudad migration (assessed by x-ray) of caudal-thoracic epidural catheters occurred in 64% of patients (1 d to 10 mth old); however >1 level of migration occurred only in infants ≤6 kg (Simpao 2019 **Level IV**, n=85). In older children with a thoracic epidural catheter, catheter migration was also related to patient size: 1.1 level change in those <40 kg and less change of 0.3 level in those ≥40 kg (where catheters fell out in 10% of patients) (Strandness 2015 **Level IV**, n=59).

MRI anatomical studies have shown the largest dura to spinal cord distance is mid thoracic at T5/6 and the smallest at the L2/3 region (Wani 2018 **Level IV**, n=88 patients). A formula for the mean skin to epidural space distance at L3/4 in ≤6 y olds based on MRI data (9 + 0.62 x weight kg=depth in mm) may be more accurate than previously reported formulas based on depth of needle insertion (Franklin 2015 **Level IV**, n=70).

Furthermore, MRI has shown spinal cerebrospinal fluid (CSF) volumes per kg are less in children (0–18 y) than previously predicted (Jang 2019 **Level IV**, n=500 [248 thoracolumbar]). Thoracolumbar CSF volume (T1 to end of dural sac) reduced with increasing age (r 0.66: <1 y mean 1.95 mL/kg vs >12 y 0.99), height (r 0.72), and weight (r 0.73). In young children 0–3 y, MRI study demonstrated the median epidural space volume per vertebral segment: the lumbar value was 1.18 mL/kg (95%CI 0.94 to 1.43) and the thoracic value was half that at 0.60 mL/kg (95%CI 0.38 to 0.75) (Forestier 2017 **Level IV**, n=20).

Ultrasound can identify normal and abnormal spinal anatomy in children (6–12 y) post myelomeningocoele repair, facilitating selection of the optimal intervertebral space for epidural catheter placement (Ponde 2018 **Level IV**, n=12).

Ultrasound is a reliable predictor of depth to loss of resistance (or depth of epidural space), offers visibility of the needle and catheter, and may reduce bone contacts (Guay 2019a **Level I** [Cochrane], 1 RCT overlap with Tsui 2010 **Level IV SR** [PRISMA], 1 RCT: Tachibana 2012 **Level II**, n=20 JS 1). US prescanning vs landmark technique in children (mean age 10 y) having a Nuss procedure decreased the time to insert a thoracic epidural catheter (by ≈1 min: median 1.67 min vs 2.75) (not including pre-scanning time). Whilst continuous US scanning in neonates to 6 y olds reduced epidural lumbar or thoracic catheter insertion time (mean 2.7 min vs 3.9) (Guay 2019a **Level I** [Cochrane], 1 RCT: Willschke 2006 **Level II**, n=64 JS 1).

Local anaesthetics

Continuous epidural infusions of bupivacaine are effective and safe in children (Walker 2018 **Level IV**, n=13,120 [epidural catheters]; Wong 2013a **Level IV**, n=3,152 [epidurals]; Ecoffey 2010 **Level IV**, n=10,098; Llewellyn 2007 **Level IV**, n=10,633). In children <4 y having abdominal surgery, bupivacaine 0.25% epidural infusion (0.1 mL/kg/h) vs morphine infusion were similarly effective (Wolf 1993 **Level II**, n=32, JS 3). In children aged 7–12 y having lower extremity major orthopaedic surgery, patient-controlled epidural analgesia (PCEA) ropivacaine 0.2% vs continuous infusion both achieved low pain scores (≤1/10) in the first 48 h postoperatively (Antok 2003 **Level II**, n=48, JS 2). Total ropivacaine dose was reduced with PCEA (0.2 mg/kg/h vs 0.4 mg/kg/h) but no differences in adverse effects were detected.

In neonates, due to reduced clearance and the potential for accumulation of bupivacaine, the hourly dose should be reduced, and the duration of therapy limited to 24–48 h (Larsson 1997 **Level IV**; Ivani 2015 **GL**). Postnatal age and weight influence the pharmacokinetic profile of levobupivacaine, with slower absorption and clearance in neonates and infants (Chalkiadis 2006 **Level IV**, n=86). Total plasma levobupivacaine concentrations after caudal epidural bolus in 3–6 mth old infants peaked at 1 h post 2 mg/kg at 0.30 mg/L (range: 0.20–0.70) (Vashisht 2019 **Level IV PK**, n=8). During subsequent infusion of 47 h duration, the total plasma level increased (with rising alpha-1 acid glycoprotein); however free plasma concentrations plateaued at steady state early, remained low at 0.03 mg/L and were cleared rapidly over ≈12 h post cessation. In infants >6 mth, although plasma levobupivacaine concentrations increased, they remained low after 24 h of epidural infusion (Lerman 2003 **Level II**, n=120, JS 5). Epidural infusions of ropivacaine were effective and safe in neonates (Bosenberg 2005 **Level IV**) and children (Berde 2008 **Level IV**) with minimal drug accumulation.

Postoperative continuous epidural infusion with chloroprocaine 1% (0.4–3 mL/h) or 1.5% (0.25–1.5 mL/kg/h) for 7–118 h has been used in neonates, infants and children having various surgeries, (Veneziano 2016 **Level IV**, n=21 [15 ≤6 mth]; Ross 2015 **Level IV**, n=18 [≤6 mth]; Kamata 2014 **CR**), and was similarly effective to ropivacaine 0.1% in infants (≤6 mth) post-thoracotomy (Muhly 2015 **Level III-2**, n=54). No serious adverse events related to epidural analgesia were reported in any of the three studies. As an ester local anaesthetic which is rapidly metabolised in plasma at all ages including neonates, chloroprocaine may have a lower risk of accumulation and LAST than amide local anaesthetics in neonates and young infants with immature hepatic enzymes (Veneziano 2017 **NR**).

For infants (median age 59 d) having a Kasai portoenterostomy, epidural local anaesthetic (with various adjuvants: fentanyl or hydromorphone with clonidine in 56%) vs no epidural had lower pain scores from 6–30 h (highest median score 0.2/10 vs 2.1), were more likely to be extubated in theatre (88% vs 59%) and had shorter LOS (median 6 d vs 8) (Phelps 2019 **Level III-2**, n=47).

In children (5 mth to 12 y) having ureteric reimplantation surgery, patients with a caudal epidural catheter threaded 5–7cm vs lumbar epidural catheters (bupivacaine 0.125%/fentanyl 2 mcg/mL infusions at 0.1–0.3 mL/kg/h) had less interventions for bladder spasms (mean 1.8/patient vs 8) and wound pain (mean 8.8/patient vs 11.4) (Sommerfield 2016 **Level III-2**, n=135 [catheter]).

In infants (<12 mth) having a laparotomy, epidural analgesia vs systemic analgesia resulted in similar opioid administration 0–48 h and similarly adequate pain scores for 0–72 h postoperatively but with less sedation (13% vs 30%) (Martin 2019 **Level III-2**, n=82).

Epidural opioids alone

Epidural opioids alone have a limited role. Epidural morphine provided prolonged analgesia but no improvement in the quality of analgesia vs systemic opioids (Bozkurt 2004 **Level II**, n=32, JS 1). Without a systemic or epidural local anaesthetic comparator, epidural morphine 0.1 mg/kg vs epidural

tramadol 2 mg/kg had similar pain scores and time to first rescue analgesic but with higher rates of adverse effects (Demiraran 2005 **Level II**, n=80, JS 3). Epidural fentanyl 1 mcg/mL alone was less effective than both levobupivacaine 0.0625% and 0.125% alone and levobupivacaine/fentanyl combined (Lerman 2003 **Level II**, n=114, JS 5). Bolus doses of epidural morphine 20–30 mcg/kg were less effective than epidural infusions of fentanyl 1–2 mcg/mL and local anaesthetic (Reinoso-Barbero 2002 **Level II**, n=30, JS 1; Kart 1997 **Level II**, n=30, JS 5). IV Ketoprofen improved analgesia vs saline when given in conjunction with epidural sufentanil (Kokki 1999 **Level II**, n=54, JS 5).

10.6.3.2 | Caudal analgesia

Despite innovation and increasing use of PNB, caudal analgesia remains a commonly performed regional technique (comprising 27–40% of audited blocks), especially in the smaller paediatric patient (Ecoffey 2010 **Level IV**, n=8,493 [caudal]; Walker 2018 **Level IV**, n=38,116 single injection caudal and 2,016 lumbosacral caudal catheters), although single injection caudal block has been used effectively in older children weighing 30 to 50 kg (Keplinger 2016 **Level IV**, n=20). Single injection caudal block provides intra and postoperative analgesia and is generally used for surgery on the lower abdomen, perineum and lower limbs (see Table 10.9 and for comparison with PNBs Section 10.6.2.1). Large series have reported a high success rate (particularly in children aged <7 y) and a low incidence of serious complications (Walker 2018 **Level IV**, n=40,132 [PRAN]; Suresh 2015a **Level IV**, n=18,650 [PRAN]; Ecoffey 2010 **Level IV**, n=8,493; Giaufre 1996 **Level IV**, n=12,111). The complication rate for single injection caudal blocks was 1.9% (95%CI 1.7% to2.1): most commonly these were failure 1% (95%CI 0.8 to 1.1), blood aspiration 0.6% (95%CI 0.5 to 0.8) and a positive test dose indicating intravascular injection 0.1% (95%CI 0.1 to 0.2) (Suresh 2015a **Level IV**, n=18,650). There was one seizure (in a 1 mth old) and one cardiac arrest (in a 36 mth old), and no complications that led to long term sequelae. Total plasma concentrations have been documented post administration of ropivacaine 3.1 mg/kg in larger children (30-50 kg) and were low, 1.16 mg/L (range 0.65 to 2.61), peaking at 1 h (95%CI 0.5 to 1.5) (Keplinger 2016 **Level IV**, n=20).

Caudal bupivacaine, levobupivacaine and ropivacaine produced similar times to onset of block and quality of postoperative analgesia (Sharma 2018 **Level II**, n=90, JS 3; Praveen 2017 **Level II**, n=60, JS 4; Cinar 2015 **Level II**, n=80, JS 2; Ingelmo 2006 **Level II**, n=86, JS 5; Frawley 2006 **Level II**, n=310, JS 5; Ivani 2005 **Level II**, n=60, JS 5; Breschan 2005 **Level II**, n=182, JS 3).

Concentration-dependent differences have been noted for individual agents. Ropivacaine 0.175% was superior to lower concentrations and was as effective as a 0.2% solution but produced less motor block (Khalil 2006 **Level II**, n=74, JS 5). In children aged 1–3 y having inguinal surgery, six concentrations of levobupivacaine were administered (0.08–0.18%, 1 mL/kg) (Yao 2009 **Level II**, n=60, JS 5); for caudal analgesia, this study established the EC_{50} as 0.109% (95%CI 0.098 to 0.120) and the EC95 as 0.151% (95%CI 0.135 to 0.193).

The PRAN data provides information of large variation in local anaesthetic dosing practices for caudal blocks (IQR, 1.23 to 1.98 mg bupivacaine/kg) (Suresh 2015a **Level IV**, n=17,867 [dosing known]). This was not explained by weight differences (r 0.5; 95%CI 0.48 to 0.52). This may in part reflect the desire for differential block heights. Importantly, 25% recipients received doses >2 mg/kg of bupivacaine equivalents and 5.4% received >2.5 mg/kg that could be potentially unsafe.

The volume administered directly influences the height of block achieved. The spread of caudal block has been measured clinically (assessing dermatomes and myotomes) and the vertebral height measured by US, contrast and MRI studies (see Table 10.9). Dosing in volume based on weight is practical. For effective caudal analgesia, volumes of 0.5–0.7 mL/kg are used for sacral dermatome surgery and 0.8–1 mL/kg for lumbar and lower abdominal dermatome surgery. Higher volume 1.2–1.5 mL/kg blocks are effective for abdominal and thoracic surgery; spread above the T12 dermatome occurs most reliably in neonates and infants.

Table 10.9 | Block height following caudal injection in children using different formulae

Surgery type Patient number and age	Local anaesthetic agent (%) and additives	Volume used vs suggested formula	Block height achieved
Clinical			
Study	McGown 1982 **Level IV**		
Upper abdominal; lower abdominal; lumbosacral; sacral n=500 Height assessed in 360 aged 6 mth–10 y	Lidocaine 1% (with adrenaline 5 mcg/mL)	1.65 mL/kg 1.1 mL/kg 0.55 mL/kg	T2–T8 T8–T12 L1–S3
Outcome/conclusion	Volume/weight calculation successful for 430 (86%)		
Study	Satoyoshi 1984 **Level IV**		
Abdominal Paediatric cadaver radio-opaque contrast study: n=16 Clinical: n=21 Aged 1 mth–11 y	Bupivacaine 0.25–0.375% or Mepivacaine 0.75–1.5%	1 mL/kg or Spiegel formula (x1–1.5) Developed new formula: mL=[(cm in distance from C7 to sacral hiatus) – 13]	New formula achieved T4–5 height assessed by response to painful stimulus
Outcome/conclusion	Reduced thoraco-abdominal musculature movement; abdominal surgery successfully completed		
Study	Coad 1989 **Level II**, n=60, JS 3		
Inguinal n=48 (including 2 failures); mean age 2 1 y	Bupivacaine 0.25% Bupivacaine 0.25% Bupivacaine 0.5%	1 mL/kg vs formula ([Age in years]+2)mL	
Outcome/conclusion	No difference found for weight- vs formula-based dosing with similar postoperative pain scores.		
Study	Verghese 2002 **Level II**, n=50, JS 4		
Orchidopexy n=50 aged <6 y	Bupivacaine 0.25% Vs Bupivacaine 0.2% (both with adrenaline 5 mcg/mL and sodium bicarbonate 8.4% 0.1 mL/10 mL)	0.8 mL/kg vs 1 mL/kg	35% to T 10 vs 70% to T10 (assessed with spermatic cord traction test)
Outcome/conclusion	Higher volume lower concentration had less response to spermatic cord traction. The sample was too small to detect a difference in postoperative rescue analgesia (fentanyl 7 vs 17% p=0.4; paracetamol 59 vs 74% p=0.37).		

Surgery type Patient number and age	Local anaesthetic agent (%) and additives	Volume used vs suggested formula	Block height achieved
Ultrasound			
Study	Lundblad 2011 **Level IV**		
Subumbilical surgery: urogenital, anal, foot, and inguinal n=50 aged 0–4 y	Ropivacaine 0.2%	All received 1.5 mL/kg with volume/kg noted once T12 reached: Formula generated by US was lower than studies with dermatomal testing: mL per spinal segment=(0.154 x kg) minus 0.094	Block ≥T12 vertebral level on US in 93% neonates, 73% infants and 25% young children.
Outcome/conclusion	Inverse relationship with age (r 0.8) and weight (r 1.0).		
Study	Brenner 2011 **Level II**, n=75, JS 5		
Anal, penile and inguinal n=75, median age 21–32 mth	Ropivacaine 0.2% if <12 mth Ropivacaine 0.35% if >12 mth	0.7 mL/kg 1.0 mL/kg 1.3 mL/kg	Median vertebral height L2; same for age <12 or >12 mth.
Outcome/conclusion	Weak inverse correlation with weight, height, BMI.		
X-ray contrast study			
Study	Chan 2010a **Level II**, n=73, JS 4		
Orchidopexy n=73; aged 1–5 y	Ropivacaine 0.225% vs Ropivacaine 0.15%	 1 mL/kg 1.5 mL/kg	Median height (range) T6 (T3–11) T11 (T8–L2);
Outcome/conclusion	No difference in recovery times, postoperative pain scores or adverse effects Higher volume/lower concentration had longer time to acetaminophen rescue (9.2 vs 6.1 h; p<001) and reduced requirement (50 vs 76%; p=0.03).		
Study	Koo 2010 **Level III-2**, n=83		
Perineal, inguinal, orchidopexy n=87 recruited: 83 had caudal aged 6 mth–4.5 y	Ropivacaine 0.2%	0.5 mL/kg 1 mL/kg 1.25 mL/kg	Median height (range) L2 (L4–T12) T12 (L1–T8) T10 (L2–T7)

Surgery type Patient number and age	Local anaesthetic agent (%) and additives	Volume used vs suggested formula	Block height achieved
Outcome/conclusion	More segments were covered per mL administered with younger age: mean number of segments (SD) of 1.3 (0.4) for <1 y, 1.1 (0.3) for 1–3 y and 0.8 (0.4) for >3 y. Dosed according to surgical type; effective for surgery in 100%, with low median postoperative pain scores (>2 h), 4% required analgesic rescue.		
Study	Thomas 2010 **Level III-2**, n=45		
Perineal/lower limb, inguinal n=45; aged 1–7 y abdominal	Bupivacaine 0.25%	0.5 mL/kg 0.75 mL/kg 1 mL/kg	Median height SEM L2 0.44 L1 0.32 T12 0.43
Outcome/conclusion	Contrast study 1 mL/kg of caudal injectate reliably achieved one vertebral level higher than 0.5 mL/kg (L2 vs L3 for 93% of patients)		
Study	Forestier 2017 **Level IV**, n=20		
Normal MRIs of spine and sacrum assessed to measure: volume of spinal canal/caudal space, dural sac, and spinal cord. From this data volume of epidural space and cerebrospinal fluid was calculated.	N/A	Median epidural volume by weight 1.30 mL/kg 1.57 mL/kg 1.78 mL/kg Median epidural volume by height 0.146 mL/cm 0.172 mL/cm 0.204 mL/cm	Predicted height L1 T10 T6 L1 T10 T6
Outcome/conclusion	The epidural space volume showed a linear relationship to both height (r 0.83) and weight (r 0.82)		

Anatomical variations

Commonly used anatomical landmarks (posterior superior iliac spines and sacral hiatus) when scanned by US do not form an equilateral triangle in children ≤7 y old (Abukawa 2015 **Level IV**, n=282) and infants (<9mth) (Mirjalili 2015 **Level IV**, n=26); the latter reported the sacral cornua were identifiable by US in all 26 infants, but could not be palpated in 4 (15%).

In an MRI study of children (<12 y), the distance between the sacro-coccygeal ligament and the dural sac correlated with weight (r 0.77), height (r 0.77), age (r 0.76) and most strongly with body surface area (r 0.80) (Lee 2017b **Level IV**, n=141). From this data, a formula to calculate the sacro-coccygeal ligament to dural sac distance (95%CI lower limit) based on BSA was developed: 25 x BSA (mm). In a neonatal cadaveric study, the mean distance from the sacral hiatus apex to the dural sac was 10.5 mm (range 4.9 to 26.2); there was a correlation between neonatal length and distance from apex of sacral hiatus to dural sac (r 0.39) such that for every

1 cm increase in neonate length, the distance increased by 3.3% (van Schoor 2018 **Level IV**, n=39). In a further series of anaesthetised children, the dural sac ended below S2/3 in 7.6% of patients (Shin 2009 **Level IV**, n=317).

Ultrasound guidance

US allows the real-time visualization of local anaesthetic spread during caudal injection (Lam 2016 **Level IV SR** [PRISMA], 11 studies [caudal], n=1,101]). Continuous US scanning vs landmark technique reduced time to perform a caudal (mean 2.42 min vs 2.73) (Lam 2016 **Level IV SR** [PRISMA], 1 RCT: Wang 2013 **Level II**, n=140 JS 3). Two subsequent RCTs in children (1–12 y) found continuous US-guided caudal injection vs landmark technique resulted in higher success on first puncture (80–93% vs 63–66%) and lower rates of vascular puncture (0–1.5% vs 11–12%) and subcutaneous bulging (0% vs 8–12%), but with a similar success rate (no movement, HR and RR change ≤20%) and mean time to perform caudal (Karaca 2019 **Level II**, n=266, JS 3; Ahiskalioglu 2018a **Level II**, n=134 JS 3).

For the use of US and other techniques to facilitate caudal epidural catheter placement, see Section 10.6.3.1 above.

10.6.3.3 | Adjuvants for epidural and caudal

Opioid and nonopioid adjuvants have been added to caudal local anaesthetic with the aim of improving the efficacy or duration of analgesia. The neurotoxicity of nonopioid spinal additives has not been systematically evaluated in neonates and children (Walker 2012c **NR**). Preservative-free morphine and clonidine are registered drugs for use in the epidural space; the remaining drugs listed below are used off label (Suresh 2018b **GL**). However, these recommendations by the European/American Society of Regional Anaesthesia endorse clonidine, dexmedetomidine, preservative-free morphine and ketamine as neuraxial adjuvants.

Epidural adjuvants

Opioids

A combination of local anaesthetic and opioid is frequently used in epidural infusions but there are limited data available to assess the relative merits of different regimens. Fentanyl 1–2 mcg/mL addition to local anaesthetic infusions had both improved analgesia (less IV opioid rescue) (Lovstad 2001 **Level III-2**) and similar analgesic effect (Lerman 2003 **Level II**, n=114, JS 5) but increased nausea and vomiting (Cho 2009 **Level II**, n=108, JS 5; Lovstad 2001 **Level III-2**). Addition of fentanyl 5 mcg/mL to bupivacaine 0.1% provided similar analgesia but increased adverse effects vs clonidine 1.2 mcg/mL with bupivacaine 0.1% (Cucchiaro 2006 **Level II**, n=47, JS 3). In children with cerebral palsy (mean age 11 y) having single event multi-level surgery (SEMLS), epidural bupivacaine 0.125% (0.25 mL/kg/h initial rate) with fentanyl 2 mcg/mL vs clonidine 2.5 mcg/mL was similarly effective over 72 h in terms of diazepam use, frequency and severity of muscle spasm, pain scores and epidural bolus requirement (Chalkiadis 2016 **Level II**, n=50, JS 4). Vomiting, antiemetic use and oxygen desaturations were more common with epidural fentanyl, whilst blood pressure and heart rate were lower in epidural clonidine recipients. For children (3–12 y old) (86% with cerebral palsy) having lower limb orthopaedic surgery, an intraoperative epidural dose of dexmedetomidine 1 mcg/kg vs fentanyl 1 mcg/kg in addition to ropivacaine 0.2% PCEA achieved lower pain scores at 6 h (median 0/10 vs 1) but not at 12–48 h (Park 2017b **Level II**, n=60, JS 5). Total ropivacaine dose, and the incidence of minor adverse effects (eg emergence agitation and nausea and vomiting) were similar. In cerebral palsy patients (3–17y) having SEMLS, adding baclofen (3 mcg/kg bolus followed by 0.5 mcg/kg/h) to 0.1% bupivacaine (with clonidine in 26–40% and fentanyl in 8–11% of patients) for continuous epidural infusion did not reduce supplemental opioid or benzodiazepine administration, pain scores or length of stay (Nemeth 2015 **Level III-2**, n=44).

Following a postoperative epidural infusion of ropivacaine 0.2% 0.15 mL/kg/h with fentanyl 0.375 mcg/kg/h (for median 38 h), fentanyl plasma levels reached a secondary peak 3–6 h post cessation, and remained detectable for longer in infants and toddlers (3 mth – 3y) than in older children (3–12 y) (mean residence time: 22.9 h vs 11.5) (Karas-Trzeciak 2015 **Level IV PK**, n=43). There was marked variability in post-infusion fentanyl PKs, which was greater in infants and toddlers than older children.

Epidural infusion of sufentanil (0.015 mcg/kg/mL)/ropivacaine 0.15% achieved similar pain scores following paediatric urological surgery with reduced rescue analgesic use but with more pruritus vs fentanyl (0.1 mcg/kg/mL)/ropivacaine 0.15% (Cho 2008 **Level II**, n=64, JS 4).

The addition of morphine 10 mcg/mL to an epidural local anaesthetic infusion was more effective than clonidine 0.6 mcg/mL (Cucchiaro 2003 **Level II**, n=26, JS 5), but higher doses of clonidine improved analgesia when added to epidural ropivacaine infusion (De Negri 2001 **Level II**, n=60, JS 4).

Tramadol 2 mg/kg has been added to ropivacaine 0.2% via the epidural route and was superior to ropivacaine alone (Inanoglu 2010 **Level II**, n=44, JS 5).

For the use of epidural morphine and hydromorphone in scoliosis surgery and pectus excavatum repair, see Section 10.6.6.

Caudal adjuvants

Opioids

Addition of morphine to caudal local anaesthetic prolonged analgesia but dose-related adverse effects were relatively common (Cesur 2007 **Level II**, n=135, JS 5; Bozkurt 1997 **Level IV**). Morphine 7.5 mcg/kg added to 0.125% levobupivacaine resulted in a lower incidence of vomiting than higher morphine doses and provided effective postoperative analgesia (Dostbil 2014 **Level II**, n=240, JS 5). Morphine 20 mcg/kg added to bupivacaine 0.166% (with adrenaline 1:600,000) 1 mL/kg was more effective (lower pain scores and fewer patients requiring rescue analgesics) than bupivacaine/adrenaline alone or with clonidine 1 mcg/kg, although with higher rates of PONV (Fernandes 2012 **Level II**, n=80, JS 5). Single injection caudal with bupivacaine 0.25% (1 mL/kg) and morphine (30–50 mcg/kg) vs IV fentanyl for infants and children (0.5–12 y) having laparoscopic surgery prolonged time to first rescue analgesia, and halved postoperative fentanyl consumption (mean 24 h cumulative dose 1.1 mcg/kg vs 2.3) (Kundu 2015 **Level III-2**, n=65).

Clinically significant respiratory depression has been reported, particularly with higher morphine doses and in younger patients (de Beer 2003 **NR**). Adverse effects are potentially fewer with lipid soluble opioids but, while fentanyl may prolong caudal analgesia (Constant 1998 **Level II**, n=59, JS 5), others have shown no benefit (Kawaraguchi 2006 **Level II**, n=35, JS 3; Baris 2003 **Level II**, n=75, JS 3; Joshi 1999 **Level II**, n=56, JS 2).

Adrenaline (epinephrine)

Adding adrenaline (epinephrine) to bupivacaine has minimal effect on the duration of analgesia, particularly in older children (Ansermino 2003 **Level I**, 3 RCTs, n=407). The influences of caudal adrenaline and/or clonidine on the absorption characteristics of caudal levobupivacaine has been evaluated (Chalkiadis 2013 **Level IV**, n=240). Adrenaline (5 mcg/mL) decreased the rate of levobupivacaine systemic absorption, reducing peak concentration by half but with minimal impact on levobupivacaine's time-concentration profile. Adrenaline (2.5 mcg/mL) addition to caudal ropivacaine slowed the T_{max}, and reduced the peak ropivacaine concentration by 35% (Van Obbergh 2003 **PK**).

Alpha-2 agonists

Addition of clonidine (1–2 mcg/kg) to caudal local anaesthetic, as assessed by two systematic reviews, prolongs analgesia by a mean difference of 3.7 (95%CI 2.7 to 4.7) and 4 h (2.8 to 5.1),

with fewer patients requiring rescue analgesics (RR 0.72; 95%CI 0.57 to 0.90) (Schnabel 2011b **Level I** [PRISMA], 20 RCTs, n=993) and (OR 0.22; 95%CI 0.13 to 0.37) (Engelman 2013 **Level I** [PRISMA], 18 RCTs, n=782) (14 RCT overlap). In assessing the sedative effects of clonidine as a caudal additive, these systematic reviews conflict; one finding positive association (OR 2.48; 95%CI 1.63 to 3.69) (Engelman 2012 **Level I** [PRISMA], 3 RCTs [sedation], n unspecified) and the other none (RR 4.76; 95% CI 0.24 to 93.19) (Schnabel 2011b **Level I** [PRISMA], 4 RCTs [sedation], n=142). Both found no reduction of PONV.

Subsequent studies of infraumbilical surgery in 1–12 y olds have similar findings for caudal clonidine where:

- 1, 2 and 3 mcg/kg dose dependently spared levobupivacaine: from 0.2% to ED50s of 0.11, 0.08 and 0.04% respectively (Disma 2011 **Level II**, n=120, JS 4). The optimal dose was 2 mcg/kg with longer time to first analgesic rescue, reduced rescue analgesic requirement and less emergence agitation vs 1 mcg/kg, with more sedation in 3 mcg/kg recipients (30% vs 10 vs 0).
- 2 mcg/kg vs fentanyl 1 mcg/kg added to ropivacaine were similarly effective, with more adverse events (POV, desaturation and bradycardia) in fentanyl treated (Shukla 2011 **Level II**, n=90, JS 4). 1mcg/kg combined with fentanyl 1 mcg/kg was superior to caudal fentanyl 1 mcg/kg (added to local anaesthetic) with prolonged analgesia duration and reduced pain scores from 1–12 h (by 0.5–1.8/13) (Jarraya 2016 **Level II**, n=40, JS 2).
- 1 mcg/kg was superior to caudal midazolam 30 mcg/kg, with both superior to bupivacaine alone with ≈2 fold increase in analgesic duration (12.1 h vs 10.1 vs 4.9) and less use of 3 rescue medications (4% vs 28 vs 60) (Sanwatsarkar 2017 **Level II**, n=75, JS 5). Intraoperative haemodynamic changes and postoperative sedation were similar between groups, however all received midazolam premedication.
- In addition to caudal local anaesthetic, caudal clonidine 1 mcg/kg was superior to IV clonidine and placebo in prolonging duration of analgesia (16.7 h vs 9.4 vs 4.2) and reducing the number of patients requiring rescue analgesia (0–24 h) (80% vs 96 vs 100%), with no difference in sedation (Potti 2017 **Level II**, n=75, JS 4).
- While clonidine (2 mcg/mL) differed from adrenaline with faster systemic absorption of levobupivacaine; but both agents had minimal impact upon levobupivacaine's time-concentration profile overall (Chalkiadis 2013 **PK**).

Three overlapping systematic reviews document similar positive benefit of caudal dexmedetomidine 1–2 mcg/kg as an adjuvant to local anaesthetic in children aged 0.5–12 y having various surgeries:

- The duration of postoperative analgesia vs local anaesthetic alone is prolonged (WMD 8.2 h; 95%CI 5.0 to 11.4) (5 RCTs, n=270) (Trifa 2018 **Level I** [PRISMA], 21 RCTs, n=1,590; Tong 2014b **Level I** [PRISMA], 6 RCTs, n=328) (6 RCT overlap) and (SMD 3.19; 95%CI: 2.16 to 4.22) (Tu 2019 **Level I** [PRISMA], 10 RCTs, n=691) (overlap 3 & 8 RCTs respectively). Subanalysis reveals no difference between 1 mcg/kg (SMD 3.76; 95%CI 2.16 to 5.37) vs 2 mcg/kg dose (SMD 1.73; 95%CI 1.73 to 2.89). Dexmedetomidine addition also reduces the need for rescue analgesia vs bupivacaine alone at 6 h (RR 0.09; 95%CI 0.05 to 0.17), 12 h (RR 0.50; 95%CI 0.32 to 0.79) and 24 h (0.66; 95%CI 0.51 to 0.85), with no difference in PONV.
- A dose related increase in emergence time and sedation scores is consistently reported, without increased risk of respiratory depression (Trifa 2018 **Level I** [PRISMA], 21 RCTs, n=1,590). Compared to other caudal adjuvants, dexmedetomidine provides similar analgesia to clonidine (2 RCTs) and dexamethasone (1 RCT), and is superior to opioids (fentanyl 4 RCTs; morphine 1 RCT) with longer duration of analgesia, lower use of rescue analgesia and lower pain scores.

For unilateral inguinal hernia repair, the addition of dexmedetomidine 1 mcg/kg by caudal or IV route to levobupivacaine was similarly effective vs placebo in doubling the median time to first rescue analgesia (14.2 h vs 12.4 vs 6.0), reducing the number of patients requiring rescue analgesia (63% vs 70% vs 93%) and reducing the incidence of emergence agitation (3% vs 3% vs 27%) (Yao 2018 **Level II**, n=90, JS 5). Emergence time was mildly delayed (by 6 and 7 min) vs placebo, with no difference in PACU LOS; no bradycardia, hypotension or motor block was observed.

For hypospadias repair with caudal bupivacaine 0.25%, combination dexmedetomidine 1 mcg/kg/dexamethasone 0.1 mg/kg vs dexmedetomidine 1 mcg/kg vs dexamethasone 0.1 mg/kg increased the mean duration of analgesia (11.5 h vs 7.4 vs 4.5), lowered pain scores from 0.5 to 6 h, but with increased sedation in both dexmedetomidine groups from 0.5 to 12 h postoperatively (Hassan 2018 **Level II**, n=63, JS 5).

Dexamethasone

Three systematic reviews have concluded that adjuvant dexamethasone caudally (0.1–0.2 mg/kg) or IV (mostly 0.5 mg/kg with one study 1.5 mg/kg) vs placebo prolongs the time to first rescue analgesia following a single injection caudal block in children (mostly ≤10 y) having lower abdominal/perineal or lower limb orthopaedic surgery (Zhu 2018a **Level I** [PRISMA], 7 RCTs, n=647; Chong 2018 **Level I** [PRISMA], 14 RCTs, n=1,315; Kawakami 2017 **Level I** [PRISMA], 6 RCTs [IV only] n=424) (6 & 4 RCT overlap). The largest review found prolongation with both caudal (WMD 5.4 h; 95%CI 3.5 to 7.3 9 RCTs) and IV routes (WMD 5.5 h; 95%CI 3.6 to 7.5) (5 RCTs) (Chong 2018 **Level I** [PRISMA], 14 RCTs, n=1,315). Dexamethasone reduces pain scores postoperatively at 6 h (WMD -1.31; 95%CI -2.07 to -0.54) (6 RCTs) and 24 h (WMD -0.80; 95%CI -1.37 to -0.24) (5 RCTs), but not at PACU, 12 h, or 48 h. It reduces the number of patients needing rescue analgesia in PACU (RR 0.30; 95%CI 0.18 to 0.51) (5 RCTs) and post PACU (RR 0.46; 95%CI 0.23 to 0.92) (9 RCTs), and reduces PONV (RR 0.47; 95%CI 0.30 to 0.73). No increased risk of adverse effects with dexamethasone were reported in these reviews. Subsequent RCTs have similar results for 0.1 mg/kg via caudal (Parameswari 2017 **Level II**, n=130, JS 3) and 0.25 mg/kg by IV route (Salami 2017 **Level II**, n=94, JS 5). While a further RCT was positive for 0.1 mg/kg caudal over IV route (Dongare 2018 **Level II**, n=60, JS 1).

Magnesium

Adding magnesium (Mg) 50 mg caudally vs control reduces the number of patients requiring rescue analgesia postoperatively (RR 0.45; 95%CI 0.24 to 0/86) (Kawakami 2018 **Level I** [PRISMA], 6 RCTs [Mg], n=371). Duration of analgesia is prolonged with caudal magnesium (3/5 RCTs), with a mixed effect on postoperative pain scores (6 RCTs); there were no serious adverse events reported, with a similar rate of minor adverse events (eg shivering, sedation, motor block). In a further RCT, the combination of caudal Mg 50 mg/ dexmedetomidine 1 mcg/kg increased time to first analgesic request vs Mg 50 mg alone vs dexmedetomidine alone which were also superior to no adjuvant (Sayed 2018b **Level II**, n=120, JS 3). Dexmedetomidine recipients in both arms had more sedation for 1–1.5 h.

Ketamine

The addition of caudal ketamine 0.25–0.5 mg/kg to local anaesthetic prolongs time to first analgesic request vs local anaesthetic alone (MD 5.6 h; 95%CI: 5.45 to 5.76) without prolonging motor block (Schnabel 2011a **Level I** [PRISMA], 13 RCTs [paediatric], n=584), increases duration of block with ketamine 0.5 mg/kg (SMD 2.25; 95%CI 1.53 to 3) and reduces postoperative analgesic requirements (OR 0.26; 95%CI 0.1 to 0.7) (Dahmani 2011 **Level I** [QUORUM], 10 RCTs [caudal], n=686) (6 RCT overlap). Some adverse effects were more frequent in the ketamine group (eg sedation) but not significantly different to placebo for PONV (OR 1.17; 95%CI 0.7 to 2) (Schnabel 2011a **Level I**

[PRISMA], 13 RCTs [paediatric], n=584) or psychomimetic effects (OR 1.72; 95%CI 0.7 to 4.3) (Dahmani 2011 **Level I** [QUORUM], 10 RCTs [paediatric], n=686). A subanalysis of S-ketamine added to caudal anaesthesia was performed showing similar prolongation of block vs racemic ketamine (Dahmani 2011 **Level I** [QUORUM], 4 RCTs [S-ketamine], n unspecified). A subsequent RCT found similar results (Aliena 2018 **Level II**, n=58, JS 4). A significant concern that continues to limit the use of neuraxial ketamine is local neurotoxicity *in vitro* (Walker 2012c **NR;** Werdehausen 2011 **BS**).

Tramadol, neostigmine and midazolam

Caudal tramadol 1–2 mg/kg added to local anaesthetic prolongs the time to first rescue analgesic (4.5 h: 95%CI 2.8 to 6.1) at the expense of increased vomiting (OR 2.5; 95%CI 1.3 to 4.6) with no IV comparator (Engelman 2012 **Level I** [PRISMA], 9 RCTs [tramadol], n=258). Caudal tramadol 2 mg/kg added to bupivacaine and levobupivacaine was similarly effective for inguinoscrotal surgery (Sezen 2014 **Level II**, n=68, JS 5).

Caudal tramadol 1 mg/kg added to bupivacaine vs bupivacaine 0.25% alone prolonged duration of analgesia (9.6 h vs 7.2), reduced the amount of rescue paracetamol used to 24 h and had lower rise of IL-6, CRP and cortisol over 24 to 72 h postoperatively (Sayed 2018a **Level II**, n=60 JS 5).

Tramadol 2mg/kg/bupivacaine 0.25% vs fentanyl 2 mcg/kg/bupivacaine 0.25% prolonged duration of analgesia (10–18 h vs 7–11 h) with lower pain scores from 4–10 h, but more PONV (8 vs 0%) (Solanki 2016 **Level II**, n=100, JS 2).

Neostigmine added in doses of 1–4 mcg/kg extends the time to first analgesic rescue request by 2.5 times that of clonidine (MD 10 h; 95%CI 7.8 to 12.2) without any dose-dependent effect evident. This is at the expense of increased vomiting (OR 1.8; 95%CI 1.1 to 2.8) (Engelman 2012 **Level I**, 7 RCTs [neostigmine], n=533). Neostigmine (administered with adrenaline 5 mcg/mL) without local anaesthetic demonstrated analgesic efficacy for 20–50 mcg/kg (but not 10 mcg/kg), with a dose-dependent increase in PONV (Batra 2003 **Level II**, n=120, JS 2). Adding neostigmine 2 mcg/kg, midazolam 50 mcg/kg or ketamine 0.5 mg/kg to bupivacaine 0.25% (1 mL/kg) for a single injection caudal all prolonged duration of analgesia (21 h vs 18.3 vs 12.8 vs 7.2), and reduced postoperative pain scores (mean 2.6/10 vs 3.1 vs 4.4 vs 5.6), but with increased vomiting with neostigmine and ketamine (25% vs 15% vs 5% vs 5%) (Shirmohammadie 2019 **Level II**, n=80, JS 3).

Caudal midazolam 50 mcg/kg/bupivacaine vs caudal fentanyl 1 mcg/kg/bupivacaine vs bupivacaine alone had similar 0–24 h analgesic requirement, with higher sedation scores over the initial 1.5 h (Baris 2003 **Level II**, n=75, JS 3). This dose added to bupivacaine prolonged time to first rescue analgesic (similar to neostigmine 2 mcg/kg and ketamine 0.5 mg/kg) with no difference in sedation scores over 24 h vs plain bupivacaine (Kumar 2005 **Level II**, n=80, JS 4). Compared to plain bupivacaine, midazolam 50 mcg/kg vs morphine 50 mcg/kg added to bupivacaine prolonged the duration of analgesia (mean duration: 8 h vs 21 vs 15 respectively) with similar prolongation of sedation to 12 h (Gulec 1998 **Level II**, n=60, JS 1).

10.6.3.4 | Other outcomes of Paediatric Regional Analgesia

Stress response

Perioperative regional analgesia modifies the stress response to surgery in children (Nasr 2013 **Level II**, n=40, JS 3; Humphreys 2005 **Level II**, n=59, JS 2; Wolf 1998 **Level II**, n=26, JS 1). Suppression of the stress response may necessitate a local anaesthetic block that is more intense or extensive than required for analgesia, and therefore the risks of increased adverse effects or toxicity must be balanced against any potential benefit (Wolf 1998 **Level II**, n=26, JS 1). Use of caudal opioids alone (morphine 30 mcg/kg) was less effective than plain bupivacaine 0.25% in attenuating cortisol and glucose responses following hypospadias surgery (Teyin 2006 **Level II**, n=28, JS 3). Sufentanil added to bupivacaine modified the stress response to cardiac surgery (Sendasgupta 2009 **Level II**, n=30, JS 3).

Respiratory outcomes including apnoea

Improvements in respiratory outcome with regional analgesia have not been established in controlled comparative trials. Reductions in respiratory rate and oxygen saturation were less marked during epidural analgesia vs with systemic opioids but the degree of difference was of limited clinical significance (Wolf 1993 **Level II**, n=32, JS 2). Case series report improvements in respiratory function and/or a reduced need for mechanical ventilation with regional analgesia techniques (Raghavan 2008 **Level IV**; Aspirot 2008 **Level IV;** Hodgson 2000 **Level IV;** McNeely 1997 **Level IV**). A review summarises the use of awake caudal or combined spinal epidural vs epidural as a supplement to general anaesthesia in 560 neonates having multiple surgery types with multiple outcomes (surgical efficacy, postoperative respiratory events, other) (Maitra 2014 **NR**). A meta-analysis of PRA (spinal, caudal or epidural) vs general anaesthesia for inguinal herniorrhaphy in ex-premature infants reported a reduction in postoperative apnoea with PRA when infants having preoperative sedation were excluded (RR 0.53; 95%CI 0.34 to 0.82) (4 studies n=129); the groups did not differ in the need for postoperative ventilation (3 RCTs, n=98) (Jones 2015 **Level I** [Cochrane], 7 RCTs, n=203). A subsequent multicentre RCT assessing PRA (spinal, caudal, or combined spinal and caudal) vs general anaesthesia (sevoflurane <1 h) for infants (≤60 wk post-menstrual age) having hernia repair qualifies these findings (Davidson 2015 **Level II**, n=722, JS 3). Prematurity was the strongest predictor of apnoea (OR 22; 95%CI 4 to 109), and PRA reduced early (0 to 0.5 h) (1 vs 3%) (OR 0.20; 95%CI 0.05 to 0.91) but not late apnoea (0.5 to 12 h). Neurodevelopmental outcomes did not differ between the regional anaesthesia and general anaesthesia groups at 2 y (Davidson 2015 **Level II**, n=532, JS 3) and 5 y of age (McCann 2019 **Level II**, n=447, JS 3).

10.6.3.5 | Safety and complications of Paediatric Regional Analgesia

Performance of PRA under general anaesthesia vs awake

The safety of performing paediatric regional anaesthesia (PRA) under general anaesthesia or deep sedation has been demonstrated in six large prospective multi-regional audits (Walker 2018 **Level IV**, n=104,393; Taenzer 2014a **Level IV**, n=53,564; Wong 2013a **Level IV**, n=3,152; Polaner 2012 **Level IV**, n=14,917; Ecoffey 2010 **Level IV**, n=31,142; Llewellyn 2007 **Level IV**, n=10,633; Giaufre 1996 **Level IV,** n=24,409) (see Table 10.10). Placement of regional anaesthesia/analgesia under general anaesthesia is confirmed to be as safe as placement in sedated and awake children (Walker 2018 **Level IV**, n=104,393 in 91,701 children). The combined incidence for major adverse events (LAST and neurological deficit together) was 2.2/10,000 (95%CI 1.5 to 3.4) for blocks placed under GA and 15.2/10,000 (95%CI 7.8 to 28.4) for blocks placed when awake or sedated.

Overall complications

The earlier audits reported rates of overall complications for regional analgesia of 0.09% (Giaufre 1996 **Level IV**, n=24,409), 0.12 % (95%CI 0.09 to 0.17) (Ecoffey 2010 **Level IV**, n=31,142) and in PRAN audits: 0.2% (Polaner 2012 **Level IV**, n=14,917) to 1.2% (95%CI 1.1 to 1.3) (Taenzer 2014b **Level IV**, n=53,564); with the most recent providing specific adverse effect and not overall complication incidence (Walker 2018 **Level IV**, n=104,393).

Younger age is associated with higher incidence of complications: neonates and infants vs older children (OR 2.9; 95%CI 1.2 to 7.0) (Wong 2013a **Level III-2**, n=3,152); 1.13% for neonates vs 0.3–0.8% older children, particularly dosing error (0.3% <12 mth vs 0.07% >12 mth) (Llewellyn 2007 **Level IV**, n=10,633); and 0.4% for infants <6 mth vs 0.1% >6 mth of age (Ecoffey 2010 **Level IV**, n=3,860 [infant] vs 27,272 [older]). A higher incidence of complications with neuraxial catheters (inclusive of catheter malfunction, catheter contamination and vascular puncture) of 13.3% (95%CI 9.8 to 17.4%) was reported in neonates in a USA multicentre safety analysis (Long 2016

Level IV, n=307). No complications resulted in long term sequelae, and the risk of a serious complication was estimated as 0.3/10,000 (95%CI 0.08 to 1.8). In young children having a laparotomy and epidural ropivacaine/sufentanil for postoperative analgesia, the epidural catheter was removed early in 35%, the most common reasons being inadequate analgesia and technical failure; further adverse effects were documented in 16 patients (18%) (Bravenboer-Monster 2019 **Level IV**, n=90).

Table 10.10 | Incidence of adverse effects in large-scale audits of paediatric regional analgesia

Study	Walker 2018		
Denominator	104,393 blocks; 41,004 neuraxial GA 94%,	Years audited	PRAN Apr 2007 – Sept 2015
Adverse effects type and incidence			
LAST	LAST 0.76 in 10,000: 3 seizures, 4 cardiac arrests	Dural tap, PDPH	rates of dural tap: 86/10,000 lumbar 66/10000 thoracic and 10/10000 for caudal approach; 7/11 patients with PDPH had an epidural blood patch
PONS	Permanent neurological deficits: 0 (95%CI 0 to 0.4/10,000) Transient neurological deficits (primarily sensory): 2.4/10,000 (95%CI 1.6 to 3.6); 92% resolving by 3 mth	Drug error	NS
Death, cardio-respiratory event/ arrest	NS	Pressure sore	NS
Bleeding Infection	0 haematomas associated with neuraxial catheters (95%CI 0 to 3.5/10,000); 1 epidural haematoma with a paravertebral catheter 29/92 catheter associated infections treated with antibiotics	Compartment syndrome	NS
Study	Wong 2013a		
Denominator	3,152 epidurals	Years audited	Jan 1997–Dec 2011

Adverse effects type and incidence			
LAST	0 (1 intravascular catheter; unrecognised)	Dural tap, PDPH, intrathecal placement	1 PDPH; blood patch NS; 1 IT placement-unrecognised
PONS	1 permanent with residual left sided 3–4/5 weakness of L5–S1 (blood staining of dural sac)	Drug error	3
Death, cardio-respiratory event/arrest	1 fatal cardiac arrest; 1 respiratory depression	Pressure sore	3
Bleeding	NS (bar that in patient with PONS above)	Compartment syndrome	1
Infection	11 local of skin: 5 required antibiotics		
Study	Ecoffey 2010		
Denominator	31,142 blocks; 11,418 neuraxial GA 96%	Years audited	(ADARPEF II) Nov 2005–Oct 2006
Adverse effects type and incidence			
LAST	5.1/10,000; (95%CI 3 to 8); 1 convulsion; 15 cardiac: 2 ECG change, 13 arrhythmia; (Positive test doses within 134 reports excluded from adverse event assessment)	Dural tap, PDPH, total spinal anaesthesia	10 dural taps 0 PDPH 1 total spinal anaesthesia
PONS	5 of short duration (18 h–3 wk); 0 permanent	Drug error	1 leading to LAST in infant
Death, cardio-respiratory event/arrest	0 deaths/cardiac arrests; 1 total and 2 high spinals: requiring short term ventilation <12 h	Pressure sore	NS
Bleeding	NS	Compartment syndrome	NS
Infection	1 local		
Study	Llewellyn 2007		
Denominator	10,633 epidurals	Years audited	Mar 2001–Dec 2005
Adverse effects type and incidence			
LAST	1 seizure post 2 boluses; 1 seizure/LAST at 24 h high end dosing	Dural tap, PDPH, blood patch	5 PDPH, 1 blood patch

PONS	1 permanent (peripheral nerve); 1 cauda equina; 5 resolved over 4–10 mth (2 concurrent spinal cord insult: 1 haematoma with rods, 1 impaired blood supply)	Drug error	13
Death, cardio-respiratory event/ arrest	0 deaths/cardiac arrests; 2 respiratory arrests 1 total spinal and 1 with opioid and epidural bolus; ventilated <24 h	Pressure sore	33
Bleeding	(1 possible haematoma mentioned above in PONS in patient with 2 epidural catheters attributed to rod placement in scoliosis surgery)	Compartment syndrome	4 (not masked by epidural)
Infection	2 epidural abscess; 1 meningism; 25 local		
Study	Giaufre 1996		
Denominator	24,409 blocks; 15,013 neuraxial	Years audited	May 1993–April 1994 (ADARPEF I)
Adverse effects type and incidence			
LAST	7 LAST: 2 convulsions; 1 arrhythmia; 2 delayed arrhythmia (with overdose); 2 "subclinical"	Dural tap, PDPH	2 dural puncture; 2 PDPH; 4 total spinal
PONS	2 transient <8 h	Drug error	NS
Death, cardio-respiratory event/ arrest	1 apnoea secondary to excess epidural morphine	Pressure sore	NS
Bleeding	NS	Compartment syndrome	NS
Infection	1 local burn from skin preparation solution/heated mattress; 1 rectal puncture (with caudal) without sequelae		
Infection	11 local of skin: 5 required antibiotics		

Notes: *ADARPEF: French-Language Society of Paediatric Anaesthesiologists; LAST: local anaesthetic systemic toxicity; NS: none specified; PDPH: postdural puncture headache; PONS: postoperative neurological symptoms; PRAN: Paediatric Regional Anesthesia Network.*

Local anaesthetic systemic toxicity

Accidental intravascular injection and LAST remain high-risk complications of caudal and epidural analgesia. It is reported to occur rarely: 0.76 to 5 in 10,000 (see Table 10.10) and may be less common in paediatric populations than in adults (Neal 2018 **GL**). As the sacrum is largely cartilaginous during infancy and early childhood, vascular puncture can occur (38 in 6,011) (Polaner 2012 **Level IV**) and there is an increased risk of injecting local anaesthetic into the highly vascular medullary space of the sacrum (Veyckemans 1992 **Level IV**). Sevoflurane attenuated cardiovascular responses to adrenaline 0.5 mcg/kg IV less than halothane and may be a better agent to facilitate detection (Kozek-Langenecker 2000 **Level III-2**). Changes in T-wave amplitude can be observed in 91% of patients within 1 min of IV injection of 0.1 mL/kg of lidocaine 1%/adrenaline 5 mcg/mL (and >25% change measured in 94%) (Varghese 2009 **Level II**, n=68, JS 4); this is a sensitive way of detecting intravascular injection. Almost all regional blocks are performed under general anaesthesia in children but there is no clear evidence that this obscures early signs of LAST (Taenzer 2014b **Level IV;** Bernards 2008 **Level IV**). In the PRAN audit, 5 of 7 LAST events occurred in association with neuraxial block (see Section 10.6.1.3 for detail of the peripheral block associated events): 3 caudal single injections, 1 subarachnoid block and 1 thoracic epidural (Walker 2018 **Level IV**, n=59,069 [neuraxial]). Four were infants resulting in a greater risk of severe LAST for <6mth vs >6 mth of OR 7.4 (95%CI 1.3 to 39.3).

Paediatric patients with LAST (neonates to 18 y) have been successfully resuscitated with 20% lipid emulsion (Presley 2013 **Level IV SR** [14 case reports]; Gitman 2019 **NR**). In conjunction with advanced life support resuscitation, it is recommended as an early intervention (Neal 2018 **GL;** AAGBI 2010 **GL**) (see also Section 4.4.3). Dosing recommendations are the same as for adults: if <70 kg, 1.5 mL/kg bolus (can be repeated twice every 5 min for persistent cardiovascular collapse) and infusion 0.25 mL/kg/min (increased to 0.5 mL/kg/min if hypotension persists), continuing for 10 min after attaining circulatory stability; the maximum cumulative recommended dose is 12 mL/kg. Adverse effects when higher doses of 20% lipid emulsion were used to treat LAST have been reported: hypoxia and V/Q mismatch occurred in a 3 y old child (dose 15.5 mL/kg) (Shenoy 2014 **CR**), and severe hyperlipidaemia, metabolic acidosis and raised lactate associated with hypersomnolence, tachypnoea and tachycardia occurred in an 11 y old girl (dose 66 mL/kg) (Corwin 2017 **CR**); both patients made full recoveries.

Postoperative neurological symptoms

Neurological damage attributable to paediatric regional analgesia is rare (see Table 10.10). PRAN publication has reported an overall event rate of no permanent neurological deficits (95%CI 0 to 0.4/10,000), and very low incidence of transient neurological deficits of 2.4/10,000, with similar risk for neuraxial and peripheral blocks (Walker 2018 **Level IV**, n=104,393). The risk of transient neurological deficits or LAST combined was lower in patients having their blocks under general anaesthesia vs awake/sedated, including when adjusted for age (OR 2.93; 95% CI 1.34 to 5.52) (Walker 2018 **Level IV**, n=104,393).

The prior UK audit reports a similar incidence of postoperative neurological symptoms (PONS) to PRAN audits, with two events with residual symptoms at 12 mth: one cauda equina syndrome resulting from a drug volume error and one peripheral nerve injury (Llewellyn 2007 **Level IV**, n=10,633). Five other cases of peripheral or nerve root damage were of short duration: three resolved spontaneously, two required chronic pain referral and gabapentin but resolved by 10 mth. The two previous French audits report only transient PONS events (Ecoffey 2010 **Level IV**, n=31,142; Giaufre 1996 **Level IV,** n=24,509); a single centre audit reports one permanent PONS event likely related to epidural insertion (Wong 2013b **Level IV**, n=3,152) and a survey reports two permanent events in two infants (Flandin-Blety 1995 **Level IV**, n=2).

Care of insensate body regions is important post PRA as prolonged block/immobility may result in nerve compression, accompanied by neurological deficit or neuropathic pain (Symons 2008 **CR**).

Infection

Local skin infection is variably reported (see Table 10.10), with *Staphylococcus aureus* the most commonly identified organism (Llewellyn 2007 **Level IV**, n=10,633 [paediatric epidurals]). This UK audit reported three serious infections: two epidural abscesses and one meningism. The PRAN audit reported one epidural abscess (in a 2 mth old with a lumbar epidural catheter removed on POD 4 that required surgical intervention and fully recovered) and 92 cases of local cutaneous infection (53/10,000; 95%CI 43 to 64) (Walker 2018 **Level IV**, n=18,065 [catheters]). Most were treated with catheter removal only; 29 were treated with antibiotics. Risk of infection was higher with neuraxial vs peripheral catheters (60 vs 26/10,000) and increased by 6.7% per catheter day: the median catheter duration for cases of infection vs no infection was 4 d vs 2. There were no infections reported with single injection blocks. Additional cases of epidural abscesses associated with epidural catheters in children ≤2 y old that responded to antibiotics are reported from the UK (Desai 2016b **Level IV**, n=2) and USA (Suchar 2016 **CR**).

Bacterial colonisation of catheters was more commonly associated with caudal than lumbar catheters (Kost-Byerly 1998 **Level IV**), however, no difference was found in odds of superficial infection for caudal vs lumbar epidural catheters, or caudal vs thoracic epidural catheters (Walker 2018 **Level IV**, n=18,065 [catheters]).

Acute compartment syndrome and pressure sores

There have been reports of acute compartment syndrome (ACS) in adult epidural recipients; in 4 of 8, the epidural was not felt to have masked the ACS (Klucka 2017 **Level IV** [PRISMA], 15 studies, n=20). In children, 6 events have been reported felt to not have been masked by the single injection caudal (Klucka 2017 **Level IV** [PRISMA], 15 studies, n=20 [1 caudal epidural]) or epidural infusion (Wong 2013b **Level IV**, n=3,152 [1 ACS]) and (Llewellyn 2007 **Level IV**, n=10,633) with no events in the PRAN database (see Table 10.10). Avoiding unnecessarily dense sensory/motor block allows full assessment and may prevent delay in diagnosis of compartment syndrome (Johnson 2009 **Level IV**).

Appropriate staff education regarding pressure care and vigilant monitoring for pressure areas to prevent sores is essential for patients receiving continuous regional analgesia (Llewellyn 2007 **Level IV**).

Dural puncture and post-dural puncture headache (PDPH)

The audits report variably on dural puncture and resultant total spinal or post-dural puncture headache (PDPH) and the need for respiratory or blood patch intervention (see Table 10.10). The PRAN audit reported the risk of unintentional dural tap with an epidural needle for the different approaches as 86/10,000 (95%CI 66 to 112) for lumbar, 66/10,000 (95%CI 46 to 95) for thoracic and a low incidence 10/10,000 (95%CI 7 to 14/10,000) for caudal (Walker 2018 **Level IV**, n=54,124 [single injection & catheters]). Eleven (7%) patients with an unintentional dural tap reported PDPH, of which 7 had an epidural blood patch. An 11 mth old who required three attempts for an epidural insertion developed a CSF cutaneous fistula following removal of the epidural catheter on POD 3; this resolved following a sterile skin suture and occlusive dressing (Rusy 2018 **CR**).

Bleeding/epidural haematoma

Vascular puncture is reported in association with PRA, generally without consequence, and epidural haematomas are rare. One audit included removal of an epidural catheter in a coagulopathic patient without comment on the consequence (Wong 2013a **Level IV**). Two audits report on epidural/dural sac blood with neurological sequelae; the former related to surgical rod

placement (Llewellyn 2007 **Level IV**) and the latter attributed to epidural placement (Wong 2013a **Level IV**). The PRAN audit has reported no epidural haematoma related to epidural catheter insertion/infusion (Walker 2018 **Level IV**, n=18,065 [epidural]). Two reports of bleeding complications and motor deficit with neuraxial blocks have required surgical intervention: an anterior spinal artery arteriovenous fistula/pseudoaneurysm related to an epidural needle and spinal cord trauma was reported in a 5 y old (who fully recovered over 20 mth) (Alnaami 2013 **CR**); and an epidural haematoma in a 12 y old with sickle cell disease, choledocholithiasis and mildly deranged coagulation with a thoracic epidural catheter (who fully recovered by 6 mth) (Sathyamoorthy 2017 **CR**). Otherwise, epidural haematoma in children occurs more commonly spontaneously (40–50%), associated with anticoagulants (25–30%) and rarely in association with trauma (usually falls) (Sim 2010 **CR**) (see also Section 5.6.5).

Deaths associated with epidural use

One survey (Flandin-Blety 1995 **Level IV**, n=24,005) and one retrospective audit (Wong 2013a **Level IV**, n=3,152) have reported deaths in association with neuraxial block insertions: three infants – one related to LAST, one possibly due to cerebral air embolism, one due to spinal cord ischaemia – and one child aged 6 y with cerebral palsy and carnitine deficiency, who had cardiac arrest with intravascular catheter migration of an epidural catheter and presumed bupivacaine toxicity (Wong 2010 **CR**). No deaths have been reported in the large scale audits (see Table 10.10).

Physiological effects of caudal injection

Following caudal injection of local anaesthetic with adrenaline (1 mL/kg, max 20 mL injected over 1 min) in infants and children (2.3 mth to 8.6 y), there was a transient rise in epidural pressure that returned to baseline within 60 s (Goeller 2016 **Level IV**, n=31). Caudal injection under general anaesthetic of both 1 mL/kg and 1.5 mL/kg of ropivacaine 0.15% increased optic nerve sheath diameter (a surrogate for intracranial pressure) with a similar peak of 14% and 19% respectively 10 min following injection, normalising at 30 min (Lee 2017a **Level II**, n=80, JS 5).

Complications of caudal analgesia

An attempted US-guided caudal block in a 1 mth old infant having an inguinal hernia repair failed in the context of an ongoing cerebrospinal spinal fluid leak presumably secondary to a lumbar puncture on d 13 of life (Bruce 2015 **CR**). Rectal puncture is a risk of caudal injection that may be increased by the presence of faecal loading and rectal distension (Sathianathan 2015 **CR**).

10.6.4 | Intrathecal opioids

Following cardiac surgery, IT morphine 20 mcg/kg prolonged time to first analgesia and decreased postoperative morphine requirements but did not alter time to discharge from intensive care (Suominen 2004 **Level II**, n=80, JS 5). Addition of IT tetracaine and morphine to IV remifentanil decreased pain scores and analgesic requirements after early extubation (Golianu 2005 **Level II**, n=45, JS 3). Spinal morphine 2 mcg/kg vs placebo added to bupivacaine increased time to first rescue analgesic (12 h ± 3.2 vs 8 ± 3.5) and reduced need for supplementary analgesia (17 vs 60%) following hypospadias repair (Apiliogullari 2009 **Level II**, n=54, JS 5). In 3–17 y olds having ureteroneocystostomy or pyeloplasty, IT morphine (mean 4.4 mcg/kg) vs opioid via PCA/NCA resulted in less patients receiving rescue opioid 0–16 h postoperatively (0–8 h: 14% vs 96 and 8–16 h: 33% vs 92), less rescue opioid (oral morphine equivalents: 5 mcg/kg/h vs 10), and similar adverse event rates (eg nausea and vomiting, pruritus: 75% vs 67%) including hypoxia (as a surrogate for respiratory depression: 9% vs 8%) (Putnam 2015 **Level III-3**, n=128). In children and adolescents (0.5 to 20 y) having laparoscopic urological surgery, IT morphine (4–5 mcg/kg) vs bupivacaine infiltration of port sites resulted in similar perioperative systemic opioid

requirement (Srinivasan 2016 **Level III-3**, n=130). Early postoperative opioid requirements, adverse effects and LOS were not reported.

In infants undergoing lower abdominal and urological surgery, addition of fentanyl 1 mcg/kg (but not lower doses) to IT local anaesthetic prolonged the duration of analgesia and reduced supplemental analgesic requirements (Batra 2008 **Level II**, n=58, JS 5). Fentanyl 0.2 mcg/kg added to local anaesthetic prolonged block duration and reduced analgesic requirements after hernia repair in infants (Duman 2010 **Level II**, n=50, JS 4).

Dose-responsiveness for IT opioids is not evident in adults; studies are too few to assess this in children.

For the use of IT morphine in scoliosis surgery, see Section 10.6.6.

10.6.5 | Topical therapies

As is the case for addition of adjuvant to injectate, topical application can lead to systemic absorption. Thus for effective comparison, a systemic comparator arm is desirable but rarely employed in the below summarised RCTs.

Studies relevant to photobiomodulation use in paediatric dental, cleft and tonsillectomy are not discussed here but are included in the adult Section 7.4.

10.6.5.1 | Tonsillectomy

Following tonsillectomy, topical application of bupivacaine and ropivacaine reduces pain scores at 4–6 h vs saline (-1.3/10; 95%CI -1.67 to -0.9) (Grainger 2008 **Level I**, 2 RCTs [paediatric], n=71). Regular dosing with lidocaine spray (1 RCT, n=40) vs saline improves pain scores post tonsillectomy in children until the third postoperative day (Fedorowicz 2013 **Level I [**Cochrane], 6 RCTs [1 adult, 1 mixed, 4 paediatric], n=593 [397 children]).

No benefit was seen following single topical application of tramadol 5% over 0–24 h, but thereafter pain scores were reduced for 7 d (Akbay 2010 **Level II**, n=40, JS 5). Single tonsillar applications of tramadol 40 mg vs ketamine 20 mg were superior to placebo (artificial saliva), with similar pain scores and rescue analgesic requirements (0–24 h) (Tekelioglu 2013 **Level II**, n=60, JS 5). Tonsillar application of ketamine 20 mg vs morphine 20 mg alone and in combination were superior to placebo (artificial saliva) with reduced rescue paracetamol use (0–24 h), but pain scores were only reduced in PACU (Canbay 2008 **Level II**, n=60, JS 5).

Cryotherapy (ice lollipop) over 4 h reduced pain post-tonsillectomy in children 2–12 y at 0.5 and 1 hr (Keefe 2018 **Level I** [PRISMA], 1 RCT**:** Sylvester 2011 **Level II**, n=87, JS 3).

10.6.5.2 | Acute otitis media

Acute otitis media is common in children. Topical local anaesthetic drops (benzocaine/ antipyrine or lidocaine) used in acute otitis media, in addition to PO analgesia, are effective vs saline at 10 min (RR 2.13; 95%CI 1.19 to 3.80) and 30 min after instillation (RR 1.43; 95% CI 1.12 to 1.81) (2 RCTs, n=117) (Foxlee 2011 **Level I** [Cochrane], 5 RCTs, n=391). Superiority of local anaesthetic (amethocaine/ antipyrine) vs naturopathic drops (3–4 herbal extracts in olive oil) is not established in three RCTs (in addition to paracetamol in one RCT and amoxicillin in one RCT) (3 RCTs, n=274 [analysed]).

10.6.5.3 | Acute mouth ulceration

In painful acute mouth ulceration in children, topical viscous lidocaine 2% did not improve oral intake, with similar requirement for rescue analgesic at 1 h vs placebo (Hopper 2014 **Level II**, n=100,

JS 5). Lidocaine 2% gel was massaged onto mouth ulcers and reduced pain by 19.7/100 (18.3) at 3 min vs placebo in children prior to dental work (Coudert 2014 **Level II**, n=64, JS 5).

Topical therapies (commonly Maalox®: lidocaine, aluminium hydroxide combined with diphenhydramine syrup) are used 2nd line (to paracetamol and/or ibuprofen) by 42% of USA paediatric emergency physicians at 15 centres (MacLellan 2017 **Level IV**, n=150 [surveyed]).

10.6.3.4 | Nasogastric tube insertion

For efficacy of sweet solutions in nasogastric tube insertion in neonates see Section 10.7.1.5. For evidence of efficacy of topical and nebulised local anaesthetic and IN ketamine in children see Section 10.7.2.6.

10.6.3.5 | Circumcision

Ring block is more effective (across all operative stages) than DPNB and both are more effective than EMLA® which is more effective than placebo in awake infant circumcision (1 RCT, n=54) (Suresh 2014 **Level I** [PRISMA], 5 RCTs [EMLA®], n=266). EMLA® has shorter time to analgesic rescue vs DPNB (4 RCTs, n=212); including in older children who received general anaesthesia (Salgado Filho 2013 **Level II**, n=41, JS 4). EMLA®/sucrose 25% 2 mL /lidocaine ring block was more effective vs EMLA®/sucrose/DPNB and EMLA®/sucrose (Sharara-Chami 2017 **Level II**, n=70, JS 5).

One study measured methaemoglobin plasma concentrations after EMLA® 2 gm application for 90 min; these were elevated at 6 h but did not require treatment (Suresh 2014 **Level I** [PRISMA], 1 RCT: Lander 1997 **Level II**, n=54, JS 1). Of note, a neonate who developed acquired methaemoglobinaemia following circumcision with topical EMLA® cream (and lidocaine infiltration) was successfully treated with methylene blue (Kuiper-Prins 2016 **CR**).

10.6.6 | Use of Paediatric Regional Analgesia (PRA) in Specific Paediatric Surgical Procedures

There are numerous small observational and interventional studies of variable quality assessing various PRA techniques for many surgeries as outlined below. Despite this body of work, heterogeneity in interventional and control arms (in PRA technique, medication combinations and dosing) makes comparison of studies and performing meta-analyses difficult. Two qualitative systematic reviews by the same author group concluded that more evidence is needed to establish the effects of PRA techniques, on the postoperative pain outcomes for specific procedures (Kendall 2018 **Level I** [PRISMA], 40 RCTs, n=2,408; Suresh 2014 **Level I** [PRISMA], 73 RCTs, n=5,125).

Penile surgery: circumcision and hypospadias repair

Policy statements from the Royal Australasian College of Physicians (RACP 2010 **GL**), the British Association of Paediatric Urologists (BAPU 2007 **GL**) and the American Academy of Pediatrics (American Academy of Pediatrics Task Force on Circumcision 2012 **GL**) emphasise the need for effective analgesia for neonatal circumcision.

In boys (infants to adolescent) who also received a general anaesthetic, a dorsal penile nerve block (DPNB) provides similar analgesia to a caudal block with similar need for rescue analgesia (RR 1.25; 95%CI 0.64 to 2.44) (4 RCTs, n=336) (Cyna 2008 **Level I** [Cochrane], 10 RCTs [5 RCTs DPNB], n=721; Canakci 2017 **Level II**, n=60 JS 1), and is as or more effective with a longer duration than post EMLA® cream application (Suresh 2014 **Level I** [PRISMA], 5 RCTs [EMLA®], n=266). PONV rates are also similar (RR 1.88; 95%CI 0.70 to 5.04) (4 RCTs, n=336) with more leg weakness in caudal recipients (RR 10.7; 95%CI 1.3 to 86.1) (2 RCTs, n=110) (Cyna 2008 **(Level I** [Cochrane], 10 RCTs, n=721). However

in a single (PRAN participant) institution, DPNBs (landmark technique; surgically inserted at cessation) were inferior to caudal blocks (often containing clonidine) with higher pain scores (OR 2.7; 95%CI 1.7 to 4.4) and perioperative opioid requirement (OR 5.2; 95%CI 3.3 to 8.1) (Chan 2018 **Level III-2**, n=738). Caudal block vs parenteral analgesia does not reduce PONV (RR 0.61; 95%CI 0.36 to 1.05) or the need for early or later rescue analgesia (RR 0.41; 95%CI 0.12 to 1.43) (Cyna 2008 **Level I** [Cochrane], 4 RCTs [parenteral], n=235). There is no clear analgesic intervention recommendation; the clinical decision is influenced by perceived failure rates, risk/benefit of parenteral analgesia and side effects especially leg weakness in children old enough to walk (Suresh 2014 **Level I** [PRISMA], 13 RCTs [circumcision]; Cyna 2008 **Level I** [Cochrane], 10 RCTs [caudal], n=721; Brady-Fryer 2004 **Level I** [Cochrane], 35 RCTs [14 DPNB], n=1,984; Bellieni 2013 **NR** 14 RCTs [9 DPNB], n=1,192) (2-3 RCT overlap).

Landmark technique DPNB has a failure rate of 10% (Faraoni 2010 **Level II**, n=40, JS 3) to 30% (O'Sullivan 2011 **Level II**, n=66, JS 5; Chan 2018 **Level III-2**). For US-guided DPNB there are at least two described techniques (Qian 2015; Sandeman 2007). Compared to landmark technique, US-guided DPNB reduced postoperative pain scores and increased time to first analgesic 9.5 h vs 1 (Faraoni 2010 **Level II**, n=40, JS 3), reduced postoperative analgesic requirements (6 vs 38%), with improved success rates (eg to 97%: O'Sullivan 2011 **Level II**, n=66, JS 5; Qian 2015) and reported increase in procedure time (Sandeman 2011 **Level III-2**, n=216 [101 DPNB]) by ≈10 min (Faraoni 2010 **Level II**, n=40, JS 3).

There are insufficient controlled trials (DPNB vs placebo or sham, topical local anaesthetic or ring block; local anaesthetic vs placebo or ring block; ring block vs no treatment) to rank the efficacy of local anaesthetic techniques for circumcision in awake neonates (Brady-Fryer 2004 **Level I** [Cochrane], 35 RCTs, n=1,984; Bellieni 2013 **NR**) (2 RCT overlap). As topical local anaesthetic cream only partially attenuates the pain response to circumcision, more effective analgesic techniques are recommended. In one further RCT, EMLA® cream/PO sucrose 25% 2 mL/ lidocaine ring block was more effective than EMLA®/PO sucrose/lidocaine DPNB (surgically inserted) and EMLA®/sucrose (Sharara-Chami 2017 **Level II**, n=70, JS 5).

For circumcision, nerve stimulator-guided pudendal nerve block vs DPNB had lower pain scores, reduced analgesic requirement and provided longer duration of analgesia (Naja 2011 **Level II**, n=60, JS 3) up to 18 h (Tutuncu 2018 **Level II**, n=85, JS 5). For hypospadias repair, nerve stimulator-guided pudendal nerve block vs caudal block had lower pain scores, reduced analgesic requirement and provided longer duration of analgesia vs local anaesthetic alone (Kendigelen 2016 **Level II**, n=81 JS 5) and with clonidine 1 mcg/kg (Naja 2013 **Level II**, n=80, JS 5). Studies conflict in their results for DPNB vs caudal block for this surgery: a high success rate with both blocks was reported (DPNB 93% vs caudal 98%), with higher postoperative analgesic requirements for DPNB vs caudal (70% vs 44%) (Seyedhejazi 2011 **Level II**, n=85, JS 2); while a second RCT had longer time to first rescue analgesia for DPNB vs caudal (5 h vs 3.7) and reduced morphine requirement 0–48 h (Kundra 2012 **Level II**, n=54, JS 4).

An association has been suggested between caudal analgesia and postoperative complications including urethrocutaneous fistula or glanular dehiscence in hypospadias: 19% vs 0 DPNB recipients (Kundra 2012 **Level II**, n=54, JS4); aOR 13.4 (95%CI 1.8 to 101.8) (Taicher 2017 **Level III-2**, n=326 [230 caudal]); OR 2.1 (95% CI 1.14 to 3.8) for postoperative complications overall, but similar fistula incidence (Kim 2016 **Level III-2**, n=342 [216 caudal]) countered by OR 0.75 (95%CI 0.33 to 1.68) (Zaidi 2015 **Level III-2**, n=135 [45 fistulae]) and similar complication rates in hypospadias surgical patients who received caudal vs DPNB (OR 2.4; 95%CI 0.9 to 6.4) (Braga 2017 **Level III-2**, n=518 [367 caudal]) including vs GA alone (Splinter 2019 **Level III-2**, n=764 [825 procedures; 87% caudal]). The latter studies proposed additional factors that were positively associated in the univariate analysis such as hypospadias type (eg proximal meatus), surgery type and duration.

Caution must be exercised in interpreting these retrospective observational studies assessing association for clinical significance, and the outcome scrutinised for biological plausibility.

Inguinal surgery

Inguinal surgery includes inguinal hernia repair, hydrocoele and testicular operations. All abdominal wall truncal blocks and caudals have been used for this surgery (see earlier individual sections for II/IHNB, PVB, ESPB, TAPB, TMQLB comparisons eg with surgical site infiltration and see also Section 10.6.3.2 for caudal).

Two systematic reviews of inguinal surgery conflict in their conclusions on the analgesic efficacy of single injection caudal block vs II/IH nerve block and/or wound infiltration. The first found single injection caudal block with local anaesthetic reduces the number of patients requiring rescue analgesia early 0–4 h (RR 0.81; 95%CI 0.66 to 0.99) (13 RCTs, n=789) and late 4–24 h (RR 0.81; 95%CI 0.69 to 0.96) (9 RCTs, n=532) on POD 0 (Shanthanna 2014 **Level I** [PRISMA], 17 RCTs, n unspecified). In this setting, caudal block increases motor block (RR 2.59; 95%CI 1.29 to 5.20) (6 RCTs, n=469) and urinary retention (RR 2.23; 95%CI 1.27 to 3.91) (5 RCTs, n=429). The parallel lower quality systematic review found no difference in pain intensity at 1 h, or use of rescue analgesia (Baird 2013 **Level III-2 SR**, 13 studies n=733) (9 RCT overlap). The efficacy of different volumes of caudal local anaesthetic has been assessed for inguinal surgery. One RCT found 0.75 mL/kg was more effective than 0.5 mL/kg (Akpoduado 2017 **Level II**, n=56, JS 3); while another found no difference between 0.6 vs 0.8 and 1 mL/kg (Marjanovic 2017 **Level II**, n=40, JS 2).

Failure rates for II/IHNB are variable (as they are for caudal see Section 10.6.3.2), reported as 30–39% for landmark technique (Lim 2002 **Level II**, n=90, JS 3; Weintraud 2008 **Level III-2**, n=62). While US-guidance may reduce failure rates for II/IHNB (eg to 6%: Weintraud 2009 **Level II**, n=66, JS 3; Willschke 2005 **Level II**, n=100, JS 3) and possibly improve safety over the landmark technique (Suresh 2014 **Level I** [PRISMA], 15 [II/IHNB], n=1,046).

The effect of the addition of clonidine 1–2 mcg/kg to blocks for this surgery has not been adequately assessed (Suresh 2014 **Level I** [PRISMA], 22 RCTs [inguinal: 2 clonidine], n=1,598; Seyedhejazi 2014 **Level II**, n=66, JS 2). See also PNB Adjuvant Section 10.6.2.6 and Neuraxial adjuvant Section 10.6.3.3.

Umbilical hernia repair

Analgesia for this common paediatric surgery is covered in the rectus sheath block (RSB) section (see 10.6.2.3), with no data specific to TAPB for this surgery to date.

Pectus excavatum repair

Pectus excavatum repair (including minimally invasive repair of pectus excavatum, Nuss and Ravitch procedures) is painful surgery typically performed in adolescents. Thoracic epidural has been shown to be effective (Frawley 2016 **Level IV**, n=217 [all epidural]), and similar or superior to systemic analgesia. Epidural analgesia (bupivacaine or ropivacaine with fentanyl or hydromorphone) vs PCA (morphine, fentanyl or hydromorphone) for Nuss surgery reduced postoperative pain scores at 12 h (WMD -1.12/10; 95%CI -1.61 to -0.62) (4 studies, n=196) and 48 h (WMD -0.85; 95%CI -1.62 to -0.07) (6 studies, n=365) but not at other times; with no differences between secondary outcomes (eg rescue analgesia, adverse events, LOS) (Stroud 2014 **Level III-3 SR**, 6 studies, n=430). While three epidural infusion regimens have been compared: bupivacaine 0.125%/fentanyl 5 mcg/mL was least effective with higher pain scores by ≈0.9/10 vs bupivacaine 0.125%/hydromorphone 10 mcg/mL vs ropivacaine 0.1%/hydromorphone 20 mcg/mL on POD 1, but not later (Siddiqui 2016 **Level III-2**, n=72).

With the expansion of available regional analgesic techniques, there is no consensus on postoperative pain management for pectus excavatum repair: 91% of respondents in an international survey (North America, Europe, Asia and Australia) reported thoracic epidural as

the primary analgesic modality for minimally invasive pectus excavatum repair or Nuss procedure, with 27% concomitantly using PCA opioid (Muhly 2014 **Level IV**, n=58). While USA registry data reported less frequent use of epidurals (34%); pain scores and postoperative opioid consumption were lower with an epidural catheter vs no regional analgesic technique or a wound catheter, and achieved similar analgesia to paravertebral catheters (Muhly 2019 **Level III-2**, n=331 [114 epidural]; Stroud 2014 **Level III-2**, n=331*)*. Epidural recipients had longer time to ambulation (vs PVB CPNCs), higher rates of urinary catheterisation and longer LOS (median 4 d vs 3). While LOS was similar vs PCA only in a low quality RCT, where epidural failure rate was 22%, PCA was used during transition from epidural to orals for 19% and no detail of infusion adjuvant or opioid use for either arm was provided (Desai 2016a **Level II**, n=110, JS 1). Longer LOS for epidural recipients by 1–3 d is consistently reported in small and retrospective pectus excavatum surgery studies below.

Pain outcomes were mixed where thoracic epidural infusion:

- Provided equivalent analgesia vs PVB CPNC infusions (US-guided; bilateral) (Muhly 2019 **Level III-2**, n=331 [56 paravertebral, 114 epidural] Hall Burton 2014 **Level III-2**, n=20);
- Resulted in lower pain scores and opioid use postoperatively vs PVB CPNCs and intercostal nerve catheters, but LOS was shortest with PVB CPNCs (mean 2.0 d vs 4.0 vs 4.9) (Loftus 2016 **Level III-2**, n=137);
- (With adjuvant hydromorphone 10 mcg/mL) achieved similar pain scores vs wound catheter recipients (who also received hydromorphone PCA, low dose gabapentin 100–200 mg three times daily and clonidine patch 50 mcg/d) (Choudhry 2016 **Level III-3**, n=32);
- Achieved lower pain scores vs wound catheter recipients (Kabagambe 2018 **Level III-2**, n=31; Thaker 2019 **Level III-3**, n=124) but higher PCA requirements in a study exploring the addition of preoperative self-hypnosis training (Manworren 2018 **Level III-2**, n=53);
- (With adjuvant hydromorphone) had higher (Keller 2016 **Level III-2**, n=52) or similar postoperative opioid use and pain scores vs intercostal nerve cryoablation (Harbaugh 2018a **Level III-2**, n=32);
- Had similar pain scores vs single injection intercostal nerve block (0.25% bupivacaine) and/or PCA (Schlatter 2019 **Level III-2**, n=173);
- Resulted in higher pain scores from POD 2–5 vs IV parecoxib 1 mg/kg (max 40 mg) BD (Yang 2015 **Level III-2**, n=120 [14 parecoxib]);
- (With adjuvant clonidine 0.6 mcg/mL)/ketorolac/PCA had similar pain scores but greater opioid use vs multimodal analgesia with no regional analgesia (paracetamol, NSAID, PCA, gabapentin, clonidine patch, diazepam) (Man 2017 **Level III-3**, n=50); and
- Resulted in greater postoperative opioid requirement and more minutes in severe pain (≥7/10) vs multimodal analgesia (including some receiving intraoperative methadone [0.1 mg/kg max 7.5 mg]) (Singhal 2016 **Level III-3**, n=124). There was no difference in adverse effects, although respiratory depression was not reported.

While two non-epidural studies show benefit for PRA in addition to PCA opioid, where US-guided bilateral intercostal nerve blocks reduced early pain scores (0–6 h) and opioid requirements in PACU and 0–24 h vs saline blocks (Luo 2017 **Level II**, n=62, JS 4) and US-guided bilateral single injection thoracic PVB reduced pain scores by >2.5/10 vs PCA opioid alone at all time points with lower PCA opioid use 0–48 h postoperatively (Qi 2014 **Level II**, n=30, JS 2).

Scoliosis surgery

Intrathecal and epidural opioids in posterior spinal fusion for idiopathic scoliosis

Studies of IT opioid dosing in children and adolescents having scoliosis surgery have used larger doses on a per kg basis than adult studies. Doses of ≥9 mcg/kg are associated with respiratory complications and PICU admission.

IT opioids given preoperatively reduced blood loss and provided good analgesia in the immediate perioperative period: morphine 5–15 mcg/kg and/or sufentanil 1 mcg/kg (Eschertzhuber 2008 **Level II**, n=46, JS 5) and morphine 12 mcg/kg (Lesniak 2013 **Level III-3**, n=256). IT morphine (7.5 mcg/kg) vs extended release epidural morphine (150 mcg/kg) had similar time to first PCA use and postoperative IV PCA morphine use 0–48 h (Cohen 2017 **Level II**, n=71, JS 4). Pain scores differed relating to the kinetics of the epidural preparation and were lower with IT morphine from 0–4 h, similar from 8–24 h, and lower with extended release epidural morphine from 28–36 h.

IT morphine prolonged time to first IV morphine: 22.9 h for ≥20 mcg/kg (mean 24) vs 16.7 h for 9–19 mcg/kg (mean 14) vs 6.6 h with no IT morphine (Tripi 2008 **Level III-2**, n=407). This was at the expense of respiratory depression (15.2% vs 2.7 vs 1.5) and PICU admission (17.4% vs 2 vs 0). Pruritus (4–9%) and PONV incidence (25–30%) was similar. IT morphine (3–7 mcg/kg) combined with 2–5 d epidural infusion of ropivacaine and/or fentanyl (Ravish 2012 **Level III-3**, n=146) or bupivacaine/hydromorphone epidural infusion (Milbrandt 2009 **Level III-2**, n=138) provided superior analgesia vs IV PCA opioid alone.

Continuous epidural infusion with hydromorphone only 5 mcg/mL at 60–80 mcg/h (with 10 mcg bolus q30 min prn) achieved adequate analgesia in 95% of adolescents (Hong 2016 **Level IV**, n=56). No serious adverse effects were reported but subsequently, the same group compared IT morphine vs a lower dose epidural hydromorphone infusion (40–60 mcg/h and 5 mcg bolus q30 min prn), where 9 mcg/kg IT (Li 2018b **Level III-3**, n=56) reduced pain scores on POD 0, while 12 mcg/kg IT (Hong 2017 **Level III-2**, n=40) only lowered PACU pain scores. In both studies, the IT group had shorter time to ambulation and urinary catheter removal. Two serious adverse events occurred in the IT 9 mcg/kg group: one respiratory depression and one with severe hypotension/bradycardia and both required ICU admission (Li 2018b **Level III-3**, n=56).

Epidural local anaesthetic and or opioid in mixed scoliosis surgery

In children and adolescents having thoracolumbar spinal surgery (9 RCTs posterior spinal fusion [PSF] & 1 RCT anterior surgery for idiopathic scoliosis; 1 RCT of selective dorsal rhizotomy in cerebral palsy patients), epidural analgesia (local anaesthetic, opioid or both) vs systemic analgesia reduces pain scores at 72 h at rest (MDs -0.65/10 to -1.32) (5 RCTs, n=157) and on movement (MDs -1.07/10 to -1.51) (2 RCTs [1 anterior; 1 posterior approach], n=60), with more patients opening their bowels within 48 h (RR 11.5; 95%CI 2.4 to 56.3) (2 RCTs, n=60) (Guay 2019b **Level I** [Cochrane], 11 RCTs, n=559). There was no difference in POV (0–48 h), time to ambulation or hospital LOS.

Dual epidural catheter techniques have been effective after anterior (Guay 2019b **Level I** [Cochrane], 1 RCT: Blumenthal 2006 **Level II**, n=30, JS 3), and posterior (Guay 2019b **Level I** [Cochrane], 1 RCT: Blumenthal 2005 **Level II**, n=30, JS 3; Lavelle 2010 **Level III-2**, n=55) spinal fusion with improved dermatomal spread after combined surgical approach (Ekatodramis 2002 **Level IV**, n=23). PCEA has been effective with a high level of patient satisfaction in selected cases (Saudan 2008 **Level IV**, n=98). There is however a significant epidural failure rate within 24 h of 8.5–37% due to incorrect placement, patency issues and the long wound length (Guay 2019b **Level I** [Cochrane], 1 RCT: Gauger 2009 **Level II**, n=38, JS 3; Ravish 2012 **Level III-3**, n=146).

In a comparison of two epidural morphine administration techniques for PSF for idiopathic scoliosis, patient-controlled intermittent epidural bolus (PCIEB) (50 mcg/kg initial bolus and q1 h

prn) vs PCEA (20 mcg/kg initial bolus then 10 mcg/kg/h with 5 mcg/kg q30 min prn) had no difference in pain scores with less morphine in 24 h (median 5 mg vs 12.5), PON (16% vs 50%), POV (8% vs 35%) and pruritus (17% vs 40%) (Erdogan 2017 **Level II**, n=44, JS 5).

In patients with neuromuscular disorders and restrictive lung disease having PSF, epidural analgesia with ropivacaine 0.2% (4–6 mL/h) and systemic analgesia vs systemic analgesia alone (NSAIDs and pentazocine) reduced pain scores and frequency of rescue analgesia use in the first 3 d postoperatively (Saito 2015 **Level III-3**, n=10).

Wound catheter use in scoliosis surgery

Continuous bupivacaine infusion via a wound catheter reduced basal morphine use in idiopathic scoliosis surgery (Ross 2011 **Level III-3**, n=244 [129 wound catheter]).

Cardiothoracic surgery

In paediatric cardiac surgery, caudal injection of various medications and combinations reduced intraoperative and postoperative analgesia vs control in 9 studies and pain scores in three of five studies (Maharramova 2019 **Level IV SR** [PRISMA], 17 studies, n=2,159). In two of three studies caudal/general anaesthesia vs general anaesthesia alone reduced the perioperative stress response (cortisol, blood glucose or IL-6 levels), and caudal vs control reduced LOS in four of four studies; the authors concluded the data quality was too poor to make any recommendations for caudal analgesia use in this surgery.

Tonsillectomy

The assessment and comparison of efficacy of analgesia in tonsillectomy trials is challenged by the variation in surgical technique both within and between trials. Due to the proximity of significant vascular structures and nerves, peritonsillar infiltration and nerve block have inherent risks which can result in severe complications (Kang 2001 **Level IV**, n=2; Weksler 2001 **CR**). RCTs of infiltration with agents that are effective systemically should have a systemic arm for comparison that permits assessment of additive risk vs analgesic benefit.

For discussion of topical local anaesthetic and topical ketamine in children see Section 10.6.5 and adult Section 8.6.7.3

Local anaesthetic infiltration or application

Various local anaesthetics by infiltration (5 RCTs) or topical application (2 RCTs) produced modest reductions in pain (SMD 7–19/100 mm) vs placebo following tonsillectomy; this is a pooled value with no subgroup analyses for paediatric patients (Grainger 2008 **Level I**, 13 RCTs [7 RCTs paediatric, n≈356]) (see also adult Section 8.6.7.3). Infiltration with local anaesthetic solutions containing adrenaline may reduce blood loss (Johr 2015 **NR**). Compared to placebo, bupivacaine 0.25–0.5% infiltration alone (3 RCTs) and with adrenaline (3 RCTs) results in fewer children requiring additional analgesia across 0–4 h postoperatively (RR 0.62; 95%CI 0.48 to 0.80) (4 RCTs, n=163) and lower pain scores at 12–48 h (5 RCTs, n=204), but with no difference in PONV (3 RCTS, n=121) (Sun 2010 **Level I**, 7 RCTs, n=286) (2 RCT overlap). However, patients who received infiltration with bupivacaine 0.25% 5 mL vs pre-emptive administration of IV tramadol 3 mg/kg had higher postoperative pain scores by 0.83/10 (95% CI 0.47 to 1.2) and required more postoperative rescue analgesia (81% vs 57), with no difference in PONV (Teunkens 2019 **Level II**, n=200, JS 4).

Systemic or peritonsillar infiltration of dexamethasone

Peritonsillar infiltration pre-incision of dexamethasone as a comparator arm (and not as an adjuvant) (in single doses of 0.3 to 1 mg/kg, with 0.5 mg/kg the most studied dose) was superior to or equivalent to various active therapies, with all superior to placebo (Titirungruang 2019 **Level I**, 7 RCTs [dexamethasone infiltration], n=728). In these heterogeneous RCTs, dexamethasone infiltration vs placebo reduced postoperative pain at 0–24 h (OR -0.77; 95 %CI -1.02 to -0.53) (6

RCTs, n=528) and on POD 1 (OR -1.06; 95%CI -1.6 to -0.52) (7 RCTs, n=676) and reduced PONV (OR 0.56; 95%CI 0.36 to 0.87) (7 RCTs, n=728).

Details of the active therapies in these RCTs reveals dexamethasone infiltration pre-incision:

- Resulted in lower pain intensity vs IV 0.5 mg/kg (max 24 mg) with both routes superior to placebo (Gao 2015 **Level II**, n=240, JS 4);
- Was similar to bupivacaine 0.25% (3–5 mL) infiltration and postoperative topical lidocaine spray (applied four times daily) with all treatment arms superior to placebo (Kaygusuz 2003 **Level II**, n=40, JS 2);
- Lowered pain scores over 1 wk vs levobupivacaine infiltration 0.25% (with 5mcg/mL epinephrine/adrenaline) with both superior to placebo; both active therapies increased time to first analgesia similarly (Aysenur 2014 **Level II**, n=60, JS 4);
- 0.3 mg/kg (max dose unspecified) was superior to placebo in lowering pain scores but inferior to tramadol infiltration 0.1 mg/kg (with no systemic comparator) (Topal 2017 **Level II**, n=60, JS 2).

An earlier systematic review with 1 RCT overlap drew the same conclusions (Vlok 2017 **Level I**, 3 RCTs [2 paediatric, n=309]).

In contrast to the Cochrane review of systemic use of dexamethasone presented in 10.4.10, IV dexamethasone 0.5 mg/kg (max 16 mg)/saline block (a comparator arm) was less effective than pre-emptive local anaesthetic infiltration/IV placebo which reduced pain scores and analgesia requirements 0–24 h and PONV in PACU (3.1% vs 15.6%) and 24 h (9.2% vs 26.6%) (Naja 2017 **Level II**, n=129, JS 5). The combination of glossopharyngeal nerve block with IV dexamethasone 0.15 mg/kg (max 8 mg) for tonsillectomy provided superior postoperative analgesia to either in isolation (Mohamed 2009 **Level II**, n=150, JS 3). However, glossopharyngeal nerve block in 2 children has been associated with postoperative airway obstruction (which terminated the proposed RCT) (Bean-Lijewski 1997 **Level III-3**, n=8).

Peritonsillar infiltration or systemic NMDA antagonists

Three systematic reviews of peritonsillar infiltration of ketamine for tonsillectomy (see Section 10.4.7.1) summarise between 3 and 10 RCTs with 2 to 10 RCT overlap. The effect for peritonsillar infiltration is positive vs placebo for pain scores at 60 min (WMD -1.71/10; 95% CI -2.12 to -0.22) and reduced analgesic rescue (RR 0.51; 95%CI 0.26 to 0.9), with no systemic arm for comparison (Tong 2014a **Level I**, 10 RCTs, n=522). Adding IV ketamine 0.5 mg/kg to peritonsillar bupivacaine 0.25% was more effective than IV placebo/peritonsillar bupivacaine infiltration, and IV placebo/placebo infiltration with significantly lower pain scores from 1–24 h, and longer time to first analgesia (Inanoglu 2009 **Level II**, n=90, JS 5). A subsequent study compared peritonsillar ketamine administration vs PR and IV routes vs IV tramadol with similar pain scores in all four treatment arms (Yenigun 2015 **Level III-1**, n=120).

The addition of peritonsillar magnesium 2–5mg/kg to local anaesthetic reduced pain scores (4 RCTs, n=230) and the number of analgesic requests (WMD −0.68; 95% CI −1.17 to −0.18) (3 RCTs, n=180) (Vlok 2017 **Level I**, 4 RCTs [Mg], n=230).

Peritonsillar tramadol and pethidine

Adjuvant use of peritonsillar infiltration of tramadol added to local anaesthetic was beneficial to pain scores (0.25–24 h), with no difference in PONV (Vlok 2017 **Level I**, 1 RCT: Honarmand 2015 **Level II**, n=120, JS 5). Adjuvant use of peritonsillar infiltration of pethidine added to local anaesthetic reduced pain scores (at 3 h) and increased time to first analgesic use (Vlok 2017 **Level I**, 1 RCT: Elhakim 1997 **Level II**, n=80, JS 4).

Ophthalmological Surgery

Peribulbar block

Compared to intraoperative opioids, pre-emptive peribulbar block reduced the occurrence of intraoperative oculocardiac reflex and PONV during strabismus (Chhabra 2005 **Level II**, n=109, JS3) and other paediatric ophthalmic surgery with lower postoperative pain scores from 0.5–6 h (; Subramaniam 2003 **Level II**, n=85, JS 3; Deb 2001 **Level II**, n=50, JS 1). A peribulbar block may eliminate the need for opioid in children down to 5 wk of age undergoing vitreoretinal surgery (Patel 2012 **Level IV**, n=6).

Sub Tenon block

For vitreoretinal surgery, a sub Tenon block vs intraoperative opioids reduced the occurrence of the oculocardiac reflex with longer time to first rescue analgesic vs IV fentanyl (Chhabra 2009 **Level II**, n=196, JS 5); with benefit (Ramachandran 2014 **Level II**, n=67, JS 3; Kachko 2010 **Level II**, n=79, JS 1; Gupta 2007 **Level II**, n=45, JS 2; Steib 2005 **Level II,** n=40 JS 5) and no benefit to the reflex and PONV for strabismus surgery (Tuzcu 2015 **Level II**, n=40, JS 3).

For strabismus surgery, a sub Tenon block yielded a small clinical improvement in early postoperative pain scores at 30 min only (and not from 1–2 h) vs no block (Tuzcu 2015 **Level II**, n=40, JS 3); with reduced postoperative analgesic requirements vs placebo (Steib 2005 **Level II**, n=40, JS 5). Pain scores after sub Tenon block with bupivacaine did not differ vs topical lidocaine 3.5% gel or placebo (Enyedi 2017 **Level II**, n=50, JS 5). Sub Tenon block reduced emergence agitation post strabismus surgery vs placebo (10.4% vs 27.2%) independent of anaesthesia maintenance type (sevoflurane vs propofol/remifentanil) (Seo 2011 **Level II**, n=250, JS 5).

For paediatric cataract surgery, sub Tenon blocks were superior to IV opioid with reduced oculocardiac reflex, lower pain scores and longer time to first analgesic (median 16 h [range 2–13] vs 4 [0.5–8.5]) (Ghai 2009 **Level II**, n=114, JS 5).

The relative risks of the different eye block approaches have not been fully evaluated and a meta-analyses for the various techniques has not yet been performed.

Cleft lip and palate repair

Infraorbital nerve block for cleft lip repair

For paediatric cleft lip repair, there is low quality evidence that an infraorbital nerve block with lidocaine or bupivacaine may reduce postoperative pain vs placebo (SMD -3.54; 95%CI -6.13 to -0.95) and vs IV analgesia (SMD -1.50; 95%CI -2.40 to -0.60) (Feriani 2016 **Level I** (Cochrane], 8 RCTs, n=353). An infra-orbital nerve block vs surgical site infiltration reduces supplemental analgesia requirements (RR 0.05; 95%CI 0.01 to 0.18) and prolongs analgesia duration (MD 8.26 h; 95%CI 5.41 to 11.11). The addition of clonidine 1 mcg/kg to bupivacaine in a bilateral infraorbital nerve block prolonged duration of analgesia (11.1 h vs 9.3); with no systemic comparator (Feriani 2016 **Level I** [Cochrane], 1 RCT: Jindal 2011 **Level II**, n=50, JS 5). Adding opioids to bupivacaine infraorbital nerve block (with no systemic comparators) increases duration of analgesia from 18 to 24 h for fentanyl and from 29 to 35 h for pethidine (Feriani 2016 **Level I** [Cochrane], 2 RCTs: Mane 2011 **Level II**, n=45, JS 5; Jonnavithula 2007 **Level II**, n=40, JS 2). Infraorbital nerve block reduces postoperative opioid requirement and emergence agitation but not pain scores vs placebo (Kendall 2018 **Level I** [PRISMA] 1 RCT: Wang 2015 **Level II**, n=100, JS 4). Future studies should standardise the observation time and the instruments used to measure outcomes, have larger sample sizes and stratify children by age group (Feriani 2016 **Level I** [Cochrane], 8 RCTs, n=353).

Bilateral suprazygomatic maxillary nerve block and palatal block

For cleft palate repair, bilateral suprazygomatic maxillary nerve block (SZMNB) with ropivacaine vs saline reduced postoperative opioid requirements (Mesnil 2010 **Level III-3**, n=33), halved the 48 h IV morphine (mean 104 mcg/kg; 95%CI 69 to 140 vs 205 mcg/kg; 95%CI 131 to 280) and reduced

the need for morphine infusion postoperatively (3.6% vs 31) (Chiono 2014 **Level II**, n=57, JS 4). Minor adverse events related to the SZMNB have been reported: bleeding at the puncture site, localised swelling (Mostafa 2018 **Level II**, n=60, JS 4) and an infrazygomatic cheek haematoma which appeared on POD 1 and resolved by POD 5 (Chiono 2014 **Level II**, n=57, JS 4). US-guidance permitted confirmation of needle location and assessed local anaesthetic spread (Sola 2012 **Level IV**, n=25 [50 blocks]). Levobupivacaine 0.2% and bupivacaine 0.2% SZMNBs provide equivalent postoperative analgesia (Mostafa 2018 **Level II**, n=60, JS 4).

Palatal block (combined nasopalatine, greater and lesser palatine nerve block) vs no block reduced pain scores following cleft palate repair, and delayed time to first analgesia (18 h vs 6) with less demands for rescue analgesia (Jonnavithula 2010 **Level II**, n=45, JS 3). The addition of dexmedetomidine 1 mcg/kg to bupivacaine 0.25% for greater palatine nerve blocks reduced pain scores across 0–24 h vs bupivacaine 0.25% alone and prolonged time to first analgesia (mean 22 h vs 14.2) with no side effects (Obayah 2010 **Level II**, n=30, JS 3).

Bilateral SZMNB vs bilateral infraorbital nerve block for cleft lip and vs palatal block for cleft palate surgery achieved similar postoperative pain scores, opioid consumption, complication and failure rates (Echaniz 2019 **Level II**, n=120 [102 children], JS 4).

Interventions for the iliac bone graft donor site for cleft palate repair are described in Section 10.6.2.1 lower limb blocks.

Dental procedures

Outpatient dental procedures

Topical anaesthetics should be used prior to local anaesthetic injection to minimise discomfort with needle penetration and injection (Kuhnisch 2017 **GL**). Local anaesthetic infiltration reduced pain following dental extractions (Anand 2005 **Level III-2**); adding morphine 25 mcg/kg to the local anaesthetic did not improve the quality or duration of analgesia (Bhananker 2008 **Level II**, n=42, JS 3). There is low quality evidence suggesting similar efficacy for local anaesthetics during routine dental treatments with articaine achieving slightly more pain score reduction than lidocaine post procedure (SMD 0.37) (4 RCTs, n=397) (Tong 2018 **Level I** [PRISMA], 6 RCTs, n=541); while inferior alveolar nerve block was superior to buccal infiltration for mandibular molar extraction (1 RCT, n=113) (Klingberg 2017 **Level I** [PRISMA], 8 RCTs, n unspecified) (3 RCT overlap). Use of local anaesthesia for dental work is documented in children with rare medical diseases (Dougall 2017 **Level IV SR** [PRISMA], 3 studies, n=83).

The use of a computer assisted injection devices delivery device vs conventional infiltration was not painful, with high success rates (Giannetti 2018 **Level IV**, n=66; Sixou 2015 **Level IV**, n=278 [421 procedures]) and similar onset of effect for submucosal and buccal injection for 1st permanent molar work (Kandiah 2012 **Level II**, n=30, JS 3) and less painful for buccopalatal injection (Feda 2010 **Level II**, n=40 JS 1). A vibrating device did not reduce pain scores during local anaesthetic injection (Raslan 2018 **Level II**, n=40, JS 2; Roeber 2011 **Level II**, n=90, JS 4). A needleless jet system was inferior to standard local anaesthetic infiltration, as it required more local anaesthetic supplementation and more patients reported post procedure pain (Arapostathis 2010 **Level III-2**, n=87 [174 procedures-split mouth design]).

Eutectic Mixture of Local Anaesthetics (EMLA®) with audiovisual aid distraction reduced pain scores during needle insertion and was superior to EMLA® alone, or topical benzocaine (20%) with and without audiovisual aid distraction (mean 4.7/10 vs 5.7 vs 5.9 vs 7.4) (Agarwal 2017 **Level II**, n=120, JS 1). Acupuncture at L14 improved pain levels with local anaesthetic injection (buccal infiltration, intraligament injection and block analgesia): mean 2.3/10 (95%CI 1.5 to 3.1) vs 3.9 (95%CI 3.0 to 4.7) (Usichenko 2016 **Level II**, n=49, JS 4). A Cochrane review did not find positive benefit for hypnosis (Al-Harasi 2010 **Level I** [Cochrane], 3 RCTs, n=69). The addition of preoperative

systemic analgesic prior to orthodontic separator placement (without general anaesthesia) is likely of benefit (Ashley 2016 **Level I** [Cochrane], 5 RCTs, n=190).

See also adult Section 8.6.7.2 Acute postoperative dental pain.

Dental procedures under general anaesthesia

RCTs of local anaesthetic for children undergoing dental work with a general anaesthetic were heterogeneous regarding injection site (intra-ligamental vs surgical site infiltration vs topical) and varied in supplemental analgesics and follow-up (Parekh 2014 **Level I** [Cochrane], 14 RCTs, n=1,152). This precluded pooling of results, with a suggestion for further good quality RCTs. The addition of local anaesthetic to IV ketorolac in dental restoration or extraction under general anaesthetic does not improve quality of recovery vs IV ketorolac alone and young children may bite or chew the anaesthetic cheek or lip (Townsend 2009 **Level II**, n=27, JS 5). 'Best Clinical Practice Guidelines' by the European Academy of Paediatric Dentistry recommend the routine use of local anaesthetic agents with vasoconstrictors to slow systemic absorption, prolong analgesic effect and provide additional haemostasis (Kuhnisch 2017 **GL**).

KEY MESSAGES

1. Topical local anaesthetic does not adequately control pain associated with circumcision in awake neonates (**U**) (**Level I** [Cochrane Review]).
2. Caudal local anaesthetic, dorsal penile nerve block (**U**) (**Level I** [Cochrane Review]) and ring block (**N**) (**Level II**) provide effective perioperative analgesia for circumcision in infants to adolescents.
3. Caudal local anaesthetic in addition to general anaesthesia for circumcision does not reduce postoperative nausea and vomiting or the need for early rescue or other analgesia in children (infants to adolescents) when compared to parenteral analgesia (**U**) (**Level I** [Cochrane Review]).
4. In acute otitis media, topical local anaesthetic drops are effective in children compared to placebo and equivalent to naturopathic drops (**S**) (**Level I** [Cochrane Review]).
5. For paediatric cleft lip repair, infraorbital nerve block with lidocaine or bupivacaine may reduce postoperative pain versus placebo; duration is increased when opioids are added (with no systemic comparator) (**N**) (**Level I** [Cochrane Review]).
6. Epidural analgesia compared to systemic analgesia after spinal surgery in children improves pain up to 72 hours postoperatively (N) (Level I[Cochrane Review]).
7. Local anaesthetics (by infiltration or nerve block) reduce pain scores post dental procedures (**N**) (**Level I** [PRISMA]).
8. Ketamine added to caudal local anaesthetic for paediatric day-stay surgery prolongs analgesia but not motor block (**U**) (**Level I** [PRISMA]); however concerns regarding neurotoxicity remain.
9. Dexamethasone (caudal, perineural or IV) prolongs the duration of analgesia of local anaesthetic caudal (**N**) (**Level I** [PRISMA]) and peripheral nerve blocks (**N**) (**Level II**).
10. Magnesium added to caudal local anaesthetic blocks improves analgesia in children (**N**) (**Level I** [PRISMA]).

11. Clonidine (**U**) and dexmedetomidine (**N**) improve analgesia in children when added to local anaesthetic caudal blocks, epidural infusions (**Level I** [PRISMA]) and peripheral nerve blocks (**N**) (**Level II**).
12. Peritonsillar dexamethasone or peritonsillar ketamine may reduce pain scores following paediatric tonsillectomy compared to placebo (in trials with no systemic comparator arms) (**N**) (**Level I**).
13. Ultrasound guidance for epidural catheter insertion is a reliable predictor of depth to loss of resistance (or of epidural space), offers visibility of the needle and catheter and may reduce bone contacts (**N**) (**Level IV SR**).
14. In children having cardiac surgery, caudal injections with various medication combinations vs control reduces postoperative analgesia requirements and pain scores (**N**) (**Level IV SR** [PRISMA]).
15. In children having scoliosis surgery, the addition of epidural local anaesthetic infusion to intravenous PCA morphine improves pain scores and patient satisfaction (**U**) (**Level I**) and decreases postoperative nausea (**U**) (**Level II**).
16. Peripheral nerve blocks (**S**) (**Level I** [PRISMA]), wound infiltration and caudal local anaesthetic provide effective analgesia after day-stay paediatric inguinal surgery (**S**) (**Level II**).
17. Epidural infusions of local anaesthetic in children provide similar levels of analgesia compared to systemic opioid infusion (**U**) (**Level II**) and intravenous PCA (**U**) (**Level III-3 SR**).
18. Epidural opioids alone are less effective than epidural local anaesthetic or combinations of local anaesthetic and opioid in children (**U**) (**Level II**).
19. Intrathecal opioids provide prolonged analgesia after surgery in children and reduce blood loss during paediatric spinal fusion (**U**) (**Level II**). High doses of intrathecal morphine in children have been associated with respiratory failure and intensive care admission (**N**) (**Level III-2**).
20. Paediatric regional analgesia (peripheral nerve and neuraxial blocks as single injections and continuous catheters) are effective (**Level II**) and safe analgesic techniques in children (**S**) (**Level IV**); continous peripheral nerve catheters have been used in hospital and following discharge, with low secondary failure rates (**N**) (**Level IV**).
21. Ultrasound guidance to assist peripheral block and catheter placement has increased block success (**Level II**) but not impacted the incidence of local anaesthetic systemic toxicity or neurological complications in children; the latter having decreased independently over time (**N**) (**Level IV**).
22. Continuous wound catheter infusions of local anaesthetic are effective (**N**) (**Level II**) and safe analgesic techniques (**N**) (**Level IV**).
23. Caudal local anaesthetic blocks provide effective analgesia for lower abdominal, perineal and lower limb surgery (**Level II**) and have a low incidence of serious complications (**S**) (**Level IV**).
24. Continuous ultrasound-guided caudal injection versus landmark technique increases success of first puncture and lowers risk of vascular puncture and inadvertent subcutaneous injection (**N**) (**Level II**); while permitting real-time visualisation of injectate spread (**N**) (**Level IV**).

25. Sub Tenon block for paediatric ocular surgery achieved longer time to first analgesic administration versus placebo or intravenous opioid (**N**) (**Level II**).
26. Complications of epidural infusions are rare; the rates are slightly higher in neonates and infants versus older children (S) (**Level III-2**).
27. Continuous epidural infusions provide effective postoperative analgesia in children of all ages (**U**) (**Level III-2**).
28. Continuous epidural infusions are safe in children of all ages (**S**) (**Level III-2**) if appropriate doses and equipment are used by experienced practitioners, with adequate monitoring and management of complications (**U**) (**Level IV**).
29. Thoracic epidural, paravertebral catheters, wound catheters and intercostal nerve blocks all provide effective analgesia for pectus excavatum repair surgery, with longer hospital stays in thoracic epidural recipients (**N**) (**Level III-3**).
30. Placement of paediatric regional analgesia (peripheral nerve and neuraxial blocks as single injections and catheters) in children under general anaesthesia is not associated with an increased rate of complications (**S**) (**Level IV**).

The following tick boxes represents conclusions based on clinical experience and expert opinion:

☑ An association between urethral fistula formation complicating hypospadias repair and caudal block has not been consistently reported; variation in anatomical presentation and surgical technique are more biologically plausible risk factors (**N**).

☑ Lipid emulsion (20%) has been used in successful resuscitation of paediatric patients (neonates to 18 years) with local anaesthetic systemic toxicity; dosing recommendations are the same as for adults and higher doses have led to adverse effects (**N**).

☑ Dosing practices for peripheral nerve blocks vary and concerningly doses sometimes approach or exceed the accepted safe dose limit; this occurs more commonly in younger children (**N**).

10.7 | Management of procedural pain in children

Procedure-related pain is a frequent and distressing component of medical care for children, their families and hospital staff (Atkinson 2009 **NR**; Kennedy 2008 **NR**). Repeated interventions are often required and the level of pain and memory of the first procedure affect the pain (Taddio 2009 **Level II**, n=240, JS 5; Noel 2012 **Level IV**), fear (de Vos 2012 **Level IV**) and distress (Chen 2000 **NR**) associated with subsequent procedures (Kennedy 2008 **NR**). Poorly managed procedural pain may also result in greater anxiety, pain and avoidance of health care as adults (Young 2005 **NR**). Studies suggest that minor procedures are still undertaken in children, particularly neonates and infants, in the elective and emergency hospital setting without evidence-supported pain management interventions (Bueno 2017 **Level IV SR,** 68 videos; Cruz 2016 **Level IV SR,** 18 studies, n=3,156; Ali 2014 **Level IV**; Codipietro 2011 **Level IV**; Losacco 2011 **Level IV**; Hoyle 2011 **Level IV**; MacLean 2007 **Level IV**).

The aim of procedural pain management is to minimise physical discomfort, pain, movement and psychological disturbance without compromising patient safety. Management may include analgesic agents via different routes of administration, concurrent sedation or general anaesthesia and nonpharmacological methods. The choice of technique will depend on the age and previous experience of the child, the type of procedure, the expected intensity and duration of pain, the treatment environment and available resources (Atkinson 2009 **NR**; Murat 2003 **GL**). Sedation alone must not be seen as an alternative to appropriate analgesia, particularly when pain is expected after completion of the procedure. Further information is available from evidence based guidelines produced by various anaesthetic, paediatric and emergency physician associations (Green 2019b **GL**; Lago 2017 **GL;** Cote 2016 **GL;** Mace 2008 **GL;** RACP 2005 **GL**).

10.7.1 | Procedural pain in the neonate

10.7.1.1 | Blood sampling, skin puncture and intravenous cannulation

Effective pain management is a desirable standard of care for preterm and term neonates and may improve their clinical and neurodevelopmental outcomes (Hall 2014 **NR**). Multiple interventions have been assessed and their use is strongly supported; combining interventions appears to be more effective and is recommended (Lago 2017 **GL**). Neonates in NICUs require frequent painful procedures (mean 7.5–17.3 per day) (6 studies); however pain management strategies in these studies are inconsistently applied (Cruz 2016 **Level IV**, 18 studies, n=3,156). Many studies continue to be published on interventions such as breastfeeding, sweet solutions, non-nutritive sucking (NNS) and kangaroo care (ventral skin to skin contact with an adult); where these studies do not alter the conclusions of published systematic reviews, they have not been referenced.

Different techniques of blood sampling

In term neonates, venipuncture is less painful than heel lance (HL) (SMD -0.76; 95%CI -1.00 to -0.52) (5 RCTs, n=288), including when a sweet solution is administered (SMD -0.38; 95%CI -0.69 to -0.07) (3 RCTs, n=170) with less pain behaviour exhibited during and after the procedure and fewer attempts required (SMD 0.34; 95% CI -0.43 to -0.25) (4 RCTs, n=254) (Shah 2011b **Level I** [Cochrane], 6 RCTs, n=478). Spring-loaded automated devices for HL reduced the pain behaviour exhibited vs manual lance (Shah 2003 **Level II**, n=80, JS 5).

Topical local anaesthesia

Evidence-based recommendations could not be made regarding the use of topical local anaesthetics for the prevention of needle related procedural pain in newborns (Foster 2017 **Level I** [Cochrane], 8 RCTs, n=506). This includes for venipuncture, IV cannulation, arterial puncture, arterial cannulation, HL, lumbar puncture (LP), supra-pubic aspiration of urine, peripherally inserted central catheter (PICC) placement and intramuscular injection. Subsequently, for infants (<3 mth), EMLA® vs placebo, sucrose or breastfeeding did not reduce pain during (6 RCTs, n=742) or at the end (4 RCTs, n=226) of venipuncture (Shahid 2019 **Level I** [PRISMA], 10 RCTs, n=907) (1 RCT overlap). None of the RCTs reported clinical symptoms of methaemoglobinaemia; in two RCTs (n=134) methaemoglobin levels were <5%. However, acquired methaemoglobinaemia in a neonate following circumcision with EMLA® (dose unknown) and lidocaine infiltration, which was successfully treated with methylene blue has been reported (Kuiper-Prins 2016 **CR**).

Breastfeeding, supplemental breastmilk and sweet solutions

Breastfeeding

In term neonates, breastfeeding reduces pain scores, behavioural (cry), and physiological (heart rate) responses to skin puncture procedures when compared to positioning (swaddling and placement in a crib), holding by the mother, maternal kangaroo care, no intervention, placebo, pacifier use and PO sucrose or both, topical local anaesthetics and music therapy (Benoit 2017a **Level I** [PRISMA], 21 RCTs, n=1,764; Shah 2012 **Level III-1 SR** [Cochrane], 10 RCTs [breastfeeding], n=1,076) (0 RCT overlap). The effect in preterm neonates is not clear; studies are of limited number, and preterm neonates often cannot breastfeed and are more likely to receive repeated painful procedures.

Supplemental breastmilk

Studies of supplemental/expressed breast milk report mixed effects vs sweet tasting solutions (5 RCTs), placebo (6 RCTs) and no intervention (3 RCTs), and inferiority to pacifier use and rocking (1 RCT each) (Benoit 2017a **Level I** [PRISMA], 21 RCTs, n=1,764; Shah 2012 **Level III-1 SR** [Cochrane], 10 studies [supplemental breast milk], n=1,002) (0 study overlap).

Sweet solutions

A systematic review pooled data for meta-analysis on all sweet solutions (sucrose 106 studies, glucose 62 studies, non-sucrose sweetener 2 studies, honey and fructose 1 study each) for procedural pain in neonates (Harrison 2017 **Level III-1 SR** [PRISMA], 168 studies, n unspecified). Sweet solutions overall vs placebo reduced composite pain scores (SMD -0.90; 95%CI -1.09 to -0.70) (50 studies, n=3,341) and cry duration (SMD -23.18 s; 95%CI -28.89 to -17.47) (29 studies, n=1,775).

The most frequently studied intervention for managing procedural pain in preterm and term infants is sucrose with or without NNS. Studies vary in concentration and volume of sucrose administered, comparison group intervention and outcomes measured, meaning meta-analysis for each research question typically only combines a few studies or pool heterogeneous data.

Studies specific to sucrose mostly support an analgesic effect at higher concentrations (>20%) for HL (39 RCTs), venipuncture (10 RCTs), and intramuscular (IM) injection (4 RCTs); this effect may be greater when combined with other interventions (eg NNS, swaddling) (Stevens 2016 **Level I** [Cochrane], 74 RCTs, n=7,049). There is high quality evidence in this review for the following:

- For HL, 24% sucrose (0.5–2 mL) with NNS or sucrose 0.5 mL orally vs placebo in preterm and term infants reduces pain score at 30 s (WMD -1.70/21; 95%CI -2.13 to -1.26) (3 RCTs, n=278) and 60 s post procedure (WMD -2.14/21; 95%CI -3.34 to -0.94) (2 RCTs, n=164);
- 24% sucrose (2 mL) vs placebo for term neonates reduces pain score during venipuncture (WMD -2.79/21; 95%CI -3.76 to -1.83) (1 RCT, n=213);

- 24% sucrose (2mL) vs placebo for term neonates reduces pain score during IM injection (WMD -1.05/21; 95%CI -1.98 to -0.12) (1 RCT, n=232);
- Evidence for effectiveness of sucrose for arterial puncture (1 RCT) and SC injection (2 RCTs) is inconclusive.

Debate continues as to the optimal dose and administration of sucrose with one RCT documenting a minimum effective dose of 0.1 mL of 24% sucrose (Stevens 2018 **Level II**, n=248, JS 3).

A separate review focussing on the efficacy and safety of *repeated* sucrose over multiple procedures in neonates found limited evidence supporting its use to reduce pain scores and behaviours (cry), with no adverse effects reported; no meta-analysis was possible (Gao 2016 **Level I** [PRISMA], 8 RCTs, n=782).

Sweet non-sucrose solutions via dropper, syringe or pacifier have shown efficacy for procedural pain in preterm and term infants (Bueno 2013 **Level I** [PRISMA], 38 RCTs [35 glucose; artificial sweetener, fructose, glycine, honey, maltitol, 1 RCT each; 36 skin puncture], n=3,785):

- Glucose 10–50% (0.2–2mL) vs no intervention or water reduces pain scores during and/or after HL (6 RCTs, n=322; no meta-analysis);
- Glucose 20–30% (1–2 mL) vs water for HL reduces pain scores (WMD −3.61/21; 95%CI -4.58 to -2.63) (2 RCTs, n=124);
- Artificial sweetener, maltitol or fructose vs water or no intervention for HL reduces pain scores (1 RCT each);
- Maltitol, artificial sweetener or honey vs water for HL reduces cry duration (1 RCT each);
- Glucose 25–30% (1–2mL) vs glucose 10%, water, no intervention or EMLA® reduces pain scores for venipuncture (11 RCTs, n=1,250, no meta-analysis);
- Glucose 25–50% (1–2 mL) vs water for venipuncture reduces cry response (RR 0.80; 95%CI 0.66 to 0.96: NNT 6; 95%CI 3 to 20) (3 RCTs, n=130).

A further systematic review of Chinese studies on all sweet solutions for neonatal procedural pain found similar results to the above reviews (Huang 2019 **Level III-1 SR** [PRISMA], 31 studies, n=4,999) (0 study overlap).

Paracetamol

Paracetamol given 30–60 min prior vs placebo does not reduce pain with HL (3 RCTs), and findings are conflicting for eye examination (2 RCTs) (for further discussion, see 10.7.1.4); no meta-analysis was possible due to study heterogeneity (Ohlsson 2016 **Level I** [Cochrane], 9 RCTs, n=728). A subsequent RCT found paracetamol was not more effective than sucrose 24% for managing pain during PICC placement in preterm neonates (Roofthooft 2017 **Level II**, n=60, JS 4).

Opioids

Background morphine infusions in ventilated neonates had limited efficacy for acute procedural interventions in intensive care (Bellu 2008 **Level I** [Cochrane], 2 RCTs [procedures], n=965). An RCT of PO morphine (100 mcg/kg) vs placebo in non-ventilated premature infants for HL or eye examination was stopped early due to a high rate of respiratory depression requiring resuscitation (20% vs 0%) (Monk 2019 **Level II**, n=31, JS 5). IN Fentanyl (mean dose 1.3 mcg/kg) has been used in neonates in NICU having painful procedures (78% PICC insertion); respiratory depression occurred in 26% (McNair 2018 **Level IV**, n=23).

Combination intervention in neonates: pharmacological

In preterm neonates, topical local anaesthesia EMLA® combined with PO sucrose 30% was more effective than sucrose alone in reducing venipuncture-related pain (Biran 2011 **Level II**, n=76, JS 3). In term neonates, the addition of liposomal lidocaine for venipuncture to sucrose did not confer additional benefit (Taddio 2011 **Level II**, n=330, JS 5).

For PICC placement, IV morphine bolus with topical amethocaine provided more effective analgesia than morphine or amethocaine alone in preterm neonates (Taddio 2006 **Level II**, n=132, JS 5). In ventilated term and preterm neonates pre-treated with EMLA®, a glucose 30% pacifier combination was inferior to sevoflurane (Bueno 2013 **Level I** [PRISMA], 1 RCT [sevoflurane]: Michel 2010 **Level II**, n=59, JS 2).

Nonpharmacological intervention alone and in combination

Many nonpharmacological interventions have been studied for procedural pain in preterm and term neonates including NNS, swaddling/tucking, rocking/holding and kangaroo care. However, study designs are heterogeneous and prone to bias due to difficulty blinding interventions; caution interpreting results is required. A systematic review assessed the efficacy of nonpharmacological interventions on pain reactivity (behavioural responses within 30 s of painful procedure) and immediate pain regulation (behavioural response >30 s after painful procedure) (Pillai Riddell 2015c **Level III-I SR** [Cochrane], 63 studies [32 HL, 17 vaccination, 8 venipuncture], n=4,905). It found:

- NNS vs control reduces pain reactivity in term neonates (SMD -1.20; 95%CI -2.01 to -0.38) (5 studies, n=270) and improves immediate pain regulation in preterm (SMD -0.43; 95%CI -0.63 to -0.23) (5 studies, n=260) and term neonates (SMD -0.90; 95%CI -1.54 to -0.25) (7 studies, n=325);
- Swaddling/facilitated tucking vs control reduced pain reactivity in preterm neonates (SMD -0.89; 95%CI -1.37 to -0.40) (8 studies, n=331);
- Rocking and holding vs control improved immediate pain regulation in term neonates (SMD -0.75; 95%CI -1.20 to -0.30) (2 studies, n=81);
- NNS with pacifier/sucrose appeared superior to NNS alone (1 study, n=24), and facilitated tucking appeared to have an additive effect to NNS in preterm neonates (1 study n=45);
- There were smaller benefits for the following interventions: environmental modification (eg low noise and lighting, clustering procedures) and touch/massage interventions in preterm infants; swaddling/facilitated tucking and familiar odours (familiarisation with vanilla 24 h prior to procedure) in term infants;
- Subsequent to this review, olfactory stimulation from lavender, breast milk and amniotic fluid vs control for HL reduced pain scores (2.91/7 vs 3.31 vs 3.90 vs 5.20) (Akcan 2016 **Level II**, n=102, JS 2).

For vaccination, individual studies report NNS to be inferior to PO sucrose 20% (Liaw 2011 **Level II**, n=165, JS 3) and glucose 25% (Lima 2017 **Level II**, n=78, JS 2), whilst external warming was superior to NNS alone and PO sucrose 25% alone (Gray 2012 **Level II**, n=47, JS 3).

Two RCTs combined interventions for repeated HL in preterm infants. NNS/PO sucrose provides better pain relief than NNS or PO sucrose alone (Gao 2018 **Level II**, n=91, JS 3), whilst PO sucrose 20% is superior to facilitated tucking, but facilitated tucking/sucrose does not confer additional benefit to sucrose alone (Cignacco 2012 **Level II**, n=71, JS 5).

Kangaroo care appeared to be safe and reduce pain response to HL, venipuncture, and IM injections; however, the degree of benefit was difficult to estimate and may not be large (Johnston 2017 **Level III-I SR** [Cochrane], 25 studies, n=2,001). For all procedures on preterm neonates, kangaroo care vs standard care reduced pain score at 30 s (MD -3.21/21; 95%CI -3.94 to -2.47) (6 studies, n=267) and 60 s (MD -1.64/21; 95%CI -2.86 to -0.43) (4 studies, n=156). No difference was seen between mothers and alternative kangaroo care providers in preterm neonates. Single studies in this review comparing kangaroo care with other active interventions demonstrated similar efficacy to breastfeeding but superiority to PO dextrose and glucose solutions. Kangaroo care combined with breastfeeding, or PO sucrose/dextrose solutions was superior to kangaroo

care alone. A subsequent RCT found kangaroo care remained efficacious across three procedures (HL) with similar efficacy to PO sucrose 24% (Campbell-Yeo 2019 **Level II**, n=242, JS 3).

For HL, passive music therapy (played lullaby) was superior to no music for preterm neonates and, combined with NNS, was superior vs either alone, with lower pain and stress scores in both preterm and term neonates (Wright 2013 **Level I**, 2 RCTs [heel lance], n=87).

Acupuncture (invasive or non-invasive) for preterm and term neonates receiving HL did not reduce pain intensity (Stadler 2019 **Level I** [PRISMA], 5 RCTs, n=265). Distress during acupuncture itself was not reported. A subsequent RCT found auricular non-invasive magnetic acupuncture vs placebo reduced pain scores during (mean 5.9/21 vs 8.3) but not after HL in preterm and term neonates (Chen 2017a **Level II**, n=26, JS 3).

Applying mechanical vibration (5 s of 100 Hz) to the foot prior to HL, in addition to use of a pacifier with sucrose and heel warming, did not impact upon pain scores vs pacifier and sucrose alone (Baba 2010 **Level II**, n=20, JS 3).

For venipuncture, pre-recorded maternal voice was an effective intervention for reducing term neonates' physiological response to pain (Azarmnejad 2017 **Level III-1**, n=60).

10.7.1.2 | Lumbar puncture

For infant lumbar puncture (LP), surveyed clinicians working in paediatric EDs at five USA centres reported frequent use of NNS (67%), with low use of other interventions (<30% for sucrose, topical and injectable lidocaine) (Hoyle 2011 **Level IV**, n=156). A further USA centre audited local anaesthetic use for LP in children aged 0–24 mth with 0% use in neonates, 54% in infants but 99% in toddlers (Gorchynski 2011 **Level IV**, n=223). A Canadian ED survey revealed minimal use of PO sucrose in infants, and low use of topical local anaesthetic, across the paediatric age range (Ali 2014 **Level IV**, n=72 [EDs]). The poor translation of evidence into practice is disappointing with the data known regarding the consequences of poor analgesia (Kennedy 2008 **NR**) and the suggested positive association of local anaesthetic use with increased first pass success and atraumatic taps (Kennedy 2014 **NR**).

EMLA® reduced the physiological and behavioural response with needle insertion for LP in preterm and term neonates (Foster 2017 **Level I** [Cochrane], 1 RCT: Kaur 2003 **Level II**, n=60, JS 5).

10.7.1.3 | Urine sampling

EMLA® reduced pain scores in neonates and young infants undergoing suprapubic aspiration (Nahum 2007 **Level II**, n=52, JS 5). Oral sucrose 24% vs water reduced cry incidence (29 vs 78%) and pain scores during transurethral catheterisation in neonates (Stevens 2016 **Level I** [Cochrane], 1 RCT [catheterisation]: Rogers 2006 **Level II**, n=80, JS 5).

Four RCTs have compared pain from transurethral catheterisation to suprapubic aspiration. Transurethral catheterisation after urethral application of lidocaine 2% was less painful than suprapubic aspiration after skin application of EMLA® (Kozer 2006 **Level II**, n=58, JS 3). Transurethral catheterisation with lubrication only was less painful than suprapubic aspiration without topical local anaesthesia in preterm neonates (Badiee 2014 **Level II**, n=80 [uncircumcised males only], JS 2; El-Naggar 2010 **Level II**, n=48, JS 3) but not when compared to suprapubic aspiration with EMLA® in preterm and term neonates (Ghaffari 2014 **Level II**, n=90, JS 3).

10.7.1.4 | Ocular examination for retinopathy of prematurity

Screening for retinopathy of prematurity (ROP) causes pain in neonates (Belda 2004 **Level IV**). Topical local anaesthetic reduces pain scores (Dempsey 2011 **Level III-1 SR** [Cochrane], 2 studies,

n=168). A systematic review on the efficacy of sucrose found mixed results for eye examination (Stevens 2016 **Level I** [Cochrane], 7 RCTs [ROP], n=259):

- Oral sucrose 24–33%/NNS is more effective than sterile water/NNS in reducing pain scores (WMD -2.47/21; 95%CI -3.27 to -1.66) (3 RCTs, n=114);
- Sucrose did not affect cry (2 RCTs) or HR (2 RCTs);
- Two RCTs report short-lived reduction in oxygen saturation in PO sucrose treated infants, during but not persisting after eye examination.

A review including lower level evidence concluded that topical local anaesthetic/sweet tasting solution and a nonpharmaocological (adjunct) intervention was superior to topical local anaesthetic alone (MD -3.67/21; 95%CI -5.86 to -1.47) (17 studies) (Disher 2018 **Level III-1** [NMA], 29 studies, n=1,487) (2 & 7 study overlap with above). A fourth review included two RCTs comparing paracetamol to placebo for eye examination which have conflicting results whilst a third RCT reported higher pain scores for paracetamol vs sucrose 24% (Ohlsson 2016 **Level I** [Cochrane], 3 RCTs [ROP], n=213) (overlap 0, 0 & 3 RCTs).

10.7.1.5 | Nasogastric tube insertion

The evidence for efficacy of PO sucrose reducing pain from nasogastric/orogastric insertion is inconclusive (Stevens 2016 **Level I** [Cochrane], 3 RCTs [nasogastric], n=164). The highest quality evidence is for sucrose 24% vs sterile water lowering mean pain score 30 s post orogastric tube insertion (WMD -1.30/21; 95%CI -2.31 to -0.29) (1 RCT) but not during or 1 min post procedure (Pandey 2013 **Level II**, n=105, JS 5). A subsequent review that included lower level evidence concluded sweet solutions (sucrose 24 to 30% or glucose 25%) vs no intervention or placebo reduced pain score during or immediately after gastric tube insertion (MD -2.18/21; 95% CI -3.86 to -0.51) (4 studies, n=344) (Chen 2017b **Level III-1 SR**, 6 studies, n=441 [630 insertions]) (3 RCT overlap).

10.7.1.6 | Nasal CPAP prong insertion

Topical lidocaine 2% vs control did not reduce pain intensity or cortisol levels for preterm neonates having nasal CPAP prongs inserted (Soliman 2016 **Level II**, n=60, JS 3).

10.7.2 | Procedural pain in infants and older children

10.7.2.1 | Venipuncture and intravenous cannulation

Venipuncture causes significant distress in many children (Kennedy 2008 **NR**). Both pharmacological and nonpharmacological interventions have supportive evidence.

Hospital initiatives

In a large children's hospital, a system-wide initiative implemented a new standard of care for needle procedures that required staff to consistently offer 4 strategies: topical anaesthetics; PO sucrose or breastfeeding for infants 0–12 mth old; age-appropriate comfort positioning; and age-appropriate distraction (Friedrichsdorf 2018 **Level III-3**, n=20,758). This reduced wait times for services and increased patient satisfaction. Staff concerns about implementation (such as wait times) were allayed by the results. Using a similar multidisciplinary approach for venipuncture (including universal offering of EMLA®, child preparation, carer education, comfort positioning and age-appropriate distraction), the majority of carers were satisfied (91%) with the process and 82% reported the procedure eliminated the fear of needle-related procedures in their children (Yamamoto-Hanada 2015 **Level IV**, n=132).

Topical local anaesthesia

Topical local anaesthesia (via cream/gel, patch, iontophoresis and needleless compression device delivery) reduces pain associated with venipuncture and IV cannulation in all age groups (Zempsky 2008 **Level I**, 52 RCTs, n unspecified).

Amethocaine (tetracaine) gel is more effective than EMLA® cream (RR 0.78; 95%CI 0.62 to 0.98) with more rapid onset (Lander 2006 **Level I** [Cochrane], 6 RCTs, n=634), although does not improve first time cannulation success rate (Pywell 2015 **Level I** [PRISMA], 3 RCTs, n=922) (1 RCT overlap). A heated lidocaine/tetracaine patch was superior to both placebo (2 RCTs, n=109) and EMLA® (1 RCT, n=200) (Croxtall 2010 **Level I**, 3 RCTs [paediatric], n=309) and associated with a higher first-time venipuncture/cannulation success rate than EMLA® (Cozzi 2017 **Level II**, n=356, JS 3). Application of a heat pack after EMLA® does not increase first time success rate (Schreiber 2018 **Level II**, n=400, JS 3). EMLA® was more effective than a Valsalva manoeuvre in children (5–12y), both being more effective than control (1/10 vs 2.15 vs 2.55) (Akdas 2014 **Level II**, n=60, JS 2).

Iontophoresis of lidocaine 1–4% is superior to placebo (4 RCTs, n=420) and is equivalent to or superior to EMLA® (2 RCTs, n=144) with a time to onset of 10 min (Zempsky 2008 **Level I**, 52 RCTs, n unspecified). Liposomal lidocaine 4% cream was similar with only 15 min application to placebo (Brenner 2013 **Level II**, n=120, JS 5), but after 30 min was both similar to amethocaine 4% (Poonai 2012 **Level II**, n=60, JS 5) and superior to placebo (1 RCT, n=142) (Zempsky 2008 **Level I**, 52 RCTs, n unspecified). It had a more rapid onset, was as effective as EMLA® (3 RCTs, n=240) and was as effective as buffered lidocaine (1 RCT, n=69) (Zempsky 2008 **Level I**, 52 RCTs, n unspecified). Sonophoresis prior to application of liposomal lidocaine accelerated the onset time from 30 to 5 min (1 RCT, n=60) and sonophoresis/liposomal lidocaine was superior to sonophoresis/placebo cream (1 RCT, n=77).

Intradermal delivery of powdered lidocaine (0.5–1 mg) under high pressure (20 bar) via a needleless device (CO_2 or helium driven) was effective within 3 min and produced more effective skin anaesthesia than EMLA® in one RCT (Jimenez 2006 **Level II**, n=116, JS 3), but was less effective than EMLA® in another (Stoltz 2017, **Level II**, n=150, JS 3). Powdered lidocaine 0.5 mg was more effective than 0.25 mg (1 RCT, n=307) and placebo (2 RCTs, n=452) (Zempsky 2008 **Level I**, 52 RCTs, n unspecified; Schmitz 2015 **Level II**, n=517, JS 5), and associated with infrequent mild adverse events such as erythema and petechiae (Schmitz 2015 **Level II**, n=517, JS 5). In children (1–6 y) intradermal needleless pressure-injected lidocaine was more effective than vapocoolant spray and placebo (Lunoe 2015 **Level II**, n=205, JS 3). A cooling and rapidly vibrating device (Buzzy®) combined with intradermal needleless pressure-injected lidocaine provided no benefit vs intradermal needleless pressure-injected lidocaine alone, both for the administration of lidocaine and venipuncture (Kearl 2015 **Level III-2**, n=356).

Nitrous oxide (N_2O)

N_2O at 20–75% reduced pain and anxiety associated with venipuncture/IV cannulation and, in one study, shortened time to achieve access with fewer attempts (Tobias 2013a **Level IV SR**, 5 studies [venipuncture/cannulation], n unspecified). N_2O 70% for 3 and 5 min reduced pain scores by >50% (Furuya 2009 **Level II**, n=73, JS 5). The combination of N_2O 40–50% and topical EMLA® for IV cannulation is more effective in reducing pain scores and increased satisfaction vs either method alone (Pedersen 2013 **Level I** [PRISMA], 3 RCTs [IV cannulation], n=233). This systematic review also included five large case series of N_2O use in mixed minor procedures, supporting the safety of N_2O 50–70% administration in children. Minor adverse events were reported in 4–8% of patients and serious or potentially serious adverse events were reported in less than 0.5% of patients. (Pedersen 2013 **Level IV SR** [PRISMA], 5 studies, n=53,108).

Dexmedetomidine

IN Dexmedetomidine (2 mcg/kg) 30 min prior reduced pain scores during venous cannulation when given via mucosal atomisation device (MAD) vs dropper administration (Xie 2017b **Level II**, n=106, JS 3).

Sweet-tasting solutions in older children

For school aged children, chewing sweetened gum before needle-related painful procedures (2 RCTs, n=111) or during the procedure (2 RCTs, n=103) did not reduce pain scores during the procedure (Harrison 2015 **Level I** [Cochrane], 8 RCTs, n=808). In toddlers/preschool children (6 RCTs, n=520) there was insufficient evidence of an analgesic effect for sweet tasting solutions or substances during acutely painful procedures.

Combination pharmacological intervention

The combination of EMLA® and N_2O 50% reduced procedure duration with more successful IV placements than EMLA®/low-dose PO midazolam 0.3 mg/kg (max 15 mg) 40 min prior (Ekbom 2011 **Level II**, n=90, JS 4). Notably, the usual PO midazolam dose is 0.5 mg/kg and, at 40 min, offset of effect is relevant.

Nonpharmacological intervention

Skin cooling techniques

Evidence on the use of skin cooling techniques in children is conflicting. Vapocoolant sprays did not reduce pain from venipuncture or IV cannulation in children vs placebo or no treatment (3 studies, n=387) (Hogan 2014 **Level III-1 SR** [PRISMA], 12 studies, n=1,266 [4 paediatric, n=509]). Pain or discomfort from application of vapocoolant spray was not assessed in children. Two subsequent meta-analyses of the same 2 paediatric RCTs (n=165, both RCTs included in the above review) similarly reported no pain reduction with vapocoolant sprays vs placebo (Zhu 2018b **Level I**, 11 RCTs, n=1,410; Griffith 2016 **Level I** [Cochrane], 9 RCTs, n=1,070). In two separate RCTs, a vapocoolant spray (5-fluoropropane/4-fluoroethane: Painease®) applied 10 s prior to IV cannulation was similarly effective to 3 min application of ice in older children (9–18 y) (Waterhouse 2013 **Level II**, n=95, JS 4) and vapocoolant spray was superior to control but inferior to EMLA® (Dalvandi 2017 **Level II**, n=40, JS 3). Ice application (0° C) for 3 min has previously been reported to improve pain-related behaviours in children aged 6–12 y undergoing venipuncture (Movahedi 2006 **Level III-2**). With use of a metal applicator (Coolsense®: refrigerated to -2°C requiring 10 s application time), 94% of children aged 6–18 y rated their pain score during cannulation <3/10; patient and carer satisfaction with the device was high (Ragg 2017 **Level IV**, n=100).

Vibration alone or combined with cooling

The efficacy of the Buzzy® device (vibration alone or combined with cooling) vs no intervention for children (3–18y) having needle-related procedures has been assessed (Ballard 2019 **Level I** [PRISMA], 9 RCTs [7 IV cannulation/venipuncture, 2 vaccine injection], n=1,138). Buzzy® reduces:

- Self-reported pain intensity (SMD -1.12; 95%CI -1.53 to -0.71) (6 RCTs, n=609);
- Parent-reported pain intensity (SMD -0.94; 95%CI -1.62 to -0.27) (5 RCTs, n=398);
- Observer-reported pain intensity (SMD -1.19; 95%CI -1.90 to -0.47) (4 RCTs, n=329).

Smaller meta-analyses suggest a beneficial effect on parent and observer-reported anxiety, but not success of procedure on first attempt, or adverse effects. Additionally, Buzzy® vs distraction cards (1 RCT, n=110) and Buzzy®/topical anaesthesia vs vapocoolant spray/topical anaesthesia (1 RCT, n=81) improve self and parent-reported pain intensity, whilst Buzzy®/comfort plan is not superior to topical anaesthetic /comfort plan for IV cannulation (1 RCT, n=224).

The following RCTs with mixed results were not included in the above review where Buzzy®:

- Added to distraction cards for venipuncture was more effective than the hypnoanalgesic *'Magic Glove'* technique in 3–10 y olds (mean pain score 3.65/10 vs 4.67) (Susam 2018 **Level II**, n=64, JS 3);
- Vs a handheld computer game for venipuncture resulted in similar median pain scores in 4–12 y olds (3/10 vs 2) (Cozzi 2018 **Level II**, n=200, JS 3);
- Vs virtual reality (VR) for venipuncture resulted in similar pain scores in 7–12 y olds (mean 2.0/10 vs 1.5) (Gerceker 2018 **Level II**, n=121, JS 3);
- Alone or combined with animated cartoons vs control for 5–12 y olds having venipuncture did not reduce pain scores (Bergomi 2018 **Level II**, n=150, JS 3);
- Was not as effective as EMLA® patch in reducing pain intensity for children (18 mth to 16 y) having IV cannulation (mean 8.5/18 vs 7.2) (Bourdier 2019 **Level II**, n=607, JS 3);
- Resulted in lower pain scores than ShotBlocker®, bubble blowing or control in children aged 5–10 y receiving IM injection in the ED (mean 3.87/10 vs 4.14 vs 4.75 vs 6.72) (Yilmaz 2019 **Level II**, n=160, JS 3).

A second review included lower level evidence and evaluated vibratory stimulation *by any method* to reduce needle related procedure pain in children (0–18 y) (Ueki 2019 **Level III-1**, 21 studies, n=1,727) (7 RCT overlap). It found vibratory stimulation vs control reduced self-rated pain intensity (SMD -0.55; 95%CI -0.92 to -0.18) (13 studies, n=1,589), observer-rated pain intensity (SMD -0.47; 95%CI -0.76 to -0.18) (16 studies, n=1,721) and observer-rated anxiety (SMD -1.03; 95%CI -1.85 to -0.20) (4 studies, n=624). There was no difference in success of procedure on first attempt or adverse effects.

Distraction

A customised multimodal distraction device (Ditto®) designed for children aged 3–12 y provides procedural preparation stories and distraction content. Compared to standard distraction, combined Ditto® procedural preparation and distraction significantly reduced nursing staff and carer reported pain and distress (Miller 2016 **Level II**, n=98, JS 3). Carers also reported combined Ditto® procedural preparation and distraction as more effective than either in isolation.

Immersive virtual reality (Sony Snow World®) use in children aged 7–17 y significantly reduced time spent thinking about pain, pain unpleasantness and worst pain; patients reported more fun than controls (Atzori 2018 **Level III-2**, n=15). Patients aged 10–21 y used Bear Blast® with VR goggles during venipuncture and experienced less pain and anxiety than controls (Gold 2018 **Level II**, n=143, JS 3). Secondary analysis revealed patients with a high anxiety sensitivity experienced less anxiety with VR vs control, while patients with low anxiety sensitivity did not. For further discussion of distraction techniques including virtual reality see Section 10.7.5 Nonpharmacological Strategies in Adolescents and Children.

Other techniques

For older infants up to 36 mth having needle procedures, NNS improved immediate pain regulation (behavioural response >30 s post procedure: SMD -1.34; 95%CI -2.14 to -0.54) (2 studies, n=151) (Pillai Riddell 2015c **Level III-2 SR** [Cochrane], 63 studies, n=4,905). Touch/massage-related strategies and structured non-parent involvement also improved immediate pain regulation.

For pain during venipuncture in 6–12 y olds, acupressure and EMLA® reduced FLACC scores similarly with both better than routine care (mean 2.65/10 vs 2.75 vs 7.75) (Pour 2017 **Level II**, n=120, JS 3). Medical clowning (also termed clown care by therapeutic clowns or "clown doctors") for children aged 2–10 y reduced mean crying duration vs control (1.3 min vs 3.8) (Meiri 2016 **Level III-1**, n=100). Clowning also lowered parental assessment of child's anxiety about future blood tests assessed the following day vs both control and EMLA®, but did not reduce pain

scores. In a further venipuncture study, medical clowning vs standard care reduced pain scores in older 7–15 y old children (1.5/10 vs 2.7), but not in younger 4–6 y olds (Kristensen 2018 **Level III-2**, n=111).

Therapeutic dog presence for venipuncture in 4–11 y olds reduced observer-reported distress and patients' cortisol levels, but not pain scores during the procedure or parental anxiety (Vagnoli 2015 **Level II**, n=50, JS 2).

Children with an intellectual disability having venipuncture or IV cannulation experienced more pain and anxiety despite receiving more pain and anxiety interventions (eg EMLA®, distraction, physical or verbal comforting) (Pascolo 2018 **Level III-2**, n=141).

10.7.2.2 | Lumbar puncture and bone marrow aspiration

Numerous techniques are used to alleviate the pain and distress occurring in children undergoing lumbar puncture (LP) alone or combined with bone marrow aspiration (BMA) in the ED and oncology settings (Kennedy 2014 **NR**). Interventions have usually been assessed in isolation. Despite positive benefits, use of analgesic intervention in EDs has penetrated poorly (Ali 2014 **Level IV**). Combining techniques is recommended best practice: topical local anaesthesia, local anaesthesia infiltration by slow injection, and PO sucrose with NNS in infants; and, for older children, adding distraction (see Section 10.4.5) and anxiolysis with midazolam and/or further analgesia with N_2O (Kennedy 2014 **NR**). Deeper sedation techniques and general anaesthesia are also used. The choice of intervention is best determined by the setting, the local resources and skills, and assessment of the individual child.

Topical local anaesthesia and nitrous oxide (N_2O) (alone or in combination)

Several RCTs and case series have reported on the safety of N_2O 50–70% for mixed minor procedures in children (see Section 10.7.2.1). Nitrous oxide is often co-administered with other agents or strategies. For LP:

- In infants <3 mth, needle-free jet injection of lidocaine vs saline resulted in lower pain scores (mean 4.1/10 vs 4.8) and slightly reduced cry duration (by 10 s) (Ferayorni 2012 **Level II**, n=55, JS 5);
- In infants <4 mth, needle free injection of lidocaine was of similar efficacy to EMLA® in reducing pain intensity during needle insertion (Caltagirone 2018 **Level II**, n=58, JS 5);
- For 3–21 y olds, topical local anaesthesia with EMLA® vs placebo reduced median propofol requirements 4 mg/kg (95%CI 3.5 to 4.4) vs 4.9 mg/kg (95%CI 4.3 to 5.6), decreased movement at skin puncture (8% vs 84%) and reduced heart rate change (mean 1 bpm vs 8.3) (Whitlow 2015 **Level III-2**, n=25);
- In 5–14y old children with leukaemia, self-administered N_2O/oxygen mixture (ratio unspecified) reduced self-reported pain intensity vs control (mean 1.05/10 vs 8) (Liu 2019 **Level II**, n=114, JS 5);
- In an oncology LP clinic (2–29 y olds), N_2O 40–70% with or without topical local anaesthesia was 98% successful, with minimal sedation (Livingston 2017 **Level IV**, n=78 [LPs n=350]).

For LP and BMA:

- Coadministration of local anaesthesia and sedative/anxiolytic has been used both infrequently (18% and 8.2%) (Onody 2006 **Level IV**, n=3,964) and frequently (98.7% and 64.5%) (Annequin 2000 **Level IV**, n=286 [LPs] & n=231 [BMAs]). The latter study described low pain scores during LP and BMA (respective median procedural pain scores – patient 5/100 and 12.5; nurse 0/10 and 2) with a low need overall for restraint, 18.2% initially and 6% during the procedure.

Fentanyl alone

Oral transmucosal fentanyl is not licensed for paediatric use but 10–15 mcg/kg reduced pain scores vs placebo dosette for LP/BMA (Schechter 1995 **Level II**, n=48, JS 4). As yet, IN use is unreported for this procedural indication.

Single or double agent sedation vs general anaesthesia

For oncology LP/BMA, general anaesthesia is considered by some to be best practice (eg with propofol/fentanyl) (Ghasemi 2013 **Level IV**), while volatile-based general anaesthesia (sevoflurane/N_2O) was preferred to sedation, with less distress and pain for children requiring multiple procedures (Crock 2003 **Level III-3**). Propofol has been used by an ED physician-led sedation team for these procedures (Lamond 2010 **Level IV SR**, 1 study [ED physician], n=87 [291 procedures]). In two small cross-over trials of children with leukaemia undergoing LPs/BMAs, adding IV fentanyl 1 mcg/kg to propofol sedation improved satisfaction, recovery time by 10 min (Cechvala 2008 **Level II**, n=22, JS 5) and analgesia (Nagel 2008 **Level II**, n=25, JS 5). The addition of fentanyl 0.5–1 mcg/kg was propofol sparing with less movement during the procedure and shorter recovery times but no difference in post LP/BMA pain scores (Anghelescu 2013 **Level II**, n=162, JS 5).

Oral or IV ketamine was effective and associated with less distress vs placebo or IV midazolam during LP and/or BMA in children with cancer (Rayala 2019 **Level II**, n=52, JS 2; Tobias 1992b **Level III-3;** Evans 2005 **Level IV**). In the ED setting, IV ketamine 1 mg/kg alone vs with IV midazolam 0.1 mg/kg was similarly effective (Dilli 2008 **Level II**, n=99, JS 3), whilst for oncology patients, IV ketamine 1mg/kg/midazolam 0.1mg/kg vs IV pethidine 1mg/kg/midazolam 0.1mg/kg resulted in lower median pain scores at the beginning of BMA/biopsy (3/10 vs 7) (Abdolkarimi 2016 **Level II**, n=57, JS 4). Adding ketamine 0.5 mg/kg to propofol (administered by non-anaesthetists) vs propofol alone was propofol sparing, resulted in better observer scored intraprocedural pain scores and reduced recovery time (Chiaretti 2011 **Level II**, n=121, JS 3). In an outpatient oncology unit, thiamylal/pentazocine vs ketamine/midazolam (routes unspecified) for LP/BMA was used by paediatricians with similar efficacy, but with increased transient desaturation (36 vs 22%) and oxygen supplementation (82 vs 36%) (Nakagawa 2018 **Level III-2**, n=35 [268 procedures]). Protocolised administration by non-anaesthetists of propofol sedation vs ketamine/midazolam resulted in a higher sedation failure rate (12 vs 0%), but a lower rate of emergence symptoms (9.2 vs 50%) (Chayapathi 2018 **Level II**, n=152, JS 3). Pain outcomes were not assessed. A study of a standardised sedation procedure with IV midazolam and S(+) ketamine for BMA reported 2% prevalence of hypoxia requiring intervention and 3% prevalence of minor complications (Sauer 2019 **Level IV**, n=107). The qualifications of the practitioner administering sedation were not specified.

Nonpharmacological intervention

See also Section 10.7.5 for nonpharmacological techniques.

Child distress during a course of consecutive LPs/BMAs increased over time and was positively related with parental distress (Caes 2014a **Level IV**, n=28 [242 procedures]). Additionally, parental distress about LPs/BMAs decreased over time with low-catastrophising parents but remained high with high-catastrophising parents. In another study by the same group, parental catastrophic thinking contributed to increased parental distress during, but less pain attending behaviour before LP/BMA (Caes 2014b **Level IV**, n=46).

Massage therapy just prior to IT chemotherapy or BMA was associated with greater reduction in children's pain and anxiety vs control when evaluated prior to treatment and 20 min after (Celebioglu 2015 **Level III-2**, n=25). IV sedation was also given to both groups; however the amount of hypnoanalgesia administered was not reported.

Authors concluded that all youth with cancer having invasive medical procedures should receive preparatory information to reduce distress and increase coping and compliance (low quality evidence, strong recommendation), and psychological interventions such as distraction, hypnosis, and combined cognitive behavioural therapy (CBT) interventions to reduce pain and distress (high quality evidence, strong recommendation) (Flowers 2015 **GL**). Psychosocial intervention (preparation and CBT) was associated with less mean anticipatory and total behavioural distress ratings (OSBD-R) in patients receiving BMA or LP. Reduced behavioural distress ratings from one procedure to the next were observed when psychosocial interventions (preparation and CBT) with a child-life specialist were given for the second procedure (Hsiao 2019 **Level III-3**, n=18).

Reduction of post-dural puncture headache (PDPH) incidence

Risk of PDPH after LP was higher with traumatic vs atraumatic needles (RR 2.14; 95%CI 1.72 to 2.67) (36 RCTs, n=9,378); however the paediatric sub-analysis revealed no difference (2 RCTs, n=315) (Arevalo-Rodriguez 2017 **Level I** [Cochrane], 66 RCTs, n=17,067 [3 paediatric, n= 475]). With the exception of one adult RCT, there was no difference with different gauge traumatic needles (multiple sub-analyses, 10 RCTs [1 paediatric], n=2,288) or different gauge atraumatic needles (multiple sub-analyses, 13 RCTs, n=3,134 [paediatric unspecified]). Subsequently, a lower risk of PDPH was confirmed with atraumatic vs traumatic needles (RR 0.40; 95%CI 0.34 to 0.47) (n=24,901) but again, no difference in the paediatric sub-analysis (2 RCTs, n=782) (Nath 2018 **Level I** [PRISMA], 110 RCTs [2 paediatric, unspecified number of mixed adult/paediatric], n=31,412 [1,065 paediatric]) (39 RCTs overlap [2 paediatric]).

Lower level evidence have mixed findings. Following diagnostic LP in children, less PDPH resulted with use of a 27-guage atraumatic vs 26-g traumatic needle (0.4% vs 4.5%) (Apiliogullari 2010 **Level III-2**, n=414). In children having IT chemotherapy, the incidence of PDPH with a 22-g traumatic vs 25-g atraumatic needle was similar (11 vs 7%) (Lowery 2008 **Level III-2**). With guideline change from 22-g spinal needles to 25-g (type unspecified) for diagnostic LPs/chemotherapy administration and 27-g for spinal anaesthesia, epidural blood patch rates decreased from 0.8% (5 y data) to 0.2–0.3% (10 y data) (Kokki 2012b **Level III-3**). Injected mean blood volumes of 0.27 mL/kg (range 0.16–0.53 mL/kg) for epidural blood patch achieved complete persistent resolution of headache in 83% of 42 patients (see also Section 8.6.5).

The use of atraumatic needles for LP is strongly recommended in patients (including children) of all ages (Rochwerg 2018 **GL**).

10.7.2.3 | Botulinum toxin (intramuscular) or steroid (intra-articular) injection

IM botulinum toxin for spasticity and intra-articular steroid injections are acutely painful procedures, and general anaesthesia should be considered for these procedures, especially when multiple injections are performed.

Nitrous oxide (N_2O)

Use of N_2O 70% in isolation reduced patient, parent and nurse-reported pain scores vs PR midazolam 0.35–0.5 mg/kg (Zier 2008 **Level II**, n=50, JS 4). Using topical EMLA® and N_2O 50% in children reduced pain in only 50% of the 51 procedures (n=39) with the remainder experiencing severe pain intensity (≥9/13) (Brochard 2009 **Level IV**). N_2O 50%/oxygen treatment for botox or joint injections was superior to inhaled nitrogen 50%/oxygen mix, with lower pain scores (by 50%) and fewer patients requiring rescue with propofol or sevoflurane (18 vs 55%) (Reinoso-Barbero 2011 **Level II**, n=100, JS 4). Use of N_2O 50–70% in a small series of children having joint injection achieved adequate analgesia in most (89%) children (Cleary 2002 **Level IV**, n=55).

Local anaesthetic

Girls had lower post procedural pain scores with topical local anaesthesia (EMLA® or Numby®) plus subcutaneous buffered lidocaine vs topical local anaesthesia alone for corticosteroid knee joint injections, but boys did not (Weiss 2015 **Level II**, n=63, JS 2).

The use of vapocoolant spray (used in 89%) or topical local anaesthetic (used in 2%), as well as younger age, and body region injected (leg, thigh, hand) was associated with increased pain with botulinum toxin injection for spasticity (Fisher 2018b **Level IV**, n=249 [563 procedures]).

Other sedative agents

IV ketamine with or without midazolam in addition to topical local anaesthesia was successfully used for botulinum toxin injection to treat spasticity with a low prevalence of minor adverse effects (Chow 2016 **Level IV**, n=87 [152 procedures]). PR midazolam and ketamine in addition to topical local anaesthesia has also been used successfully for botulinum toxin injection (Nilsson 2017 **Level IV**, n=61 [128 procedures]).

Impact of localisation techniques

For botulinum toxin injection, US-guidance may help localise muscles more accurately (Py 2009 **Level IV**) and reduce procedure related pain vs use of electrical stimulation US-guidance (Bayon-Mottu 2014 **Level III-2**, n=107 [155 procedures]).

Nonpharmacological intervention

Medical clowning has been used for intra-articular steroid injections (Weintraub 2014 **Level IV)**. For botulinum toxin injections, results are mixed; medical clowning vs standard care was associated with lower pain scores in one study (Ben-Pazi 2017 **Level III-2**, n=45) but not in another (Houx 2019 **Level III-2**, n=88). Virtual reality has been used for botulinum toxin injection (Chau 2018 **Level IV**, n=14).

10.7.2.4 | Urethral catheterisation and micturating (voiding) cystourethrogram

Children with stronger medical fears were more anxious during the micturating cystourethrogram (MCUG) as reported by their parents and examining technologists and demonstrated more procedural distress as measured by their vocalisations (Fox 2016 **Level IV**, n=34).

Local anaesthesia — topical and installation

Lidocaine 2% gel is no better than non-anaesthetic gel in reducing pain from transurethral bladder catheterisation (Chua 2017c **Level I** [PRISMA], 5 RCTs, n=369). A subsequent RCT similarly reported lidocaine 2% gel was not better than usual care with high reported median pain scores (8/10 vs 9) and the authors thus emphasised that analgesia for this procedure needs to improve (Uspal 2018 **Level II**, n=73, JS 3); however high pain scores are not universally reported (Chua 2017c **Level I** [PRISMA], 5 RCTs, n=369).

Nitrous oxide (N_2O)

N_2O use is associated with low pain and distress scores in children undergoing urethral catheterisation and/or MCUG (Pedersen 2013 **Level IV SR** [PRISMA], 2 studies [catheterisation], n≈5,000).

Intranasal fentanyl alone

IN fentanyl 2 mcg/kg, administered slowly by dropper 10 min prior to catheterisation for MCUG, with no distraction, resulted in similarly low pain scores vs water (mean 2.6/10 vs 2.9) (Chung 2010 **Level II**, n=69, JS 5). Nasal irritation was reported by 6 and 14% respectively.

Midazolam

Midazolam administered PO or IN vs no treatment for urinary catheterisation in 4–24 mth olds was associated with lower parent and nurse-reported pain/distress (mean 33.6/100 vs 71.7) and shorter cry duration (median 0 s vs 240) (Weiser 2014 **Level III-2**, n=51).

Sucrose

Sucrose 75% 4 mL vs water for children (3 mth–3 y) did not reduce pain intensity with transurethral bladder catheterisation (London 2019 **Level II**, n=40, JS 5).

Other

Pain scores were not different when olive oil/calcium hydroxide (oleocalcareous) liniment vs a dry compress was used to aid removal of a urine collection bag (Lamy 2019 **Level II**, n=135, JS 3).

Nonpharmacological intervention

Preparing the child for the MCUG using a story booklet alone or with play preparation reduced distress (Phillips 1998 **Level III-2**). Hypnosis was superior to play preparation, with reduced distress and procedure duration (Butler 2005 **Level II**, n=44, JS 3).

10.7.2.5 | Chest drain and intercostal catheter insertion and removal following surgery or for pneumothorax management

Chest drains and intercostal catheters are inserted for a variety of reasons perioperatively and for management of pneumothorax.

The incidence of paediatric spontaneous pneumothorax is low; it can be primary [PSP] or secondary [SSP] due to asthma, cystic fibrosis and congenital cystic adenomatoid malformations. Pain is commonly present (along with dyspnoea); overall hospital admission rates for PSP and SSP (reported by the British Thoracic Society) are 5.8 and 16.7/100 000 for women and men (respectively), without paediatric subgroup data (MacDuff 2010 **GL**). Most paediatric patients are admitted (81% of 219 presentations) and have non-surgical management with oxygen, needle aspiration (PSP 27% and SSP 9%) and/or intercostal catheter (ICC) insertion (PSP 48% and SSP 67%), with 38% PSP and 47% SSP requiring surgery (Robinson 2015 **Level IV**, n=162 children [120 with PSP]).

Pain service involvement in patients with PSP/SSP in the acute phase of care has decreased – likely related to the use of less painful small bore or micro/pig tail catheters; duration of care postoperatively has also shortened with change in surgical technique from open to limited axillary (LATS) or video-assisted thoracic surgery (VATS) procedures. VATS had lower analgesic requirement and shorter period of follow-up vs LATS (Butterworth 2007 **Level III-3**, n=31). Analgesic intervention follows stepwise escalation with paracetamol, nsNSAID and opioids PO or IV including by PCA. Following antibiotic or talc pleurodesis, nsNSAIDs are generally avoided (with no positive or negative data to support this practice) but are used post-bleb or apical pleural abrasion or resection.

Removal of chest drains/ICCs can cause significant pain and distress. For chest drain/ICC removal (inserted for various indications), IV morphine, topical anaesthesia with EMLA® and N_2O reduced pain but did not provide adequate analgesia in children (and adults) (Bruce 2006a **Level III-2**; Bruce 2006b **Level IV SR**, 14 studies, n=758 [1 study, 1 RCT, paediatric n=144]). For children aged <7 y having chest drain removal post cardiothoracic surgery, pain scores were similarly high during the procedure (7/10) with EMLA® applied 3 h prior and IV placebo vs placebo cream and IV morphine 0.1 mg/kg 30 mins prior (Rosen 2000 **Level II**, n=120, JS 2). IN Ketamine 0.5 mg/kg combined with IN sufentanil 0.5 mcg/kg has been used in children for drain removal (Nielsen 2014 **Level IV**).

Following paediatric cardiac surgery, a nursing education program improved timely use of periprocedural intervention including analgesic and nonpharmacological therapies for ICC removal (Ring 2017 **Level IV**, n= 68 staff surveyed & 21 charts reviewed). Similarly, introduction of a procedural treatment protocol (play therapist, topical local anaesthetic and targeted pharmacological intervention based on the tool's estimate of risk) reduced the number of patients that were inconsolable after chest drain and pacing wire removal (Craske 2013 **Level III-3**, n=163).

10.7.2.6 | Nasogastric tube insertion

Nasogastric tube (NGT) insertion causes pain and distress particularly in children (Juhl 2005 **Level IV**).

Topical local anaesthesia

In adults, topical gel and/or nebulised anaesthesia of the nose and pharynx reduces pain associated with NGT insertion (OR 0.42; 95%CI 0.20 to 0.88) (Kuo 2010 **Level I**, 5 RCTs, n=212; Uri 2011 **Level II**, n=62, JS 5) and reduced NGT insertion time (Chan 2010b **Level II**, n=206, JS 5). Lidocaine/phenylephrine spray (10 mg/1mg for 6–12 kg, 20 mg/2 mg for >12 kg) was not superior to saline spray in infants and young children (6 mth–5 y) (median 9/10 vs 9) (Craig 2019 **Level II**, n=107, JS 5). An RCT in children aged 1–5 y of nebulised lidocaine was terminated early due to the distress associated with nebulisation; this may outweigh its potential benefit (Babl 2009 **Level II,** n=36, JS 5).

Ketamine

In adults, IN ketamine 50 mg reduced pain scores vs placebo for NGT insertion (Nejati 2010 **Level II**, n=72, JS 5). In mostly preschool aged children having NGT insertion (for repeat gastric aspirates), IN ketamine 2 mg/kg and IN midazolam 0.5 mg/kg (max 10 mg) vs placebo achieved sedation for 71 min (95%CI 64 to 80) and reduced pain scores and the need for physical restraint (4% vs 100), with low post-procedure agitation rates (11% of procedures) (Buonsenso 2014 **Level II**, n=36 [108 procedures], JS 5).

10.7.2.7 | Dental procedures

For pharmacological interventions see the various analgesic subsections in 10.4 and for local anaesthetic interventions see Section 10.6.6

Nonpharmacological interventions for dental procedures

In children <18 y having dental procedures, distraction techniques including music, virtual reality, magic tricks, exposure to positive dental images and relaxation training have been studied with mixed results for pain, anxiety and behaviour outcomes (Goettems 2017 **Level I**, 13 RCTs, n unspecified) including during local anaesthetic infiltration (Sridhar 2019 **Level II**, n=66, JS 3) and pulpotomy (Shetty 2019 **Level III-1**, n=120). Acupuncture (at the LI 4 meridian point bilaterally) in children and adolescents (4–18 y) reduced self-reported pain intensity (2.3/10 vs 3.9) during local anaesthetic injection for dental treatment (Usichenko 2016 **Level II**, n=49 [98 injections], JS 3).

10.7.2.8 | Intraosseous pin removal

Topical local anaesthetic vs placebo in children (3–16 y) having interosseous pin removal did not reduce pain intensity (Dulai 2016 **Level II**, n=281, JS 5).

Children who have sustained burns injuries often require repeated, painful and distressing dressing changes (see also Section 8.5). Considerable interindividual variation occurs and analgesia needs to be titrated to effect as requirements differ according to the surface area involved, the location, the stage of healing and need for grafts, and the child's previous experiences (Palmer 2014 **NR**). It is important to consider significant coexistent post-traumatic stress symptoms or disorder (Stoddard 2011 **Level III-1;** Stoddard 2006 **Level IV**) and anxiety and depression (van Baar 2011 **Level III-2**). Additionally, parental post-traumatic stress symptoms and parental guilt predict more child distress, and parental general anxiety/depression predict less child coping (Brown 2019 **Level IV**, n=87). Long term post-traumatic stress symptoms may be reduced by adequate early opioid administration (Sheridan 2014b **Level IV**). In the early phases, general anaesthesia may be preferred for dressing changes, stepping down to procedural interventions on the ward and then as outpatients (Palmer 2014 **NR**).

Burn dressing types

Numerous dressings for superficial and partial thickness burns have been assessed and the optimal choice is unclear (Wasiak 2013 **Level I** [Cochrane], 6 RCTs [paediatric], n=364). In paediatric patients, biosynthetic dressings are superior to silver sulphadiazine in reducing daily opioid requirements (1 RCT, n=20), the time to healing, number of dressing changes and hospital stay (2 RCTs, n=109) but were similar to hydrocolloid dressing (Duoderm®) in terms of pain scores and time to healing (1 RCT, n=72).

Pharmacological interventions for burn dressing

Opioids

Opioids are frequently required and prescribed for burns dressing changes, with little published data. Compared to placebo, oral transmucosal fentanyl (≈10 mcg/kg) compared favourably with PO morphine (Robert 2003 **Level II**, n=8, JS 4), PO hydromorphone 60 mcg/kg (Sharar 1998 **Level II**, n=14, JS 4) and PO oxycodone 0.2 mg/kg in reduction of pain associated with dressing changes (Sharar 2002 **Level III-2**). IN fentanyl 1.4 mcg/kg reduced pain scores similarly with similar recovery time vs PO morphine 1 mg/kg in paediatric burns dressing change (Borland 2005 **Level II**, n=28, JS 4).

Ketamine

IN Ketamine 0.5 mg/kg combined with IN sufentanil 0.5 mcg/kg has been used in children for burn dressing change (Nielsen 2014 **Level IV**, n=7). IV Ketamine administration by non-anaesthetists was audited, where doses of 6–800 mg were given to children weighing 3–111 kg for procedures of 1–105 min duration (Owens 2006 **Level IV**, n=347). Ten events occurred that required intervention (2.9% incidence): eight were airway related and responded to repositioning, supplemental oxygen or bag-mask ventilation and two hypotensive events responded to fluid administration.

For burns dressing changes in children aged 1–5 y, PO ketamine 5 mg/kg with midazolam 0.5 mg/kg vs combination PO midazolam 0.5 mg/kg/paracetamol 10 mg/kg/codeine 1 mg/kg may provide superior analgesia: mean pain scores 7.4/13 (95%CI 4 to 12) vs 8.9 (95%CI 4 to 13) (Norambuena 2013 **Level II**, n=60, JS 4).

Dexmedetomidine

IN dexmedetomidine 2 mcg/kg has been used as premedication prior to burns reconstructive surgery (Talon 2009 **Level II**, n=50, JS 3) but no conclusion can be drawn as to the impact upon pain outcomes. Use in deep sedation is described below.

Deep sedation/analgesia

Three doses of PR ketamine (4, 6 and 8 mg/kg) with PR midazolam 0.5mg/kg for burns wound care sedated children with low pain scores (median 0 vs 0 vs 0) and a dose dependent effect on recovery (mean 25 vs 27 vs 36 min) (Grossmann 2019 **Level II**, n=201, JS 4). Propofol 2mg/kg/ketamine 1mg/kg was comparable to propofol 2mg/kg/remifentanil bolus 0.1 mcg/kg and infusion 0.05 mcg/kg/min for burns dressing changes, but with longer recovery time (median 22.5 min (IQR 20.3–25) vs 10.3 (IQR 9.1–11.5)); pain outcomes were not reported (Seol 2015 **Level II**, n=50, JS 5). IV Ketamine 0.8–2 mg/kg with propofol 0.8–2.5 mg/kg or dexmedetomidine 0.4–1.2 mcg/kg has also been used for short duration (10 min) dressing change (Canpolat 2012 **Level III-1**).

Nonpharmacological interventions for burn dressing

Nonpharmacological strategies such as distraction, virtual reality (VR), preparation, parental presence and hypnosis may be effective (see also Section 10.7.5). Studies vary substantially in the specifics of interventions and comparison groups and are difficult to blind.

Child life therapy

Child life (previously termed educational play) therapy (preparation, education and distraction delivered by a therapist) for pain and anxiety management vs standard care for initial burn dressing change reduced a combined scaled pain and anxiety score (mean 1.7/20 vs 2.9) and pain scores alone (median 5.3/13 vs 6.0), but not anxiety scores alone (Children's Fear Scale); nor did it improve wound outcomes or reduce need for grafting (Hyland 2015 **Level II**, n=100, JS 3). In a cohort of patients with low procedural pain scores, directed medical play vs standard preparation reduced maximum pain score during burns dressing change (median 2/10 vs 3) (Moore 2015 **Level III-1**, n=21).

Distraction

The use of therapeutic clowning increased compliance with dressing change vs standard care assessed by behavioural response (mean 4.8/15 vs 11.0) (Yildirim 2019 **Level II**, n=50, JS 3).

Child life therapists using computer tablet distraction vs their standard intervention during hydrotherapy for burns dressing changes in 4–12 y olds did not reduce self-reported pain scores, but reduced nurse-reported pain and emotional response during and after the procedure (Burns-Nader 2017 **Level II**, n=30, JS 3).

Multimodal procedural preparation (video shown on screen device: "Bobby got a burn") and multimodal distraction (screen device using games: "touch and find" stories with multisensory visual, auditory, and vibratory feedback: Ditto®) lowered pain scores (child by 20–27%, parent by 29–37% and nursing staff by 16–34%) vs a hand-held video game device or standard distraction (varied use of TV, video games, stories, toys, nursing staff soothing and care giver support) (Miller 2010 **Level II**, n=80, JS 3). Across three procedures, multimodal distraction reduced pain scores, while multimodal procedural preparation, video or standard distraction did not. Ditto™ vs standard distraction (in addition to varying pharmacological agents) did not impact significantly on pain or anxiety ratings during the first three dressing changes (Brown 2014b **Level II**, n=117, JS 3).

Adding animated cartoon watching to PO ibuprofen vs ibuprofen alone was not associated with improved pain scores during burns dressing change (Feng 2018 **Level III-2**, n=54).

A multidisciplinary group of clinicians identified barriers to routine iPad® use for distraction during burns dressing change including competing demands of clinicians, differing views on the relevance of distraction, and lack of experience and confidence with iPad® use (Green 2018 **Level IV**, n=15). The authors suggested that effective use of iPads in this context required training and guidelines for clinicians.

Immersive VR gaming vs standard distraction reduced nurse observer-rated pain scores (mean 2.9/10 vs 4.7) and rescue use of N_2O (15 vs 43%) (Kipping 2012 **Level II**, n=41, JS 3). Augmented reality gaming achieved lower patient pain scores vs basic cognitive therapy intervention (2.9/10 vs 5.4) (Mott 2008 **Level III-1**). When immersive VR games were added to routine analgesia, patient pain scores with burn dressing changes decreased (Das 2005 **Level IV**, n=7).

Other nonpharmacological interventions

Pain scores with burn dressing changes reduced with music ("active alternate engagement") (Klassen 2008 **Level III-2 SR**, 1 RCT [paediatric burn dressing change], n=14; Fratianne 2001 **Level II**, n=24, JS 3) and massage therapy (O'Flaherty 2012 **Level IV**; Hernandez-Reif 2001 **Level IV**). Twice weekly massage for 15–20 min for 5 wk lowered heart and respiratory rate, with positive response (becoming relaxed or falling asleep in 93%, verbally requesting more in 20%) (O'Flaherty 2012 **Level IV**) and decreased pain and anxiety by 58% vs no change in patients receiving standard care (Parlak Gurol 2010 **Level III-1**).

Hypnosis had no effect on pain and wound healing for burn dressing changes, but reduced preprocedural anxiety on the second of three burns dressing changes (MD -0.8/10; 95%CI -1.5 to -0.1) (Chester 2018 **Level II**, n=62, JS 3).

Nonpharmacological interventions for physiotherapy in burns rehabilitation

Use of PlayStation II EyeToy™ to facilitate body movement vs standard therapy in 5–18 y olds did not increase range of motion gains; as rehabilitation progressed, standard therapy did increase pain scores while EyeToy™ did not (r 0.18 vs 0.05) (Parry 2015 **Level II**, n=17 [31 limbs], JS 1). Xbox Kinect™ plus standard physiotherapy in 5–12 y olds achieved greater improvements in active range of motion between discharge and follow-up vs standard physiotherapy and had higher fun and enjoyment scores; pain outcomes were not reported (Lozano 2018 **Level III-2**, n=66).

In adult and paediatric burn patients having physiotherapy, immersive VR SnowWorld® reduced mean worst pain intensity by 20% (54/100 ± 3 vs 44 ± 4), pain unpleasantness by 26% (41/100 ± 4 vs 30 ± 3), and time spent thinking about pain by 37% (47/100 ± 4 vs 30 ± 3) (Sharar 2007 **Level II**, n=88 [66 children], JS 3). Repeated use of SnowWorld® in addition to pharmacotherapy by children with burns having physiotherapy reduced cognitive, sensory and affective pain scores (by 44, 27 and 32%) with patients experiencing three-fold more fun than when no immersive VR was used, although there was no difference in the maximum range of motion achieved (Schmitt 2011 **Level II**, n=54, JS 3).

Distraction through purposeful activity with play and games vs "exercise by rote" modulated the pain experience and improved range of motion achieved during physiotherapy for hand burns in children (Omar 2012 **Level II**, n=30, JS 2).

10.7.3 | Vaccine injection pain in infants and children

Vaccine injections are the most commonly performed medical procedures worldwide, and concern about pain caused by vaccine injection is a barrier to future vaccine uptake; managing vaccine injection pain therefore has immediate and long term implications for the health and wellbeing of individuals and populations (Taddio 2015a **NR**). There is supportive evidence for various interventions. Most studies focus on assessing the effects of a single intervention in an RCT or quasi-randomised study design, and control groups often include active treatments. Outcomes assessed depend on stage of development and include patient distress (using behavioural pain/distress scales, cry duration and/or physiological variables), by carer, health professional or researcher, and self-reported pain and fear at different time points, typically prior to injection, in the acute phase (usually within 1 min of injection) and recovery phase (usually

1–3 min post injection). Translation of evidence to practice is slow but can be improved with a (telephone-based) educational outreach program (Schechter 2010 **Level IV**), assessment of lay and medical perceptions and practice (Harrison 2014 **Level IV**) and then use of innovative techniques to effect change eg social media (Center for Pediatric Pain Research **NR**). Guidelines for evidence-based recommendations across the lifespan are available (McMurtry 2016 **GL;** Taddio 2015c **GL**; WHO 2015 **GL**). Work is also being done to develop painless modes of vaccine delivery (eg IN, PO, transdermal) (Garg 2018 **NR**).

10.7.3.1 | Procedural modifications

Procedural modifications were assessed in a systematic review with the following findings (Taddio 2015d **Level III-1 SR**, 31 studies, n unspecified):

- IM injection without aspiration vs with aspiration reduces acute distress in infants (18 mth) (SMD -0.82; 95%CI -1.18 to -0.46) (2 studies, n=313);
- Simultaneous vs sequential injections reduces acute distress in infants (<1 y) (SMD -0.56; 95%CI -0.87 to -0.25) (2 studies, n=172);
- Injecting the most painful vaccine last reduces acute distress in infants (6 mth) (SMD -0.69; 95%CI -0.98 to -0.40) (2 studies, n=196);
- Vastus lateralis vs deltoid injection reduces acute and recovery phase distress in infants (<1 y) (SMD -0.7; 95%CI -1.0 to -0.4) (1 study, n=185);
- Subsequently, term infants (<4 mth) who received HBV vaccine first vs DTaP vaccine first had lower pain scores (MD -4.13/7; 95%CI -1.9 to -6.4) and HR, and higher oxygen saturation (Kumar 2016 **Level II**, n=130, JS 4).

A wider (23-guage 25 mm vs 25-g 25 mm) needle reduces pain intensity (MBPS: MD 0.70/15; 95%CI 0.39 to 1.01) and cry duration (MD 8s; 95%CI 2.86 s to 13.14) in infants (<6 mth) receiving DTwP vaccines in the thigh; however this effect is probably not clinically relevant, and the generalisability of this result is uncertain (Beirne 2018 **Level I** [Cochrane], 1 RCT: Bharti 2010 **Level II**, n=320, JS 3). Longer needles of 25 mm (23 or 25-g) vs 16 mm (25-g) resulted in both fewer severe (NNT=25) and non-severe (NNT=5-6) reactions (Beirne 2018 **Level I** [Cochrane], 1 RCT: Diggle 2006 **Level II**, n=458, JS 3). Applying pressure has a positive effect in adults and may be of use in children (Schechter 2007 **NR**, 1 negative RCT, 2 positive unpublished RCTs, n unspecified). In an additional RCT, fast injection vs slow injection in infants (2-6 mth) receiving DTaP-IPV-Hib (0.5ml) reduced mean pain scores (MBPS: 6/15 vs 7.4) but not cry duration or parent-reported pain (Taddio 2016 **Level II**, n=120, JS 3).

Evidence based guidelines strongly recommend not aspirating on vaccine injection and injecting the most painful vaccine last for all children (18 y); weaker recommendations include simultaneous injection for 1 y but not 1-3 y olds, and vastus lateralis (rather than deltoid) injection site for 11 mth (Taddio 2015c **GL**).

10.7.3.2 | Topical local anaesthesia

Topical local anaesthesia for infants and children (0-12 y) is recommended (Taddio 2015c **GL**). For infants (age unspecified), topical local anaesthesia (EMLA® in 12 of 13 studies) vs control (placebo in 6 of 13 studies) reduced acute distress from vaccine injection (SMD -0.91; 95%CI -1.36 to -0.47) (13 studies, n=1,424), but not for children (4-12 y), although this finding was qualified by a positive result if one study (n=39) at high risk of bias was removed from the meta-analysis (SMD -0.47; 95%CI -0.73 to -0.21) (2 studies, n=230) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified). Meta-analyses for adolescents (12 y) was not possible; two included studies had conflicting results. Despite this, selective use of topical local anaesthesia has been recommended in older

children (Taddio 2015c **GL;** Schechter 2007 **NR**). Topical local anaesthesia vs placebo in infants and children did not affect immune response to vaccines (MMR, DTaP-IPV-Hib HBV, BCG vaccines) as measured by antibody response (4 studies, n=833) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified).

10.7.3.3 | Sweet solutions

Two systematic reviews (14 study overlap) support efficacy of sweet solutions for vaccination injection in infants <2 y old:

- For 1–12 mth olds, PO sucrose (12–75%) and glucose (30–40%) 1-2 mL vs water, saline or no treatment reduces incidence of cry and crying duration (MD -13.5; 95%CI -16.8 to -10.2) (Kassab 2019 **Level III-1 SR** [Cochrane], 14 studies, n=1,551);
- PO sucrose vs control for <2 y olds was associated with lower acute distress (SMD -0.37; 95%CI -0.67 to -0.06) (18 studies, n=881) and acute and recovery distress (SMD -0.76; 95%CI -1.19 to -0.34) (18 studies, n=2,071); PO sucrose 2 mL was typically given (15 of 18 studies) 2 min prior to injection (15 of 18 studies) and was effective in concentrations of 20-33% (9/18 studies) but not 12% (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified);
- PO glucose 1–2 mL (25–50%) vs control for <1 y olds reduces acute + recovery distress (SMD -0.69; 95%CI -1.03 to -0.35) (6 studies, n=818) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified);
- Sweet solutions combined with NNS (1 study) or breastfeeding (1 study) in infants <3 mth was not superior to either intervention alone (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified).

In further individual studies not included or subsequent to the above reviews:

- PO glucose 25% 2 mL vs NNS in neonates receiving HBV vaccine reduced pain score (mean 3.3/7 vs 5.6) and crying time (mean 10.9 s vs 33.9), however increased HR (147 vs 137) (Lima 2017 **Level II**, n=78, JS 2);
- Infants (2–4 mth old) who received oral rotavirus vaccine (contains 71.5% sucrose) vs sucrose 24% prior to vaccine injection had no difference in observer-reported pain scores (mean 7.4/15 vs 7.7), parent or clinician reported pain scores, or cry duration (Taddio 2015b **Level II**, n=120, JS 5);
- For 2–6 mth old, high-dose PO sucrose 50–75% (2 mL) was equivalent to water in terms of pain scores and crying time (Curry 2012 **Level II**, n=113, JS 5);
- For older infants (15 mth MMR vaccination) sucrose 30% vs water reduced cry duration (mean 18 s vs 33) (Despriee 2016 **Level II**, n=114, JS 3).

Sweet solutions (sucrose or glucose) are strongly recommended for infants (2 y) receiving vaccines, with weaker recommendations to combine with NNS or breastfeeding (Taddio 2015c **GL**). In older children, there is insufficient evidence to support the use of sweet solutions (sucrose) in 1–4 y olds (6 studies, n=520), and no evidence of analgesic effect of sweet solutions (sweetened chewing gum) in school aged children (2 studies, n=111) (Harrison 2015 **Level III-1 SR**, 8 studies, n=808 [n vaccination unspecified]).

10.7.3.4 | Nonpharmacological intervention for vaccine injection

Preparation and education

A systematic review found supportive evidence for the following nonpharmacological interventions (Pillai Riddell 2015b **Level III-1 SR**, 13 studies, n=972 [children] & 53 [nurses] & 197 [expectant parents]):

- Educating nurses administering vaccines improved use of pain management interventions (SMD 0.66; 95%CI 0.47 to 0.85) (1 study: Chan 2013 **Level III-1**, n=53 [459 procedures]);
- Parental presence reduced pre-vaccine injection distress in infants and children (1–7 y) (SMD -0.85; 95%CI -1.35 to -0.35) (3 studies, n=67);
- Parental education *before vaccination day* improved use of interventions pre-vaccination (RR 2.08; 95%CI 1.51 to 2.86) (2 studies, n=300) and reduced acute distress (SMD -0.35; 95%CI -0.57 to -0.13) (3 studies, n=350) in infants 2 y old;
- Parental education *on vaccination day* improved use of interventions (SMD 1.02; 95%CI 0.22 to 1.83) (4 studies, n=183), (RR 2.42; 95%CI 1.47 to 3.99) (4 studies, n=239) and reduced periprocedural distress (SMD -0.48; 95%CI -0.82 to -0.15) (4 studies, n=262) in infants and children 6 y old.

The effect of information provision has been assessed in further RCTs:

- Information provision to new mothers prior to leaving hospital on vaccine pain management given by factsheet vs control (baby general health information) did not improve knowledge scores or utilisation of pain management interventions 2 mth later (Taddio 2014 **Level II**, n=120, JS 3);
- Post-natal education for parents with a pain pamphlet and/or pain video vs general vaccine information increased the use of pain management interventions (breastfeeding, sucrose, topical local anaesthesia) at infant (6 mth) vaccination (pain pamphlet + pain video 63%, pain pamphlet only 61%, general vaccine information 53%) (Taddio 2018 **Level II**, n=2,549, JS 3);
- Excluding toddler (18 mth) pain scores during the regulatory phase of vaccine injection, parental psychological distress (assessed by BSI-18) had no moderating effect on the impact of a parent education video (ABCDs of pain management) when assessing various outcomes (parental soothing behaviours, parental worry, infant (6 mth) and toddler reactivity and regulatory phase pain scores) (Gennis 2018 **Level II**, n=128, JS 5);
- For parents of older children (4–6y), automated parent-training via a 10 min interactive computer program + distraction, vs distraction only vs no treatment did not reduce child distress or pain. However, it did improve parental knowledge, parents' behaviours during vaccination, and children's engagement in distraction and deep breathing during vaccination (Cohen 2015 **Level II**, n=90, JS 3).

Parents who were educated on pain management strategies for an RCT most commonly used strategies such as acting calm, holding the child and distraction, whilst strategies such as PO sucrose, topical local anaesthetic cream and pacifier use were uncommon; reasons cited for this included parents thinking these strategies were unnecessary, forgot to use strategy, or they were not easily accessible at the vaccine clinic (McNair 2017 **Level IV**, n=130).

In a review of YouTube videos of children receiving vaccination injections, 73% of infants (<12 mth) received at least one pain management strategy during injection, with distraction (66%) the most common strategy; no videos showed breastfeeding or the use of a sweet solution (Harrison 2014 **Level IV SR**, n=142 [videos]).

Feeding interventions

Two systematic reviews found supportive evidence for breastfeeding in infants <12 mth old (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified) and beyond the neonatal period (Harrison 2016 **Level III-1 SR** [Cochrane], 10 studies, n=1,066) (6 study overlap):

- For infants <12 mth, breastfeeding during vaccination injection vs control reduces acute phase distress (SMD -1.78; 95%CI -2.35 to -1.22) (8 studies, n=792), and acute and recovery phase distress (SMD -1.89; 95%CI -3.19 to -0.59) (n=424) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified);

- For infants <12 mth, breastfeeding before vaccination injection (if not used during) vs control reduces acute phase distress (SMD -1.43; 95%CI -2.14 to -0.72) (2 studies, n=100) and acute and recovery phase distress (SMD -1.47; 95%CI -2.05 to -0.90) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified);
- Beyond the neonatal period (mostly 1–6 mth old), breastfeeding vs water or no treatment reduces cry time (MD -38 s; 95%CI -50 to -26) (6 studies, n=547), and pain scores (SMD -1.7; 95%CI -2.2 to -1.3) (5 studies, n=310) but not HR (2 studies, n=186) (Harrison 2016 **Level III-1 SR** [Cochrane], 10 studies, n=1,066);
- Additionally, there was supportive evidence for breastfeeding reducing cry time and pain scores vs massage and cuddling, PO glucose 25%, topical local anaesthesia (EMLA®) and vapocoolant spray (1 study each) (Harrison 2016 **Level III-1 SR** [Cochrane], 10 studies, n=1,066).

Subsequent RCTs continue to support a beneficial effect of breastfeeding (Dar 2019 **Level II**, n=60, JS 3; Gad 2019 **Level II**, n=120, JS 2; Fallah 2017 **Level II**, n=120, JS 3; Hashemi 2016 **Level II**, n=131, JS 2). Additionally, formula feeding of infants (4–10 wk) during vaccine injection vs no treatment reduced cry duration (MD -32.9 s; 95%CI -58.0 to -7.8) and recovery phase pain scores (MD -3.78/7; 95%CI -2.52 to -5.05) (Bos-Veneman 2018 **Level II**, n=48, JS 2).

Physical interventions

Various physical interventions have been assessed in a systematic review (Taddio 2015d **Level III-1 SR**, 31 studies, n unspecified):

- In neonates, kangaroo care vs lying supine reduces acute and recovery phase distress (SMD -0.65; 95%CI -1.05 to -0.25 and SMD -0.89; 95%CI -1.26 to -0.52 respectively) (3 studies, n=736);
- Excluding one high risk bias study, for infants (6 wk–6 mth) holding by parent during vaccination vs lying supine and not being held reduces acute distress (SMD -1.25; 95%CI -2.05 to -0.46) (2 studies, n=181);
- For infants (0–4 mth) holding by parent after vaccination (if not held during) reduced acute and recovery distress (SMD -0.65; 95%CI -1.08 to -0.22) (2 studies, n=417);
- For infants (0–4 mth), NNS reduces acute distress (SMD -1.88; 95%CI -2.57 to -1.18) (2 studies, n=186);
- Manual tactile stimulation (pressure, rubbing/stroking, tapping) vs no treatment does not reduce acute distress in infants (3 studies, n=301), or self-reported pain in older children and adults (3 studies, n=893);
- For children (4–6 y), sitting upright vs lying supine reduces fear (SMD -0.39; 95%CI -0.77 to -0.01) (1 RCT: Lacey 2008 **Level II**, n=107, JS 2) but not pain;
- For children (4–7 y) vibrating device with cold reduces pain (SMD -1.23; 95%CI -1.58 to -0.87) (2 studies, n=145) but not fear;
- For vaccination for older children (7 y) and adults, a muscle tension intervention reduces risk of fainting during injection (RR 0.11; 95%CI 0.02 to 0.79) (2 studies, n=38).

Application of cold and vibration (using the Buzzy® device) vs no treatment reduced self-reported pain scores in paediatric patients receiving vaccination (3–18y) (SMD -0.76; 95%CI -1.09 to -0.43) (2 RCTs, n=144) (Ballard 2019 **Level I** [PRISMA], 9 RCTs, n=1,138) (1 RCT overlap), whilst vapocoolant sprays were not effective in reducing pain for infants (3 mth old) (1 study, n=74) or older children (3–17 y) (4 studies, n=228) (Shah 2015 **Level III-1 SR**, 6 studies [vapocoolant in children], n unspecified).

Further studies to the above reviews have been published on physical interventions:

- Facilitated tucking vs holding in supine position in term neonates receiving HBV vaccine reduces pain score (mean 2.83/7 vs 6.47) but not HR, RR or oxygen saturation (Kucukoglu 2015 **Level II**, n=60, JS 2);
- White noise vs no intervention for premature neonates (born at 28–32 wk) receiving their 2nd dose of HBV vaccine reduced pain scores (mean 8.14/21 vs 14.35) and peak HR (mean 154/min vs 166) and RR (mean 50/min vs 61) (Kucukoglu 2016 **Level III-1**, n=75**);**
- ShotBlocker /swaddling vs swaddling alone for healthy term neonates receiving HBV vaccine reduces pain scores during (mean 1.64/7 vs 2.96) and 3 min after (mean 0.74/7 vs 1.42) injection, but not HR or RR (Caglar 2017 **Level II**, n=100, JS 3);
- Maternal kangaroo care vs swaddling for infants (ex-term and preterm) reduces pain scores at 1 min (median 2.5/7 vs 5) and 5 min (0/7 vs 4) post vaccine injection, as well as cry duration (median 42.5 s vs 135) (Pandita 2018 **Level II**, n=61, JS 3);
- Holding infants (6–12 wk post-natal age) in the supine vs upright position reduced crying (52 vs 70%), irritability (43 vs 58%) and distressed facial expression (46 vs 60%) 30 s after vaccine injection (Yin 2017 **Level III-2**, n=282);
- There was no difference in pain scores, and cry duration between infants (4–6 mth) receiving 10 s manual pressure, rapid injection without aspiration, or both; all study groups were superior to standard care (Gol 2017 **Level II**, n=128, JS 3);
- In older children (4–12 y) ShotBlocker vs placebo and typical care was not found to be more effective in reducing self-reported or observer-reported pain scores, distress behaviours (crying, screaming or requiring adult restraint) or observer-reported distress (Cobb 2009 **Level II**, n=89, JS 2).

Physical interventions that are strongly recommended include kangaroo care for 1 mth old, breastfeeding during vaccination injection for 2y old, holding for 3 y old, and sitting up for 3–18y olds; weaker recommendations include to use NNS during vaccination injection for 2 y olds, vibrating device with cold for 3–18 y olds, and muscle tension for 7–18 y olds, and recommend against manual tactile stimulation and warming the vaccine for all ages (Taddio 2015c **GL**).

Psychological interventions

Parental responses during injection such as excessive reassurance, criticism or apology increase distress, whereas humour and distraction tend to decrease distress (Schechter 2007 **NR**, 4 studies, n unspecified). Parental stress promoting behaviours had a stronger relationship than soothing behaviours and emotional availability with infant reactivity (immediate response) and regulation (non-immediate response), suggesting that teaching parents what not to do may be at least as important as teaching parents what to do (Badovinac 2018 **Level IV**, n=220). Furthermore, care-giver behaviour and poorer pain regulation at 12 mth vaccination predicted forward to pre-school vaccination coping, and care-giver behaviour also showed relationships to broader child cognitive behavioural abilities (Campbell 2018 **Level IV**, n=760). Healthcare staff can also influence a child's vaccination experience, and should purposefully use coping promoting strategies (Pedro 2016 **Level IV**, n=220 [4–7y]).

Three systematic reviews have assessed psychological interventions for vaccine injection:

- For 0–3 y olds, directed video distraction vs control reduces acute and recovery phase distress (SMD -0.68; 95%CI -1.04 to -0.32) (4 studies, n=126) and pre-vaccination distress (SMD -0.49; 95%CI -7.6 to -0.22) (4 studies, n=216) (Pillai Riddell 2015a **Level III-1 SR**, 10 studies, n=1,259);

- Directed toy distraction vs control for 0–3 y olds reduces peri-vaccination distress (SMD -0.47; 95%CI -0.91 to -0.02) (1 study, n=81), whilst non-directed toy distraction vs control does not reduce acute distress as the confidence interval includes zero (SMD -0.93; 95%CI -1.86 to 0.00) (4 studies, n=290) (Pillai Riddell 2015a **Level III-1 SR**, 10 studies, n=1,259);
- Verbal distraction vs control reduces distress in children (3–7 y) (SMD -1.22; 95%CI -1.87 to -0.58) (2 studies, n=46) but not pain (Birnie 2015 **Level III-1 SR**, 22 studies, n 1,717);
- Breathing with a toy reduces pain in children (3–9 y) (SMD -0.49; 95%CI -0.85 to -0.13) (6 studies, n=368) but not fear (Birnie 2015 **Level III-1 SR**, 22 studies, n=1,717);
- Video distraction vs control reduces distress in children (2–12 y) (SMD -1.22; 95%CI -1.87 to -0.58) (5 studies, n=328) but not pain (Birnie 2015 **Level III-1 SR**, 22 studies, n=1,717);
- Music distraction vs control reduces pain in children (3–7 y) (SMD -0.45; 95%CI -0.71 to -0.18) (4 studies, n=417) but not in adolescents (1 study n=118) (Birnie 2015 **Level III-1 SR**, 22 studies, n=1,717);
- There is no benefit for breathing techniques without a toy for pain or fear in children (3–7 y olds) (2 studies, n=136), coughing with injection for pain in 4–5 y olds (1 study n=136), false suggestion for pain or distress in 4–7 y olds (2 studies, n=240) or repeated reassurance for pain, distress or fear in 3–7y olds (2 studies, n=82) (Birnie 2015 **Level III-1 SR**, 22 studies, n=1,717);
- Psychological interventions for needle-related procedural pain in older children and adolescents (2–19 y) are effective (11 unique RCTs studying immunisation or injection: distraction 7 RCTs, combined CBT 6 RCTs, suggestion 1 RCT), but a sub-group analysis on vaccine injection was not done (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550) (0 & 10 RCT overlap).

Further studies published on psychological interventions for vaccine injection pain found:

- Parent participation to deliver distraction during vaccination in 4–6 y olds vs medical assistant delivered distraction did not change self-reported pain or satisfaction scores, parent-reported pain or satisfaction scores, or observer-reported pain scores (Franck 2015 **Level II**, n=76, JS 3);
- Music therapy for children (4–6 y) vs no treatment did not reduce parent ratings of child's pain but did reduce child distress behaviours during and after vaccination and parent distress promoting behaviours before, during and after vaccination (Yinger 2016 **Level II**, n=58, JS 2);
- Relaxation therapy and guided imagery had similar effects on cortisol reactivity, self-reported stress, pain intensity and pain unpleasantness in females (11–12 y) receiving the HPV vaccine (Nilsson 2015 **Level III-2**, n=37).

There is no data for needle phobia interventions alone; *in vivo* exposure based therapy for children (7–17y) with other phobias reduced specific fear (SMD -1.71; 95%CI -2.72 to -0.70) (4 studies, n=235), whilst imagined exposure based therapy in children (7–17y) reduced specific fear post-treatment (SMD -0.88; 95%CI -1.7 to -0.05) (2 studies, n=41) and at 3 mth (SMD -0.89; 95%CI -1.73 to -0.04) (1 study, n=24) (McMurtry 2015 **Level III-1 SR**, 11 studies, n=620).

The following psychological interventions are recommended: verbal signal of impending procedure, suggestion and reassurance for all children (0–17 y); directed video distraction, directed or non-directed toy distraction for 3 y; verbal, video or music distraction and breathing with a toy for 3–12 y olds; and recommend against a planned cough during injection for 3–17 y olds (Taddio 2015c **GL**). For patients with high levels of needle fear *in vivo* exposure-based therapy, and if this is not used, non-*in vivo* (imagined) exposure-based therapy is strongly recommended for children 7–17 y old (McMurtry 2016 **GL**).

Combination intervention

Various combinations of interventions have been studied in vaccine injection pain. Further reviews and studies are summarised here:

- In infants <3 mth, topical anaesthesia with breastfeeding vs topical anaesthesia alone reduced acute and recovery phase distress (SMD -0.83; 95%CI -1.36 to -0.30) (Gupta 2013 **Level II**, n=90, JS 3), whilst there was no benefit for sweet tasting solutions with NNS vs either alone (1 study), or breastfeeding and sweet tasting solutions vs either alone (1 study) (Shah 2015 **Level III-1 SR**, 55 studies, n unspecified);
- PO sucrose, oral tactile stimulation (with a pacifier or a bottle) and parental holding reduced the duration of crying in infants (2 mth) receiving multiple immunisations (Reis 2003 **Level II**, n=116, JS 5);
- EMLA® combined with N_2O 50% was superior to either alone for observed pain in infants (<24 mth) during and post vaccination injection (Carbajal 2008 **Level II**, n=55, JS 5);
- EMLA® and breastfeeding was similarly effective to vapocoolant spray and breastfeeding, and both combinations were superior to breastfeeding alone in terms of cry duration (36 s vs 33 s vs 68 s) and pain intensity at 1 min (mean 1.4/6 vs 1.8 vs 3.2) and 3 min (mean 0.9/6 vs 0.6 vs 2.3) post vaccine injection (Gupta 2017 **Level II**, n=90, JS 3);
- Combination of video/ sucrose/topical lidocaine administered to infants at each of their vaccinations up to 12 mth old reduced pain scores during vaccine injection vs video/sucrose, video alone and placebo (mean 6.3/15 vs 6.7 vs 6. 7 vs 6.7 respectively) suggesting benefit from this combination of interventions was derived from topical lidocaine only (Taddio 2017b **Level II**, n=352, JS 5);
- The same four groups all received video/sucrose/topical lidocaine for vaccinations at 15 mth old, and there was no difference in pain scores across groups before, during and after vaccination injection, suggesting consistency in vaccine pain management interventions in the first year of life does not confer benefit at 15 mth (Taddio 2017a **Level II**, n=352, JS 5).

10.7.4 | Procedural pain management in the emergency department

Clinical guidelines from various bodies have been developed for procedural pain management in the ED. The American College of Emergency Physicians has published a guideline for unscheduled procedural sedation in children and adults; it focusses on safety of delivering sedation in this context rather than on individual drug efficacy, and is applicable to the use of various sedatives (Green 2019b **GL**).

10.7.4.1 | Laceration repair

All oral agents as specified in Sections 10.4.1 to 10.4.3 have been used in children having laceration repair, usually to supplement topical or injected local anaesthetic. IN fentanyl use is not yet specifically reported for laceration repair.

Topical local anaesthesia

Topical local anaesthetic application for wound closure can avoid the distress caused by intradermal injection; importantly cocaine-containing preparations are no longer recommended (Tayeb 2017 **Level III-1 SR** [Cochrane], 25 RCTs [2 paediatric, 19 mixed paediatric/adult], n=3,278 [paediatric unspecified]). Numerous topical local anaesthetic agents have been assessed. Only a descriptive analysis is possible as studies have high risk of bias, mostly involve only single comparisons and only 15 of 25 RCTs report pain scores. The most widely used topical agent applied to paediatric wounds is lidocaine-adrenaline-amethocaine (tetracaine) preparation (abbreviated to ALA in Australia and LAT or LET in the USA). This combination appears as effective as tetracaine-

adrenaline-cocaine (3 RCTs, n=341), buffered lidocaine-adrenaline infiltration (1 RCT, n≈66), infiltrated lidocaine (1 RCT, n=40) and as a gel or solution with no other comparator (1 RCT, n=194).

Topical ALA solution applied to wounds at triage reduced treatment time by 31 min vs controls (Priestley 2003 **Level II**, n=161, JS 4) and pain associated with subsequent intradermal injection of lidocaine (Singer 2000 **Level II**, n=43, JS 5).

Local anaesthesia infiltration

In mainly adult patients, pain on injection of local anaesthesia is reduced by warming (to 37–43°C) (Hogan 2011 **Level I** [PRISMA], 1 RCT [paediatric], n=44) or buffering with sodium bicarbonate (increasing the pH of lidocaine to ≥7.35) (Cepeda 2010 **Level I** [Cochrane], 2 RCTs [mixed age], n=165 and 1 RCT [paediatric], n=7) (see also Section 4.4.2).

Alternatives to suturing: tissue adhesives and hair apposition

Tissue adhesives vs suturing for simple lacerations produce similar cosmetic results (9 RCTs, n=889), and less parent-reported pain (WMD -13.4/100; 95%CI -20 to -6.9) (5 RCTs, n=434) with shorter procedure time (WMD -4.7 min; 95%CI -7.2 to -2.1) (6 RCTs, n=584) and may be more acceptable to children (Farion 2003 **Level I** [Cochrane], 13 RCTs [paediatric], n unspecified). The risk of dehiscence is increased slightly with tissue adhesive vs standard wound care (NNH 40; 95%CI 20 to 1,168) but it is offered to parents as a preferred initial intervention. Hair apposition was as effective as suturing for simple scalp lacerations (Hock 2002 **Level II**, n=189, JS 3), and can be performed effectively by doctors and nurses (Ong 2008 **Level II**, n=164, JS 3).

Children who received topical local anaesthetic (ALA) prior to tissue adhesive application were more likely to have a pain-free procedure vs placebo by self or observer report (RR 0.54; 95%CI 0.37 to 0.80) (Harman 2013 **Level II**, n=221, JS 5).

Midazolam

Midazolam is a useful adjunct in the procedural sedation pharmacotherapy armamentarium for laceration repair in younger or noncooperative children. IN administration stings and the PO route is generally preferred, although efficacy may be more variable (influenced by first-pass metabolism and duration of fasting). Compared to PO route or aerosolised buccal delivery prior to laceration repair in young children (0.5–7 y), aerosolised delivery IN had faster onset and achieved adequate sedation, at the expense of nasal irritation and being less readily accepted than the PO route (Klein 2011 **Level II**, n=169, JS 5). PO midazolam 0.7 mg/kg vs PO ketamine 5 mg/kg for children (1–10 y) having laceration repair resulted in similar parent-reported pain scores (3.7/10 vs 5.1) (Rubinstein 2016 **Level II**, n=68, JS 5).

Nitrous oxide (N_2O) and ketamine alone or in comparison

Inhaled N_2O 50–70% (with oxygen) is commonly used for laceration repair and minor surgery in children and reduces pain and anxiety, with large case series affirming the utility and safety of the technique for this and other indications (Tobias 2013a **Level I SR**, 1 RCT [laceration], n=30; Pedersen 2013 **Level IV SR** [PRISMA], 1 RCT [laceration], n=204 & multiple studies [laceration], n unspecified; Heinrich 2015 **Level IV**, n=210; Babl 2010 **Level IV**, n=504). Ketamine is also commonly used as dissociative sedation and analgesia for laceration repair. Common doses used as sole agent in the ED are 0.5–1 mg/kg IV and 3–5 mg/kg IM; coadministration of atropine or benzodiazepine is no longer recommended (Green 2011 **GL**). PO and IN routes are also used (see below).

For facial laceration repair in the ED by a plastic surgeon, in children and adolescents (1–16 y; 60% unfasted), N_2O 50% with lidocaine infiltration vs lidocaine infiltration alone reduced pain scores during lidocaine infiltration (mean 1.9 /10 vs 9.7) and suturing (2/10 vs 8.8); in controls forceful restraint was applied in 100% vs patients receiving N_2O where only 15% required mild restraint (Bar-Meir 2006 **Level III-2**, n=60). Minor adverse effects (mostly nausea) occurred in 29%

of patients receiving N_2O. N_2O 50–70% and IV ketamine 2 mg/kg had similar analgesic efficacy, with deeper sedation and longer median duration by 13.5 min in those ketamine treated (Lee 2012 **Level II**, n=32, JS 3). The addition of PO ketamine 5 mg/kg to PO midazolam 0.5 mg/kg vs midazolam alone for laceration repair, resulted in similar pain scores during local anaesthetic injection (parent and researcher: 4/10), with increased sedation and time to discharge for the combination group (MD 65 min; 95%CI 22 to 107) (Barkan 2014 **Level II**, n=60, JS 5). IN Ketamine 9 mg/kg achieved adequate sedation for laceration repair in young children, whilst doses of 3mg/kg and 6 mg/kg did not (Tsze 2012 **Level II**, n=12, JS 2).

The safety of ketamine has been documented in a large paediatric ED series (n=8,282) with low rates of emergence reactions (clinically important 1.4 vs "any" 7.6%), vomiting 8.4% and respiratory events 3.9% (Green 2009c **Level IV**). Variables independently associated with increased risk of respiratory effects included age <2 y (OR 2.00; 95%CI 1.47 to 2.72) and ≥13 y (OR 2.72; 95%CI 1.97 to 3.75), high IV dosing (initial dose ≥2.5 mg/kg or total dose ≥5.0 mg/kg) (OR 2.18; 95%CI 1.59 to 2.99) and co-administered anticholinergic (OR 1.82; 95%CI 1.36 to 2.42) or benzodiazepine (OR 1.39; 95%CI 1.08 to 1.78). Oropharyngeal procedures, ASA class ≥3 and use of IV vs IM route were not associated with increased risk.

10.7.4.2 | Closed fracture reduction

Closed fracture reduction is a major procedure, which may be performed in EDs with a variety of analgesic techniques including N_2O (Pedersen 2013 **Level IV SR** [PRISMA], 4 studies, total n=45,120), ketamine IV or IM (Babl 2010 **Level IV**, n=2,002 [1,622 N_2O & 340 ketamine]), opioids (IV morphine, IN or IV fentanyl and IV alfentanil), propofol or combinations of these agents (Migita 2006 **Level I SR**, 5 RCTs, n=526; Hoeffe 2017 **Level IV,** n=90; Schofield 2013 **Level IV**). The majority of studies assess procedural pain scores and not postprocedural impact. Paediatric guidelines for procedural sedation have been produced by the American College of Emergency Physicians (Green 2019b **GL).** Different regimens may result in no or mild sedation through to heavy sedation or even anaesthesia. Comparison of specific regimens studied are summarised below:

Ketamine

- With PO oxycodone 0.2 mg/kg pre-treatment, IV ketamine 1 mg/kg with IV midazolam 0.1 mg/kg vs N_2O 50% and haematoma block (1% buffered lidocaine 2.5 mg/kg) had similar parental and child pain scores, but later readiness for discharge (mean 83 min vs 16); minor adverse effects were frequent in both groups (vomiting 24% vs 26; headache 11% vs 13) with the ketamine/midazolam group reporting more ataxia (24% vs 9) nightmares (20% vs 7) and hallucinations (29% vs 4) (Luhmann 2006 **Level II**, n=102, JS 3);
- IV Ketamine/midazolam vs IV etomidate/fentanyl achieved lower observer pain scores, similar amnesia and greater parental satisfaction, despite longer recovery time (Lee-Jayaram 2010 **Level II**, n=23, JS 5);
- In children (3–14 y) receiving IV midazolam 0.2 mg/kg (max 10 mg), IV morphine 0.1 mg/kg and 0.05 mg/kg prn (max 5 mg) vs IV ketamine 2mg/kg (max 70 mg) resulted in similar pain scores following the procedure (median 2/10 vs 2); sedation scores were not reported (Barcelos 2015 **Level II**, n=25, JS 3);
- An ED dose finding study for IV ketamine for procedural sedation/anaesthesia in 3–18 y olds (71% fracture/dislocation reduction) suggested similar median sedation depth (Ramsay sedation scores 5.5–6/6) and duration (23–24.5 min) with an initial dose of 1.5 or 2 mg/kg vs 1 mg/kg, but greater need for redosing with 1 mg/kg (16% vs 3% with 1.5mg/kg and 5% with 2 mg/kg) (Kannikeswaran 2016 **Level II**, n=125, JS 5);

- In another dose finding sedation study, the ED_{95} dose for bolus IV ketamine for closed forearm fracture reduction was estimated at 0.7 mg/kg for 2–5 y olds and 6–11 y olds, with 0.8 mg/kg for 12–17 y olds (Chinta 2015 **Level IV**, n=60);
- Following ED intervention for fracture reduction, laceration repair and other painful procedures (where procedural pain scores were not assessed), ketamine mostly single agent (or combined with midazolam) vs fentanyl/midazolam had similar vomiting rates (20% vs 14), low incidence of emergence reaction (1% vs 0) and lower incidence of post-hospital behavioural disturbance (McQueen 2009 **Level III-3**, n=554 [294 fracture reductions]).

Intranasal and inhaled analgesia

- IN fentanyl 1.5 mcg/kg added to N_2O 70% did not improve analgesia over N_2O alone in children (2–16 y) with low procedural pain scores and short procedure duration (mean 3.62 min; 84% fracture manipulation) (Seiler 2019 **Level II**, n=402, JS 5);
- IN diamorphine 0.1 mg/kg with N_2O 50% has been used successfully for closed fracture reduction in the ED (Kurien 2016 **Level IV**, n=100);
- Inhaled N_2O for closed fracture reduction in children and adolescents is safe but its efficacy is reported to be mixed (Pedersen 2013 **Level IV SR** [PRISMA], 6 studies, n=54,127 [closed fracture reduction unspecified]; Babl 2010, n=2,002 [393 closed fracture reduction]; Hennrikus 1995 **Level IV**, n=100; Hennrikus 1994 **Level IV**, n=54);
- Methoxyflurane via Penthrox® inhaler in children (5–13 y) requiring mostly upper extremity fracture reduction was an effective analgesic with rapid onset (<30 s), but variable effectiveness for procedural sedation; minor adverse events (eg cough, agitation, blurry vision) occurred in 5 of 14 patients (Babl 2007 **Level IV**, n=14);
- Dexmedetomidine IN or IV use is not yet reported for this indication (McMorrow 2012 **NR**).

For children and adolescents (21 y old) with a forearm or lower extremity fracture, the use of procedural sedation (23% vs 18) by paediatric and general ED physicians was similar. Paediatric ED physicians were more likely to use fentanyl (62% vs 19), the IV route (91% vs 67), and a combination of agents (90% vs 44) (Cimpello 2004 **Level III-2**, n=718). Patient age and characteristics of a displaced fracture (but not ethnicity: African-American or Caucasian) were predictors of use of conscious sedation (midazolam and fentanyl, or ketamine) for closed forearm fracture reduction in children and adolescents (18 y) presenting to a paediatric ED (VanderBeek 2006 **Level IV**, n=503).

Opioid/propofol and ketamine/propofol combinations

Opioid/propofol or ketamine/propofol (ketofol) combinations for deeper procedural sedation are increasingly used in paediatric EDs. In various paediatric procedural sedation settings, adverse effects of propofol use (of 0.5–2mg/kg and higher) have been reported at rates of: cardiovascular (hypotension 15.4% and bradycardia 0.1%); respiratory (desaturation 9.3%, apnoea 1.9%, assisted ventilation 1.4%, unplanned intubation 0.02%, laryngospasm 0.1%); and post-procedure vomiting (0.14%) (Lamond 2010 **Level IV SR**, 60 studies, n=17,066). Of the seven included ED studies, six were for fracture reduction (2 RCTs, n=204; 4 case series, n≈610) with coadministration of opioid (morphine or fentanyl) and supplemental oxygen. Desaturation rates varied from 5–31%, with lower rates of airway intervention (such as jaw manoeuvres and bag-mask assistance) and no intubations. Ketofol has been compared to propofol only (with and without opioid pre-treatment) for fracture reduction with focus upon satisfaction with procedural sedation, and respiratory (9–28% depending how defined) and other adverse effects (Weisz 2017 **Level II**, n=183, JS 3; Shah 2011a **Level II**, n=140, JS 5; David 2011 **Level II**, n=220, JS 5). Pharmacokinetic modelling has been done for ketofol with dosing recommendations for longer duration procedures (Coulter 2014 **PK**).

Regional anaesthesia/analgesia

Haematoma blocks and Bier's block (or IV regional anaesthesia/block [IVRA/IVRB]) are used for closed forearm fracture reduction in the ED. A survey of orthopaedic surgeons and paediatric ED physicians found 78% of respondents had used a local anaesthetic technique for closed reduction of a forearm fracture but only 17% reported frequent use; of respondents who had used local anaesthetic techniques, haematoma blocks (93%) and Bier's blocks (20%) were the most common (Constantine 2007 **Level IV**, n=85). A subsequent survey of paediatric ED physicians found that 35% of respondents had used a Bier's block and 4% a haematoma block (Schofield 2013 **Level IV**, n=111). Local anaesthetic IVRB is highly effective and safe (Migita 2006 **Level I SR**, 3 RCTs [IVRB], n=560; Murat 2003 **Level III-3 SR**, 5 studies, n=1,178; Chua 2017a **Level IV**, n=1,788) but data on optimal dosing, safety and comparisons of efficacy are limited, and serious complications may arise with faulty equipment, inappropriate local anaesthetic use, or inadequate monitoring and training of staff.

Trans-arterial axillary brachial plexus block (1% lidocaine with adrenaline 0.7 mL/kg) achieved similar procedural pain scores to ketamine/midazolam deep sedation in children (>8 y) having closed reduction of a forearm fracture in the ED (mean 6.4 /13 vs 7.5); 11/20 blocks were assessed as incomplete (residual motor block) (Kriwanek 2006 **Level II**, n=43, JS 2).

Ultrasound (US)-guided ulnar, radial, and median nerve blocks in the forearm for hand injuries managed procedurally in the ED (fractures, dislocations, crush injuries, complex lacerations) have been used successfully in children and adolescents (7–17 y old) (Mori 2019 **Level IV**, n=6; Frenkel 2015 **Level IV**, n=10). US-guided intra-articular lidocaine injection to the glenohumeral joint has been used successfully for analgesia to reduce an anterior shoulder dislocation in a 17 y old male (Breslin 2014 **CR**).

10.7.4.3 | Psychological interventions

In addition to pharmacological interventions, procedural planning for children in the ED should include age-appropriate psychological interventions, such as distraction techniques (see below Section 10.7.5).

10.7.5 | Nonpharmacological strategies in children and adolescents

For further information on nonpharmacological strategies for specific procedures, see sections 10.7.1–4 above.

Distraction

Distraction can be passive (eg listening to music, being read a book, watching a screen, kaleidoscope, distraction boxes) or active (eg guided imagery, handheld video games, non-immersive or immersive virtual reality). Distraction reduces self-reported needle-related procedure pain (SMD -0.56; 95% CI -0.78 to -0.33) (30 RCTs, n=2,802), and self-reported needle-related distress (SMD -0.82; 95%CI -1.45 to -0.18) (4 RCTs, n=426) (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550). Further reviews including lower level evidence generally support distraction techniques for various needle procedures, laceration repair and bone marrow aspiration (Bukola 2017 **Level III-I SR**, 7 studies, n=312; Wente 2013 **Level III-2 SR**, 10 studies, n=1,164; Koller 2012 **Level III-2 SR**, 37 studies, n=1,575; Landier 2010 **Level III-2 SR**, 26 studies, n=1,675).

A systematic review assessed immersive virtual reality for 21 y olds undergoing medical procedures (Eijlers 2019 **Level III-1 SR** [PRISMA], 17 studies, n=859). It found immersive VR vs usual care reduced:

- Self-reported pain scores (SMD -1.30; 95%CI -0.68 to -1.91) (14 studies);
- Self-reported anxiety (SMD -1.32; 95%CI -0.21 to -2.44) (7 studies);

- Carer (SMD -0.47; 95%CI -0.22 to -0.72) (4 studies), and professional-reported pain scores (SMD -0.82; 95%CI -0.48 to -1.15) (3 studies);
- Self-reported pain scores in burns care (SMD -0.66; 95%CI -0.40 to -0.91) (5 studies) and venous access (SMD -0.32; 95%CI -0.01 to -0.62) (2 studies) but not oncological care (3 studies).

Subsequently, VR vs standard of care reduced pain scores in 4–11 y having venipuncture in the ED (Chan 2019a **Level II**, n=123, JS 3) and pathology (Chan 2019a **Level II**, n=131, JS 3), whilst, immersive VR was not superior to nurse led distraction in 7–16 y olds for venous cannulation but had higher satisfaction (100% vs 85) (Walther-Larsen 2019 **Level II**, n=64, JS 3).

A retrospective series analysed three comfort measures (distraction, positioning and medication) and used number of attempts to complete a procedure (IV cannulation, gastrointestinal tube placement, incisional procedures, urinary catheterisation) as a measure of efficacy in minimising distress (Dastgheyb 2018 **Level IV**, n=74,276). Higher success rates occurred with distraction in younger children, particularly <1 y, whilst in older children (>4 y) higher success rates occurred with positioning; however, differences between comfort measures for each procedure and age group were generally small.

Hypnosis

Hypnosis requires the skills of a trained health professional and time for the child to learn the technique. Hypnosis vs control for needle-related procedural pain reduces pain scores (SMD -1.4; 95%CI -2.32 to -0.48) (5 RCTs, n=176), distress scores (SMD-2.53; 95%CI -3.93 to -1.12) (5 RCTs, n=176) and behavioural measures of distress (SMD -1.15; 95%CI -1.76 to -0.53) (6 RCTs, n=193) (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550). For children undergoing cancer-related procedures, hypnosis is an effective pain-control technique (Tome-Pires 2012 **Level I SR**, 10 RCTs [cancer procedural pain], n=394) (5 RCT overlap). A subsequent review of oncology patients found hypnosis reduced pain scores vs usual treatment (pooled effect size Cohen's d 2.16; 95%CI 1.41 to 2.92) and controls having attention focus (Cohen's d 2.24; 95%CI 1.66 to 2.82) but not vs active control groups (eg music, play, audiobooks) (Nunns 2018 **Level I** [PRISMA], 15 RCTs, n=585 [8 hypnosis, n=337]) (6 RCT overlap with above reviews).

Cognitive behavioral therapies (CBT)

Combined CBT (defined as combining at least one cognitive strategy with at least one behavioral strategy) may include parent coaching, parent positioning, child distraction and suggestion (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550):

- Reduces observer-reported pain (SMD -0.52; 95%CI -0.73 to -0.30) (4 RCTs, n=385) and behavioral distress (SMD -0.40; 95%CI 0.67 to -0.14) (11 RCTs, n=1,105);
- Does not reduce not self-reported pain (14 RCTs, n=1,359), self-reported distress (6 RCTs, n=234) observer-reported distress (6 RCTs, n=765) or behavioral measures of pain (2 RCTs, n=95);
- The same review found breathing interventions reduced self-reported pain (SMD -1.04; 95%CI -1.86 to -0.22) (4 RCTs, n=298), however preparation and information (4 RCTs, n=313), and suggestion (3 RCTs, n=218) showed no effect for any pain or distress outcome. No conclusion could be made on memory alteration (1 RCT, n=15).

A second systematic review further explored memory reframing interventions in children (3–18 y) (Noel 2018 **Level III-1 SR**, 3 studies, n=158). It found a memory reframing intervention vs control on the day of a subsequent needle procedure did improve memory of fear (SMD -0.60; 95%CI -1.05 to -0.15) but did not improve memory of pain, anticipatory fear or acute fear (2 studies, n=50 [oncology LP] & 45 [dental injection]); memory reframing intervention following a needle procedure (immediately and at follow-up) did improve memory of pain (SMD -0.53;

95%CI -1.03 to -0.02) (1 study, n=63 [vaccination]); outcomes regarding subsequent procedures were not assessed.

Relaxation and biofeedback vs control for 12 y olds receiving venipuncture did not lower pain intensity during the procedure (Forsner 2014 **Level III-2**, n=109).

In children (8–14 y) having cancer-related procedures, a 4-session intervention of preprocedural relaxation plus biofeedback was associated with progressively reduced state anxiety across the sessions, and improvement in heart rate variability; 81% of participants reported the combination of relaxation and biofeedback helped them feel in control of their bodies prior to the procedure (Shockey 2013 **Level IV**, n=12). Of patients (7–18 y) undergoing needle-related procedures (venipuncture, IV cannula insertion and Botox injection), 83.3% of those who used 'Brighthearts' (a biofeedback assisted relaxation application) reported the app was helpful and would use it again, 100% of parents and 96% of healthcare providers indicated they would use it again, and 64% of the healthcare providers perceived that it assisted with ease of procedure performance (Burton 2018 **Level IV**, n=107 [30 patients 27 parents 50 health professionals]).

Music therapy

Music therapy includes passive listening to recorded or played music and active participation of the patient with music. In children aged 1 mth–20 y, music therapy has a positive impact on pain (8 RCTs, n=882) and anxiety (6 RCTs, n=324) or both (5 RCTs, n=279) with various procedures (venipuncture/IV cannulation, bone marrow aspiration, dental/oral and other surgery) (Klassen 2008 **Level I**, 19 RCTs [5 active, 14 passive], n=1,513). On meta-analysis, music therapy reduces pain (SMD -0.39; 95%CI -0.66 to -0.11) (5 RCTs, n=465) and anxiety (SMD -0.39; 95%CI -0.76 to -0.03) (5 RCTs, n=284). A further RCT on IV cannulation in the ED shows the addition of passive music therapy to standard care (topical local anaesthetic, nurse explanation and reassurance) achieves lower pain and anxiety scores vs standard care alone (Hartling 2013 **Level II**, n=42, JS 3).

Other nonpharmacological interventions

Inviting parental presence for procedures (with and without sedation) is common practice. A child being positioned vertically and held by a parent vs being restrained by staff supine on an exam table reduced distress during IV cannulation (Sparks 2007 **Level II**, n=118, JS 4). During venipuncture, fearful parental expression and being reassured uninformatively (told "don't worry") increased children's fear, while informative reassurance and distraction use decreased it (McMurtry 2010 **Level IV**, n=100). Preprocedural preparation of the parent and child in a developmentally appropriate way is considered best practice and is being incorporated within hospital and national guidelines (Duff 2012 **GL**), as is staff and parent training in the use of nonprocedural talk (RACP 2005 **GL**) and use of child-friendly language for preparation/explanation (Stock 2012 **GL**). Nurse or play therapist coaches or hospital employed "child life interventionists" are also being employed to educate, distract and plan procedural intervention strategies for children and their parents informally and formally (LeBlanc 2014 **NR**).

KEY MESSAGES

Neonates

1. In term neonates, venipuncture is less painful than heel lance (**N**) (**Level I** [Cochrane Review]).
2. Sucrose (**S**) (**Level I** [Cochrane Review]) and non-sucrose sweet solutions (mostly glucose) (**N**) (**Level I** [PRISMA]) reduce pain scores and behavioural response for skin-breaking procedures in neonates.
3. Providing physical comfort measures, including kangaroo care (maternal or alternative skin to skin provider), non-nutritive sucking (alone or combined with sweet-tasting solutions), facilitated tucking (swaddling) or rocking and holding (**N**) reduces pain experienced by term and preterm neonates having skin-breaking procedures (**S**) (**Level I** [Cochrane Review]).
4. Pain from ocular examination for retinopathy of prematurity is reduced by sucrose and non-nutritive sucking (**N**) (**Level I** [Cochrane Review]) and topical local anaesthetic (**N**) (**Level III-1 SR** [Cochrane Review]).
5. Kangaroo care (or skin to skin contact) in neonates reduces the distress of vaccine injection (**N**) (**Level III-1 SR**).
6. Sucrose reduces distress after gastric tube placement in neonates (**N**) (**Level III-1 SR**).

Infants and children

7. Breastfeeding (<2 years of age) reduces pain intensity and crying duration for skin-breaking procedures including vaccine injection compared to positioning, holding by mother, maternal skin to skin contact (<1 months), topical anaesthetics, music therapy, pacifier use (<4 months), placebo, no intervention and/or oral sucrose (**S**) (**Level I** [Cochrane Review]).
8. Non-nutritive sucking reduces pain after needle-related procedures in infants and young children (<3 years) (**N**) (**Level I** [Cochrane Review]).
9. Oral sucrose and glucose reduce cry incidence and duration (**U**) (**Level III-1 SR** [Cochrane Review]**)** and distress (**N**) (**Level III-1 SR**) of vaccine injection in infants.
10. Distraction in infants and young children (<3 years) reduces vaccine injection pain (**N**) (**Level III-1 SR**).
11. Procedural modifications reduced distress of vaccine injection including injection without aspiration (18 months), simultaneous injection of multiple vaccines (12 months) and injection of most painful vaccine last (6 months) (**N**) (**Level III-1 SR**).
12. Topical local anaesthetic reduces distress of vaccine injection in infants (**N**) (**Level III-1 SR**).
13. Parental presence reduces prevaccine injection distress in infants and children (**N**) (**Level III-1 SR**).
14. Parental education before or on vaccination day increases use of evidence-based pain management strategies and reduces distress in infants and children (**N**) (**Level III-1 SR**).
15. Physical interventions including holding by parent (during or after) and non-nutritive sucking in infants (0–4 months) reduces the distress of vaccine injection (**N**) (**Level III-1 SR**).
16. The efficacy of supplemental/expressed breast milk for procedural pain management is unclear (**N**) (**Level III-1 SR**).
17. Needle-free pressure injected lidocaine is quick in onset and reduces pain from subsequent needle-related procedures in infants and children (**N**) (**Level II**).

Children and adolescents

18. EMLA® is an effective topical local anaesthetic for children but amethocaine is superior for reducing needle-insertion pain (**U**) (**Level I** [Cochrane Review]).
19. Topical local anaesthetic application (**U**) **(Level I** [Cochrane Review]), inhalation of nitrous oxide 50–70% or the combination of both (**U**) (**Level I** [PRISMA]) provides effective and safe analgesia for minor procedures in children.
20. Distraction (including with video, toys, music or stories) and hypnosis reduces needle related pain (**S**) and distress (**N**) in children and adolescents (**Level I** [Cochrane Review]).
21. Buzzy (which combines vibration and cold) (**N**) (**Level I** [PRISMA]) and vibration by other methods (**S**) (**Level III-1 SR**) reduces needle-related procedure pain, including vaccine injection in children.
22. Active and passive music therapy reduces pain and anxiety associated with various needle-related procedures in children (**U**) (**Level I**).
23. Immersive virtual reality reduces pain of medical procedures including wound dressing care and venipuncture (**N**) (**Level III-1 SR** [PRISMA]).
24. Immersive virtual reality for medical procedures in children reduces self-reported pain and anxiety (**N**) (**Level III-1 SR**).
25. Ketamine is effective for paediatric procedural pain management (**Q**) (**Level IV**).
26. Hospital wide initiatives to implement evidence-based standards of care for needle related procedures can improve service delivery and patient satisfaction (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Using combinations of evidence-supported single pain management strategies for painful procedures is strongly recommended (**N**).

☑ It is of concern that minor procedures are still undertaken in children, particularly neonates and infants, in the elective and emergency hospital setting with minimal or no pain management intervention (**N**).

☑ Inadequate monitoring, lack of adequate resuscitation skills and equipment, and the use of multiple medicine combinations has been associated with major adverse outcomes during paediatric procedural analgesia and sedation (**U**).

☑ Pain caused by injection is a barrier to vaccine uptake; thus managing vaccine injection pain has immediate and long term implications for the wellbeing and health of individuals and society (**N**).

☑ Based on data from other specific phobias, exposure-based therapy (*in vivo* or imagined) is recommended for children and adolescents (7–17 years) with needle phobia receiving vaccine injections (**N**).

☑ Hypnosis requires teaching by a trained professional, but distraction can be readily provided by staff or parents and should be routinely offered in the paediatric setting (**U**).

☑ For children and adolescents, sitting upright may reduce procedural pain and distress (**N**).

10.8 | Acute pain in children with cancer

Acute pain in children with cancer may be due to tissue destruction from the cancer itself, its consequences (eg infection), or from its treatment (eg chemotherapy, radiotherapy, painful procedures, surgery), and may be primarily nociceptive or neuropathic. It is a common symptom in children with cancer (Ye 2019 **Level IV**, n=205; Tutelman 2018 **Level IV**, n=230; Friedrichsdorf 2014 **NR**; Fortier 2014 **Level IV**, n=45) and may be more common in children from low-income households (64% vs 42) (Ilowite 2018 **Level IV**, n=78). It is associated with significant fear and distress (Ljungman 1999 **Level IV**), and difficulty in pursuing and achieving personal goals (Schwartz 2017 **Level III-2**, n=199). Self-reported pain scores by children with cancer have been of higher intensity than nurse-reported pain scores (2 studies), whilst agreement with parent/carer-reported pain scores varied (9 studies) (Cheng 2018 **Level III-2 SR**, 33 studies, n=3,063 [children paired with parents/nurses]). Use of symptom self-report wherever possible is recommended.

Compared with adults (see Section 8.9), the pattern and sources of acute pain differ significantly in children with cancer. The WHO guideline *Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses* (WHO 2012 **GL**) addresses pain in cancer and other medical conditions (such as HIV/AIDS, sickle cell disease, burns, trauma and phantom limb pain). It recommends a two-step analgesic management approach, abolishing the middle step that previously contained codeine. In 2019, this guideline was withdrawn by the WHO, however it remains endorsed by organisations in Australia, New Zealand and internationally until it is replaced.

10.8.1 | Cancer-related pain

10.8.1.1 | Tumour-related pain

Pain due to tumour is present at diagnosis in the majority of children (Miser 1987 **Level IV**) and often resolves with initial disease modifying therapy. Systematic reviews for cancer pain management have not identified any paediatric RCTs of paracetamol (Wiffen 2017b **Level I** [Cochrane], 3 RCTs [0 RCTs in children]), NSAIDs (Cooper 2017b **Level I** [Cochrane], 0 RCTs), opioids (Wiffen 2017a **Level I** [Cochrane], 0 RCTs) and pharmacological interventions (Eccleston 2019 **Level I**, 0 RCTs [cancer]) and pharmacokinetic, pharmacodynamic and pharmacogenomic data on commonly used drugs in children with cancer is limited (Constance 2017 **NR**). Thus, recommendations for their use are based on low quality evidence, extrapolation from different populations, and expert opinion.

Breakthrough pain

Breakthrough cancer pain in children is usually of sudden onset, severe and of short duration (Friedrichsdorf 2014 **NR**; WHO 2012 **GL**). For incident and breakthrough pain treatment, IR opioids are recommended at 10–15% of total daily dose. Commonly PO or IV morphine is used but all other opioids have been administered including via more rapid onset routes eg fentanyl transmucosally, SL or IN (Triarico 2019 **NR**; Coombes 2017 **Level IV**, n=26). "End of dose" pain is managed with escalation of background dosing, as in adults.

Background pain

For background pain, morphine is the most commonly used opioid; hydromorphone IR and oxycodone IR and controlled or extended release use starting at typical initial doses has also been described (Snaman 2016 **NR**). Transdermal buprenorphine has been used in 2–17 y olds with suggested weight-based doses starting at 8.75 mcg/h (<15 kg), 17.5 mcg/h (15–30 kg) and 35

mcg/h (>30 kg), titrated up to a maximum of 70 mcg/h (Ruggiero 2013 **Level IV**, n=16; Michel 2011 **Level IV SR**, 2 studies [cancer pain], n=4). Use of SL buprenorphine (2.5–10 mcg/k 12 hly) has also been described (Michel 2011 **Level IV SR**, 1 study, n=13).

Transdermal fentanyl has been used for cancer-related pain in previously opioid-tolerant children (2–19 y old in and outpatients) receiving a minimum of 30 mg/day PO morphine for a variable time period prior (Finkel 2005 **Level IV**, n=199 [132 cancer]; Hunt 2001 **Level IV**, n=41; Noyes 2001 **Level IV**, n=13; Collins 1999 **Level IV PK**, n=13). Opioid naïve cancer patients with pain (not controlled by paracetamol/ibuprofen) were admitted for TD fentanyl uptitration (Othman 2016 **Level IV**, n=64). They commenced 12 mcg/h (if <15 kg) or 25 mcg/h (if >30 kg or 15–30 kg with severe pain) with IV morphine rescue administration 50–100 mcg/kg; 16% required up titration within 15 d (max dose reached 50 mcg/h) (Othman 2016 **Level IV**, n=64). Transdermal fentanyl mean clearance and volume of distribution were similar to adults in older children (7–18 y) (Collins 1999 **Level IV PK**, n=13).

Opioid rotation/switch (mostly from morphine, hydrocodone or hydromorphone) to methadone has been described in children and adolescents (1–18 y) as both inpatients and outpatients (Madden 2018 **Level IV**, n=52; Mott 2018 **Level IV**, n=16; Davies 2008 **Level IV**, n=17). Inpatient rotation/switch is usually done in more opioid-tolerant patients and with more aggressive dosing. Initial dose calculations include 0.1 mg/kg/dose or using conversion ratios (usually 10 to 25:1) dependent on the context (eg pain intensity, inpatient vs outpatient and morphine equivalent daily dose). Methadone has also been used as an adjunct opioid (typical initial dose 1 mg nocte) (Mott 2018 **Level IV**, n=16). QT_c prolongation in small case series without complication has been reported; the clinical significance is unclear (Madden 2019 **Level IV**, n=42; Madden 2017 **Level IV**, n=25; Anghelescu 2016 **Level IV**, n=37). There are single case reports of hypoglycaemia (Gjedsted 2015 **CR**) and central sleep apnoea (Amos 2013 **CR**) in children with cancer on methadone. For further discussion re methadone also adult Section 4.3.1.

IV bisphosphonates (mostly zoledronate) have been used for pain related to bone metastases and primary bone malignancies (Anghelescu 2019a **Level IV**, n=35).

Lidocaine infusions can be considered in patients with cancer pain that is refractory to opioid escalation (Berde 2016 **NR**). However it has a narrow therapeutic range and is not titratable to pain intensity; infusion rates >2 mg/kg/h (33 mcg/kg/min) or plasma concentrations >6 mcg/mL are likely to carry a substantial risk of seizures, and many factors (eg hepatic or renal dysfunction) may confer risk at lower infusion rates or plasma concentrations (see also 10.4.11 Systemic lidocaine infusions).

Epidural and subarachnoid infusions (mostly opioid, local anaesthetic and/or baclofen), through a tunnelled indwelling catheter connected to an external pump, are the most commonly reported regional techniques for invasive tumour pain, where systemic analgesia has become ineffective or intolerable (Rork 2013 **NR**). Fully implantable systems have been used in adolescents (Rork 2013 **NR**; Bengali 2014 **CR**). Other reported regional techniques include local anaesthetic delivered by tunnelled femoral nerve and brachial plexus catheters (Rork 2013 **NR**). Neuro-destructive techniques, such as coeliac plexus or splanchnic nerves blocks with neurolytic agents (Rork 2013 **NR**), surgical cordotomy (Steel 2017 **CR**) and stereotactic mesencephalotomy (Ivanishvili 2016 **CR**) have been reported.

Neuropathic pain

Neuropathic pain in children is often treatment-related (see below); cancer-related neuropathic pain usually occurs with invasion or compression of nerves, plexus or spinal cord (by sarcomas) or following limb-sparing surgery (Collins 1995 **NR**). It requires multimodal and adjuvant therapy (alpha-2-delta ligands, antidepressants and opioids; see respective sections in adult Section 4 and paediatric 10.4.4 and 10.4.9) including nonpharmacological approaches (see Section 10.7.5)

with physiotherapy and psychology (Friedrichsdorf 2014 **NR**; Anghelescu 2014 **Level IV**). Methadone has been used in the acute setting for new onset neuropathic pain, to assist weaning and postoperatively (Anghelescu 2011a **Level IV**).

Nonpharmacological interventions

Various nonpharmacological therapies have been studied in children and adolescents with cancer pain including creative art therapy (1 RCT), aromatherapy (1 study), physical activity (1 study), massage and touch therapy (3 studies) (Jibb 2015 **Level IV SR**, 32 studies [6 cancer pain], n=1,171 [n=143 cancer pain]) and scrambler (TENS-like) therapy (Park 2017a **CR**) with mixed results.

A web-based intervention (C-TIPS) delivering information to carers of children with cancer in their home focussed on pharmacological and nonpharmacological pain management and coping strategies (Chung 2018b **Level IV**, n=30). An electronic tablet device in 8–18 y olds (Fortier 2016 **Level IV**, n=12) and a smart phone application in 12–18 y olds (Jibb 2017 **Level IV**, n=40) aimed at children and adolescents with cancer-related pain have been developed to provide real-time pain self-management support.

10.8.1.2 | Pain in the terminal stages

In the terminal stages of cancer, pain is common (Wolfe 2015 **Level IV**, n=104; Goldman 2006 **Level IV**, n=185; Wolfe 2000 **Level IV**, n=103) and poorly managed pain is associated with higher levels of long term parental grief (van der Geest 2014 **Level IV**, n=89; Kreicbergs 2005 **Level IV**, n=449). Feeding back to patients, families, and health providers of self- and carer-reported child symptoms and health-related quality of life did not improve child distress or health-related quality of life (Wolfe 2014 **Level II**, n=90, JS 3).

Opioid requirements may escalate (Hewitt 2008 **Level IV**, n=185; Sirkia 1998 **Level IV**, n=100), and benefit has been reported with the use of PCA opioids to allow rapid dose titration (Anghelescu 2015b **Level IV**, n=159; Schiessl 2008 **Level IV**), with the addition of low dose IV ketamine infusion (Taylor 2014 **Level IV**, n=14; Finkel 2007 **Level IV**, n=11) and intervention with continuous nerve catheter infusions (Anghelescu 2010 **Level IV**, n=10) (see Sections 10.4.5, 10.5 and 10.6). Outpatient PCA opioids have also been administered (using the Computerised Ambulatory Drug Delivery device CADD), enabling children to stay at home during the terminal stages of their illness (Mherekumombe 2015 **Level IV**, n=37 [33 cancer]; Anghelescu 2015c **Level IV**, n=45). Methadone has been used in small series of children/young adults with cancer for terminal care and pain unresponsive to escalation of other opioids (Mott 2018 **Level IV**, n=16; Anghelescu 2011a **Level IV**; Davies 2008 **Level IV**).

10.8.2 | Procedure-related pain

Children, their parents, physicians and nurses all rate procedural interventions and treatment as a significant source of pain (Ljungman 1999 **Level IV**; Ljungman 1996 **Level IV**). Multiple diagnostic and therapeutic interventions are required during the course of treatment and require pain management matched to the procedure type and needs of the child.

10.8.2.1 | Lumbar punctures, bone marrow aspirations, blood sampling

See Sections 10.7.2 for pharmacological intervention and 10.7.5 for nonpharmacological intervention used in paediatric oncology care.

10.8.2.2 | Central venous port access

For pain relief during central venous port access in children with cancer, EMLA® was evaluated as superior to placebo (Miser 1994 **Level II**, n=47, JS 5). When added to topical anaesthesia with EMLA® for port access, neither PO morphine 0.25 mg/kg (Heden 2011 **Level II**, n=50, JS 5) nor PO paracetamol 40 mg/kg (maximum 2 g) (Heden 2014 **Level II**, n=51, JS 5) impacted upon pain, fear and distress scores, which were equally low in placebo treated patients. Outcomes for second and subsequent procedures were improved if adequate analgesia was provided for the first procedure (Weisman 1998 **Level III-2**). Individual studies suggest various modes of distraction (eg virtual reality, bubble blowing, book reading) are equivalent or superior to active controls for port access (4 studies [age 2–19 y]) (Jibb 2015 **Level IV SR**, 32 studies, n=1,171).

Parents showed increased non-verbal caring behaviours with repeated port access procedures (Bai 2018 **Level IV**, n=43 [105 procedures]), which can reduce child distress during the procedure (Bai 2017 **Level IV**, n=43).

10.8.3 | Treatment-related pain

Pain during active treatment is common (Levine 2017 **Level IV**, n=258), worse than post-treatment pain (Tutelman 2018 **Level IV**, n=230), and a source of high distress and suffering to children with cancer (Levine 2017 **Level IV**, n=258; Ljungman 2000 **Level IV**; Collins 2000 **Level IV**). Parental acceptance of pain has been shown to predict decreased child distress, and an instrument to measure parental acceptance of pain during their child's treatment has been developed (Thorsell Cederberg 2017 **Level IV**, n=243). Parental trait anxiety predicts a higher frequency of parent-reported pain episodes, lower child health-related quality of life and increased parental solicitous behaviours (Link 2016 **Level IV**, n=353 [parents] & n=137 [children]).

10.8.3.1 | Mucositis

Oral mucositis is a common painful condition occurring in 52–80% of children receiving chemotherapy (Mazhari 2019 **Level III-3 SR** [PRISMA], 9 studies, n=504; He 2018 **Level III-3 SR** [PRISMA], 8 studies, n=373). It can be difficult to assess (Tomlinson 2008 **NR**), and is a frequent indication for IV opioid therapy. Opioid requirements are often high and escalate with the severity of mucositis (Coda 1997 **Level II**, n=119, JS 5; Dunbar 1995 **Level IV**).

Opioids

A systematic review concludes that morphine by PCA or continuous infusion provides similar analgesia (no difference in pain scores), and PCA use results in reduced hourly and overall morphine intake and duration of pain by 1.9 d (95%CI 0.25 to 3.5) with a stated concern of bias due to drop out rates in these studies (Clarkson 2010 **Level I** [Cochrane], 3 RCTs [1 paediatric], n=184). PCA morphine and pethidine (Oudot 2011 **Level II**, n=29, JS 5) and PCA morphine and hydromorphone had similar efficacy (Collins 1996 **Level II**, n=10, JS 4) but PCA sufentanil was less effective than PCA morphine or hydromorphone (Coda 1997 **Level II**, n=199, JS 5). Prolonged administration is often required (6–74 d) (Dunbar 1995 **Level IV**). If excessive or dose-limiting adverse effects occur, rotation to another opioid (morphine to fentanyl or fentanyl to hydromorphone) can produce improvement in the majority of patients, without loss of pain control (Drake 2004 **Level IV**).

Ketamine

Ketamine 20–40 mcg/kg/mL improved pain scores when added to PCA/NCA morphine (James 2010 **Level IV**) and also decreased morphine consumption when patients were requiring ≈1 mg/kg of morphine per day (White 2011 **Level III-3**). In a small case series of children with mucositis,

topical morphine 0.025–0.4 mg/kg was used in a dose-response study and reduced pain scores by ≥36% in six of seven children (Nielsen 2012 **Level IV**). Plasma levels were low, suggesting minimal systemic absorption.

Laser and photodynamic therapy

Low level laser therapy for oral mucositis, both as a prophylactic and therapeutic intervention in children and adolescents (<18 y) has been shown to be effective, however its effect on pain from oral mucositis is variably reported and unclear (Mazhari 2019 **Level III-3 SR** [PRISMA], 4 studies [low level laser therapy], n=504 [n=244]; He 2018 **Level III-3 SR** [PRISMA], 8 studies, n=373) (8 study overlap). Photodynamic therapy (methylene blue + low level laser therapy) was not superior to low level laser therapy alone in children (<18 y) (Ribeiro da Silva 2018 **Level II**, n=29, JS 3).

Honey

Honey was not superior to control for moderate to severe mucositis in teenagers, despite showing benefit in adults (Yang 2019 **Level I** [PRISMA] [NMA], 17 RCTs [5 paediatric], n=1,265 [276 paediatric]).

Cryotherapy, cytokines and growth factors

Systematic reviews on the use of cryotherapy (Riley 2015 **Level I** [Cochrane], 14 RCTs [1 mixed adult and children], n=1,280) and cytokines and growth factors (Riley 2017 **Level I** [Cochrane], 35 studies [4 paediatric], n=3,102) for the prevention of mucositis found insufficient evidence to support their use in children and adolescents.

Other therapies

Palifermin (IV keratinocyte growth factor) reduced the incidence (OR 4.1; 95%CI 2.4 to 7.0) (5 studies) and severity (SMD 0.64; 95%CI 0.30 to 0.97) (3 studies) of oral mucositis in children (<18 y) (Mazhari 2019 **Level III-3 SR** [PRISMA], 9 studies [5 palifermin], n=504 [n=260]) and one RCT found that Mucosyte® mouthwash (verbascoside, polyvinylpyrrolidone, sodium hyaluronidate) vs placebo reduced pain intensity (D 3 median 1/10 vs 2; D 8 median 0/10 vs 1) and analgesic requirements in 5–18 y olds with mild to moderate oral mucositis (Bardellini 2016 **Level II**, n=56, JS 3).

There is limited evidence in children that topical vs ingested vitamin E improved mucositis (1 RCT, n=40), while debridement in addition to standard care reduced severity and days to resolution (1 RCT, n=80) (Clarkson 2010 **Level I** [Cochrane], 32 RCTs [4 paediatric], n=1,505 [n=176]).

For further reading, see adult section 8.9.8.2 regarding acute mucositis pain.

10.8.3.2 | Neuropathic pain

Neuropathic pain during treatment can occur acutely secondary to chemotherapy, where it may be dose limiting (eg vincristine) or after surgery (Anghelescu 2019b **NR**). It may be more common than expected and poorly documented. In an adolescent and young adult cohort (13–39 y, median 18 y) screened for neuropathic pain, 26% of patients receiving treatment and 11% post treatment had neuropathic pain, and only 26% had the diagnosis documented in their medical record (Acquazzino 2017 **Level IV**, n=78). Of patients undergoing definitive surgery (amputation or limb sparing, mostly lower limb) for osteosarcoma, 81% were diagnosed with neuropathic pain (based on pain descriptors eg tingling, burning, shooting and pins and needles); mean duration of documented neuropathic pain was 6.5 wk (Anghelescu 2017 **Level IV**, n=37).

Gabapentin (reported doses ≈10–45 mg/kg/d) and amitriptyline or nortriptyline (reported doses ≈0.3–0.45 mg/kg/d) are the recommended first line agents for neuropathic pain in children with cancer; reported doses are typically lower than in adults (on a per kg basis) (Anghelescu 2019b **NR**). Opioids (Windsor 2019 **NR**) including methadone, ketamine infusions and lidocaine (patch or infusion) (Anghelescu 2019b **NR**) have also been used, as have multimodal interventions including

pharmacological (mostly with an opioid and gabapentin) and nonpharmacological therapy (Anghelescu 2014 **Level IV**, n=66).

Anti-glycolipid disialoganglioside (GD)-2 agents (typically given over 10–20 h/d for several days) have improved outcomes in patients with high-risk neuroblastoma. However, neuropathic pain (thought to be due to complement activation) during infusion can be severe and dose limiting. Morphine by NCA/PCA (Ari 2018 **Level IV**, n=16) and hydromorphone/dexmedetomidine infusions (Gorges 2015 **Level IV**, n=6) have been used in a ward environment to manage this neuropathic pain. Anti-GD2 therapy with Hu14.18K322A monoclonal antibody that causes less complement activation resulted in lower opioid requirements over 4 d (IV morphine equivalent, median 1.57 mg/kg vs 2.41) (Anghelescu 2015a **Level III-3**, n=28).

10.8.3.3 | Postoperative pain

Postoperative pain related to surgical procedures for diagnostic biopsies, insertion of long term IV access devices and tumour resection is also a frequent source of treatment-related pain. Analgesic intervention using all modalities including preoperative gabapentin and postoperative wound and CPNC local anaesthetic infusions have been described for limb salvage surgery (Anghelescu 2010 **Level IV, ** n=150) and for upper limb forequarter amputation (Kaddoum 2013 **Level IV**, n=4). Subsequently, in children and adolescents (10–17 y) having a lower limb amputation for osteosarcoma, perioperative gabapentin (300 mg three times daily for 30 d) (as part of a multimodal analgesic regimen) vs placebo resulted in similar reduction of early perioperative pain scores, and reduced the incidence of phantom limb pain at 60 d postoperatively (43% vs 77%) (Wang 2018 **Level II**, n=45, JS 5). (See also adult Section phantom limb pain 8.1.5)

In children with cancer requiring morphine infusions, the highest rate of breakthrough pain was found in postoperative cases, of which 92% had solid tumours (Flogegard 2003 **Level IV**). In children with thoracic, abdominal or lower limb cancer, supplemental IV opioid boluses (either nurse-administered or via PCA) were safely combined with epidural bupivacaine and fentanyl infusion to control postoperative pain. Of 117 patients, 1 developed respiratory depression (due to a dosing error) but patients were closely monitored and had pre-existing tolerance to opioids (Anghelescu 2008 **Level IV**).

10.8.3.4 | Vertebral compression fracture

Balloon kyphoplasty has been used to manage intractable pain in teenagers from vertebral compression fractures secondary to chemotherapy and steroid-induced osteoporosis/ osteopaenia (Hoashi 2017 **Level IV**, n=3). For further reading, see adult Section 8.9.7.6.

KEY MESSAGES

1. PCA and continuous opioid infusions are equally effective in the treatment of pain in mucositis in children, but opioid consumption and duration of pain is less with PCA (**U**) (**Level I** [Cochrane Review]).
2. Topical local anaesthetic application for children having central venous port access is effective and analgesia is not further improved by oral analgesics (morphine or paracetamol) (**U**) (**Level II**).
3. Self-reported pain scores by children with cancer were higher in intensity compared with nurse-reported pain scores, with variable agreement with parent/carer-reported pain scores (**N**) (**Level III-2 SR**).
4. There is limited evidence that low-level laser therapy reduces the severity of mucositis in children (**U**) (**Level III-2 SR** [PRISMA]).
5. QT interval prolongation with methadone in children with cancer has been reported without complication; the clinical significance is not clear (**N**) (**Level IV**).
6. Poorly managed pain in children during the terminal stages of cancer is associated with higher levels of long term parental grief (**N**) (**Level IV**).
7. Outpatient intravenous PCA opioid has been used to help children in the terminal stages of cancer stay at home (**N**) (**Level IV**).
8. Transdermal fentanyl patch use may be appropriate in opioid tolerant children with cancer (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ In paediatric cancer pain management, the same therapeutic approaches as in adults are used, although evidence is limited (**U**).

☑ The World Health Organization has removed codeine from the management approach to paediatric cancer pain reducing the number of tiers from three to two: with tier one including nonopioid analgesics and adjuvants and tier two including strong opioids; in 2019 the WHO withdrew the reference document, but it remains endorsed by organisations throughout Australia, New Zealand and internationally until it is replaced (**Q**).

☑ Caution must be taken during uptitration of transdermal systems due to the pharmacokinetic profile of transdermal delivery that has slow penetration and delayed uptake from the stratum corneum (**N**).

10.9 | Other acute pain conditions in children

10.9.1 | Management of pain due to trauma in children

10.9.1.1 | Early and prehospital trauma pain

Prehospital care of paediatric patients suffering moderate to severe trauma is administered by a range of people with varying levels of healthcare expertise including parents, carers or family members, childcare or school staff, and emergency medical services. The provision of first aid is an important component of pain management. Administration of analgesics (and sedatives) by emergency medical services is strongly recommended (ACEP 2016 **GL**; Gausche-Hill 2014 **GL**). Despite this, and evidence that it is effective, administration of analgesia for moderate to severe trauma in the prehospital setting is reported to be low. In a systematic review on the efficacy and safety of analgesics used for injured children and adolescents (<18 y) in the prehospital setting only a descriptive review was possible (Samuel 2015 **Level IV SR**, 19 studies [13 paediatric, 6 mixed adult/paediatric], n>67,287). The authors made the following conclusions:

- Overall rates of analgesic administration were low;
- Fentanyl 1-3 mcg/kg (route unspecified) had an accepted efficacy, and although other analgesics have a documented benefit (eg morphine, methoxyflurane, nitrous oxide), no comparisons could be made;
- Rates of reported adverse effects in studies and large case series are low, but there is insufficient evidence to assess the safety profile of analgesics in this setting.

Further studies report variable documentation of pain assessment (18-81%) and consistently low administration rates of any analgesics (6.4-45%), despite a high prevalence of moderate to severe pain intensity (up to 74%) when it is documented (Browne 2016a **Level III-3**, n=7,340; Hewes 2018 **Level IV**, n=276,925; Schauer 2018 **Level IV**, n=3,439; Lord 2016 **Level IV**, n=38,167; Murphy 2016a **Level IV**, n=6,371; Rutkowska 2015 **Level IV**, n=1493; Johnson 2014 **Level IV**, n=5,057). There were two exceptions, where an ambulance service gave an analgesic agent to 79−92% of children (<15 y) who reported pain (Jennings 2015 **Level IV**, n=15,016; Galinski 2011 **Level IV**, n=433). Younger age (Hewes 2018 **Level IV**, n=276,925; Lord 2016 **Level IV**, n=38,167; Murphy 2016a **Level IV,** n=6,371; Johnson 2014 **Level IV**, n=5,057; Watkins 2006 **Level IV**, n=45), and in two USA studies, non-white ethnicity (Hewes 2018 **Level IV**, n=276,925; Johnson 2014 **Level IV**, n=5,057) were associated with less pain score documentation and provision of analgesics.

Children (≤17 y old) compared to adults were less likely to have their pain assessed (OR 0.80; 95%CI 0.76 to 0.85) (Ramgopal 2018 **Level III-2**, n=371,746) and be administered opioid analgesia by an ambulance service (Bendall 2011b **Level III-2**, n=97,705; Hennes 2005 **Level III-2**, n=5,383). A further study found factors associated with opioid administration in children were vascular access (OR 11.89; 95%CI 7.33 to 19.29), longer patient transport time (OR 1.07; 95%CI 1.04 to 1.11) and pain score documentation (OR 2.23; 95%CI 1.40 to 3.55) (Browne 2016b **Level IV**, n=1,368).

Barriers to managing acute pain in children identified by paramedics include concern/difficulty administering analgesia (by IV, PO or inhalational route) to a distressed and uncooperative child, difficulty assessing pain in children, limited education, training, and experience managing children, as well as risk of adverse reactions with analgesics (Whitley 2017 **Level IV**, n=127; Rahman 2015 **Level IV**, n=191; Murphy 2014a **Level IV**, n=16; Williams 2012 **Level IV**, n=16; Watkins 2006 **Level IV**, n=52 [surveyed]).

Self-reported self-efficacy scores in ambulance officers for assessing pain in toddlers and children improved immediately following the implementation of a pain management protocol (self-report pain scale and analgesic dosing guide) in one RCT, with some improvement

maintained 13 mth later (Jaeger 2017 **Level II**, n=264, JS 2). Education combined with protocol implementation was not superior to protocol implementation alone. However, an attempt to improve the assessment of pain and provision of analgesia by implementing prehospital pain management protocols (use of age appropriate pain scales, decreased minimum age for opioid administration and updated fentanyl dosing) was unsuccessful in another study (Browne 2016a **Level III-3**, n=7,340).

The most commonly reported analgesics used by Australian prehospital emergency medical services for children and adolescents with acute pain were inhaled methoxyflurane, IN fentanyl and IV morphine; all have been found to be effective analgesics in this setting (Bendall 2011a **Level III-2**, n=3,312; Murphy 2017 **Level IV**, n=94; Lord 2016 **Level IV**, n=38,167; Jennings 2015 **Level IV**, n=15,016; Babl 2006 **Level IV**, n=105). The most frequently administered analgesic was methoxyflurane with one study reporting no serious adverse effects with its use; mild adverse effects occurred in 36% (mostly drowsiness) with deep sedation occurring in 33% of patients under 5 y (Babl 2006 **Level IV**, n=105). Ketamine has also been used with doses of 0.25−1 mg/kg via IV and IN routes and a higher IM dose of 5 mg/kg (Schauer 2018 **Level IV**, n=3,439; Bredmose 2009a **Level IV**, n=164). IN S-ketamine 0.45−1.25 mg/kg has been used in 7−17 y olds (Johansson 2013 **Level IV**, n=6 [paediatric]).

In children with acute pain (mostly from limb injury) presenting to the ED, the majority of parents and carers (72-78%) reported trying to manage their child's pain, but only 28-56% administered an analgesic (Conrad 2019 **Level IV**, n=338; Whiston 2018 **Level IV**, n=743; Rogovik 2007a **Level III-2**, n=310; Maimon 2007 **Level IV**, n=214). Reasons reported for not giving analgesics included concern about masking signs and symptoms, the child not showing signs of pain, not wanting to delay being seen by a physician, no analgesics available and did not have time (Conrad 2019 **Level IV**, n=338; Whiston 2018 **Level IV**, n=743; Maimon 2007 **Level IV**, n=214).

10.9.1.2 | Trauma pain in hospital

The majority of literature on hospital management of paediatric trauma focuses on ED management of isolated limb injuries; literature on multi-trauma pain management is limited. This section is on management of pain from a traumatic injury; for management of procedural pain with closed fracture reduction or laceration repair see Section 10.7.4.

Multi-trauma

In children and adolescents (<18 y) with severe trauma (injury severity score [ISS] 12/75), only 32% received analgesia during resuscitation in the ED (mostly opioids; 67% during primary survey) (Anantha 2014 **Level III-2**, n=203). Patients who received analgesia vs those who did not were more likely to be in a car accident (58% vs 42), and have parents present during resuscitation (17% vs 6), had a higher median ISS (22/75 vs 17), shorter duration in the ED (141 min vs 195) and longer ICU (median 3 d vs 1) and hospital stay (median 6 d vs 4).

Isolated limb injuries

For children with suspected fractures presenting to the ED, fast-tracking is occurring to facilitate rapid analgesic administration and direct referral for X-ray from triage. To avoid the distress associated with IV access or IM injection, alternative administration routes for analgesics are being increasingly used in this setting. Despite this, reported analgesic administration is variable. In children and adolescents (3–18 y) with a limb or clavicle area injury (62% fractures), analgesic administration rate was low (29%) and sufficient analgesia (assessed as adherence to protocol for paediatric ED analgesia) was only prescribed in 16.4% of patients; the median time to initiation of an analgesic medication after arrival in the ED was 2 h (Rogovik 2007a **Level III-2**, n=310). In children and adolescents (<18 y) with a closed long bone fracture, mean time to first analgesia was 70 min, and severity of pain assessed at triage did not influence the provision of

analgesia (Weng 2010 **Level IV**, n=211). In a cohort of children and adolescents (<18 y, 90% with extremity fracture) presenting to USA EDs, 72% received analgesia, and 55% of these patients received opioids; younger age (<3 y) and children who were admitted to hospital were less likely to receive analgesics in the ED (Yackey 2018 **Level IV**, n=1,341). Further evidence suggests younger children may be at increased risk of poorly managed pain: when presenting to the ED with an isolated painful injury (82% long bone fracture), infants (6–24 mth) vs school age children (6–10 y) were more likely to receive no analgesia (65% vs 48) and less likely to receive opioid analgesia (17 vs 44%) (Alexander 2003 **Level III-2**, n=180).

Ethnicity, and its association with pain and its management in the ED has been assessed. In children (mean age 7.6 y) with a long bone fracture presenting to two USA EDs, mean initial pain scores were not statistically different across ethnic groups (4.7–7/10), except for patients who identified as Somali, who reported lower pain scores (4/10) (Ortega 2012 **Level IV**, n=880). In the same cohort, patients were less likely to receive a discharge prescription for an opioid analgesic if they identified as biracial (RR 0.45), African-American/non-Hispanic (RR 0.59) or Hispanic/Latino (RR 0.61) vs patients who identified as white/non-Hispanic (Ortega 2013b **Level IV**, n=878). In Northern Israel, Arabic and Jewish patients (3–15 y olds) presenting to a paediatric ED with severe pain (7/10) from a fracture or dislocation received opioid analgesia at similar rates (99%, mostly PO oxycodone) through a nurse driven pain protocol; ethnicity of the nurse did not influence opioid administration (Shavit 2016 **Level III-2**, n=3,782).

In an ED, 91% of carers consented to their child (4–17 y; 70% musculoskeletal injury) receiving an analgesic (Whiston 2018 **Level IV**, n=743). Of those who refused, the most common reason was that their child refused the medication. Thus, carer refusal was not thought to be a major barrier to children's pain management in this context.

System interventions to improve pain management have been studied with mixed results:

- A physician pain reminder (pain scale form added to chart) did not enhance the prescription of analgesics to children and adolescents (3–18 y) with a limb or clavicle area injury (62% fractures, mean pain score on arrival: 4.4/10) (Rogovik 2007b **Level III-2**, n=310);
- In children (mean age 6 y) presenting to the ED with a supracondylar fracture, implementation of a medical directive to triage nursing staff (to assess and document pain scores and administer paracetamol or ibuprofen for pain 7/10) increased rate of analgesic administration within 60 min of presentation from 15 to 54% and reduced median time to analgesic administration from 72.5 min to 11 min; rate of opioid administration was not reported (Porter 2015 **Level III-3**, n=184). Increasing awareness of splinting through posters aimed at medical staff in the ED did not increase the rate of back slab application before X-ray (29% vs 33);
- A computerised reminder triggered with X-ray ordering increased splint application prior to X-ray (from 22% to 49) in patients (<16 y) with a forearm fracture requiring manipulation (Mills 2016 **Level III-3**, n=298). However, this did not change analgesia provision within the first hour of presentation;
- Implementation of a pain protocol for triage nurses to assess pain, document intensity and administer paracetamol for suspected long bone fractures reduced median time to first analgesia from 71.5 to 26 min; the initial analgesic was paracetamol in 52% (median time to paracetamol 20 min) and an opioid in 47% (77% IN fentanyl) (median time to opioid analgesia 29 min) (Schuman 2018 **Level III-3**, n=1,011).

Various combinations of opioids (PO, IN, or IV), sedatives, NSAIDs and paracetamol for fracture pain management in the ED have been studied; these studies are summarised below. Also see Section 10.4.4 Conventional and Atypical opioids.

Intranasal fentanyl

IN Fentanyl for fracture pain has been studied to assess its analgesic efficacy and speed of onset, whilst the effects of introducing an IN fentanyl protocol to the ED on quality of care has also been assessed:

- Following limb fracture, IN fentanyl 1–2 mcg/kg effectively reduces pain in the ED (Murphy 2014b **Level I** [Cochrane], 3 RCTs, n=313; Setlur 2018 **Level IV SR** [PRISMA], 6 studies [limb injury], n=2081; Mudd 2011 **Level IV SR**, 3 studies [limb injury], n=150) (2 & 2 study overlap). It is effective in the usual concentration 50 mcg/mL vs high concentration 300 mcg/mL (lower volumes required) (1 RCT, n=189), and is equivalent to IV (1 RCT, n=65) and IM morphine (1 RCT, n=45) with more rapid onset;
- IN Fentanyl 1.5–2 mcg/kg achieves similar pain score reduction to IN ketamine 1–2 mg/kg at 15–30 min; minor adverse effects (eg dizziness, bad taste) were less common with IN fentanyl (41–61% vs 78–100%)(Frey 2019 **Level II**, n=90, JS 5; Reynolds 2017 **Level II**, n=87, JS 3; Graudins 2015 **Level II**, n=80, JS 5).
- Introduction of an IN fentanyl protocol for suspected fracture pain reduced time to opioid analgesia vs IV morphine by 8.5–29 min (Schoolman-Anderson 2018 **Level III-3**, n=132; Schacherer 2015 **Level III-3**, n=94; Holdgate 2010 **Level III-3**, n=181; Borland 2008 **Level III-3**, n=617). Reduced rates of unnecessary IV cannulation (Schoolman-Anderson 2018 **Level III-3**) and length of ED stay (Schacherer 2015 **Level III-3**, n=94) were also reported;
- In a paediatric ED with an IN fentanyl pain pathway for children and adolescents (3–21 y) with a long bone fracture, where the pathway could have been utilised, 41% did not receive IN fentanyl, with consequences including unnecessary IV cannulation for IV morphine administration (Arnautovic 2018 **Level IV**, n=1,374).

Transmucosal/nebulised fentanyl

- Transmucosal (transbuccal) fentanyl 10–15 mcg/kg was equi-efficacious vs IV morphine 0.1 mg/kg over 15–75 min (Mahar 2007 **Level II**, n=95, JS 3);
- Nebulised fentanyl 3–4 mcg/kg was similarly effective vs IV fentanyl 1.5 mcg/kg (Miner 2007 **Level II**, n=41, JS 3) and vs IV morphine 0.1 mg/kg (Furyk 2009 **Level II**, n=77, JS 4) (both RCTs in Thompson 2016 **Level I** [PRISMA], 7 RCTs [2 paediatric limb injury], n=475 [n=118]).

Paracetamol, NSAIDs and oral opioids

- Ibuprofen for fracture pain in the ED was superior (Clark 2007 **Level** II, n=300, JS 3) or similar to (Friday 2009 **Level II**, n=68, JS 3) paracetamol/codeine and similarly effective to ibuprofen/codeine (Le May 2013 **Level II**, n=81, JS 5), oxycodone and oxycodone/ibuprofen (Koller 2007 **Level II**, n=66, JS 5);
- In a further study, children and adolescents (6–17 y) presenting to ED with a musculoskeletal injury (38% fracture) analgesia with PO morphine 0.2 mg/kg/ibuprofen 10 mg/kg vs morphine/placebo vs ibuprofen/placebo did not provide adequate analgesia in 70% of patients (Le May 2017 **Level II**, n=456, JS 5);
- PO oxycodone was more effective and produced less itching than codeine but early administration at triage was required as having X-rays, rather than examination or casting, was identified as the most painful period (Charney 2008 **Level II**, n=107, JS 5);
- PO morphine 0.5 mg/kg alone and combined with SL midazolam 0.2 mg/kg for displaced long bone fractures reduced pain scores similarly, but at the expense of increased sedation for 59% patients with combination treatment vs 23% with morphine alone (Wille-Ledon 2011 **Level II**, n=58, JS 5);

- SL Ketorolac 0.5 mg/kg vs SL tramadol 2 mg/kg were both effective for moderate to severe fracture pain; the lack of comparison with other analgesics limits the usefulness of this study (Neri 2013 **Level II**, n=131, JS 5).

See also paediatric Section 10.4.2 and adult Section 4.2.1 on NSAIDs, including effects on bone healing.

Diamorphine and hydromorphone

IN Diamorphine 0.1 mg/kg drops and spray provide rapid effective analgesia for fracture pain (Regan 2013 **Level III-3**, n=297; Kendall 2015 **Level IV**, n=226) with similar efficacy but more rapid onset vs IM morphine 0.2 mg/kg (Kendall 2001 **Level II**, n=404, JS 3). A pharmacokinetic study has been done of IV vs IN diamorphine in children with fractures (Kidd 2009 **PK**, n=24).

IN Hydromorphone 0.03–0.06 mg/kg has been used to treat acute pain (49% limb fracture requiring closed or open reduction) in the ED (Tsze 2019b **Level IV**, n=35)

Ketamine

IN Ketamine 1–2 mg/kg achieves similar pain reduction to IN fentanyl 1.5–2 mcg/kg but with more frequent minor adverse effects (see fentanyl section above) (Frey 2019 **Level II**, n=90, JS 5; Reynolds 2017 **Level II**, n=87, JS 3; Graudins 2015 **Level II**, n=80, JS 5). In children (3–13 y) with an isolated limb injury (75% fractures) and moderate to severe pain intensity at triage, IN ketamine (mean total dose 1 mg/kg) reduced pain scores from baseline to 30 min post ketamine (median 74.5/100 vs 30) which was maintained at 60 min (median 25/100) (Yeaman 2013 **Level IV**, n=28). All patients were rated as awake or mildly sedated (University of Michigan Sedation Scale 0–1), and minor side effects were common (dizziness 36%, bad taste 29%, dysphoria 14%).

Methoxyflurane (Penthrane®)

Although no longer used as an anaesthetic agent (Brown 2012 **NR**), methoxyflurane is available as a self-administered Penthrox® inhaler which dispenses 0.2–0.4% methoxyflurane (Medical Developments International 2001). In adolescents who presented with minor trauma and moderate pain to the ED, methoxyflurane was effective vs placebo (Coffey 2014 **Level II**, n=300 [90 adolescents], JS 5). In smaller series, methoxyflurane reduced pain scores associated with extremity injuries by 2.5–4.7/10 with high satisfaction, but did not provide analgesia for subsequent fracture manipulation (Grindlay 2009 **Level IV SR**, 6 studies, n=293) (see also Section 4.5.2).

Regional analgesia

The following studies have reported on the efficacy of regional analgesia for limb injuries in the ED and during hospital admission:

- Children and adolescents (15 mth−18 y) who received a fascia iliaca block with ropivacaine 0.5% (0.5–0.75 mL/kg) vs IV morphine 0.1 mg/kg for femoral fracture in the ED had a lower rate of failure of analgesia (failure to achieve pain score <4/10) 30 min post intervention, lower combined pain scores to 6 h (difference 15%; 95%CI 6 to 24%), and longer duration of analgesia (median time to next analgesic administration 313 min vs 60) (Black 2013 **Level II SR** [Cochrane], 1 RCT: Wathen 2007 **Level II**, n=55, JS 3);
- In patients (15 mth–22 y) presenting to a paediatric ED with a femoral fracture, 61% received a fascia iliaca compartment nerve block (FICNB; landmark technique) for pain management (Neubrand 2014 **Level III-2**, n=259). Those who received a FICNB/systemic analgesia vs systemic analgesia alone were older (median age 8.0 y vs 5.3), and in the 6 h post-intervention had lower pain scores (median 1/10 vs 2.5) and parenteral medication use (median doses 1 vs 2). There was no difference in the prevalence of adverse events, however, two patients receiving FICNB had seizures: one patient had an intracranial haemorrhage; the other resolved with intralipid;

- In patients presenting to ED with an isolated femoral fracture, single shot US-guided femoral nerve block vs systemic analgesia resulted in longer time to next analgesic dose (6.1 h vs 2.2), lower subsequent analgesic dose frequency (0.15 vs 0.30/h), and lower morphine requirements (6.5 vs 14.8 mcg/kg/h, route unspecified) (Turner 2014 **Level III-3**, n=81);
- A single shot femoral nerve block has been used for femoral fracture management in infants as young as 3 mth old (Frenkel 2012 **CR**);
- Continuous femoral nerve blockade in children (15 mth–14 y) with femoral fractures for up to 6 d has been used successfully (Johnson 1994 **Level IV**, n=23; Tobias 1994 **Level IV**, n=4).

Alpha-2-delta ligands

Pregabalin 1.25–2.5 mg/kg/d, as part of a multimodal analgesic regimen, has been used in a 4 y old girl with a severe crush injury requiring foot amputation (Wossner 2017 **CR**).

See also paediatric alpha-2-delta ligands Section 10.4.9.

10.9.1.3 | Trauma pain post-discharge

Nearly 60% of patients (mean age 7.6 y) presenting to two USA EDs with a long bone fracture were given an opioid prescription on discharge (Ortega 2018 **Level IV**, n=873). Socioeconomic status (measured by household income) did not influence this; however, the rate of over the counter analgesic (paracetamol and ibuprofen) prescription decreased as household income increased. In a similar cohort from the same centre, fracture severity and opioid discharge prescription provision were lower in younger children (<4 y), but in children requiring closed reduction of their fracture in the ED, analgesic discharge prescription did not differ with age (Ortega 2013a **Level IV**, n=877).

For fracture pain management post discharge from the ED, ibuprofen (either regularly or as needed) was similarly effective to paracetamol (Shepherd 2009 **Level II**, n=72, JS 3), paracetamol/codeine (Drendel 2009 **Leve II**, n=336, JS 5) and PO morphine (Poonai 2014 **Level II**, n=134, JS 5) with less minor adverse effects (eg nausea, vomiting, drowsiness) than codeine (30% vs 51) and morphine (31% vs 56).

Carer administered analgesia

For children (5–10 y) treated in the ED with an extremity or clavicle fracture, parent administered analgesia in the first two days post-discharge was low (65% received ≤1 dose/d) (Zisk 2008 **Level IV**, n=50). Analgesia administration correlated with parental postoperative pain scores on d 1 (r 0.41) and d 2 (r 0.23) and child pain report only on day 2 (r 0.22). However, active and loud behaviour tool items correlated more strongly with analgesia administration than the quiet withdrawn behaviours items suggestive of pain.

Both a web-based module and an online video were superior to standard of care (verbal instructions) in improving caregiver knowledge about pain management of a child's fracture but did not improve functional outcomes (eg number of school or carer work days missed) (Golden-Plotnik 2018 **Level IV**, n=311).

10.9.2 | Management of acute burn injury in children

Following the initial injury, burn patients experience both background and procedural pain; itch is also a significant symptom (Nelson 2019 **NR**). Higher acute pain intensity is associated with delayed re-epithelialisation (Brown 2014a **NR**) and may influence psychological outcomes. Some children require treatment throughout the rehabilitation phase including reconstructive

surgeries, and physical and occupational therapies for months or years, and may experience pain with these treatments (Nelson 2019 **NR**).

Children who sustain a burns injury in early childhood can have long term changes in somatosensory and pain processing, including reduced stress-induced activation of endogenous pain inhibitory mechanisms (Pardesi 2017 **NR**). Furthermore, on quantitative sensory testing, 9–16 y olds who had sustained a moderate burn injury (5–10% total body surface area, mostly 2nd degree) in infancy (6–24 mth) had altered responses to mechanical (increased detection threshold, lowered pain threshold, greater perceptual sensitisation), but not thermal (warm) stimuli. In contrast, severe burn injury (>10% total body surface area, mostly 2nd or 3rd degree) only showed perceptual sensitisation to a tonic heat stimulus and no difference in response to mechanical stimuli (Wollgarten-Hadamek 2009 **Level III-2**, n=72).

See also the adult Section 8.5.

10.9.2.1 | Early and prehospital burn pain

First aid measures reduce pain from burn injury in the initial stages (Varley 2016 **NR;** ANZBA 2014 **GL**). Placing the burnt area under cool running water for ≥20 min should be performed (up to 3 h post initial burn) with application of longitudinally (not circumferentially) placed thin film plastic "cling" wrap (or clean sheets, if unavailable). Additionally, analgesic medication is recommended as part of the initial resuscitation management of severe burns (ANZBA 2014 **GL**). In children and adolescents (0–15 y) admitted to a burns centre within 24 h of injury, pre-burn centre analgesic administration (paracetamol, NSAID and/or opioid) increased over time (68 to 79% from 2002–2004 to 2007–2008); flame burns and more extensive burns were predictors of receiving pre-burn centre analgesics, whilst transfer/referral by ambulance services or general practitioners were predictors of not receiving pre-burn centre analgesics (Baartmans 2016 **Level III-3**, n=622). In children (0–4 y) with burns, median pain scores reduced with treatment by an ambulance service (initial 6.5/10 vs final 1/10); in addition to nonpharmacological measures, 49% were administered analgesics (paracetamol, ibuprofen, methoxyflurane or morphine) by PO, IM, IV or inhaled routes (Fein 2014 **Level IV**, n=117). Most patients (83%) received no analgesia prior to ambulance arrival.

10.9.2.2 | Background burn pain

Psychological impact

The full impact of children and adolescents' acute pain experience whilst recovering from a burn injury is unknown, but it may influence psychosocial function both immediately and long term (Nelson 2019 **NR**). Burn injured children (8–17 y) who use internalisation as a pain coping strategy may be more vulnerable to the development of a long term anxiety disorder (Rimmer 2015 **Level IV**, n=187). Girls were more likely than boys to use internalisation or seeking social support as coping strategies, whilst children whose burn injury occurred at 10 y old were more likely to use information seeking and positive self-statements vs <5 y olds. Post-traumatic stress symptoms and post-traumatic stress disorder are common in youth following burn injury (18–25% prevalence) and can be observed in children as young as 12 mth (Nelson 2019 **NR**). In children and adolescents admitted to hospital with burn injuries, higher morphine doses during admission correlated with a reduction in post-traumatic stress symptoms over 3–6 mth in young children (age 1–4 y: r -0.32) (Stoddard 2009 **Level IV**, n=11), 6 mth in older children (age 6–16 y: r -0.44) (Saxe 2001 **Level IV**, n=24) and 4 y (age range 1.5–17.1 y; survival curves stratified according to number of opioid units and size of burn) (Sheridan 2014b **Level IV**, n=147). Separation anxiety, but not pain intensity, may be a mediator between increased morphine doses during admission and a reduction in post-traumatic stress symptoms 3 mth post burn injury (age 6–18 y) (Saxe 2006 **Level IV**, n=61).

Patterns of pain and analgesic prescribing practices

In 0–4 y olds with a small mean total body surface area burn (6.3%), observer-reported mean background pain scores were low. However, 21–28% of morning and afternoon pain scores were moderate for background pain and 25% had moderate and 66% severe procedural pain scores (de Jong 2014 **Level IV**, n=168).

A survey of burn centres treating children and adolescents (18y) found the most commonly used analgesics for inpatient background and breakthrough pain were: IV morphine (49–65%), paracetamol with codeine (41–52%) and paracetamol alone (29–49%); for outpatient pain management, paracetamol with codeine and paracetamol alone were most commonly used (Martin-Herz 2003 **Level IV**, n=111). Sustained release opioids were used in school age children and adolescents by 27% and 46% of respondents respectively, whilst antipruritics (mostly antihistamines) and anxiolytics were used in 53–66% and 17–40% of respondents across all age groups. Distraction was the most common nonpharmacological strategy used (36–67% of respondents), with other strategies including music/art therapy (27–29%), relaxation (13–42%) and massage (7–11%). In a survey of centres that care for critically ill paediatric burns patients, the most common sedatives and analgesics used were midazolam, fentanyl, morphine, ketamine and diphenhydramine; routine use of scoring systems to assess pain and sedation were common (90%), but only 63% of centres had a sedation policy, and only 54% of respondents reported noticing withdrawal signs and symptoms in their patient population (Singleton 2015 **Level IV**, n=41 [centres]).

Children and adolescents (mean age 5.3 y, range 0.5–16) with severe burns (mean total body surface area [TBSA] burned: 48.3%, range 10–95%) and ventilated in intensive care (mean duration 25 d, range 8–112) received morphine and midazolam infusions for background pain and anxiety which reached mean peaks of 0.40 mg/kg/h and 0.15 mg/kg/h respectively, on average 14 d after admission; at extubation, mean morphine and midazolam infusion rates were 0.22 mg/kg/h and 0.10 mg/kg/h respectively (Sheridan 2001 **Level IV**, n=28). Ketamine infusion (40–200 mcg/kg/h) as part of a multimodal analgesic regimen has been used for 37 d in a 9 y old with severe burns (White 2007 **CR**). IV clonidine has been used in an 11 y old burns patient as part of a multimodal analgesic regimen (Lyons 1996 **CR**).

Development and implementation of a paediatric pain and anxiety guideline resulted in adequate background and procedural pain and anxiety scores with no complications related to overmedication of patients (Sheridan 1997 **Level IV**, n=125).

Perioperative analgesia

Tumescent local anaesthesia (high volume/low concentration 0.05%–0.1% lidocaine: 7 mg/kg max) for surgical acute burn management resulted in all patients requiring no opioid or ketamine (0–24 h) postoperatively, and 80% of patients required no analgesia at all (Bussolin 2003 **Level III-3**, n=60). For burns contracture release surgery with lateral thigh donor sites, a single injection lateral femoral cutaneous nerve (LFCN) US-guided peripheral nerve block (PNB) and US-guided fascia iliaca compartment nerve block (FICNB) with continuous infusion reduced postoperative pain scores vs local anaesthesia infiltration in 6–9 y olds (Shank 2016 **Level II**, n=19, JS 3). Dual peripheral nerve catheters (axillary and sciatic) successfully managed postoperative pain for toe to hand transfer reconstructive surgery following severe burns in a 3 y old (Dadure 2004 **CR**). The combined bupivacaine maintenance infusion dose was 5 mg/kg/d for 48 h and serial plasma bupivacaine levels remained below toxic levels.

Procedural interventions

See Section 10.7.2.9

Subacute interventions

There was no difference in observer-rated pain scores in patients (5 wk–13 y) admitted to a burns unit having massage sessions with a carrier oil or aromatherapy oil vs standard nursing care (van Dijk 2018 **Level II**, n=284, JS 3).

Regular massage therapy (15 min twice a wk) vs standard treatment reduced the severity of pain, itch and less so state anxiety in adolescents (12–18 y) post burn over a 5 wk period (Parlak Gurol 2010 **Level III-2**, n=63).

Similar to previously published prevalence rates in paediatric non-burn populations, phantom limb pain following amputation for burn injury occurred in 38% of patients, where amitriptyline was commonly used (Thomas 2003 **Level IV**, n=34). See also adult Section 8.1.5.

10.9.2.3 | Pruritus

Pruritus is a common symptom following burn injury in children that often presents in the acute phase of recovery. A behavioural post-burn pruritus scale (Toronto Pediatric Itch Scale) has been developed for infants and children 5 y old (Everett 2015 **Level IV EH**, n=30 patients [3 raters]). A self-report tool (Itch man scale) has been validated in children 6 y old (Morris 2012 **Level IV**, n=45). In a cohort of paediatric burn survivors (mean age 7.8 y; mean TBSA 41%), pruritus was present in 93% at discharge with a mean intensity of 5.7/10, decreasing to 63% and 2.5/10 respectively at 2 y follow-up (Schneider 2015 **Level IV**, n=430). In a subsequent cohort, 72% of patients (13 y) reported itch following burns injury, predictors of itch included time since burn, depth of injury, TBSA burned and skin grafting (Nieuwendijk 2018 **Level IV**, n=413). In preschool children with minor burns (mean age 1.6 y; mean TBSA burn 4%) assessed within 32 d of injury, parents reported pruritus in 47%, with the majority (78%) being mild; weak correlations were found between pruritus and ethnic minorities (Black, Latino/Hispanic, Asian or other), greater TBSA of burn, and more days elapsed since burn (Stewart 2019 **Level IV**, n=256). Significant improvements in multiple outcomes following burn injury including itch and pain have been observed in children (mean age 7 y) over 2 y (Wurzer 2017 **Level IV**, n=167) and preschool children (<5 y) up to 4 y, with the greatest rate of recovery occurring in the first 6 mth (Kazis 2016 **Level IV**, n=456).

In addition to, or instead of antihistamines in paediatric burns (inpatient and outpatient settings), alpha-2-delta ligands reduced itch and pain: gabapentin 15 mg/kg/d (prescribed for 53% of patients) (Nieuwendijk 2018 **Level IV**, n=413) and 24–34 mg/kg/d (where 23 patients poorly responding to gabapentin had pregabalin 3.7–6.5 mg/kg/d added) (Kaul 2018 **Level IV**, n=136).

Evidence based guidelines for post-burn pruritus recommend cetirizine and cimetidine as first line and loratadine as second line peripherally acting agents, gabapentin as a first line centrally acting agent, and laser therapy and pressure garments as possible nonpharmacological interventions (Goutos 2010 **GL**). Combination therapy is commonly used and should be implemented in a judicious stepwise fashion that includes peripherally acting, centrally acting and nonpharmacological interventions early.

KEY MESSAGES

1. For paediatric trauma patients in the prehospital setting, frequency of administration of analgesics is low (**N**) (**Level IV SR**) and documentation of pain assessment is variable (**N**) (**Level IV**).
2. Intranasal fentanyl is equivalent to intravenous or intramuscular morphine in reducing pain associated with paediatric fracture presenting to the emergency department (**U**) (**Level II**).
3. Intranasal ketamine (1–2 mg/kg) achieves similar pain reduction to intranasal fentanyl (1.5–2 mcg/kg) for isolated limb fracture pain, but with an increased frequency of minor side effects (eg dizziness, bad taste) (**N**) (**Level II**).
4. The introduction of an intranasal fentanyl protocol for limb injury can reduce the time to first analgesia in the emergency department, compared to intravenous morphine (**N**) (**Level III-3**).
5. Single shot fascia iliaca compartment block is effective in managing femoral fracture pain (**N**) (**Level III-3**).
6. Methoxyflurane, intranasal or intravenous fentanyl and intravenous morphine are effective and commonly used prehospital to manage pain from trauma (**N**) (**Level IV)**; intravenous or intranasal ketamine is also an effective analgesic in the prehospital setting (**U**) (**Level IV**).
7. Younger children (<3 years) with an isolated limb injury receive less analgesia in the emergency department than older children (**N**) (**Level IV**).
8. In children and adolescents admitted to hospital with burns, higher morphine doses during admission predict reduced post-traumatic stress symptoms (**N**) (**Level IV**).
9. Pruritus following burn injury in children is common; predictors for pruritus include greater total body surface area of burn and greater number of days since burn injury (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Administration of analgesia by emergency medical services and emergency departments for trauma patients (including those with burns) is strongly recommended as part of the initial resuscitation along with first aid measures such as cooling and dressings for burns and splint application for trauma (**N**).

☑ Gabapentin and pregabalin are used to manage pruritus and neuropathic pain following burn injury in children (**N**).

10.9.3 | Paediatric migraine

Migraine is common in children: 9.1% over all age ranges, more prevalent in girls (10.5%) vs boys (7.6%); with increased prevalence in both female and male adolescents (aged >14 y) by 2.7% and 1.3% respectively (IHS 2018 **GL**; Wober-Bingol 2013 **Level IV**, n=210,524). However, headache is an infrequent presentation to the paediatric ED (1%) (Orr 2018c **NR**; Sheridan 2014a **NR)**. Of paediatric ED headache presentations, primary headache makes up 27–40%, and migraine accounts 34–74% of primary headaches (Hsiao 2014 **Level IV,** n=43,913; Conicella 2008 **Level IV**, n=55,273). Of migraineurs presenting to the ED, 85% of children and adolescents were discharged home; with low re-presentation rates: 5.5% return within 3 d (Bachur 2015 **Level IV**, n=32,124). Paediatric vs adult migraine may be shorter in duration (2–72 h vs 4–72 h), bilateral and typically frontotemporal (IHS 2018 **GL**; Sheridan 2014a **NR**). The general management principles of acute paediatric migraine are the same as for adults (see Section 8.6.5): environmental modification and nonpharmacological/psychological intervention should be considered (see below 10.9.3.3 and Section 10.7.5).

Guidelines for the treatment of migraine in children and adolescents acknowledge the lack of large paediatric efficacy and safety studies, summarise the same trials and make similar recommendations (Oskoui 2019 **GL**; Gelfand 2018 **GL**; Rastogi 2018 **GL**; NICE 2015 **GL**; Alfonzo 2015 **GL**; Sheridan 2014a **NR**). Triptan trials in children and adolescents have led to licensed use ≥6 y for rizatriptan in the USA and ≥12 y for the other triptans in the USA, Canada and Europe (Faber 2017 **NR**). The New Zealand and Australian product information statements (Medsafe and Australian Register of Therapeutic Goods) for the various triptans state there is inadequate data for children <18 y, without specifying a licensing age cut off.

The challenges in assessing efficacy of various agents include the high placebo response rate (eg 28–58% for pain freedom at 2 h), trials using different enrichment strategies (longer time since migraine diagnosed, longer duration of untreated headache [eg 4 h] and placebo administration with exclusion of placebo responders) and the use of different outcomes: headache relief vs pain freedom or if recurs vs relief of other symptoms (see below and also Section 8.6.5.2 for definitions of outcomes used in the below studies).

10.9.3.1 | Oral and Intranasal therapies

The evidence available for the standard of care first line abortive therapy using simple PO analgesia for acute paediatric migraine is limited. Trial data for triptans is of better quality; triptans (with NNT 6 for adolescents and NNT 13 for children) are recommended in most guidelines as either first line, in combination or second line abortive therapy.

A Cochrane review of acute migraine treatments in children (<12 y) and adolescents (12–17 y) assessing the primary outcome of pain freedom at 2 h post intervention is summarised below according to child vs adolescent age groups (Richer 2016 **Level I** [Cochrane], 27 RCTs, n=9,158):

Children (<12 y)

- Paracetamol 15 mg/kg is not superior to placebo (RR 1.40; 95%CI 0.75 to 2.58); there is no difference in headache relief, rescue medication use, headache recurrence or adverse events (1 RCT, n=88);
- Ibuprofen 7.5–10 mg/kg is superior to placebo (RR 1.87; 95%CI 1.15 to 3.04: NNT 4) (2 RCTs, n=172). It also improves headache relief (RR 1.49; 95%CI 1.11 to 2.00) (2 RCTs, n=125), but not rescue medication use (2 RCTs, n=164) or headache recurrence (1 RCT, n=38);
- Triptans are superior to placebo (RR 1.67; 95%CI 1.06 to 2.62: NNT 13) (3 RCTs, n=345). However, there was no difference in secondary outcomes of headache relief (3 RCTs,

n=345), rescue medication use (2 RCTs, n=145), nausea (3 RCTs, n=345), vomiting (3 RCTs, n=345) or adverse events (3 RCTs, n=420).

Adolescents (12–17 y)

- Ibuprofen has not been adequately assessed. One RCT found it is not superior to placebo for pain freedom at 2 h, headache recurrence, rescue medication or adverse events, but does achieve superior headache relief (RR 2.5; 95%CI 1.02 to 6.10) (1 RCT, n=32);
- Triptans are superior to placebo for pain freedom at 2 h (RR 1.32; 95%CI 1.19 to 1.47: NNT 6) (21 RCTs, n=6,761), but with increased minor adverse events (risk difference 0.13; 95% CI 0.08 to 0.18: NNH 8) (21 RCTs, n=7,876);
- Triptans are also superior to placebo for headache relief (RR 1.14; 95%CI 1.04 to 1.24) (20 RCTs, n=6,182), rescue medication use (RR 0.79; 95%CI 0.72 to 0.87) (18 RCTs, n=5,066) and headache recurrence (RR 0.79; 95%CI 0.68 to 0.93) (15 RCTs, n=2,463); there is no difference in nausea (RR 0.94; 95%CI 0.79 to 1.12) (17 RCTs, n=4,975) or vomiting (RR 0.73; 95%CI 0.48 to 1.12) (14 RCTs, n=4,037);
- Subgroup analysis reveals individual triptans are superior to placebo in achieving pain freedom at 2 h
    - PO Rizatriptan 5 mg (RR 1.34; 95%CI 1.13 to 1.60) (4 RCTs, n=1,438);
    - Sumatriptan PO 25, 50, 100 mg and IN 5, 10, 20 mg (RR 1.27; 95%CI 1.10 to 1.48) (10 RCTs, n=2,299);
    - Zolmitriptan PO 2.5, 5 , 10 mg and IN 0.5, 2.5, 5 mg (RR 1.66; 95%CI 1.16 to 2.38) (4 RCTs, n=1,480);
    - Whilst PO almotriptan (1 RCT), eletriptan (1 RCT) and naratriptan (1 RCT) have not demonstrated superiority to placebo;

The authors concluded it is not possible to recommend one triptan over another.

Subsequent to the above Cochrane review, in adolescents (12–17 y) IN zolmitriptan 5 mg vs placebo achieved pain-freedom at 2 h (30% vs 17), headache relief at 2 h (51% vs 39) and reduced rescue medication use up to 24 h post-treatment (20.3% vs 31.6) (Winner 2016 **Level II**, n=798, JS 4). Mild to moderate adverse events were more common with zolmitriptan (25.5% vs 9.9%); most commonly disturbed taste.

Three dose combinations of sumatriptan/naproxen (10/60, 30/180 and 85/500 mg) in adolescents (12–17 y) achieved pain freedom at 2 h for 29, 27 and 24% vs 10% of placebo treated patients (Derosier 2012 **Level II**, n=589, JS 5). The higher 85/500 mg dose has shown efficacy in two subsequent repeated use studies of adolescents (12–17 y) with recurrent migraine. When instructed to take early (within 1 h) vs placebo, pain freedom at 2 h was higher (37% vs 18); there was no difference in sustained pain-free response up to 24 h (86% vs 78), but more adverse effects (eg neck spasm/tightness, drowsiness, throat tightness) with sumatriptan/naproxen (10.8% vs 3) (Winner 2015 **Level II**, n=94 [347 migraines], JS 4). While in a case series, 42% achieved pain freedom at 2 h (McDonald 2011 **Level IV**, n=622 adolescents [12,957 exposures]).

Pharmacokinetics of triptans in adolescents

Iontophoretic sumatriptan patch (6.5 mg delivered over 4 h to upper arm or thigh skin) in adolescents (12–17 y) resulted in similar systemic exposure vs adults (Gutman 2016 **Level III-3 PK**, n=37). IN zolmitriptan (5 mg) in adolescents (12–17 y) and adults resulted in similar plasma concentrations of zolmitriptan and its active metabolite (Zhou 2017 **Level IV PK**, n=30). The authors used a simulation model to predict dosing in young children, but absorption kinetics from the smaller nasal mucosa is unknown making the model's clinical application questionable.

10.9.3.2 | Intravenous (IV) therapies

Intravenous (IV) therapies for acute childhood migraine are administered in the ED, outpatient infusion clinics or during inpatient admission. In practice, they are usually second or third line interventions in varying combinations given to patients who have not responded adequately to PO/IN intervention. Various medications and combinations have been reported as mostly level III and IV evidence making assessment of efficacy difficult.

Second line single and combination IV therapies

In 5–17 y olds, IV fluid bolus 10 mL/kg (0.9% sodium chloride) alone or with nurse administered placebo reduced migraine intensity 30 min post bolus (-12.5/100; 95%CI -17.2 to -7.8); expectation of additional drug treatment did not influence the effectiveness of IV fluid bolus (Richer 2014 **Level II**, n=47, JS 3). After failing at home treatments, IV prochlorperazine 0.15 mg/kg (max 10 mg) was superior to IV ketorolac 0.5 mg/kg (max 30 mg) in 5–18 y olds with complete resolution within 1 h in 85% vs 55% (SMD 30%; 95%CI 8 to 52%) (Brousseau 2004 **Level II**, n=62, JS 5).

When used in the ED for children and adolescents (<19 y) with ketorolac and usually diphenhydramine (given to 65–89%), treatment failure (defined as subsequent opioid administration) occurred less following IV prochlorperazine vs IV metoclopramide vs IV promethazine (8.7% vs 25 vs 43) (Sheridan 2018b **Level III-2**, n=67).

For paediatric patients, a standardised IV regimen including fluid bolus 20 mL/kg (0.9% sodium chloride: max 1 L)/ketorolac 0.5 mg/kg (max 30 mg)/prochlorperazine or metoclopramide 0.15 mg/kg (max 10 mg) or diphenhydramine 1 mg/kg (max 50 mg) vs a combination of various other regimens reduced pain scores (by 6.9/10 vs 5.3), ED LOS (4.4 h vs 5.3) and hospital admission rate (3% vs 32) without changes in ED return rate (Leung 2013 **Level III-3**, n=252). In 12–21 y olds who received an IV fluid bolus 20 mL/kg (± ketorolac), the addition of IV prochlorperazine (dose unspecified) vs IV chlorpromazine 0.1 mg/kg (max unspecified) had lower treatment failure (15% vs 40), hospital admission (4.7% vs 16) and rescue medication use (9.9% vs 29.3) (Kanis 2014 **Level III-3**, n=349).

In children, adolescents and young adults (mean age 15 y) attending an outpatient infusion centre, headache resolution was achieved 30 min post combination IV therapy with fluid bolus/ketorolac/metoclopramide or prochlorperazine and/or dexamethasone in 79% of visits; treatment success was less likely in those with increasing frequency of migraine headaches and medication overuse headache (Orr 2018b **Level IV**, n=543 [837 visits]). For severe migraine in <18 y olds, IV prochlorperazine 0.15 mg/kg (max 10 mg) and IV diphenhydramine 0.5 mg/kg (max 25 mg) administered in the ED resulted in a 14 and 21% treatment failure rate (further rescue therapy, hospitalisation or return visit to the ED within 48 h) (Trottier 2012 **Level IV**, n=79; Trottier 2010 **Level IV**, n=92). For 6–18 y olds with a step-up protocol dependent on medications taken prior, ED discharge rates were higher after intervention with combination IV ketorolac /IV antiemetic (prochlorperazine or ondansetron) (77% of 300 visits) vs IV ketorolac alone (56% of 39 visits) vs IV antiemetic alone (58% of 50 visits) vs PO or IN therapies (47% of 285 visits) (Aravamuthan 2017 **Level IV**, n=700 visits).

Third line IV therapies for refractory or status migrainosus

IV dihydroergotamine 0.1–1.0 mg/kg 6–8 hly and IV antiemetic (prochlorperazine, metoclopramide or ondansetron) administered to inpatients (<18 y) achieved complete or near complete headache resolution in 21–80% in 3 case series (Nelson 2017 **Level IV**, n=124 [145 admissions]; Kabbouche 2009 **Level IV**, n=32; Linder 1994 **Level IV**, n=30). Minor adverse effects were common (34–91%), including nausea and vomiting despite coadministered antiemetic therapy.

Mean length of stay was 3–3.7 d; one series reported mean admission cost of $US 7,569 (Nelson 2017 **Level IV**, n=145 [admissions]).

IV magnesium bolus 1–2 g max over 15–30 min administered in the ED substantially reduced pain severity in 35–48% of paediatric patients with severe migraine (Orr 2018 **Level IV SR**, 21 studies [2 magnesium IV, n=65]). See adult sections for NMDA antagonists Section 4.6.1.3 and Headache 8.6.5.1 and Migraine 8.6.5.2.

IV sodium valproate has been used in three case series: IV bolus 500–1000 mg in children and adolescents (<19 y) in the ED (Sheridan 2015 **Level IV**, n=12; Reiter 2005 **Level IV**, n=58) and IV bolus 20 mg/kg and infusion 1 mg/kg/h for 24 h in admitted children and adolescents (<18 y) (Zafar 2018 **Level IV**, n=83). In the first two series, pain scores reduced by a mean of 36 and 40% with low prevalence of minor adverse events (0 and 14%) eg dizziness and nausea. The third series reported complete resolution of migraine in 66% of patients, with nausea (8.4%) and vomiting (2.4%) the only adverse effects.

IV lidocaine (mean bolus 2.9 mg/kg and mean maximum infusion 1.6 mg/kg/h) administered in PICU for status migrainosus in children and adolescents (10–19 y) achieved 50% reduction in migraine pain intensity at 16.3 h (mean) with resolution at 19.3 h (mean) (Ayulo 2018 **Level IV**, n=31). Complete resolution occurred in 90.3% with one non-serious event (self-resolving chest pain and anxiety) and no serious side effects (see also Section 10.4.11 Systemic lidocaine infusions).

Low dose bolus IV propofol 0.25 mg/kg (1–5 doses) added to IV fluid bolus 20 mL/kg vs standard IV combination therapy of IV fluid bolus/ ketorolac 0.5 mg/kg (max 30 mg)/ diphenhydramine 1 mg/kg (max 50 mg)/metoclopramide 0.1 mg/kg (max 10 mg) in 7–19 y olds in the ED achieved similar pain reduction (51% vs 59) with less rebound headache at 24 h (7% vs 25) (Sheridan 2018a **Level II**, n=74, JS 2). This study was limited by the 5 minutely titration of propofol to a pain score of <4/10 and does not specify sedation scores or the mean dose or range given vs the fixed dosing of standard therapy.

10.9.3.3 | Nonpharmacological interventions for headache

Stress is considered a common trigger for headaches in children and adolescents (Bougea 2018 **NR**). Various preventive stress management strategies have been studied including yoga, relaxation therapy, biofeedback, hypnosis, massage therapy and acupuncture. Although many of these studies have positive results, their design is limited by small sample sizes, absence of controls and lack of follow-up. Whilst these strategies can be used for acute migraine management, many require skills that need to be developed with time and there is a literature gap on their use in this context.

Psychological interventions are effective as a preventive strategy for headache (Trautmann 2006 **Level I**, 23 RCTs [10 migraine/12 migraine & tension type/1 tension type only], n=999). Individual and group relaxation training, including progressive muscle relaxation (16 RCTs with 4 including stress/pain management strategies), biofeedback (7 RCTs) and cognitive behavioural therapy (10 RCTs) reduce the intensity of headache by ≥50% in 70% of adolescents vs 30% of waitlist controls. Treatment success is maintained for at least 1 y, although comparative efficacy with pharmacological treatments has not been investigated. An overlapping Cochrane review draws a similar conclusion for reduced headache frequency (RR 2.4; 95%CI 1.7 to 3.3) (15 RCTs, n=644) (Fisher 2018a **Level I** [Cochrane], 47 RCTs [23 headache], n=2,884) (14 RCT overlap). No impact on disability is demonstrated (6 RCTs, n=446). A meta-analysis on biofeedback only for prevention in paediatric (<18 y) migraine has been performed (Stubberud 2016 **Level I**, 5 RCTs, n=137) (1 & 3 RCT overlap). Biofeedback (EMG, peripheral skin temperature and blood-volume pulse biofeedback) vs waitlist control reduces migraine frequency (MD -1.97; 95%CI -2.72 to -1.21) (3 RCTs, n=72), attack duration (MD -3.94; 95%CI -5.57 to -2.31) (2 RCTs, n=48) and headache intensity (MD -

1.77/10; 95%CI -2.42 to -1.11) (2 RCTs, n=52), but is not superior to active treatment arms or effective as an adjuvant therapy.

Use of mind body techniques of transcendental meditation and hypnotherapy vs progressive muscle relaxation had similar reduction in headache frequency at 3 (37–44%) and 9 mth (42–53%) (Jong 2019 **Level II**, n=131, JS 3).

Following insertion of gold auricular acupuncture needles in 8–18 y olds presenting to the ED with severe migraine, mean pain scores reduced (from 7.63/10 to 0.55) only at 15 min, with 4 patients refusing treatment and 2 withdrawing post treatment initiation (Graff 2018 **Level IV**, n=19).

KEY MESSAGES

1. In children (<12 years), effective acute migraine treatments include ibuprofen and triptans (**Q**) (**Level I** [Cochrane]), however there is a significant placebo response rate in this setting.
2. In adolescents (12–17 years), triptans are effective acute migraine treatments, however there is a significant placebo response rate in this setting. One triptan cannot be recommended over another (**Q**) (**Level I** [Cochrane]).
3. Nonpharmacological preventive therapies including relaxation training and cognitive behavioural therapy reduce the frequency and intensity of headache in adolescents for 1 year (**S**) (**Level I** [Cochrane]). Biofeedback also reduces migraine attack duration (**S**) (**Level I**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Guidelines for the treatment of migraine in children and adolescents recommend environment modification, paracetamol, ibuprofen, naproxen (or other nonselective NSAIDs), dopamine antagonists (if nausea prominent), fluid therapy and triptans (**U**).

☑ Evidence is limited for standard of care second line therapies (single and multiple IV therapies including fluids and antiemetics) and third line therapies (such as IV dihydroergotamine, magnesium, sodium valproate, lidocaine or propofol) for acute childhood migraine (**N**).

☑ The use of psychological interventions and stress management strategies have not been assessed in acute migraine episodes; it must be recognised that many of these skills need to be developed over time (**N**).

10.9.4 | Acute abdominal pain in children

All medical causes of acute abdominal conditions are discussed in adult Section 8.6.1 (including renal and ureteral stones, biliary colic and acute pancreatitis, dysmenorrhoea, irritable bowel syndrome and colic). These also affect children and teenagers but are not reviewed separately here. The data for recurrent abdominal pain is presented below.

As for adults, early pain relief (usually in the form of opioids) does not interfere with the diagnostic process in acute abdominal pain in children (Green 2005 **Level II**, n=108, JS 5; Kim 2002 **Level II**, n=60, JS 5).

For abdominal pain associated with Henoch-Schonlein Purpura, see 10.4.10.1; and for the principles of management of abdomincal pain associated with haematological disorders see 10.9.5.

For CAMT interventions for infantile colic see Section 10.11.4.

10.9.4.1 | Recurrent abdominal pain (abdominal migraine)

Recurrent abdominal pain (RAP) or abdominal migraine presents to primary care and EDs and is functional and a diagnosis of exclusion (Brusaferro 2018 **NR**). It occurs usually in male school-aged children, sometimes adolescents, rarely in adults. RAP is characterised by recurrent attacks of acute abdominal pain, nausea, vomiting and often headaches.

There is currently no good evidence for the efficacy of any pharmacological treatment (tricyclic antidepressants, antibiotics, 5-HT4 receptor agonists, antispasmodics, antihistamines, H2 receptor antagonists, serotonin antagonists, selective serotonin re-uptake inhibitors, dopamine receptor antagonists, and hormones) in RAP in children (Martin 2017 **Level I** [Cochrane], 16 RCTs, n=1,024).

Probiotics are effective in improving pain in children with RAP vs placebo (NNT 8) (7 RCTs, n=722), however, based on moderate quality evidence (Newlove-Delgado 2017 **Level I** [Cochrane] 19 RCTs, n= 1,453). There is no convincing evidence that fibre-based interventions improve pain in children with RAP.

Cognitive Behavioural Therapy (CBT) (4 RCTs, n=175) and hypnotherapy/guided imagery (4 RCTs, n=146) reduce pain (in part or fully) in the short term (immediately to 1 or 3 mth) in children and adolescents presenting with RAP (Abbott 2017 **Level I** [Cochrane], 18 RCTs [10 CBT, 4 hypnosis], n=928).

KEY MESSAGES

1. Probiotics improve pain in children with recurrent abdominal pain versus placebo (**N**) (**Level I** [Cochrane Review]) with no good evidence for positive effect of various pharmacological treatments (**N**) (**Level I** [Cochrane Review]).
2. Cognitive behavioural therapy (CBT) and hypnotherapy reduce pain short term (over 1 to 3 months) in children and adolescents with recurrent abdominal pain (**N**) (**Level I** [Cochrane Review]).

10.9.5 | Acute pain associated with haematological disorders in children

10.9.5.1 | Sickle Cell Disease (SCD) in Children

Sickle cell disease (SCD) affects all age groups. Neonatal screening to reduce the global disease burden is routine in countries with high prevalence. As is the case for adults, there is interindividual variability in the impact upon paediatric patients. Hydroxyurea prophylaxis, transcranial doppler and red cell exchange transfusion programs have had positive benefit, reducing vaso-occlusive crises (VOC) and emergency department (ED) presentation frequency and mortality (Lovett 2017 **NR**; Yawn 2015 **GL**), with subsequent reduced need for in hospital pain service input. The majority of ED visits and hospital admissions for patients with SCD are pain related (Glassberg 2017 **GL**).

The principles of care are the same as for adults and involve individual care plans and step-up analgesic administration for at home and in hospital analgesic escalation, combined with simultaneous treatment of the precipitants of infection, dehydration and hypoxia (Glassberg 2017 **GL**; Yawn 2015 **GL**; NICE 2012 **GL**). Paediatric centres have developed clinical care pathways eg those from www.chop.edu/clinical-pathway/sickle-cell-disease-with-pain-clinical-pathway and (Kavanagh 2015 **Level III-2**, n=289 [ED visits for VOC]). With clinical pathway introduction in an urban paediatric centre, time to first analgesic medication, time to first opioid and use of IV ketorolac improved (Ender 2014 **Level III-2**, n=68). Early achievement of maximum opioid analgesia improved hospitalisation outcomes in children (Payne 2018 **Level III-3**, n=108 [236 admissions]).

See adult Section 8.6.4 Acute pain associated with haematological disorders.

Pharmacogenomics relevant to SCD

There is increased prevalence of poor CYP2D6 metaboliser phenotype in people of African descent. Children with sickle cell disease have had CYP2D6 geno-phenotyping where 44% had intermediate and 5.3% poor phenotype (Yee 2013 **Level IV**, n=75). This is an important consideration when choosing analgesic therapies for this patient group, where 27% of children ≤17 y with SCD have received codeine (Han 2018 **Level IV**, n=581 ≤ 19 y [opioid recipients]).

NSAIDs and opioid use in children with SCD

The use of an oral at home opioid protocol reduced the number of ED visits, time spent in the ED and hospital admissions over 12 mth for sickle cell pain (Conti 1996 **Level IV**, n=9; Friedman 1986 **Level IV**, n=15). Admission rates were lower following an initial paediatric ED intervention with nsNSAID/opioid combination vs opioid only (33% vs 64) (Cacciotti 2017 **Level III-3**, n=176). A paediatric ED treatment protocol administering PO paracetamol 15 mg/kg/ibuprofen 10 mg/kg/morphine 0.3 mg/kg for pain scores >5/10 reduced the number of patients requiring subsequent IV insertion for parenteral therapy, length of stay in the ED and hospital admission (Paquin 2019 **Level IV**, n=97 [147 visits]). Sustained-release PO morphine for children admitted with VOC was as effective as a continuous IV morphine infusion (Jacobson 1997 **Level II**, n=56, JS 5). However, in children treated with PO morphine vs IV morphine infusion, incidence of acute sickle chest syndrome and plasma concentrations of morphine and morphine-6-glucuronide (M6G) were significantly higher (Kopecky 2004 **Level II**, n=50, JS 4).

IV morphine PCA with bolus and background (mean 20 mcg/kg/h) has been used for children admitted with VOCs (Jacob 2008 **Level IV**, n=10 [48 admissions]). Postoperative PCA morphine requirements in children with SCD were almost double those of nonsickle children (Crawford 2006a **Level III-3**, n=22 [12 SCD]).

Acute kidney injury in SCD

Children with VOC with acute kidney injury had longer LOS; the risk of developing AKI increased for every additional day of ketorolac receipt (OR 1.63; 95%CI 1.08 to 2.47) (Baddam 2017 **Level III-3**, n=33 AKI patient events vs 164 without AKI).

Pruritus management related to opioid infusions

For children receiving morphine infusions for sickle cell crises, naloxone 1 mcg/kg/h more effectively decreased pruritus than 0.25 mcg/kg/h (Koch 2008 **Level IV**, n=16).

Intranasal opioid analgesia in SCD

IN fentanyl has been incorporated into clinical practice guidelines for VOC paediatric ED presentations (Carden 2018 **Level IV**, n=60; Kavanagh 2015 **Level III-2**, n=289 visits). IN fentanyl was a suitable alternative with reduced time to initiation of opioid analgesia (Kelly 2018 **Level III-2**, n=105 [487 visits]; Kavanagh 2015 **Level III-2**, n=128 [289 visits]). IN fentanyl vs placebo decreased pain scores at 20 min only (and not at 10 or 30) (Fein 2017 **Level II**, n=49, JS 5). IN fentanyl use increased the

proportion of patients discharged from the ED and reduced time to initiation of subsequent IV opioid including by PCA (Kavanagh 2015 **Level III-2**, n=289 visits); however in another study it did not reduce the need for IV opioid analgesia (Kelly 2018 **Level III-2**, n=487 visits).

IN diamorphine has been used for sickle cell crises and was effective in reducing pain scores (Telfer 2009 **Level IV**, n=21). It was introduced in an ED protocol as initial therapy 0.1 mg/kg (with optional IV morphine 100 mcg/kg). Subsequently the protocol was revised to coadministration with PO morphine 0.4 mg/kg (which could be repeated at 1 h) to reduce need for IV insertion.

Chronic opioid use in SCD including methadone

Over a 5 y period, children with SCD aged 0–9 y had a low prevalence of opioid use 8.5% vs teenagers 46.3% and adults 48.7 to 58.3% (Han 2018 **Level IV**, n=3,882 [2,123 ≤19 y]). Most patients (87% of children and 55% of adults) used <5 mg PO MED, but some used >30 mg PO MED (3% paediatric and 23% of adults). A subgroup of patients experience frequent painful VOCs with subsequent increased ED presentations and hospital admissions with pain recurrence that may require daily opioids (LeBlanc 2018 **Level IV**, n=16). Adolescents with frequent recurrent (chronic) pain related to SCD were treated with methadone for several months. Doses commenced at 12.5 mg and were uptitrated to a maximum of 30 mg/d, with reduced hospitalisations from 0.35± 0.19 to 0.19 ± 0.17/mth.

Corticosteroid use in SCD

In children, a 2 d course of IV methylprednisolone 15 mg/kg/d vs placebo decreased the duration of severe pain associated with acute VOCs; but patients who received methylprednisolone had more rebound attacks after therapy was discontinued (Dunlop 2006 **Level II** [Cochrane], 1 RCT (paediatric): Griffin 1994 **Level II**, n=36 [116 VOCs], JS 5).

Ketamine infusion in SCD

Beneficial use of low-dose IV ketamine infusion 0.05–0.4 mg/kg/h is described for children and adolescents with VOC usually in addition to or to replace opioid IV PCA (Puri 2019 **Level IV**, n=4; Sheehy 2015 **Level IV**, n=7; Zempsky 2010 **Level IV**, n=5) with reduction in pain scores and opioid requirement (Nobrega 2018 **Level IV**, n=80 [181 infusions]). A single dose given over 10 min of IV ketamine 1 mg/kg was non-inferior to IV morphine 0.1 mg/kg for VOC pain in children (Lubega 2018 **Level II**, n=240, JS 5). Both therapies impacted similarly on change in maximal pain scores by 66.4% vs 61.3; the reduction was achieved earlier for ketamine (at 20 min vs 34), but was shorter in duration (60 min vs 120) with increased transient side effects (37.5% vs 3.3).

Dexmedetomidine infusion in SCD

In children with refractory pain due to VOC despite nsNSAID/IV opioid/ketamine 0.1–0.3 mg/kg/h infusion, dexmedetomidine infusion 0.2–0.4 mcg/kg/h for up to 6 d duration has been used (Sheehy 2015 **Level IV**, n=3).

Inhaled nitric oxide

Nitric oxide deficiency or defective nitric oxide-dependent mechanisms may underlie many of the processes leading to vaso-occlusion. An early paediatric study suggested inhaled nitric oxide may be of benefit in painful acute VOC (Weiner 2003 **Level II**, n=25, JS 4); however, in young adults admitted with VOC, there was no difference between inhlaed nitric oxide vs nitrogen placebo in time to VOC resolution or LOS (Gladwin 2011 **Level II**, n=150, JS 5).

Inhlaed nitrous oxide (N_2O)

Despite the frequency of use of inhaled N_2O in paediatrics, there is no current data on the use of this agent specifically in VOC in children.

Rehydration

Hydration supplementation of patients with VOC is commonly practiced. Most children (84%) with VOC in the ED received fluids; a subanalysis of those who received normal saline bolus revealed less improvement in pain scores (Carden 2019 **Level IV**, n=400 [261 bolus]).

Oxygen

Oxygen supplementation is a standard of care despite old trials not supporting efficacy (see adult Section 8.6.4.1). Nocturnal oxygen desaturation was associated with a higher rate of painful VOC in children (Hargrave 2003 **Level IV**). Comorbid obstructive sleep apnoea (OSA) in children is associated with serious complications of SCD (Katz 2018 **Level III-3**, n=272 SCD [136 OSA]); a 6 wk pilot trial reports no rebound pain on CPAP cessation (Marshall 2009 **Level II**, n=24, JS 3).

Magnesium

Magnesium IV or PO therapy has no effect on reducing pain or LOS in adults or children with VOC (Than 2019 **Level I** [Cochrane], 5 RCTs [3 paediatric & 2 mixed], n=386).

Lidocaine infusion

IV Lidocaine 1–2 mg/kg/h (17-33 mcg/kg/min) for 2 d has been used for VOC (resistant to PCA morphine) with analgesic benefit (Puri 2019 **Level IV**, n=2 [3 occasions]).

Vitamin D supplementation

Vitamin D deficiency has been associated with vaso-occlusive crises and acute pain in children and adolescents (1–20 y) with sickle cell disease (Adegoke 2017 **Level IV**, n=123; Lee 2015 **Level IV**, n=95). Vitamin D supplementation for acute pain management in this population has not been studied.

Nonpharmacological interventions

Psychological therapies such as relaxation, hypnosis and cognitive behavioural therapy (CBT) reduce pain immediately after treatment for other recurrent acute pain presentations; but 2–4 sessions of CBT in patients with SCD focusing on coping skills (1 RCT), pain management (1 RCT) or a family intervention (1 RCT) were not beneficial at 1–12 mth follow-up (Fisher 2018a **Level I** [Cochrane], 3 RCTs [SCD], n=174). In a further Cochrane review, CBT for adolescents with SCD did not reduce pain frequency (1 RCT, n=53) or health care utilisation (2 RCTs, n=68) (Anie 2015 **Level I** [Cochrane], 5 RCTs [adolescents & young adults], n=260) (2 RCT overlap). Internet delivered CBT was feasible and the impact on pain burden vs control (internet delivered pain education) can be assessed (Palermo 2018 **Level II**, n=25, JS 3). Although adherence to use of a smart phone app to guide CBT was low (12%), if the app was used on a day of high pain, next-day pain was reduced vs waitlist controls (Schatz 2015 **Level II**, n=46, JS 3).

Massage therapy in youth with SCD improved function and reduced pain, depression and anxiety (Lemanek 2009 **Level II**, n=34, JS 1). However, the parents (who performed the massage therapy) had higher levels of anxiety and depression following the intervention. In children admitted with VOC, yoga vs listening to relaxing music reduced pain but not anxiety scores with the first but not subsequent sessions (Moody 2017 **Level II**, n=73, JS 2).

Prevention of painful VOC in children

Hydroxyurea (or hydroxycarbamide) 15–25 mg/kg for 10–24 mth vs placebo improved pain outcomes: pain scores (1 RCT n=193) with reduced frequency of pain crises (4 RCTs, n=577), acute chest syndrome (RR 0.43; 95% CI 0.29 to 0.63) (2 RCTs, n=492) and hospitalisations (1 RCT, n=60) (Nevitt 2017 **Level I** [Cochrane], 8 RCTs [6 paediatric only & 2 mixed], n=899). Hydroxyurea improves only fetal haemoglobin level vs control (observation: 1 RCT [paediatric], n=22) or when added to

magnesium therapy (1 RCT [mixed], n=44). Guidelines based upon this data as to when to institute hydroxyurea therapy in children (and adults) are available (Qureshi 2018 **GL**).

Zinc supplementation reduces the incidence of painful VOC in children and adults (Nagalla 2018 **Level I** [Cochrane], 1 RCT [zinc], n=145). While the evidence in children for piracetam is insufficient to support its use (Al Hajeri 2016 **Level I** [Cochrane], 3 RCTs, n=169) and is negative for prasugrel (Heeney 2016 **Level II**, n=341, JS 5).

10.9.5.2 | Haemophilia

As in adults, pain in children with haemophilia A (Factor VII) and B (Factor IX deficiency) is either recurrent acute, related to spontaneous or injury-related bleeding into joints, muscles (and rarely viscera), or chronic with secondary painful arthropathies. Preventative use of recombinant factor concentrates has had greater positive impact on pain management in affected children vs acute 'on demand' treatment (Usuba 2019, **Level III-3**, n=401).

There is no data or evidence base specifically for haemophilia but guidelines as referenced in the adult Section (See 8.6.4.2) are available (Holstein 2012 **Level IV**, n=1,678 children & 5,103 adults). The principles involve rest, ice, compression and elevation, paracetamol and escalated therapy at home or in hospital including adjuvants and nonpharmacological intervention. The use of analgesic medication needs to be encouraged (Rambod 2016 **Level IV**, n=154), possibly through education of parents of young affected children and guideline creation by haematologists in conjunction with primary care and pain specialists.

KEY MESSAGES

Sickle cell disease

1. Hydroxyurea decreases the frequency of acute vaso-occlusive crises, life-threatening complications and hospitalisations in children with sickle cell disease (**S**) (**Level I** [Cochrane Review]).
2. Intravneous or oral magnesium does not reduce pain of vaso-occlusive crises associated with sickle cell crises or length of hospital stay (**N**) (**Level I** [Cochrane Review]).
3. Attention must be paid to acute kidney injury risk in sicker inpatients with sickle cell disease receiving multiple doses of nsNSAID (**N**) (**Level III-3**).
4. Parenteral corticosteroids reduced the duration of severe pain in children with vaso-occlusive crises in sickle cell disease at the expense of more rebound attacks post cessation (**Q**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

Sickle cell disease

☑ It is standard of care for oral and IV paracetamol, nsNSAIDs and opioids to form part of an individual at home or hospital care plan for children with vaso-occlusive crises. Upon admission this is escalated to parenteral nsNSAID and opioid therapy (**N**).

☑ There is no evidence that fluid replacement therapy reduces pain in children with VOC, although it is common practice (**N**).

- ☑ The impact on painful vaso-occlusive crises of oxygen supplementation in patients with and without obstructive sleep apnoea and CPAP in patients with obstructive sleep apnoea requires assessment (**N**).
- ☑ Most children with sickle cell disease are not on opioids for chronic or frequent recurrent pain (while adolescents are, at similar rates to affected adults). In patients with sickle cell disease, postoperative opioid requirements may be higher (**N**).
- ☑ Adjunctive low-dose ketamine and IV lidocaine infusions reduce pain intensity and opioid requirements in refractory pain of acute vaso-occlusive crisis in children with sickle cell disease (**N**).

Haemophilia

- ☑ In children with haemophilia, on demand and preventative use of recombinant factor concentrates has improved pain-related quality of life measures. Otherwise the principles of pain management in acute bleeds in affected children and adults involve rest, ice, compression and elevation and stepwise escalation of analgesia. Parents of young affected children need education regarding analgesic medication (**N**).

10.10 | The overweight or obese child or adolescent

10.10.1 | Definitions of obesity

Obesity in childhood has been defined in various ways. The ideal definition based on percentage body fat is not practical for epidemiological use (Cole 2000 **Level IV**, n=192,727). Body mass index [BMI] is widely used but has limitations. In children, it varies substantially with age and sex (Chidambaran 2018 **NR**), does not discriminate between lean and fat mass, provides poor height standardisation for weight, and is not a consistent marker of body fat across ethnic groups (Hudda 2019 **Level IV**). Internationally, BMI cut-offs used for overweight and obesity vary. Both Australia (ABS 2018 **Level IV**) and New Zealand (NZ MoH 2018 **Level IV**) use the International Obesity Taskforce cut-offs developed for children aged 2–18 y (Cole 2000 **Level IV**, n=192,727). These are linked to adult BMI cut-offs at 18 y which have been related to health risk. The WHO defines BMI cut-offs for overweight and obesity in SD above the WHO median growth standard (0–5 y: overweight 2 SD; obese 3 SD) (de Onis 2010 **Level III-3**) and the WHO median growth reference (5–19 y: overweight 1 SD; obese 2 SD) (de Onis 2007 **Level IV**, n=30,018).

10.10.2 | Prevalence of childhood obesity

Global age standardised obesity prevalence increased in girls and boys respectively from 0.7 and 0.9% in 1975 to 5.6 and 7.8% in 2016 (NCD-RisC 2017 **Level IV**). The latter equates to 50 million obese girls and 74 million obese boys worldwide. In several countries, the prevalence of obesity was ≥20% such as the Middle East, North Africa, the Caribbean and Polynesian region and >30% in the Pacific Islands. The trends in mean BMI have accelerated in South East Asia, with flattening for North Western Europe and the high income English speaking countries.

In the USA, childhood (2–19 y) obesity prevalence increased from 5.5% (1976–1980) to 17.1% (2003–04) and 18.5% (2015–16) (National Center for Health Statistics 2019 **Level IV**). In Australia and New Zealand, the increase in obesity has been less marked. In Australia, obesity prevalence in 5–17 y olds increased from 5% (1995) to 8% (2007–08) (ABS 2009 **NR**); when combined with those overweight, the prevalence rates were 22% in 1995 increasing to 25% in 2007–08 and have remained stable since (ABS 2018 **Level IV**). In New Zealand, the prevalence of obesity in 2–14 y olds has increased from 8.4% (2006–07) to 12.4% (2017–18); when combined with those overweight the total prevalence was 21% in 2006–07, increasing to 31.9% in 2017–18 (NZ MoH 2018 **Level IV**).

10.10.3 | Morbidity associated with paediatric obesity

Obesity is a risk factor for morbidity in children including: sleep-disordered breathing [SDB] incorporating obstructive sleep apnoea [OSA], dyslipidaemia, hypertension, atherosclerosis, left ventricular hypertrophy, impaired glucose tolerance and type 2 diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (Chidambaran 2018 **NR**). The most immediately relevant condition to acute pain management is SDB/OSA, and the increased risk of ventilatory impairment with opioids and other sedative/hypnotics. The prevalence of OSA varied from 13–36% in obese children and adolescents, and was 24–77% in obese children and adolescents with symptoms of SDB (Baker 2017 **Level IV**, n=224 [148 obese]; Verhulst 2008 **NR**, 6 case series, n=269).

See also Section 10.4.4.5 for information regarding mortality in obese children related to codeine and for adults see sections 9.4 and 9.5.

10.10.4 | Medication dosing in paediatric obesity

When dosing a medication, its volume of distribution, clearance and pharmacodynamics should be considered (Anderson 1997 **NR**). Obesity can influence all three of these factors through its effects on body size, body composition and organ function, as well as being a risk factor for comorbid disease. Its influence is unpredictable and can place the patient at risk of both underdosing and overdosing of medication (Samuels 2016 **NR**). For example, the volume of distribution for lipophilic drugs may be increased, unchanged or reduced, and for hydrophilic drugs may be unchanged or reduced (Chidambaran 2018 **NR**). In paediatrics, the influence of maturation and growth on volume of distribution, clearance and pharmacodynamics must also be considered.

Barriers to appropriate drug dosing in overweight and obese children include: a paucity of paediatric bariatric pharmacokinetic data (Chidambaran 2018 **NR**); the range of doses calculated for a given drug from the many size descriptors that have been proposed (Chidambaran 2018 **NR**); a requirement to use different size descriptors for initial dosing and maintenance dosing for some drugs (Anderson 2017a **NR PK**); and cumbersome dosing calculations that may lead to temptation of arbitrary or "educated guess" dose adjustment in the clinical setting (Callaghan 2015 **Level III-2**). Given the barriers to accurate dosing in overweight and obese children, authors have emphasised the importance of judicious dosing and titration to effect wherever possible (Baines 2011 **NR**; Samuels 2006 **NR**).

Lean body mass and ideal body weight have been recommended for dosing many drugs in overweight and obese patients. A nomogram (https://onlinelibrary.wiley.com/doi/full/10.1111/anae.12860) developed from UK data of children >5 y old was created to facilitate calculations of lean body mass and ideal body weight in a perioperative setting or urgent drug dose calculation scenario (Callaghan 2015 **Level III-2**). It was quicker to use, with less mistakes and similar accuracy compared to calculations using equations. Other proposed size descriptors for various drugs have included: total body weight, dosing weight, adjusted body weight, predicted body weight, PK mass, fat free mass, normal fat mass, body surface area and BMI (Anderson 2017a **NR**).

Normal fat mass is a size descriptor that partitions total body mass into fat and fat-free components. It uses allometric theory to calculate the fraction of fat mass that will make fat equivalent to fat-free mass. The value of normal fat mass is drug specific and specific to a PK parameter (eg Vd or CL) (Anderson 2017a **NR PK**). Calculating normal fat mass for drug dosing has been proposed as a principle-based approach that explains size and body composition effects on PKs of all drugs in children and adults of all sizes.

Concerns have been raised about an increased risk of toxicity in obese patients when weight-based dosing exceeds the recommended maximum dose. An example is paracetamol, where CYP2E1, the enzyme responsible for metabolising paracetamol to its toxic metabolite N-acetyl-p-benzoquinone-imine (NAPBQI), may be induced in obesity and increase the production of NAPBQI (Hakim 2019 **Level IV PK**). However, the influence of obesity on paracetamol toxicity, if any, is unknown. Obesity has been described as a chronic inflammatory state and associated with other changes in the enzyme activity of metabolic and elimination pathways (Brill 2012 **NR**). However, the clinical relevance of many of these changes is questionable, and very little paediatric data is available.

10.10.5 | Weight/mass adjusted dosing for individual drugs

The terms weight and mass are used interchangeably in the literature (eg ideal body mass = ideal body weight). Due to limited data in overweight and obese children and adolescents, suggestions are typically based on studies of obese adults and normal weight children (See Table 10.11).

Table 10.11 | Dosing suggestions for common analgesics relevant to body weight

Analgesic	Initial dosing	Maintenance dosing	Dosing not specified as initial or maintenance	References
Morphine	Ideal BW	Ideal BW		Mortensen 2011
			Ideal BW	Chidambaran 2018
Fentanyl	Total BW	Lean BW		Mortensen 2011
			Lean body mass/PK mass	Chidambaran 2018
Alfentanil	Total BW	Lean BW		Mortensen 2011
			Lean BW/Total BW	Chidambaran 2018
Sufentanil	Total BW	Total BW		Mortensen 2011
			Total BW	Chidambaran 2018
Remifentanil	Lean BW	Lean BW		Mortensen 2011
			Lean body mass/Ideal BW	Chidambaran 2018
Ketamine	Nil	Nil		
Lidocaine	Total BW	Ideal BW		Chidambaran 2018
Paracetamol			Total BW with allometric scaling (single dose only)	Hakim 2019

BW=body weight

KEY MESSAGES

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ When dosing medication in the overweight or obese child or adolescent, age of the patient, each individual drug and the dose type (initial or maintenance) must be considered (**N**).

☑ Given the barriers to accurate dosing in overweight and obese children, judicious dosing and titration to effect wherever possible is recommended. This requires consideration of both pharmacokinetic and pharmacodynamic factors (**N**).

☑ Young and obese children with history of obstructive sleep apnoea syndrome/sleep-disordered breathing are at higher risk of developing serious opioid-induced ventilatory impairment and death (**U**) (**Level IV**).

10.11 | Complementary and alternative medicines and therapies in children

Complementary medicines and therapies are defined as evidence-based health care approaches developed outside of conventional Western medicine; they are used in conjunction with conventional care (McClafferty 2017 **NR**). Alternative medicines and therapies are used in place of conventional care. Complementary and alternative medicines and therapies (CAMTs) are commonly used in the community. Increasingly, complementary medicines and therapies are used as part of integrative approaches to hospital-based healthcare in the paediatric population. Therefore, there is a need for health care professionals managing acute pain to be informed about CAMTs and, where relevant, their potential drug interactions. The evidence for CAMTs is limited by the large degree of heterogeneity of the various interventions and small sample sizes resulting in low level power to detect differences.

See also adult Section on CAMs 4.14. Studies relevant to photobiomodulation use in paediatric dental, cleft and tonsillectomy are not discussed here but are included in the adult Section 7.4.

10.11.1 | Natural products

Aromatherapy

Studies on aromatherapy for paediatric acute pain show mixed results (Dimitriou 2017 **Level I** [PRISMA], 9 RCTs [2 paediatric], n=644 [112]; Lakhan 2016 **Level III-3** [PRISMA], 12 studies [3 paediatric], n=1,019) (2 study overlap):

- In 6–12 y olds post-tonsillectomy, lavender essential oil (in addition to paracetamol every 6 h) rubbed onto the palms and inhaled 6 h prn did not reduce pain intensity, but did reduce paracetamol use (1 RCT: Soltani 2013 **Level II**, n=48, JS 2);
- In infants (3–36 mth) following craniofacial surgery, massage with mandarin oil vs massage with a carrier oil did not reduce pain scores, HR or mean arterial pressure (1 RCT: de Jong 2012 **Level II**, n=60, JS 3);
- In 3–6 y olds having various surgery types (mostly thoraco-abdominal), *rosa damascena* essential oil vs sweet almond oil (placed on a small pad, adjacent to the head) postoperatively every 3 h for 12 h reduced mean pain scores 3–12 h postoperatively (1 RCT: Marofi 2015 **Level II**, n=64, JS2).

Melatonin

Melatonin is a neurohormone synthesised endogenously by the pineal gland from the amino acid tryptophan. Antinociceptive effects of melatonin have been demonstrated in animal models and, in addition to acting on melatonin receptors (MT1/MT2), other proposed analgesic mechanisms include modulation of opioid, benzodiazepine, alpha adrenergic, serotonergic and cholinergic receptors (Srinivasan 2012 **NR**). Although exogenous melatonin is commonly used in paediatrics, clinical studies on its use as an analgesic in children are lacking (Marseglia 2015a **NR**). In children 1–14 y, PO melatonin 0.5 mg/kg (max 5 mg) vs placebo 30 min prior to venipuncture reduced preprocedural anxiety (mean 1.3/5 vs 2.2) and pain scores during venipuncture (for ≤3 y olds, mean 2.5/10 vs 3.2; and for >3 y olds, mean 1.2/10 vs 2.1) (Marseglia 2015b **Level II**, n=60, JS 5).

Honey

Honey in children vs placebo reduces pain and analgesic use for up to 5–10 d post-tonsillectomy; regimens of honey administered varied substantially in volume (4–15 mL), frequency (daily to

hourly) and duration (1–10 d) (Lal 2017 **Level I** [QUOROM], 8 RCTs, n=545; Hwang 2016b **Level I** [PRISMA], 4 RCTs, n=264) (4 RCT overlap). The analgesic medication regimens used in included studies was not clear.

For neonates having a heel lance, honey vs water reduced cry duration (Bueno 2013 **Level III-1** [PRISMA], 1 study: Ramenghi 2001 **Level III-1**, n=15).

See Section 10.7.1–2 for use of sweet solutions in procedural pain in children.

Turmeric and Ginger (Zingiberaceae)

Zingiberaceae include *Curcuma longa* (turmeric), *Zingiber officinale* (ginger), *Curcuma zanthorrhiza* (Javanese ginger) and *Alpinia galanga* (galangal). Curcumin (diferuloyl methane) is the principal curcuminoid of the Indian spice turmeric, while the anti-inflammatory components of ginger are gingerol and zingerone. The available systematic reviews have assessed efficacy for pain in adults. There have been no peer reviewed publications in children regarding analgesic efficacy (although conference abstracts reflect growing interest for use of turmeric in juvenile arthritis). Efficacy of ginger in nausea and vomiting is not presented here.

Supplements and vitamins

Fish oil (500 mg/d) and vitamin B1 (100 mg/d) alone or in combination vs placebo improved pain intensity and reduced duration of pain in 13–18 y old girls with dysmenorrhoea; comparisons between active arms were not reported (Hosseinlou 2014 **Level II**, n=240, JS 3). In adolescents with dysmenorrhoea, zinc 50 mg/d during menstruation reduced the mean duration of pain in 3 menstrual cycles, and mean pain scores in two of three menstrual cycles (Zekavat 2015 **Level II**, n=120, JS 5).

Perioperative enteral docosahexaenoic acid (DHEA) 37.5 mg/kg two times daily vs sunflower oil in neonates (>34/40 wk gestational age) having cardiovascular surgery (without cardiopulmonary bypass eg Blalock-Taussig shunt or aortoplasty) reduced postoperative IV buprenorphine requirements (14.6 mcg/kg vs 25.2) and duration (2 d vs 4.5) (Bernabe-Garcia 2016 **Level II**, n=35, JS 4).

Vitamin D supplementation for acute pain management in children has not been studied (see paediatric sickle cell disease Section 10.9.5.1 for comment on Vitamin D deficiency in sickle cell disease).

10.11.2 | Acupuncture

Acupuncture (invasive [skin breaking] or non-invasive eg pressure, laser or transcutaneous electrical) for preterm and term neonates receiving heel lance does not reduce pain intensity (Stadler 2019 **Level I** [PRISMA], 5 RCTs, n=265). Individual RCTs found mixed results: two RCTs showed reduced pain scores with acupuncture, one RCT showed no difference vs control, and two RCTs showed increased pain with acupuncture. A subsequent RCT found auricular non-invasive magnetic acupuncture vs placebo reduced pain scores during (mean 5.9/21 vs 8.3) but not after heel lance in preterm and term neonates (Chen 2017a **Level II**, n=26, JS 3).

Perioperative acupuncture (including electroacupuncture) vs control in children and adolescents (<18 y) having tonsillectomy reduces pain intensity (4–48 h) (4 RCTs, n=234 [3 paediatric, n=201]) and analgesic consumption postoperatively (4 RCTs, n=232 [3 paediatric, n=199]) (Cho 2016 **Level I** [PRISMA], 12 RCTs, n=1,025 [11 paediatric, n=910]). Similar results are reported by an overlapping systematic review of RCTs and non-RCTs (Pouy 2019 **Level IV SR**, 9 RCTs and 3 studies, n=910 children) (9 RCT overlap).

For bilateral myringotomy and tympanostomy tube insertion, intraoperative acupuncture vs control in 1–6 y olds reduced postoperative pain, agitation and analgesic use, with increased time to first analgesic request (Lin 2009 **Level II**, n=60, JS 3).

For percutaneous kidney biopsy in 7–26 y olds, there was no difference in pain scores between laser acupuncture vs placebo groups (during or after the procedure) where all pain scores were low (<2/10) (Oates 2017 **Level II**, n=66, JS 5). Change in self-reported pain scores from during the procedure to after the procedure were mildly greater with laser (-0.8/10 vs -0.5).

For dental treatment, acupuncture (at the LI4 point bilaterally) in children and adolescents 4–18 y reduced self-reported pain intensity (2.3/10 vs 3.9) during local anaesthetic injection (Usichenko 2016 **Level II**, n=49 [98 injections], JS 3).

For 8–18 y olds presenting to the ED with severe migraine, pain scores reduced (mean from 7.63/10 to 0.55) at 15 min following insertion of gold auricular acupuncture needles, with 4 patients refusing treatment and 2 withdrawing post treatment initiation (Graff 2018 **Level IV**, n=23).

Acupuncture has been used in postoperative patients 0.5–18 y admitted to intensive care (Wu 2009 **Level IV**, n=20) and in 10–17 y olds with appendicitis in the ED (Nager 2015 **Level IV**, n=6); however efficacy was not adequately assessed.

For further discussion of acupuncture for acute pain in adults see Section 7.3.

10.11.3 | Mind-body practices

10.11.3.1 | Hypnosis

Hypnosis encompasses a variety of interventions (eg self-hypnosis, hypnotic guided imagery), and requires the skills of a trained health professional and time for the child to learn the technique. It has been studied mostly for procedural pain management. Hypnosis vs control for needle-related procedural pain reduces pain intensity (SMD: -1.4; 95%CI -2.32 to -0.48) (5 RCTs, n=176), distress (SMD: -2.53; 95%CI -3.93 to -1.12) (5 RCTs, n=176) and behavioural measures of distress (SMD: -1.15; 95%CI -1.76 to -0.53) (6 RCTs, n=193) (Birnie 2018 **Level I** [Cochrane], 59 RCTs, n=5,550). For children undergoing cancer-related procedures hypnosis is an effective pain-control technique (Tome-Pires 2012 **Level I**, 10 RCTs [cancer procedural pain], n=394) (5 RCT overlap). A subsequent review of oncology patients found hypnosis reduces pain scores vs treatment as usual (Cohen's d 2.16; 95%CI 1.41 to 2.92) and vs controls having attention focus (Cohen's d 2.24; 95%CI 1.66 to 2.82) but not vs active control groups (eg music, play, audiobooks) (Nunns 2018 **Level I** [PRISMA], 15 RCTs [8 hypnosis], n=585 [337]) (6 & 6 RCT overlap).

Hypnosis had no effect on pain and wound healing for burn dressing changes but reduced preprocedural anxiety on the second of three burns dressing changes (MD -0.8/10; 95%CI -1.5 to -0.1) (Chester 2018 **Level II**, n=62, JS 3).

Hypnosis interventions have been studied for postoperative pain (including Nuss procedure, spinal fusion, tonsillectomy) with mixed results, and no conclusions on its efficacy can be drawn in this setting (Accardi 2009 **Level III-3 SR**, 13 studies [3 postoperative], n=528; Duparc-Alegria 2018 **Level II**, n=120, JS 2; Manworren 2018 **Level III-2**, n=53). See also adult section 7.1.4 Hypnosis.

10.11.3.2 | Mindfulness-based interventions (attention and meditation)

Mindful attention vs guided imagery helped children 10–14 y focus their attention on experimental pain (cold pressor) without increasing pain intensity or decreasing tolerance (Petter 2013 **Level II EH**, n=82, JS 2). While, mindful attention vs guided imagery in adolescents 13–18 y prior to experiencing experimental pain (cold pressor) did not change pain intensity or tolerance; however, when considering regular meditators in the sample, the mindful attention group vs control did experience lower pain intensity (Petter 2014 **Level II EH**, n=198, JS 2).

Instructor taught Mantram meditation (commenced prior to infusion commencement) has been used successfully by children 3–14 y with high risk neuroblastoma experiencing pain from anti-glycolipid disialoganglioside (GD)-2 monoclonal antibody infusions (Ahmed 2014 **Level IV**, n=34). See also adult sections 7.1.3 Mindfulness-based interventions and 7.1.5 Attentional techniques.

10.11.3.3 | Guided imagery, relaxation and biofeedback

Postoperative guided imagery (at least 3 times a week)/standard care vs standard care alone reduced pain intensity following spinal fusion surgery for scoliosis in 11–20 y olds (Charette 2015 **Level II**, n=40, JS 3). Preoperative relaxation-guided imagery vs control in 6–12 y olds (having inguinal hernia repair, phimosis repair or endoscopy) reduced mean pain scores 2 h postoperatively (4.5/10 vs 7.7) (Vagnoli 2019 **Level II**, n=60, JS 3).

Relaxation and biofeedback vs control for 12 y olds receiving venipuncture did not lower pain intensity during the procedure (Forsner 2014 **Level III-2**, n=109). Relaxation therapy and guided imagery had similar effects on cortisol reactivity, self-reported stress, pain intensity and pain unpleasantness in females 11–12 y receiving the HPV vaccine (Nilsson 2015 **Level III-2**, n=37).

In children 8–14 y having cancer-related procedures, a 4-session intervention of preprocedural relaxation plus biofeedback progressively reduced state anxiety across the sessions, with improvement in heart rate variability; 81% of participants reported the combination of relaxation and biofeedback helped them feel in control of their bodies prior to the procedure (Shockey 2013 **Level IV**, n=12). In patients 7–18 y undergoing needle-related procedures and using 'Brighthearts' (a biofeedback assisted relaxation application), 83% reported the app was helpful and would use it again, 100% of parents and 96% of healthcare providers indicated they would use it again, and 64% of the healthcare providers perceived that it assisted with the ease of performing a procedure (Burton 2018 **Level IV**, n=107 [30 patients, 27 parents, 50 health providers]).

10.11.3.1 | Physical and other complementary therapies

Other complementary therapies have been assessed for acute pain management with studies reporting mixed results: massage therapy (Staveski 2018 **Level II**, n=60, JS 3; de Jong 2012 **Level II**, n=60, JS 3), Therapeutic Touch (Johnston 2013 **Level II**, n=55, JS 2), Reiki (Kundu 2014 **Level II**, n=38, JS 5), yoga (Moody 2017 **Level II**, n=70, JS 3), reflexology (Koc 2015 **Level II**, n=60, JS 2) and Korean hand therapy (Ochi 2015 **Level IV**, n=29). Conclusions on their effectiveness cannot be made due to small samples and study designs prone to bias.

See also adult sections regarding massage and yoga in 7.5 Physical therapies.

10.11.4 | Infantile colic

Infantile colic can be defined as excessive crying in the first few months of life; the most cited clinical diagnostic criteria is the rule of 3s: crying for longer than 3 h/d for ≥3 d/wk for at least 3 wk (Biagioli 2016 **Level III-1 SR** [Cochrane], 18 RCTs, n=1,014). In mothers who had used complementary medicine (mostly homeopathic remedies, probiotics or herbal medicines) to treat their infant's colic where 73% was alongside conventional medicine treatments, 66% felt it was effective and 47% reported no side effects (Di Gaspero 2019 **Level IV**, n=152).

Oral herbal, antifoaming, sweet solution or anticholinergic agents

Various pain-relieving agents to treat colic have been studied: herbal agents (defined as plant derived remedies), (6 studies, n=427), simethicone (4 studies, n=166), sweet solution [sucrose or glucose] (3 studies, n=120), dicyclomine (5 studies, n=137) and cimetropium bromide (2 studies,

n=126) (Biagioli 2016 **Level III-1** [Cochrane], 18 RCTs, n=1,014). Although some of these studies found positive results, reported benefits are inconsistent, and study designs are prone to bias, with the authors concluding that none of these agents could be recommended. Additionally, a subsequent systematic review of systematic reviews found supporting evidence specifically for fennel extract, but methodological issues with studies call this result into question (Perry 2019 **Level I** [PRISMA], 16 SRs [5 herbal medicine SRs], n RCTs unspecified).

Probiotics

Three systematic reviews have reported on the efficacy of probiotics for infantile colic. These draw the same conclusion: *Lactobacillus reuteri* (10^8 colony forming units daily for 21 or 28 d) is effective at reducing cry/fuss time >50%: RR 2.34 (95%CI unspecified) (5 RCTs, n=317) (Schreck Bird 2017 **Level I** [PRISMA], 5 RCTs, n=388); RR 1.67 (95%CI 1.10 to 2.81) (6 RCTs, n=391) (Dryl 2018 **Level I** [PRISMA], 7 RCTs, n=471); RR 1.71 (95%CI 1.35 to 2.15) (4 RCTs, n=293) (Sung 2018 **Level I** [PRISMA], 4 RCTs, n=345) (4 RCT overlap). Most infants included in these RCTs were breastfed (although not all exclusively). There is insufficient evidence for probiotics in formula fed infants (Sung 2018 **Level I** [PRISMA], 1 RCT [formula fed], n=66 (21 d)]. A systematic review of systematic reviews identified a further 4 older reviews that drew similar conclusions (Perry 2019 **Level I** [PRISMA], 16 SRs [7 probiotic], n RCTs unspecified). A Cochrane review assessed probiotics for prevention of colic in infants (<1 mth old at recruitment) where probiotics vs placebo did not reduce the number of new cases of infantile colic (3 RCTs, n=1,148), but did reduce the duration of crying (MD -32.6 min/d; 95%CI -55.6 to -9.54) (3 RCTs, n=707); there was no difference in the incidence of serious adverse effects (6 RCTs, n=1,851) (Ong 2019 **Level I** [Cochrane], 6 RCTs, n=1,886) (0 RCT overlap).

Dietary modifications

Various dietary modifications for infantile colic have been studied including maternal low allergen diets for breastfed infants (2 studies), lactase enzyme supplementation (3 studies), and hydrolysed formula (6 studies) (Gordon 2018 **Level III-1** [Cochrane], 15 studies, n=1,121). The authors concluded that reported benefits for hydrolysed formula were inconsistent, and overall, due to small samples and high risk of bias, no intervention was able to be recommended.

Skeletal manipulation

Individual studies report positive outcomes for skeletal manipulative therapies to treat infantile colic. However, studies were small and methodologically biased and these flaws make the results inconclusive; only one study assessed for adverse effects and reported none (Perry 2019 **Level I** [PRISMA], 16 SRs [6 manipulation]; Dobson 2012 **Level I** [Cochrane], 6 RCTs, n=325).

Acupuncture

There is no conclusive evidence to support the safety and efficacy of acupuncture to treat colic in infants (1–25 wk old) (Skjeie 2018 **Level I** [PRISMA], 3 RCTs, n=307; Lee 2018 **Level I**, 4 RCTs, n=357) (3 RCT overlap).

KEY MESSAGES

1. Hypnosis for needle-related procedural pain (including for cancer-related procedures) reduces pain intensity (**S**) and distress (**N**) versus control (**Level I** [Cochrane Review]).
2. Preventive use of probiotics does not reduce infantile colic incidence, but does reduce crying duration versus placebo (**N**) (**Level I** [Cochrane Review]).
3. The probiotic *Lactobacillus reuteri* reduces cry/fuss time in breastfed infants with colic; there is insufficient evidence in formula fed infants (**N**) (**Level I** [PRISMA]).
4. Oral administration of honey versus control in children reduces pain and analgesic use after tonsillectomy (**N**) (**Level I** [PRISMA]).
5. Perioperative acupuncture (including electroacupuncture) versus control in children having tonsillectomy reduces postoperative pain intensity (in the first 48 h) and analgesic consumption (**N**) (**Level I** [PRISMA]).
6. Acupuncture (invasive or non-invasive) versus control for preterm and term neonates receiving heel lance does not reduce pain intensity (**N**) (**Level I** [PRISMA]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Complementary and alternative medicines and therapies encompass a wide variety of interventions with common use in the community; complementary medicines and therapies are increasingly used as part of integrative approaches to hospital-based healthcare in the paediatric population (**N).**

☑ The evidence on complementary and alternative medicines and therapies is characterised by small sample sizes and study designs prone to bias and caution is urged in interpreting results. Additionally, the safety and potential drug interactions of many complementary and alternative medicines and therapies have not been adequately assessed (**N**).

References

AAGBI (2010) *Management of Severe Local Anaesthetic Toxicity.* https://anaesthetists.org/Home/Resources-publications/Guidelines/Management-of-severe-local-anaesthetic-toxicity Accessed 10 February 2020

AAP (2001) Acetaminophen Toxicity in Children. *Pediatrics* **108**(4): 1020-24.

Abbott RA, Martin AE, Newlove-Delgado TV et al (2017) Psychosocial interventions for recurrent abdominal pain in childhood. *Cochrane Database Syst Rev* **1**: Cd010971.

Abdolkarimi B, Zareifar S, Golestani Eraghi M et al (2016) Comparison Effect of Intravenous Ketamine with Pethidine for Analgesia and Sedation during Bone Marrow Procedures in Oncologic Children: A Randomized, Double-Blinded, Crossover Trial. *Int J Hematol Oncol Stem Cell Res* **10**(4): 206-11.

ABS (2009) *Children who are overweight or obesehorn.* https://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/LookupAttach/4102.0Publication24.09.093/$File/41020_Childhoodobesity.pdf Accessed 12 August 2020

ABS (2018) *National Health Survey: First Results, 2017-18* https://www.abs.gov.au/ausstats/abs@.nsf/mf/4364.0.55.001 Accessed 15 December 2019

Abu Elyazed MM, Mostafa SF, Abdullah MA et al (2016) The effect of ultrasound-guided transversus abdominis plane (TAP) block on postoperative analgesia and neuroendocrine stress response in pediatric patients undergoing elective open inguinal hernia repair. *Paediatr Anaesth* **26**(12): 1165-71.

Abukawa Y, Hiroki K, Morioka N et al (2015) Ultrasound versus anatomical landmarks for caudal epidural anesthesia in pediatric patients. *BMC Anesthesiol* **15**: 102.

Accardi MC & Milling LS (2009) The effectiveness of hypnosis for reducing procedure-related pain in children and adolescents: a comprehensive methodological review. *J Behav Med* **32**(4): 328–39.

ACEP (2016) Out-of-Hospital Use of Analgesia and Sedation. *Ann Emerg Med* **67**(2): 305-6.

Acheampong P & Thomas SH (2016) Determinants of hepatotoxicity after repeated supratherapeutic paracetamol ingestion: systematic review of reported cases. *Br J Clin Pharmacol* **82**(4): 923-31.

Achuff BJ, Moffett BS, Acosta S et al (2019) Hypotensive Response to IV Acetaminophen in Pediatric Cardiac Patients. *Pediatr Crit Care Med* **20**(6): 527-33.

Acquazzino MA, Igler EC, Dasgupta M et al (2017) Patient-reported neuropathic pain in adolescent and young adult cancer patients. *Pediatr Blood Cancer* **64**(3).

Adegoke SA, Oyelami OA, Adekile A et al (2017) Influence of serum 25-hydroxyvitamin D on the rate of pain episodes in Nigerian children with sickle cell anaemia. *Paediatr Int Child Health* **37**(3): 217-21.

Adhikary SD, Pruett A, Forero M et al (2018) Erector spinae plane block as an alternative to epidural analgesia for post-operative analgesia following video-assisted thoracoscopic surgery: A case study and a literature review on the spread of local anaesthetic in the erector spinae plane. *Indian J Anaesth* **62**(1): 75-78.

Admiraal R, van Kesteren C, Boelens JJ et al (2014) Towards evidence-based dosing regimens in children on the basis of population pharmacokinetic pharmacodynamic modelling. *Arch Dis Child* **99**(3): 267–72.

Agarwal N, Dhawan J, Kumar D et al (2017) Effectiveness of Two Topical Anaesthetic Agents used along with Audio Visual Aids in Paediatric Dental Patients. *J Clin Diagn Res* **11**(1): ZC80-ZC83.

Ahiskalioglu A, Yayik AM, Ahiskalioglu EO et al (2018a) Ultrasound-guided versus conventional injection for caudal block in children: A prospective randomized clinical study. *J Clin Anesth* **44**: 91-96.

Ahiskalioglu A, Yayik AM, Alici HA et al (2018b) Ultrasound guided transmuscular quadratus lumborum block for congenital hip dislocation surgery: Report of two pediatric cases. *J Clin Anesth* **49**: 15-16.

Ahmed M, Modak S & Sequeira S (2014) Acute pain relief after Mantram meditation in children with neuroblastoma undergoing anti-GD2 monoclonal antibody therapy. *J Pediatr Hematol Oncol* **36**(2): 152-5.

Ahmed M, Sobithadevi D, Mostafa S et al (2015) Pain evaluation in preterm infants using skin conductance algesimeter. *Medical Research Archives* **2**(1).

AIHW (2019) *Alcohol, tobacco & other drugs in Australia.* https://www.aihw.gov.au/reports/alcohol/alcohol-tobacco-other-drugs-australia Accessed 8 January 2020

Ajjan N & Shenton S (2016) Comparing oral paracetamol doses in paediatrics with the new BNF-C dosing. *Arch Dis Child* **101**(9): e2.

Akbay BK, Yildizbas S, Guclu E et al (2010) Analgesic efficacy of topical tramadol in the control of postoperative pain in children after tonsillectomy. *J Anesth* **24**(5): 705–08.

Akcan E & Polat S (2016) Comparative Effect of the Smells of Amniotic Fluid, Breast Milk, and Lavender on Newborns' Pain During Heel Lance. *Breastfeed Med* **11**(6): 309-14.

Akdas O, Basaranoglu G, Ozdemir H et al (2014) The effects of Valsalva maneuver on venipuncture pain in children: comparison to EMLA((R)) (lidocaine-prilocaine cream). *Ir J Med Sci* **183**(4): 517-20.

Akinci G, Hatipoglu Z, Gulec E et al (2019) Effects of Ultrasound-Guided Thoracic Paravertebral Block on Postoperative Pain in Children Undergoing Percutaneous Nephrolithotomy. *Turk J Anaesthesiol Reanim* **47**(4): 295-300.

Akpoduado DD, Imarengiaye CO & Edomwonyi NP (2017) Caudal analgesia for herniotomy: Comparative evaluation of two dose schemes of bupivacaine. *Niger J Clin Pract* **20**(2): 205-10.

Aksu C & Gurkan Y (2018a) Opioid sparing effect of Erector Spinae Plane block for pediatric bilateral inguinal hernia surgeries. *J Clin Anesth* **50**: 62-63.
Aksu C & Gurkan Y (2018b) Ultrasound guided erector spinae block for postoperative analgesia in pediatric nephrectomy surgeries. *J Clin Anesth* **45**: 35-36.
Aksu C & Gurkan Y (2018c) Ultrasound guided quadratus lumborum block for postoperative analgesia in pediatric ambulatory inguinal hernia repair. *J Clin Anesth* **46**: 77-78.
Aksu C & Gurkan Y (2019a) Erector spinae plane block: A new indication with a new approach and a recommendation to reduce the risk of pneumothorax. *J Clin Anesth* **54**: 130-31.
Aksu C & Gurkan Y (2019b) Ultrasound-guided bilateral erector spinae plane block could provide effective postoperative analgesia in laparoscopic cholecystectomy in paediatric patients. *Anaesth Crit Care Pain Med* **38**(1): 87-88.
Aksu C, Sen MC, Akay MA et al (2019c) Erector Spinae Plane Block vs Quadratus Lumborum Block for pediatric lower abdominal surgery: A double blinded, prospective, and randomized trial. *J Clin Anesth* **57**: 24-28.
Al Hajeri A & Fedorowicz Z (2016) Piracetam for reducing the incidence of painful sickle cell disease crises. *Cochrane Database Syst Rev* **2**: CD006111.
Al-Harasi S, Ashley PF, Moles DR et al (2010) Hypnosis for children undergoing dental treatment. *Cochrane Database Syst Rev*(8): Cd007154.
Albokrinov AA & Fesenko UA (2014) Spread of dye after single thoracolumbar paravertebral injection in infants. A cadaveric study. *Eur J Anaesthesiol* **31**(6): 305-9.
Alencar AJ, Sanudo A, Sampaio VM et al (2012) Efficacy of tramadol versus fentanyl for postoperative analgesia in neonates. *Arch Dis Child Fetal Neonatal Ed* **97**(1): F24–29.
Alexander J & Manno M (2003) Underuse of analgesia in very young pediatric patients with isolated painful injuries. *Ann Emerg Med* **41**(5): 617-22.
Alfonzo M & Chen L (2015) Acute Migraine Management in Children. *Pediatr Emerg Care* **31**(10): 722-7.
Alhashemi JA & Daghistani MF (2006) Effects of intraoperative i.v. acetaminophen vs i.m. meperidine on post-tonsillectomy pain in children. *Br J Anaesth* **96**(6): 790–95.
Alhashemi JA & Daghistani MF (2007) Effect of intraoperative intravenous acetaminophen vs. intramuscular meperidine on pain and discharge time after paediatric dental restoration. *Eur J Anaesthesiol* **24**(2): 128–33.
Ali MA & Abdellatif AA (2013) Prevention of sevoflurane related emergence agitation in children undergoing adenotonsillectomy: A comparison of dexmedetomidine and propofol. *Saudi J Anaesth* **7**(3): 296–300.
Ali S, Chambers AL, Johnson DW et al (2014) Paediatric pain management practice and policies across Alberta emergency departments. *Paediatr Child Health* **19**(4): 190–94.
Ali SM, Shahrbano S & Ulhaq TS (2008) Tramadol for pain relief in children undergoing adenotonsillectomy: a comparison with dextromethorphan. *Laryngoscope* **118**(9): 1547–49.
Aliena SP, Lini C & Chirayath JJ (2018) Comparison of postoperative analgesic effect of caudal bupivacaine with and without ketamine in Pediatric subumbilical surgeries. *J Anaesthesiol Clin Pharmacol* **34**(3): 324-27.
Aliyu I, Kyari F & Ibrahim Z (2016) Hypoglycemia in a Child with Tramadol Poisoning. *Saudi J Med Med Sci* **4**(1): 35-37.
Allegaert K, Cossey V, Debeer A et al (2005a) The impact of ibuprofen on renal clearance in preterm infants is independent of the gestational age. *Pediatr Nephrol* **20**(6): 740–43.
Allegaert K, Mian P, Lapillonne A et al (2019) Maternal paracetamol intake and fetal ductus arteriosus constriction or closure: a case series analysis. *Br J Clin Pharmacol* **85**(1): 245-51.
Allegaert K & Naulaers G (2010) Haemodynamics of intravenous paracetamol in neonates. *Eur J Clin Pharmacol* **66**(9): 855-8.
Allegaert K, Naulaers G, Vanhaesebrouck S et al (2013) The paracetamol concentration-effect relation in neonates. *Paediatr Anaesth* **23**(1): 45–50.
Allegaert K, Palmer GM & Anderson BJ (2011a) The pharmacokinetics of intravenous paracetamol in neonates: size matters most. *Arch Dis Child* **96**(6): 575–80.
Allegaert K, Rochette A & Veyckemans F (2011b) Developmental pharmacology of tramadol during infancy: ontogeny, pharmacogenetics and elimination clearance. *Paediatr Anaesth* **21**(3): 266–73.
Allegaert K, van de Velde M & van den Anker J (2014) Neonatal clinical pharmacology. *Paediatr Anaesth* **24**(1): 30–38.
Allegaert K & van den Anker JN (2016) Neonatal pain management: still in search for the Holy Grail. *Int J Clin Pharmacol Ther* **54**(7): 514-23.
Allegaert K & van den Anker JN (2017) Perinatal and neonatal use of paracetamol for pain relief. *Semin Fetal Neonatal Med* **22**(5): 308-13.
Allegaert K, van den Anker JN, de Hoon JN et al (2008) Covariates of tramadol disposition in the first months of life. *Br J Anaesth* **100**(4): 525–32.
Allegaert K, Vanhole C, de Hoon J et al (2005b) Nonselective cyclo-oxygenase inhibitors and glomerular filtration rate in preterm neonates. *Pediatr Nephrol* **20**(11): 1557–61.
Allely CS (2013) Pain sensitivity and observer perception of pain in individuals with autistic spectrum disorder. *ScientificWorldJournal* **2013**: 916178.

Allen JD, Casavant MJ, Spiller HA et al (2017) Prescription Opioid Exposures Among Children and Adolescents in the United States: 2000-2015. *Pediatrics* **139**(4).
Almenrader N, Larsson P, Passariello M et al (2009) Absorption pharmacokinetics of clonidine nasal drops in children. *Paediatr Anaesth* **19**(3): 257–61.
Alnaami I, Lam FC, Steel G et al (2013) Arteriovenous fistula and pseudoaneurysm of the anterior spinal artery caused by an epidural needle in a 5-year-old patient. *J Neurosurg Pediatr* **11**(3): 340-5.
Altamimi MI, Choonara I & Sammons H (2015) Inter-individual variation in morphine clearance in children. *Eur J Clin Pharmacol* **71**(6): 649-55.
Ambuel B, Hamlett KW, Marx CM et al (1992) Assessing distress in pediatric intensive care environments: the COMFORT scale. *J Pediatr Psychol* **17**(1): 95–109.
American Academy of Pediatrics Task Force on Circumcision (2012) Circumcision policy statement. *Pediatrics* **130**(3): 585-6.
Amory C, Mariscal A, Guyot E et al (2003) Is ilioinguinal/iliohypogastric nerve block always totally safe in children? *Paediatr Anaesth* **13**(2): 164-6.
Amos LB & D'Andrea LA (2013) Severe central sleep apnea in a child with leukemia on chronic methadone therapy. *Pediatr Pulmonol* **48**(1): 85–87.
Anagnostis EA, Sadaka RE, Sailor LA et al (2011) Formulation of buprenorphine for sublingual use in neonates. *J Pediatr Pharmacol Ther* **16**(4): 281-4.
Anand KJ, Anderson BJ, Holford NH et al (2008) Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. *Br J Anaesth* **101**(5): 680–89.
Anand KJ, Barton BA, McIntosh N et al (1999) Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. *Arch Pediatr Adolesc Med* **153**(4): 331–38.
Anand KJ, Clark AE, Willson DF et al (2013a) Opioid analgesia in mechanically ventilated children: results from the multicenter Measuring Opioid Tolerance Induced by Fentanyl study. *Pediatr Crit Care Med* **14**(1): 27–36.
Anand KJ, Clark AE, Willson DF et al (2013b) Opioid analgesia in mechanically ventilated children: results from the multicenter Measuring Opioid Tolerance Induced by Fentanyl study. *Pediatr Crit Care Med* **14**(1): 27–36.
Anand KJ, Hall RW, Desai N et al (2004) Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet* **363**(9422): 1673–82.
Anand KJ, Willson DF, Berger J et al (2010) Tolerance and withdrawal from prolonged opioid use in critically ill children. *Pediatrics* **125**(5): e1208–25.
Anand P, Wilson R & Sheehy EC (2005) Intraligamental analgesia for post-operative pain control in children having dental extractions under general anaesthesia. *Eur J Paediatr Dent* **6**(1): 10–15.
Anantha RV, Stewart TC, Rajagopalan A et al (2014) Analgesia in the management of paediatric and adolescent trauma during the resuscitative phase: the role of the pediatric trauma centre. *Injury* **45**(5): 845-9.
Ancora G, Lago P, Garetti E et al (2013) Efficacy and safety of continuous infusion of fentanyl for pain control in preterm newborns on mechanical ventilation. *J Pediatr* **163**(3): 645-51 e1.
Ancora G, Lago P, Garetti E et al (2017) Follow-up at the corrected age of 24 months of preterm newborns receiving continuous infusion of fentanyl for pain control during mechanical ventilation. *Pain* **158**(5): 840-45.
Andersen RD, Langius-Eklof A, Nakstad B et al (2017) The measurement properties of pediatric observational pain scales: A systematic review of reviews. *Int J Nurs Stud* **73**: 93-101.
Anderson B, Kanagasundarum S & Woollard G (1996) Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model. *Anaesth Intensive Care* **24**(6): 669–73.
Anderson BJ & Allegaert K (2009) Intravenous neonatal paracetamol dosing: the magic of 10 days. *Paediatr Anaesth* **19**(4): 289–95.
Anderson BJ & Dare T (2014a) We need to confirm, not relearn old information. *Paediatr Anaesth* **24**(6): 549–52.
Anderson BJ & Holford NH (2011) Tips and traps analyzing pediatric PK data. *Paediatr Anaesth* **21**(3): 222–37.
Anderson BJ & Holford NH (2017a) What is the best size predictor for dose in the obese child? *Paediatr Anaesth* **27**(12): 1176-84.
Anderson BJ, McKee AD & Holford NH (1997) Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. *Clin Pharmacokinet* **33**(5): 313-27.
Anderson BJ, Thomas J, Ottaway K et al (2017b) Tramadol: keep calm and carry on. *Paediatr Anaesth* **27**(8): 785-88.
Anderson BJ & van den Anker J (2014b) Why is there no morphine concentration-response curve for acute pain? *Paediatr Anaesth* **24**(3): 233–8.
Anderson BJ, van Lingen RA, Hansen TG et al (2002) Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. *Anesthesiology* **96**(6): 1336–45.
Anderson BJ, Woollard GA & Holford NH (2001) Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy. *Eur J Clin Pharmacol* **57**(8): 559–69.
Anderson KT, Bartz-Kurycki MA, Ferguson DM et al (2018) Too much of a bad thing: Discharge opioid prescriptions in pediatric appendectomy patients. *J Pediatr Surg* **53**(12): 2374-77.
Andreoli SP (2004) Acute renal failure in the newborn. *Semin Perinatol* **28**(2): 112–23.

Andrews KA, Desai D, Dhillon HK et al (2002) Abdominal sensitivity in the first year of life: comparison of infants with and without prenatally diagnosed unilateral hydronephrosis. *Pain* **100**(1–2): 35–46.
Anghelescu DL, Burgoyne LL, Faughnan LG et al (2013) Prospective randomized crossover evaluation of three anesthetic regimens for painful procedures in children with cancer. *J Pediatr* **162**(1): 137–41.
Anghelescu DL, Burgoyne LL, Oakes LL et al (2005) The safety of patient-controlled analgesia by proxy in pediatric oncology patients. *Anesth Analg* **101**(6): 1623–27.
Anghelescu DL, Faughnan LG, Baker JN et al (2010) Use of epidural and peripheral nerve blocks at the end of life in children and young adults with cancer: the collaboration between a pain service and a palliative care service. *Paediatr Anaesth* **20**(12): 1070–77.
Anghelescu DL, Faughnan LG, Hankins GM et al (2011a) Methadone use in children and young adults at a cancer center: a retrospective study. *J Opioid Manag* **7**(5): 353–61.
Anghelescu DL, Faughnan LG, Jeha S et al (2011b) Neuropathic pain during treatment for childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* **57**(7): 1147–53.
Anghelescu DL, Faughnan LG, Oakes LL et al (2012) Parent-controlled PCA for pain management in pediatric oncology: is it safe? *J Pediatr Hematol Oncol* **34**(6): 416–20.
Anghelescu DL, Faughnan LG, Popenhagen MP et al (2014) Neuropathic pain referrals to a multidisciplinary pediatric cancer pain service. *Pain Manag Nurs* **15**(1): 126–31.
Anghelescu DL, Goldberg JL, Faughnan LG et al (2015a) Comparison of pain outcomes between two anti-GD2 antibodies in patients with neuroblastoma. *Pediatr Blood Cancer* **62**(2): 224-28.
Anghelescu DL, Pankayatselvan V, Nguyen R et al (2019a) Bisphosphonate Use in Pediatric Oncology for Pain Management. *Am J Hosp Palliat Care* **36**(2): 138-42.
Anghelescu DL, Patel RM, Mahoney DP et al (2016) Methadone prolongs cardiac conduction in young patients with cancer-related pain. *J Opioid Manag* **12**(2): 131-8.
Anghelescu DL, Ross CE, Oakes LL et al (2008) The safety of concurrent administration of opioids via epidural and intravenous routes for postoperative pain in pediatric oncology patients. *J Pain Symptom Manage* **35**(4): 412–19.
Anghelescu DL, Snaman JM, Trujillo L et al (2015b) Patient-controlled analgesia at the end of life at a pediatric oncology institution. *Pediatr Blood Cancer* **62**(7): 1237-44.
Anghelescu DL, Steen BD, Wu H et al (2017) Prospective study of neuropathic pain after definitive surgery for extremity osteosarcoma in a pediatric population. *Pediatr Blood Cancer* **64**(3).
Anghelescu DL & Tesney JM (2019b) Neuropathic Pain in Pediatric Oncology: A Clinical Decision Algorithm. *Paediatr Drugs* **21**(2): 59-70.
Anghelescu DL, Zhang K, Faughnan LG et al (2015c) The Safety and Effectiveness of Patient-controlled Analgesia in Outpatient Children and Young Adults With Cancer: A Retrospective Study. *J Pediatr Hematol Oncol* **37**(5): 378-82.
Anie KA & Green J (2015) Psychological therapies for sickle cell disease and pain. *Cochrane Database Syst Rev*(5): CD001916.
Annequin D, Carbajal R, Chauvin P et al (2000) Fixed 50% nitrous oxide oxygen mixture for painful procedures: A French survey. *Pediatrics* **105**(4): E47.
Anouar J, Mohamed S, Sofiene A et al (2016) The analgesic effect of clonidine as an adjuvant in dorsal penile nerve block. *Pan Afr Med J* **23**: 213.
Ansermino M, Basu R, Vandebeek C et al (2003) Nonopioid additives to local anaesthetics for caudal blockade in children: a systematic review. *Paediatr Anaesth* **13**(7): 561–73.
Antila H, Manner T, Kuurila K et al (2006) Ketoprofen and tramadol for analgesia during early recovery after tonsillectomy in children. *Paediatr Anaesth* **16**(5): 548–53.
Antok E, Bordet F, Duflo F et al (2003) Patient-controlled epidural analgesia versus continuous epidural infusion with ropivacaine for postoperative analgesia in children. *Anesth Analg* **97**(6): 1608–11.
ANZBA (2014) Initial Management of Severe Burns.
ANZCA (2015) *Stop before you block guide.* http://www.anzca.edu.au/documents/stop-blocking-flyer-a4-p1 Accessed 10 February 2020
APAGBI (2012) Good practice in postoperative and procedural pain management, 2nd edition. *Paediatr Anaesth* **22 Suppl 1**: 1–79.
Apiliogullari S, Duman A, Gok F et al (2010) Spinal needle design and size affect the incidence of postdural puncture headache in children. *Paediatr Anaesth* **20**(2): 177–82.
Apiliogullari S, Duman A, Gok F et al (2009) Efficacy of a low-dose spinal morphine with bupivacaine for postoperative analgesia in children undergoing hypospadias repair. *Paediatr Anaesth* **19**(11): 1078–83.
Aranda JV, Salomone F, Valencia GB et al (2017) Non-steroidal Anti-inflammatory Drugs in Newborns and Infants. *Pediatr Clin North Am* **64**(6): 1327-40.
Aranda JV & Thomas R (2006) Systematic review: intravenous Ibuprofen in preterm newborns. *Semin Perinatol* **30**(3): 114–20.
Arapostathis KN, Dabarakis NN, Coolidge T et al (2010) Comparison of acceptance, preference, and efficacy between jet injection INJEX and local infiltration anesthesia in 6 to 11 year old dental patients. *Anesth Prog* **57**(1): 3–12.

Aravamuthan BR, Mar SS & Williams KG (2017) Factors Associated With Discharge After Initial Emergency Treatment of Pediatric Migraine. *Pediatr Emerg Care* **33**(9): 620-29.

Arevalo-Rodriguez I, Munoz L, Godoy-Casasbuenas N et al (2017) Needle gauge and tip designs for preventing post-dural puncture headache (PDPH). *Cochrane Database Syst Rev* **4**: Cd010807.

Ari P, Kars M, Meany H et al (2018) Treatment of Transient Peripheral Neuropathy During Chimeric 14.18 Antibody Therapy in Children With Neuroblastoma: A Case Series. *J Pediatr Hematol Oncol* **40**(2): e113-e16.

Arikoglu T, Aslan G, Yildirim DD et al (2017) Discrepancies in the diagnosis and classification of nonsteroidal anti-inflammatory drug hypersensitivity reactions in children. *Allergol Int* **66**(3): 418-24.

Arirachakaran A, Siripaiboonkij M, Pairuchvej S et al (2018) Comparative outcomes of epidural steroids versus placebo after lumbar discectomy in lumbar disc herniation: a systematic review and meta-analysis of randomized controlled trials. *Eur J Orthop Surg Traumatol* **28**(8): 1589-99.

Arnautovic T, Sommese K, Mullan PC et al (2018) Evaluating the Implementation Barriers of an Intranasal Fentanyl Pain Pathway for Pediatric Long-Bone Fractures. *Pediatr Emerg Care* **34**(7): 473-78.

Ashley PF, Parekh S, Moles DR et al (2016) Preoperative analgesics for additional pain relief in children and adolescents having dental treatment. *Cochrane Database Syst Rev*(8): CD008392.

Aslan N, Yildizdas D, Arslan D et al (2019) Intravenous Paracetamol Overdose: A Pediatric Case Report. *Pediatr Emerg Care* **35**(2): e42-e43.

Aspirot A, Puligandla PS, Bouchard S et al (2008) A contemporary evaluation of surgical outcome in neonates and infants undergoing lung resection. *J Pediatr Surg* **43**(3): 508–12.

Assouline RB, Tramèr RM, Kreienbühl RL et al (2016) Benefit and harm of adding ketamine to an opioid in a patient-controlled analgesia device for the control of postoperative pain: systematic review and meta-analyses of randomized controlled trials with trial sequential analyses. *PAIN* **157**(12): 2854-64.

Atee M, Hoti K & Hughes JD (2018) A Technical Note on the PainChek System: A Web Portal and Mobile Medical Device for Assessing Pain in People With Dementia. *Front Aging Neurosci* **10**: 117.

Atef A & Fawaz AA (2008) Peritonsillar infiltration with tramadol improves pediatric tonsillectomy pain. *Eur Arch Otorhinolaryngol* **265**(5): 571–74.

Atkinson P, Chesters A & Heinz P (2009) Pain management and sedation for children in the emergency department. *BMJ* **339**: b4234.

Atzori B, Hoffman HG, Vagnoli L et al (2018) Virtual Reality Analgesia During Venipuncture in Pediatric Patients With Onco-Hematological Diseases. *Front Psychol* **9**: 2508.

Aveline C, Le Hetet H, Le Roux A et al (2015) A survey of the administration of prednisolone versus ibuprofen analgesic protocols after ambulatory tonsillectomy. *Anaesth Crit Care Pain Med* **34**(5): 281-7.

Ayatollahi V, Behdad S, Hatami M et al (2012) Comparison of peritonsillar infiltration effects of ketamine and tramadol on post tonsillectomy pain: a double-blinded randomized placebo-controlled clinical trial. *Croat Med J* **53**(2): 155–61.

Aydogan MS, Korkmaz MF, Ozgul U et al (2013) Pain, fentanyl consumption, and delirium in adolescents after scoliosis surgery: dexmedetomidine vs midazolam. *Paediatr Anaesth* **23**(5): 446–52.

Aysenur D, Mine C, Ozgur Y et al (2014) Pre-emptive peritonsillar dexamethasone vs. levobupivacaine infiltration for relief of post-adenotonsillectomy pain in children: a controlled clinical study. *Int J Pediatr Otorhinolaryngol* **78**(9): 1467–71.

Ayulo MA, Jr., Phillips KE & Tripathi S (2018) Safety and Efficacy of IV Lidocaine in the Treatment of Children and Adolescents With Status Migraine. *Pediatr Crit Care Med* **19**(8): 755-59.

Azarmnejad E, Sarhangi F, Javadi M et al (2017) The effectiveness of familiar auditory stimulus on hospitalized neonates' physiologic responses to procedural pain. *Int J Nurs Pract* **23**(3).

Baarslag MA, Ista E, de Leeuw T et al (2018) Clinically effective implementation of intravenous paracetamol as primary analgesia after major surgery in neonates and young infants. *Arch Dis Child* **103**(12): 1168-69.

Baartmans MG, de Jong AE, van Baar ME et al (2016) Early management in children with burns: Cooling, wound care and pain management. *Burns* **42**(4): 777-82.

Baba LR, McGrath JM & Liu J (2010) The efficacy of mechanical vibration analgesia for relief of heel stick pain in neonates: a novel approach. *J Perinat Neonatal Nurs* **24**(3): 274–83.

Babl F, Barnett P, Palmer G et al (2007) A pilot study of inhaled methoxyflurane for procedural analgesia in children. *Paediatr Anaesth* **17**(2): 148–53.

Babl FE, Belousoff J, Deasy C et al (2010) Paediatric procedural sedation based on nitrous oxide and ketamine: sedation registry data from Australia. *Emerg Med J* **27**(8): 607–12.

Babl FE, Goldfinch C, Mandrawa C et al (2009) Does nebulized lidocaine reduce the pain and distress of nasogastric tube insertion in young children? A randomized, double-blind, placebo-controlled trial. *Pediatrics* **123**(6): 1548–55.

Babl FE, Jamison SR, Spicer M et al (2006) Inhaled methoxyflurane as a prehospital analgesic in children. *Emerg Med Australas* **18**(4): 404–10.

Baccei ML (2010) Modulation of developing dorsal horn synapses by tissue injury. *Ann NY Acad Sci* **1198**: 159–67.

Bachur RG, Monuteaux MC & Neuman MI (2015) A comparison of acute treatment regimens for migraine in the emergency department. *Pediatrics* **135**(2): 232-8.
Baddam S, Aban I, Hilliard L et al (2017) Acute kidney injury during a pediatric sickle cell vaso-occlusive pain crisis. *Pediatric Nephrology* **32**(8): 1451-56.
Badiee Z, Sadeghnia A & Zarean N (2014) Suprapubic Bladder Aspiration or Urethral Catheterization: Which is More Painful in Uncircumcised Male Newborns? *Int J Prev Med* **5**(9): 1125-30.
Badovinac S, Gennis H, Riddell RP et al (2018) Understanding the Relative Contributions of Sensitive and Insensitive Parent Behaviors on Infant Vaccination Pain. *Children (Basel)* **5**(6).
Baeriswyl M, Zeiter F, Piubellini D et al (2018) The analgesic efficacy of transverse abdominis plane block versus epidural analgesia: A systematic review with meta-analysis. *Medicine (Baltimore)* **97**(26): e11261.
Bai J, Harper FWK, Penner LA et al (2017) Parents' Verbal and Nonverbal Caring Behaviors and Child Distress During Cancer-Related Port Access Procedures: A Time-Window Sequential Analysis. *Oncol Nurs Forum* **44**(6): 675-87.
Bai J, Swanson KM, Harper FWK et al (2018) Longitudinal Analysis of Parent Communication Behaviors and Child Distress during Cancer Port Start Procedures. *Pain Manag Nurs* **19**(5): 487-96.
Bailey B, Gravel J & Daoust R (2012) Reliability of the visual analog scale in children with acute pain in the emergency department. *Pain* **153**(4): 839–42.
Bailey L, Sun J, Courtney M et al (2015) Improving postoperative tonsillectomy pain management in children--a double blinded randomised control trial of a patient analgesia information sheet. *Int J Pediatr Otorhinolaryngol* **79**(5): 732-9.
Baines D (2011) Anaesthetic considerations for the obese child. *Paediatr Respir Rev* **12**(2): 144-7.
Baird R, Guilbault MP, Tessier R et al (2013) A systematic review and meta-analysis of caudal blockade versus alternative analgesic strategies for pediatric inguinal hernia repair. *J Pediatr Surg* **48**(5): 1077-85.
Baker M, Scott B, Johnson RF et al (2017) Predictors of Obstructive Sleep Apnea Severity in Adolescents. *JAMA Otolaryngol Head Neck Surg* **143**(5): 494-99.
Bakshi SG, Doctor JR, Trivedi BD et al (2017) Transversus abdominis plane catheters for postoperative pain relief in pediatric patients. *J Anaesthesiol Clin Pharmacol* **33**(1): 121-22.
Ballard A, Khadra C, Adler S et al (2019) Efficacy of the Buzzy Device for Pain Management During Needle-related Procedures: A Systematic Review and Meta-Analysis. *Clin J Pain* **35**(6): 532-43.
Balyan R, Mecoli M, Venkatasubramanian R et al (2017a) CYP2D6 pharmacogenetic and oxycodone pharmacokinetic association study in pediatric surgical patients. *Pharmacogenomics* **18**(4): 337-48.
Balyan R, Zhang X, Chidambaran V et al (2017b) OCT1 genetic variants are associated with postoperative morphine-related adverse effects in children. *Pharmacogenomics* **18**(7): 621-29.
Bandstra NF & Chambers CT (2008) Pain assessment in children. In: *Clinical Pain Management: Practice and Procedures* 2nd edn. Breivik H, Campbell WI and Nicholas MK (eds). London, Hodder Arnold. 447–61.
Bar-Meir E, Zaslansky R, Regev E et al (2006) Nitrous oxide administered by the plastic surgeon for repair of facial lacerations in children in the emergency room. *Plast Reconstr Surg* **117**(5): 1571-5.
Barcelos A, Garcia PC, Portela JL et al (2015) Comparison of two analgesia protocols for the treatment of pediatric orthopedic emergencies. *Rev Assoc Med Bras (1992)* **61**(4): 362-7.
Bardellini E, Amadori F, Schumacher RF et al (2016) Efficacy of a Solution Composed by Verbascoside, Polyvinylpyrrolidone (PVP) and Sodium Hyaluronate in the Treatment of Chemotherapy-induced Oral Mucositis in Children With Acute Lymphoblastic Leukemia. *J Pediatr Hematol Oncol* **38**(7): 559-62.
Baris S, Karakaya D, Kelsaka E et al (2003) Comparison of fentanyl-bupivacaine or midazolam-bupivacaine mixtures with plain bupivacaine for caudal anaesthesia in children. *Paediatr Anaesth* **13**(2): 126–31.
Barkan S, Breitbart R, Brenner-Zada G et al (2014) A double-blind, randomised, placebo-controlled trial of oral midazolam plus oral ketamine for sedation of children during laceration repair. *Emerg Med J* **31**(8): 649–53.
Bartu AE, Ilett KF, Hackett LP et al (2012) Buprenorphine exposure in infants of opioid-dependent mothers at birth. *Aust N Z J Obstet Gynaecol* **52**(4): 342-7.
Basco WT, Jr., Ebeling M, Garner SS et al (2015) Opioid Prescribing and Potential Overdose Errors Among Children 0 to 36 Months Old. *Clin Pediatr (Phila)* **54**(8): 738-44.
Basker S, Singh G & Jacob R (2009) Clonidine in paediatrics - a review. *Indian J Anaesth* **53**(3): 270–80.
Batra YK, Arya VK, Mahajan R et al (2003) Dose response study of caudal neostigmine for postoperative analgesia in paediatric patients undergoing genitourinary surgery. *Paediatr Anaesth* **13**(6): 515–21.
Batra YK, Lokesh VC, Panda NB et al (2008) Dose-response study of intrathecal fentanyl added to bupivacaine in infants undergoing lower abdominal and urologic surgery. *Paediatr Anaesth* **18**(7): 613–19.
Bauer AZ, Kriebel D, Herbert MR et al (2018) Prenatal paracetamol exposure and child neurodevelopment: A review. *Horm Behav* **101**: 125-47.
Baxter KJ, Hafling J, Sterner J et al (2018) Effectiveness of gabapentin as a postoperative analgesic in children undergoing appendectomy. *Pediatr Surg Int* **34**(7): 769-74.
Bayon-Mottu M, Gambart G, Deries X et al (2014) Pain during injections of botulinum toxin in children: Influence of the localization technique. *Ann Phys Rehabil Med* **57**(9-10): 578-86.

Bean-Lijewski JD (1997) Glossopharyngeal nerve block for pain relief after pediatric tonsillectomy: retrospective analysis and two cases of life-threatening upper airway obstruction from an interrupted trial. *Anesth Analg* **84**(6): 1232–38.

Becke K, Albrecht S, Schmitz B et al (2005) Intraoperative low-dose S-ketamine has no preventive effects on postoperative pain and morphine consumption after major urological surgery in children. *Paediatr Anaesth* **15**(6): 484–90.

Beggs S (2015) Long-Term Consequences of Neonatal Injury. *Can J Psychiatry* **60**(4): 176-80.

Beirne PV, Hennessy S, Cadogan SL et al (2018) Needle size for vaccination procedures in children and adolescents. *Cochrane Database Syst Rev* **8**: Cd010720.

Belda S, Pallas CR, De la Cruz J et al (2004) Screening for retinopathy of prematurity: is it painful? *Biol Neonate* **86**(3): 195–200.

Bell J, Paget SP, Nielsen TC et al (2019a) Prescription opioid dispensing in Australian children and adolescents: a national population-based study. *Lancet Child Adolesc Health* **3**(12): 881-88.

Bell TM, Raymond J, Vetor A et al (2019b) Long-term prescription opioid utilization, substance use disorders, and opioid overdoses after adolescent trauma. *J Trauma Acute Care Surg* **87**(4): 836-40.

Bellieni CV, Alagna MG & Buonocore G (2013) Analgesia for infants' circumcision. *Ital J Pediatr* **39**: 38.

Bellieni CV, Vannuccini S & Petraglia F (2018) Is fetal analgesia necessary during prenatal surgery? *J Matern Fetal Neonatal Med* **31**(9): 1241-45.

Bellis JR, Pirmohamed M, Nunn AJ et al (2014) Dexamethasone and haemorrhage risk in paediatric tonsillectomy: a systematic review and meta-analysis. *Br J Anaesth* **113**(1): 23–42.

Bellon M, Le Bot A, Michelet D et al (2016) Efficacy of Intraoperative Dexmedetomidine Compared with Placebo for Postoperative Pain Management: A Meta-Analysis of Published Studies. *Pain Ther* **5**(1): 63-80.

Bellu R, de Waal KA & Zanini R (2008) Opioids for neonates receiving mechanical ventilation. *Cochrane Database Syst Rev* **1**: CD004212.

Beltramini A, Galinski M, Chabernaud JL et al (2019) Pain Assessment in Children Younger Than 8 Years in Out-of-Hospital Emergency Medicine: Reliability and Validity of EVENDOL Score. *Pediatr Emerg Care* **35**(2): 125-31.

Bembich S, Brovedani P, Cont G et al (2015) Pain activates a defined area of the somatosensory and motor cortex in newborn infants. *Acta Paediatr* **104**(11): e530-3.

Bembich S, Marrazzo F, Barini A et al (2016) The cortical response to a noxious procedure changes over time in preterm infants. *Pain* **157**(9): 1979-87.

Ben-Pazi H, Cohen A, Kroyzer N et al (2017) Clown-care reduces pain in children with cerebral palsy undergoing recurrent botulinum toxin injections- A quasi-randomized controlled crossover study. *PLoS One* **12**(4): e0175028.

Bendall JC, Simpson PM & Middleton PM (2011a) Effectiveness of prehospital morphine, fentanyl, and methoxyflurane in pediatric patients. *Prehosp Emerg Care* **15**(2): 158–65.

Bendall JC, Simpson PM & Middleton PM (2011b) Prehospital analgesia in New South Wales, Australia. *Prehosp Disaster Med* **26**(6): 422–26.

Bender JL, Radhakrishnan A, Diorio C et al (2011) Can pain be managed through the Internet? A systematic review of randomized controlled trials. *Pain* **152**(8): 1740–50.

Bengali R, Huang MS & Gulur P (2014) The use of an intrathecal pump to manage intractable cancer pain in a pediatric patient: a case report. *J Pediatr Hematol Oncol* **36**(3): e162–4.

Benner KW & Durham SH (2011) Meperidine restriction in a pediatric hospital. *J Pediatr Pharmacol Ther* **16**(3): 185–90.

Bennett KG, Harbaugh CM, Hu HM et al (2018) Persistent Opioid Use Among Children, Adolescents, and Young Adults After Common Cleft Operations. *J Craniofac Surg* **29**(7): 1697-701.

Benoit B, Martin-Misener R, Latimer M et al (2017a) Breast-Feeding Analgesia in Infants: An Update on the Current State of Evidence. *J Perinat Neonatal Nurs* **31**(2): 145-59.

Benoit B, Martin-Misener R, Newman A et al (2017b) Neurophysiological assessment of acute pain in infants: a scoping review of research methods. *Acta Paediatr* **106**(7): 1053-66.

Berde C, Koka A & Donado-Rincon C (2016) Lidocaine Infusions and Other Options for Opioid-Resistant Pain Due to Pediatric Advanced Cancer. *Pediatr Blood Cancer* **63**(7): 1141-3.

Berde CB, Lehn BM, Yee JD et al (1991) Patient-controlled analgesia in children and adolescents: a randomized, prospective comparison with intramuscular administration of morphine for postoperative analgesia. *J Pediatr* **118**(3): 460-6.

Berde CB, Walco GA, Krane EJ et al (2012) Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. *Pediatrics* **129**(2): 354–64.

Berde CB, Yaster M, Meretoja O et al (2008) Stable plasma concentrations of unbound ropivacaine during postoperative epidural infusion for 24-72 hours in children. *Eur J Anaesthesiol* **25**(5): 410–17.

Bergomi P, Scudeller L, Pintaldi S et al (2018) Efficacy of Non-pharmacological Methods of Pain Management in Children Undergoing Venipuncture in a Pediatric Outpatient Clinic: A Randomized Controlled Trial of Audiovisual Distraction and External Cold and Vibration. *J Pediatr Nurs* **42**: e66-e72.

Bernabe-Garcia M, Lopez-Alarcon M, Salgado-Sosa A et al (2016) Enteral Docosahexaenoic Acid Reduces Analgesic Administration in Neonates Undergoing Cardiovascular Surgery. *Ann Nutr Metab* **69**(2): 150-60.

Bernards CM, Hadzic A, Suresh S et al (2008) Regional anesthesia in anesthetized or heavily sedated patients. *Reg Anesth Pain Med* **33**(5): 449–60.
Berta E, Spanhel J, Smakal O et al (2008) Single injection paravertebral block for renal surgery in children. *Paediatr Anaesth* **18**(7): 593–97.
Best KM, Boullata JI & Curley MAQ (2015) Risk factors associated with iatrogenic opioid and benzodiazepine withdrawal in critically ill pediatric patients: a systematic review and conceptual model. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* **16**(2): 175-83.
Bhananker SM, Azavedo LF & Splinter WM (2008) Addition of morphine to local anesthetic infiltration does not improve analgesia after pediatric dental extractions. *Paediatr Anaesth* **18**(2): 140–44.
Bharti B, Grewal A, Kalia R et al (2010) Vaccine related reactogenicity for primary immunization: a randomized controlled trial of 23(wider) vs. 25(narrower) gauge needles with same lengths. *Indian J Pediatr* **77**(11): 1241–46.
Biagioli E, Tarasco V, Lingua C et al (2016) Pain-relieving agents for infantile colic. *Cochrane Database Syst Rev* **9**: Cd009999.
Bianciotto M, Chiappini E, Raffaldi I et al (2013) Drug use and upper gastrointestinal complications in children: a case-control study. *Arch Dis Child* **98**(3): 218-21.
Bieri D, Reeve RA, Champion GD et al (1990) The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: development, initial validation, and preliminary investigation for ratio scale properties. *Pain* **41**(2): 139–50.
Bigal LM, Bibeau K & Dunbar S (2019) Tramadol Prescription over a 4-Year Period in the USA. *Curr Pain Headache Rep* **23**(10): 76.
Bilgili B, Bozkurt I, Bozkurt P et al (2012) Prolonged apnea and sedation in premature babies with the use of oral tramadol. *J Clin Case Rep* **2**(10): 163.
Binswanger IA & Glanz JM (2015) Pharmaceutical Opioids in the Home and Youth: Implications for Adult Medical Practice. *Substance abuse* **36**(2): 141-43.
Biran V, Gourrier E, Cimerman P et al (2011) Analgesic effects of EMLA cream and oral sucrose during venipuncture in preterm infants. *Pediatrics* **128**(1): e63–70.
Birchley G (2009) Opioid and benzodiazepine withdrawal syndromes in the paediatric intensive care unit: a review of recent literature. *Nurs Crit Care* **14**(1): 26–37.
Birnie KA, Chambers CT, Taddio A et al (2015) Psychological Interventions for Vaccine Injections in Children and Adolescents: Systematic Review of Randomized and Quasi-Randomized Controlled Trials. *Clin J Pain* **31**(10 Suppl): S72-89.
Birnie KA, Hundert AS, Lalloo C et al (2019) Recommendations for selection of self-report pain intensity measures in children and adolescents: a systematic review and quality assessment of measurement properties. *Pain* **160**(1): 5-18.
Birnie KA, Noel M, Chambers CT et al (2018) Psychological interventions for needle-related procedural pain and distress in children and adolescents. *Cochrane Database Syst Rev* **10**: Cd005179.
Black KJ, Bevan CA, Murphy NG et al (2013) Nerve blocks for initial pain management of femoral fractures in children. *Cochrane Database Syst Rev*(12): Cd009587.
Blackburn L, Almenrader N, Larsson P et al (2014) Intranasal clonidine pharmacokinetics. *Paediatr Anaesth* **24**(3): 340-2.
Blais C, Fiset D, Furumoto-Deshaies H et al (2019) Facial Features Underlying the Decoding of Pain Expressions. *J Pain* **20**(6): 728-38.
Blanca-Lopez N, Cornejo-Garcia JA, Perez-Alzate D et al (2015) Hypersensitivity Reactions to Nonsteroidal Anti-inflammatory Drugs in Children and Adolescents: Selective Reactions. *J Investig Allergol Clin Immunol* **25**(6): 385-95.
Blumenthal S, Borgeat A, Nadig M et al (2006) Postoperative analgesia after anterior correction of thoracic scoliosis: a prospective randomized study comparing continuous double epidural catheter technique with intravenous morphine. *Spine* **31**(15): 1646–51.
Blumenthal S, Min K, Nadig M et al (2005) Double epidural catheter with ropivacaine versus intravenous morphine: a comparison for postoperative analgesia after scoliosis correction surgery. *Anesthesiology* **102**(1): 175–80.
Boretsky K, Visoiu M & Bigeleisen P (2013) Ultrasound-guided approach to the paravertebral space for catheter insertion in infants and children. *Paediatr Anaesth* **23**(12): 1193-8.
Borgeat A, Ofner C, Saporito A et al (2018) The effect of nonsteroidal anti-inflammatory drugs on bone healing in humans: A qualitative, systematic review. *J Clin Anesth* **49**: 92-100.
Borland ML, Bergesio R, Pascoe EM et al (2005) Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. *Burns* **31**(7): 831–37.
Borland ML, Clark LJ & Esson A (2008) Comparative review of the clinical use of intranasal fentanyl versus morphine in a paediatric emergency department.[Erratum appears in Emerg Med Australas. 2009 Apr;21(2):166 Note: Dosage error in article text], [Erratum appears in Emerg Med Australas. 2009 Jun;21(3):246 Note: Dosage error in article text]. *Emergency Medicine Australasia* **20**(6): 515–20.

Borodovsky JT, Levy S, Fishman M et al (2018) Buprenorphine Treatment for Adolescents and Young Adults With Opioid Use Disorders: A Narrative Review. *J Addict Med* **12**(3): 170-83.
Borys D, Stanton M, Gummin D et al (2015) Tapentadol toxicity in children. *Pediatrics* **135**(2): e392-6.
Bos-Veneman NGP, Otter M & Reijneveld SA (2018) Using feeding to reduce pain during vaccination of formula-fed infants: a randomised controlled trial. *Arch Dis Child* **103**(12): 1132-37.
Bosenberg AT, Thomas J, Cronje L et al (2005) Pharmacokinetics and efficacy of ropivacaine for continuous epidural infusion in neonates and infants. *Paediatr Anaesth* **15**(9): 739–49.
Bougea A, Spantideas N & Chrousos GP (2018) Stress management for headaches in children and adolescents: A review and practical recommendations for health promotion programs and well-being. *J Child Health Care* **22**(1): 19-33.
Bourdier S, Khelif N, Velasquez M et al (2019) Cold Vibration (Buzzy) Versus Anesthetic Patch (EMLA) for Pain Prevention During Cannulation in Children: A Randomized Trial. *Pediatr Emerg Care*.
Bouwmeester NJ, Anand KJ, van Dijk M et al (2001) Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. *Br J Anaesth* **87**(3): 390–99.
Bouwmeester NJ, Anderson BJ, Tibboel D et al (2004) Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. *Br J Anaesth* **92**(2): 208–17.
Bouwmeester NJ, Hop WC, van Dijk M et al (2003a) Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism. *Intensive Care Med* **29**(11): 2009–15.
Bouwmeester NJ, van den Anker JN, Hop WC et al (2003b) Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants. *Br J Anaesth* **90**(5): 642–52.
Boyd CJ, McCabe SE, Cranford JA et al (2006) Adolescents' motivations to abuse prescription medications. *Pediatrics* **118**(6): 2472-80.
Bozkurt P (2005) Use of tramadol in children. *Paediatr Anaesth* **15**(12): 1041–47.
Bozkurt P, Kaya G & Yeker Y (1997) Single-injection lumbar epidural morphine for postoperative analgesia in children: a report of 175 cases. *Reg Anesth* **22**(3): 212–17.
Bozkurt P, Kaya G, Yeker Y et al (2004) Effectiveness of morphine via thoracic epidural vs intravenous infusion on postthoracotomy pain and stress response in children. *Paediatr Anaesth* **14**(9): 748–54.
Brady-Fryer B, Wiebe N & Lander JA (2004) Pain relief for neonatal circumcision. *Cochrane Database Syst Rev* **4**: CD004217.
Braga LH, Jegatheeswaran K, McGrath M et al (2017) Cause and Effect versus Confounding-Is There a True Association between Caudal Blocks and Tubularized Incised Plate Repair Complications? *J Urol* **197**(3 Pt 2): 845-51.
Brahmbhatt A, Adeloye T, Ercole A et al (2012) Assessment of post-operative pain in children: who knows best? *Pediatr Rep* **4**(1): e10.
Brandlistuen RE, Ystrom E, Nulman I et al (2013) Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol* **42**(6): 1702-13.
Brands B, Paglia-Boak A, Sproule BA et al (2010) Nonmedical use of opioid analgesics among Ontario students. *Can Fam Physician* **56**(3): 256-62.
Bravenboer-Monster K, Keyzer-Dekker C, van Dijk M et al (2019) Efficacy of Epidural Analgesia after Laparotomy in Children. *Eur J Pediatr Surg* **29**(2): 209-14.
Bray RJ, Woodhams AM, Vallis CJ et al (1996) Morphine consumption and respiratory depression in children receiving postoperative analgesia from continuous morphine infusion or patient controlled analgesia. *Paediatr Anaesth* **6**(2): 129–34.
Breau LM & Burkitt C (2009) Assessing pain in children with intellectual disabilities. *Pain Res Manag* **14**(2): 116–20.
Breau LM, Finley GA, McGrath PJ et al (2002a) Validation of the Non-communicating Children's Pain Checklist-Postoperative Version. *Anesthesiology* **96**(3): 528–35.
Breau LM, McGrath PJ, Camfield CS et al (2002b) Psychometric properties of the non-communicating children's pain checklist-revised. *Pain* **99**(1-2): 349–57.
Breau LM, McGrath PJ, Stevens B et al (2006) Judgments of pain in the neonatal intensive care setting: a survey of direct care staffs' perceptions of pain in infants at risk for neurological impairment. *Clin J Pain* **22**(2): 122–29.
Bredmose PP, Grier G, Davies GE et al (2009a) Pre-hospital use of ketamine in paediatric trauma. *Acta Anaesthesiol Scand* **53**(4): 543–45.
Bredmose PP, Lockey DJ, Grier G et al (2009b) Pre-hospital use of ketamine for analgesia and procedural sedation. *Emerg Med J* **26**(1): 62–64.
Brenchley J & Ramlakhan S (2006) Intranasal alfentanil for acute pain in children. *Emerg Med J* **23**(6): 488.
Brenner L, Marhofer P, Kettner SC et al (2011) Ultrasound assessment of cranial spread during caudal blockade in children: the effect of different volumes of local anaesthetics. *Br J Anaesth* **107**(2): 229–35.
Brenner SM, Rupp V, Boucher J et al (2013) A randomized, controlled trial to evaluate topical anesthetic for 15 minutes before venipuncture in pediatrics. *Am J Emerg Med* **31**(1): 20–25.
Breschan C, Jost R, Krumpholz R et al (2005) A prospective study comparing the analgesic efficacy of levobupivacaine, ropivacaine and bupivacaine in pediatric patients undergoing caudal blockade. *Paediatr Anaesth* **15**(4): 301–06.

Breslin K, Boniface K & Cohen J (2014) Ultrasound-guided intra-articular lidocaine block for reduction of anterior shoulder dislocation in the pediatric emergency department. *Pediatr Emerg Care* **30**(3): 217-20.
Bressolle F, Rochette A, Khier S et al (2009) Population pharmacokinetics of the two enantiomers of tramadol and O-demethyl tramadol after surgery in children. *Br J Anaesth* **102**(3): 390–99.
Brewer CL & Baccei ML (2018) Enhanced Postsynaptic GABAB Receptor Signaling in Adult Spinal Projection Neurons after Neonatal Injury. *Neuroscience* **384**: 329-39.
Brill MJ, Diepstraten J, van Rongen A et al (2012) Impact of obesity on drug metabolism and elimination in adults and children. *Clin Pharmacokinet* **51**(5): 277-304.
Brochard S, Blajan V, Lempereur M et al (2009) Effectiveness of nitrous oxide and analgesic cream (lidocaine and prilocaine) for prevention of pain during intramuscular botulinum toxin injections in children. *Ann Phys Rehabil Med* **52**(10): 704–16.
Bronco A, Pietrini D, Lamperti M et al (2014) Incidence of pain after craniotomy in children. *Paediatr Anaesth* **24**(7): 781–87.
Brooks MR & Golianu B (2016) Perioperative management in children with chronic pain. *Paediatr Anaesth* **26**(8): 794-806.
Brousseau DC, Duffy SJ, Anderson AC et al (2004) Treatment of pediatric migraine headaches: a randomized, double-blind trial of prochlorperazine versus ketorolac. *Ann Emerg Med* **43**(2): 256–62.
Brown EA, De Young A, Kimble R et al (2019) Impact of Parental Acute Psychological Distress on Young Child Pain-Related Behavior Through Differences in Parenting Behavior During Pediatric Burn Wound Care. *J Clin Psychol Med Settings* **26**(4): 516-29.
Brown KA, Laferriere A, Lakheeram I et al (2006) Recurrent hypoxemia in children is associated with increased analgesic sensitivity to opiates. *Anesthesiology* **105**(4): 665–9.
Brown NJ, Kimble RM, Gramotnev G et al (2014a) Predictors of re-epithelialization in pediatric burn. *Burns* **40**(4): 751–8.
Brown NJ, Kimble RM, Rodger S et al (2014b) Play and heal: randomized controlled trial of Ditto intervention efficacy on improving re-epithelialization in pediatric burns. *Burns* **40**(2): 204–13.
Brown T (2012) Farewell! Some halogenated inhalation anesthetics: chloroform, trichlorethylene. *Paediatr Anaesth* **23**: 1097–100.
Browne LR, Shah MI, Studnek JR et al (2016a) Multicenter Evaluation of Prehospital Opioid Pain Management in Injured Children. *Prehosp Emerg Care* **20**(6): 759-67.
Browne LR, Studnek JR, Shah MI et al (2016b) Prehospital Opioid Administration in the Emergency Care of Injured Children. *Prehosp Emerg Care* **20**(1): 59-65.
Bruce E, Franck L & Howard RF (2006a) The efficacy of morphine and Entonox analgesia during chest drain removal in children. *Paediatr Anaesth* **16**(3): 302–08.
Bruce EA, Howard RF & Franck LS (2006b) Chest drain removal pain and its management: a literature review. *J Clin Nurs* **15**(2): 145–54.
Brummelte S, Grunau RE, Chau V et al (2012) Procedural pain and brain development in premature newborns. *Ann Neurol* **71**(3): 385–96.
Brunette KE, Anderson BJ, Thomas J et al (2011) Exploring the pharmacokinetics of oral ketamine in children undergoing burns procedures. *Paediatr Anaesth* **21**(6): 653–62.
Brusaferro A, Farinelli E, Zenzeri L et al (2018) The Management of Paediatric Functional Abdominal Pain Disorders: Latest Evidence. *Paediatr Drugs* **20**(3): 235-47.
Bryskin RB, Londergan B, Wheatley R et al (2015) Transversus Abdominis Plane Block Versus Caudal Epidural for Lower Abdominal Surgery in Children: A Double-Blinded Randomized Controlled Trial. *Anesth Analg* **121**(2): 471-8.
Bu X, Yang L & Zuo Y (2015) Efficacy and safety of perioperative parecoxib for acute postoperative pain treatment in children: a meta-analysis. *Front Med* **9**(4): 496-507.
Bucaretchi F, Fernandes CB, Branco MM et al (2014) Acute liver failure in a term neonate after repeated paracetamol administration. *Rev Paul Pediatr* **32**(1): 144–48.
Bucher HU, Moser T, von Siebenthal K et al (1995) Sucrose reduces pain reaction to heel lancing in preterm infants: a placebo-controlled, randomized and masked study. *Pediatr Res* **38**(3): 332-5.
Bueno M, Moreno-Ramos MC, Forni E et al (2019) Adaptation and Initial Validation of the Premature Infant Pain Profile-Revised (PIPP-R) in Brazil. *Pain Manag Nurs* **20**(5): 512-15.
Bueno M, Nishi ET, Costa T et al (2017) Blood Sampling in Newborns: A Systematic Review of YouTube Videos. *J Perinat Neonatal Nurs* **31**(2): 160-65.
Bueno M, Yamada J, Harrison D et al (2013) A systematic review and meta-analyses of nonsucrose sweet solutions for pain relief in neonates. *Pain Res Manag* **18**(3): 153–61.
Bukola IM & Paula D (2017) The Effectiveness of Distraction as Procedural Pain Management Technique in Pediatric Oncology Patients: A Meta-analysis and Systematic Review. *J Pain Symptom Manage* **54**(4): 589-600.e1.
Buonsenso D, Barone G, Valentini P et al (2014) Utility of intranasal Ketamine and Midazolam to perform gastric aspirates in children: a double-blind, placebo controlled, randomized study. *BMC Pediatr* **14**: 67.

Burghardt LC, Ayers JW, Brownstein JS et al (2013) Adult prescription drug use and pediatric medication exposures and poisonings. *Pediatrics* **132**(1): 18-27.
Burns-Nader S, Joe L & Pinion K (2017) Computer tablet distraction reduces pain and anxiety in pediatric burn patients undergoing hydrotherapy: A randomized trial. *Burns* **43**(6): 1203-11.
Burton KLO, Morrow AM, Beswick BV et al (2018) The Feasibility of Using the BrightHearts Biofeedback-Assisted Relaxation Application for the Management of Pediatric Procedural Pain: A Pilot Study. *Pain Pract* **18**(8): 979-87.
Buskila D, Neumann L, Zmora E et al (2003) Pain sensitivity in prematurely born adolescents. *Arch Pediatr Adolesc Med* **157**(11): 1079–82.
Bussolin L, Busoni P, Giorgi L et al (2003) Tumescent local anesthesia for the surgical treatment of burns and postburn sequelae in pediatric patients. *Anesthesiology* **99**(6): 1371-5.
Butkovic D, Kralik S, Matolic M et al (2007) Postoperative analgesia with intravenous fentanyl PCA vs epidural block after thoracoscopic pectus excavatum repair in children. *Br J Anaesth* **98**(5): 677–81.
Butler L, Symons B, Henderson S et al (2005) Hypnosis reduces distress and duration of an invasive medical procedure for children. *Pediatrics* **115**(1): e77–85.
Butler S (2013) Buprenorphine-Clinically useful but often misunderstood. *Scand J Pain* **4**(3): 148-52.
Butterworth SA, Blair GK, LeBlanc JG et al (2007) An open and shut case for early VATS treatment of primary spontaneous pneumothorax in children. *Can J Surg* **50**(3): 171-4.
Buttner W & Finke W (2000) Analysis of behavioural and physiological parameters for the assessment of postoperative analgesic demand in newborns, infants and young children: a comprehensive report on seven consecutive studies. *Paediatr Anaesth* **10**(3): 303–18.
Cacciotti C, Vaiselbuh S & Romanos-Sirakis E (2017) Pain Management for Sickle Cell Disease in the Pediatric Emergency Department: Medications and Hospitalization Trends. *Clin Pediatr (Phila)* **56**(12): 1109-14.
Caes L, Goubert L, Devos P et al (2014a) The relationship between parental catastrophizing about child pain and distress in response to medical procedures in the context of childhood cancer treatment: a longitudinal analysis. *J Pediatr Psychol* **39**(7): 677–86.
Caes L, Vervoort T, Devos P et al (2014b) Parental distress and catastrophic thoughts about child pain: implications for parental protective behavior in the context of child leukemia-related medical procedures. *Clin J Pain* **30**(9): 787-99.
Caglar S, Buyukyilmaz F, Cosansu G et al (2017) Effectiveness of ShotBlocker for Immunization Pain in Full-Term Neonates: A Randomized Controlled Trial. *J Perinat Neonatal Nurs* **31**(2): 166-71.
Cairns R, Karanges EA, Wong A et al (2019) Trends in self-poisoning and psychotropic drug use in people aged 5-19 years: a population-based retrospective cohort study in Australia. *BMJ Open* **9**(2): e026001.
Callaghan LC & Walker JD (2015) 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* **70**(2): 176-82.
Caltagirone R, Raghavan VR, Adelgais K et al (2018) A Randomized Double Blind Trial of Needle-free Injected Lidocaine Versus Topical Anesthesia for Infant Lumbar Puncture. *Acad Emerg Med* **25**(3): 310-16.
Campbell L, Pillai Riddell R, Cribbie R et al (2018) Preschool children's coping responses and outcomes in the vaccination context: child and caregiver transactional and longitudinal relationships. *Pain* **159**(2): 314-30.
Campbell-Yeo M, Johnston CC, Benoit B et al (2019) Sustained efficacy of kangaroo care for repeated painful procedures over neonatal intensive care unit hospitalization: a single-blind randomized controlled trial. *Pain* **160**(11): 2580-88.
Canakci E, Yagan O, Tas N et al (2017) Comparison of preventive analgesia techniques in circumcision cases: Dorsal penile nerve block, caudal block, or subcutaneous morphine? *J Pak Med Assoc* **67**(2): 159-65.
Canbay O, Celebi N, Uzun S et al (2008) Topical ketamine and morphine for post-tonsillectomy pain. *Eur J Anaesthesiol* **25**(4): 287–92.
Canpolat DG, Esmaoglu A, Tosun Z et al (2012) Ketamine-propofol vs ketamine-dexmedetomidine combinations in pediatric patients undergoing burn dressing changes. *J Burn Care Res* **33**(6): 718–22.
Cao J, Shi X, Miao X et al (2009) Effects of premedication of midazolam or clonidine on perioperative anxiety and pain in children. *Biosci Trends* **3**(3): 115–18.
Caparrotta TM, Antoine DJ & Dear JW (2018) Are some people at increased risk of paracetamol-induced liver injury? A critical review of the literature. *Eur J Clin Pharmacol* **74**(2): 147-60.
Capici F, Ingelmo PM, Davidson A et al (2008) Randomized controlled trial of duration of analgesia following intravenous or rectal acetaminophen after adenotonsillectomy in children. *Br J Anaesth* **100**(2): 251–55.
Carbajal R, Biran V, Lenclen R et al (2008) EMLA cream and nitrous oxide to alleviate pain induced by palivizumab (Synagis) intramuscular injections in infants and young children. *Pediatrics* **121**(6): e1591–98.
Carden MA, Brousseau DC, Ahmad FA et al (2019) Normal saline bolus use in pediatric emergency departments is associated with poorer pain control in children with sickle cell anemia and vaso-occlusive pain. *Am J Hematol* **94**(6): 689-96.

Carden MA, Patil P, Ahmad ME et al (2018) Variations in pediatric emergency medicine physician practices for intravenous fluid management in children with sickle cell disease and vaso-occlusive pain: A single institution experience. *Pediatr Blood Cancer* **65**(1).
Cardile S, Martinelli M, Barabino A et al (2016) Italian survey on non-steroidal anti-inflammatory drugs and gastrointestinal bleeding in children. *World J Gastroenterol* **22**(5): 1877-83.
Cardona-Grau D, Bush RA, Le HK et al (2019) Reducing Opioid Prescriptions in Outpatient Pediatric Urological Surgery. *J Urol* **201**(5): 1012-16.
Carney J, Finnerty O, Rauf J et al (2010) Ipsilateral transversus abdominis plane block provides effective analgesia after appendectomy in children: a randomized controlled trial. *Anesth Analg* **111**(4): 998–1003.
Carr AS, Brennan L, Courtman S et al (2009) *Association of Paediatric Anaesthetists of Great Britain and Ireland. Guidelines on the prevention of post-operative vomiting in children.* http://www.apagbi.org.uk/sites/default/files/APA_Guidelines_on_the_Prevention_of_Postoperative_Vomiting_in_Children.pdf Accessed 8 September 2015
Carre P, Joly A, Cluzel Field B et al (2000) Axillary block in children: single or multiple injection? *Paediatr Anaesth* **10**(1): 35-9.
Castarlenas E, Jensen MP, von Baeyer CL et al (2017) Psychometric Properties of the Numerical Rating Scale to Assess Self-Reported Pain Intensity in Children and Adolescents: A Systematic Review. *Clin J Pain* **33**(4): 376-83.
Cavkaytar O, Arik Yilmaz E, Karaatmaca B et al (2015) Different Phenotypes of Non-Steroidal Anti-Inflammatory Drug Hypersensitivity during Childhood. *Int Arch Allergy Immunol* **167**(3): 211-21.
Cavkaytar O, du Toit G & Caimmi D (2019) Characteristics of NSAID-induced hypersensitivity reactions in childhood. *Pediatr Allergy Immunol* **30**(1): 25-35.
Cechvala MM, Christenson D, Eickhoff JC et al (2008) Sedative preference of families for lumbar punctures in children with acute leukemia: propofol alone or propofol and fentanyl. *J Pediatr Hematol Oncol* **30**(2): 142–47.
Ceelie I, de Wildt SN, van Dijk M et al (2013) Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. *JAMA* **309**(2): 149–54.
Celebioglu A, Gurol A, Yildirim ZK et al (2015) Effects of massage therapy on pain and anxiety arising from intrathecal therapy or bone marrow aspiration in children with cancer. *Int J Nurs Pract* **21**(6): 797-804.
Center for Pediatric Pain Research *Strategies for Helping Children with Shots and Needles.* http://pediatric-pain.ca/it-doesnt-have-to-hurt Accessed August 2015
Cepeda MS, Tzortzopoulou A, Thackrey M et al (2010) Adjusting the pH of lidocaine for reducing pain on injection. *Cochrane Database Syst Rev*(12): CD006581.
Cesur M, Alici HA, Erdem AF et al (2007) Effects of reduction of the caudal morphine dose in paediatric circumcision on quality of postoperative analgesia and morphine-related side-effects. *Anaesth Intensive Care* **35**(5): 743–47.
Cha MH, Eom JH, Lee YS et al (2012) Beneficial effects of adding ketamine to intravenous patient-controlled analgesia with fentanyl after the Nuss procedure in pediatric patients. *Yonsei Med J* **53**(2): 427-32.
Chakraborty A, Goswami J & Patro V (2015) Ultrasound-guided continuous quadratus lumborum block for postoperative analgesia in a pediatric patient. *A A Case Rep* **4**(3): 34-6.
Chalam KS, Patnaik SS, Sunil C et al (2015) Comparative study of ultrasound-guided paravertebral block with ropivacaine versus bupivacaine for post-operative pain relief in children undergoing thoracotomy for patent ductus arteriosus ligation surgery. *Indian J Anaesth* **59**(8): 493-8.
Chalkiadis GA, Abdullah F, Bjorksten AR et al (2013) Absorption characteristics of epidural levobupivacaine with adrenaline and clonidine in children. *Paediatr Anaesth* **23**(1): 58–67.
Chalkiadis GA & Anderson BJ (2006) Age and size are the major covariates for prediction of levobupivacaine clearance in children. *Paediatr Anaesth* **16**(3): 275–82.
Chalkiadis GA, Sommerfield D, Low J et al (2016) Comparison of lumbar epidural bupivacaine with fentanyl or clonidine for postoperative analgesia in children with cerebral palsy after single-event multilevel surgery. *Dev Med Child Neurol* **58**(4): 402-8.
Chalmers DJ, Bielsky A, Wild TT et al (2015) Continuous local anesthetic infusion for children with spina bifida undergoing major reconstruction of the lower urinary tract. *J Pediatr Urol* **11**(2): 72 e1-5.
Chan AK, Cheung CW & Chong YK (2010a) Alpha-2 agonists in acute pain management. *Expert Opin Pharmacother* **11**(17): 2849–68.
Chan CP & Lau FL (2010b) Should lidocaine spray be used to ease nasogastric tube insertion? A double-blind, randomised controlled trial. *Hong Kong Med J* **16**(4): 282–86.
Chan DK & Parikh SR (2014) Perioperative ketorolac increases post-tonsillectomy hemorrhage in adults but not children. *Laryngoscope* **124**(8): 1789–93.
Chan E, Hovenden M, Ramage E et al (2019a) Virtual Reality for Pediatric Needle Procedural Pain: Two Randomized Clinical Trials. *J Pediatr* **209**: 160-67.e4.
Chan GCK, Leung J & Hall W (2019b) Non-medical use of pharmaceutical opioids with and without other illicit substances in Australia: Prevalence and correlates. *Drug Alcohol Rev* **38**(2): 151-58.

Chan KH, Shah A, Moser EA et al (2018) Comparison of Intraoperative and Early Postoperative Outcomes of Caudal vs Dorsal Penile Nerve Blocks for Outpatient Penile Surgeries. *Urology* **118**: 164-71.
Chan S, Pielak K, McIntyre C et al (2013) Implementation of a new clinical practice guideline regarding pain management during childhood vaccine injections. *Paediatr Child Health* **18**(7): 367-72.
Chang P, Fabrizi L, Olhede S et al (2016) The Development of Nociceptive Network Activity in the Somatosensory Cortex of Freely Moving Rat Pups. *Cereb Cortex* **26**(12): 4513-23.
Charette S, Fiola JL, Charest MC et al (2015) Guided Imagery for Adolescent Post-spinal Fusion Pain Management: A Pilot Study. *Pain Manag Nurs* **16**(3): 211-20.
Charney RL, Yan Y, Schootman M et al (2008) Oxycodone versus codeine for triage pain in children with suspected forearm fracture: a randomized controlled trial. *Pediatr Emerg Care* **24**(9): 595–600.
Chau B, Chi B & Wilson T (2018) Decreasing pediatric pain and agitation during botulinum toxin injections for spasticity with virtual reality: Lessons learned from clinical use. *J Pediatr Rehabil Med* **11**(3): 199-204.
Chau CM, Ranger M, Sulistyoningrum D et al (2014) Neonatal pain and COMT Val158Met genotype in relation to serotonin transporter (SLC6A4) promoter methylation in very preterm children at school age. *Front Behav Neurosci* **8**: 409.
Chaudhary V, Chauhan S, Choudhury M et al (2012) Parasternal intercostal block with ropivacaine for postoperative analgesia in pediatric patients undergoing cardiac surgery: a double-blind, randomized, controlled study. *J Cardiothorac Vasc Anesth* **26**(3): 439-42.
Chayapathi V, Kalra M, Bakshi AS et al (2018) A comparison of ketamine + midazolam to propofol for procedural sedation for lumbar puncture in pediatric oncology by nonanesthesiologists-a randomized comparative trial. *Pediatr Blood Cancer* **65**(8): e27108.
Cheelo M, Lodge CJ, Dharmage SC et al (2015) Paracetamol exposure in pregnancy and early childhood and development of childhood asthma: a systematic review and meta-analysis. *Arch Dis Child* **100**(1): 81-9.
Chen CK, Teo SC, Phui VE et al (2015) Analgesic efficacy of transversus abdominis plane block in neonates and early infants for colostomy and reversal of colostomy. *Agri* **27**(4): 210-4.
Chen E, Joseph M & Zeltzer L (2000) Behavioral and cognitive interventions in the treatment of acute pain in children. *Pediatr Clin North Am* **47**(3): 513–25.
Chen JY, Jia JE, Liu TJ et al (2013) Comparison of the effects of dexmedetomidine, ketamine, and placebo on emergence agitation after strabismus surgery in children. *Can J Anaesth* **60**(4): 385–92.
Chen KL, Lindrea KB, Quah-Smith I et al (2017a) Magnetic noninvasive acupuncture for infant comfort (MAGNIFIC) - a single-blinded randomised controlled pilot trial. *Acta Paediatr* **106**(11): 1780-86.
Chen L, Zhang M, Yung J et al (2018) Safety of Rectal Administration of Acetaminophen in Neonates. *Can J Hosp Pharm* **71**(6): 364-69.
Chen S, Zhang Q, Xie RH et al (2017b) What is the Best Pain Management During Gastric Tube Insertion for Infants Aged 0-12months: A Systematic Review. *J Pediatr Nurs* **34**: 78-83.
Cheng L, Wang L, He M et al (2018) Perspectives of children, family caregivers, and health professionals about pediatric oncology symptoms: a systematic review. *Support Care Cancer* **26**(9): 2957-71.
Chester SJ, Tyack Z, De Young A et al (2018) Efficacy of hypnosis on pain, wound-healing, anxiety, and stress in children with acute burn injuries: a randomized controlled trial. *Pain* **159**(9): 1790-801.
Cheung HM & Yew DTW (2019) Effects of Perinatal Exposure to Ketamine on the Developing Brain. *Front Neurosci* **13**: 138.
Chhabra A, Pandey R, Khandelwal M et al (2005) Anesthetic techniques and postoperative emesis in pediatric strabismus surgery. *Reg Anesth Pain Med* **30**(1): 43–47.
Chhabra A, Sinha R, Subramaniam R et al (2009) Comparison of sub-Tenon's block with i.v. fentanyl for paediatric vitreoretinal surgery. *Br J Anaesth* **103**(5): 739–43.
CHI (2019) *Patient and Nurse Controlled Analgesia Oxycodone.* https://www.olchc.ie/Healthcare-Professionals/Nursing-Practice-Guidelines/Oxycodone-PCA-NCA-Prescription-2019.pdf Accessed 15 December 2019
Chiam E, Weinberg L, Bailey M et al (2016) The haemodynamic effects of intravenous paracetamol (acetaminophen) in healthy volunteers: a double-blind, randomized, triple crossover trial. *Br J Clin Pharmacol* **81**(4): 605-12.
Chiam E, Weinberg L & Bellomo R (2015) Paracetamol: a review with specific focus on the haemodynamic effects of intravenous administration. *Heart Lung Vessel* **7**(2): 121-32.
Chiaretti A, Genovese O, Antonelli A et al (2008) Patient-controlled analgesia with fentanil and midazolam in children with postoperative neurosurgical pain. *Childs Nerv Syst* **24**(1): 119–24.
Chiaretti A, Ruggiero A, Barbi E et al (2011) Comparison of propofol versus propofol-ketamine combination in pediatric oncologic procedures performed by non-anesthesiologists. *Pediatr Blood Cancer* **57**(7): 1163–67.
Chidambaran V, Olbrecht V, Hossain M et al (2014) Risk Predictors of Opioid-Induced Critical Respiratory Events in Children: Naloxone Use as a Quality Measure of Opioid Safety. *Pain Med*.
Chidambaran V, Pilipenko V, Spruance K et al (2017a) Fatty acid amide hydrolase-morphine interaction influences ventilatory response to hypercapnia and postoperative opioid outcomes in children. *Pharmacogenomics* **18**(2): 143-56.

Chidambaran V & Sadhasivam S (2012) Pediatric acute and surgical pain management: recent advances and future perspectives. *Int Anesthesiol Clin* **50**(4): 66–82.
Chidambaran V, Sadhasivam S & Mahmoud M (2017b) Codeine and opioid metabolism: implications and alternatives for pediatric pain management. *Curr Opin Anaesthesiol* **30**(3): 349-56.
Chidambaran V, Tewari A & Mahmoud M (2018) Anesthetic and pharmacologic considerations in perioperative care of obese children. *J Clin Anesth* **45**: 39-50.
Chidambaran V, Venkatasubramanian R, Zhang X et al (2017c) ABCC3 genetic variants are associated with postoperative morphine-induced respiratory depression and morphine pharmacokinetics in children. *Pharmacogenomics J* **17**(2): 162-69.
Chiew AL, Gluud C, Brok J et al (2018) Interventions for paracetamol (acetaminophen) overdose. *Cochrane Database Syst Rev* **2**: CD003328.
Chiew AL, Reith D, Pomerleau A et al (2020) Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. *Med J Aust* **212**(4): 175-83.
Chin KJ, Alakkad H, Adhikary SD et al (2013) Infraclavicular brachial plexus block for regional anaesthesia of the lower arm. *Cochrane Database Syst Rev* **8**: CD005487.
Chin KJ, Cubillos JE & Alakkad H (2016) Single, double or multiple-injection techniques for non-ultrasound guided axillary brachial plexus block in adults undergoing surgery of the lower arm. *Cochrane Database Syst Rev* **9**: CD003842.
Chinta SS, Schrock CR, McAllister JD et al (2015) Rapid administration technique of ketamine for pediatric forearm fracture reduction: a dose-finding study. *Ann Emerg Med* **65**(6): 640-48.e2.
Chiono J, Raux O, Bringuier S et al (2014) Bilateral suprazygomatic maxillary nerve block for cleft palate repair in children: a prospective, randomized, double-blind study versus placebo. *Anesthesiology* **120**(6): 1362–69.
Cho HK, Kim KW, Jeong YM et al (2014) Efficacy of ketamine in improving pain after tonsillectomy in children: meta-analysis. *PLoS One* **9**(6): e101259.
Cho HK, Park IJ, Jeong YM et al (2016) Can perioperative acupuncture reduce the pain and vomiting experienced after tonsillectomy? A meta-analysis. *Laryngoscope* **126**(3): 608-15.
Cho HK, Park IJ, Yoon HY et al (2018a) Efficacy of Adjuvant Magnesium for Posttonsillectomy Morbidity in Children: A Meta-analysis. *Otolaryngol Head Neck Surg* **158**(1): 27-35.
Cho HK, Yoon HY, Jin HJ et al (2018b) Efficacy of dexmedetomidine for perioperative morbidities in pediatric tonsillectomy: A metaanalysis. *Laryngoscope* **128**(5): E184-E93.
Cho JE, Kim JY, Hong JY et al (2009) The addition of fentanyl to 1.5 mg/ml ropivacaine has no advantage for paediatric epidural analgesia. *Acta Anaesthesiol Scand* **53**(8): 1084–87.
Cho JE, Kim JY, Kim JE et al (2008) Epidural sufentanil provides better analgesia from 24 h after surgery compared with epidural fentanyl in children. *Acta Anaesthesiol Scand* **52**(10): 1360–63.
Choi SH, Lee WK, Lee SJ et al (2008) Parent-controlled analgesia in children undergoing cleft palate repair. *J Korean Med Sci* **23**(1): 122–25.
Chong C, Schug SA, Page-Sharp M et al (2009) Development of a sublingual/oral formulation of ketamine for use in neuropathic pain: preliminary findings from a three-way randomized, crossover study. *Clin Drug Investig* **29**(5): 317–24.
Chong MA, Szoke DJ, Berbenetz NM et al (2018) Dexamethasone as an Adjuvant for Caudal Blockade in Pediatric Surgical Patients: A Systematic Review and Meta-analysis. *Anesth Analg* **127**(2): 520-28.
Chorney JM & McMurtry CM (2014) Behavioural measures of pain. In: *Oxford Textbook of Paediatric Pain* 1st edn. McGrath P (eds). Oxford. 253-69.
Choudhry DK, Brenn BR, Sacks K et al (2016) Continuous chest wall ropivacaine infusion for analgesia in children undergoing Nuss procedure: a comparison with thoracic epidural. *Paediatr Anaesth* **26**(6): 582-9.
Choudhry DK, Brenn BR, Sacks K et al (2017) Evaluation of Gabapentin and Clonidine Use in Children Following Spinal Fusion Surgery for Idiopathic Scoliosis: A Retrospective Review. *J Pediatr Orthop*.
Chow C & Choong CT (2016) Ketamine-based procedural sedation and analgesia for botulinum toxin A injections in children with cerebral palsy. *Eur J Paediatr Neurol* **20**(2): 319-22.
Chu Y-C, Lin S-M, Hsieh Y-C et al (2006) Intraoperative administration of tramadol for postoperative nurse-controlled analgesia resulted in earlier awakening and less sedation than morphine in children after cardiac surgery. *Anesth Analg* **102**(6): 1668–73.
Chua ISY, Chong SL & Ong GYK (2017a) Intravenous regional anaesthesia (Bier's block) for pediatric forearm fractures in a pediatric emergency department-Experience from 2003 to 2014. *Injury* **48**(12): 2784-87.
Chua KP, Shrime MG & Conti RM (2017b) Effect of FDA Investigation on Opioid Prescribing to Children After Tonsillectomy/Adenoidectomy. *Pediatrics* **140**(6).
Chua ME, Firaza PNB, Ming JM et al (2017c) Lidocaine Gel for Urethral Catheterization in Children: A Meta-Analysis. *J Pediatr* **190**: 207-14.e1.
Chung CP, Callahan ST, Cooper WO et al (2018a) Outpatient Opioid Prescriptions for Children and Opioid-Related Adverse Events. *Pediatrics* **142**(2): e20172156.

Chung CP, Callahan ST, Cooper WO et al (2019) Individual short-acting opioids and the risk of opioid-related adverse events in adolescents. *Pharmacoepidemiol Drug Saf* **28**(11): 1448-56.

Chung S, Lim R & Goldman RD (2010) Intranasal fentanyl versus placebo for pain in children during catheterization for voiding cystourethrography. *Pediatr Radiol* **40**(7): 1236–40.

Chung WW, Agbayani CG, Martinez A et al (2018b) Improving Children's cancer pain management in the home setting: Development and formative evaluation of a web-based program for parents. *Comput Biol Med* **101**: 146-52.

CHW (2019) *Guideline: Pain Management - CHW Practice Guideline.* http://www.schn.health.nsw.gov.au/_policies/pdf/2006-8215.pdf Accessed 15 December 2019

Ciftci T, Daskaya H, Yildirim MB et al (2014) A minimally painful, comfortable, and safe technique for hemodialysis catheter placement in children: Superficial cervical plexus block. *Hemodial Int* **18**(3): 700–04.

Cignacco EL, Sellam G, Stoffel L et al (2012) Oral sucrose and "facilitated tucking" for repeated pain relief in preterms: a randomized controlled trial. *Pediatrics* **129**(2): 299–308.

Cimpello LB, Khine H & Avner JR (2004) Practice patterns of pediatric versus general emergency physicians for pain management of fractures in pediatric patients. *Pediatr Emerg Care* **20**(4): 228-32.

Cinar SO, Isil CT, Sahin SH et al (2015) Caudal ropivacaine and bupivacaine for postoperative analgesia in infants undergoing lower abdominal surgery. *Pak J Med Sci* **31**(4): 903-8.

Clark E, Plint A, C., Correll R et al (2007) A randomised, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics* **119**(3): 460–67.

Clarkson JE, Worthington HV, Furness S et al (2010) Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* **8**: CD001973.

Cleary AG, Ramanan AV, Baildam E et al (2002) Nitrous oxide analgesia during intra-articular injection for juvenile idiopathic arthritis. *Arch Dis Child* **86**(6): 416–18.

Clebone A, Burian BK & Polaner DM (2017) A Time-Out Checklist for Pediatric Regional Anesthetics. *Reg Anesth Pain Med* **42**(1): 105-08.

Coad NR & Hain WR (1989) Caudal anaesthesia for postoperative pain relief in children: a comparative trial of different regimens using plain bupivacaine. *Ann R Coll Surg Engl* **71**(4): 245–48.

Cobb JE & Cohen LL (2009) A randomized controlled trial of the ShotBlocker for children's immunization distress. *Clin J Pain* **25**(9): 790-6.

Cocelli LP, Ugur BK, Durucu C et al (2012) Comparison of pre-emptive tonsillar lodge infiltration with ropivacaine versus intravenous tramadol in pediatric tonsillectomies: a randomized placebo-controlled study. *Int J Pediatr Otorhinolaryngol* **76**(5): 653–57.

Coda BA, O'Sullivan B, Donaldson G et al (1997) Comparative efficacy of patient-controlled administration of morphine, hydromorphone, or sufentanil for the treatment of oral mucositis pain following bone marrow transplantation. *Pain* **72**(3): 333–46.

Codipietro L, Bailo E, Nangeroni M et al (2011) Analgesic techniques in minor painful procedures in neonatal units: a survey in northern Italy. *Pain Pract* **11**(2): 154–59.

Coffey F, Wright J, Hartshorn S et al (2014) STOP!: a randomised, double-blind, placebo-controlled study of the efficacy and safety of methoxyflurane for the treatment of acute pain. *Emerg Med J* **31**(8): 613-8.

Cohen LL, Rodrigues NP, Lim CS et al (2015) Automated parent-training for preschooler immunization pain relief: a randomized controlled trial. *J Pediatr Psychol* **40**(5): 526-34.

Cohen M, Zuk J, McKay N et al (2017) Intrathecal Morphine Versus Extended-Release Epidural Morphine for Postoperative Pain Control in Pediatric Patients Undergoing Posterior Spinal Fusion. *Anesth Analg* **124**(6): 2030-37.

Cok OY, Erkan AN, Eker HE et al (2015) Practical regional blocks for nasal fracture in a child: blockade of infraorbital nerve and external nasal branch of anterior ethmoidal nerve. *J Clin Anesth* **27**(5): 436-8.

Cole TJ, Bellizzi MC, Flegal KM et al (2000) Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ (Clinical research ed.)* **320**(7244): 1240-43.

Collins JJ, Byrnes ME, Dunkel IJ et al (2000) The measurement of symptoms in children with cancer. *J Pain Symptom Manage* **19**(5): 363–77.

Collins JJ, Dunkel IJ, Gupta SK et al (1999) Transdermal fentanyl in children with cancer pain: feasibility, tolerability, and pharmacokinetic correlates. *J Pediatr* **134**(3): 319–23.

Collins JJ, Geake J, Grier HE et al (1996) Patient-controlled analgesia for mucositis pain in children: a three-period crossover study comparing morphine and hydromorphone. *J Pediatr* **129**(5): 722–28.

Collins JJ, Grier HE, Kinney HC et al (1995) Control of severe pain in children with terminal malignancy. *J Pediatr* **126**(4): 653–57.

Cometa MA, Esch AT & Boezaart AP (2011) Did continuous femoral and sciatic nerve block obscure the diagnosis or delay the treatment of acute lower leg compartment syndrome? A case report. *Pain Med* **12**(5): 823–28.

Cong X, Delaney C & Vazquez V (2013a) Neonatal nurses' perceptions of pain assessment and management in NICUs: a national survey. *Adv Neonatal Care* **13**(5): 353–60.

Cong X, McGrath JM, Cusson RM et al (2013b) Pain assessment and measurement in neonates: an updated review. *Adv Neonatal Care* **13**(6): 379–95.

Conicella E, Raucci U, Vanacore N et al (2008) The child with headache in a pediatric emergency department. *Headache* **48**(7): 1005-11.
Conrad C, Soni P, Coorg V et al (2019) Prehospital Analgesic Administration by Parents for Pain Relief in Children. *Pediatr Emerg Care* **35**(5): 359-62.
Constance JE, Campbell SC, Somani AA et al (2017) Pharmacokinetics, pharmacodynamics and pharmacogenetics associated with nonsteroidal anti-inflammatory drugs and opioids in pediatric cancer patients. *Expert Opin Drug Metab Toxicol* **13**(7): 715-24.
Constant I, Gall O, Gouyet L et al (1998) Addition of clonidine or fentanyl to local anaesthetics prolongs the duration of surgical analgesia after single shot caudal block in children. *Br J Anaesth* **80**(3): 294–98.
Constantine E, Steele DW, Eberson C et al (2007) The use of local anesthetic techniques for closed forearm fracture reduction in children: a survey of academic pediatric emergency departments. *Pediatr Emerg Care* **23**(4): 209–11.
Conti C, Tso E & Browne B (1996) Oral morphine protocol for sickle cell crisis pain. *Md Med J* **45**(1): 33–35.
Cook-Sather SD, Li J, Goebel TK et al (2014) TAOK3, a novel genome-wide association study locus associated with morphine requirement and postoperative pain in a retrospective pediatric day surgery population. *Pain* **155**(9): 1773-83.
Coombes L, Burke K & Anderson AK (2017) The use of rapid onset fentanyl in children and young people for breakthrough cancer pain. *Scand J Pain* **17**: 256-59.
Cooper TE, Fisher E, Gray AL et al (2017a) Opioids for chronic non-cancer pain in children and adolescents. *Cochrane Database of Systematic Reviews* **7**: CD012538.
Cooper TE, Heathcote LC, Anderson B et al (2017b) Non-steroidal anti-inflammatory drugs (NSAIDs) for cancer-related pain in children and adolescents. *Cochrane Database Syst Rev* **7**: Cd012563.
Cooper TE, Wiffen PJ, Heathcote LC et al (2017c) Antiepileptic drugs for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev* **8**: Cd012536.
Corwin DJ, Topjian A, Banwell BL et al (2017) Adverse events associated with a large dose of intravenous lipid emulsion for suspected local anesthetic toxicity. *Clin Toxicol (Phila)* **55**(6): 603-07.
Cote CJ, Posner KL & Domino KB (2014) Death or neurologic injury after tonsillectomy in children with a focus on obstructive sleep apnea: houston, we have a problem! *Anesth Analg* **118**(6): 1276-83.
Cote CJ & Wilson S (2016) Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures: Update 2016. *Pediatrics* **138**(1).
Coudert AE, Ostertag A, Baaroun V et al (2014) Phase III, randomized, double-blind, placebo-controlled trial of topical 2 % lidocaine for the prevention and treatment of oral mucosal pain in children. *Clin Oral Investig* **18**(4): 1189-94.
Coulter FL, Hannam JA & Anderson BJ (2014) Ketofol simulations for dosing in pediatric anesthesia. *Paediatr Anaesth* **24**(8): 806–12.
Courtemanche AB & Black WR (2016) Everyday expressions of pain in children with and without autism spectrum disorder. *Research in Autism Spectrum Disorders* **26**: 65-70.
Cousin M, Chiriac A, Molinari N et al (2016) Phenotypical characterization of children with hypersensitivity reactions to NSAIDs. *Pediatr Allergy Immunol* **27**(7): 743-48.
Cozzi G, Borrometi F, Benini F et al (2017) First-time success with needle procedures was higher with a warm lidocaine and tetracaine patch than an eutectic mixture of lidocaine and prilocaine cream. *Acta Paediatr* **106**(5): 773-78.
Cozzi G, Crevatin F, Dri V et al (2018) Distraction Using Buzzy or Handheld Computers During Venipuncture. *Pediatr Emerg Care*.
Craig SS, Seith RW, Cheek JA et al (2019) Lidocaine and phenylephrine versus saline placebo nasal spray for the pain and distress of nasogastric tube insertion in young children and infants: a randomised, double-blind, controlled trial. *Lancet Child Adolesc Health* **3**(6): 391-97.
Craske J, Dooley F, Griffiths L et al (2013) Introducing LAPPS (Liverpool Anticipatory Procedural Pain Score): the pragmatic development of an innovative approach to predicting and treating procedural pain and distress in children. *J Child Health Care* **17**(2): 114–24.
Cravero JP, Agarwal R, Berde C et al (2019) The Society for Pediatric Anesthesia recommendations for the use of opioids in children during the perioperative period. *Paediatr Anaesth* **29**(6): 547-71.
Crawford MW, Galton S & Naser B (2006a) Postoperative morphine consumption in children with sickle-cell disease. *Paediatr Anaesth* **16**(2): 152–57.
Crawford MW, Hickey C, Zaarour C et al (2006b) Development of acute opioid tolerance during infusion of remifentanil for pediatric scoliosis surgery. *Anesth Analg* **102**(6): 1662–67.
Cregg N, Conway F & Casey W (1996) Analgesia after otoplasty: regional nerve blockade vs local anaesthetic infiltration of the ear. *Can J Anaesth* **43**(2): 141–47.
Crellin DJ, Harrison D, Santamaria N et al (2015) Systematic review of the Face, Legs, Activity, Cry and Consolability scale for assessing pain in infants and children: is it reliable, valid, and feasible for use? *Pain* **156**(11): 2132-51.
Crellin DJ, Harrison D, Santamaria N et al (2018) The Psychometric Properties of the FLACC Scale Used to Assess Procedural Pain. *J Pain* **19**(8): 862-72.
Crock C, Olsson C, Phillips R et al (2003) General anaesthesia or conscious sedation for painful procedures in childhood cancer: the family's perspective. *Arch Dis Child* **88**(3): 253–57.

Crosta QR, Ward TM, Walker AJ et al (2014) A review of pain measures for hospitalized children with cognitive impairment. *J Spec Pediatr Nurs* **19**(2): 109–18.
Croxtall JD (2010) Lidocaine/tetracaine medicated plaster: in minor dermatological and needle puncture procedures. *Drugs* **70**(16): 2113–20.
Cruz MD, Fernandes AM & Oliveira CR (2016) Epidemiology of painful procedures performed in neonates: A systematic review of observational studies. *Eur J Pain* **20**(4): 489-98.
Cucchiaro G, Adzick SN, Rose JB et al (2006) A comparison of epidural bupivacaine-fentanyl and bupivacaine-clonidine in children undergoing the Nuss procedure. *Anesth Analg* **103**(2): 322–27.
Cucchiaro G, Dagher C, Baujard C et al (2003) Side-effects of postoperative epidural analgesia in children: a randomized study comparing morphine and clonidine. *Paediatr Anaesth* **13**(4): 318–23.
Cucchiaro G & Ganesh A (2007) The effects of clonidine on postoperative analgesia after peripheral nerve blockade in children. *Anesth Analg* **104**(3): 532-7.
Currie CL & Wild TC (2012) Adolescent use of prescription drugs to get high in Canada. *Can J Psychiatry* **57**(12): 745-51.
Curry DM, Brown C & Wrona S (2012) Effectiveness of oral sucrose for pain management in infants during immunizations. *Pain Manag Nurs* **13**(3): 139–49.
Cyna AM & Middleton P (2008) Caudal epidural block versus other methods of postoperative pain relief for circumcision in boys. *Cochrane Database Syst Rev* **4**: CD003005.
Czarnecki ML, Ferrise AS, Jastrowski Mano KE et al (2008) Parent/nurse-controlled analgesia for children with developmental delay. *Clin J Pain* **24**(9): 817–24.
Czarnecki ML, Hainsworth KR, Simpson PM et al (2018) Parent/Nurse-Controlled Analgesia Compared with Intravenous PRN Opioids for Postsurgical Pain Management in Children with Developmental Delay: A Randomized Controlled Trial. *Pain Med* **19**(4): 742-52.
Czarnecki ML, Jandrisevits MD, Theiler SC et al (2004) Controlled-release oxycodone for the management of pediatric postoperative pain. *J Pain Symptom Manage* **27**(4): 379–86.
Czarnecki ML, Salamon KS, Jastrowski Mano KE et al (2011) A preliminary report of parent/nurse-controlled analgesia (PNCA) in infants and preschoolers. *Clin J Pain* **27**(2): 102–07.
Czarnetzki C, Elia N, Lysakowski C et al (2008) Dexamethasone and risk of nausea and vomiting and postoperative bleeding after tonsillectomy in children: a randomized trial. *JAMA* **300**(22): 2621–30.
Dadure C, Acosta C & Capdevila X (2004) Perioperative pain management of a complex orthopedic surgical procedure with double continuous nerve blocks in a burned child. *Anesth Analg* **98**(6): 1653–55.
Dadure C, Bringuier S, Nicolas F et al (2006) Continuous epidural block versus continuous popliteal nerve block for postoperative pain relief after major podiatric surgery in children: a prospective, comparative randomized study. *Anesth Analg* **102**(3): 744–49.
Dadure C, Bringuier S, Raux O et al (2009) Continuous peripheral nerve blocks for postoperative analgesia in children: feasibility and side effects in a cohort study of 339 catheters. *Can J Anaesth* **56**(11): 843–50.
Dahan A, Aarts L & Smith TW (2010) Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. *Anesthesiology*. **112:** 13.
Dahmani S, Brasher C, Stany I et al (2010) Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies. *Acta Anaesthesiol Scand* **54**(4): 397–402.
Dahmani S, Michelet D, Abback PS et al (2011) Ketamine for perioperative pain management in children: a meta-analysis of published studies. *Paediatr Anaesth* **21**(6): 636–52.
Dalvandi A, Ranjbar H, Hatamizadeh M et al (2017) Comparing the effectiveness of vapocoolant spray and lidocaine/procaine cream in reducing pain of intravenous cannulation: A randomized clinical trial. *Am J Emerg Med* **35**(8): 1064-68.
Damian MA, Hammer GB, Elkomy MH et al (2020) Pharmacokinetics of Dexmedetomidine in Infants and Children After Orthotopic Liver Transplantation. *Anesth Analg* **130**(1): 209-16.
Dar JY, Goheer L & Shah SA (2019) Analgesic Effect Of Direct Breastfeeding During BCG Vaccination In Healthy Neonates. *J Ayub Med Coll Abbottabad* **31**(3): 379-82.
Dart RC, Bartelson BB & Adams EH (2014) Nonmedical use of tapentadol immediate release by college students. *Clin J Pain* **30**(8): 685-92.
Dart RC, Surratt HL, Le Lait MC et al (2016) Diversion and Illicit Sale of Extended Release Tapentadol in the United States. *Pain Med* **17**(8): 1490-6.
Das DA, Grimmer KA, Sparnon AL et al (2005) The efficacy of playing a virtual reality game in modulating pain for children with acute burn injuries: a randomized controlled trial [ISRCTN87413556]. *BMC Pediatr* **5**(1): 1.
Dastgheyb S, Fishlock K, Daskalakis C et al (2018) Evaluating comfort measures for commonly performed painful procedures in pediatric patients. *J Pain Res* **11**: 1383-90.
Dautremont EA, Ebramzadeh E, Beck JJ et al (2017) Opioid Prescription and Usage in Adolescents Undergoing Orthopaedic Surgery in the United States: A Systematic Review. *JBJS Rev* **5**(8): e5.
David H & Shipp J (2011) A randomized controlled trial of ketamine/propofol versus propofol alone for emergency department procedural sedation. *Ann Emerg Med* **57**(5): 435–41.

Davidson A & Flick RP (2013) Neurodevelopmental implications of the use of sedation and analgesia in neonates. *Clin Perinatol* **40**(3): 559–73.
Davidson AJ, Morton NS, Arnup SJ et al (2015) Apnea after Awake Regional and General Anesthesia in Infants: The General Anesthesia Compared to Spinal Anesthesia Study--Comparing Apnea and Neurodevelopmental Outcomes, a Randomized Controlled Trial. *Anesthesiology* **123**(1): 38-54.
Davidson AJ & Sun LS (2018) Clinical Evidence for Any Effect of Anesthesia on the Developing Brain. *Anesthesiology* **128**(4): 840-53.
Davies D, DeVlaming D & Haines C (2008) Methadone analgesia for children with advanced cancer. *Pediatr Blood Cancer* **51**(3): 393–97.
Davis MP (2011) Fentanyl for breakthrough pain: a systematic review. *Expert Rev Neurother* **11**(8): 1197–216.
Dawes JM, Cooke EM, Hannam JA et al (2017) Oral morphine dosing predictions based on single dose in healthy children undergoing surgery. *Paediatr Anaesth* **27**(1): 28-36.
de Beer DA & Thomas ML (2003) Caudal additives in children--solutions or problems? *Br J Anaesth* **90**(4): 487–98.
De Cassai A & Tonetti T (2018) Local anesthetic spread during erector spinae plane block. *J Clin Anesth* **48**: 60-61.
de Graaf J, van Lingen RA, Simons SH et al (2011) Long-term effects of routine morphine infusion in mechanically ventilated neonates on children's functioning: five-year follow-up of a randomized controlled trial. *Pain* **152**(6): 1391–97.
de Graaf J, van Lingen RA, Valkenburg AJ et al (2013) Does neonatal morphine use affect neuropsychological outcomes at 8 to 9 years of age? *Pain* **154**(3): 449–58.
de Jong A, Baartmans M, Bremer M et al (2010) Reliability, validity and clinical utility of three types of pain behavioural observation scales for young children with burns aged 0-5 years. *Pain* **150**(3): 561–67.
de Jong AE, Bremer M, van Komen R et al (2014) Pain in young children with burns: extent, course and influencing factors. *Burns* **40**(1): 38-47.
de Jong M, Lucas C, Bredero H et al (2012) Does postoperative 'M' technique massage with or without mandarin oil reduce infants' distress after major craniofacial surgery? *J Adv Nurs* **68**(8): 1748-57.
De Jose Maria B, Banus E, Navarro Egea M et al (2008) Ultrasound-guided supraclavicular vs infraclavicular brachial plexus blocks in children. *Paediatr Anaesth* **18**(9): 838–44.
de Knegt N & Scherder E (2011) Pain in adults with intellectual disabilities. *Pain* **152**(5): 971–74.
De la Cuadra-Fontaine JC, Concha M, Vuletin F et al (2018) Continuous Erector Spinae Plane block for thoracic surgery in a pediatric patient. *Paediatr Anaesth* **28**(1): 74-75.
de Martino M & Chiarugi A (2015) Recent Advances in Pediatric Use of Oral Paracetamol in Fever and Pain Management. *Pain Ther* **4**(2): 149-68.
de Martino M, Chiarugi A, Boner A et al (2017) Working Towards an Appropriate Use of Ibuprofen in Children: An Evidence-Based Appraisal. *Drugs* **77**(12): 1295-311.
De Negri P, Ivani G, Visconti C et al (2001) The dose-response relationship for clonidine added to a postoperative continuous epidural infusion of ropivacaine in children. *Anesth Analg* **93**(1): 71–76.
de Onis M, Blossner M & Borghi E (2010) Global prevalence and trends of overweight and obesity among preschool children. *Am J Clin Nutr* **92**(5): 1257-64.
de Onis M, Onyango AW, Borghi E et al (2007) Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* **85**(9): 660-7.
de Vos G, Shankar V, Nazari R et al (2012) Fear of repeated injections in children younger than 4 years receiving subcutaneous allergy immunotherapy. *Ann Allergy Asthma Immunol* **109**(6): 465–69.
De Windt AC, Asehnoune K, Roquilly A et al (2010) An opioid-free anaesthetic using nerve blocks enhances rapid recovery after minor hand surgery in children. *Eur J Anaesthesiol* **27**(6): 521–25.
Deb K, Subramaniam R, Dehran M et al (2001) Safety and efficacy of peribulbar block as adjunct to general anaesthesia for paediatric ophthalmic surgery. *Paediatr Anaesth* **11**(2): 161-7.
Deindl P, Unterasinger L, Kappler G et al (2013) Successful implementation of a neonatal pain and sedation protocol at 2 NICUs. *Pediatrics* **132**(1): e211–18.
Delgado-Noguera MF, Forero Delgadillo JM, Franco AA et al (2018) Corticosteroids for septic arthritis in children. *Cochrane Database Syst Rev* **11**: CD012125.
Demiraran Y, Ilce Z, Kocaman B et al (2006) Does tramadol wound infiltration offer an advantage over bupivacaine for postoperative analgesia in children following herniotomy? *Paediatr Anaesth* **16**(10): 1047–50.
Demiraran Y, Kocaman B & Akman RY (2005) A comparison of the postoperative analgesic efficacy of single-dose epidural tramadol versus morphine in children. *Br J Anaesth* **95**(4): 510–13.
DeMoss P, Ramsey LH & Karlson CW (2018) Phantom Limb Pain in Pediatric Oncology. *Front Neurol* **9**: 219.
Dempsey E & McCreery K (2011) Local anaesthetic eye drops for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity. *Cochrane Database Syst Rev* **9**: CD007645.
DePeter KC, Blumberg SM, Dienstag Becker S et al (2017) Does the Use of Ibuprofen in Children with Extremity Fractures Increase their Risk for Bone Healing Complications? *J Emerg Med* **52**(4): 426-32.
Derbyshire SW (2006) Can fetuses feel pain? *BMJ* **332**(7546): 909–12.

DeRienz RT, Baker DD, Kelly NE et al (2018) Child Fatalities Due to Heroin/Fentanyl Exposure: What the Case History Missed. *J Anal Toxicol* **42**(8): 581-85.
Derosier FJ, Lewis D, Hershey AD et al (2012) Randomized trial of sumatriptan and naproxen sodium combination in adolescent migraine. *Pediatrics* **129**(6): e1411–20.
Dervan LA, Yaghmai B, Watson RS et al (2017) The use of methadone to facilitate opioid weaning in pediatric critical care patients: a systematic review of the literature and meta-analysis. *Paediatr Anaesth* **27**(3): 228-39.
Desai A, Alemayehu H, Weesner KA et al (2016a) Impact of Epidural Failures on the Results of a Prospective, Randomized Trial. *Eur J Pediatr Surg* **26**(2): 160-3.
Desai R, Dickson U, Rodrigues D et al (2016b) Epidural abscess after epidural analgesia in children: report of two cases. *Eur J Anaesthesiol* **33**(11): 866-67.
Despriee AW & Langeland E (2016) The effect of sucrose as pain relief/comfort during immunisation of 15-month-old children in health care centres: a randomised controlled trial. *J Clin Nurs* **25**(3-4): 372-80.
Dewhirst E, Fedel G, Raman V et al (2014) Pain management following myringotomy and tube placement: intranasal dexmedetomidine versus intranasal fentanyl. *Int J Pediatr Otorhinolaryngol* **78**(7): 1090–94.
Di Gaspero NC, Razlog R, Patel R et al (2019) Perceived effectiveness of complementary medicine by mothers of infants with colic in Gauteng. *Health SA* **24**: 1175.
Di Pede A, Morini F, Lombardi MH et al (2014) Comparison of regional vs. systemic analgesia for post-thoracotomy care in infants. *Paediatr Anaesth* **24**(6): 569–73.
Diercks GR, Comins J, Bennett K et al (2019) Comparison of Ibuprofen vs Acetaminophen and Severe Bleeding Risk After Pediatric Tonsillectomy: A Noninferiority Randomized Clinical Trial. *JAMA Otolaryngol Head Neck Surg* **145**(6): 494-500.
Diggle L, Deeks JJ & Pollard AJ (2006) Effect of needle size on immunogenicity and reactogenicity of vaccines in infants: randomised controlled trial. *BMJ* **333**(7568): 571.
Dilli D, Dallar Y & Sorgui NH (2008) Intravenous ketamine plus midazolam vs. intravenous ketamine for sedation in lumbar puncture: a randomized controlled trial. *Indian Pediatr* **45**(11): 899–904.
Dimitriou V, Mavridou P, Manataki A et al (2017) The Use of Aromatherapy for Postoperative Pain Management: A Systematic Review of Randomized Controlled Trials. *Journal of PeriAnesthesia Nursing* **32**(6): 530-41.
Disher T, Cameron C, Mitra S et al (2018) Pain-Relieving Interventions for Retinopathy of Prematurity: A Meta-analysis. *Pediatrics* **142**(1).
Disma N, Frawley G, Mameli L et al (2011) Effect of epidural clonidine on minimum local anesthetic concentration (ED50) of levobupivacaine for caudal block in children. *Paediatr Anaesth* **21**(2): 128–35.
Dobson D, Lucassen PL, Miller JJ et al (2012) Manipulative therapies for infantile colic. *Cochrane Database Syst Rev* **12**: Cd004796.
Doherty C & Mc Donnell C (2012) Tenfold medication errors: 5 years' experience at a university-affiliated pediatric hospital. *Pediatrics* **129**(5): 916–24.
Donado C, Solodiuk J, Rangel SJ et al (2019) Patient- and Nurse-Controlled Analgesia: 22-Year Experience in a Pediatric Hospital. *Hosp Pediatr* **9**(2): 129-33.
Donaldson CD, Nakawaki B & Crano WD (2015) Variations in parental monitoring and predictions of adolescent prescription opioid and stimulant misuse. *Addict Behav* **45**: 14-21.
Dostbil A, Gursac Celik M, Aksoy M et al (2014) The effects of different doses of caudal morphine with levobupivacaine on postoperative vomiting and quality of analgesia after circumcision. *Anaesth Intensive Care* **42**(2): 234–38.
Dougall A, Hayes M & Daly B (2017) A systematic review of the use of local analgesia in medically compromised children and adolescents. *Eur Arch Paediatr Dent* **18**(5): 331-43.
Doyle E, Morton NS & McNicol LR (1994a) Comparison of patient-controlled analgesia in children by i.v. and s.c. routes of administration. *Br J Anaesth* **72**(5): 533–36.
Doyle E, Mottart KJ, Marshall C et al (1994b) Comparison of different bolus doses of morphine for patient-controlled analgesia in children. *Br J Anaesth* **72**(2): 160–63.
Drake R, Longworth J & Collins JJ (2004) Opioid rotation in children with cancer. *J Palliat Med* **7**(3): 419–22.
Drake-Brockman TF, Russell P, Gibson C et al (2016) Regional nerve blockade in an Australian tertiary paediatric centre. *Anaesth Intensive Care* **44**(5): 646-7.
Drendel A, L., Gorelick M, H., Weisman S, J. et al (2009) A randomized clinical trial of ibuprofen versus acetaminophen with codeine for acute pediatric arm fracture pain. *Ann Emerg Med* **54**: 553–60.
Drover DR, Hammer GB & Anderson BJ (2012) The pharmacokinetics of ketorolac after single postoperative intranasal administration in adolescent patients. *Anesth Analg* **114**(6): 1270–76.
Dryl R & Szajewska H (2018) Probiotics for management of infantile colic: a systematic review of randomized controlled trials. *Arch Med Sci* **14**(5): 1137-43.
Dubois A, Michelon C, Rattaz C et al (2017) Daily living pain assessment in children with autism: Exploratory study. *Research in Developmental Disabilities* **62**: 238-46.
Duedahl TH & Hansen EH (2007) A qualitative systematic review of morphine treatment in children with postoperative pain. *Paediatr Anaesth* **17**(8): 756–74.

Duerden EG, Grunau RE, Guo T et al (2018) Early Procedural Pain Is Associated with Regionally-Specific Alterations in Thalamic Development in Preterm Neonates. *J Neurosci* **38**(4): 878-86.
Duff AJ, Gaskell SL, Jacobs K et al (2012) Management of distressing procedures in children and young people: time to adhere to the guidelines. *Arch Dis Child* **97**(1): 1–4.
Dulai SK, Firth K, Al-Mansoori K et al (2016) Does Topical Anesthetic Reduce Pain During Intraosseous Pin Removal in Children? A Randomized Controlled Trial. *J Pediatr Orthop* **36**(2): 126-31.
Duman A, Apiliogullari S & Duman I (2010) Effects of intrathecal fentanyl on quality of spinal anesthesia in children undergoing inguinal hernia repair. *Paediatr Anaesth* **20**(6): 530–36.
Dunbar PJ, Buckley P, Gavrin JR et al (1995) Use of patient-controlled analgesia for pain control for children receiving bone marrow transplant. *J Pain Symptom Manage* **10**(8): 604–11.
Dunlop RJ & Bennett KC (2006) Pain management for sickle cell disease. *Cochrane Database Syst Rev* **2**: CD003350.
Duparc-Alegria N, Tiberghien K, Abdoul H et al (2018) Assessment of a short hypnosis in a paediatric operating room in reducing postoperative pain and anxiety: A randomised study. *J Clin Nurs* **27**(1-2): 86-91.
Eccleston C, Fisher E, Cooper TE et al (2019) Pharmacological interventions for chronic pain in children: an overview of systematic reviews. *Pain* **160**(8): 1698-707.
Echaniz G, De Miguel M, Merritt G et al (2019) Bilateral suprazygomatic maxillary nerve blocks vs. infraorbital and palatine nerve blocks in cleft lip and palate repair: A double-blind, randomised study. *Eur J Anaesthesiol* **36**(1): 40-47.
Ecoffey C, Lacroix F, Giaufre E et al (2010) Epidemiology and morbidity of regional anesthesia in children: a follow-up one-year prospective survey of the French-Language Society of Paediatric Anaesthesiologists (ADARPEF). *Paediatr Anaesth* **20**(12): 1061–69.
Egunsola O, Wylie CE, Chitty KM et al (2019) Systematic Review of the Efficacy and Safety of Gabapentin and Pregabalin for Pain in Children and Adolescents. *Anesth Analg* **128**(4): 811-19.
Ehrentraut JH, Kern KD, Long SA et al (2014) Opioid misuse behaviors in adolescents and young adults in a hematology/oncology setting. *J Pediatr Psychol* **39**(10): 1149-60.
Eijlers R, Utens E, Staals LM et al (2019) Systematic Review and Meta-analysis of Virtual Reality in Pediatrics: Effects on Pain and Anxiety. *Anesth Analg* **129**(5): 1344-53.
Eisenach JC, De Kock M & Klimscha W (1996) alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). *Anesthesiology* **85**(3): 655–74.
Eiszner JR, Atanda A, Jr., Rangavajjula A et al (2016) A case series of peripheral nerve blocks in pediatrics and young adults with skeletal dysplasia. *Paediatr Anaesth* **26**(5): 553-6.
Ekatodramis G, Min K, Cathrein P et al (2002) Use of a double epidural catheter provides effective postoperative analgesia after spine deformity surgery. *Can J Anaesth* **49**(2): 173–77.
Ekbom K, Kalman S, Jakobsson J et al (2011) Efficient intravenous access without distress: a double-blind randomized study of midazolam and nitrous oxide in children and adolescents. *Arch Pediatr Adolesc Med* **165**(9): 785–91.
Ekemen S, Yelken B, Ilhan H et al (2008) A comparison of analgesic efficacy of tramadol and pethidine for management of postoperative pain in children: a randomized, controlled study. *Pediatr Surg Int* **24**(6): 695–98.
El-Deeb A, El-Morsy GZ, Ghanem AAA et al (2013) The effects of intravenous lidocaine infusion on hospital stay after major abdominal pediatric surgery. A randomized double-blinded study. *Egyptian Journal of Anaesthesia* **29**(3): 225-30.
El-Morsy GZ, El-Deeb A, El-Desouky T et al (2012) Can thoracic paravertebral block replace thoracic epidural block in pediatric cardiac surgery? A randomized blinded study. *Ann Card Anaesth* **15**(4): 259–63.
El-Naggar W, Yiu A, Mohamed A et al (2010) Comparison of pain during two methods of urine collection in preterm infants. *Pediatrics* **125**(6): 1224–29.
El-Tahtawy A, Kokki H & Reidenberg BE (2006) Population pharmacokinetics of oxycodone in children 6 months to 7 years old. *J Clin Pharmacol* **46**(4): 433–42.
Elens L, Norman E, Matic M et al (2016) Genetic Predisposition to Poor Opioid Response in Preterm Infants: Impact of KCNJ6 and COMT Polymorphisms on Pain Relief After Endotracheal Intubation. *Ther Drug Monit* **38**(4): 525-33.
Elhakim M, Abdul Salam AY, Eid A et al (1997) Inclusion of pethidine in lidocaine for infiltration improves analgesia following tonsillectomy in children. *Acta Anaesthesiol Scand* **41**(2): 214-7.
Elkomy MH, Alruwaili N, Elmowafy M et al (2019) Assessment of Ketamine Adult Anesthetic Doses in Pediatrics Using Pharmacokinetic Modeling and Simulations. *Pharmacotherapy* **39**(4): 454-62.
Ellis J, Martelli B, Lamontagne C et al (2011) Improved practices for safe administration of intravenous bolus morphine in a pediatric setting. *Pain Manag Nurs* **12**(3): 146–53.
Elshammaa N, Chidambaran V, Housny W et al (2011) Ketamine as an adjunct to fentanyl improves postoperative analgesia and hastens discharge in children following tonsillectomy - a prospective, double-blinded, randomized study. *Paediatr Anaesth* **21**(10): 1009–14.
Ely LE, Chen-Lim MM, Carpenter MK et al (2016) Pain Assessment of Children with Autism Spectrum Disorders. *Journal of Developmental & Behavioral Pediatrics* **37**(1): 53-61.

EMA (2013) *Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation.* http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001829.jsp&mid=WC0b01ac058004d5c1 Accessed 15 February 2020

EMA (2015) *Codeine not to be used in children below 12 years for cough and cold* https://www.ema.europa.eu/en/news/codeine-not-be-used-children-below-12-years-cough-cold Accessed 17 February 2020

Emmott AS, West N, Zhou G et al (2017) Validity of Simplified Versus Standard Self-Report Measures of Pain Intensity in Preschool-Aged Children Undergoing Venipuncture. *J Pain* **18**(5): 564-73.

Emons MI, Petzke F, Stamer UM et al (2016) Current practice of acute pain management in children-a national follow-up survey in Germany. *Paediatr Anaesth* **26**(9): 883-90.

Ender KL, Krajewski JA, Babineau J et al (2014) Use of a clinical pathway to improve the acute management of vaso-occlusive crisis pain in pediatric sickle cell disease. *Pediatr Blood Cancer* **61**(4): 693–96.

Engelhardt T, Steel E, Johnston G et al (2003) Tramadol for pain relief in children undergoing tonsillectomy: a comparison with morphine. *Paediatr Anaesth* **13**(3): 249–52.

Engelhardt T, Zaarour C, Naser B et al (2008) Intraoperative low-dose ketamine does not prevent a remifentanil-induced increase in morphine requirement after pediatric scoliosis surgery. *Anesth Analg* **107**(4): 1170–5.

Engelman E & Marsala C (2012) Bayesian enhanced meta-analysis of post-operative analgesic efficacy of additives for caudal analgesia in children. *Acta Anaesthesiol Scand* **56**(7): 817–32.

Engelman E & Marsala C (2013) Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. *Br J Anaesth* **110**(1): 21–27.

Enyedi LB, Wallace DK & de LDG (2017) A double-masked randomized trial of postoperative local anesthetic for pain control in pediatric strabismus surgery. *J AAPOS* **21**(2): 107-11.

Erdogan MA, Ozgul U, Ucar M et al (2017) Patient-controlled Intermittent Epidural Bolus Versus Epidural Infusion for Posterior Spinal Fusion After Adolescent Idiopathic Scoliosis: Prospective, Randomized, Double-blinded Study. *Spine (Phila Pa 1976)* **42**(12): 882-86.

Ergonenc T, Can H & Gokhan Beyaz S (2017) Ultrasound-guided interscalene brachial plexus block in a child with acute upper respiratory infection : A case report. *Anaesthesist* **66**(10): 782-85.

Eriksson M & Campbell-Yeo M (2019) Assessment of pain in newborn infants. *Semin Fetal Neonatal Med* **24**(4): 101003.

Erskine A, Wiffen PJ & Conlon JA (2015) As required versus fixed schedule analgesic administration for postoperative pain in children. *Cochrane Database Syst Rev*(2): Cd011404.

Eschertzhuber S, Hohlrieder M, Keller C et al (2008) Comparison of high- and low-dose intrathecal morphine for spinal fusion in children. *Br J Anaesth* **100**(4): 538–43.

Etminan M, Sadatsafavi M, Jafari S et al (2009) Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. *Chest* **136**(5): 1316–23.

Eustace N & O'Hare B (2007) Use of nonsteroidal anti-inflammatory drugs in infants. A survey of members of the Association of Paediatric Anaesthetists of Great Britain and Ireland. *Paediatr Anaesth* **17**(5): 464–69.

Evans D, Turnham L, Barbour K et al (2005) Intravenous ketamine sedation for painful oncology procedures. *Paediatr Anaesth* **15**(2): 131–38.

Everett T, Parker K, Fish J et al (2015) The construction and implementation of a novel postburn pruritus scale for infants and children aged five years or less: introducing the Toronto Pediatric Itch Scale. *J Burn Care Res* **36**(1): 44-9.

Eyers S, Weatherall M, Jefferies S et al (2011) Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. *Clin Exp Allergy* **41**(4): 482–89.

Faasse MA, Lindgren BW, Frainey BT et al (2015) Perioperative effects of caudal and transversus abdominis plane (TAP) blocks for children undergoing urologic robot-assisted laparoscopic surgery. *J Pediatr Urol* **11**(3): 121 e1-7.

Faber AJ, Lagman-Bartolome AM & Rajapakse T (2017) Drugs for the acute treatment of migraine in children and adolescents. *Paediatr Child Health* **22**(8): 454-58.

Fabrizi L, Slater R, Worley A et al (2011) A shift in sensory processing that enables the developing human brain to discriminate touch from pain. *Curr Biol* **21**(18): 1552–58.

Fabrizi L, Verriotis M, Williams G et al (2016) Encoding of mechanical nociception differs in the adult and infant brain. *Sci Rep* **6**: 28642.

Faerber J, Zhong W, Dai D et al (2017) Comparative Safety of Morphine Delivered via Intravenous Route vs. Patient-Controlled Analgesia Device for Pediatric Inpatients. *J Pain Symptom Manage* **53**(5): 842-50.

Falanga IJ, Lafrenaye S, Mayer SK et al (2006) Management of acute pain in children: safety and efficacy of a nurse-controlled algorithm for pain relief. *Acute Pain* **8**(2): 45–54.

Fallah R, Naserzadeh N, Ferdosian F et al (2017) Comparison of effect of kangaroo mother care, breastfeeding and swaddling on Bacillus Calmette-Guerin vaccination pain score in healthy term neonates by a clinical trial. *J Matern Fetal Neonatal Med* **30**(10): 1147-50.

Faraoni D, Gilbeau A, Lingier P et al (2010) Does ultrasound guidance improve the efficacy of dorsal penile nerve block in children? *Paediatr Anaesth* **20**(10): 931-6.

Farid IS, Heiner EJ & Fleissner PR (2010) Comparison of femoral nerve block and fascia iliaca block for analgesia following reconstructive knee surgery in adolescents. *J Clin Anesth* **22**(4): 256–59.
Farion KJ, Osmond MH, Hartling L et al (2003) Tissue adhesives for traumatic lacerations: a systematic review of randomized controlled trials. *Acad Emerg Med* **10**(2): 110-8.
Faye PM, De Jonckheere J, Logier R et al (2010) Newborn infant pain assessment using heart rate variability analysis. *Clin J Pain* **26**(9): 777–82.
FDA (2003) Labeling for oral and rectal over-the-counter drug products containing aspirin and nonaspirin salicylates; Reye's Syndrome warning. Final rule. *Fed Regist* **68**(74): 18861-9.
FDA (2013a) *FDA Drug Safety Communication: FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen.* https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-rare-serious-skin-reactions-pain-relieverfever-reducer Accessed 22 February 2020
FDA (2013b) *Safety review update of codeine use in children; new Boxed Warning and contraindication on use after tonsillectomy and/or adenoidectomy* https://www.fda.gov/media/85072/download Accessed 20 February 2020
FDA (2017) *Drug Safety Communications: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women.* https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-restricts-use-prescription-codeine-pain-and-cough-medicines-and Accessed 17 February 2020
FDA (2018a) *FDA acts to protect kids from serious risks of opioid ingredients contained in some prescription cough and cold products by revising labeling to limit pediatric use.* https://www.fda.gov/news-events/press-announcements/fda-acts-protect-kids-serious-risks-opioid-ingredients-contained-some-prescription-cough-and-cold Accessed 23 October 2019
FDA (2018b) *Prescribing information: OXYCONTIN® (oxycodone hydrochloride) extended-release tablets, for oral use, CII. Reference no: 4326201* https://www.fda.gov/media/131026/download Accessed 17 February 2020
Feda M, Al Amoudi N, Sharaf A et al (2010) A comparative study of children's pain reactions and perceptions to AMSA injection using CCLAD versus traditional injections. *J Clin Pediatr Dent* **34**(3): 217–22.
Fedorowicz Z, van Zuuren EJ, Nasser M et al (2013) Oral rinses, mouthwashes and sprays for improving recovery following tonsillectomy. *Cochrane Database Syst Rev*(9): CD007806.
Fein DM, Avner JR, Scharbach K et al (2017) Intranasal fentanyl for initial treatment of vaso-occlusive crisis in sickle cell disease. *Pediatr Blood Cancer* **64**(6): 06.
Fein M, Quinn J, Watt K et al (2014) Prehospital paediatric burn care: New priorities in paramedic reporting. *Emerg Med Australas* **26**(6): 609-15.
Feng Z, Tang Q, Lin J et al (2018) Application of animated cartoons in reducing the pain of dressing changes in children with burn injuries. *Int J Burns Trauma* **8**(5): 106-13.
Fenn NE, 3rd & Plake KS (2017) Opioid and Benzodiazepine Weaning in Pediatric Patients: Review of Current Literature. *Pharmacotherapy* **37**(11): 1458-68.
Ferayorni A, Yniguez R, Bryson M et al (2012) Needle-free jet injection of lidocaine for local anesthesia during lumbar puncture: a randomized controlled trial. *Pediatr Emerg Care* **28**(7): 687–90.
Feriani G, Hatanaka E, Torloni MR et al (2016) Infraorbital nerve block for postoperative pain following cleft lip repair in children. *Cochrane Database Syst Rev* **4**: CD011131.
Ferlic PW, Singer G, Kraus T et al (2012) The acute compartment syndrome following fractures of the lower leg in children. *Injury* **43**(10): 1743–46.
Fernandes AM, De Campos C, Batalha L et al (2014) Pain assessment using the adolescent pediatric pain tool: a systematic review. *Pain Res Manag* **19**(4): 212-8.
Fernandes ML, Pires KC, Tiburcio MA et al (2012) Caudal bupivacaine supplemented with morphine or clonidine, or supplemented with morphine plus clonidine in children undergoing infra-umbilical urological and genital procedures: a prospective, randomized and double-blind study. *J Anesth* **26**(2): 213–18.
Filan PM, Hunt RW, Anderson PJ et al (2012) Neurologic outcomes in very preterm infants undergoing surgery. *J Pediatr* **160**(3): 409–14.
Finkel JC, Finley A, Greco C et al (2005) Transdermal fentanyl in the management of children with chronic severe pain: results from an international study. *Cancer* **104**(12): 2847–57.
Finkel JC, Goldberg J, Rosenburg R et al (2019) First evaluation of tapentadol oral solution for the treatment of moderate to severe acute pain in children aged 6 to <18. *J Pain Res* **12**: 1925-36.
Finkel JC, Pestieau SR & Quezado ZM (2007) Ketamine as an adjuvant for treatment of cancer pain in children and adolescents. *J Pain* **8**(6): 515–21.
Fisher E, Law E, Dudeney J et al (2018a) Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database Syst Rev* **9**: CD003968.
Fisher MT, Zigler CK & Houtrow AJ (2018b) Factors affecting procedural pain in children during and immediately after intramuscular botulinum toxin injections for spasticity. *J Pediatr Rehabil Med* **11**(3): 193-97.
Fisher WJ, Bingham RM & Hall R (1999) Axillary brachial plexus block for perioperative analgesia in 250 children. *Paediatr Anaesth* **9**(5): 435–38.
Fitzgerald M (2005) The development of nociceptive circuits. *Nat Rev Neurosci* **6**(7): 507–20.

Fitzgerald M (2015) What do we really know about newborn infant pain? *Exp Physiol* **100**(12): 1451-7.
Fitzgerald M, Millard C & MacIntosh N (1988) Hyperalgesia in premature infants. *Lancet* **1**(8580): 292.
Fitzgerald M & Walker SM (2009) Infant pain management: a developmental neurobiological approach. *Nat Clin Pract Neurol* **5**(1): 35–50.
Flandin-Blety C & Barrier G (1995) Accidents following extradural analgesia in children. The results of a retrospective study. *Paediatr Anaesth* **5**(1): 41–46.
Flogegard H & Ljungman G (2003) Characteristics and adequacy of intravenous morphine infusions in children in a paediatric oncology setting. *Med Pediatr Oncol* **40**(4): 233–38.
Flowers SR & Birnie KA (2015) Procedural Preparation and Support as a Standard of Care in Pediatric Oncology. *Pediatr Blood Cancer* **62 Suppl 5**: S694-723.
Foeldvari I, Szer IS, Zemel LS et al (2009) A prospective study comparing celecoxib with naproxen in children with juvenile rheumatoid arthritis. *J Rheumatol* **36**(1): 174–82.
Ford NC, Ren D & Baccei ML (2018) NALCN channels enhance the intrinsic excitability of spinal projection neurons. *Pain* **159**(9): 1719-30.
Forestier J, Castillo P, Finnbogason T et al (2017) Volumes of the spinal canal and caudal space in children zero to three years of age assessed by magnetic resonance imaging: implications for volume dosage of caudal blockade. *Br J Anaesth* **119**(5): 972-78.
Forrester MB (2009) Cases of pediatric ingestion of celecoxib reported to Texas poison control centers in 2000-2007. *Hum Exp Toxicol* **28**(4): 191–94.
Forsner M, Norstrom F, Nordyke K et al (2014) Relaxation and guided imagery used with 12-year-olds during venipuncture in a school-based screening study. *J Child Health Care* **18**(3): 241–52.
Fortier MA, Chung WW, Martinez A et al (2016) Pain buddy: A novel use of m-health in the management of children's cancer pain. *Comput Biol Med* **76**: 202-14.
Fortier MA, Wahi A, Bruce C et al (2014) Pain management at home in children with cancer: a daily diary study. *Pediatr Blood Cancer* **61**(6): 1029–33.
Foster JP, Taylor C & Spence K (2017) Topical anaesthesia for needle-related pain in newborn infants. *Cochrane Database Syst Rev* **2**: Cd010331.
Fournier-Charriere E, Tourniaire B, Carbajal R et al (2012) EVENDOL, a new behavioral pain scale for children ages 0 to 7 years in the emergency department: design and validation. *Pain* **153**(8): 1573–82.
Fox JK, Halpern LF, Dangman BC et al (2016) Children's anxious reactions to an invasive medical procedure: The role of medical and non-medical fears. *J Health Psychol* **21**(8): 1587-96.
Foxlee R, Johansson AC, Wejfalk J et al (2011) Topical analgesia for acute otitis media. *Cochrane Database Syst Rev* **3**: CD005657.
Franck LS, Berberich FR & Taddio A (2015) Parent participation in a childhood immunization pain reduction method. *Clin Pediatr (Phila)* **54**(3): 228-35.
Franck LS, Ridout D, Howard R et al (2011) A comparison of pain measures in newborn infants after cardiac surgery. *Pain* **152**(8): 1758–65.
Franklin AD, Lorinc AN, Shotwell MS et al (2015) Evaluation of the skin to epidural and subarachnoid space distance in young children using magnetic resonance imaging. *Reg Anesth Pain Med* **40**(3): 245-8.
Fratianne RB, Prensner JD, Huston MJ et al (2001) The effect of music-based imagery and musical alternate engagement on the burn debridement process. *J Burn Care Rehabil* **22**(1): 47–53.
Frawley G, Frawley J & Crameri J (2016) A review of anesthetic techniques and outcomes following minimally invasive repair of pectus excavatum (Nuss procedure). *Paediatr Anaesth* **26**(11): 1082-90.
Frawley GP, Downie S & Huang GH (2006) Levobupivacaine caudal anesthesia in children: a randomized double-blind comparison with bupivacaine. *Paediatr Anaesth* **16**(7): 754–60.
Fredrickson MJ, Paine C & Hamill J (2010) Improved analgesia with the ilioinguinal block compared to the transversus abdominis plane block after pediatric inguinal surgery: a prospective randomized trial. *Paediatr Anaesth* **20**(11): 1022–27.
Frenette E (2011) Restless legs syndrome in children: a review and update on pharmacological options. *Curr Pharm Des* **17**(15): 1436-42.
Frenkel O, Liebmann O & Fischer JW (2015) Ultrasound-guided forearm nerve blocks in kids: a novel method for pain control in the treatment of hand-injured pediatric patients in the emergency department. *Pediatr Emerg Care* **31**(4): 255-9.
Frenkel O, Mansour K & Fischer JW (2012) Ultrasound-guided femoral nerve block for pain control in an infant with a femur fracture due to nonaccidental trauma. *Pediatr Emerg Care* **28**(2): 183-4.
Frey TM, Florin TA, Caruso M et al (2019) Effect of Intranasal Ketamine vs Fentanyl on Pain Reduction for Extremity Injuries in Children: The PRIME Randomized Clinical Trial. *JAMA Pediatr* **173**(2): 140-46.
Friday J, H., Kanegaye J, T. & McCaslin I (2009) Ibuprofen provides analgesia equivalent to acetaminophen-codeine in the treatment of acute pain in children with extremity injuries: a randomised clinical trial. *Acad Emerg Med* **16**(8): 711–16.

Friedman EW, Webber AB, Osborn HH et al (1986) Oral analgesia for treatment of painful crisis in sickle cell anemia. *Ann Emerg Med* **15**(7): 787–91.
Friedrichsdorf SJ, Eull D, Weidner C et al (2018) A hospital-wide initiative to eliminate or reduce needle pain in children using lean methodology. *Pain Rep* **3**(Suppl 1): e671.
Friedrichsdorf SJ, Nugent AP & Strobl AQ (2013) Codeine-associated pediatric deaths despite using recommended dosing guidelines: three case reports. *J Opioid Manag* **9**(2): 151–55.
Friedrichsdorf SJ & Postier A (2014) Management of breakthrough pain in children with cancer. *J Pain Res* **7**: 117–23.
Friedrichsdorf SJ, Postier A, Eull D et al (2015a) Pain Outcomes in a US Children's Hospital: A Prospective Cross-Sectional Survey. *Hosp Pediatr* **5**(1): 18-26.
Friedrichsdorf SJ, Postier AC, Foster LP et al (2015b) Tramadol versus codeine/acetaminophen after pediatric tonsillectomy: A prospective, double-blinded, randomized controlled trial. *J Opioid Manag* **11**(4): 283-94.
Frigon C, Mai R, Valois-Gomez T et al (2006) Bowel hematoma following an iliohypogastric-ilioinguinal nerve block. *Paediatr Anaesth* **16**(9): 993-6.
Fukuda T, Chidambaran V, Mizuno T et al (2013) OCT1 genetic variants influence the pharmacokinetics of morphine in children. *Pharmacogenomics* **14**(10): 1141–51.
Funk RS, Brown JT & Abdel-Rahman SM (2012) Pediatric pharmacokinetics: human development and drug disposition. *Pediatr Clin North Am* **59**(5): 1001–16.
Furuya A, Ito M, Fukao T et al (2009) The effective time and concentration of nitrous oxide to reduce venipuncture pain in children. *J Clin Anesth* **21**(3): 190–93.
Furyk JS, Grabowski WJ & Black LH (2009) Nebulized fentanyl versus intravenous morphine in children with suspected limb fractures in the emergency department: a randomized controlled trial. *Emerg Med Australas* **21**(3): 203-9.
Gabrielli S, Langlois A & Ben-Shoshan M (2018) Prevalence of Hypersensitivity Reactions in Children Associated with Acetaminophen: A Systematic Review and Meta-Analysis. *Int Arch Allergy Immunol* **176**(2): 106-14.
Gad RF, Dowling DA, Abusaad FE et al (2019) Oral Sucrose Versus Breastfeeding in Managing Infants' Immunization-Related Pain: A Randomized Controlled Trial. *MCN Am J Matern Child Nurs* **44**(2): 108-14.
Gaither JR, Shabanova V & Leventhal JM (2018) US National Trends in Pediatric Deaths From Prescription and Illicit Opioids, 1999-2016. *JAMA Network Open* **1**(8): e186558-e58.
Galinkin J, Koh JL, Committee on D et al (2014) Recognition and management of iatrogenically induced opioid dependence and withdrawal in children. *Pediatrics* **133**(1): 152–55.
Galinski M, Picco N, Hennequin B et al (2011) Out-of-hospital emergency medicine in pediatric patients: prevalence and management of pain. *Am J Emerg Med* **29**(9): 1062-6.
Gammal RS, Crews KR, Haidar CE et al (2016) Pharmacogenetics for Safe Codeine Use in Sickle Cell Disease. *Pediatrics* **138**(1).
Ganesh A, Rose JB, Wells L et al (2007) Continuous peripheral nerve blockade for inpatient and outpatient postoperative analgesia in children. *Anesth Analg* **105**(5): 1234–42.
Gao H, Gao H, Xu G et al (2016) Efficacy and safety of repeated oral sucrose for repeated procedural pain in neonates: A systematic review. *Int J Nurs Stud* **62**: 118-25.
Gao H, Li M, Gao H et al (2018) Effect of non-nutritive sucking and sucrose alone and in combination for repeated procedural pain in preterm infants: A randomized controlled trial. *Int J Nurs Stud* **83**: 25-33.
Gao W, Zhang QR, Jiang L et al (2015) Comparison of local and intravenous dexamethasone for postoperative pain and recovery after tonsillectomy. *Otolaryngol Head Neck Surg* **152**(3): 530-5.
Garg N & Aggarwal A (2018) Advances Towards Painless Vaccination and Newer Modes of Vaccine Delivery. *Indian J Pediatr* **85**(2): 132-38.
Garra G, Singer AJ, Domingo A et al (2013) The Wong-Baker pain FACES scale measures pain, not fear. *Pediatr Emerg Care* **29**(1): 17–20.
Garrido MJ, Habre W, Rombout F et al (2006) Population pharmacokinetic/pharmacodynamic modelling of the analgesic effects of tramadol in pediatrics. *Pharm Res* **23**(9): 2014-23.
Gauger VT, Voepel-Lewis TD, Burke CN et al (2009) Epidural analgesia compared with intravenous analgesia after pediatric posterior spinal fusion. *J Pediatr Orthop* **29**(6): 588–93.
Gausche-Hill M, Brown KM, Oliver ZJ et al (2014) An Evidence-based Guideline for prehospital analgesia in trauma. *Prehosp Emerg Care* **18 Suppl 1**: 25-34.
Gazal G & Mackie IC (2007) A comparison of paracetamol, ibuprofen or their combination for pain relief following extractions in children under general anaesthesia: a randomized controlled trial. *Int J Paediatr Dent* **17**(3): 169–77.
Geary T, Negus A, Anderson BJ et al (2012) Perioperative management of the child on long-term opioids. *Paediatr Anaesth* **22**(3): 189–202.
Gelfand AA (2018) Pediatric and Adolescent Headache. *Continuum (Minneap Minn)* **24**(4, Headache): 1108-36.
Gennis H, Pillai Riddell R, O'Neill MC et al (2018) Parental Psychological Distress Moderates the Impact of a Video Intervention to Help Parents Manage Young Child Vaccination Pain. *J Pediatr Psychol* **43**(10): 1170-78.
George JA, Lin EE, Hanna MN et al (2010) The effect of intravenous opioid patient-controlled analgesia with and without background infusion on respiratory depression: a meta-analysis. *J Opioid Manag* **6**(1): 47–54.

George JA, Park PS, Hunsberger J et al (2016) An Analysis of 34,218 Pediatric Outpatient Controlled Substance Prescriptions. *Anesth Analg* **122**(3): 807-13.
Gerceker GO, Binay S, Bilsin E et al (2018) Effects of Virtual Reality and External Cold and Vibration on Pain in 7- to 12-Year-Old Children During Phlebotomy: A Randomized Controlled Trial. *J Perianesth Nurs* **33**(6): 981-89.
Geva A & Brigger MT (2011) Dexamethasone and tonsillectomy bleeding: a meta-analysis. *Otolaryngol Head Neck Surg* **144**(6): 838–43.
Ghaffari V, Fattahi S, Taheri M et al (2014) The comparison of pain caused by suprapubic aspiration and transurethral catheterization methods for sterile urine collection in neonates: a randomized controlled study. *ScientificWorldJournal* **2014**: 946924.
Ghai B, Ram J, Makkar JK et al (2009) Subtenon block compared to intravenous fentanyl for perioperative analgesia in pediatric cataract surgery. *Anesth Analg* **108**(4): 1132–8.
Gharavi B, Schott C, Nelle M et al (2007) Pain management and the effect of guidelines in neonatal units in Austria, Germany and Switzerland. *Pediatr Int* **49**(5): 652–58.
Ghasemi A, Gharavi Fard M & Sabzevari A (2013) General anesthesia for lumbar puncture and bone marrow aspiration /biopsy in children with cancer. *Iran J Ped Hematol Oncol* **3**(2): 54–58.
Giannetti L, Forabosco E, Spinas E et al (2018) Single tooth anaesthesia: a new approach to the paediatric patient. A clinical experimental study. *Eur J Paediatr Dent* **19**(1): 40-43.
Giaufre E, Dalens B & Gombert A (1996) Epidemiology and morbidity of regional anesthesia in children: a one-year prospective survey of the French-Language Society of Pediatric Anesthesiologists. *Anesth Analg* **83**(5): 904–12.
Gibb IA & Anderson BJ (2008) Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasma concentration. *Arch Dis Child* **93**(3): 241-7.
Girotra S, Kumar S & Rajendran KM (1990) Postoperative analgesia in children who have genito-urinary surgery. A comparison between caudal buprenorphine and bupivacaine. *Anaesthesia* **45**(5): 406-8.
Girotra S, Kumar S & Rajendran KM (1993a) Caudal buprenorphine for postoperative analgesia in children: a comparison with intramuscular buprenorphine. *Acta Anaesthesiol Scand* **37**(4): 361-4.
Girotra S, Kumar S & Rajendran KM (1993b) Comparison of caudal morphine and buprenorphine for post-operative analgesia in children. *Eur J Anaesthesiol* **10**(4): 309-12.
Gish EC, Harrison D, Gormley AK et al (2011) Dosing evaluation of continuous intravenous fentanyl infusions in overweight children: a pilot study. *J Pediatr Pharmacol Ther* **16**(1): 39–46.
Gitman M, Fettiplace MR, Weinberg GL et al (2019) Local Anesthetic Systemic Toxicity: A Narrative Literature Review and Clinical Update on Prevention, Diagnosis, and Management. *Plast Reconstr Surg* **144**(3): 783-95.
Gjedsted J & Dall R (2015) Severe hypoglycemia during methadone escalation in an 8-year-old child. *Acta Anaesthesiol Scand* **59**(10): 1394-6.
Gladwin MT, Kato GJ, Weiner D et al (2011) Nitric oxide for inhalation in the acute treatment of sickle cell pain crisis: a randomized controlled trial. *JAMA* **305**(9): 893-902.
Glassberg JA (2017) Improving Emergency Department-Based Care of Sickle Cell Pain. *Hematology Am Soc Hematol Educ Program* **2017**(1): 412-17.
Glover CD, Paek JS, Patel N et al (2015) Postoperative pain and the use of ultrasound-guided regional analgesia in pediatric supracondylar humerus fractures. *J Pediatr Orthop B* **24**(3): 178-83.
Goeller JK, Joselyn A, Martin DP et al (2016) Epidural pressure changes following caudal blockade: a prospective, observational study. *J Anesth* **30**(4): 578-82.
Goettems ML, Zborowski EJ, Costa FD et al (2017) Nonpharmacologic Intervention on the Prevention of Pain and Anxiety During Pediatric Dental Care: A Systematic Review. *Acad Pediatr* **17**(2): 110-19.
Goksan S, Hartley C, Emery F et al (2015) fMRI reveals neural activity overlap between adult and infant pain. *Elife* **4**: e06356.
Gol I & Altug Ozsoy S (2017) Effects of Rapid Vaccine Injection Without Aspiration and Applying Manual Pressure Before Vaccination on Pain and Crying Time in Infants. *Worldviews Evid Based Nurs* **14**(2): 154-62.
Gold JI & Mahrer NE (2018) Is Virtual Reality Ready for Prime Time in the Medical Space? A Randomized Control Trial of Pediatric Virtual Reality for Acute Procedural Pain Management. *J Pediatr Psychol* **43**(3): 266-75.
Golden-Plotnik S, Ali S, Drendel AL et al (2018) A Web-based module and online video for pain management education for caregivers of children with fractures: A randomized controlled trial. *Cjem* **20**(6): 882-91.
Goldman A, Hewitt M, Collins GS et al (2006) Symptoms in children/young people with progressive malignant disease: United Kingdom Children's Cancer Study Group/Paediatric Oncology Nurses Forum survey. *Pediatrics* **117**(6): e1179-86.
Golianu B & Hammer GB (2005) Pain management for pediatric thoracic surgery. *Curr Opin Anaesthesiol* **18**(1): 13–21.
Gomes T, Tadrous M, Mamdani MM et al (2018) The Burden of Opioid-Related Mortality in the United States. *JAMA network open* **1**(2): e180217-e17.
Goot BH, Kaufman J, Pan Z et al (2018) Morphine Pharmacokinetics in Children With Down Syndrome Following Cardiac Surgery. *Pediatr Crit Care Med* **19**(5): 459-67.
Gorchynski J & McLaughlin T (2011) The routine utilization of procedural pain management for pediatric lumbar punctures: are we there yet? *J Clin Med Res* **3**(4): 164–67.

Gordon M, Biagioli E, Sorrenti M et al (2018) Dietary modifications for infantile colic. *Cochrane Database Syst Rev* **10**: Cd011029.
Gorges M, West N, Deyell R et al (2015) Dexmedetomidine and hydromorphone: a novel pain management strategy for the oncology ward setting during anti-GD2 immunotherapy for high-risk neuroblastoma in children. *Pediatr Blood Cancer* **62**(1): 29-34.
Goutos I, Clarke M, Upson C et al (2010) Review of therapeutic agents for burns pruritus and protocols for management in adult and paediatric patients using the GRADE classification. *Indian J Plast Surg* **43**(Suppl): S51-62.
Graff DM & McDonald MJ (2018) Auricular Acupuncture for the Treatment of Pediatric Migraines in the Emergency Department. *Pediatr Emerg Care* **34**(4): 258-62.
Graham GG, Davies MJ, Day RO et al (2013) The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* **21**(3): 201–32.
Grainger J & Saravanappa N (2008) Local anaesthetic for post-tonsillectomy pain: a systematic review and meta-analysis. *Clin Otolaryngol* **33**(5): 411–19.
Graudins A, Meek R, Egerton-Warburton D et al (2015) The PICHFORK (Pain in Children Fentanyl or Ketamine) trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries. *Ann Emerg Med* **65**(3): 248–54 e1.
Gray L, Lang CW & Porges SW (2012) Warmth is analgesic in healthy newborns. *Pain* **153**(5): 960–66.
Green E, Cadogan J & Harcourt D (2018) A qualitative study of health professionals' views on using iPads to facilitate distraction during paediatric burn dressing changes. *Scars Burn Heal* **4**: 2059513118764878.
Green G, Hartley C, Hoskin A et al (2019a) Behavioural discrimination of noxious stimuli in infants is dependent on brain maturation. *Pain* **160**(2): 493-500.
Green R, Bulloch B, Kabani A et al (2005) Early analgesia for children with acute abdominal pain. *Pediatrics* **116**(4): 978-83.
Green SM & Cote CJ (2009a) Ketamine and neurotoxicity: clinical perspectives and implications for emergency medicine. *Ann Emerg Med* **54**(2): 181–90.
Green SM, Roback MG, Kennedy RM et al (2011) Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med* **57**(5): 449–61.
Green SM, Roback MG, Krauss B et al (2009b) Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children. *Ann Emerg Med* **54**(2): 158–68.e1–4.
Green SM, Roback MG, Krauss B et al (2009c) Predictors of emesis and recovery agitation with emergency department ketamine sedation: an individual-patient data meta-analysis of 8,282 children. *Ann Emerg Med* **54**(2): 171–80; e1–4.
Green SM, Roback MG, Krauss BS et al (2019b) Unscheduled Procedural Sedation: A Multidisciplinary Consensus Practice Guideline. *Ann Emerg Med* **73**(5): e51-e65.
Griffin TC, McIntire D & Buchanan GR (1994) High-dose intravenous methylprednisolone therapy for pain in children and adolescents with sickle cell disease. *N Engl J Med* **330**(11): 733–37.
Griffith RJ, Jordan V, Herd D et al (2016) Vapocoolants (cold spray) for pain treatment during intravenous cannulation. *Cochrane Database Syst Rev* **4**: Cd009484.
Grindlay J & Babl FE (2009) Review article: efficacy and safety of methoxyflurane analgesia in the emergency department and prehospital setting. *Emerg Med Australas* **21**(1): 4–11.
Groenewald CB (2019a) Opioid-prescribing Patterns for Pediatric Patients in the United States. *Clin J Pain* **35**(6): 515-20.
Groenewald CB, Rabbitts JA, Gebert JT et al (2016) Trends in opioid prescriptions among children and adolescents in the United States: a nationally representative study from 1996 to 2012. *Pain* **157**(5): 1021-7.
Groenewald CB, Zhou C, Palermo TM et al (2019b) Associations Between Opioid Prescribing Patterns and Overdose Among Privately Insured Adolescents. e20184070.
Grosek S, Mozina M, Grabnar I et al (2009) Diagnostic and therapeutic value of naloxone after intoxication with tramadol in a young girl. *Pediatr Int* **51**(6): 842–43.
Grossmann B, Nilsson A, Sjoberg F et al (2019) Rectal ketamine during paediatric burn wound dressing procedures: a randomised dose-finding study. *Burns* **45**(5): 1081-88.
Grunau RE, Whitfield MF, Petrie-Thomas J et al (2009) Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. *Pain* **143**(1-2): 138–46.
Grunau RV & Craig KD (1987) Pain expression in neonates: facial action and cry. *Pain* **28**(3): 395–410.
Grunau RV, Whitfield MF, Petrie JH et al (1994) Early pain experience, child and family factors, as precursors of somatization: a prospective study of extremely premature and fullterm children. *Pain* **56**(3): 353–59.
Guay J, Suresh S & Kopp S (2019a) The use of ultrasound guidance for perioperative neuraxial and peripheral nerve blocks in children. *Cochrane Database Syst Rev* **2**: CD011436.
Guay J, Suresh S, Kopp S et al (2019b) Postoperative epidural analgesia versus systemic analgesia for thoraco-lumbar spine surgery in children. *Cochrane Database Syst Rev* **1**: CD012819.

Guinsburg R, de Araujo Peres C, Branco de Almeida MF et al (2000) Differences in pain expression between male and female newborn infants. *Pain* **85**(1-2): 127-33.
Gulec S, Buyukkidan B, Oral N et al (1998) Comparison of caudal bupivacaine, bupivacaine-morphine and bupivacaine-midazolam mixtures for post-operative analgesia in children. *Eur J Anaesthesiol* **15**(2): 161–65.
Guo Q, Li R, Wang L et al (2015) Transversus abdominis plane block versus local anaesthetic wound infiltration for postoperative analgesia: A systematic review and meta-analysis. *Int J Clin Exp Med* **8**(10): 17343-52.
Guo T, Mandai K, Condie BG et al (2011) An evolving NGF-Hoxd1 signaling pathway mediates development of divergent neural circuits in vertebrates. *Nature Neuroscience* **14**(1): 31–36.
Gupta A, Daggett C, Drant S et al (2004) Prospective randomized trial of ketorolac after congenital heart surgery. *J Cardiothorac Vasc Anesth* **18**(4): 454–57.
Gupta N, Kumar R, Kumar S et al (2007) A prospective randomised double blind study to evaluate the effect of peribulbar block or topical application of local anaesthesia combined with general anaesthesia on intra-operative and postoperative complications during paediatric strabismus surgery. *Anaesthesia* **62**(11): 1110–13.
Gupta NK, Upadhyay A, Agarwal A et al (2013) Randomized controlled trial of topical EMLA and breastfeeding for reducing pain during wDPT vaccination. *Eur J Pediatr* **172**(11): 1527–33.
Gupta NK, Upadhyay A, Dwivedi AK et al (2017) Randomized controlled trial of topical EMLA and vapocoolant spray for reducing pain during wDPT vaccination. *World J Pediatr* **13**(3): 236-41.
Gupta P, Whiteside W, Sabati A et al (2012) Safety and efficacy of prolonged dexmedetomidine use in critically ill children with heart disease*. *Pediatr Crit Care Med* **13**(6): 660–66.
Gurkan Y, Aksu C, Kus A et al (2017) One operator's experience of ultrasound guided lumbar plexus block for paediatric hip surgery. *J Clin Monit Comput* **31**(2): 331-36.
Gurnaney H, Kraemer FW, Maxwell L et al (2014) Ambulatory continuous peripheral nerve blocks in children and adolescents: a longitudinal 8-year single center study. *Anesth Analg* **118**(3): 621–27.
Gurney J, Richiardi L, McGlynn KA et al (2017) Analgesia use during pregnancy and risk of cryptorchidism: a systematic review and meta-analysis. *Human reproduction (Oxford, England)* **32**(5): 1118-29.
Gutman D, Hellriegel E, Aycardi E et al (2016) A Phase I, Open-Label, Single-Dose Safety, Pharmacokinetic, and Tolerability Study of the Sumatriptan Iontophoretic Transdermal System in Adolescent Migraine Patients. *Headache* **56**(8): 1300-9.
Habashy C, Springer E, Hall EA et al (2018) Methadone for Pain Management in Children with Cancer. *Paediatr Drugs* **20**(5): 409-16.
Haddadi S, Marzban S, Karami MS et al (2014) Comparing the duration of the analgesic effects of intravenous and rectal acetaminophen following tonsillectomy in children. *Anesth Pain Med* **4**(1): e13175.
Hadden KL, LeFort S, O'Brien M et al (2015) A comparison of observers' and self-report pain ratings for children with cerebral palsy. *J Dev Behav Pediatr* **36**(1): 14-23.
Hadden KL, LeFort S, O'Brien M et al (2016) Validity of the Child Facial Coding System for the Assessment of Acute Pain in Children With Cerebral Palsy. *J Child Neurol* **31**(5): 597-602.
Hadley G, Maconochie I & Jackson A (2010) A survey of intranasal medication use in the paediatric emergency setting in England and Wales. *Emerg Med J* **27**(7): 553–54.
Hakim M, Anderson BJ, Walia H et al (2019) Acetaminophen pharmacokinetics in severely obese adolescents and young adults. *Paediatr Anaesth* **29**(1): 20-26.
Hall Burton DM & Boretsky KR (2014) A comparison of paravertebral nerve block catheters and thoracic epidural catheters for postoperative analgesia following the Nuss procedure for pectus excavatum repair. *Paediatr Anaesth* **24**(5): 516–20.
Hall RW & Anand KJ (2014) Pain management in newborns. *Clin Perinatol* **41**(4): 895-924.
Hamill JK, Rahiri JL, Liley A et al (2016) Rectus sheath and transversus abdominis plane blocks in children: a systematic review and meta-analysis of randomized trials. *Paediatr Anaesth* **26**(4): 363-71.
Hamunen K & Kontinen V (2005) Systematic review on analgesics given for pain following tonsillectomy in children. *Pain* **117**(1-2): 40–50.
Han J, Zhou J, Saraf SL et al (2018) Characterization of opioid use in sickle cell disease. *Pharmacoepidemiol Drug Saf* **27**(5): 479-86.
Hannam JA, Anderson BJ, Mahadevan M et al (2014) Postoperative analgesia using diclofenac and acetaminophen in children. *Paediatr Anaesth* **24**(9): 953–61.
Hannam JA, Anderson BJ & Potts A (2018) Acetaminophen, ibuprofen, and tramadol analgesic interactions after adenotonsillectomy. *Paediatr Anaesth* **28**(10): 841-51.
Hansen MS, Mathiesen O, Trautner S et al (2012) Intranasal fentanyl in the treatment of acute pain--a systematic review. *Acta Anaesthesiol Scand* **56**(4): 407–19.
Hansen TG, Henneberg SW & Hole P (1996) Age-related postoperative morphine requirements in children following major surgery--an assessment using patient-controlled analgesia (PCA). *Eur J Pediatr Surg* **6**(1): 29–31.
Harbaugh CM, Johnson KN, Kein CE et al (2018a) Comparing outcomes with thoracic epidural and intercostal nerve cryoablation after Nuss procedure. *J Surg Res* **231**: 217-23.

Harbaugh CM, Lee JS, Hu HM et al (2018b) Persistent Opioid Use Among Pediatric Patients After Surgery. *Pediatrics* **141**(1).
Harbaugh CM, Vargas G, Streur CS et al (2019) Eliminating Unnecessary Opioid Exposure After Common Children's Surgeries. *JAMA Surg*.
Hargrave DR, Wade A, Evans JP et al (2003) Nocturnal oxygen saturation and painful sickle cell crises in children. *Blood* **101**(3): 846–48.
Harma A, Aikio O, Hallman M et al (2016) Intravenous Paracetamol Decreases Requirements of Morphine in Very Preterm Infants. *J Pediatr* **168**: 36-40.
Harman S, Zemek R, Duncan MJ et al (2013) Efficacy of pain control with topical lidocaine-epinephrine-tetracaine during laceration repair with tissue adhesive in children: a randomized controlled trial. *CMAJ* **185**(13): E629–34.
Haroon M (2005) Should children with Henoch-Schonlein purpura and abdominal pain be treated with steroids? *Arch Dis Child* **90**(11): 1196-8.
Harrison D, Larocque C, Bueno M et al (2017) Sweet Solutions to Reduce Procedural Pain in Neonates: A Meta-analysis. *Pediatrics* **139**(1).
Harrison D, Reszel J, Bueno M et al (2016) Breastfeeding for procedural pain in infants beyond the neonatal period. *Cochrane Database Syst Rev* **10**: Cd011248.
Harrison D, Sampson M, Reszel J et al (2014) Too many crying babies: a systematic review of pain management practices during immunizations on YouTube. *BMC Pediatr* **14**: 134.
Harrison D, Yamada J, Adams-Webber T et al (2015) Sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years. *Cochrane Database Syst Rev*(5): Cd008408.
Hartenstein S, Proquitte H, Bauer S et al (2010) Neonatal abstinence syndrome (NAS) after intrauterine exposure to tramadol. *J Perinat Med* **38**(6): 695–96.
Hartley C, Duff EP, Green G et al (2017) Nociceptive brain activity as a measure of analgesic efficacy in infants. *Sci Transl Med* **9**(388).
Hartling L, Newton AS, Liang Y et al (2013) Music to reduce pain and distress in the pediatric emergency department: a randomized clinical trial. *JAMA Pediatrics* **167**(9): 826–35.
Harvey A, Reddihough D, Scheinberg A et al (2018) Oral medication prescription practices of tertiary-based specialists for dystonia in children with cerebral palsy. *J Paediatr Child Health* **54**(4): 401-04.
Hashemi F, Taheri L, Ghodsbin F et al (2016) Comparing the effect of swaddling and breastfeeding and their combined effect on the pain induced by BCG vaccination in infants referring to Motahari Hospital, Jahrom, 2010-2011. *Appl Nurs Res* **29**: 217-21.
Hassan PF, Hassan AS & Elmetwally SA (2018) Caudal Analgesia for Hypospadias in Pediatrics: Comparative Evaluation of Adjuvants Dexamethasone and Dexmedetomidine Combination versus Dexamethasone or Dexmedetomidine to Bupivacaine: A Prospective, Double-Blinded, Randomized Comparative Study. *Anesth Essays Res* **12**(3): 644-50.
Hassanian-Moghaddam H, Farajidana H, Sarjami S et al (2013) Tramadol-induced apnea. *Am J Emerg Med* **31**(1): 26–31.
Hassanian-Moghaddam H, Farnaghi F & Rahimi M (2015) Tramadol overdose and apnea in hospitalized children, a review of 20 cases. *Res Pharm Sci* **10**(6): 544-52.
Hatfield LA & Ely EA (2015) Measurement of acute pain in infants: a review of behavioral and physiological variables. *Biol Res Nurs* **17**(1): 100-11.
Hathway GJ, Vega-Avelaira D & Fitzgerald M (2012) A critical period in the supraspinal control of pain: opioid-dependent changes in brainstem rostroventral medulla function in preadolescence. *Pain* **153**(4): 775–83.
Hauer J & Houtrow AJ (2017) Pain Assessment and Treatment in Children With Significant Impairment of the Central Nervous System. *Pediatrics* **139**(6).
Hayden JC, Bardol M, Doherty DR et al (2019) Optimizing clonidine dosage for sedation in mechanically ventilated children: A pharmacokinetic simulation study. *Paediatr Anaesth* **29**(10): 1002-10.
Hayes J, Dowling JJ, Peliowski A et al (2016) Patient-Controlled Analgesia Plus Background Opioid Infusion for Postoperative Pain in Children: A Systematic Review and Meta-Analysis of Randomized Trials. *Anesth Analg* **123**(4): 991-1003.
Haynes G, Brahen NH & Hill HF (1993) Plasma sufentanil concentration after intranasal administration to paediatric outpatients. *Can J Anaesth* **40**(3): 286.
He M, Zhang B, Shen N et al (2018) A systematic review and meta-analysis of the effect of low-level laser therapy (LLLT) on chemotherapy-induced oral mucositis in pediatric and young patients. *European Journal of Pediatrics* **177**(1): 7-17.
He XY, Cao JP, Shi XY et al (2013) Dexmedetomidine versus morphine or fentanyl in the management of children after tonsillectomy and adenoidectomy: a meta-analysis of randomized controlled trials. *Ann Otol Rhinol Laryngol* **122**(2): 114–20.
Hedeland RL, Andersen J, Askbo N et al (2014) Early predictors of severe acetaminophen-induced hepatotoxicity in a paediatric population referred to a tertiary paediatric department. *Acta Paediatr* **103**(11): 1179–86.
Heden L, von Essen L & Ljungman G (2014) Effect of high-dose paracetamol on needle procedures in children with cancer - a RCT. *Acta Paediatr* **103**(3): 314–19.

Heden LE, von Essen L & Ljungman G (2011) Effect of morphine in needle procedures in children with cancer. *Eur J Pain* **15**(10): 1056–60.
Heeney MM, Hoppe CC, Abboud MR et al (2016) A Multinational Trial of Prasugrel for Sickle Cell Vaso-Occlusive Events. *N Engl J Med* **374**(7): 625-35.
Heiba MH, Atef A, Mosleh M et al (2012) Comparison of peritonsillar infiltration of tramadol and lidocaine for the relief of post-tonsillectomy pain. *J Laryngol Otol* **126**(11): 1138–41.
Heiderich TM, Leslie AT & Guinsburg R (2015) Neonatal procedural pain can be assessed by computer software that has good sensitivity and specificity to detect facial movements. *Acta Paediatr* **104**(2): e63-9.
Heinrich M, Menzel C, Hoffmann F et al (2015) Self-administered procedural analgesia using nitrous oxide/oxygen (50:50) in the pediatric surgery emergency room: effectiveness and limitations. *Eur J Pediatr Surg* **25**(3): 250-6.
Hennes H, Kim MK & Pirrallo RG (2005) Prehospital pain management: a comparison of providers' perceptions and practices. *Prehosp Emerg Care* **9**(1): 32–9.
Hennrikus WL, Shin AY & Klingelberger CE (1995) Self-administered nitrous oxide and a hematoma block for analgesia in the outpatient reduction of fractures in children. *J Bone Joint Surg Am* **77**(3): 335-9.
Hennrikus WL, Simpson RB, Klingelberger CE et al (1994) Self-administered nitrous oxide analgesia for pediatric fracture reductions. *J Pediatr Orthop* **14**(4): 538-42.
Herd DW, Anderson BJ & Holford NH (2007) Modeling the norketamine metabolite in children and the implications for analgesia. *Paediatr Anaesth* **17**(9): 831–40.
Herd DW, Anderson BJ, Keene NA et al (2008) Investigating the pharmacodynamics of ketamine in children. *Paediatr Anaesth* **18**(1): 36–42.
Hermann C, Hohmeister J, Demirakca S et al (2006) Long-term alteration of pain sensitivity in school-aged children with early pain experiences. *Pain* **125**(3): 278–85.
Hernandez MA, Palazzi L, Lapalma J et al (2018a) Erector spinae plane block for inguinal hernia repair in preterm infants. *Paediatr Anaesth* **28**(3): 298-99.
Hernandez MA, Palazzi L, Lapalma J et al (2018b) Erector Spinae Plane Block for Surgery of the Posterior Thoracic Wall in a Pediatric Patient. *Reg Anesth Pain Med* **43**(2): 217-19.
Hernandez-Reif M, Field T, Largie S et al (2001) Childrens' distress during burn treatment is reduced by massage therapy. *J Burn Care Rehabil* **22**(2): 191–95; discussion 90.
Hester NK (1979) The preoperational child's reaction to immunization. *Nurs Res* **28**(4): 250–55.
Hewes HA, Dai M, Mann NC et al (2018) Prehospital Pain Management: Disparity By Age and Race. *Prehosp Emerg Care* **22**(2): 189-97.
Hewitt M, Goldman A, Collins GS et al (2008) Opioid use in palliative care of children and young people with cancer. *J Pediatr* **152**(1): 39–44.
Hicks CL, von Baeyer CL, Spafford PA et al (2001) The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain* **93**(2): 173–83.
Higashizawa T & Koga Y (2001) Effect of infraorbital nerve block under general anesthesia on consumption of isoflurane and postoperative pain in endoscopic endonasal maxillary sinus surgery. *J Anesth* **15**(3): 136-8.
Hiller A, Helenius I, Nurmi E et al (2012) Acetaminophen improves analgesia but does not reduce opioid requirement after major spine surgery in children and adolescents. *Spine (Phila Pa 1976)* **37**(20): E1225–31.
Hiller A, Meretoja OA, Korpela R et al (2006) The analgesic efficacy of acetaminophen, ketoprofen, or their combination for pediatric surgical patients having soft tissue or orthopedic procedures. *Anesth Analg* **102**(5): 1365–71.
Hippard HK, Govindan K, Friedman EM et al (2012) Postoperative analgesic and behavioral effects of intranasal fentanyl, intravenous morphine, and intramuscular morphine in pediatric patients undergoing bilateral myringotomy and placement of ventilating tubes. *Anesth Analg* **115**(2): 356–63.
Hirschfeld G & Zernikow B (2013) Cut points for mild, moderate, and severe pain on the VAS for children and adolescents: what can be learned from 10 million ANOVAs? *Pain* **154**(12): 2626–32.
Hirschfeld G, Zernikow B, Kraemer N et al (2012) Development of somatosensory perception in children: a longitudinal QST-study. *Neuropediatrics* **43**(1): 10–16.
Hoashi JS, Thomas SM, Goodwin RC et al (2017) Balloon Kyphoplasty for Managing Intractable Pain in Pediatric Pathologic Vertebral Fractures. *J Pediatr Orthop* **37**(4): e286-e91.
Hock MO, Ooi SB, Saw SM et al (2002) A randomized controlled trial comparing the hair apposition technique with tissue glue to standard suturing in scalp lacerations (HAT study). *Ann Emerg Med* **40**(1): 19–26.
Hodgson R, Bosenberg A & Hadley L (2000) Congenital diaphragmatic hernia repair--impact of delayed surgery and epidural analgesia. *S Afr J Surg* **38**(2): 31–34.
Hoeffe J, Doyon Trottier E, Bailey B et al (2017) Intranasal fentanyl and inhaled nitrous oxide for fracture reduction: The FAN observational study. *Am J Emerg Med* **35**(5): 710-15.
Hogan ME, Smart S, Shah V et al (2014) A systematic review of vapocoolants for reducing pain from venipuncture and venous cannulation in children and adults. *J Emerg Med* **47**(6): 736-49.
Hogan ME, vanderVaart S, Perampaladas K et al (2011) Systematic review and meta-analysis of the effect of warming local anesthetics on injection pain. *Ann Emerg Med* **58**(1): 86–98 e1.

Hohmeister J, Demirakca S, Zohsel K et al (2009) Responses to pain in school-aged children with experience in a neonatal intensive care unit: cognitive aspects and maternal influences. *Eur J Pain* **13**(1): 94–101.
Hohmeister J, Kroll A, Wollgarten-Hadamek I et al (2010) Cerebral processing of pain in school-aged children with neonatal nociceptive input: an exploratory fMRI study. *Pain* **150**(2): 257–67.
Holdgate A, Cao A & Lo KM (2010) The implementation of intranasal fentanyl for children in a mixed adult and pediatric emergency department reduces time to analgesic administration. *Acad Emerg Med* **17**(2): 214-7.
Holford NH, Ma SC & Anderson BJ (2012) Prediction of morphine dose in humans. *Paediatr Anaesth* **22**(3): 209–22.
Holstein K, Klamroth R, Richards M et al (2012) Pain management in patients with haemophilia: a European survey. *Haemophilia* **18**(5): 743–52.
Holsti L & Grunau RE (2007) Initial validation of the Behavioral Indicators of Infant Pain (BIIP). *Pain* **132**(3): 264–72.
Holsti L, Grunau RE, Whifield MF et al (2006) Behavioral responses to pain are heightened after clustered care in preterm infants born between 30 and 32 weeks gestational age. *Clin J Pain* **22**(9): 757–64.
Honarmand A, Safavi M, Kashefi P et al (2013) Comparison of effect of intravenous ketamine, peritonsillar infiltration of tramadol and their combination on pediatric posttonsillectomy pain: A double-blinded randomized placebo-controlled clinical trial. *Res Pharm Sci* **8**(3): 177–83.
Honarmand A, Safavi M, Naghibi K et al (2015) Preemptive peritonsillar infiltration with bupivacaine in combination with tramadol improves pediatric post-tonsillectomy pain better than using bupivacaine or tramadol alone: A randomized, placebo-controlled, double blind clinical trial. *Adv Biomed Res* **4**: 132.
Honey BL, Benefield RJ, Miller JL et al (2009) Alpha2-receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients. *Ann Pharmacother* **43**(9): 1506–11.
Hong JY, Kim WO, Koo BN et al (2010) Fentanyl-sparing effect of acetaminophen as a mixture of fentanyl in intravenous parent-/nurse-controlled analgesia after pediatric ureteroneocystostomy. *Anesthesiology* **113**(3): 672–77.
Hong R, Gauger V, Caird MS et al (2016) Narcotic-only Epidural Infusion for Posterior Spinal Fusion Patients: A Single-Center, Retrospective Review. *J Pediatr Orthop* **36**(5): 526-9.
Hong RA, Gibbons KM, Li GY et al (2017) A retrospective comparison of intrathecal morphine and epidural hydromorphone for analgesia following posterior spinal fusion in adolescents with idiopathic scoliosis. *Paediatr Anaesth* **27**(1): 91-97.
Hopper SM, McCarthy M, Tancharoen C et al (2014) Topical lidocaine to improve oral intake in children with painful infectious mouth ulcers: a blinded, randomized, placebo-controlled trial. *Ann Emerg Med* **63**(3): 292–99.
Horn PL, Wrona S, Beebe AC et al (2010) A retrospective quality improvement study of ketorolac use following spinal fusion in pediatric patients. *Orthop Nurs* **29**(5): 342–43.
Hornik CP, Gonzalez D, van den Anker J et al (2018) Population Pharmacokinetics of Intramuscular and Intravenous Ketamine in Children. *J Clin Pharmacol*.
Horvat CM, Au AK, Conley YP et al (2017) ABCB1 genotype is associated with fentanyl requirements in critically ill children. *Pediatr Res* **82**(1): 29-35.
Hosseinlou A, Alinejad V, Alinejad M et al (2014) The effects of fish oil capsules and vitamin B1 tablets on duration and severity of dysmenorrhea in students of high school in Urmia-Iran. *Glob J Health Sci* **6**(7 Spec No): 124-9.
Houx L, Dubois A, Brochard S et al (2019) Do clowns attenuate pain and anxiety undergoing botulinum toxin injections in children? *Ann Phys Rehabil Med*.
Howard R, Carter B, Curry J et al (2008a) Pain assessment. *Paediatr Anaesth* **18**(Suppl 1): 14–18.
Howard RF, Carter B, Curry J et al (2008b) Association of Paediatric Anaesthetists: good practice in postoperative and procedural pain. *Paediatr Anaesth* **18**(Suppl 1): 1–81.
Howard RF, Lloyd-Thomas A, Thomas M et al (2010) Nurse-controlled analgesia (NCA) following major surgery in 10,000 patients in a children's hospital. *Paediatr Anaesth* **20**(2): 126–34.
Howard RF, Walker SM, Mota PM et al (2005) The ontogeny of neuropathic pain: postnatal onset of mechanical allodynia in rat spared nerve injury (SNI) and chronic constriction injury (CCI) models. *Pain* **115**(3): 382–89.
Howell TK & Patel D (2003) Plasma paracetamol concentrations after different doses of rectal paracetamol in older children A comparison of 1 g vs. 40 mg x kg(-1). *Anaesthesia* **58**(1): 69–73.
Hoyle JD, Jr., Rogers AJ, Reischman DE et al (2011) Pain intervention for infant lumbar puncture in the emergency department: physician practice and beliefs. *Acad Emerg Med* **18**(2): 140–44.
HQSC (2019) *Opioid Atlas Maps 2017.* https://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/opioids/ Accessed 17 February 2020
Hsiao HJ, Chen SH, Jaing TH et al (2019) Psychosocial interventions for reduction of distress in children with leukemia during bone marrow aspiration and lumbar puncture. *Pediatr Neonatol* **60**(3): 278-84.
Hsiao HJ, Huang JL, Hsia SH et al (2014) Headache in the pediatric emergency service: a medical center experience. *Pediatr Neonatol* **55**(3): 208-12.
Hu J, Modanloo S, Squires JE et al (2019) The Validity of Skin Conductance For Assessing Acute Pain in Infants: A Scoping Review. *Clin J Pain* **35**(8): 713-24.
Huang RR, Xie RH, Wen SW et al (2019) Sweet Solutions for Analgesia in Neonates in China: A Systematic Review and Meta-Analysis. *Can J Nurs Res* **51**(2): 116-27.

Hudda MT, Fewtrell MS, Haroun D et al (2019) Development and validation of a prediction model for fat mass in children and adolescents: meta-analysis using individual participant data. *Bmj* **366**: l4293.
Hullett B, Salman S, O'Halloran SJ et al (2012) Development of a population pharmacokinetic model for parecoxib and its active metabolite valdecoxib after parenteral parecoxib administration in children. *Anesthesiology* **116**(5): 1124–33.
Hullett BJ, Chambers NA, Pascoe EM et al (2006) Tramadol vs morphine during adenotonsillectomy for obstructive sleep apnea in children. *Paediatr Anaesth* **16**(6): 648-53.
Hummel P, Puchalski M, Creech SD et al (2008) Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. *J Perinatol* **28**(1): 55–60.
Humphreys N, Bays SM, Parry AJ et al (2005) Spinal anesthesia with an indwelling catheter reduces the stress response in pediatric open heart surgery. *Anesthesiology* **103**(6): 1113–20.
Hungerford JL, O'Brien N, Moore-Clingenpeel M et al (2019) Remifentanil for Sedation of Children With Traumatic Brain Injury. *J Intensive Care Med* **34**(7): 557-62.
Hunsberger JB, Hsu A, Yaster M et al (2019) Physicians Prescribe More Opioid Than Needed to Treat Pain in Children After Outpatient Urological Procedures: An Observational Cohort Study. *Anesth Analg*: epub ahead of print.
Hunseler C, Balling G, Rohlig C et al (2014) Continuous infusion of clonidine in ventilated newborns and infants: a randomized controlled trial. *Pediatr Crit Care Med* **15**(6): 511-22.
Hunt A, Goldman A, Devine T et al (2001) Transdermal fentanyl for pain relief in a paediatric palliative care population. *Palliat Med* **15**(5): 405-12.
Hunt A, Goldman A, Seers K et al (2004) Clinical validation of the paediatric pain profile. *Dev Med Child Neurol* **46**(1): 9–18.
Hunt A, Wisbeach A, Seers K et al (2007) Development of the paediatric pain profile: role of video analysis and saliva cortisol in validating a tool to assess pain in children with severe neurological disability. *J Pain Symptom Manage* **33**(3): 276–89.
Hussein MM (2018) Ultrasound-guided quadratus lumborum block in pediatrics: trans-muscular versus intra-muscular approach. *J Anesth* **32**(6): 850-55.
Hwang SH, Park IJ, Cho YJ et al (2016a) The efficacy of gabapentin/pregabalin in improving pain after tonsillectomy: A meta-analysis. *Laryngoscope* **126**(2): 357-66.
Hwang SH, Song JN, Jeong YM et al (2016b) The efficacy of honey for ameliorating pain after tonsillectomy: a meta-analysis. *Eur Arch Otorhinolaryngol* **273**(4): 811-8.
Hyland EJ, D'Cruz R, Harvey JG et al (2015) An assessment of early Child Life Therapy pain and anxiety management: A prospective randomised controlled trial. *Burns* **41**(8): 1642-52.
Ibach BW, Miller JL, Woo S et al (2017) Characterization of Tolerance in Children during Fentanyl Continuous Infusions. *J Pediatr Intensive Care* **6**(2): 83-90.
IHS HCC (2018) Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* **38**(1): 1-211.
Ilett KF, Hackett LP, Gower S et al (2012) Estimated dose exposure of the neonate to buprenorphine and its metabolite norbuprenorphine via breastmilk during maternal buprenorphine substitution treatment. *Breastfeed Med* **7**: 269-74.
Ilowite MF, Al-Sayegh H, Ma C et al (2018) The relationship between household income and patient-reported symptom distress and quality of life in children with advanced cancer: A report from the PediQUEST study. *Cancer* **124**(19): 3934-41.
Inanoglu K, Ozbakis Akkurt BC, Turhanoglu S et al (2009) Intravenous ketamine and local bupivacaine infiltration are effective as part of a multimodal regime for reducing post-tonsillectomy pain. *Med Sci Monit* **15**(10): CR539–43.
Inanoglu K, Ozcengiz D, Gunes Y et al (2010) Epidural ropivacaine versus ropivacaine plus tramadol in postoperative analgesia in children undergoing major abdominal surgery: a comparison. *J Anesth* **24**(5): 700–04.
Ince I, Aksoy M, Dostbil A et al (2017) Can we use lower volume of local anesthetic for infraclavicular brachial plexus nerve block under ultrasound guidance in children? *J Clin Anesth* **41**: 132-36.
Ingelmo PM, Locatelli BG, Sonzogni V et al (2006) Caudal 0.2% ropivacaine is less effective during surgery than 0.2% levobupivacaine and 0.2% bupivacaine: a double-blind, randomized, controlled trial. *Paediatr Anaesth* **16**(9): 955–61.
Iodice FG, Thomas M, Walker I et al (2011) Analgesia in fast-track paediatric cardiac patients. *Eur J Cardiothorac Surg* **40**(3): 610–13.
Ivani G, De Negri P, Lonnqvist PA et al (2005) Caudal anesthesia for minor pediatric surgery: a prospective randomized comparison of ropivacaine 0.2% vs levobupivacaine 0.2%. *Paediatr Anaesth* **15**(6): 491–94.
Ivani G, Suresh S, Ecoffey C et al (2015) The European Society of Regional Anaesthesia and Pain Therapy and the American Society of Regional Anesthesia and Pain Medicine Joint Committee Practice Advisory on Controversial Topics in Pediatric Regional Anesthesia. *Reg Anesth Pain Med* **40**(5): 526-32.
Ivanishvili Z, Pujara S, Honey CM et al (2016) Stereotactic mesencephalotomy for palliative care pain control: A case report, literature review and plea to rediscover this operation. *Br J Neurosurg* **30**(4): 444-7.

Jabbour HJ, Naccache NM, Jawish RJ et al (2014) Ketamine and magnesium association reduces morphine consumption after scoliosis surgery: prospective randomised double-blind study. *Acta Anaesthesiol Scand* **58**(5): 572–79.
Jacob E & Mueller BU (2008) Pain experience of children with sickle cell disease who had prolonged hospitalizations for acute painful episodes. *Pain Med* **9**(1): 13–21.
Jacobson SJ, Kopecky EA, Joshi P et al (1997) Randomised trial of oral morphine for painful episodes of sickle-cell disease in children. *Lancet* **350**(9088): 1358–61.
Jaeger A, Dudley N, Holsti M et al (2017) Impact of an Offline Pain Management Protocol on Prehospital Provider Self-Efficacy: A Randomized Trial. *Pediatr Emerg Care* **33**(6): 388-95.
James F, Edwards R, James N et al (2017) The Royal College of Emergency Medicine composite pain scale for children: level of inter-rater agreement. *Emerg Med J* **34**(6): 360-63.
James PJ, Howard RF & Williams DG (2010) The addition of ketamine to a morphine nurse- or patient-controlled analgesia infusion (PCA/NCA) increases analgesic efficacy in children with mucositis pain. *Paediatr Anaesth* **20**(9): 805–11.
Jang YE, Lee JH, Seo YS et al (2019) Lumbosacral and thoracolumbosacral cerebrospinal fluid volume changes in neonates, infants, children, and adolescents: A retrospective magnetic resonance imaging study. *Paediatr Anaesth* **29**(1): 92-97.
Jarraya A, Elleuch S, Zouari J et al (2016) Postoperative analgesia in children when using clonidine in addition to fentanyl with bupivacaine given caudally. *Pan Afr Med J* **24**: 182.
Jay MA, Thomas BM, Nandi R et al (2017) Higher risk of opioid-induced respiratory depression in children with neurodevelopmental disability: a retrospective cohort study of 12 904 patients. *Br J Anaesth* **118**(2): 239-46.
Jennings PA, Lord B & Smith K (2015) Clinically meaningful reduction in pain severity in children treated by paramedics: a retrospective cohort study. *Am J Emerg Med* **33**(11): 1587-90.
Jibb LA, Nathan PC, Stevens BJ et al (2015) Psychological and Physical Interventions for the Management of Cancer-Related Pain in Pediatric and Young Adult Patients: An Integrative Review. *Oncol Nurs Forum* **42**(6): E339-57.
Jibb LA, Stevens BJ, Nathan PC et al (2017) Implementation and preliminary effectiveness of a real-time pain management smartphone app for adolescents with cancer: A multicenter pilot clinical study. *Pediatr Blood Cancer* **64**(10).
Jimenez N, Anderson GD, Shen DD et al (2012) Is ethnicity associated with morphine's side effects in children? Morphine pharmacokinetics, analgesic response, and side effects in children having tonsillectomy. *Paediatr Anaesth* **22**(7): 669–75.
Jimenez N, Bradford H, Seidel KD et al (2006) A comparison of a needle-free injection system for local anesthesia versus EMLA for intravenous catheter insertion in the pediatric patient. *Anesth Analg* **102**(2): 411–14.
Jindal P, Khurana G, Dvivedi S et al (2011) Intra and postoperative outcome of adding clonidine to bupivacaine in infraorbital nerve block for young children undergoing cleft lip surgery. *Saudi J Anaesth* **5**(3): 289–94.
Jo YY, Hong JY, Choi EK et al (2011) Ketorolac or fentanyl continuous infusion for post-operative analgesia in children undergoing ureteroneocystostomy. *Acta Anaesthesiol Scand* **55**(1): 54–59.
Johansson J, Sjoberg J, Nordgren M et al (2013) Prehospital analgesia using nasal administration of S-ketamine--a case series. *Scand J Trauma Resusc Emerg Med* **21**: 38.
Johnson CM (1994) Continuous femoral nerve blockade for analgesia in children with femoral fractures. *Anaesth Intensive Care* **22**(3): 281-3.
Johnson DJ & Chalkiadis GA (2009) Does epidural analgesia delay the diagnosis of lower limb compartment syndrome in children? *Paediatr Anaesth* **19**(2): 83–91.
Johnson PN, Miller J & Harrison D (2012) Evaluation of initial methadone dosing for prevention of iatrogenic opioid abstinence syndrome in children. *J Pediatr Intensive Care* **1**(2): 105-13.
Johnson TJ, Schultz BR & Guyette FX (2014) Characterizing analgesic use during air medical transport of injured children. *Prehosp Emerg Care* **18**(4): 531-8.
Johnston C, Campbell-Yeo M, Disher T et al (2017) Skin-to-skin care for procedural pain in neonates. *Cochrane Database Syst Rev* **2**: Cd008435.
Johnston C, Campbell-Yeo M, Rich B et al (2013) Therapeutic touch is not therapeutic for procedural pain in very preterm neonates: a randomized trial. *Clin J Pain* **29**(9): 824-9.
Johnston CC, Stevens B, Craig KD et al (1993) Developmental changes in pain expression in premature, full-term, two- and four-month-old infants. *Pain* **52**(2): 201–08.
Johnston CC, Stevens BJ, Boyer K et al (2003) Development of psychologic responses to pain and assessment of pain in infants and toddlers. In: *Pain in Infants, Children and Adolescents* 2nd edn. Schecter NL, Berde CB and Yaster M (eds). Baltimore, Lippincott Williams and Wilkins. pp 105–27.
Johnston CC, Stevens BJ, Franck LS et al (1999) Factors explaining lack of response to heel stick in preterm newborns. *J Obstet Gynecol Neonatal Nurs* **28**(6): 587–94.
Johr M (2015) Regional anaesthesia in neonates, infants and children: an educational review. *Eur J Anaesthesiol* **32**(5): 289-97.
Johr M & Sossai R (1999) Colonic puncture during ilioinguinal nerve block in a child. *Anesth Analg* **88**(5): 1051-2.

Jones GT, Power C & Macfarlane GJ (2009) Adverse events in childhood and chronic widespread pain in adult life: Results from the 1958 British Birth Cohort Study. *Pain* **143**(1–2): 92–96.
Jones HE, Finnegan LP & Kaltenbach K (2012) Methadone and buprenorphine for the management of opioid dependence in pregnancy. *Drugs* **72**(6): 747–57.
Jones L, Fabrizi L, Laudiano-Dray M et al (2017) Nociceptive Cortical Activity Is Dissociated from Nociceptive Behavior in Newborn Human Infants under Stress. *Curr Biol* **27**(24): 3846-51 e3.
Jones LJ, Craven PD, Lakkundi A et al (2015) Regional (spinal, epidural, caudal) versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy in early infancy. *Cochrane Database Syst Rev*(6): Cd003669.
Jong MC, Boers I, van Wietmarschen HA et al (2019) Hypnotherapy or transcendental meditation versus progressive muscle relaxation exercises in the treatment of children with primary headaches: a multi-centre, pragmatic, randomised clinical study. *Eur J Pediatr* **178**(2): 147-54.
Jonnavithula N, Durga P, Kulkarni DK et al (2007) Bilateral intra-oral, infra-orbital nerve block for postoperative analgesia following cleft lip repair in paediatric patients: comparison of bupivacaine vs bupivacaine-pethidine combination. *Anaesthesia* **62**(6): 581-5.
Jonnavithula N, Durga P, Madduri V et al (2010) Efficacy of palatal block for analgesia following palatoplasty in children with cleft palate. *Paediatr Anaesth* **20**(8): 727-33.
Jooste EH, Hammer GB, Reyes CR et al (2017) Phase IV, Open-Label, Safety Study Evaluating the Use of Dexmedetomidine in Pediatric Patients Undergoing Procedure-Type Sedation. *Front Pharmacol* **8**: 529.
Jordan AE, Blackburn NA, Des Jarlais DC et al (2017) Past-year prevalence of prescription opioid misuse among those 11 to 30years of age in the United States: A systematic review and meta-analysis. *J Subst Abuse Treat* **77**: 31-37.
Joshi W, Connelly NR, Dwyer M et al (1999) A comparison of two concentrations of bupivacaine and adrenaline with and without fentanyl in paediatric inguinal herniorrhaphy. *Paediatr Anaesth* **9**(4): 317–20.
Juhl GA & Conners GP (2005) Emergency physicians' practices and attitudes regarding procedural anaesthesia for nasogastric tube insertion. *Emerg Med J* **22**(4): 243–45.
Kabagambe SK, Goodman LF, Chen YJ et al (2018) Subcutaneous local anesthetic infusion could eliminate use of epidural analgesia after the Nuss procedure. *Pain Manag* **8**(1): 9-13.
Kabbouche MA, Powers SW, Segers A et al (2009) Inpatient treatment of status migraine with dihydroergotamine in children and adolescents. *Headache* **49**(1): 106-9.
Kachko L, Katz J, Axer-Siegel R et al (2010) Sub-Tenon's ropivacaine block for pain relief after primary strabismus surgery. *Curr Eye Res* **35**(6): 529–35.
Kaddoum RN, Burgoyne LL, Pereiras JA et al (2013) Nerve sheath catheter analgesia for forequarter amputation in paediatric oncology patients. *Anaesth Intensive Care* **41**(5): 671–77.
Kamata M, Corridore M & Tobias JD (2014) Thoracic epidural infusion with chloroprocaine for postoperative analgesia following epicardial pacemaker placement in an infant. *J Pain Res* **7**: 609-13.
Kamata M & Tobias JD (2016) Remifentanil: applications in neonates. *J Anesth* **30**(3): 449-60.
Kanabar DJ (2017) A clinical and safety review of paracetamol and ibuprofen in children. *Inflammopharmacology* **25**(1): 1-9.
Kandiah P & Tahmassebi JF (2012) Comparing the onset of maxillary infiltration local anaesthesia and pain experience using the conventional technique vs. the Wand in children. *Br Dent J* **213**(9): E15.
Kane J, Colvin J, Bartlett A et al (2018) Opioid-Related Critical Care Resource Use in US Children's Hospitals. *Pediatrics* **141**: e20173335.
Kang PB, Phuah HK, Zimmerman RA et al (2001) Medial medullary injury during adenoidectomy. *J Pediatr* **138**(5): 772-4.
Kang Z, Xie W, Xie W et al (2018) Comparison of neurotoxicity of dexmedetomidine as an adjuvant in brachial plexus block in rats of different age. *Neurotoxicol Teratol* **69**: 21-26.
Kanis JM & Timm NL (2014) Chlorpromazine for the treatment of migraine in a pediatric emergency department. *Headache* **54**(2): 335-42.
Kannikeswaran N, Lieh-Lai M, Malian M et al (2016) Optimal dosing of intravenous ketamine for procedural sedation in children in the ED-a randomized controlled trial. *Am J Emerg Med* **34**(8): 1347-53.
Kaplowitz N (2004) Acetaminophen hepatoxicity: what do we know, what don't we know, and what do we do next? *Hepatology* **40**(1): 23–26.
Karabulut B & Paytoncu S (2019) Efficacy and Safety of Oral Paracetamol vs. Oral Ibuprofen in the Treatment of Symptomatic Patent Ductus Arteriosus in Premature Infants. *Paediatr Drugs* **21**(2): 113-21.
Karaca O, Pinar HU, Gokmen Z et al (2019) Ultrasound-Guided versus Conventional Caudal Block in Children: A Prospective Randomized Study. *Eur J Pediatr Surg* **29**(6): 533-38.
Karagol EHI, Yilmaz O, Topal E et al (2015) Nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease in adolescents. *Int Forum Allergy Rhinol* **5**(5): 392-8.
Karas-Trzeciak M, Grabowski T, Woloszczuk-Gebicka B et al (2015) Fentanyl with ropivacaine infusion for postoperative pain relief in infants and children. Kinetics of epidural fentanyl. *Paediatr Anaesth* **25**(8): 818-23.
Kargi E, Isikdemir A, Tokgoz H et al (2010) Comparison of local anesthetic effects of tramadol with prilocaine during circumcision procedure. *Urology* **75**(3): 672–75.

Karl HW, Tyler DC & Miser AW (2012) Controlled trial of morphine vs hydromorphone for patient-controlled analgesia in children with postoperative pain. *Pain Med* **13**(12): 1658–59.
Karlsen AP, Pedersen DM, Trautner S et al (2014) Safety of intranasal fentanyl in the out-of-hospital setting: a prospective observational study. *Ann Emerg Med* **63**(6): 699–703.
Karnik PP, Dave NM, Shah HB et al (2019) Comparison of ultrasound-guided transversus abdominis plane (TAP) block versus local infiltration during paediatric laparoscopic surgeries. *Indian J Anaesth* **63**(5): 356-60.
Kart T, Walther-Larsen S, Svejborg TF et al (1997) Comparison of continuous epidural infusion of fentanyl and bupivacaine with intermittent epidural administration of morphine for postoperative pain management in children. *Acta Anaesthesiol Scand* **41**(4): 461–65.
Kassab M, Foster JP, Foureur M et al (2019) Sweet-tasting solutions for needle-related procedural pain in infants one month to one year of age. *Cochrane Database Syst Rev* **12**: CD008411.
Kattail D, Macmillan A, Musavi L et al (2018) Pain Management for Nonsyndromic Craniosynostosis: Adequate Analgesia in a Pediatric Cohort? *J Craniofac Surg* **29**(5): 1148-53.
Katz T, Schatz J & Roberts CW (2018) Comorbid obstructive sleep apnea and increased risk for sickle cell disease morbidity. *Sleep Breath* **22**(3): 797-804.
Kaul I, Amin A, Rosenberg M et al (2018) Use of gabapentin and pregabalin for pruritus and neuropathic pain associated with major burn injury: A retrospective chart review. *Burns* **44**(2): 414-22.
Kaur G, Gupta P & Kumar A (2003) A randomized trial of eutectic mixture of local anesthetics during lumbar puncture in newborns. *Arch Pediatr Adolesc Med* **157**(11): 1065–70.
Kaushal B, Chauhan S, Saini K et al (2019) Comparison of the Efficacy of Ultrasound-Guided Serratus Anterior Plane Block, Pectoral Nerves II Block, and Intercostal Nerve Block for the Management of Postoperative Thoracotomy Pain After Pediatric Cardiac Surgery. *J Cardiothorac Vasc Anesth* **33**(2): 418-25.
Kavanagh PL, Sprinz PG, Wolfgang TL et al (2015) Improving the Management of Vaso-Occlusive Episodes in the Pediatric Emergency Department. *Pediatrics* **136**(4): e1016-25.
Kawakami H, Mihara T, Nakamura N et al (2017) Effect of an Intravenous Dexamethasone Added to Caudal Local Anesthetics to Improve Postoperative Pain: A Systematic Review and Meta-analysis With Trial Sequential Analysis. *Anesth Analg* **125**(6): 2072-80.
Kawakami H, Mihara T, Nakamura N et al (2018) Effect of magnesium added to local anesthetics for caudal anesthesia on postoperative pain in pediatric surgical patients: A systematic review and meta-analysis with Trial Sequential Analysis. *PLoS One* **13**(1): e0190354.
Kawaraguchi Y, Otomo T, Ota C et al (2006) A prospective, double-blind, randomized trial of caudal block using ropivacaine 0.2% with or without fentanyl 1 microg kg-1 in children. *Br J Anaesth* **97**(6): 858–61.
Kay RM, Directo MP, Leathers M et al (2010) Complications of ketorolac use in children undergoing operative fracture care. *J Pediatr Orthop* **30**(7): 655–58.
Kay RM, Leathers M, Directo MP et al (2011) Perioperative ketorolac use in children undergoing lower extremity osteotomies. *J Pediatr Orthop* **31**(7): 783–86.
Kaygusuz I & Susaman N (2003) The effects of dexamethasone, bupivacaine and topical lidocaine spray on pain after tonsillectomy. *Int J Pediatr Otorhinolaryngol* **67**(7): 737-42.
Kazis LE, Lee AF, Rose M et al (2016) Recovery Curves for Pediatric Burn Survivors: Advances in Patient-Oriented Outcomes. *JAMA Pediatr* **170**(6): 534-42.
Kearl YL, Yanger S, Montero S et al (2015) Does Combined Use of the J-tip(R) and Buzzy(R) Device Decrease the Pain of Venipuncture in a Pediatric Population? *J Pediatr Nurs* **30**(6): 829-33.
Keefe KR, Byrne KJ & Levi JR (2018) Treating pediatric post-tonsillectomy pain and nausea with complementary and alternative medicine. *Laryngoscope* **128**(11): 2625-34.
Keller BA, Kabagambe SK, Becker JC et al (2016) Intercostal nerve cryoablation versus thoracic epidural catheters for postoperative analgesia following pectus excavatum repair: Preliminary outcomes in twenty-six cryoablation patients. *J Pediatr Surg* **51**(12): 2033-38.
Kelly GS, Stewart RW, Strouse JJ et al (2018) Intranasal fentanyl improves time to analgesic delivery in sickle cell pain crises. *Am J Emerg Med* **36**(7): 1305-07.
Kelly JJ, Donath S, Jamsen K et al (2006) Postoperative sleep disturbance in pediatric patients using patient-controlled devices (PCA). *Paediatr Anaesth* **16**(10): 1051–56.
Kelly LE, Rieder M, van den Anker J et al (2012) More codeine fatalities after tonsillectomy in North American children. *Pediatrics* **129**(5): e1343–47.
Kelly LE, Sommer DD, Ramakrishna J et al (2015) Morphine or Ibuprofen for post-tonsillectomy analgesia: a randomized trial. *Pediatrics* **135**(2): 307-13.
Kendall J, Maconochie I, Wong IC et al (2015) A novel multipatient intranasal diamorphine spray for use in acute pain in children: pharmacovigilance data from an observational study. *Emerg Med J* **32**(4): 269–73.
Kendall JM, Reeves BC & Latter VS (2001) Multicentre randomised controlled trial of nasal diamorphine for analgesia in children and teenagers with clinical fractures. *BMJ* **322**(7281): 261–65.

Kendall MC, Alves LJC, Suh EI et al (2018) Regional anesthesia to ameliorate postoperative analgesia outcomes in pediatric surgical patients: an updated systematic review of randomized controlled trials. *Local Reg Anesth* **11**: 91-109.

Kendigelen P, Tutuncu AC, Emre S et al (2016) Pudendal Versus Caudal Block in Children Undergoing Hypospadias Surgery: A Randomized Controlled Trial. *Reg Anesth Pain Med* **41**(5): 610-5.

Kennedy RM (2014) Effective management of children's pain and anxiety in the ED. In: *Oxford Textbook of Paediatric Pain* edn. McGrath PJ, Stevens BJ, Walker SE and Zempsky WT (eds). Oxford, Oxford University Press.

Kennedy RM, Luhmann J & Zempsky WT (2008) Clinical implications of unmanaged needle-insertion pain and distress in children. *Pediatrics* **122 Suppl 3**: S130–33.

Keplinger M, Marhofer P, Klug W et al (2016) Feasibility and pharmacokinetics of caudal blockade in children and adolescents with 30-50 kg of body weight. *Paediatr Anaesth* **26**(11): 1053-59.

Khalil S, Lingadevaru H, Bolos M et al (2006) Caudal regional anesthesia, ropivacaine concentration, postoperative analgesia, and infants. *Anesth Analg* **102**(2): 395–99.

Khalili GR, Shafa A & Yousefi R (2016) Comparison of the Effects of Preemptive Intravenous and Rectal Acetaminophen on Pain Management after Inguinal Herniorrhaphy in Children: A Placebo-Controlled Study. *Middle East J Anaesthesiol* **23**(5): 543-8.

Khan FA, Memon GA & Kamal RS (2002) Effect of route of buprenorphine on recovery and postoperative analgesic requirement in paediatric patients. *Paediatr Anaesth* **12**(9): 786-90.

Khanna IK & Pillarisetti S (2015) Buprenorphine - an attractive opioid with underutilized potential in treatment of chronic pain. *J Pain Res* **8**: 859-70.

Kidd S, Brennan S, Stephen R et al (2009) Comparison of morphine concentration-time profiles following intravenous and intranasal diamorphine in children. *Arch Dis Child* **94**(12): 974–78.

Kidon M, Blanca-Lopez N, Gomes E et al (2018) EAACI/ENDA Position Paper: Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents. *Pediatric Allergy and Immunology* **29**(5): 469-80.

Kilinc L, Türk B, Türk HS et al (2019) Peritonsillar dexamethasone–bupivacaine vs. bupivacaine infiltration for post-tonsillectomy pain relief in children: a randomized, double-blind, controlled study. *European Archives of Oto-Rhino-Laryngology* **276**(7): 2081-89.

Kim HS, Kim CS, Kim SD et al (2011) Fascia iliaca compartment block reduces emergence agitation by providing effective analgesic properties in children. *J Clin Anesth* **23**(2): 119-23.

Kim MH, Im YJ, Kil HK et al (2016) Impact of caudal block on postoperative complications in children undergoing tubularised incised plate urethroplasty for hypospadias repair: a retrospective cohort study. *Anaesthesia* **71**(7): 773-8.

Kim MK, Strait RT, Sato TT et al (2002) A randomized clinical trial of analgesia in children with acute abdominal pain. *Acad Emerg Med* **9**(4): 281-7.

Kim SH, Lee MH, Seo H et al (2013) Intraoperative infusion of 0.6-0.9 microg.kg(-1).min(-1) remifentanil induces acute tolerance in young children after laparoscopic ureteroneocystostomy. *Anesthesiology* **118**(2): 337-43.

Kimland E, Nydert P, Odlind V et al (2012) Paediatric drug use with focus on off-label prescriptions at Swedish hospitals - a nationwide study. *Acta Paediatr* **101**(7): 772-8.

Kingsnorth S, Orava T, Provvidenza C et al (2015) Chronic Pain Assessment Tools for Cerebral Palsy: A Systematic Review. *Pediatrics* **136**(4): e947-60.

Kipping B, Rodger S, Miller K et al (2012) Virtual reality for acute pain reduction in adolescents undergoing burn wound care: A prospective randomized controlled trial. *Burns* **38**(5): 650–57.

Klassen JA, Liang Y, Tjosvold L et al (2008) Music for pain and anxiety in children undergoing medical procedures: a systematic review of randomized controlled trials. *Ambul Pediatr* **8**(2): 117–28.

Kleiber N, Mathot RAA, Ahsman MJ et al (2017) Population pharmacokinetics of intravenous clonidine for sedation during paediatric extracorporeal membrane oxygenation and continuous venovenous hemofiltration. *Br J Clin Pharmacol* **83**(6): 1227-39.

Klein EJ, Brown JC, Kobayashi A et al (2011) A randomized clinical trial comparing oral, aerosolized intranasal, and aerosolized buccal midazolam. *Ann Emerg Med* **58**(4): 323–29.

Klingberg G, Ridell K, Brogardh-Roth S et al (2017) Local analgesia in paediatric dentistry: a systematic review of techniques and pharmacologic agents. *Eur Arch Paediatr Dent* **18**(5): 323-29.

Klucka J, Stourac P, Stouracova A et al (2017) Compartment syndrome and regional anaesthesia: Critical review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* **161**(3): 242-51.

Kluger M, Penrose S, Bjorksten AR et al (2016) Accuracy of dispersing tramadol capsules for oral administration in young children. *Anaesth Intensive Care* **44**(6): 742-44.

Koc T & Gozen D (2015) The Effect of Foot Reflexology on Acute Pain in Infants: A Randomized Controlled Trial. *Worldviews Evid Based Nurs* **12**(5): 289-96.

Koch J, Manworren R, Clark L et al (2008) Pilot study of continuous co-infusion of morphine and naloxone in children with sickle cell pain crisis. *Am J Hematol* **83**(9): 728–31.

Koenig J, Jarczok MN, Ellis RJ et al (2014) Heart rate variability and experimentally induced pain in healthy adults: a systematic review. *Eur J Pain* **18**(3): 301-14.
Koh JL, Fanurik D, Harrison RD et al (2004) Analgesia following surgery in children with and without cognitive impairment. *Pain* **111**(3): 239–44.
Kokki H (2010) Ketoprofen pharmacokinetics, efficacy, and tolerability in pediatric patients. *Paediatr Drugs* **12**(5): 313–29.
Kokki H, Kokki M & Sjovall S (2012a) Oxycodone for the treatment of postoperative pain. *Expert Opin Pharmacother* **13**(7): 1045–58.
Kokki H, Kumpulainen E, Lehtonen M et al (2007) Cerebrospinal fluid distribution of ibuprofen after intravenous administration in children. *Pediatrics* **120**(4): e1002–08.
Kokki H, Rasanen I, Lasalmi M et al (2006) Comparison of oxycodone pharmacokinetics after buccal and sublingual administration in children. *Clin Pharmacokinet* **45**(7): 745–54.
Kokki H, Tuovinen K & Hendolin H (1999) The effect of intravenous ketoprofen on postoperative epidural sufentanil analgesia in children. *Anesth Analg* **88**(5): 1036–41.
Kokki M, Sjovall S & Kokki H (2012b) Epidural blood patches are effective for postdural puncture headache in pediatrics--a 10-year experience. *Paediatr Anaesth* **22**(12): 1205–10.
Koller D & Goldman RD (2012) Distraction techniques for children undergoing procedures: a critical review of pediatric research. *J Pediatr Nurs* **27**(6): 652–81.
Koller DM, Myers AB, Lorenz D et al (2007) Effectiveness of oxycodone, ibuprofen, or the combination in the initial management of orthopedic injury-related pain in children. *Pediatr Emerg Care* **23**(9): 627–33.
Koo BN, Hong JY & Kil HK (2010) Spread of ropivacaine by a weight-based formula in a pediatric caudal block: a fluoroscopic examination. *Acta Anaesthesiol Scand* **54**(5): 562–65.
Kopecky EA, Jacobson S, Joshi P et al (2004) Systemic exposure to morphine and the risk of acute chest syndrome in sickle cell disease. *Clin Pharmacol Ther* **75**(3): 140–46.
Kost-Byerly S, Tobin JR, Greenberg RS et al (1998) Bacterial colonization and infection rate of continuous epidural catheters in children. *Anesth Analg* **86**(4): 712–16.
Kowalski ML (2019) Heterogeneity of NSAID-Exacerbated Respiratory Disease: has the time come for subphenotyping? *Curr Opin Pulm Med* **25**(1): 64-70.
Kozek-Langenecker SA, Marhofer P, Jonas K et al (2000) Cardiovascular criteria for epidural test dosing in sevoflurane- and halothane-anesthetized children. *Anesth Analg* **90**(3): 579–83.
Kozer E, Rosenbloom E, Goldman D et al (2006) Pain in infants who are younger than 2 months during suprapubic aspiration and transurethral bladder catheterization: a randomized, controlled study. *Pediatrics* **118**(1): e51–56.
Kraft WK (2018) Buprenorphine in Neonatal Abstinence Syndrome. *Clin Pharmacol Ther* **103**(1): 112-19.
Krechel SW & Bildner J (1995) CRIES: a new neonatal postoperative pain measurement score. Initial testing of validity and reliability. *Paediatr Anaesth* **5**(1): 53–61.
Kreicbergs U, Valdimarsdottir U, Onelov E et al (2005) Care-related distress: a nationwide study of parents who lost their child to cancer. *J Clin Oncol* **23**(36): 9162-71.
Krekels EH, DeJongh J, van Lingen RA et al (2011) 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* **50**(1): 51–63.
Krishnaswami S, Hutmacher MM, Robbins JL et al (2012) Dosing celecoxib in pediatric patients with juvenile rheumatoid arthritis. *J Clin Pharmacol* **52**(8): 1134–49.
Kristensen HN, Lundbye-Christensen S, Haslund-Thomsen H et al (2018) Acute Procedural Pain in Children: Intervention With the Hospital Clown. *Clin J Pain* **34**(11): 1032-38.
Kriwanek KL, Wan J, Beaty JH et al (2006) Axillary block for analgesia during manipulation of forearm fractures in the pediatric emergency department a prospective randomized comparative trial. *J Pediatr Orthop* **26**(6): 737-40.
Krylborn J, Anell-Olofsson ME, Bitkover C et al (2015) Plasma levels of levobupivacaine during continuous infusion via a wound catheter after major surgery in newborn infants: An observational study. *Eur J Anaesthesiol* **32**(12): 851-6.
Kucukoglu S, Aytekin A, Celebioglu A et al (2016) Effect of White Noise in Relieving Vaccination Pain in Premature Infants. *Pain Manag Nurs* **17**(6): 392-400.
Kucukoglu S, Kurt S & Aytekin A (2015) The effect of the facilitated tucking position in reducing vaccination-induced pain in newborns. *Ital J Pediatr* **41**: 61.
Kuhnisch J, Daublander M, Klingberg G et al (2017) Best clinical practice guidance for local analgesia in paediatric dentistry: an EAPD policy document. *Eur Arch Paediatr Dent* **18**(5): 313-21.
Kuiper-Prins E, Kerkhof GF, Reijnen CG et al (2016) A 12-Day-Old Boy with Methemoglobinemia After Circumcision with Local Anesthesia (Lidocaine/Prilocaine). *Drug Saf Case Rep* **3**(1): 12.
Kumar M, Upadhyay A, Singh J et al (2016) Effect of change in sequence of administration of DTwP and Hepatitis B vaccines on perception of pain in infants: A randomized control trial. *Vaccine* **34**(15): 1816-22.
Kumar P, Rudra A, Pan AK et al (2005) Caudal additives in pediatrics: a comparison among midazolam, ketamine, and neostigmine coadministered with bupivacaine. *Anesth Analg* **101**(1): 69–73.

Kumar Raja D, Anantanarayanan P, Christabel A et al (2014) Donor site analgesia after anterior iliac bone grafting in paediatric population: a prospective, triple-blind, randomized clinical trial. *Int J Oral Maxillofac Surg* **43**(4): 422-7.
Kumpulainen E, Valitalo P, Kokki M et al (2010) Plasma and cerebrospinal fluid pharmacokinetics of flurbiprofen in children. *Br J Clin Pharmacol* **70**(4): 557–66.
Kundra P, Yuvaraj K, Agrawal K et al (2012) Surgical outcome in children undergoing hypospadias repair under caudal epidural vs penile block. *Paediatr Anaesth* **22**(7): 707–12.
Kundu A, Lin Y, Oron AP et al (2014) Reiki therapy for postoperative oral pain in pediatric patients: pilot data from a double-blind, randomized clinical trial. *Complement Ther Clin Pract* **20**(1): 21-5.
Kundu R, Baidya DK, Arora MK et al (2015) Caudal bupivacaine and morphine provides effective postoperative analgesia but does not prevent hemodynamic response to pneumoperitoneum for major laparoscopic surgeries in children. *J Anesth* **29**(4): 618-21.
Kuo YW, Yen M, Fetzer S et al (2010) Reducing the pain of nasogastric tube intubation with nebulized and atomized lidocaine: a systematic review and meta-analysis. *J Pain Symptom Manage* **40**(4): 613–20.
Kurien T, Price KR, Pearson RG et al (2016) Manipulation and reduction of paediatric fractures of the distal radius and forearm using intranasal diamorphine and 50% oxygen and nitrous oxide in the emergency department: a 2.5-year study. *Bone Joint J* **98-b**(1): 131-6.
Kussman BD & Sethna NF (1998) Pethidine-associated seizure in a healthy adolescent receiving pethidine for postoperative pain control. *Paediatr Anaesth* **8**(4): 349–52.
Kyllonen M, Olkkola KT, Seppala T et al (2005) Perioperative pharmacokinetics of ibuprofen enantiomers after rectal administration. *Paediatr Anaesth* **15**(7): 566–73.
Lacey CM, Finkelstein M & Thygeson MV (2008) The impact of positioning on fear during immunizations: supine versus sitting up. *J Pediatr Nurs* **23**(3): 195–200.
LactMed Database (2019) *Tramadol.* https://www.ncbi.nlm.nih.gov/books/NBK501260/ Accessed 17 February 2020
Lagercrantz H & Changeux JP (2009) The emergence of human consciousness: from fetal to neonatal life. *Pediatr Res* **65**(3): 255–60.
Lago P, Garetti E, Bellieni CV et al (2017) Systematic review of nonpharmacological analgesic interventions for common needle-related procedure in newborn infants and development of evidence-based clinical guidelines. *Acta Paediatr* **106**(6): 864-70.
Lakhan SE, Sheafer H & Tepper D (2016) The Effectiveness of Aromatherapy in Reducing Pain: A Systematic Review and Meta-Analysis. *Pain Res Treat* **2016**: 8158693.
Lal A, Chohan K, Chohan A et al (2017) Role of honey after tonsillectomy: a systematic review and meta-analysis of randomised controlled trials. *Clin Otolaryngol* **42**(3): 651-60.
Lam DK, Corry GN & Tsui BC (2016) Evidence for the Use of Ultrasound Imaging in Pediatric Regional Anesthesia: A Systematic Review. *Reg Anesth Pain Med* **41**(2): 229-41.
Lambert P, Cyna AM, Knight N et al (2014) Clonidine premedication for postoperative analgesia in children. *Cochrane Database Syst Rev* **1**: CD009633.
Lamond DW (2010) Review article: Safety profile of propofol for paediatric procedural sedation in the emergency department. *Emerg Med Australas* **22**(4): 265–86.
Lamy C, Loizeau V, Couquet C et al (2019) Pain experienced by infants and toddlers at urine collection bag removal: A randomized, controlled, clinical trial. *Int J Nurs Stud* **95**: 1-6.
Lancaster JL, Jones TM, Kay AR et al (2003) Paediatric day-case otoplasty: local versus general anaesthetic. *Surgeon* **1**(2): 96–98.
Lander J, Brady-Fryer B, Metcalfe JB et al (1997) Comparison of ring block, dorsal penile nerve block, and topical anesthesia for neonatal circumcision: a randomized controlled trial. *Jama* **278**(24): 2157-62.
Lander JA, Weltman BJ & So SS (2006) EMLA and amethocaine for reduction of children's pain associated with needle insertion. *Cochrane Database Syst Rev* **3**: CD004236.
Landier W & Tse AM (2010) Use of complementary and alternative medical interventions for the management of procedure-related pain, anxiety, and distress in pediatric oncology: an integrative review. *J Pediatr Nurs* **25**(6): 566–79.
Langford DJ, Gross JB, Doorenbos AZ et al (2020) Evaluation of the Impact of an Online Opioid Education Program for Acute Pain Management. *Pain Med* **21**(1): 55-60.
Larsson BA, Lonnqvist PA & Olsson GL (1997) Plasma concentrations of bupivacaine in neonates after continuous epidural infusion. *Anesth Analg* **84**(3): 501–05.
Larsson P, Eksborg S & Lonnqvist PA (2012) Onset time for pharmacologic premedication with clonidine as a nasal aerosol: a double-blind, placebo-controlled, randomized trial. *Paediatr Anaesth* **22**(9): 877–83.
Larsson P, Nordlinder A, Bergendahl HT et al (2011) Oral bioavailability of clonidine in children. *Paediatr Anaesth* **21**(3): 335-40.
Lavelle ED, Lavelle WF, Goodwin R et al (2010) Epidural analgesia for postoperative pain control after adolescent spinal fusion procedures which violated the epidural space. *J Spinal Disord Tech* **23**(5): 347–50.
Lavonas EJ, Reynolds KM & Dart RC (2010) Therapeutic acetaminophen is not associated with liver injury in children: a systematic review. *Pediatrics* **126**(6): e1430–44.

Lawrence J, Alcock D, McGrath P et al (1993) The development of a tool to assess neonatal pain. *Neonatal Netw* **12**(6): 59–66.
Le May S, Ali S, Khadra C et al (2016) Pain Management of Pediatric Musculoskeletal Injury in the Emergency Department: A Systematic Review. *Pain Res Manag* **2016**: 4809394.
Le May S, Ali S, Plint AC et al (2017) Oral Analgesics Utilization for Children With Musculoskeletal Injury (OUCH Trial): An RCT. *Pediatrics* **140**(5).
Le May S, Ballard A, Khadra C et al (2018) Comparison of the psychometric properties of 3 pain scales used in the pediatric emergency department: Visual Analogue Scale, Faces Pain Scale-Revised, and Colour Analogue Scale. *Pain* **159**(8): 1508-17.
Le May S, Gouin S, Fortin C et al (2013) Efficacy of an ibuprofen/codeine combination for pain management in children presenting to the emergency department with a limb injury: a pilot study. *J Emerg Med* **44**(2): 536–42.
LeBlanc CK (2014) Child Life Interventions in paediatric pain. In: *Oxford Textbook of Paediatric Pain* edn. McGrath PJ, Stevens BJ, Walker SE and Zempsky WT (eds). Oxford, Oxford University Press.
LeBlanc Z, Vance C, Payne J et al (2018) Management of severe chronic pain with methadone in pediatric patients with sickle cell disease. *Pediatr Blood Cancer* **65**(8): e27084.
Lebrun-Vignes B, Guy C, Jean-Pastor MJ et al (2018) Is acetaminophen associated with a risk of Stevens-Johnson syndrome and toxic epidermal necrolysis? Analysis of the French Pharmacovigilance Database. *Br J Clin Pharmacol* **84**(2): 331-38.
Lee B, Koo BN, Choi YS et al (2017a) Effect of caudal block using different volumes of local anaesthetic on optic nerve sheath diameter in children: a prospective, randomized trial. *Br J Anaesth* **118**(5): 781-87.
Lee BH, Lehmann CU, Jackson EV et al (2009) Assessing controlled substance prescribing errors in a pediatric teaching hospital: an analysis of the safety of analgesic prescription practice in the transition from the hospital to home. *J Pain* **10**(2): 160-6.
Lee D, Lee H, Kim J et al (2018) Acupuncture for Infantile Colic: A Systematic Review of Randomised Controlled Trials. *Evid Based Complement Alternat Med* **2018**: 7526234.
Lee GY & Stevens BJ (2014) Neonatal and infant pain assessment In: *Oxford Textbook of Paediatric Pain* 1st edn. McGrath P (eds). Oxford. 353 - 69.
Lee HJ, Min JY, Kim HI et al (2017b) Measuring the depth of the caudal epidural space to prevent dural sac puncture during caudal block in children. *Paediatr Anaesth* **27**(5): 540-44.
Lee HM, Choi KW, Byon HJ et al (2019) Systemic Lidocaine Infusion for Post-Operative Analgesia in Children Undergoing Laparoscopic Inguinal Hernia Repair: A Randomized Double-Blind Controlled Trial. *J Clin Med* **8**(11).
Lee JH, Kim K, Kim TY et al (2012) A randomized comparison of nitrous oxide versus intravenous ketamine for laceration repair in children. *Pediatr Emerg Care* **28**(12): 1297–301.
Lee MG, Kim HJ, Lee KH et al (2016) The Influence of Genotype Polymorphism on Morphine Analgesic Effect for Postoperative Pain in Children. *Korean J Pain* **29**(1): 34-9.
Lee MT, Licursi M & McMahon DJ (2015) Vitamin D deficiency and acute vaso-occlusive complications in children with sickle cell disease. *Pediatr Blood Cancer* **62**(4): 643-7.
Lee-Jayaram JJ, Green A, Siembieda J et al (2010) Ketamine/midazolam versus etomidate/fentanyl: procedural sedation for pediatric orthopedic reductions. *Pediatr Emerg Care* **26**(6): 408–12.
Lehtonen P, Sten T & Aitio O (2010) Glucuronidation of racemic O-desmethytramadol, the active metabolite of tramadol. *Eur J Pharm Sci* **41**(3-4): 523-30.
Lemanek KL, Ranalli M & Lukens C (2009) A randomized controlled trial of massage therapy in children with sickle cell disease. *J Pediatr Psychol* **34**(10): 1091-6.
Lemming K, Fang G & Buck ML (2019) Safety and Tolerability of Lidocaine Infusions as a Component of Multimodal Postoperative Analgesia in Children. *J Pediatr Pharmacol Ther* **24**(1): 34-38.
Lerman J, Nolan J, Eyres R et al (2003) Efficacy, safety, and pharmacokinetics of levobupivacaine with and without fentanyl after continuous epidural infusion in children: a multicenter trial. *Anesthesiology* **99**(5): 1166–74.
Lesko SM, Louik C, Vezina RM et al (2002) Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics* **109**(2): E20.
Lesko SM & Mitchell AA (1995) An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *JAMA* **273**(12): 929–33.
Lesko SM & Mitchell AA (1999) The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics* **104**(4): e39.
Lesniak AB, Tremblay P, Dalens BJ et al (2013) Intrathecal morphine reduces blood loss during idiopathic scoliosis surgery: retrospective study of 256 pediatric cases. *Paediatr Anaesth* **23**(3): 265–70.
Leung S, Bulloch B, Young C et al (2013) Effectiveness of standardized combination therapy for migraine treatment in the pediatric emergency department. *Headache* **53**(3): 491–97.
Levine DR, Mandrell BN, Sykes A et al (2017) Patients' and Parents' Needs, Attitudes, and Perceptions About Early Palliative Care Integration in Pediatric Oncology. *JAMA Oncol* **3**(9): 1214-20.
Lewis SR, Nicholson A, Cardwell ME et al (2013) Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. *Cochrane Database Syst Rev* **7**: CD003591.

Li A, Yuen VM, Goulay-Dufay S et al (2018a) Pharmacokinetic and pharmacodynamic study of intranasal and intravenous dexmedetomidine. *Br J Anaesth* **120**(5): 960-68.
Li H, Mandema J, Wada R et al (2012a) Modeling the onset and offset of dental pain relief by ibuprofen. *J Clin Pharmacol* **52**(1): 89–101.
Li J & Baccei ML (2011a) Neonatal tissue damage facilitates nociceptive synaptic input to the developing superficial dorsal horn via NGF-dependent mechanisms. *Pain* **152**(8): 1846–55.
Li J & Baccei ML (2011b) Pacemaker neurons within newborn spinal pain circuits. *J Neurosci* **31**(24): 9010–22.
Li J, Kritzer E, Ford NC et al (2015) Connectivity of pacemaker neurons in the neonatal rat superficial dorsal horn. *J Comp Neurol* **523**(7): 1038-53.
Li X, Zhou M, Xia Q et al (2016) Parecoxib sodium reduces the need for opioids after tonsillectomy in children: a double-blind placebo-controlled randomized clinical trial. *Can J Anaesth* **63**(3): 268-74.
Li X, Zuo Y & Dai Y (2012b) Children's seizures caused by continuous intravenous infusion of tramadol analgesia: two rare case reports. *Paediatr Anaesth* **22**(3): 308–09.
Li Y, Hong RA, Robbins CB et al (2018b) Intrathecal Morphine and Oral Analgesics Provide Safe and Effective Pain Control After Posterior Spinal Fusion for Adolescent Idiopathic Scoliosis. *Spine (Phila Pa 1976)* **43**(2): E98-e104.
Liaw JJ, Zeng WP, Yang L et al (2011) Nonnutritive sucking and oral sucrose relieve neonatal pain during intramuscular injection of hepatitis vaccine. *J Pain Symptom Manage* **42**(6): 918–30.
Liew Z, Ritz B, Rebordosa C et al (2014) Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatr* **168**(4): 313–20.
Lim SL, Ng Sb A & Tan GM (2002) Ilioinguinal and iliohypogastric nerve block revisited: single shot versus double shot technique for hernia repair in children. *Paediatr Anaesth* **12**(3): 255-60.
Lima AG, Santos VS, Nunes MS et al (2017) Glucose solution is more effective in relieving pain in neonates than non-nutritive sucking: A randomized clinical trial. *Eur J Pain* **21**(1): 159-65.
Lin YC, Tassone RF, Jahng S et al (2009) Acupuncture management of pain and emergence agitation in children after bilateral myringotomy and tympanostomy tube insertion. *Paediatric Anaesthesia* **19**(11): 1096–101.
Lindemalm S, Nydert P, Svensson JO et al (2009) Transfer of buprenorphine into breast milk and calculation of infant drug dose. *J Hum Lact* **25**(2): 199-205.
Linder SL (1994) Treatment of childhood headache with dihydroergotamine mesylate. *Headache* **34**(10): 578-80.
Link CJ & Fortier MA (2016) The Relationship Between Parent Trait Anxiety and Parent-reported Pain, Solicitous Behaviors, and Quality of Life Impairment in Children With Cancer. *J Pediatr Hematol Oncol* **38**(1): 58-62.
Liossi C, Failo A, Schoth DE et al (2018) The effectiveness of online pain resources for health professionals: a systematic review with subset meta-analysis of educational intervention studies. *Pain* **159**(4): 631-43.
Liossi C, White P, Franck L et al (2007) Parental pain expectancy as a mediator between child expected and experienced procedure-related pain intensity during painful medical procedures. *Clin J Pain* **23**(5): 392–99.
Liow NY, Gimeno H, Lumsden DE et al (2016) Gabapentin can significantly improve dystonia severity and quality of life in children. *Eur J Paediatr Neurol* **20**(1): 100-7.
Lipp AK, Woodcock J, Hensman B et al (2004) Leg weakness is a complication of ilio-inguinal nerve block in children. *Br J Anaesth* **92**(2): 273-4.
Litalien C & Jacqz-Aigrain E (2001) Risks and benefits of nonsteroidal anti-inflammatory drugs in children: a comparison with paracetamol. *Paediatr Drugs* **3**(11): 817–58.
Littlejohn C, Pang D, Power C et al (2012) Is there an association between preterm birth or low birthweight and chronic widespread pain? Results from the 1958 Birth Cohort Study. *Eur J Pain* **16**(1): 134–39.
Litz CN, Farach SM, Fernandez AM et al (2017) Percutaneous ultrasound-guided vs. intraoperative rectus sheath block for pediatric umbilical hernia repair: A randomized clinical trial. *J Pediatr Surg* **52**(6): 901-06.
Liu HC, Lian QQ, Wu FF et al (2017) Population Pharmacokinetics of Dexmedetomidine After Short Intravenous Infusion in Chinese Children. *Eur J Drug Metab Pharmacokinet* **42**(2): 201-11.
Liu Q, Chai XM, Zhang JJ et al (2019) A Fixed Nitrous Oxide and Oxygen Mixture for Analgesia in Children With Leukemia With Lumbar Puncture-induced Pain: A Randomized, Double-blind Controlled Trial. *J Pain Symptom Manage* **57**(6): 1043-50.
Liu W, Dutta S, Kearns G et al (2015) Pharmacokinetics of hydrocodone/acetaminophen combination product in children ages 6-17 with moderate to moderately severe postoperative pain. *J Clin Pharmacol* **55**(2): 204-11.
Liu W, Liu J, Tan X et al (2018) Ultrasound-guided lower forearm median nerve block in open surgery for trigger thumb in 1- to 3-year-old children: A randomized trial. *Paediatr Anaesth* **28**(2): 134-41.
Liu Y, Seipel C, Lopez ME et al (2013) A retrospective study of multimodal analgesic treatment after laparoscopic appendectomy in children. *Paediatr Anaesth* **23**(12): 1187–92.
Livingston M, Lawell M & McAllister N (2017) Successful use of nitrous oxide during lumbar punctures: A call for nitrous oxide in pediatric oncology clinics. *Pediatr Blood Cancer* **64**(11).
Livingstone MJ, Groenewald CB, Rabbitts JA et al (2017) Codeine use among children in the United States: a nationally representative study from 1996 to 2013. *Paediatr Anaesth* **27**(1): 19-27.
Ljungman G, Gordh T, Sorensen S et al (1999) Pain in paediatric oncology: interviews with children, adolescents and their parents. *Acta Paediatr* **88**(6): 623–30.

Ljungman G, Gordh T, Sorensen S et al (2000) Pain variations during cancer treatment in children: a descriptive survey. *Pediatr Hematol Oncol* **17**(3): 211–21.
Ljungman G, Kreuger A, Gordh T et al (1996) Treatment of pain in pediatric oncology: a Swedish nationwide survey. *Pain* **68**(2–3): 385–94.
Llewellyn N & Moriarty A (2007) The national pediatric epidural audit. *Paediatr Anaesth* **17**(6): 520–33.
Loftus PD, Elder CT, Russell KW et al (2016) Paravertebral regional blocks decrease length of stay following surgery for pectus excavatum in children. *J Pediatr Surg* **51**(1): 149-53.
London K, Watson H, Kwok S et al (2019) Oral sucrose for analgesia in children aged between 3 months and 3 years undergoing transurethral bladder catheterisation: A randomised, double-blinded, clinical trial. *J Paediatr Child Health*.
Long JB, Birmingham PK, De Oliveira GS, Jr. et al (2014) Transversus abdominis plane block in children: A multicenter safety analysis of 1994 cases from the PRAN (Pediatric Regional Anesthesia Network) database. *Anesth Analg* **119**(2): 395–99.
Long JB, Joselyn AS, Bhalla T et al (2016) The Use of Neuraxial Catheters for Postoperative Analgesia in Neonates: A Multicenter Safety Analysis from the Pediatric Regional Anesthesia Network. *Anesth Analg* **122**(6): 1965-70.
Long LS, Ved S & Koh JL (2009) Intraoperative opioid dosing in children with and without cerebral palsy. *Paediatr Anaesth* **19**(5): 513–20.
Lonnqvist PA, Ecoffey C, Bosenberg A et al (2017) The European society of regional anesthesia and pain therapy and the American society of regional anesthesia and pain medicine joint committee practice advisory on controversial topics in pediatric regional anesthesia I and II: what do they tell us? *Curr Opin Anaesthesiol* **30**(5): 613-20.
Lopez MM, Zech D, Linton JL et al (2018) Dexmedetomidine Decreases Postoperative Pain and Narcotic Use in Children Undergoing Alveolar Bone Graft Surgery. *Cleft Palate Craniofac J* **55**(5): 688-91.
Lord B, Jennings PA & Smith K (2016) The epidemiology of pain in children treated by paramedics. *Emerg Med Australas* **28**(3): 319-24.
Lord SM, Tardif HP, Kepreotes EA et al (2019) The Paediatric electronic Persistent Pain Outcomes Collaboration (PaedePPOC): establishment of a binational system for benchmarking children's persistent pain services. *Pain* **160**(7): 1572-85.
Losacco V, Cuttini M, Greisen G et al (2011) Heel blood sampling in European neonatal intensive care units: compliance with pain management guidelines. *Arch Dis Child Fetal Neonatal Ed* **96**(1): F65–68.
Lotsch J, Walter C, Parnham MJ et al (2013) Pharmacokinetics of non-intravenous formulations of fentanyl. *Clin Pharmacokinet* **52**(1): 23–36.
Lovett PB, Sule HP & Lopez BL (2017) Sickle Cell Disease in the Emergency Department. *Hematol Oncol Clin North Am* **31**(6): 1061-79.
Lovstad RZ & Stoen R (2001) Postoperative epidural analgesia in children after major orthopaedic surgery. A randomised study of the effect on PONV of two anaesthetic techniques: low and high dose i.v. fentanyl and epidural infusions with and without fentanyl. *Acta Anaesthesiol Scand* **45**(4): 482–88.
Lowery S & Oliver A (2008) Incidence of postdural puncture headache and backache following diagnostic/therapeutic lumbar puncture using a 22G cutting spinal needle, and after introduction of a 25G pencil point spinal needle. *Paediatr Anaesth* **18**(3): 230–34.
Lozano EI & Potterton JL (2018) The use of Xbox Kinect in a Paediatric Burns Unit. *S Afr J Physiother* **74**(1): 429.
Lu Q, Krull KR, Leisenring W et al (2011) Pain in long-term adult survivors of childhood cancers and their siblings: a report from the Childhood Cancer Survivor Study. *Pain* **152**(11): 2616-24.
Lubega FA, DeSilva MS, Munube D et al (2018) Low dose ketamine versus morphine for acute severe vaso occlusive pain in children: a randomized controlled trial. *Scand J Pain* **18**(1): 19-27.
Luhmann JD, Schootman M, Luhmann SJ et al (2006) A randomized comparison of nitrous oxide plus hematoma block versus ketamine plus midazolam for emergency department forearm fracture reduction in children. *Pediatrics* **118**(4): e1078–86.
Lundblad M, Lonnqvist PA, Eksborg S et al (2011) Segmental distribution of high-volume caudal anesthesia in neonates, infants, and toddlers as assessed by ultrasonography. *Paediatr Anaesth* **21**(2): 121–27.
Lundblad M, Trifa M, Kaabachi O et al (2016) Alpha-2 adrenoceptor agonists as adjuncts to peripheral nerve blocks in children: a meta-analysis. *Paediatr Anaesth* **26**(3): 232-8.
Lunoe MM, Drendel AL, Levas MN et al (2015) A Randomized Clinical Trial of Jet-Injected Lidocaine to Reduce Venipuncture Pain for Young Children. *Ann Emerg Med* **66**(5): 466-74.
Luo M, Liu X, Ning L et al (2017) Comparison of Ultrasonography-guided Bilateral Intercostal Nerve Blocks and Conventional Patient-controlled Intravenous Analgesia for Pain Control After the Nuss Procedure in Children: A Prospective Randomized Study. *Clin J Pain* **33**(7): 604-10.
Lynn AM, Bradford H, Kantor ED et al (2007) Postoperative ketorolac tromethamine use in infants aged 6-18 months: the effect on morphine usage, safety assessment, and stereo-specific pharmacokinetics. *Anesth Analg* **104**(5): 1040–51.
Lynn AM, Nespeca MK, Bratton SL et al (2000) Intravenous morphine in postoperative infants: intermittent bolus dosing versus targeted continuous infusions. *Pain* **88**(1): 89–95.

Lyons B, Casey W, Doherty P et al (1996) Pain relief with low-dose intravenous clonidine in a child with severe burns. *Intensive Care Med* **22**(3): 249–51.
Lyttle MD, Verma S & Isaac R (2012) Transdermal fentanyl in deliberate overdose in pediatrics. *Pediatr Emerg Care* **28**(5): 463–64.
Maaskant J, Raymakers-Janssen P, Veldhoen E et al (2016) The clinimetric properties of the COMFORT scale: A systematic review. *Eur J Pain* **20**(10): 1587-611.
MacDuff A, Arnold A, Harvey J et al (2010) Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. *Thorax* **65 Suppl 2**(Suppl 2): ii18-31.
Mace SE, Brown LA, Francis L et al (2008) Clinical policy: critical issues in the sedation of pediatric patients in the emergency department. *J Emerg Nurs* **34**(3): e33–107.
Machoki MS, Millar AJ, Albetyn H et al (2015) Local anesthetic wound infusion versus standard analgesia in paediatric post-operative pain control. *Pediatr Surg Int* **31**(11): 1087-97.
Machotta A, Risse A, Bercker S et al (2003) Comparison between instillation of bupivacaine versus caudal analgesia for postoperative analgesia following inguinal herniotomy in children. *Paediatr Anaesth* **13**(5): 397–402.
MacLean S, Obispo J & Young KD (2007) The gap between pediatric emergency department procedural pain management treatments available and actual practice. *Pediatr Emerg Care* **23**(2): 87–93.
MacLellan J, Ali S, Curtis S et al (2017) Analgesia for acute gingivostomatitis: a national survey of pediatric emergency physicians. *CJEM* **19**(1): 32-38.
Madadi P, Hildebrandt D, Gong IY et al (2010) Fatal hydrocodone overdose in a child: pharmacogenetics and drug interactions. *Pediatrics* **126**(4): e986–89.
Madadi P, Koren G, Cairns J et al (2007) Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. *Can Fam Physician* **53**(1): 33–35.
Madden K, Jo E, Williams JL et al (2019) Corrected QT Interval Prolongation in Pediatric and Young Adult Patients on Methadone for Cancer-Related Pain. *J Pain Symptom Manage* **58**(4): 678-84.
Madden K, Mills S, Dibaj S et al (2018) Methadone as the Initial Long-Acting Opioid in Children with Advanced Cancer. *J Palliat Med* **21**(9): 1317-21.
Madden K, Park M, Liu D et al (2017) The frequency of QTc prolongation among pediatric and young adult patients receiving methadone for cancer pain. *Pediatr Blood Cancer* **64**(11).
Mahant S, Keren R, Localio R et al (2014) Dexamethasone and risk of bleeding in children undergoing tonsillectomy. *Otolaryngol Head Neck Surg* **150**(5): 872-9.
Mahar PJ, Rana JA, Kennedy CS et al (2007) A randomized clinical trial of oral transmucosal fentanyl citrate versus intravenous morphine sulfate for initial control of pain in children with extremity injuries. *Pediatr Emerg Care* **23**(8): 544-8.
Maharramova M & Taylor K (2019) A Systematic Review of Caudal Anesthesia and Postoperative Outcomes in Pediatric Cardiac Surgery Patients. *Semin Cardiothorac Vasc Anesth* **23**(2): 237-47.
Mahgoobifard M, Mirmesdagh Y, Imani F et al (2014) The analgesic efficacy of preoperative oral Ibuprofen and acetaminophen in children undergoing adenotonsillectomy: a randomized clinical trial. *Anesth Pain Med* **4**(1): e15049.
Maimon MS, Marques L & Goldman RD (2007) Parental administration of analgesic medication in children after a limb injury. *Pediatr Emerg Care* **23**(4): 223-6.
Maitra S, Baidya DK, Pawar DK et al (2014) Epidural anesthesia and analgesia in the neonate: a review of current evidences. *J Anesth* **28**(5): 768–79.
Maitre NL, Stark AR, McCoy Menser CC et al (2017) Cry presence and amplitude do not reflect cortical processing of painful stimuli in newborns with distinct responses to touch or cold. *Arch Dis Child Fetal Neonatal Ed* **102**(5): F428-F33.
Malviya S, Voepel-Lewis T, Burke C et al (2006a) The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. *Paediatr Anaesth* **16**(3): 258–65.
Malviya S, Voepel-Lewis T, Ramamurthi RJ et al (2006b) Clonidine for the prevention of emergence agitation in young children: efficacy and recovery profile. *Paediatr Anaesth* **16**(5): 554–59.
Malviya S, Voepel-Lewis T, Tait AR et al (2001) Pain management in children with and without cognitive impairment following spine fusion surgery. *Paediatr Anaesth* **11**(4): 453–58.
Man JY, Gurnaney HG, Dubow SR et al (2017) A retrospective comparison of thoracic epidural infusion and multimodal analgesia protocol for pain management following the minimally invasive repair of pectus excavatum. *Paediatr Anaesth* **27**(12): 1227-34.
Mandema JW & Stanski DR (1996) Population pharmacodynamic model for ketorolac analgesia. *Clin Pharmacol Ther* **60**(6): 619–35.
Mane RS, Sanikop CS, Dhulkhed VK et al (2011) Comparison of bupivacaine alone and in combination with fentanyl or pethidine for bilateral infraorbital nerve block for postoperative analgesia in paediatric patients for cleft lip repair: A prospective randomized double blind study. *J Anaesthesiol Clin Pharmacol* **27**(1): 23–26.

Manworren RCB, Anderson MN, Girard ED et al (2018) Postoperative Pain Outcomes After Nuss Procedures: Comparison of Epidural Analgesia, Continuous Infusion of Local Anesthetic, and Preoperative Self-Hypnosis Training. *J Laparoendosc Adv Surg Tech A* **28**(10): 1234-42.
Marechal C, Honorat R & Claudet I (2011) Serotonin syndrome induced by tramadol intoxication in an 8-month-old infant. *Pediatr Neurol* **44**(1): 72–74.
Marhofer P, Sitzwohl C, Greher M et al (2004) Ultrasound guidance for infraclavicular brachial plexus anaesthesia in children. *Anaesthesia* **59**(7): 642–46.
Marinkovic D, Simin JM, Draskovic B et al (2016) Efficiency of Ultrasound Guided Lower Limb Peripheral Nerve Blocks in Perioperative Pain Management for Knee Arthroscopy in Children. A Randomized Study. *Med Pregl* **69**(1-2): 5-10.
Marjanovic V, Budic I, Stevic M et al (2017) A Comparison of Three Different Volumes of Levobupivacaine for Caudal Block in Children Undergoing Orchidopexy and Inguinal Hernia Repair. *Med Princ Pract* **26**(4): 331-36.
Marofi M, Sirousfard M, Moeini M et al (2015) Evaluation of the effect of aromatherapy with Rosa damascena Mill. on postoperative pain intensity in hospitalized children in selected hospitals affiliated to Isfahan University of Medical Sciences in 2013: A randomized clinical trial. *Iran J Nurs Midwifery Res* **20**(2): 247-54.
Marquardt KA, Alsop JA & Albertson TE (2005) Tramadol exposures reported to statewide poison control system. *Ann Pharmacother* **39**(6): 1039-44.
Marseglia L, D'Angelo G, Manti S et al (2015a) Analgesic, anxiolytic and anaesthetic effects of melatonin: new potential uses in pediatrics. *Int J Mol Sci* **16**(1): 1209-20.
Marseglia L, Manti S, D'Angelo G et al (2015b) Potential Use of Melatonin in Procedural Anxiety and Pain in Children Undergoing Blood Withdrawal. *J Biol Regul Homeost Agents* **29**(2): 509-14.
Marshall BD, Green TC, Yedinak JL et al (2016) Harm reduction for young people who use prescription opioids extra-medically: Obstacles and opportunities. *Int J Drug Policy* **31**: 25-31.
Marshall MJ, Bucks RS, Hogan AM et al (2009) Auto-adjusting positive airway pressure in children with sickle cell anemia: results of a phase I randomized controlled trial. *Haematologica* **94**(7): 1006-10.
Martin AE, Newlove-Delgado TV, Abbott RA et al (2017) Pharmacological interventions for recurrent abdominal pain in childhood. *Cochrane Database Syst Rev* **3**: Cd010973.
Martin DP, Samora WP, 3rd, Beebe AC et al (2018) Analgesic effects of methadone and magnesium following posterior spinal fusion for idiopathic scoliosis in adolescents: a randomized controlled trial. *J Anesth* **32**(5): 702-08.
Martin LD, Adams TL, Duling LC et al (2019) Comparison between epidural and opioid analgesia for infants undergoing major abdominal surgery. *Paediatr Anaesth* **29**(8): 835-42.
Martin-Herz SP, Patterson DR, Honari S et al (2003) Pediatric pain control practices of North American Burn Centers. *J Burn Care Rehabil* **24**(1): 26-36.
Marzuillo P, Calligaris L, Amoroso S et al (2018) Narrative review shows that the short-term use of ketorolac is safe and effective in the management of moderate-to-severe pain in children. *Acta Paediatr* **107**(4): 560-67.
Marzuillo P, Guarino S & Barbi E (2014) Paracetamol: a focus for the general pediatrician. *Eur J Pediatr* **173**(4): 415-25.
Masarwa R, Levine H, Gorelik E et al (2018) Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies. *Am J Epidemiol* **187**(8): 1817-27.
Mason KP, Zurakowski D, Zgleszewski SE et al (2008) High dose dexmedetomidine as the sole sedative for pediatric MRI. *Paediatr Anaesth* **18**(5): 403-11.
Massimo L, Haupt R & Enrica M (1985) Control of pain with sublingual buprenorphine in children with cancer. *European Paediatric Haematology and Oncology* **2**(1): 224-24.
Mata-Gomez J, Guerrero-Dominguez R, Garcia-Santigosa M et al (2015) Ultrasound-guided paravertebral block for pyloromyotomy in 3 neonates with congenital hypertrophic pyloric stenosis. *Braz J Anesthesiol* **65**(4): 302-5.
Matava CT, Crawford MW, Pehora C et al (2014) Early postoperative patient-controlled analgesia ratio predicts 24-hour morphine consumption and pain in children undergoing scoliosis surgery. *J Opioid Manag* **10**(1): 39–45.
Mattila I, Patila T, Rautiainen P et al (2016) The effect of continuous wound infusion of ropivacaine on postoperative pain after median sternotomy and mediastinal drain in children. *Paediatr Anaesth* **26**(7): 727-33.
Maunuksela EL, Korpela R & Olkkola KT (1988a) Comparison of buprenorphine with morphine in the treatment of postoperative pain in children. *Anesth Analg* **67**(3): 233-9.
Maunuksela EL, Korpela R & Olkkola KT (1988b) Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain of children. *Br J Anaesth* **60**(1): 48-55.
Maxwell EN, Johnson B, Cammilleri J et al (2019) Intravenous Acetaminophen-Induced Hypotension: A Review of the Current Literature. *Ann Pharmacother* **53**(10): 1033-41.
Maxwell LG, Kaufmann SC, Bitzer S et al (2005) 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. *Anesth Analg* **100**(4): 953–58.
Mayell A, Srinivasan I, Campbell F et al (2014) Analgesic effects of gabapentin after scoliosis surgery in children: a randomized controlled trial. *Paediatr Anaesth*.
Mazhari F, Shirazi AS & Shabzendehdar M (2019) Management of oral mucositis in pediatric patients receiving cancer therapy: A systematic review and meta-analysis. *Pediatric Blood & Cancer* **66**(3): e27403.

Mazor SS, Feldman KW, Sugar NF et al (2008) Pediatric tramadol ingestion resulting in seizurelike activity: a case series. *Pediatr Emerg Care* **24**(6): 380–81.
Mc Donnell C (2011) Opioid medication errors in pediatric practice: four years' experience of voluntary safety reporting. *Pain Res Manag* **16**(2): 93–98.
McAdam D, Muro K & Suresh S (2005) The use of infraorbital nerve block for postoperative pain control after transsphenoidal hypophysectomy. *Reg Anesth Pain Med* **30**(6): 572-3.
McCabe SE, Veliz P & Schulenberg JE (2016) Adolescent context of exposure to prescription opioids and substance use disorder symptoms at age 35: a national longitudinal study. *Pain* **157**(10): 2173-8.
McCabe SE, Veliz PT, Boyd CJ et al (2019) A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. *Drug Alcohol Depend* **194**: 377-85.
McCabe SE, West BT & Boyd CJ (2013a) Leftover prescription opioids and nonmedical use among high school seniors: a multi-cohort national study. *J Adolesc Health* **52**(4): 480-5.
McCabe SE, West BT & Boyd CJ (2013b) Motives for medical misuse of prescription opioids among adolescents. *The journal of pain : official journal of the American Pain Society* **14**(10): 1208-16.
McCabe SE, West BT, Veliz P et al (2017) Trends in Medical and Nonmedical Use of Prescription Opioids Among US Adolescents: 1976-2015. *Pediatrics* **139**(4).
McCann ME, de Graaff JC, Dorris L et al (2019) Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial. *Lancet* **393**(10172): 664-77.
McClafferty H, Vohra S, Bailey M et al (2017) Pediatric Integrative Medicine. *Pediatrics* **140**(3).
McDonald EM, Kennedy-Hendricks A, McGinty EE et al (2017) Safe Storage of Opioid Pain Relievers Among Adults Living in Households With Children. *Pediatrics* **139**(3): e20162161.
McDonald SA, Hershey AD, Pearlman E et al (2011) Long-term evaluation of sumatriptan and naproxen sodium for the acute treatment of migraine in adolescents. *Headache* **51**(9): 1374–87.
McDonnell C, Pehora C & Crawford MW (2012) PCA-derived factors that may be predictive of postoperative pain in pediatric patients: a possible role for the PCA ratio. *J Opioid Manag* **8**(1): 39–44.
McEwan A, Sigston PE, Andrews KA et al (2000) A comparison of rectal and intramuscular codeine phosphate in children following neurosurgery. *Paediatr Anaesth* **10**(2): 189–93.
McGown RG (1982) Caudal analgesia in children. Five hundred cases for procedures below the diaphragm. *Anaesthesia* **37**(8): 806–18.
McGrath PA, Seifert CE, Speechley KN et al (1996) A new analogue scale for assessing children's pain: an initial validation study. *Pain* **64**(3): 435–43.
McGrath PJ, Walco GA, Turk DC et al (2008) Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. *J Pain* **9**(9): 771–83.
McHoney M, Wade AM, Eaton S et al (2011) Clinical outcome of a randomized controlled blinded trial of open versus laparoscopic Nissen fundoplication in infants and children. *Ann Surg* **254**(2): 209–16.
McIntyre RE, Hardcastle C, Eng RL et al (2012) Effect of dexamethasone on postoperative morbidity after dental rehabilitation in children. *Can J Anaesth* **59**(1): 34–40.
McKnight ER, Bonny AE, Lange HLH et al (2017) Statewide opioid prescriptions and the prevalence of adolescent opioid misuse in Ohio. *The American journal of drug and alcohol abuse* **43**(3): 299-305.
McLay JS, Engelhardt T, Mohammed BS et al (2018) The pharmacokinetics of intravenous ketorolac in children aged 2 months to 16 years: A population analysis. *Paediatr Anaesth* **28**(2): 80-86.
McMorrow SP & Abramo TJ (2012) Dexmedetomidine sedation: uses in pediatric procedural sedation outside the operating room. *Pediatr Emerg Care* **28**(3): 292–96.
McMurtry CM, Chambers CT, McGrath PJ et al (2010) When "don't worry" communicates fear: Children's perceptions of parental reassurance and distraction during a painful medical procedure. *Pain* **150**(1): 52–58.
McMurtry CM, Noel M, Taddio A et al (2015) Interventions for Individuals With High Levels of Needle Fear: Systematic Review of Randomized Controlled Trials and Quasi-Randomized Controlled Trials. *Clin J Pain* **31**(10 Suppl): S109-23.
McMurtry CM, Taddio A, Noel M et al (2016) Exposure-based Interventions for the management of individuals with high levels of needle fear across the lifespan: a clinical practice guideline and call for further research. *Cogn Behav Ther* **45**(3): 217-35.
McNair C, Fung M, Taddio A et al (2017) Parent-led interventions in reducing infant vaccination pain after participation in a longitudinal randomized control trial. *Paediatr Child Health* **22**(4): 217-19.
McNair C, Graydon B & Taddio A (2018) A cohort study of intranasal fentanyl for procedural pain management in neonates. *Paediatr Child Health* **23**(8): e170-e75.
McNeely J, Farber N, Rusy L et al (1997) Epidural analgesia improves outcome following pediatric fundoplication. A retrospective analysis. *Reg Anesth* **22**(1): 16–23.
McNicol ED, Ferguson MC & Hudcova J (2015) Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. *Cochrane Database Syst Rev*(6): CD003348.

McNicol ED, Rowe E & Cooper TE (2018) Ketorolac for postoperative pain in children. *Cochrane Database Syst Rev* **7**: CD012294.
McNicol R (1993) Postoperative analgesia in children using continuous s.c. morphine. *Br J Anaesth* **71**(5): 752–56.
McQueen A, Wright RO, Kido MM et al (2009) Procedural sedation and analgesia outcomes in children after discharge from the emergency department: ketamine versus fentanyl/midazolam. *Ann Emerg Med* **54**(2): 191–97 e1–4.
Medical Developments International (2001) Methoxyflurane inhalation analgesic. *Material Safety Data Sheet* http://www.medicaldev.com/pdf_files/Products_Pain_Relief_Healthcare_Professionals_Medical/Penthrox_MSDS.pdf.
Medsafe (2015) *Use of Aspirin in Children is Not Recommended.* https://www.medsafe.govt.nz/profs/PUArticles/December2015/UseOfAspirinInChildren.htm Accessed 5 March 2020
Medsafe (2017) *Tramadol in Children.* https://www.medsafe.govt.nz/profs/PUArticles/March2017/TramadolinChildren.htm Accessed 17 February 2020
Medsafe (2018) *Alert Communication: Codeine – new restrictions on use in children and young adults.* https://www.medsafe.govt.nz/safety/EWS/2018/Codeine.asp Accessed 17 February 2020
Medsafe (2020) *Spotlight on tramadol, including updated advice for use in children.* https://medsafe.govt.nz/profs/PUArticles/June2020/Spotlight-on-tramadol.html Accessed 27 July 2020
Meesters N, Dilles T, Simons S et al (2019) Do Pain Measurement Instruments Detect the Effect of Pain-Reducing Interventions in Neonates? A Systematic Review on Responsiveness. *J Pain* **20**(7): 760-70.
Meiri N, Ankri A, Hamad-Saied M et al (2016) The effect of medical clowning on reducing pain, crying, and anxiety in children aged 2-10 years old undergoing venous blood drawing--a randomized controlled study. *Eur J Pediatr* **175**(3): 373-9.
Mellon RD, Simone AF & Rappaport BA (2007) Use of anesthetic agents in neonates and young children. *Anesth Analg* **104**(3): 509–20.
Ment LR, Vohr BR, Makuch RW et al (2004) Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. *J Pediatr* **145**(6): 832–34.
Merdad M, Crawford M, Gordon K et al (2012) Unexplained fever after bilateral superficial cervical block in children undergoing cochlear implantation: an observational study. *Can J Anaesth* **59**(1): 28–33.
Merkel SI, Voepel-Lewis T, Shayevitz JR et al (1997) The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs* **23**(3): 293–97.
Merry AF, Edwards KE, Ahmad Z et al (2013) Randomized comparison between the combination of acetaminophen and ibuprofen and each constituent alone for analgesia following tonsillectomy in children. *Can J Anaesth* **60**(12): 1180–89.
Mesnil M, Dadure C, Captier G et al (2010) A new approach for peri-operative analgesia of cleft palate repair in infants: the bilateral suprazygomatic maxillary nerve block. *Paediatr Anaesth* **20**(4): 343–9.
Mherekumombe MF & Collins JJ (2015) Patient-controlled analgesia for children at home. *J Pain Symptom Manage* **49**(5): 923-7.
MHRA (2003) *Aspirin and Reye's Syndrome in the under 16s.* https://webarchive.nationalarchives.gov.uk/20141206082130/http:/www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con007619.pdf Accessed 5 March 2020
Micalizzi RA, Williams LA, Pignataro S et al (2014) Review of outcomes in pediatric patients undergoing anterior cruciate ligament repairs with regional nerve blocks. *J Pediatr Nurs* **29**(6): 670-8.
Michel E, Anderson BJ & Zernikow B (2011) Buprenorphine TTS for children--a review of the drug's clinical pharmacology. *Paediatr Anaesth* **21**(3): 280–90.
Michel F, Vialet R, Hassid S et al (2010) Sevoflurane for central catheter placement in neonatal intensive care: a randomized trial. *Paediatr Anaesth* **20**(8): 712-9.
Michelet D, Andreu-Gallien J, Bensalah T et al (2012) A meta-analysis of the use of nonsteroidal antiinflammatory drugs for pediatric postoperative pain. *Anesth Analg* **114**(2): 393–406.
Michelet D, Hilly J, Skhiri A et al (2016) Opioid-Sparing Effect of Ketamine in Children: A Meta-Analysis and Trial Sequential Analysis of Published Studies. *Paediatr Drugs* **18**(6): 421-33.
Miech R, Johnston L, O'Malley PM et al (2015) Prescription Opioids in Adolescence and Future Opioid Misuse. *Pediatrics* **136**(5): e1169-77.
Migita RT, Klein EJ & Garrison MM (2006) Sedation and analgesia for pediatric fracture reduction in the emergency department: a systematic review. *Arch Pediatr Adolesc Med* **160**(1): 46-51.
Mikawa K, Nishina K, Maekawa N et al (1996) Oral clonidine premedication reduces postoperative pain in children. *Anesth Analg* **82**(2): 225–30.
Milbrandt TA, Singhal M, Minter C et al (2009) A comparison of three methods of pain control for posterior spinal fusions in adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)* **34**(14): 1499–503.
Milesi C, Cambonie G, Jacquot A et al (2010) Validation of a neonatal pain scale adapted to the new practices in caring for preterm newborns. *Arch Dis Child Fetal Neonatal Ed* **95**(4): F263–66.

Miller JW, Balyan R, Dong M et al (2018) Does intranasal dexmedetomidine provide adequate plasma concentrations for sedation in children: a pharmacokinetic study. *Br J Anaesth* **120**(5): 1056-65.
Miller K, Rodger S, Bucolo S et al (2010) Multi-modal distraction. Using technology to combat pain in young children with burn injuries. *Burns* **36**(5): 647–58.
Miller K, Tan X, Hobson AD et al (2016) A Prospective Randomized Controlled Trial of Nonpharmacological Pain Management During Intravenous Cannulation in a Pediatric Emergency Department. *Pediatr Emerg Care* **32**(7): 444-51.
Mills E, Craig S & Oakley E (2016) Effect of a Computerized Reminder on Splinting of Pediatric Upper Limb Fractures in the Emergency Department. *Pediatr Emerg Care* **32**(10): 717-22.
Min TJ, Kim WY, Jeong WJ et al (2012) Effect of ketamine on intravenous patient-controlled analgesia using hydromorphone and ketorolac after the Nuss surgery in pediatric patients. *Korean J Anesthesiol* **62**(2): 142-7.
Miner JR, Kletti C, Herold M et al (2007) Randomized clinical trial of nebulized fentanyl citrate versus i.v. fentanyl citrate in children presenting to the emergency department with acute pain. *Acad Emerg Med* **14**(10): 895–98.
Minoshima R, Kosugi S, Nishimura D et al (2015) Intra- and postoperative low-dose ketamine for adolescent idiopathic scoliosis surgery: a randomized controlled trial. *Acta Anaesthesiol Scand* **59**(10): 1260-8.
Mion G & Villevieille T (2013) Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). *CNS Neurosci Ther* **19**(6): 370–80.
Mireskandari SM & Makarem J (2011) Effect of rectal diclofenac and acetaminophen alone and in combination on postoperative pain after cleft palate repair in children. *J Craniofac Surg* **22**(5): 1955–59.
Mirjalili SA, Taghavi K, Frawley G et al (2015) Should we abandon landmark-based technique for caudal anesthesia in neonates and infants? *Paediatr Anaesth* **25**(5): 511-6.
Miro J, Castarlenas E, de la Vega R et al (2016) Validity of three rating scales for measuring pain intensity in youths with physical disabilities. *Eur J Pain* **20**(1): 130-7.
Miro J, Castarlenas E & Huguet A (2009) Evidence for the use of a numerical rating scale to assess the intensity of pediatric pain. *Eur J Pain* **13**(10): 1089–95.
Miser AW, Goh TS, Dose AM et al (1994) Trial of a topically administered local anesthetic (EMLA cream) for pain relief during central venous port accesses in children with cancer. *J Pain Symptom Manage* **9**(4): 259–64.
Miser AW, McCalla J, Dothage JA et al (1987) Pain as a presenting symptom in children and young adults with newly diagnosed malignancy. *Pain* **29**(1): 85–90.
Misurac JM, Knoderer CA, Leiser JD et al (2013) Nonsteroidal anti-inflammatory drugs are an important cause of acute kidney injury in children. *J Pediatr* **162**(6): 1153–59; 59.e1.
Mitchell A & Smith HS (2010) Applying partially occluded fentanyl transdermal patches to manage pain in pediatric patients. *J Opioid Manag* **6**(4): 290–94.
Mitchell RB, Archer SM, Ishman SL et al (2019) Clinical Practice Guideline: Tonsillectomy in Children (Update)-Executive Summary. *Otolaryngol Head Neck Surg* **160**(2): 187-205.
Moffett BS, Wann TI, Carberry KE et al (2006) Safety of ketorolac in neonates and infants after cardiac surgery. *Paediatr Anaesth* **16**(4): 424-8.
Mohamed SK, Ibraheem AS & Abdelraheem MG (2009) Preoperative intravenous dexamethasone combined with glossopharyngeal nerve block: role in pediatric postoperative analgesia following tonsillectomy. *Eur Arch Otorhinolaryngol* **266**(11): 1815–19.
Mohammed BS, Engelhardt T, Cameron GA et al (2012) Population pharmacokinetics of single-dose intravenous paracetamol in children. *Br J Anaesth* **108**(5): 823–29.
Moir MS, Bair E, Shinnick P et al (2000) Acetaminophen versus acetaminophen with codeine after pediatric tonsillectomy. *Laryngoscope* **110**(11): 1824–27.
Monitto CL, Greenberg RS, Kost-Byerly S et al (2000) The safety and efficacy of parent-/nurse-controlled analgesia in patients less than six years of age. *Anesth Analg* **91**(3): 573–79.
Monitto CL, Hsu A, Gao S et al (2017) Opioid Prescribing for the Treatment of Acute Pain in Children on Hospital Discharge. *Anesth Analg* **125**(6): 2113-22.
Monitto CL, Kost-Byerly S, White E et al (2011) 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. *Anesth Analg* **113**(4): 834–42.
Monk V, Moultrie F, Hartley C et al (2019) Efficacy and Mechanism Evaluation. In: *Oral morphine analgesia for preventing pain during invasive procedures in non-ventilated premature infants in hospital: the Poppi RCT* edn. (eds). Southampton (UK), NIHR Journals Library

Montirosso R, Del Prete A, Bellu R et al (2012) Level of NICU quality of developmental care and neurobehavioral performance in very preterm infants. *Pediatrics* **129**(5): e1129–37.
Moody K, Abrahams B, Baker R et al (2017) A Randomized Trial of Yoga for Children Hospitalized With Sickle Cell Vaso-Occlusive Crisis. *J Pain Symptom Manage* **53**(6): 1026-34.
Moore ER, Bennett KL, Dietrich MS et al (2015) The Effect of Directed Medical Play on Young Children's Pain and Distress During Burn Wound Care. *J Pediatr Health Care* **29**(3): 265-73.
Morelius E, He HG & Shorey S (2016) Salivary Cortisol Reactivity in Preterm Infants in Neonatal Intensive Care: An Integrative Review. *Int J Environ Res Public Health* **13**(3): 337.
Mori F, Barni S, Manfredi M et al (2015) Anaphylaxis to Intravenous Tramadol in a Child. *Pharmacology* **96**(5-6): 256-8.
Mori T, Nomura O & Ihara T (2019) Ultrasound-guided peripheral forearm nerve block for digit fractures in a pediatric emergency department. *Am J Emerg Med* **37**(3): 489-93.
Moriceau F, Geffard B & Duflo F (2015) Levobupivacaine for continuous femoral nerve block in paediatric patients: A plasma concentration analysis report on safety. *Anaesth Crit Care Pain Med* **34**(3): 183.
Morris V, Murphy LM, Rosenberg M et al (2012) Itch assessment scale for the pediatric burn survivor. *J Burn Care Res* **33**(3): 419-24.
Mortensen A, Lenz K, Abildstrom H et al (2011) Anesthetizing the obese child. *Paediatr Anaesth* **21**(6): 623-9.
Morton NS & Errera A (2010) APA national audit of pediatric opioid infusions. *Paediatr Anaesth* **20**(2): 119–25.
Moss A, Beggs S, Vega-Avelaira D et al (2007) Spinal microglia and neuropathic pain in young rats. *Pain* **128**(3): 215–24.
Moss JR, Watcha MF, Bendel LP et al (2014) A multicenter, randomized, double-blind placebo-controlled, single dose trial of the safety and efficacy of intravenous ibuprofen for treatment of pain in pediatric patients undergoing tonsillectomy. *Paediatr Anaesth* **24**(5): 483–89.
Mostafa MF, Herdan R & Elshazly M (2018) Comparative study of levobupivacaine and bupivacaine for bilateral maxillary nerve block during pediatric primary cleft palate surgery: a randomized double-blind controlled study. *Korean J Anesthesiol* **71**(2): 135-40.
Mott C, Sarpal A, Moss K et al (2018) Methadone for Analgesia in Children with Life-Limiting Illness: Experience from a Tertiary Children's Health Service. *Children (Basel)* **5**(7).
Mott J, Bucolo S, Cuttle L et al (2008) The efficacy of an augmented virtual reality system to alleviate pain in children undergoing burns dressing changes: a randomised controlled trial. *Burns* **34**(6): 803–08.
Moulis F, Durrieu G, Masmoudi K et al (2018) Medication errors with tramadol drops in children. *Eur J Clin Pharmacol* **74**(2): 247-48.
Movahedi AF, Rostami S, Salsali M et al (2006) Effect of local refrigeration prior to venipuncture on pain related responses in school age children. *Aust J Adv Nurs* **24**(2): 51–55.
Moyao-Garcia D, Hernandez-Palacios JC, Ramirez-Mora JC et al (2009) A pilot study of nalbuphine versus tramadol administered through continuous intravenous infusion for postoperative pain control in children. *Acta Biomed* **80**(2): 124–30.
Mudd PA, Thottathil P, Giordano T et al (2017) Association Between Ibuprofen Use and Severity of Surgically Managed Posttonsillectomy Hemorrhage. *JAMA Otolaryngol Head Neck Surg* **143**(7): 712-17.
Mudd S (2011) Intranasal fentanyl for pain management in children: a systematic review of the literature. *J Pediatr Health Care* **25**(5): 316–22.
Muhly WT, Beltran RJ, Bielsky A et al (2019) Perioperative Management and In-Hospital Outcomes After Minimally Invasive Repair of Pectus Excavatum: A Multicenter Registry Report From the Society for Pediatric Anesthesia Improvement Network. *Anesth Analg* **128**(2): 315-27.
Muhly WT, Gurnaney HG, Kraemer FW et al (2015) A retrospective comparison of ropivacaine and 2-chloroprocaine continuous thoracic epidural analgesia for management of postthoracotomy pain in infants. *Paediatr Anaesth* **25**(11): 1162-7.
Muhly WT, Maxwell LG & Cravero JP (2014) Pain management following the Nuss procedure: a survey of practice and review. *Acta Anaesthesiol Scand* **58**(9): 1134-9.
Munk-Andersen H & Laustrup TK (2013) Compartment syndrome diagnosed in due time by breakthrough pain despite continuous peripheral nerve block. *Acta Anaesthesiol Scand* **57**(10): 1328–30.
Munoz F, Cubillos J, Bonilla AJ et al (2017) Erector spinae plane block for postoperative analgesia in pediatric oncological thoracic surgery. *Can J Anaesth* **64**(8): 880-82.
Munro FJ, Fisher S, Dickson U et al (2002) The addition of antiemetics to the morphine solution in patient controlled analgesia syringes used by children after an appendicectomy does not reduce the incidence of postoperative nausea and vomiting. *Paediatr Anaesth* **12**(7): 600–03.
Munshey F, Rodriguez S, Diaz E et al (2018) Continuous erector spinae plane block for an open pyeloplasty in an infant. *J Clin Anesth* **47**: 47-49.
Munsters J, Wallstrom L, Agren J et al (2012) Skin conductance measurements as pain assessment in newborn infants born at 22-27 weeks gestational age at different postnatal age. *Early Hum Dev* **88**(1): 21–26.
Murat I, Gall O & Tourniaire B (2003) Procedural pain in children: evidence-based best practice and guidelines. *Reg Anesth Pain Med* **28**(6): 561–72.

Murphy A, Barrett M, Cronin J et al (2014a) A qualitative study of the barriers to prehospital management of acute pain in children. *Emerg Med J* **31**(6): 493-8.
Murphy A, McCoy S, O'Reilly K et al (2016a) A Prevalence and Management Study of Acute Pain in Children Attending Emergency Departments by Ambulance. *Prehosp Emerg Care* **20**(1): 52-8.
Murphy A, O'Sullivan R, Wakai A et al (2014b) Intranasal fentanyl for the management of acute pain in children. *Cochrane Database Syst Rev* **10**: Cd009942.
Murphy AP, Hughes M, McCoy S et al (2017) Intranasal fentanyl for the prehospital management of acute pain in children. *Eur J Emerg Med* **24**(6): 450-54.
Murphy T, McCheyne A & Karlsson J (2016b) Analgesic management after thoracotomy for decortication in children: a retrospective audit of 83 children managed with a paravertebral infusion-based regime. *Paediatr Anaesth* **26**(7): 722-6.
Murray N, Malla U, Vlok R et al (2018) Buprenorphine versus Morphine in Paediatric Acute Pain: A Systematic Review and Meta-Analysis. *Crit Care Res Pract* **2018**: 3792043.
Murto K, Lamontagne C, McFaul C et al (2015) Celecoxib pharmacogenetics and pediatric adenotonsillectomy: a double-blinded randomized controlled study. *Can J Anaesth* **62**(7): 785-97.
Muse D, Tarau E, Lefeber C et al (2019) Pharmacokinetics, safety, and efficacy of tapentadol oral solution for treating moderate to severe pain in pediatric patients. *J Pain Res* **12**: 1777-90.
Musu M, Finco G, Antonucci R et al (2011) Acute nephrotoxicity of NSAID from the foetus to the adult. *Eur Rev Med Pharmacol Sci* **15**(12): 1461–72.
Nagalla S & Ballas SK (2018) Drugs for preventing red blood cell dehydration in people with sickle cell disease. *Cochrane Database Syst Rev* **10**: CD003426.
Nagel K, Willan AR, Lappan J et al (2008) Pediatric oncology sedation trial (POST): A double-blind randomized study. *Pediatr Blood Cancer* **51**(5): 634–38.
Nager AL, Kobylecka M, Pham PK et al (2015) Effects of acupuncture on pain and inflammation in pediatric emergency department patients with acute appendicitis: a pilot study. *J Altern Complement Med* **21**(5): 269-72.
Nahum Y, Tenenbaum A, Isaiah W et al (2007) Effect of eutectic mixture of local anesthetics (EMLA) for pain relief during suprapubic aspiration in young infants: a randomized, controlled trial. *Clin J Pain* **23**(9): 756–59.
Naja Z, Al-Tannir MA, Faysal W et al (2011) A comparison of pudendal block vs dorsal penile nerve block for circumcision in children: a randomised controlled trial. *Anaesthesia* **66**(9): 802–07.
Naja Z, Kanawati S, Al Khatib R et al (2017) The effect of IV dexamethasone versus local anesthetic infiltration technique in postoperative nausea and vomiting after tonsillectomy in children: A randomized double-blind clinical trial. *Int J Pediatr Otorhinolaryngol* **92**: 21-26.
Naja ZM, Ziade FM, Kamel R et al (2013) The effectiveness of pudendal nerve block versus caudal block anesthesia for hypospadias in children. *Anesth Analg* **117**(6): 1401–07.
Nakagawa S, Okamoto Y, Kodama Y et al (2018) Thiamylal Plus Pentazocine Shows Similar Efficacy as Ketamine Plus Midazolam for Painful Procedures in Children With Leukemia. *J Pediatr Hematol Oncol* **40**(4): e263-e65.
Nandi R & Fitzgerald M (2005) Opioid analgesia in the newborn. *Eur J Pain* **9**(2): 105–08.
Narasimhan P, Kashyap L, Mohan VK et al (2019) Comparison of caudal epidural block with paravertebral block for renal surgeries in pediatric patients: A prospective randomised, blinded clinical trial. *J Clin Anesth* **52**: 105-10.
Nasr DA & Abdelhamid HM (2013) The efficacy of caudal dexmedetomidine on stress response and postoperative pain in pediatric cardiac surgery. *Ann Card Anaesth* **16**(2): 109–14.
Nath S, Koziarz A, Badhiwala JH et al (2018) Atraumatic versus conventional lumbar puncture needles: a systematic review and meta-analysis. *Lancet* **391**(10126): 1197-204.
National Center for Health Statistics (2019) *The state of obesity - National Obesity Monitor.* https://www.stateofobesity.org/monitor/ Accessed 3 October 2019
Naulaers G, Delanghe G, Allegaert K et al (2005) Ibuprofen and cerebral oxygenation and circulation. *Arch Dis Child Fetal Neonatal Ed* **90**(1): F75–76.
NCD-RisC (2017) Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* **390**(10113): 2627-42.
Neal JM, Barrington MJ, Fettiplace MR et al (2018) The Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity: Executive Summary 2017. *Reg Anesth Pain Med* **43**(2): 113-23.
Nejati A, Golshani K, Moradi Lakeh M et al (2010) Ketamine improves nasogastric tube insertion. *Emerg Med J* **27**(8): 582–85.
Nelson GR, Bale JF & Kerr LM (2017) Outcome and Cost of Inpatient Hospitalization for Intravenous Dihydroergotamine Treatment of Refractory Pediatric Headache. *Pediatr Neurol* **66**: 76-81.
Nelson KL, Yaster M, Kost-Byerly S et al (2010) A national survey of American Pediatric Anesthesiologists: patient-controlled analgesia and other intravenous opioid therapies in pediatric acute pain management. *Anesth Analg* **110**(3): 754–60.
Nelson L & Schwaner R (2009) Transdermal fentanyl: pharmacology and toxicology. *J Med Toxicol* **5**(4): 230–41.

Nelson S, Conroy C & Logan D (2019) The biopsychosocial model of pain in the context of pediatric burn injuries. *Eur J Pain* **23**(3): 421-34.
Nemergut ME, Yaster M & Colby CE (2013) Sedation and analgesia to facilitate mechanical ventilation. *Clin Perinatol* **40**(3): 539–58.
Nemeth BA, Montero RJ, Halanski MA et al (2015) Epidural Baclofen for the Management of Postoperative Pain in Children With Cerebral Palsy. *J Pediatr Orthop* **35**(6): 571-5.
Neri E, Maestro A, Minen F et al (2013) Sublingual ketorolac versus sublingual tramadol for moderate to severe post-traumatic bone pain in children: a double-blind, randomised, controlled trial. *Arch Dis Child* **98**(9): 721-4.
Neubrand TL, Roswell K, Deakyne S et al (2014) Fascia iliaca compartment nerve block versus systemic pain control for acute femur fractures in the pediatric emergency department. *Pediatr Emerg Care* **30**(7): 469-73.
Neunhoeffer F, Hanser A, Esslinger M et al (2017) Ketamine Infusion as a Counter Measure for Opioid Tolerance in Mechanically Ventilated Children: A Pilot Study. *Paediatr Drugs* **19**(3): 259-65.
Nevitt SJ, Jones AP & Howard J (2017) Hydroxyurea (hydroxycarbamide) for sickle cell disease. *Cochrane Database Syst Rev* **4**: Cd002202.
Newlove-Delgado TV, Martin AE, Abbott RA et al (2017) Dietary interventions for recurrent abdominal pain in childhood. *Cochrane Database Syst Rev* **3**: Cd010972.
NICE (2012) *Sickle cell disease: managing acute painful episodes in hospital.* http://guidance.nice.org.uk/CG143/Guidance/pdf/English Accessed 7 October 2019
NICE (2015) *Headaches in over 12s: diagnosis and management. Clinical guideline [CG150].* https://www.nice.org.uk/guidance/cg150/chapter/Recommendations Accessed 29 September 2019
Nielsen BN, Aagaard G, Henneberg SW et al (2012) Topical morphine for oral mucositis in children: dose finding and absorption. *J Pain Symptom Manage* **44**(1): 117–23.
Nielsen BN, Friis SM, Romsing J et al (2014) Intranasal sufentanil/ketamine analgesia in children. *Paediatr Anaesth* **24**(2): 170–80.
Niesters M, Overdyk F, Smith T et al (2013) Opioid-induced respiratory depression in paediatrics: a review of case reports. *Br J Anaesth* **110**(2): 175–82.
Nieuwendijk SMP, de Korte IJ, Pursad MM et al (2018) Post burn pruritus in pediatric burn patients. *Burns* **44**(5): 1151-58.
Niiyama Y, Yotsuyanagi T & Yamakage M (2016) Continuous wound infiltration with 0.2% ropivacaine versus a single intercostal nerve block with 0.75% ropivacaine for postoperative pain management after reconstructive surgery for microtia. *J Plast Reconstr Aesthet Surg* **69**(10): 1445-9.
Nilsson S, Brunsson I, Askljung B et al (2017) A rectally administered combination of midazolam and ketamine was easy, effective and feasible for procedural pain in children with cerebral palsy. *Acta Paediatr* **106**(3): 458-62.
Nilsson S, Forsner M, Finnstrom B et al (2015) Relaxation and guided imagery do not reduce stress, pain and unpleasantness for 11- to 12-year-old girls during vaccinations. *Acta Paediatr* **104**(7): 724-9.
Nishina K & Mikawa K (2002) Clonidine in paediatric anaesthesia. *Curr Opin Anaesthesiol* **15**(3): 309–16.
Nnaji CT, Onajin-Obembe B & Ebirim L (2017) The analgesic effects of rectal diclofenac versus rectal paracetamol following caudal-bupivacaine for pediatric day-case inguinal herniotomies: a randomized controlled prospective trial. *J Pediatr Surg* **52**(9): 1384-88.
Nobrega R, Sheehy KA, Lippold C et al (2018) Patient characteristics affect the response to ketamine and opioids during the treatment of vaso-occlusive episode-related pain in sickle cell disease. *Pediatr Res* **83**(2): 445-54.
Noel M, Chambers CT, McGrath PJ et al (2012) The influence of children's pain memories on subsequent pain experience. *Pain* **153**(8): 1563–72.
Noel M, McMurtry CM, Pavlova M et al (2018) Brief Clinical Report: A Systematic Review and Meta-analysis of Pain Memory-reframing Interventions for Children's Needle Procedures. *Pain Pract* **18**(1): 123-29.
Norambuena C, Yanez J, Flores V et al (2013) Oral ketamine and midazolam for pediatric burn patients: a prospective, randomized, double-blind study. *J Pediatr Surg* **48**(3): 629–34.
Nour C, Ratsiu J, Singh N et al (2014) Analgesic effectiveness of acetaminophen for primary cleft palate repair in young children: a randomized placebo controlled trial. *Paediatr Anaesth* **24**(6): 574–81.
Noyes M & Irving H (2001) The use of transdermal fentanyl in pediatric oncology palliative care. *Am J Hosp Palliat Care* **18**(6): 411-6.
NPS Medicinewise (2019a) *Consumer medicine information: Chemmart Tramadol (Tramadol hydrochloride).* https://www.nps.org.au/medicine-finder/chemmart-tramadol-capsules Accessed 20 January 2020
NPS Medicinewise (2019b) *Managing Pain and Opioid Medicines.* http://www.choosingwisely.org.au/getmedia/08c9c58b-2ed0-4482-9dd4-43fa976868bd/CW-Patient-resource-Opioids_1.pdf.aspx Accessed 8 January 2020
Numanoglu KV, Ayoglu H & Er DT (2014) Efficacy of tramadol as a preincisional infiltration anesthetic in children undergoing inguinal hernia repair: a prospective randomized study. *Ther Clin Risk Manag* **10**: 753–58.
Nunns M, Mayhew D, Ford T et al (2018) Effectiveness of nonpharmacological interventions to reduce procedural anxiety in children and adolescents undergoing treatment for cancer: A systematic review and meta-analysis. *Psychooncology* **27**(8): 1889-99.

NYSORA (2020) *Ultrasound-Guided Transversus Abdominis Plane and Quadratus Lumborum Blocks.* https://www.nysora.com/regional-anesthesia-for-specific-surgical-procedures/abdomen/ultrasound-guided-transversus-abdominis-plane-quadratus-lumborum-blocks/ Accessed 28 February 2020

NZ MoH (2018) *Annual Data Explorer 2017/18: New Zealand Health Survey [Data File].* https://www.health.govt.nz/news-media/news-items/publication-new-zealand-health-surveys-2017-18-annual-results Accessed 3 February 2020

O'Brien DE, Alter BJ, Satomoto M et al (2015) ERK2 Alone Drives Inflammatory Pain But Cooperates with ERK1 in Sensory Neuron Survival. *J Neurosci* **35**(25): 9491-507.

O'Conner-Von S (2008) Preparation of adolescents for outpatient surgery: using an Internet program. *AORN J* **87**(2): 374–98.

O'Donnell DP, Schafer LC, Stevens AC et al (2013) Effect of introducing the mucosal atomization device for fentanyl use in out-of-hospital pediatric trauma patients. *Prehosp Disaster Med* **28**(5): 520–22.

O'Flaherty LA, van Dijk M, Albertyn R et al (2012) Aromatherapy massage seems to enhance relaxation in children with burns: an observational pilot study. *Burns* **38**(6): 840–45.

O'Sullivan MJ, Mislovic B & Alexander E (2011) Dorsal penile nerve block for male pediatric circumcision--randomized comparison of ultrasound-guided vs anatomical landmark technique. *Paediatr Anaesth* **21**(12): 1214–18.

Oates A, Benedict KA, Sun K et al (2017) Laser acupuncture reduces pain in pediatric kidney biopsies: a randomized controlled trial. *Pain* **158**(1): 103-09.

Obayah GM, Refaie A, Aboushanab O et al (2010) Addition of dexmedetomidine to bupivacaine for greater palatine nerve block prolongs postoperative analgesia after cleft palate repair. *Eur J Anaesthesiol* **27**(3): 280-4.

Ocay DD, Otis A, Teles AR et al (2018) Safety of Patient-Controlled Analgesia After Surgery in Children And Adolescents: Concerns And Potential Solutions. *Front Pediatr* **6**: 336.

Ochi JW (2015) Korean hand therapy for tonsillectomy pain in children. *Int J Pediatr Otorhinolaryngol* **79**(8): 1263-7.

Ohlsson A & Shah PS (2016) Paracetamol (acetaminophen) for prevention or treatment of pain in newborns. *Cochrane Database Syst Rev* **10**: Cd011219.

Ohlsson A & Shah PS (2018a) Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. *Cochrane Database Syst Rev* **4**: CD010061.

Ohlsson A, Walia R & Shah SS (2018b) Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database Syst Rev* **9**: CD003481.

Oksuz G, Bilal B, Gurkan Y et al (2017) Quadratus Lumborum Block Versus Transversus Abdominis Plane Block in Children Undergoing Low Abdominal Surgery: A Randomized Controlled Trial. *Reg Anesth Pain Med* **42**(5): 674-79.

Olischar M, Palmer GM, Orsini F et al (2014) The addition of tramadol to the standard of i.v. acetaminophen and morphine infusion for postoperative analgesia in neonates offers no clinical benefit: A randomized placebo-controlled trial. *Paediatr Anaesth* **24**(11): 1149–57.

Olofsen E, Noppers I, Niesters M et al (2012) Estimation of the contribution of norketamine to ketamine-induced acute pain relief and neurocognitive impairment in healthy volunteers. *Anesthesiology* **117**(2): 353–64.

Olsson E, Anderzen-Carlsson A, Atladottir SM et al (2018) Cultural adaptation and harmonization of four Nordic translations of the revised Premature Infant Pain Profile (PIPP-R). *BMC Pediatr* **18**(1): 349.

Omar AM, Mansour MA & Kamal AS (2011) Psoas compartment block for acute postoperative pain management after hip surgery in pediatrics: a comparative study with caudal analgesia. *Reg Anesth Pain Med* **36**(2): 121–24.

Omar MT, Hegazy FA & Mokashi SP (2012) Influences of purposeful activity versus rote exercise on improving pain and hand function in pediatric burn. *Burns* **38**(2): 261–68.

Ong ME, Chan YH, Teo J et al (2008) Hair apposition technique for scalp laceration repair: a randomized controlled trial comparing physicians and nurses (HAT 2 study). *Am J Emerg Med* **26**(4): 433-8.

Ong TG, Gordon M, Banks SS et al (2019) Probiotics to prevent infantile colic. *Cochrane Database Syst Rev* **3**: Cd012473.

Onody P, Gil P & Hennequin M (2006) Safety of inhalation of a 50% nitrous oxide/oxygen premix: a prospective survey of 35 828 administrations. *Drug Saf* **29**(7): 633–40.

Orliaguet G, Hamza J, Couloigner V et al (2015) A case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol. *Pediatrics* **135**(3): e753–55.

Orr SL (2018a) The Evidence for the Role of Nutraceuticals in the Management of Pediatric Migraine: a Review. *Curr Pain Headache Rep* **22**(5): 37.

Orr SL, Kabbouche MA, Horn PS et al (2018b) Predictors of First-Line Treatment Success in Children and Adolescents Visiting an Infusion Center for Acute Migraine. *Headache* **58**(8): 1194-202.

Orr SL, Kabbouche MA, O'Brien HL et al (2018c) Paediatric migraine: evidence-based management and future directions. *Nat Rev Neurol* **14**(9): 515-27.

Ortega HW, Vander Velden H, Lin CW et al (2013a) Does age affect analgesia provision at discharge among children with long bone fractures requiring emergency care? *J Emerg Med* **45**(5): 649–57.

Ortega HW, Vander Velden H, Lin CW et al (2013b) Race, ethnicity, and analgesia provision at discharge among children with long-bone fractures requiring emergency care. *Pediatr Emerg Care* **29**(4): 492–7.

Ortega HW, Velden HV, Lin CW et al (2012) Ethnicity and reported pain scores among children with long-bone fractures requiring emergency care. *Pediatr Emerg Care* **28**(11): 1146-9.

Ortega HW, Velden HV, Truong W et al (2018) Socioeconomic Status and Analgesia Provision at Discharge Among Children With Long-Bone Fractures Requiring Emergency Care. *Pediatr Emerg Care*.
Oschman A, McCabe T & Kuhn RJ (2011) Dexmedetomidine for opioid and benzodiazepine withdrawal in pediatric patients. *Am J Health Syst Pharm* **68**(13): 1233–38.
Oskoui M, Pringsheim T, Holler-Managan Y et al (2019) Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Headache* **59**(8): 1158-73.
Othman AH, Mohamad MF & Sayed HA (2016) Transdermal Fentanyl for Cancer Pain Management in Opioid-Naive Pediatric Cancer Patients. *Pain Med*.
Oudot C, Laplanche A, Orbach D et al (2011) PCA analgesia for children with chemotherapy-related mucositis: a double-blind randomized comparison of morphine and pethidine. *Bull Cancer* **98**(2): E11–18.
Ousley R, Burgoyne LL, Crowley NR et al (2016) An audit of patient-controlled analgesia after appendicectomy in children. *Paediatr Anaesth* **26**(10): 1002-9.
Owens VF, Palmieri TL, Comroe CM et al (2006) Ketamine: a safe and effective agent for painful procedures in the pediatric burn patient. *J Burn Care Res* **27**(2): 211–16; discussion 17.
Ozalevli M, Unlugenc H, Tuncer U et al (2005) Comparison of morphine and tramadol by patient-controlled analgesia for postoperative analgesia after tonsillectomy in children. *Paediatr Anaesth* **15**(11): 979-84.
Ozawa M, Kanda K, Hirata M et al (2011) Influence of repeated painful procedures on prefrontal cortical pain responses in newborns. *Acta Paediatr* **100**(2): 198-203.
Ozer Z, Gorur K, Altunkan AA et al (2003) Efficacy of tramadol versus meperidine for pain relief and safe recovery after adenotonsillectomy. *Eur J Anaesthesiol* **20**(11): 920–24.
Ozkan D, Gonen E, Akkaya T et al (2017) Popliteal block for lower limb surgery in children with cerebral palsy: effect on sevoflurane consumption and postoperative pain (a randomized, double-blinded, controlled trial). *J Anesth* **31**(3): 358-64.
Padhye NS, Williams AL, Khattak AZ et al (2009) Heart rate variability in response to pain stimulus in VLBW infants followed longitudinally during NICU stay. *Dev Psychobiol* **51**(8): 638–49.
Page EA & Taylor KL (2017) Paravertebral block in paediatric abdominal surgery-a systematic review and meta-analysis of randomized trials. *Br J Anaesth* **118**(2): 159-66.
Palermo TM, Dudeney J, Santanelli JP et al (2018) Feasibility and Acceptability of Internet-delivered Cognitive Behavioral Therapy for Chronic Pain in Adolescents With Sickle Cell Disease and Their Parents. *J Pediatr Hematol Oncol* **40**(2): 122-27.
Palmer GM (2005) A teenager with severe asthma exacerbation following ibuprofen. *Anaesth Intensive Care* **33**(2): 261–65.
Palmer GM, Anderson BJ, Linscott DK et al (2018) Tramadol, breast feeding and safety in the newborn. *Arch Dis Child* **103**(12): 1110-13.
Palmer GM, Atkins M, Anderson BJ et al (2008) I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth* **101**(4): 523–30.
Palmer GM & Babl FE (2014) Pain management in major paediatric trauma and burns. In: *Oxford Textbook of Paediatric Pain* edn. McGrath PJ, Stevens BJ, Walker SE and Zempsky WT (eds). Oxford, Oxford University Press.
Palmer GM, Chen SP, Smith KR et al (2007) Introduction and audit of intravenous paracetamol at a tertiary paediatric teaching hospital. *Anaesth Intensive Care* **35**(5): 702–06.
Palmer GM, Luk VH, Smith KR et al (2011) Audit of initial use of the ultrasound-guided transversus abdominis plane block in children. *Anaesth Intensive Care* **39**(2): 279–86.
Palmer GM, Thalayasingam P, McNally CM et al (2012) Audit of extrapleural local anaesthetic infusion in neonates following repair of tracheo-oesophageal fistulae and oesophageal atresia via thoracotomy. *Anaesth Intensive Care* **40**(1): 172–80.
Pandey M, Datta V & Rehan HS (2013) Role of sucrose in reducing painful response to orogastric tube insertion in preterm neonates. *Indian J Pediatr* **80**(6): 476-82.
Pandita A, Panghal A, Gupta G et al (2018) Is kangaroo mother care effective in alleviating vaccination associated pain in early infantile period? A RCT. *Early Hum Dev* **127**: 69-73.
Papacci P, De Francisci G, Iacobucci T et al (2004) Use of intravenous ketorolac in the neonate and premature babies. *Paediatr Anaesth* **14**(6): 487-92.
Pappas AL, Fluder EM, Creech S et al (2003) Postoperative analgesia in children undergoing myringotomy and placement equalization tubes in ambulatory surgery. *Anesth Analg* **96**(6): 1621–24.
Paquin H, E DT, Robitaille N et al (2019) Oral morphine protocol evaluation for the treatment of vaso-occlusive crisis in paediatric sickle cell patients. *Paediatr Child Health* **24**(1): e45-e50.
Parameswari A, Krishna B, Manickam A et al (2017) Analgesic efficacy of dexamethasone as an adjuvant to caudal bupivacaine for infraumbilical surgeries in children: A prospective, randomized study. *J Anaesthesiol Clin Pharmacol* **33**(4): 509-13.

Pardesi O & Fuzaylov G (2017) Pain Management in Pediatric Burn Patients: Review of Recent Literature and Future Directions. *J Burn Care Res* **38**(6): 335-47.
Pardey Bracho GF, Pereira de Souza Neto E, Grousson S et al (2014) Opioid consumption after levobupivacaine scalp nerve block for craniosynostosis surgery. *Acta Anaesthesiol Taiwan* **52**(2): 64–69.
Pardey G, Grousson S, de Souza EP et al (2008) Levobupivacaine scalp nerve block in children. *Paediatr Anaesth* **18**(3): 271–72.
Parekh S, Gardener C, Ashley PF et al (2014) Intraoperative local anaesthesia for reduction of postoperative pain following general anaesthesia for dental treatment in children and adolescents. *Cochrane Database Syst Rev*(12): CD009742.
Park HS, Kim WJ, Kim HG et al (2017a) Scrambler therapy for the treatment of neuropathic pain related to leukemia in a pediatric patient: A case report. *Medicine (Baltimore)* **96**(45): e8629.
Park SJ, Shin S, Kim SH et al (2017b) Comparison of Dexmedetomidine and Fentanyl as an Adjuvant to Ropivacaine for Postoperative Epidural Analgesia in Pediatric Orthopedic Surgery. *Yonsei Med J* **58**(3): 650-57.
Parlak Gurol A, Polat S & Akcay MN (2010) Itching, pain, and anxiety levels are reduced with massage therapy in burned adolescents. *J Burn Care Res* **31**(3): 429–32.
Parry I, Painting L, Bagley A et al (2015) A Pilot Prospective Randomized Control Trial Comparing Exercises Using Videogame Therapy to Standard Physical Therapy: 6 Months Follow-Up. *J Burn Care Res* **36**(5): 534-44.
Pascolo P, Peri F, Montico M et al (2018) Needle-related pain and distress management during needle-related procedures in children with and without intellectual disability. *Eur J Pediatr* **177**(12): 1753-60.
Patel Z, Palte HD & Tutiven J (2012) Postoperative analgesia and infant vitreoretinal surgery. *Paediatr Anaesth* **22**(12): 1225-6.
Paul IM, Reynolds KM & Green JL (2018) Adverse events associated with opioid-containing cough and cold medications in children. *Clin Toxicol (Phila)* **56**(11): 1162-64.
Paut O, Camboulives J, Viard L et al (2000) Pharmacokinetics of transdermal fentanyl in the peri-operative period in young children. *Anaesthesia* **55**(12): 1202-7.
Paut O, Sallabery M, Schreiber-Deturmeny E et al (2001) Continuous fascia iliaca compartment block in children: a prospective evaluation of plasma bupivacaine concentrations, pain scores, and side effects. *Anesth Analg* **92**(5): 1159–63.
Payne J, Aban I, Hilliard LM et al (2018) Impact of early analgesia on hospitalization outcomes for sickle cell pain crisis. *Pediatr Blood Cancer* **65**(12): e27420.
Pedersen LK, Rahbek O, Nikolajsen L et al (2015) The revised FLACC score: Reliability and validation for pain assessment in children with cerebral palsy. *Scand J Pain* **9**(1): 57-61.
Pedersen RS, Bayat A, Steen NP et al (2013) Nitrous oxide provides safe and effective analgesia for minor paediatric procedures - a systematic review. *Dan Med J* **60**(6): A4627.
Pedro H, Barros L & Pereira AI (2016) Pediatric Immunization Distress: A Cluster Analyses of Children's, Parents', and Nurses' Behaviors During the Anticipatory Phase. *Clin J Pain* **32**(5): 394-403.
Pendeville PE, Von Montigny S, Dort JP et al (2000) Double-blind randomized study of tramadol vs. paracetamol in analgesia after day-case tonsillectomy in children. *Eur J Anaesthesiol* **17**(9): 576–82.
Perdreau E, Iriart X, Mouton JB et al (2015) Cardiogenic shock due to acute tramadol intoxication. *Cardiovasc Toxicol* **15**(1): 100–03.
Perello M, Artes D, Pascuets C et al (2017) Prolonged Perioperative Low-Dose Ketamine Does Not Improve Short and Long-term Outcomes After Pediatric Idiopathic Scoliosis Surgery. *Spine (Phila Pa 1976)* **42**(5): E304-e12.
Perry R, Leach V, Penfold C et al (2019) An overview of systematic reviews of complementary and alternative therapies for infantile colic. *Syst Rev* **8**(1): 271.
Pestieau SR, Finkel JC, Junqueira MM et al (2014) Prolonged perioperative infusion of low-dose ketamine does not alter opioid use after pediatric scoliosis surgery. *Paediatr Anaesth* **24**(6): 582–90.
Peters JW, Bandell Hoekstra IE, Huijer Abu-Saad H et al (1999) Patient controlled analgesia in children and adolescents: a randomized controlled trial. *Paediatr Anaesth* **9**(3): 235–41.
Peters JW, Koot HM, de Boer JB et al (2003) Major surgery within the first 3 months of life and subsequent biobehavioral pain responses to immunization at later age: a case comparison study. *Pediatrics* **111**(1): 129–35.
Peters JW, Schouw R, Anand KJ et al (2005) Does neonatal surgery lead to increased pain sensitivity in later childhood? *Pain* **114**(3): 444–54.
Petersen TG, Liew Z, Andersen AN et al (2018) Use of paracetamol, ibuprofen or aspirin in pregnancy and risk of cerebral palsy in the child. *Int J Epidemiol* **47**(1): 121-30.
Petter M, Chambers CT & MacLaren Chorney J (2013) The effects of mindfulness-based attention on cold pressor pain in children. *Pain Res Manag* **18**(1): 39–45.
Petter M, McGrath PJ, Chambers CT et al (2014) The effects of mindful attention and state mindfulness on acute experimental pain among adolescents. *J Pediatr Psychol* **39**(5): 521-31.
Phan H & Nahata MC (2008) Clinical uses of dexmedetomidine in pediatric patients. *Paediatr Drugs* **10**(1): 49–69.
Pharmac (2016) *Decision to delist tramadol hydrochloride oral drops 100 mg per ml.* https://www.pharmac.govt.nz/news/notification-2016-12-13-tramadol-hydrochloride/ Accessed 20 January 2020

Phelps HM, Robinson JR, Chen H et al (2019) Enhancing Recovery After Kasai Portoenterostomy With Epidural Analgesia. *J Surg Res* **243**: 354-62.
Phillips DA, Watson AR & MacKinlay D (1998) Distress and the micturating cystourethrogram: does preparation help? *Acta Paediatr* **87**(2): 175–79.
Pickard A, Davies P, Birnie K et al (2014) Systematic review and meta-analysis of the effect of intraoperative alpha(2)-adrenergic agonists on postoperative behaviour in children. *Br J Anaesth* **112**(6): 982–90.
Pickering AE, Bridge HS, Nolan J et al (2002) Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children. *Br J Anaesth* **88**(1): 72–77.
Pilgrim JL, Jenkins EL, Baber Y et al (2017) Fatal acute poisonings in Australian children (2003-13). *Addiction* **112**(4): 627-39.
Pillai Riddell R, Flora DB, Stevens SA et al (2013) Variability in infant acute pain responding meaningfully obscured by averaging pain responses. *Pain* **154**(5): 714-21.
Pillai Riddell R, Taddio A, McMurtry CM et al (2015a) Psychological Interventions for Vaccine Injections in Young Children 0 to 3 Years: Systematic Review of Randomized Controlled Trials and Quasi-Randomized Controlled Trials. *Clin J Pain* **31**(10 Suppl): S64-71.
Pillai Riddell R, Taddio A, McMurtry CM et al (2015b) Process Interventions for Vaccine Injections: Systematic Review of Randomized Controlled Trials and Quasi-Randomized Controlled Trials. *Clin J Pain* **31**(10 Suppl): S99-108.
Pillai Riddell RR, Racine NM, Gennis HG et al (2015c) Non-pharmacological management of infant and young child procedural pain. *Cochrane Database Syst Rev*(12): Cd006275.
Pinkerton R & Hardy JR (2017) Opioid addiction and misuse in adult and adolescent patients with cancer. *Intern Med J* **47**(6): 632-36.
Piotrowski A, Gach M & Wiszniewski D (2015) The use of dexmedetomidine in paediatric intensive care. *Anaesthesiol Intensive Ther* **47**(3): 263-4.
Plante J, Turgeon AF, Zarychanski R et al (2012) Effect of systemic steroids on post-tonsillectomy bleeding and reinterventions: systematic review and meta-analysis of randomised controlled trials. *BMJ* **345**: e5389.
Playfor S, Jenkins I, Boyles C et al (2006) Consensus guidelines on sedation and analgesia in critically ill children. *Intensive Care Med* **32**(8): 1125–36.
Polaner DM, Taenzer AH, Walker BJ et al (2012) Pediatric Regional Anesthesia Network (PRAN): a multi-institutional study of the use and incidence of complications of pediatric regional anesthesia. *Anesth Analg* **115**(6): 1353–64.
Polat F, Tuncel A, Balci M et al (2013) Comparison of local anesthetic effects of lidocaine versus tramadol and effect of child anxiety on pain level in circumcision procedure. *J Pediatr Urol* **9**(5): 670–74.
Ponde VC (2008) Continuous infraclavicular brachial plexus block: a modified technique to better secure catheter position in infants and children. *Anesth Analg* **106**(1): 94–96.
Ponde VC, Bedekar VV, Chavan D et al (2018) Role of ultrasound guided epidural anesthesia for lower limb surgery in children with previously repaired meningomyelocele. *Paediatr Anaesth* **28**(3): 287-90.
Ponde VC, Bedekar VV, Desai AP et al (2017) Does ultrasound guidance add accuracy to continuous caudal-epidural catheter placements in neonates and infants? *Paediatr Anaesth* **27**(10): 1010-14.
Poonai N, Alawi K, Rieder M et al (2012) A comparison of amethocaine and liposomal lidocaine cream as a pain reliever before venipuncture in children: a randomized control trial. *Pediatr Emerg Care* **28**(2): 104–08.
Poonai N, Bhullar G, Lin K et al (2014) Oral administration of morphine versus ibuprofen to manage postfracture pain in children: a randomized trial. *CMAJ*.
Poonai N, Datoo N, Ali S et al (2017) Oral morphine versus ibuprofen administered at home for postoperative orthopedic pain in children: a randomized controlled trial. *CMAJ* **189**(40): E1252-E58.
Porter RN, Chafe RE, Newhook LA et al (2015) Multiple interventions improve analgesic treatment of supracondylar humerus fractures in a pediatric emergency department. *Pain Res Manag* **20**(4): 173-8.
Potti LR, Bevinaguddaiah Y, Archana S et al (2017) Caudal Levobupivacaine Supplemented with Caudal or Intravenous Clonidine in Children Undergoing Infraumbilical Surgery: A Randomized, Prospective Double-blind Study. *Anesth Essays Res* **11**(1): 211-15.
Potts AL, Anderson BJ, Warman GR et al (2009) Dexmedetomidine pharmacokinetics in pediatric intensive care--a pooled analysis. *Paediatr Anaesth* **19**(11): 1119-29.
Potts AL, Larsson P, Eksborg S et al (2007) Clonidine disposition in children; a population analysis. *Paediatr Anaesth* **17**(10): 924-33.
Pour PS, Ameri GF, Kazemi M et al (2017) Comparison of Effects of Local Anesthesia and Two-Point Acupressure on the Severity of Venipuncture Pain Among Hospitalized 6-12-Year-Old Children. *J Acupunct Meridian Stud* **10**(3): 187-92.
Pouy S, Etebarian A, Azizi-Qadikolaee A et al (2019) The effect of acupuncture on postoperative pain, nausea and vomiting after pediatric tonsillectomy: a systematic review. *Int J Adolesc Med Health*.
Prapaitrakool S, Hollmann MW, Wartenberg HC et al (2012) Use of buprenorphine in children with chronic pseudoobstruction syndrome: case series and review of literature. *Clin J Pain* **28**(8): 722–25.

Praveen P, Remadevi R & Pratheeba N (2017) Caudal Epidural Analgesia in Pediatric Patients: Comparison of 0.25% Levobupivacaine and 0.25% Ropivacaine in Terms of Motor Blockade and Postoperative Analgesia. *Anesthesia, essays and researches* **11**(1): 223-27.

Presley JD & Chyka PA (2013) Intravenous lipid emulsion to reverse acute drug toxicity in pediatric patients. *Ann Pharmacother* **47**(5): 735-43.

Priestley S, Kelly AM, Chow L et al (2003) Application of topical local anesthetic at triage reduces treatment time for children with lacerations: a randomized controlled trial. *Ann Emerg Med* **42**(1): 34–40.

Prins SA, Van Dijk M, Van Leeuwen P et al (2008) Pharmacokinetics and analgesic effects of intravenous propacetamol vs rectal paracetamol in children after major craniofacial surgery. *Paediatr Anaesth* **18**(7): 582–92.

Provenzi L, Fumagalli M, Sirgiovanni I et al (2015) Pain-related stress during the Neonatal Intensive Care Unit stay and SLC6A4 methylation in very preterm infants. *Front Behav Neurosci* **9**: 99.

Provenzi L, Guida E & Montirosso R (2018) Preterm behavioral epigenetics: A systematic review. *Neurosci Biobehav Rev* **84**: 262-71.

Prows CA, Zhang X, Huth MM et al (2014) Codeine-related adverse drug reactions in children following tonsillectomy: a prospective study. *Laryngoscope* **124**(5): 1242–50.

Puri L, Morgan KJ & Anghelescu DL (2019) Ketamine and lidocaine infusions decrease opioid consumption during vaso-occlusive crisis in adolescents with sickle cell disease. *Curr Opin Support Palliat Care* **13**(4): 402-07.

Putnam EM, Koppera P, Malviya S et al (2015) Pain outcomes in children who received intrathecal vs intravenous opioids for pain control following major urologic surgery: a retrospective review. *Paediatr Anaesth* **25**(12): 1280-6.

Py AG, Zein Addeen G, Perrier Y et al (2009) Evaluation of the effectiveness of botulinum toxin injections in the lower limb muscles of children with cerebral palsy. Preliminary prospective study of the advantages of ultrasound guidance. *Ann Phys Rehabil Med* **52**(3): 215–23.

Pywell A & Xyrichis A (2015) Does topical Amethocaine cream increase first-time successful cannulation in children compared with a eutectic mixture of local anaesthetics (EMLA) cream? A systematic review and meta-analysis of randomised controlled trials. *Emerg Med J* **32**(9): 733-7.

Qi J, Du B, Gurnaney H et al (2014) A prospective randomized observer-blinded study to assess postoperative analgesia provided by an ultrasound-guided bilateral thoracic paravertebral block for children undergoing the Nuss procedure. *Reg Anesth Pain Med* **39**(3): 208–13.

Qian X, Jin X, Chen L et al (2015) A new ultrasound-guided dorsal penile nerve block technique for circumcision in children. *Anaesth Intensive Care* **43**(5): 662-3.

Quigley C (2002) Hydromorphone for acute and chronic pain. *Cochrane Database Syst Rev* **1**: CD003447.

Quinn BL, Seibold E & Hayman L (2015) Pain Assessment in Children With Special Needs: A Review of the Literature. *Exceptional Children* **82**(1): 44-57.

Quinn PD, Hur K, Chang Z et al (2018) Association of Mental Health Conditions and Treatments With Long-term Opioid Analgesic Receipt Among Adolescents. *JAMA Pediatr* **172**(5): 423-30.

Quiralte J, Blanco C, Delgado J et al (2007) Challenge-based clinical patterns of 223 Spanish patients with nonsteroidal anti-inflammatory-drug-induced-reactions. *J Investig Allergol Clin Immunol* **17**(3): 182–88.

Qureshi A, Kaya B, Pancham S et al (2018) Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. *Br J Haematol* **181**(4): 460-75.

Rabbitts JA, Aaron RV, Zempsky WT et al (2017) Validation of the Youth Acute Pain Functional Ability Questionnaire in Children and Adolescents Undergoing Inpatient Surgery. *J Pain* **18**(10): 1209-15.

Racoosin JA, Roberson DW, Pacanowski MA et al (2013) New evidence about an old drug--risk with codeine after adenotonsillectomy. *N Engl J Med* **368**(23): 2155–57.

RACP (2005) *Guideline Statement: Management of Procedure-related Pain in Neonates*. Sydney, Royal Australasian College of Physicians, Paediatrics & Child Health Division.

Radman M, Babic A, Runjic E et al (2019) Revisiting established medicines: An overview of systematic reviews about ibuprofen and paracetamol for treating pain in children. *Eur J Pain* **23**(6): 1071-82.

Ragg PG, Cahoon G, Yeo A et al (2017) A clinical audit to assess the efficacy of the Coolsense(R) Pain Numbing Applicator for intravenous cannulation in children. *Anaesth Intensive Care* **45**(2): 251-55.

Raghavan M & Montgomerie J (2008) Anaesthetic management of gastroschisis - a review of our practice over the past 5 years. *Paediatr Anaesth* **18**(8): 731–35.

Rahman A, Curtis S, DeBruyne B et al (2015) Emergency medical services provider comfort with prehospital analgesia administration to children. *Prehosp Disaster Med* **30**(1): 66-71.

Rajalu M, Muller UC, Caley A et al (2009) Plasticity of synaptic inhibition in mouse spinal cord lamina II neurons during early postnatal development and after inactivation of the glycine receptor alpha3 subunit gene. *Eur J Neurosci* **30**(12): 2284–92.

Rajanayagam J, Bishop JR, Lewindon PJ et al (2015) Paracetamol-associated acute liver failure in Australian and New Zealand children: high rate of medication errors. *Arch Dis Child* **100**(1): 77-80.

Ramachandran R, Rewari V, Chandralekha C et al (2014) Sub-Tenon block does not provide superior postoperative analgesia vs intravenous fentanyl in pediatric squint surgery. *Eur J Ophthalmol* **24**(5): 643–49.

Rambod M, Forsyth K, Sharif F et al (2016) Assessment and management of pain in children and adolescents with bleeding disorders: a cross-sectional study from three haemophilia centres. *Haemophilia* **22**(1): 65-71.
Ramenghi LA, Amerio G & Sabatino G (2001) Honey, a palatable substance for infants: from De Rerum Natura to evidence-based medicine. *Eur J Pediatr* **160**(11): 677-8.
Ramgopal S, Elmer J, Escajeda J et al (2018) Differences in Prehospital Patient Assessments for Pediatric Versus Adult Patients. *J Pediatr* **199**: 200-05 e6.
Ramirez L, Cros J, Marin B et al (2015) Analgesic interaction between ondansetron and acetaminophen after tonsillectomy in children: the Paratron randomized, controlled trial. *Eur J Pain* **19**(5): 661-8.
Raney EM, van Bosse HJP, Shea KG et al (2018) Current State of the Opioid Epidemic as it Pertains to Pediatric Orthopaedics From the Advocacy Committee of the Pediatric Orthopaedic Society of North America. *J Pediatr Orthop* **38**(5): e238-e44.
Ranger M, Celeste Johnston C, Rennick JE et al (2013a) A multidimensional approach to pain assessment in critically ill infants during a painful procedure. *Clin J Pain* **29**(7): 613–20.
Ranger M, Chau CM, Garg A et al (2013b) Neonatal pain-related stress predicts cortical thickness at age 7 years in children born very preterm. *PLoS One* **8**(10): e76702.
Raof RA, El Metainy SA, Alia DA et al (2017) Dexmedetomidine decreases the required amount of bupivacaine for ultrasound-guided transversus abdominis plane block in pediatrics patients: a randomized study. *J Clin Anesth* **37**: 55-60.
Rashed AN, Tomlin S, Aguado V et al (2016) Sources and magnitude of error in preparing morphine infusions for nurse-patient controlled analgesia in a UK paediatric hospital. *Int J Clin Pharm* **38**(5): 1069-74.
Rashed AN, Whittlesea C, Davies C et al (2019) Standardised concentrations of morphine infusions for nurse/patient-controlled analgesia use in children. *BMC Anesthesiol* **19**(1): 26.
Raslan N & Masri R (2018) A randomized clinical trial to compare pain levels during three types of oral anesthetic injections and the effect of Dentalvibe((R)) on injection pain in children. *Int J Paediatr Dent* **28**(1): 102-10.
Rastogi RG, Borrero-Mejias C, Hickman C et al (2018) Management of Episodic Migraine in Children and Adolescents: a Practical Approach. *Curr Neurol Neurosci Rep* **18**(12): 103.
Rattray B, Nugent DJ & Young G (2006) Celecoxib in the treatment of haemophilic synovitis, target joints, and pain in adults and children with haemophilia. *Haemophilia* **12**(5): 514–17.
Ravish M, Muldowney B, Becker A et al (2012) Pain management in patients with adolescent idiopathic scoliosis undergoing posterior spinal fusion: combined intrathecal morphine and continuous epidural versus PCA. *J Pediatr Orthop* **32**(8): 799–804.
Rayala S, Backdahl T, Reddy N et al (2019) Low-Dose Oral Ketamine for Procedural Analgesia in Pediatric Cancer Patients Undergoing Lumbar Puncture at a Resource-Limited Cancer Hospital in India. *J Palliat Med* **22**(11): 1357-63.
RCH (2017) *I.V. Lignocaine Lidocaine infusion for inpatient use for severe resistant acute pain.* https://www.rch.org.au/anaes/pain_management/iv-lignocaine-lidocaine-infusion-for-severe-resistant-pain/ Accessed 28 April 2020
Redmann AJ, Maksimoski M, Brumbaugh C et al (2018) The effect of postoperative steroids on post-tonsillectomy pain and need for postoperative physician contact. *Laryngoscope* **128**(9): 2187-92.
Rees CA, Bernhardt MB, Camp EA et al (2019) Race and ethnicity: Not factors in the prescribing of hydrocodone and codeine-containing products in two pediatric emergency departments. *J Opioid Manag* **15**(3): 229-33.
Regan L, Chapman AR, Celnik A et al (2013) Nose and vein, speed and pain: comparing the use of intranasal diamorphine and intravenous morphine in a Scottish paediatric emergency department. *Emerg Med J* **30**(1): 49–52.
Regmi U & Sapkota S (2017) Efficacy of tramadol as an adjuvant to bupivacaine for caudal analgesia in children: a randomised controlled trial. *JSAN* **4**(1): 11-15.
Reid C, Hatton R & Middleton P (2011) Case report: prehospital use of intranasal ketamine for paediatric burn injury. *Emerg Med J* **28**(4): 328–29.
Reinoso-Barbero F, Pascual-Pascual SI, de Lucas R et al (2011) Equimolar nitrous oxide/oxygen versus placebo for procedural pain in children: a randomized trial. *Pediatrics* **127**(6): e1464–70.
Reinoso-Barbero F, Saavedra B, Hervilla S et al (2002) Lidocaine with fentanyl, compared to morphine, marginally improves postoperative epidural analgesia in children. *Can J Anaesth* **49**(1): 67–71.
Reis EC, Roth EK, Syphan JL et al (2003) Effective pain reduction for multiple immunization injections in young infants. *Arch Pediatr Adolesc Med* **157**(11): 1115–20.
Reiter PD, Ng J & Dobyns EL (2012) Continuous hydromorphone for pain and sedation in mechanically ventilated infants and children. *J Opioid Manag* **8**(2): 99–104.
Reiter PD, Nickisch J & Merritt G (2005) Efficacy and tolerability of intravenous valproic acid in acute adolescent migraine. *Headache* **45**(7): 899-903.
Relland LM, Gehred A & Maitre NL (2019) Behavioral and Physiological Signs for Pain Assessment in Preterm and Term Neonates During a Nociception-Specific Response: A Systematic Review. *Pediatr Neurol* **90**: 13-23.

Relland LM, Tobias JD, Martin D et al (2017) Ultrasound-guided rectus sheath block, caudal analgesia, or surgical site infiltration for pediatric umbilical herniorrhaphy: a prospective, double-blinded, randomized comparison of three regional anesthetic techniques. *J Pain Res* **10**: 2629-34.

Reynolds SL, Bryant KK, Studnek JR et al (2017) Randomized Controlled Feasibility Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected Extremity Fractures. *Acad Emerg Med* **24**(12): 1430-40.

Riad W & Moussa A (2007) Pre-operative analgesia with rectal diclofenac and/or paracetamol in children undergoing inguinal hernia repair. *Anaesthesia* **62**(12): 1241–45.

Ribeiro da Silva VC, da Motta Silveira FM, Barbosa Monteiro MG et al (2018) Photodynamic therapy for treatment of oral mucositis: Pilot study with pediatric patients undergoing chemotherapy. *Photodiagnosis Photodyn Ther* **21**: 115-20.

Richardson MD, Palmeri NO, Williams SA et al (2016) Routine perioperative ketorolac administration is not associated with hemorrhage in pediatric neurosurgery patients. *J Neurosurg Pediatr* **17**(1): 107-15.

Richer L, Billinghurst L, Linsdell MA et al (2016) Drugs for the acute treatment of migraine in children and adolescents. *Cochrane Database Syst Rev* **4**: Cd005220.

Richer L, Craig W & Rowe B (2014) Randomized controlled trial of treatment expectation and intravenous fluid in pediatric migraine. *Headache* **54**(9): 1496-505.

Riggin L, Ramakrishna J, Sommer DD et al (2013) A 2013 updated systematic review & meta-analysis of 36 randomized controlled trials; no apparent effects of non steroidal anti-inflammatory agents on the risk of bleeding after tonsillectomy. *Clin Otolaryngol* **38**(2): 115–29.

Riley P, Glenny AM, Worthington HV et al (2015) Interventions for preventing oral mucositis in patients with cancer receiving treatment: oral cryotherapy. *Cochrane Database Syst Rev*(12): CD011552.

Riley P, Glenny AM, Worthington HV et al (2017) Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors. *Cochrane Database Syst Rev* **11**: Cd011990.

Rimmer RB, Alam NB, Bay RC et al (2015) The reported pain coping strategies of pediatric burn survivors-does a correlation exist between coping style and development of anxiety disorder? *J Burn Care Res* **36**(2): 336-43.

Ring LM & Watson A (2017) Thoracostomy Tube Removal: Implementation of a Multidisciplinary Procedural Pain Management Guideline. *J Pediatr Health Care* **31**(6): 671-83.

Robert R, Brack A, Blakeney P et al (2003) A double-blind study of the analgesic efficacy of oral transmucosal fentanyl citrate and oral morphine in pediatric patients undergoing burn dressing change and tubbing. *J Burn Care Rehabil* **24**(6): 351–55.

Robinson PD, Blackburn C, Babl FE et al (2015) Management of paediatric spontaneous pneumothorax: a multicentre retrospective case series. *Arch Dis Child* **100**(10): 918-23.

Rochwerg B, Almenawer SA, Siemieniuk RAC et al (2018) Atraumatic (pencil-point) versus conventional needles for lumbar puncture: a clinical practice guideline. *Bmj* **361**: k1920.

Rodieux F, Vutskits L, Posfay-Barbe KM et al (2018) When the Safe Alternative Is Not That Safe: Tramadol Prescribing in Children. *Front Pharmacol* **9**: 148.

Roeber B, Wallace DP, Rothe V et al (2011) Evaluation of the effects of the VibraJect attachment on pain in children receiving local anesthesia. *Pediatr Dent* **33**(1): 46–50.

Rogers A, Greenwald M, Deguzman M et al (2006) A randomized, controlled trial of sucrose analgesia in infants younger than 90 days of age who require bladder catheterization in the pediatric emergency department. *Acad Emerg Med* **13**(6): 617–22.

Rogovik AL & Goldman RD (2007a) Prehospital use of analgesics at home or en route to the hospital in children with extremity injuries. *Am J Emerg Med* **25**(4): 400–05.

Rogovik AL, Rostami M, Hussain S et al (2007b) Physician pain reminder as an intervention to enhance analgesia for extremity and clavicle injuries in pediatric emergency. *J Pain* **8**(1): 26-32.

Rolan P, Lim S, Sunderland V et al (2014) The absolute bioavailability of racemic ketamine from a novel sublingual formulation. *Br J Clin Pharmacol* **77**(6): 1011–16.

Roofthooft DWE, Simons SHP, van Lingen RA et al (2017) Randomized Controlled Trial Comparing Different Single Doses of Intravenous Paracetamol for Placement of Peripherally Inserted Central Catheters in Preterm Infants. *Neonatology* **112**(2): 150-58.

Rork JF, Berde CB & Goldstein RD (2013) Regional anesthesia approaches to pain management in pediatric palliative care: a review of current knowledge. *J Pain Symptom Manage* **46**(6): 859-73.

Rosen DA, Morris JL, Rosen KR et al (2000) Analgesia for pediatric thoracostomy tube removal. *Anesth Analg* **90**(5): 1025–8.

Ross EL, Reiter PD, Murphy ME et al (2015) Evaluation of prolonged epidural chloroprocaine for postoperative analgesia in infants. *J Clin Anesth* **27**(6): 463-9.

Ross PA, Smith BM, Tolo VT et al (2011) Continuous infusion of bupivacaine reduces postoperative morphine use in adolescent idiopathic scoliosis after posterior spine fusion. *Spine (Phila Pa 1976)* **36**(18): 1478–83.

Rothera E, Chumas P, Liddington M et al (2014) Scalp blocks in nonsyndromic craniosynostosis surgery - a retrospective case series review. *Paediatr Anaesth* **24**(8): 894-5.

Roue JM, Rioualen S, Gendras J et al (2018) Multi-modal pain assessment: are near-infrared spectroscopy, skin conductance, salivary cortisol, physiologic parameters, and Neonatal Facial Coding System interrelated during venepuncture in healthy, term neonates? *J Pain Res* **11**: 2257-67.

Roze JC, Denizot S, Carbajal R et al (2008) Prolonged sedation and/or analgesia and 5-year neurodevelopment outcome in very preterm infants: results from the EPIPAGE cohort. *Arch Pediatr Adolesc Med* **162**(8): 728–33.

Rubinstein O, Barkan S, Breitbart R et al (2016) Efficacy of oral ketamine compared to midazolam for sedation of children undergoing laceration repair: A double-blind, randomized, controlled trial. *Medicine (Baltimore)* **95**(26): e3984.

Ruggiero A, Barone G, Liotti L et al (2007) Safety and efficacy of fentanyl administered by patient controlled analgesia in children with cancer pain. *Support Care Cancer* **15**(5): 569–73.

Ruggiero A, Coccia P, Arena R et al (2013) Efficacy and safety of transdermal buprenorphine in the management of children with cancer-related pain. *Pediatr Blood Cancer* **60**(3): 433–7.

Rugyte D & Kokki H (2007) Intravenous ketoprofen as an adjunct to patient-controlled analgesia morphine in adolescents with thoracic surgery: a placebo controlled double-blinded study. *Eur J Pain* **11**(6): 694–99.

Rugyte DC, Kilda A, Karbonskiene A et al (2010) Systemic postoperative pain management following minimally invasive pectus excavatum repair in children and adolescents: a retrospective comparison of intravenous patient-controlled analgesia and continuous infusion with morphine. *Pediatr Surg Int* **26**(7): 665–69.

Rusy LM, Hainsworth KR, Nelson TJ et al (2010) Gabapentin use in pediatric spinal fusion patients: a randomized, double-blind, controlled trial. *Anesth Analg* **110**(5): 1393–8.

Rutkowska A & Skotnicka-Klonowicz G (2015) Prehospital pain management in children with traumatic injuries. *Pediatr Emerg Care* **31**(5): 317-20.

Sadeghirad B, Siemieniuk RAC, Brignardello-Petersen R et al (2017) Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomised trials. *BMJ* **358**: j3887.

Sadhasivam S, Boat A & Mahmoud M (2009) Comparison of patient-controlled analgesia with and without dexmedetomidine following spine surgery in children. *J Clin Anesth* **21**(7): 493–501.

Sadhasivam S, Chidambaran V, Olbrecht VA et al (2015a) Opioid-related adverse effects in children undergoing surgery: unequal burden on younger girls with higher doses of opioids. *Pain Med* **16**(5): 985-97.

Sadhasivam S, Chidambaran V, Olbrecht VA et al (2014) Genetics of pain perception, COMT and postoperative pain management in children. *Pharmacogenomics* **15**(3): 277–84.

Sadhasivam S, Chidambaran V, Zhang X et al (2015b) Opioid-induced respiratory depression: ABCB1 transporter pharmacogenetics. *Pharmacogenomics J* **15**(2): 119–26.

Sadhasivam S, Zhang X, Chidambaran V et al (2015c) Novel associations between FAAH genetic variants and postoperative central opioid-related adverse effects. *Pharmacogenomics J* **15**(5): 436-42.

Safavi M, Honarmand A, Habibabady MR et al (2012) Assessing intravenous ketamine and intravenous dexamethasone separately and in combination for early oral intake, vomiting and postoperative pain relief in children following tonsillectomy. *Med Arh* **66**(2): 111–5.

Sahin L, Soydinc MH, Sen E et al (2017) Comparison of 3 different regional block techniques in pediatric patients. A prospective randomized single-blinded study. *Saudi Med J* **38**(9): 952-59.

Saito W, Inoue G, Imura T et al (2015) Safety and Efficacy of Continuous Epidural Anesthesia Following Scoliosis Surgery in Respiratory-Impaired Neuromuscular Children: A Pilot Study. *Spine Deform* **3**(3): 272-76.

Sakulchit T, Kuzeljevic B & Goldman RD (2019) Evaluation of Digital Face Recognition Technology for Pain Assessment in Young Children. *Clin J Pain* **35**(1): 18-22.

Salami OF, Amanor-Boadu SD, Eyelade OR et al (2017) Effects of low-dose intravenous dexamethasone combined with caudal analgesia on post-herniotomy pain. *Niger Postgrad Med J* **24**(4): 230-35.

Saleh AH, Hassan PF, Elayashy M et al (2018) Role of dexamethasone in the para-vertebral block for pediatric patients undergoing aortic coarctation repair. randomized, double-blinded controlled study. *BMC Anesthesiol* **18**(1): 178.

Salgado Filho MF, Goncalves HB, Pimentel Filho LH et al (2013) Assessment of pain and hemodynamic response in older children undergoing circumcision: comparison of eutectic lidocaine/prilocaine cream and dorsal penile nerve block. *J Pediatr Urol* **9**(5): 638-42.

SAMHSA (2019) *Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH Series H-54).* https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf Accessed 9 March 2019

Samuel N, Steiner IP & Shavit I (2015) Prehospital pain management of injured children: a systematic review of current evidence. *Am J Emerg Med* **33**(3): 451-4.

Samuels PJ (2006) Anesthesia for adolescent bariatric surgery. *Int Anesthesiol Clin* **44**(1): 17-31.

Samuels PJ & Sjoblom MD (2016) Anesthetic considerations for pediatric obesity and adolescent bariatric surgery. *Curr Opin Anaesthesiol* **29**(3): 327-36.

Sanchez-Borges M, Caballero-Fonseca F & Capriles-Hulett A (2005a) Safety of etoricoxib, a new cyclooxygenase 2 inhibitor, in patients with nonsteroidal anti-inflammatory drug-induced urticaria and angioedema. *Ann Allergy Asthma Immunol* **95**(2): 154–58.

Sanchez-Borges M, Caballero-Fonseca F & Capriles-Hulett A (2005b) Tolerance of nonsteroidal anti-inflammatory drug-sensitive patients to the highly specific cyclooxygenase 2 inhibitors rofecoxib and valdecoxib. *Ann Allergy Asthma Immunol* **94**(1): 34–38.

Sanchez-Rodriguez E, Miro J & Castarlenas E (2012) A comparison of four self-report scales of pain intensity in 6- to 8-year-old children. *Pain* **153**(8): 1715–19.

Sandeman DJ, Bennett M, Dilley AV et al (2011) Ultrasound-guided transversus abdominis plane blocks for laparoscopic appendicectomy in children: a prospective randomized trial. *Br J Anaesth* **106**(6): 882–86.

Sandeman DJ & Dilley AV (2007) Ultrasound guided dorsal penile nerve block in children. *Anaesth Intensive Care* **35**(2): 266-9.

Sanwatsarkar S, Kapur S, Saxena D et al (2017) Comparative study of caudal clonidine and midazolam added to bupivacaine during infra-umbilical surgeries in children. *J Anaesthesiol Clin Pharmacol* **33**(2): 241-47.

Sathyamoorthy M, Walker B, Rhodes MM et al (2017) Spinal epidural hematoma following a thoracic epidural in a child with sickle cell disease. *Clin Case Rep* **5**(7): 1115-18.

Sato M (2019) Ultrasound-guided quadratus lumborum block compared to caudal ropivacaine/morphine in children undergoing surgery for vesicoureteric reflex. *Paediatr Anaesth* **29**(7): 738-43.

Sato M, Iida T, Kikuchi C et al (2017) Comparison of caudal ropivacaine-morphine and paravertebral catheter for major upper abdominal surgery in infants. *Paediatr Anaesth* **27**(5): 524-30.

Satoyoshi M & Kamiyama Y (1984) Caudal anaesthesia for upper abdominal surgery in infants and children: a simple calculation of the volume of local anaesthetic. *Acta Anaesthesiol Scand* **28**(1): 57–60.

Saudan S, Habre W, Ceroni D et al (2008) Safety and efficacy of patient controlled epidural analgesia following pediatric spinal surgery. *Paediatr Anaesth* **18**(2): 132–39.

Sauer H, Graeber S, Lieser U et al (2019) Bone marrow aspirations in oncological patients: experience from an in-house standard in paediatrics. *Wien Med Wochenschr* **169**(3-4): 82-86.

Saxe G, Geary M, Bedard K et al (2006) Separation anxiety as a mediator between acute morphine administration and PTSD symptoms in injured children. *Ann N Y Acad Sci* **1071**: 41-5.

Saxe G, Stoddard F, Courtney D et al (2001) Relationship between acute morphine and the course of PTSD in children with burns. *J Am Acad Child Adolesc Psychiatry* **40**(8): 915-21.

Sayed JA, Abd Elshafy SK, Kamel EZ et al (2018a) The impact of caudally administrated tramadol on immune response and analgesic efficacy for pediatric patients: a comparative randomized clinical trial. *Korean J Pain* **31**(3): 206-14.

Sayed JA, Kamel EZ, Riad MAF et al (2018b) Dexmedetomidine with magnesium sulphate as adjuvants in caudal block to augment anaesthesia and analgesia in paediatric lower abdominal surgeries. *Egyptian Journal of Anaesthesia* **34**(4): 115-22.

Sayed JA, MA FR & MO MA (2016) Comparison of dexamethasone or intravenous fluids or combination of both on postoperative nausea, vomiting and pain in pediatric strabismus surgery. *J Clin Anesth* **34**: 136-42.

Schacherer NM, Erikson Ramirez D, Frazier SB et al (2015) Expedited Delivery of Pain Medication for Long-Bone Fractures Using an Intranasal Fentanyl Clinical Pathway. *Pediatr Emerg Care* **31**(8): 560-3.

Schatz J, Schlenz AM, McClellan CB et al (2015) Changes in coping, pain, and activity after cognitive-behavioral training: a randomized clinical trial for pediatric sickle cell disease using smartphones. *Clin J Pain* **31**(6): 536-47.

Schauer SG, Arana AA, Naylor JF et al (2018) Prehospital Analgesia for Pediatric Trauma Patients in Iraq and Afghanistan. *Prehosp Emerg Care* **22**(5): 608-13.

Schechter NL, Bernstein BA, Zempsky WT et al (2010) Educational outreach to reduce immunization pain in office settings. *Pediatrics* **126**(6): e1514–21.

Schechter NL, Weisman SJ, Rosenblum M et al (1995) The use of oral transmucosal fentanyl citrate for painful procedures in children. *Pediatrics* **95**(3): 335–39.

Schechter NL, Zempsky WT, Cohen LL et al (2007) Pain reduction during pediatric immunizations: evidence-based review and recommendations. *Pediatrics* **119**(5): e1184–98.

Schepis TS, Teter CJ & McCabe SE (2018) Prescription drug use, misuse and related substance use disorder symptoms vary by educational status and attainment in U.S. adolescents and young adults. *Drug Alcohol Depend* **189**: 172-77.

Schiavenato M & von Baeyer CL (2012) A quantitative examination of extreme facial pain expression in neonates: The primal face of pain across time. *Pain Res Treat* **2012**: 251625.

Schiessl C, Gravou C, Zernikow B et al (2008) Use of patient-controlled analgesia for pain control in dying children. *Support Care Cancer* **16**(5): 531–36.

Schlatter MG, Nguyen LV, Tecos M et al (2019) Progressive reduction of hospital length of stay following minimally invasive repair of pectus excavatum: A retrospective comparison of three analgesia modalities, the role of addressing patient anxiety, and reframing patient expectations. *J Pediatr Surg* **54**(4): 663-69.

Schmitt YS, Hoffman HG, Blough DK et al (2011) A randomized, controlled trial of immersive virtual reality analgesia, during physical therapy for pediatric burns. *Burns* **37**(1): 61–68.

Schmitz ML, Zempsky WT & Meyer JM (2015) Safety and Efficacy of a Needle-free Powder Lidocaine Delivery System in Pediatric Patients Undergoing Venipuncture or Peripheral Venous Cannulation: Randomized Double-blind COMFORT-004 Trial. *Clin Ther* **37**(8): 1761-72.

Schnabel A, Poepping DM, Kranke P et al (2011a) Efficacy and adverse effects of ketamine as an additive for paediatric caudal anaesthesia: a quantitative systematic review of randomized controlled trials. *Br J Anaesth* **107**(4): 601–11.
Schnabel A, Poepping DM, Pogatzki-Zahn EM et al (2011b) Efficacy and safety of clonidine as additive for caudal regional anesthesia: a quantitative systematic review of randomized controlled trials. *Paediatr Anaesth* **21**(12): 1219–30.
Schnabel A, Reichl SU, Meyer-Friessem C et al (2015) Tramadol for postoperative pain treatment in children. *Cochrane Database Syst Rev*(3): CD009574.
Schnabel A, Reichl SU, Poepping DM et al (2013) Efficacy and safety of intraoperative dexmedetomidine for acute postoperative pain in children: a meta-analysis of randomized controlled trials. *Paediatr Anaesth* **23**(2): 170–79.
Schnabel A, Reichl SU, Zahn PK et al (2014) Nalbuphine for postoperative pain treatment in children. *Cochrane Database Syst Rev* **7**: CD009583.
Schneider JC, Nadler DL, Herndon DN et al (2015) Pruritus in pediatric burn survivors: defining the clinical course. *J Burn Care Res* **36**(1): 151-8.
Schofield S, Schutz J, Babl FE et al (2013) Procedural sedation and analgesia for reduction of distal forearm fractures in the paediatric emergency department: a clinical survey. *Emerg Med Australas* **25**(3): 241–47.
Schoolman-Anderson K, Lane RD, Schunk JE et al (2018) Pediatric emergency department triage-based pain guideline utilizing intranasal fentanyl: Effect of implementation. *Am J Emerg Med* **36**(9): 1603-07.
Schreck Bird A, Gregory PJ, Jalloh MA et al (2017) Probiotics for the Treatment of Infantile Colic: A Systematic Review. *J Pharm Pract* **30**(3): 366-74.
Schreiber S, Cozzi G, Patti G et al (2018) Does the Application of Heat Gel Pack After Eutectic Mixture of Local Anesthetic Cream Improve Venipuncture or Intravenous Cannulation Success Rate in Children? A Randomized Control Trial. *Pediatr Emerg Care* **34**(2): e24-e27.
Schror K (2007) Aspirin and Reye syndrome: a review of the evidence. *Paediatr Drugs* **9**(3): 195–204.
Schuman SS, Regen RB, Stuart LH et al (2018) Reducing Time to Pain Medication Administration for Pediatric Patients with Long Bone Fractures in the Emergency Department. *Pediatr Qual Saf* **3**(6): e120.
Schwaller F, Kanellopoulos AH & Fitzgerald M (2017) The developmental emergence of differential brainstem serotonergic control of the sensory spinal cord. *Sci Rep* **7**(1): 2215.
Schwaller F, Kwok C & Fitzgerald M (2016) Postnatal maturation of the spinal-bulbo-spinal loop: brainstem control of spinal nociception is independent of sensory input in neonatal rats. *Pain* **157**(3): 677-86.
Schwartz LA & Brumley LD (2017) What a Pain: The Impact of Physical Symptoms and Health Management on Pursuit of Personal Goals Among Adolescents with Cancer. *J Adolesc Young Adult Oncol* **6**(1): 142-49.
Seiler M, Staubli G & Landolt MA (2019) Combined nitrous oxide 70% with intranasal fentanyl for procedural analgosedation in children: a prospective, randomised, double-blind, placebo-controlled trial. *Emerg Med J* **36**(3): 142-47.
Sellam G, Cignacco EL, Craig KD et al (2011) Contextual factors influencing pain response to heelstick procedures in preterm infants: what do we know? A systematic review. *Eur J Pain* **15**(7): 661 e1–15.
Semple D, Russell S, Doyle E et al (1999) Comparison of morphine sulphate and codeine phosphate in children undergoing adenotonsillectomy. *Paediatr Anaesth* **9**(2): 135–38.
Sendasgupta C, Makhija N, Kiran U et al (2009) Caudal epidural sufentanil and bupivacaine decreases stress response in paediatric cardiac surgery. *Ann Card Anaesth* **12**(1): 27–33.
Seo IS, Seong CR, Jung G et al (2011) The effect of sub-Tenon lidocaine injection on emergence agitation after general anaesthesia in paediatric strabismus surgery. *Eur J Anaesthesiol* **28**(5): 334–39.
Seol TK, Lim JK, Yoo EK et al (2015) Propofol-ketamine or propofol-remifentanil for deep sedation and analgesia in pediatric patients undergoing burn dressing changes: a randomized clinical trial. *Paediatr Anaesth* **25**(6): 560-6.
Sethi N, Pant D, Dutta A et al (2016) Comparison of caudal epidural block and ultrasonography-guided transversus abdominis plane block for pain relief in children undergoing lower abdominal surgery. *J Clin Anesth* **33**: 322-9.
Setlur A & Friedland H (2018) Treatment of pain with intranasal fentanyl in pediatric patients in an acute care setting: a systematic review. *Pain Management* **8**(5): 341-52.
Seyedhejazi M, Azerfarin R, Kazemi F et al (2011) Comparing caudal and penile nerve blockade using bupivacaine in hypospadias repair surgeries in children. *Afr J Paediatr Surg* **8**(3): 294-7.
Seyedhejazi M, Sheikhzadeh D, Adrang Z et al (2014) Comparing the analgesic effect of caudal and ilioinguinal iliohypogastric nerve blockade using bupivacaine-clonidine in inguinal surgeries in children 2-7 years old. *Afr J Paediatr Surg* **11**(2): 166-9.
Sezen G, Demiraran Y, Karagoz I et al (2014) The assessment of bupivacaine-tramadol and levobupivacaine-tramadol combinations for preemptive caudal anaesthesia in children: a randomized, double-blind, prospective study. *Int J Clin Exp Med* **7**(5): 1391–96.
Shah A, Mosdossy G, McLeod S et al (2011a) A blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. *Ann Emerg Med* **57**(5): 425–33.e2.
Shah PS, Herbozo C, Aliwalas LL et al (2012) Breastfeeding or breast milk for procedural pain in neonates. *Cochrane Database Syst Rev* **12**: CD004950.

Shah V, Taddio A, Kulasekaran K et al (2003) Evaluation of a new lancet device (BD QuikHeel) on pain response and success of procedure in term neonates. *Arch Pediatr Adolesc Med* **157**(11): 1075–78.
Shah V, Taddio A, McMurtry CM et al (2015) Pharmacological and Combined Interventions to Reduce Vaccine Injection Pain in Children and Adults: Systematic Review and Meta-Analysis. *Clin J Pain* **31**(10 Suppl): S38-63.
Shah VS & Ohlsson A (2011b) Venepuncture versus heel lance for blood sampling in term neonates. *Cochrane Database Syst Rev* **10**: CD001452.
Shaheen SO, Newson RB, Ring SM et al (2010) Prenatal and infant acetaminophen exposure, antioxidant gene polymorphisms, and childhood asthma. *J Allergy Clin Immunol* **126**(6): 1141-8.e7.
Shahid S, Florez ID & Mbuagbaw L (2019) Efficacy and Safety of EMLA Cream for Pain Control Due to Venipuncture in Infants: A Meta-analysis. *Pediatrics* **143**(1).
Shanahan EC, Marshall AG & Garrett CP (1983) Adverse reactions to intravenous codeine phosphate in children. A report of three cases. *Anaesthesia* **38**(1): 40–43.
Shank ES, Martyn JA, Donelan MB et al (2016) Ultrasound-Guided Regional Anesthesia for Pediatric Burn Reconstructive Surgery: A Prospective Study. *J Burn Care Res* **37**(3): e213-7.
Shanthanna H, Singh B & Guyatt G (2014) A systematic review and meta-analysis of caudal block as compared to noncaudal regional techniques for inguinal surgeries in children. *Biomed Res Int* **2014**: 890626.
Sharar SR, Bratton SL, Carrougher GJ et al (1998) A comparison of oral transmucosal fentanyl citrate and oral hydromorphone for inpatient pediatric burn wound care analgesia. *J Burn Care Rehabil* **19**(6): 516–21.
Sharar SR, Carrougher GJ, Nakamura D et al (2007) Factors influencing the efficacy of virtual reality distraction analgesia during postburn physical therapy: preliminary results from 3 ongoing studies. *Arch Phys Med Rehabil* **88**(12 Suppl 2): S43–49.
Sharar SR, Carrougher GJ, Selzer K et al (2002) A comparison of oral transmucosal fentanyl citrate and oral oxycodone for pediatric outpatient wound care. *J Burn Care Rehabil* **23**(1): 27–31.
Sharara-Chami R, Lakissian Z, Charafeddine L et al (2017) Combination Analgesia for Neonatal Circumcision: A Randomized Controlled Trial. *Pediatrics* **140**(6).
Shargorodsky J, Hartnick CJ & Lee GS (2012) Dexamethasone and postoperative bleeding after tonsillectomy and adenotonsillectomy in children: A meta-analysis of prospective studies. *Laryngoscope* **122**(5): 1158–64.
Sharma J, Gupta R, Kumari A et al (2018) A Comparative Study of 0.25% Levobupivacaine, 0.25% Ropivacaine, and 0.25% Bupivacaine in Paediatric Single Shot Caudal Block. *Anesthesiol Res Pract* **2018**: 1486261.
Sharma K, Kumar M & Gandhi R (2019) Effect of Single-Dose Dexmedetomidine on Intraoperative Hemodynamics and Postoperative Recovery during Pediatric Adenotonsillectomy. *Anesth Essays Res* **13**(1): 63-67.
Shavit I, Brumer E, Shavit D et al (2016) Emergency Department Pain Management in Pediatric Patients With Fracture or Dislocation in a Bi-Ethnic Population. *Ann Emerg Med* **67**(1): 9-14 e1.
Sheehan WJ, Mauger DT, Paul IM et al (2016) Acetaminophen versus Ibuprofen in Young Children with Mild Persistent Asthma. *N Engl J Med* **375**(7): 619-30.
Sheehy KA, Finkel JC, Darbari DS et al (2015) Dexmedetomidine as an Adjuvant to Analgesic Strategy During Vaso-Occlusive Episodes in Adolescents with Sickle-Cell Disease. *Pain Practice* **15**(8): E90-E97.
Shenoy U, Paul J & Antony D (2014) Lipid resuscitation in pediatric patients - need for caution? *Paediatr Anaesth* **24**(3): 332-4.
Shepherd M & Aickin R (2009) Paracetamol versus ibuprofen: a randomized controlled trial of outpatient analgesia efficacy for paediatric acute limb fractures. *Emerg Med Australas* **21**(6): 484–90.
Sheridan D, Sun B, O'Brien P et al (2015) Intravenous Sodium Valproate for Acute Pediatric Headache. *J Emerg Med* **49**(4): 541-5.
Sheridan DC, Hansen ML, Lin AL et al (2018a) Low-Dose Propofol for Pediatric Migraine: A Prospective, Randomized Controlled Trial. *J Emerg Med* **54**(5): 600-06.
Sheridan DC, Laurie A, Hendrickson RG et al (2016) Association of Overall Opioid Prescriptions on Adolescent Opioid Abuse. *J Emerg Med* **51**(5): 485-90.
Sheridan DC, Laurie A, Pacheco S et al (2018b) Relative Effectiveness of Dopamine Antagonists for Pediatric Migraine in the Emergency Department. *Pediatr Emerg Care* **34**(3): 165-68.
Sheridan DC, Spiro DM & Meckler GD (2014a) Pediatric migraine: abortive management in the emergency department. *Headache* **54**(2): 235–45.
Sheridan R, Stoddard F & Querzoli E (2001) Management of background pain and anxiety in critically burned children requiring protracted mechanical ventilation. *J Burn Care Rehabil* **22**(2): 150-3.
Sheridan RL, Hinson M, Nackel A et al (1997) Development of a pediatric burn pain and anxiety management program. *J Burn Care Rehabil* **18**(5): 455-9; discussion 53-4.
Sheridan RL, Stoddard FJ, Kazis LE et al (2014b) Long-term posttraumatic stress symptoms vary inversely with early opiate dosing in children recovering from serious burns: effects durable at 4 years. *J Trauma Acute Care Surg* **76**(3): 828–32.
Shetty V, Suresh LR & Hegde AM (2019) Effect of Virtual Reality Distraction on Pain and Anxiety During Dental Treatment in 5 to 8 Year Old Children. *J Clin Pediatr Dent* **43**(2): 97-102.

Shibata M, Kawai M, Matsukura T et al (2013) Salivary biomarkers are not suitable for pain assessment in newborns. *Early Hum Dev* **89**(7): 503–06.
Shin SK, Hong JY, Kim WO et al (2009) Ultrasound evaluation of the sacral area and comparison of sacral interspinous and hiatal approach for caudal block in children. *Anesthesiology* **111**(5): 1135-40.
Shirazi M, Mahmoudi H, Nasihatkon B et al (2016) Efficacy of dexamethasone on postoperative analgesia in children undergoing hypospadias repair. *Pak J Med Sci* **32**(1): 125-9.
Shirmohammadie M, Ebrahim Soltani A, Arbabi S et al (2019) A randomized-controlled, double-blind study to evaluate the efficacy of caudal midazolam, ketamine and neostigmine as adjuvants to bupivacaine on postoperative analgesic in children undergoing lower abdominal surgery. *Acta Biomed* **89**(4): 513-18.
Shockey DP, Menzies V, Glick DF et al (2013) Preprocedural distress in children with cancer: an intervention using biofeedback and relaxation. *J Pediatr Oncol Nurs* **30**(3): 129-38.
Short JA, Barr CA, Palmer CD et al (2000) Use of diclofenac in children with asthma. *Anaesthesia* **55**(4): 334–37.
Shukla U, Prabhakar T & Malhotra K (2011) Postoperative analgesia in children when using clonidine or fentanyl with ropivacaine given caudally. *J Anaesthesiol Clin Pharmacol* **27**(2): 205–10.
SickKids (2018) *Prevention and Treatment of Opioid and Benzodiazepine Withdrawal.* https://www.sickkids.ca/clinical-practice-guidelines/clinical-practice-guidelines/Export/CLINH303/Main%20Document.pdf Accessed 17 February 2020
Siddiqui A, Tse A, Paul JE et al (2016) Postoperative epidural analgesia for patients undergoing pectus excavatum corrective surgery: a 10-year retrospective analysis. *Local Reg Anesth* **9**: 25-33.
Sikka K, Ahmed AA, Diaz D et al (2015) Automated Assessment of Children's Postoperative Pain Using Computer Vision. *Pediatrics* **136**(1): e124-31.
Silvasti M, Tarkkila P, Tuominen M et al (1999) Efficacy and side effects of tramadol versus oxycodone for patient-controlled analgesia after maxillofacial surgery. *Eur J Anaesthesiol* **16**(12): 834–39.
Sim HB, Weon YC, Park JB et al (2010) Chronic traumatic spinal epidural hematoma in a child. *Am J Phys Med Rehabil* **89**(11): 936–40.
Simons SH, van Dijk M, van Lingen RA et al (2003) Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. *JAMA* **290**(18): 2419-27.
Simpao AF, Galvez JA, Wartman EC et al (2019) The Migration of Caudally Threaded Thoracic Epidural Catheters in Neonates and Infants. *Anesth Analg* **129**(2): 477-81.
Singer AJ & Stark MJ (2000) Pretreatment of lacerations with lidocaine, epinephrine, and tetracaine at triage: a randomized double-blind trial. *Acad Emerg Med* **7**(7): 751–56.
Singhal NR, Jones J, Semenova J et al (2016) Multimodal anesthesia with the addition of methadone is superior to epidural analgesia: A retrospective comparison of intraoperative anesthetic techniques and pain management for 124 pediatric patients undergoing the Nuss procedure. *J Pediatr Surg* **51**(4): 612-6.
Singleton A, Preston RJ & Cochran A (2015) Sedation and analgesia for critically ill pediatric burn patients: the current state of practice. *J Burn Care Res* **36**(3): 440-5.
Sirkia K, Hovi L, Pouttu J et al (1998) Pain medication during terminal care of children with cancer. *J Pain Symptom Manage* **15**(4): 220-6.
Sixou JL & Marie-Cousin A (2015) Intraosseous anaesthesia in children with 4 % articaine and epinephrine 1:400,000 using computer-assisted systems. *Eur Arch Paediatr Dent* **16**(6): 477-81.
Sjoukes A, Venekamp RP, van de Pol AC et al (2016) Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. *Cochrane Database Syst Rev* **12**: CD011534.
Skaper SD (2018) Neurotrophic Factors: An Overview in Neurotrophic Factors Methods and Protocols. In: *Methods in Molecular Biology* 2017/12/10 edn. (eds). Humana Press, New York, NY, Springer Science and Business Media. 1727: 1-17.
Skjeie H, Skonnord T, Brekke M et al (2018) Acupuncture treatments for infantile colic: a systematic review and individual patient data meta-analysis of blinding test validated randomised controlled trials. *Scand J Prim Health Care* **36**(1): 56-69.
Slater R, Cantarella A, Franck L et al (2008) How well do clinical pain assessment tools reflect pain in infants? *PLoS Med* **5**(6): e129.
Slater R, Cantarella A, Gallella S et al (2006) Cortical pain responses in human infants. *J Neurosci* **26**(14): 3662–66.
Slater R, Cornelissen L, Fabrizi L et al (2010) Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. *Lancet* **376**(9748): 1225–32.
Snaman JM, Baker JN, Ehrentraut JH et al (2016) Pediatric Oncology: Managing Pain at the End of Life. *Paediatr Drugs* **18**(3): 161-80.
Sobel RE, Lovell DJ, Brunner HI et al (2014) Safety of celecoxib and nonselective nonsteroidal anti-inflammatory drugs in juvenile idiopathic arthritis: results of the phase 4 registry. *Pediatr Rheumatol Online J* **12**: 29.
Soderberg Lofdal KC, Andersson ML & Gustafsson LL (2013) Cytochrome P450-mediated changes in oxycodone pharmacokinetics/pharmacodynamics and their clinical implications. *Drugs* **73**(6): 533–43.

Sola C, Raux O, Savath L et al (2012) Ultrasound guidance characteristics and efficiency of suprazygomatic maxillary nerve blocks in infants: a descriptive prospective study. *Paediatr Anaesth* **22**(9): 841-6.
Solana MJ, Lopez-Herce J, Fernandez S et al (2015) Assessment of pain in critically ill children. Is cutaneous conductance a reliable tool? *J Crit Care* **30**(3): 481-5.
Solanki NM, Engineer SR, Jansari DB et al (2016) Comparison of caudal tramadol versus caudal fentanyl with bupivacaine for prolongation of postoperative analgesia in pediatric patients. *Saudi J Anaesth* **10**(2): 154-60.
Soliman H, Elsharkawy A & Abdel-Hady H (2016) Does Topical Lidocaine Reduce the Pain Associated With the Insertion of Nasal Continuous Positive Airway Pressure Prongs in Preterm Infants?: A Randomized, Controlled Pilot Trial. *Clin J Pain* **32**(11): 948-54.
Solodiuk JC, Scott-Sutherland J, Meyers M et al (2010) Validation of the Individualized Numeric Rating Scale (INRS): a pain assessment tool for nonverbal children with intellectual disability. *Pain* **150**(2): 231–36.
Soltani R, Soheilipour S, Hajhashemi V et al (2013) Evaluation of the effect of aromatherapy with lavender essential oil on post-tonsillectomy pain in pediatric patients: a randomized controlled trial. *Int J Pediatr Otorhinolaryngol* **77**(9): 1579-81.
Sommerfield D, Ramgolam A, Barker A et al (2016) Epidural insertion height for ureteric reimplant surgery; does location matter? *Paediatr Anaesth* **26**(10): 951-9.
Sonderman KA, Wolf LL, Madenci AL et al (2018) Opioid Prescription Patterns for Children Following Laparoscopic Appendectomy. *Ann Surg*: epub ahead of print.
Sørensen GV & Rubak SLM (2014) Anaphylaxis to Paracetamol in a Twelve-Year-Old Girl. *Pediatric Allergy, Immunology, and Pulmonology* **27**(3): 154-56.
Soreze Y, Audureau E, Decobert F et al (2017) Reduced Sufentanil Doses are Effective for Postoperative Analgesia After Ductal Closure in Extremely Premature Infants: A 10 Years Retrospective Cohort Study. *Clin J Pain* **33**(12): 1109-16.
Sottas CE & Anderson BJ (2017) Dexmedetomidine: the new all-in-one drug in paediatric anaesthesia? *Curr Opin Anaesthesiol* **30**(4): 441-51.
Southey ER, Soares-Weiser K & Kleijnen J (2009) Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever. *Curr Med Res Opin* **25**(9): 2207–22.
Sparks LA, Setlik J & Luhman J (2007) Parental holding and positioning to decrease IV distress in young children: a randomized controlled trial. *J Pediatr Nurs* **22**(6): 440–47.
Splinter WM, Bass J & Komocar L (1995) Regional anaesthesia for hernia repair in children: local vs caudal anaesthesia. *Can J Anaesth* **42**(3): 197–200.
Splinter WM, Kim J, Kim AM et al (2019) Effect of anesthesia for hypospadias repair on perioperative complications. *Paediatr Anaesth* **29**(7): 760-67.
Sridhar S, Suprabha BS, Shenoy R et al (2019) Effect of a relaxation training exercise on behaviour, anxiety, and pain during buccal infiltration anaesthesia in children: Randomized clinical trial. *Int J Paediatr Dent* **29**(5): 596-602.
Srinivasan AK, Shrivastava D, Kurzweil RE et al (2016) Port Site Local Anesthetic Infiltration Vs Single-dose Intrathecal Opioid Injection to Control Perioperative Pain in Children Undergoing Minimal Invasive Surgery: A Comparative Analysis. *Urology* **97**: 179-83.
Srinivasan V, Lauterbach EC, Ho KY et al (2012) Melatonin in antinociception: its therapeutic applications. *Curr Neuropharmacol* **10**(2): 167-78.
Stadler J, Raith W, Mileder LP et al (2019) Invasive and non-invasive acupuncture techniques for pain management in neonates: a systematic review. *Acupunct Med* **37**(4): 201-10.
Stamer UM, Musshoff F, Stuber F et al (2016) Loss-of-function polymorphisms in the organic cation transporter OCT1 are associated with reduced postoperative tramadol consumption. *Pain* **157**(11): 2467-75.
Standing JF, Ooi K, Keady S et al (2009a) Prospective observational study of adverse drug reactions to diclofenac in children. *Br J Clin Pharmacol* **68**(2): 243–51.
Standing JF, Savage I, Pritchard D et al (2009b) Diclofenac for acute pain in children. *Cochrane Database Syst Rev* **4**: CD005538.
Standing JF, Tibboel D, Korpela R et al (2011) Diclofenac pharmacokinetic meta-analysis and dose recommendations for surgical pain in children aged 1-12 years. *Paediatr Anaesth* **21**(3): 316–24.
Starship (2017) *Weaning of Opioids and Benzodiazepines.* https://www.starship.org.nz/guidelines/weaning-of-opioids-and-benzodiazepines/ Accessed 18 February 2020
Stassinos GL, Gonzales L & Klein-Schwartz W (2019) Characterizing the Toxicity and Dose-Effect Profile of Tramadol Ingestions in Children. *Pediatr Emerg Care* **35**(2): 117-20.
Staveski SL, Boulanger K, Erman L et al (2018) The Impact of Massage and Reading on Children's Pain and Anxiety After Cardiovascular Surgery: A Pilot Study. *Pediatr Crit Care Med* **19**(8): 725-32.
Steel D, Kirkman MA, Thompson DNP et al (2017) Open thoracic anterolateral cordotomy for pain relief in children: report of 2 cases. *J Neurosurg Pediatr* **20**(3): 278-83.
Steib A, Karcenty A, Calache E et al (2005) Effects of subtenon anesthesia combined with general anesthesia on perioperative analgesic requirements in pediatric strabismus surgery. *Reg Anesth Pain Med* **30**(5): 478–83.

Stempak D, Gammon J, Klein J et al (2002) Single-dose and steady-state pharmacokinetics of celecoxib in children. *Clin Pharmacol Ther* **72**(5): 490-7.
Stevens B, Johnston C, Petryshen P et al (1996) Premature Infant Pain Profile: development and initial validation. *Clin J Pain* **12**(1): 13–22.
Stevens B, Johnston C, Taddio A et al (2010) The premature infant pain profile: evaluation 13 years after development. *Clin J Pain* **26**(9): 813–30.
Stevens B, McGrath P, Gibbins S et al (2007) Determining behavioural and physiological responses to pain in infants at risk for neurological impairment. *Pain* **127**(1-2): 94–102.
Stevens B, McGrath P, Gibbins S et al (2003) Procedural pain in newborns at risk for neurologic impairment. *Pain* **105**(1-2): 27–35.
Stevens B, Yamada J, Campbell-Yeo M et al (2018) The minimally effective dose of sucrose for procedural pain relief in neonates: a randomized controlled trial. *BMC Pediatr* **18**(1): 85.
Stevens B, Yamada J, Ohlsson A et al (2016) Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev* **7**: CD001069.
Stevens BJ, Gibbins S, Yamada J et al (2014a) The Premature Infant Pain Profile-Revised (PIPP-R): Initial validation and feasibility. *Clin J Pain* **30**(3): 238–43.
Stevens BJ, Yamada J, Estabrooks CA et al (2014b) Pain in hospitalized children: Effect of a multidimensional knowledge translation strategy on pain process and clinical outcomes. *Pain* **155**(1): 60–8.
Steward DL, Grisel J & Meinzen-Derr J (2011) Steroids for improving recovery following tonsillectomy in children. *Cochrane Database Syst Rev* **8**: CD003997.
Stewart D, Caradec J, Ziegfeld S et al (2019) Predictors and Correlates of Pediatric Postburn Pruritus in Preschool Children of Ages 0 to 4. *J Burn Care Res* **40**(6): 930-35.
Stock A, Hill A & Babl FE (2012) Practical communication guide for paediatric procedures. *Emerg Med Australas* **24**(6): 641–46.
Stoddard FJ, Jr., Luthra R, Sorrentino EA et al (2011) A randomized controlled trial of sertraline to prevent posttraumatic stress disorder in burned children. *J Child Adolesc Psychopharmacol* **21**(5): 469–77.
Stoddard FJ, Jr., Sorrentino EA, Ceranoglu TA et al (2009) Preliminary evidence for the effects of morphine on posttraumatic stress disorder symptoms in one- to four-year-olds with burns. *J Burn Care Res* **30**(5): 836–43.
Stoddard FJ, Ronfeldt H, Kagan J et al (2006) Young burned children: the course of acute stress and physiological and behavioral responses. *Am J Psychiatry* **163**(6): 1084–90.
Stoecker WV, Madsen DE, Cole JG et al (2016) Boys at Risk: Fatal Accidental Fentanyl Ingestions in Children: Analysis of Cases Reported to the FDA 2004-2013. *Mo Med* **113**(6): 476-79.
Stoltz P & Manworren RCB (2017) Comparison of Children's Venipuncture Fear and Pain: Randomized Controlled Trial of EMLA(R) and J-Tip Needleless Injection System(R). *J Pediatr Nurs* **37**: 91-96.
Strandness T, Wiktor M, Varadarajan J et al (2015) Migration of pediatric epidural catheters. *Paediatr Anaesth* **25**(6): 610-3.
Streissguth AP, Treder RP, Barr HM et al (1987) Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. *Teratology* **35**(2): 211-9.
Stroud AM, Tulanont DD, Coates TE et al (2014) Epidural analgesia versus intravenous patient-controlled analgesia following minimally invasive pectus excavatum repair: a systematic review and meta-analysis. *J Pediatr Surg* **49**(5): 798–806.
Stubberud A, Varkey E, McCrory DC et al (2016) Biofeedback as Prophylaxis for Pediatric Migraine: A Meta-analysis. *Pediatrics* **138**(2).
Subramaniam R, Joshi C, Sharma A et al (2007) Analgesic efficacy of single-dose parecoxib for corneal suturing in children. *Eur J Anaesthesiol* **24**(5): 464–65.
Subramaniam R, Subbarayudu S, Rewari V et al (2003) Usefulness of pre-emptive peribulbar block in pediatric vitreoretinal surgery: a prospective study. *Reg Anesth Pain Med* **28**(1): 43-7.
Subramaniam SD, Doss B, Chanderasekar LD et al (2018) Scope of physiological and behavioural pain assessment techniques in children - a review. *Healthc Technol Lett* **5**(4): 124-29.
Subramanyam R, Varughese A, Willging JP et al (2013) Future of pediatric tonsillectomy and perioperative outcomes. *Int J Pediatr Otorhinolaryngol* **77**(2): 194-9.
Sucato DJ, Duey-Holtz A, Elerson E et al (2005) Postoperative analgesia following surgical correction for adolescent idiopathic scoliosis: a comparison of continuous epidural analgesia and patient-controlled analgesia. *Spine* **30**(2): 211–17.
Suchar A, Bailey A & Kopp V (2016) Postoperative Epidural Abscess in an Infant. *A A Case Rep* **6**(9): 277-9.
Sun J, Wu X, Meng Y et al (2010) Bupivacaine versus normal saline for relief of post-adenotonsillectomy pain in children: a meta-analysis. *Int J Pediatr Otorhinolaryngol* **74**(4): 369–73.
Sun Y, Liu J, Yuan X et al (2017) Effects of dexmedetomidine on emergence delirium in pediatric cardiac surgery. *Minerva Pediatr* **69**(3): 165-73.
Sung V, D'Amico F, Cabana MD et al (2018) Lactobacillus reuteri to Treat Infant Colic: A Meta-analysis. *Pediatrics* **141**(1).

Suominen PK, Ragg PG, McKinley DF et al (2004) Intrathecal morphine provides effective and safe analgesia in children after cardiac surgery. *Acta Anaesthesiol Scand* **48**(7): 875–82.
Suresh S, Barcelona SL, Young NM et al (2004a) Does a preemptive block of the great auricular nerve improve postoperative analgesia in children undergoing tympanomastoid surgery? *Anesth Analg* **98**(2): 330–33.
Suresh S, Barcelona SL, Young NM et al (2002) Postoperative pain relief in children undergoing tympanomastoid surgery: is a regional block better than opioids? *Anesth Analg* **94**(4): 859–62.
Suresh S & Bellig G (2004b) Regional anesthesia in a very low-birth-weight neonate for a neurosurgical procedure. *Reg Anesth Pain Med* **29**(1): 58-9.
Suresh S & De Oliveira GS, Jr. (2018a) Local anaesthetic dosage of peripheral nerve blocks in children: analysis of 40 121 blocks from the Pediatric Regional Anesthesia Network database. *Br J Anaesth* **120**(2): 317-22.
Suresh S, Ecoffey C, Bosenberg A et al (2018b) The European Society of Regional Anaesthesia and Pain Therapy/American Society of Regional Anesthesia and Pain Medicine Recommendations on Local Anesthetics and Adjuvants Dosage in Pediatric Regional Anesthesia. *Reg Anesth Pain Med* **43**(2): 211-16.
Suresh S, Long J, Birmingham PK et al (2015a) Are caudal blocks for pain control safe in children? an analysis of 18,650 caudal blocks from the Pediatric Regional Anesthesia Network (PRAN) database. *Anesth Analg* **120**(1): 151-6.
Suresh S, Schaldenbrand K, Wallis B et al (2014) Regional anaesthesia to improve pain outcomes in paediatric surgical patients: a qualitative systematic review of randomized controlled trials. *Br J Anaesth* **113**(3): 375–90.
Suresh S, Taylor LJ & De Oliveira GS, Jr. (2015b) Dose effect of local anesthetics on analgesic outcomes for the transversus abdominis plane (TAP) block in children: a randomized, double-blinded, clinical trial. *Paediatr Anaesth* **25**(5): 506-10.
Suresh S & Templeton L (2004c) Superficial cervical plexus block for vocal cord surgery in an awake pediatric patient. *Anesth Analg* **98**(6): 1656-7.
Suresh S & Voronov P (2012) Head and neck blocks in infants, children, and adolescents. *Paediatr Anaesth* **22**(1): 81-7.
Susam V, Friedel M, Basile P et al (2018) Efficacy of the Buzzy System for pain relief during venipuncture in children: a randomized controlled trial. *Acta Biomed* **89**(6-s): 6-16.
Sutters KA, Miaskowski C, Holdridge-Zeuner D et al (2010) 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* **26**(2): 95–103.
Svenson JE & Abernathy MK (2007) Ketamine for prehospital use: new look at an old drug. *Am J Emerg Med* **25**(8): 977–80.
Sylvester DC, Rafferty A, Bew S et al (2011) The use of ice-lollies for pain relief post-paediatric tonsillectomy. A single-blinded, randomised, controlled trial. *Clin Otolaryngol* **36**(6): 566-70.
Symons JA & Palmer GM (2008) Neuropathic pain and foot drop related to nerve injury after short duration surgery and caudal analgesia. *Clin J Pain* **24**(7): 647–49.
Taber SS & Mueller BA (2006) Drug-associated renal dysfunction. *Crit Care Clin* **22**(2): 357–74; viii.
Tachibana N, Yamauchi M, Sugino S et al (2012) Utility of longitudinal paramedian view of ultrasound imaging for middle thoracic epidural anesthesia in children. *J Anesth* **26**(2): 242–5.
Taddio A (2015a) Setting the Stage for Improved Practices During Vaccine Injections: A Knowledge Synthesis of Interventions for the Management of Pain and Fear. *Clin J Pain* **31**(10 Suppl): S1-2.
Taddio A, Flanders D, Weinberg E et al (2015b) A randomized trial of rotavirus vaccine versus sucrose solution for vaccine injection pain. *Vaccine* **33**(25): 2939-43.
Taddio A, Goldbach M, Ipp M et al (1995) Effect of neonatal circumcision on pain responses during vaccination in boys. *Lancet* **345**(8945): 291–92.
Taddio A, Ipp M, Vyas C et al (2014) Teaching parents to manage pain during infant immunizations: laying the foundation for better pain management practices. *Clin J Pain* **30**(11): 987–94.
Taddio A, Lee C, Yip A et al (2006) Intravenous morphine and topical tetracaine for treatment of pain in [corrected] neonates undergoing central line placement.[erratum appears in JAMA. 2006 Apr 5;295(13):1518]. *JAMA* **295**(7): 793–800.
Taddio A, McMurtry CM, Shah V et al (2015c) Reducing pain during vaccine injections: clinical practice guideline. *Cmaj* **187**(13): 975-82.
Taddio A, Riddell RP, Ipp M et al (2017a) A Longitudinal Randomized Trial of the Effect of Consistent Pain Management for Infant Vaccinations on Future Vaccination Distress. *J Pain* **18**(9): 1060-66.
Taddio A, Riddell RP, Ipp M et al (2017b) Relative effectiveness of additive pain interventions during vaccination in infants. *Cmaj* **189**(6): E227-e34.
Taddio A, Shah V, Atenafu E et al (2009) Influence of repeated painful procedures and sucrose analgesia on the development of hyperalgesia in newborn infants. *Pain* **144**(1-2): 43–48.
Taddio A, Shah V, Bucci L et al (2018) Effectiveness of a hospital-based postnatal parent education intervention about pain management during infant vaccination: a randomized controlled trial. *Cmaj* **190**(42): E1245-e52.
Taddio A, Shah V, McMurtry CM et al (2015d) Procedural and Physical Interventions for Vaccine Injections: Systematic Review of Randomized Controlled Trials and Quasi-Randomized Controlled Trials. *Clin J Pain* **31**(10 Suppl): S20-37.

Taddio A, Shah V, Stephens D et al (2011) Effect of liposomal lidocaine and sucrose alone and in combination for venipuncture pain in newborns. *Pediatrics* **127**(4): e940–47.
Taddio A, Wong H, Welkovics B et al (2016) A randomized trial of the effect of vaccine injection speed on acute pain in infants. *Vaccine* **34**(39): 4672-77.
Tadros A, Layman SM, Davis SM et al (2016) Emergency department visits by pediatric patients for poisoning by prescription opioids. *Am J Drug Alcohol Abuse* **42**(5): 550-55.
Taenzer A, Walker BJ, Bosenberg AT et al (2014a) Interscalene brachial plexus blocks under general anesthesia in children: is this safe practice?: A report from the Pediatric Regional Anesthesia Network (PRAN). *Reg Anesth Pain Med* **39**(6): 502-5.
Taenzer AH, Walker BJ, Bosenberg AT et al (2014b) Asleep versus awake: does it matter?: pediatric regional block complications by patient state: a report from the pediatric regional anesthesia network. *Reg Anesth Pain Med* **39**(4): 279–83.
Taicher BM, Routh JC, Eck JB et al (2017) The association between caudal anesthesia and increased risk of postoperative surgical complications in boys undergoing hypospadias repair. *Paediatr Anaesth* **27**(7): 688-94.
Tait AR, Bickham R, O'Brien LM et al (2016) The STBUR questionnaire for identifying children at risk for sleep-disordered breathing and postoperative opioid-related adverse events. *Paediatr Anaesth* **26**(7): 759-66.
Talon MD, Woodson LC, Sherwood ER et al (2009) Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. *J Burn Care Res* **30**(4): 599–605.
Tan L, Taylor E, Hannam JA et al (2016) Pharmacokinetics and analgesic effectiveness of intravenous parecoxib for tonsillectomy +/- adenoidectomy. *Paediatr Anaesth* **26**(12): 1126-35.
Tanne C, Javouhey E, Millet A et al (2016) Severe tramadol overdoses in children: A Case Series admitted to pediatric intensive care unit. *Journal of Clinical Toxicology* **6**(5).
Taplak AS & Bayat M (2019) Psychometric Testing of the Turkish Version of the Premature Infant Pain Profile Revised-PIPP-R. *J Pediatr Nurs* **48**: e49-e55.
Tay CL & Tan S (2002) Diclofenac or paracetamol for analgesia in paediatric myringotomy outpatients. *Anaesth Intensive Care* **30**(1): 55–59.
Tayeb BO, Eidelman A, Eidelman CL et al (2017) Topical anaesthetics for pain control during repair of dermal laceration. *Cochrane Database Syst Rev* **2**(2): CD005364.
Taylor J, Liley A & Anderson BJ (2013) The relationship between age and morphine infusion rate in children. *Paediatr Anaesth* **23**(1): 40–44.
Taylor M, Jakacki R, May C et al (2014) Ketamine PCA for treatment of end-of-life neuropathic pain in pediatrics. *Am J Hosp Palliat Care* **Epub ahead of print**.
Tekelioglu UY, Apuhan T, Akkaya A et al (2013) Comparison of topical tramadol and ketamine in pain treatment after tonsillectomy. *Paediatr Anaesth* **23**(6): 496–501.
Telfer P, Criddle J, Sandell J et al (2009) Intranasal diamorphine for acute sickle cell pain. *Arch Dis Child* **94**(12): 979–80.
Teo JH, Palmer GM & Davidson AJ (2011) Post-craniotomy pain in a paediatric population. *Anaesth Intensive Care* **39**(1): 89–94.
Ter Bruggen F, Eralp I, Jansen CK et al (2017) Efficacy of Dexmedetomidine as a Sole Sedative Agent in Small Diagnostic and Therapeutic Procedures: A Systematic Review. *Pain Pract* **17**(6): 829-40.
Teunkens A, Vermeulen K, Peters M et al (2019) Bupivacaine infiltration in children for postoperative analgesia after tonsillectomy: A randomised controlled trial. *Eur J Anaesthesiol* **36**(3): 206-14.
Teyin E, Derbent A, Balcioglu T et al (2006) The efficacy of caudal morphine or bupivacaine combined with general anesthesia on postoperative pain and neuroendocrine stress response in children. *Paediatr Anaesth* **16**(3): 290–96.
TGA (2004) *Review of Aspirin / Reye's syndrome warning statement.* https://www.tga.gov.au/sites/default/files/review-aspirin-reyes-syndrome-0404.pdf Accessed 25 December 2019
TGA (2013) *Rethinking medicines decision-making in Australian Hospitals: Guiding Principles for the quality use of off-label medicines.* http://www.catag.org.au/wp-content/uploads/2012/08/OKA9963-CATAG-Rethinking-Medicines-Decision-Making-final1.pdf Accessed 22 February 2020
TGA (2015) *Medicines Safety Update Volume 6 Number 4, August 2015: Tramadol oral drops - not for children under the age of 12 years.* https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-6-number-4-august-2015#tramadol Accessed 17 February 2020
TGA (2017) *Safety review of codeine and ultrarapid metabolisers.* https://www.tga.gov.au/alert/safety-review-codeine-use-children-and-ultra-rapid-metabolisers Accessed 17 February 2020
TGA (2019) *Significant decrease in the amount of codeine supplied to Australians.* https://www.tga.gov.au/media-release/significant-decrease-amount-codeine-supplied-australians Accessed 17 February 2020
Thaker S, McKenna E, Rader C et al (2019) Pain Management in Pectus Excavatum Surgery: A Comparison of Subcutaneous Catheters Versus Epidurals in a Pediatric Population. *J Laparoendosc Adv Surg Tech A* **29**(2): 261-66.
Than NN, Soe HHK, Palaniappan SK et al (2019) Magnesium for treating sickle cell disease. *Cochrane Database Syst Rev* **9**: CD011358.

Thienprayoon R, Porter K, Tate M et al (2017) Risk Stratification for Opioid Misuse in Children, Adolescents, and Young Adults: A Quality Improvement Project. *Pediatrics* **139**(1).
Thomas CR, Brazeal BA, Rosenberg L et al (2003) Phantom limb pain in pediatric burn survivors. *Burns* **29**(2): 139-42.
Thomas DT & Tulgar S (2018a) Ultrasound-guided Erector Spinae Plane Block in a Child Undergoing Laparoscopic Cholecystectomy. *Cureus* **10**(2): e2241.
Thomas JJ, Levek C, Quick HD et al (2018b) Utility of gabapentin in meeting physical therapy goals following posterior spinal fusion in adolescent patients with idiopathic scoliosis. *Paediatr Anaesth* **28**(6): 558-63.
Thomas ML, Roebuck D, Yule C et al (2010) The effect of volume of local anesthetic on the anatomic spread of caudal block in children aged 1-7 years. *Paediatr Anaesth* **20**(11): 1017–21.
Thompson JP & Thompson DF (2016) Nebulized Fentanyl in Acute Pain: A Systematic Review. *Ann Pharmacother* **50**(10): 882-91.
Thompson ME & Haynes B (2015) Ultrasound-guided thoracic paravertebral block catheter experience in 2 neonates. *J Clin Anesth* **27**(6): 514-6.
Thorsell Cederberg J, Weineland Strandskov S, Dahl J et al (2017) Parents' relationship to pain during children's cancer treatment - a preliminary validation of the Pain Flexibility Scale for Parents. *J Pain Res* **10**: 507-14.
Tibboel D, Anand KJ & van den Anker JN (2005) The pharmacological treatment of neonatal pain. *Semin Fetal Neonatal Med* **10**(2): 195–205.
Titirungruang C, Seresirikachorn K, Kasemsuwan P et al (2019) The use of steroids to reduce complications after tonsillectomy: a systematic review and meta-analysis of randomized controlled studies. *Eur Arch Otorhinolaryngol* **276**(2): 585-604.
Tobias JD (1994) Continuous femoral nerve block to provide analgesia following femur fracture in a paediatric ICU population. *Anaesth Intensive Care* **22**(5): 616-8.
Tobias JD (2013a) Applications of nitrous oxide for procedural sedation in the pediatric population. *Pediatr Emerg Care* **29**(2): 245–65.
Tobias JD (2014) Acute pain management in infants and children-Part 1: Pain pathways, pain assessment, and outpatient pain management. *Pediatr Ann* **43**(7): e163-8.
Tobias JD & Baker DK (1992a) Patient-controlled analgesia with fentanyl in children. *Clin Pediatr (Phila)* **31**(3): 177–79.
Tobias JD & Chrysostomou C (2013b) Dexmedetomidine: antiarrhythmic effects in the pediatric cardiac patient. *Pediatr Cardiol* **34**(4): 779-85.
Tobias JD, Phipps S, Smith B et al (1992b) Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. *Pediatrics* **90**(4): 537–41.
Toce MS, Burns MM & O'Donnell KA (2017) Clinical effects of unintentional pediatric buprenorphine exposures: experience at a single tertiary care center. *Clin Toxicol (Phila)* **55**(1): 12-17.
Toce MS, Kim H, Chung S et al (2019) Prolonged central apnoea after intravenous morphine administration in a 12-year-old male with a UGT1A1 loss-of-function polymorphism. *Br J Clin Pharmacol* **85**(1): 258-62.
Tome-Pires C & Miro J (2012) Hypnosis for the management of chronic and cancer procedure-related pain in children. *Int J Clin Exp Hypn* **60**(4): 432–57.
Tomlinson D, Judd P, Hendershot E et al (2008) Establishing literature-based items for an oral mucositis assessment tool in children. *J Pediatr Oncol Nurs* **25**(3): 139–47.
Tomlinson D, von Baeyer CL, Stinson JN et al (2010) A systematic review of faces scales for the self-report of pain intensity in children. *Pediatrics* **126**(5): e1168–98.
Tong HJ, Alzahrani FS, Sim YF et al (2018) Anaesthetic efficacy of articaine versus lidocaine in children's dentistry: a systematic review and meta-analysis. *Int J Paediatr Dent* **28**(4): 347-60.
Tong HY, Medrano N, Borobia AM et al (2017) Hepatotoxicity induced by acute and chronic paracetamol overdose in children: Where do we stand? *World J Pediatr* **13**(1): 76-83.
Tong Y, Ding XB, Wang X et al (2014a) Ketamine peritonsillar infiltration during tonsillectomy in pediatric patients: An updated meta-analysis. *Int J Pediatr Otorhinolaryngol* **78**(10): 1735-41.
Tong Y, Ren H, Ding X et al (2014b) Analgesic effect and adverse events of dexmedetomidine as additive for pediatric caudal anesthesia: a meta-analysis. *Paediatr Anaesth* **24**(12): 1224-30.
Topal E, Celiksoy MH, Catal F et al (2016) The value of the clinical history for the diagnosis of immediate nonsteroidal anti-inflammatory drug hypersensitivity and safe alternative drugs in children. *Allergy Asthma Proc* **37**(1): 57-63.
Topal K, Aktan B, Sakat MS et al (2017) Post-operative pain control after tonsillectomy: dexametasone vs tramadol. *Acta Otolaryngol* **137**(6): 618-22.
Townsend JA, Ganzberg S & Thikkurissy S (2009) The effect of local anesthetic on quality of recovery characteristics following dental rehabilitation under general anesthesia in children. *Anesth Prog* **56**(4): 115–22.
Trautmann E, Lackschewitz H & Kroner-Herwig B (2006) Psychological treatment of recurrent headache in children and adolescents--a meta-analysis. *Cephalalgia* **26**(12): 1411–26.
Tremlett MR (2013) Wither codeine? *Paediatr Anaesth* **23**(8): 677–83.
Triarico S, Capozza MA, Mastrangelo S et al (2019) Intranasal therapy with opioids for children and adolescents with cancer: results from clinical studies. *Support Care Cancer* **27**(10): 3639-45.

Trifa M, Ben Khalifa S, Jendoubi A et al (2012) Clonidine does not improve quality of ropivacaine axillary brachial plexus block in children. *Paediatr Anaesth* **22**(5): 425–29.
Trifa M, Tumin D & Tobias JD (2018) Dexmedetomidine as an adjunct for caudal anesthesia and analgesia in children. *Minerva Anestesiol* **84**(7): 836-47.
Tripi PA, Poe-Kochert C, Potzman J et al (2008) Intrathecal morphine for postoperative analgesia in patients with idiopathic scoliosis undergoing posterior spinal fusion. *Spine (Phila Pa 1976)* **33**(20): 2248-51.
Trottier ED, Bailey B, Dauphin-Pierre S et al (2010) Clinical outcomes of children treated with intravenous prochlorperazine for migraine in a pediatric emergency department. *J Emerg Med* **39**(2): 166-73.
Trottier ED, Bailey B, Lucas N et al (2012) Prochlorperazine in children with migraine: a look at its effectiveness and rate of akathisia. *Am J Emerg Med* **30**(3): 456-63.
Trzcinski S, Rosenberg RE, Vasquez Montes D et al (2019) Use of Gabapentin in Posterior Spinal Fusion is Associated With Decreased Postoperative Pain and Opioid Use in Children and Adolescents. *Clin Spine Surg* **32**(5): 210-14.
Tsoukas C, Eyster ME, Shingo S et al (2006) Evaluation of the efficacy and safety of etoricoxib in the treatment of hemophilic arthropathy. *Blood* **107**(5): 1785–90.
Tsui BC (2004) Thoracic epidural catheter placement in infants via the caudal approach under electrocardiographic guidance: simplification of the original technique. *Anesth Analg* **98**(1): 273.
Tsui BC & Finucane B (2002) Verifying accurate placement of an epidural catheter tip using electrical stimulation. *Anesth Analg* **94**(6): 1670–71; author reply 71.
Tsui BC & Pillay JJ (2010) Evidence-based medicine: Assessment of ultrasound imaging for regional anesthesia in infants, children, and adolescents. *Reg Anesth Pain Med* **35**(2 Suppl): S47–54.
Tsui BCH, Fonseca A, Munshey F et al (2019) The erector spinae plane (ESP) block: A pooled review of 242 cases. *J Clin Anesth* **53**: 29-34.
Tsutaoka BT, Ho RY, Fung SM et al (2015) Comparative Toxicity of Tapentadol and Tramadol Utilizing Data Reported to the National Poison Data System. *Ann Pharmacother* **49**(12): 1311-6.
Tsze DS, Hirschfeld G, Dayan PS et al (2018) Defining No Pain, Mild, Moderate, and Severe Pain Based on the Faces Pain Scale-Revised and Color Analog Scale in Children With Acute Pain. *Pediatr Emerg Care* **34**(8): 537-44.
Tsze DS, Hirschfeld G, von Baeyer CL et al (2015) Clinically significant differences in acute pain measured on self-report pain scales in children. *Acad Emerg Med* **22**(4): 415-22.
Tsze DS, Hirschfeld G, von Baeyer CL et al (2019a) Changes in Pain Score Associated With Clinically Meaningful Outcomes in Children With Acute Pain. *Academic Emergency Medicine* **26**(9): <xocs:firstpage xmlns:xocs=""/>.
Tsze DS, Pan SS, DePeter KC et al (2019b) Intranasal hydromorphone for treatment of acute pain in children: A pilot study. *Am J Emerg Med* **37**(6): 1128-32.
Tsze DS, Steele DW, Machan JT et al (2012) Intranasal ketamine for procedural sedation in pediatric laceration repair: a preliminary report. *Pediatr Emerg Care* **28**(8): 767–70.
Tsze DS, von Baeyer CL, Bulloch B et al (2013) Validation of self-report pain scales in children. *Pediatrics* **132**(4): e971–79.
Tu Z, Tan X, Li S et al (2019) The Efficacy and Safety of Dexmedetomidine Combined with Bupivacaine on Caudal Epidural Block in Children: A Meta-Analysis. *Med Sci Monit* **25**: 165-73.
Turkoz A, Balci ST, Can Guner M et al (2013) Anesthesia management with single injection paravertebral block for aorta coarctation in infant. *Paediatr Anaesth* **23**(11): 1078–83.
Turner AL, Stevenson MD & Cross KP (2014) Impact of ultrasound-guided femoral nerve blocks in the pediatric emergency department. *Pediatr Emerg Care* **30**(4): 227-9.
Turtle EJ, Dear JW & Webb DJ (2013) A systematic review of the effect of paracetamol on blood pressure in hypertensive and non-hypertensive subjects. *Br J Clin Pharmacol* **75**(6): 1396–405.
Tutelman PR, Chambers CT, Stinson JN et al (2018) Pain in Children With Cancer: Prevalence, Characteristics, and Parent Management. *Clin J Pain* **34**(3): 198-206.
Tuttle KL, Schneider TR, Henrickson SE et al (2016) Aspirin-exacerbated respiratory disease: not always "adult-onset". *J Allergy Clin Immunol Pract* **4**(4): 756-8.
Tutuncu AC, Kendigelen P, Ashyyeralyeva G et al (2018) Pudendal Nerve Block Versus Penile Nerve Block in Children Undergoing Circumcision. *Urol J* **15**(3): 109-15.
Tuzcu K, Coskun M, Tuzcu EA et al (2015) Effectiveness of sub-Tenon's block in pediatric strabismus surgery. *Braz J Anesthesiol* **65**(5): 349-52.
Twycross A, Voepel-Lewis T, Vincent C et al (2015) A debate on the proposition that self-report is the gold standard in assessment of pediatric pain intensity. *Clin J Pain* **31**(8): 707-12.
Tzvetkov M (2017) OCT1 pharmacogenetics in pain management: is a clinical application within reach? *Pharmacogenetics* **18**(16): 1515-23.
Uchinami Y, Sakuraya F, Tanaka N et al (2017) Comparison of the analgesic efficacy of ultrasound-guided rectus sheath block and local anesthetic infiltration for laparoscopic percutaneous extraperitoneal closure in children. *Paediatr Anaesth* **27**(5): 516-23.
Ueki S, Yamagami Y & Makimoto K (2019) Effectiveness of vibratory stimulation on needle-related procedural pain in children: a systematic review. *JBI Database System Rev Implement Rep* **17**(7): 1428-63.

Ueshima H & Otake H (2018) Clinical experiences of erector spinae plane block for children. *J Clin Anesth* **44**: 41.
Ugur KS, Karabayirli S, Demircioglu RI et al (2013) The comparison of preincisional peritonsillar infiltration of ketamine and tramadol for postoperative pain relief on children following adenotonsillectomy. *Int J Pediatr Otorhinolaryngol* **77**(11): 1825–29.
Ugur MB, Yilmaz M, Altunkaya H et al (2008) Effects of intramuscular and peritonsillar injection of tramadol before tonsillectomy: a double blind, randomized, placebo-controlled clinical trial. *Int J Pediatr Otorhinolaryngol* **72**(2): 241–48.
Uri O, Yosefov L, Haim A et al (2011) Lidocaine gel as an anesthetic protocol for nasogastric tube insertion in the ED. *Am J Emerg Med* **29**(4): 386–90.
Usichenko TI, Wolters P, Anders EF et al (2016) Acupuncture Reduces Pain and Autonomic Distress During Injection of Local Anesthetic in Children: A Pragmatic Crossover Investigation. *Clin J Pain* **32**(1): 82-6.
Uspal NG, Strelitz B, Gritton J et al (2018) Randomized Clinical Trial of Lidocaine Analgesia for Transurethral Bladder Catheterization Delivered via Blunt Tipped Applicator in Young Children. *Pediatr Emerg Care* **34**(4): 273-79.
Usuba K, Price VE, Blanchette V et al (2019) Impact of prophylaxis on health-related quality of life of boys with hemophilia: An analysis of pooled data from 9 countries. *Res Pract Thromb Haemost* **3**(3): 397-404.
Uysal HY, Takmaz SA, Yaman F et al (2011) The efficacy of intravenous paracetamol versus tramadol for postoperative analgesia after adenotonsillectomy in children. *J Clin Anesth* **23**(1): 53–57.
Vagnoli L, Bettini A, Amore E et al (2019) Relaxation-guided imagery reduces perioperative anxiety and pain in children: a randomized study. *Eur J Pediatr* **178**(6): 913-21.
Vagnoli L, Caprilli S, Vernucci C et al (2015) Can presence of a dog reduce pain and distress in children during venipuncture? *Pain Manag Nurs* **16**(2): 89-95.
Valeri BO, Gaspardo CM, Martinez FE et al (2014) Pain reactivity in preterm neonates: examining the sex differences. *Eur J Pain* **18**(10): 1431-9.
Valeri BO, Holsti L & Linhares MB (2015) Neonatal pain and developmental outcomes in children born preterm: a systematic review. *Clin J Pain* **31**(4): 355-62.
Valitalo P, Kokki M, Ranta VP et al (2017) Maturation of Oxycodone Pharmacokinetics in Neonates and Infants: a Population Pharmacokinetic Model of Three Clinical Trials. *Pharm Res* **34**(5): 1125-33.
Valitalo P, Kumpulainen E, Manner M et al (2012) Plasma and cerebrospinal fluid pharmacokinetics of naproxen in children. *J Clin Pharmacol* **52**(10): 1516–26.
Valkenburg AJ, Boerlage AA, Ista E et al (2011) The COMFORT-behavior scale is useful to assess pain and distress in 0- to 3-year-old children with Down syndrome. *Pain* **152**(9): 2059–64.
Valkenburg AJ, Calvier EA, van Dijk M et al (2016) Pharmacodynamics and Pharmacokinetics of Morphine After Cardiac Surgery in Children With and Without Down Syndrome. *Pediatr Crit Care Med* **17**(10): 930-38.
Valkenburg AJ, van den Bosch GE, de Graaf J et al (2015) Long-Term Effects of Neonatal Morphine Infusion on Pain Sensitivity: Follow-Up of a Randomized Controlled Trial. *J Pain* **16**(9): 926-33.
Valkenburg AJ, van Dijk M, de Klein A et al (2010) Pain management in intellectually disabled children: Assessment, treatment, and translational research. *Dev Disabil Res Rev* **16**(3): 248–57.
Valkenburg AJ, van Dijk M, de Leeuw TG et al (2012) Anaesthesia and postoperative analgesia in surgical neonates with or without Down's syndrome: is it really different? *Br J Anaesth* **108**(2): 295–301.
van Baar ME, Polinder S, Essink-Bot ML et al (2011) Quality of life after burns in childhood (5–15 years): Children experience substantial problems. *Burns* **37**(6): 930–38.
Van Cleve WC (2017) Pediatric Posttonsillectomy Analgesia Before and After the Black Box Warning Against Codeine Use. *JAMA Otolaryngol Head Neck Surg* **143**(10): 1052-54.
van den Anker JN & Tibboel D (2011) Pain relief in neonates: when to use intravenous paracetamol. *Arch Dis Child* **96**(6): 573–74.
van den Heuvel I, Gottschalk A, Langer M et al (2016) Feasibility, efficacy, and safety of ultrasound-guided axillary plexus blockade in pediatric patients with epidermolysis bullosa dystrophica. *Paediatr Anaesth* **26**(4): 405-8.
van der Geest IM, Darlington AS, Streng IC et al (2014) Parents' experiences of pediatric palliative care and the impact on long-term parental grief. *J Pain Symptom Manage* **47**(6): 1043-53.
van der Marel CD, Anderson BJ, Romsing J et al (2004) Diclofenac and metabolite pharmacokinetics in children. *Paediatr Anaesth* **14**(6): 443–51.
van der Marel CD, Peters JW, Bouwmeester NJ et al (2007) Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants. *Br J Anaesth* **98**(3): 372–9.
van Dijk M, Bouwmeester NJ, Duivenvoorden HJ et al (2002) Efficacy of continuous versus intermittent morphine administration after major surgery in 0-3-year-old infants; a double-blind randomized controlled trial. *Pain* **98**(3): 305–13.
van Dijk M, de Boer JB, Koot HM et al (2000) The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. *Pain* **84**(2-3): 367–77.
van Dijk M, O'Flaherty LA, Hoedemaker T et al (2018) Massage has no observable effect on distress in children with burns: A randomized, observer-blinded trial. *Burns* **44**(1): 99-107.

van Dijk M, Roofthooft DW, Anand KJ et al (2009) Taking up the challenge of measuring prolonged pain in (premature) neonates: the COMFORTneo scale seems promising. *Clin J Pain* **25**(7): 607–16.
van Dijk M & Tibboel D (2012) Update on pain assessment in sick neonates and infants. *Pediatr Clin North Am* **59**(5): 1167–81.
Van Obbergh LJ, Roelants FA, Veyckemans F et al (2003) In children, the addition of epinephrine modifies the pharmacokinetics of ropivacaine injected caudally. *Can J Anaesth* **50**(6): 593–98.
van Schoor AN, Bosman MC, Venter G et al (2018) Determining the extent of the dural sac for the performance of caudal epidural blocks in newborns. *Paediatr Anaesth* **28**(10): 852-56.
Vandenbossche JR, H; & Solanki B (2015) Single- and Multiple-dose pharmacokinetic studyes of tramadol immediate-release tablets in children and adolescents. *Clin Pharmacol Drug Dev* **4**(3): 184-92.
VanderBeek BL, Mehlman CT, Foad SL et al (2006) The use of conscious sedation for pain control during forearm fracture reduction in children: does race matter? *J Pediatr Orthop* **26**(1): 53-7.
Varghese E, Deepak KM & Chowdary KV (2009) Epinephrine test dose in children: is it interpretable on ECG monitor? *Paediatr Anaesth* **19**(11): 1090–95.
Varley A, Sarginson J & Young A (2016) Evidence-based first aid advice for paediatric burns in the United Kingdom. *Burns* **42**(3): 571-7.
Varni JW, Stucky BD, Thissen D et al (2010) PROMIS Pediatric Pain Interference Scale: an item response theory analysis of the pediatric pain item bank. *J Pain* **11**(11): 1109–19.
Vashisht R, Bendon AA, Okonkwo I et al (2019) A study of the dosage and duration for levobupivacaine infusion by the caudal-epidural route in infants aged 3-6 months. *Paediatr Anaesth* **29**(2): 161-68.
Vecchione T, Zurakowski D & Boretsky K (2016) Thoracic Paravertebral Nerve Blocks in Pediatric Patients: Safety and Clinical Experience. *Anesth Analg* **123**(6): 1588-90.
Veneziano G, Iliev P, Tripi J et al (2016) Continuous chloroprocaine infusion for thoracic and caudal epidurals as a postoperative analgesia modality in neonates, infants, and children. *Paediatr Anaesth* **26**(1): 84-91.
Veneziano G, Martin DP, Beltran R et al (2018) Dexamethasone as an Adjuvant to Femoral Nerve Block in Children and Adolescents Undergoing Knee Arthroscopy: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial. *Reg Anesth Pain Med* **43**(4): 438-44.
Veneziano G & Tobias JD (2017) Chloroprocaine for epidural anesthesia in infants and children. *Paediatr Anaesth* **27**(6): 581-90.
Venkatasubramanian R, Fukuda T, Niu J et al (2014) ABCC3 and OCT1 genotypes influence pharmacokinetics of morphine in children. *Pharmacogenomics* **15**(10): 1297–309.
Verghese ST, Hannallah RS, Rice LJ et al (2002) Caudal anesthesia in children: effect of volume versus concentration of bupivacaine on blocking spermatic cord traction response during orchidopexy. *Anesth Analg* **95**(5): 1219–23; table of contents.
Verhulst SL, Van Gaal L, De Backer W et al (2008) The prevalence, anatomical correlates and treatment of sleep-disordered breathing in obese children and adolescents. *Sleep Med Rev* **12**(5): 339-46.
Verriotis M, Chang P, Fitzgerald M et al (2016a) The development of the nociceptive brain. *Neuroscience* **338**: 207-19.
Verriotis M, Fabrizi L, Lee A et al (2016b) Mapping Cortical Responses to Somatosensory Stimuli in Human Infants with Simultaneous Near-Infrared Spectroscopy and Event-Related Potential Recording. *eNeuro* **3**(2).
Verriotis M, Jones L, Whitehead K et al (2018) The distribution of pain activity across the human neonatal brain is sex dependent. *Neuroimage* **178**: 69-77.
Veyckemans F, Anderson BJ, Wolf AR et al (2014) Intravenous paracetamol dosage in the neonate and small infant. *Br J Anaesth* **112**(2): 380–81.
Veyckemans F, Van Obbergh LJ & Gouverneur JM (1992) Lessons from 1100 pediatric caudal blocks in a teaching hospital. *Reg Anesth* **17**(3): 119–25.
Vicchio N, Mossetti V & Ivani G (2015) Evaluation of 18279 blocks in a pediatric hospital. *Anesth Pain Med* **5**(2): e22897.
Vicencio-Rosas E, Perez-Guille MG, Flores-Perez C et al (2018) Buprenorphine and pain treatment in pediatric patients: an update. *J Pain Res* **11**: 549-59.
Villalobos MA, Veneziano G, Miller R et al (2019) Evaluation of postoperative analgesia in pediatric patients after hip surgery: lumbar plexus versus caudal epidural analgesia. *J Pain Res* **12**: 997-1001.
Vilo S, Rautiainen P, Kaisti K et al (2008) Pharmacokinetics of intravenous dexmedetomidine in children under 11 yr of age. *Br J Anaesth* **100**(5): 697–700.
Vinall J, Miller SP, Chau V et al (2012) Neonatal pain in relation to postnatal growth in infants born very preterm. *Pain* **153**(7): 1374–81.
Visoiu M (2014a) Outpatient analgesia via paravertebral peripheral nerve block catheter and On-Q pump--a case series. *Paediatr Anaesth* **24**(8): 875-8.
Visoiu M (2015) Paediatric regional anaesthesia: a current perspective. *Curr Opin Anaesthesiol* **28**(5): 577-82.
Visoiu M, Boretsky KR, Goyal G et al (2012) Postoperative analgesia via transversus abdominis plane (TAP) catheter for small weight children-our initial experience. *Paediatr Anaesth* **22**(3): 281–84.
Visoiu M, Joy LN, Grudziak JS et al (2014b) The effectiveness of ambulatory continuous peripheral nerve blocks for postoperative pain management in children and adolescents. *Paediatr Anaesth* **24**(11): 1141-8.

Visoiu M & Yakovleva N (2013) Continuous postoperative analgesia via quadratus lumborum block - an alternative to transversus abdominis plane block. *Paediatr Anaesth* **23**(10): 959–61.
Vitale MG, Choe JC, Hwang MW et al (2003) Use of ketorolac tromethamine in children undergoing scoliosis surgery. an analysis of complications. *Spine J* **3**(1): 55–62.
Vlenterie R, Wood ME, Brandlistuen RE et al (2016) Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: a propensity score matched cohort study. *Int J Epidemiol* **45**(6): 1998-2008.
Vlok R, Melhuish TM, Chong C et al (2017) Adjuncts to local anaesthetics in tonsillectomy: a systematic review and meta-analysis. *J Anesth* **31**(4): 608-16.
Voepel-Lewis T, Marinkovic A, Kostrzewa A et al (2008) The prevalence of and risk factors for adverse events in children receiving patient-controlled analgesia by proxy or patient-controlled analgesia after surgery. *Anesth Analg* **107**(1): 70–75.
Voepel-Lewis T, Piscotty RJ, Jr., Annis A et al (2012) Empirical review supporting the application of the "pain assessment as a social transaction" model in pediatrics. *J Pain Symptom Manage* **44**(3): 446–57.
Voepel-Lewis T, Wagner D & Tait AR (2015a) Leftover prescription opioids after minor procedures: an unwitting source for accidental overdose in children. *JAMA Pediatr* **169**(5): 497-8.
Voepel-Lewis T, Zikmund-Fisher B, Smith EL et al (2015b) Opioid-related adverse drug events: do parents recognize the signals? *Clin J Pain* **31**(3): 198-205.
Voiriot G, Philippot Q, Elabbadi A et al (2019) Risks Related to the Use of Non-Steroidal Anti-Inflammatory Drugs in Community-Acquired Pneumonia in Adult and Pediatric Patients. *J Clin Med* **8**(6).
von Baeyer CL (2009a) Numerical rating scale for self-report of pain intensity in children and adolescents: recent progress and further questions. *Eur J Pain* **13**(10): 1005-7.
von Baeyer CL (2014) Self-report: the primary source in assessment after infancy. In: *Oxford Textbook of Paediatric Pain* 1st edn. McGrath P (eds). Oxford.
von Baeyer CL, Forsyth SJ, Stanford EA et al (2009b) Response biases in preschool children's ratings of pain in hypothetical situations. *Eur J Pain* **13**(2): 209–13.
von Baeyer CL, Jaaniste T, Vo HLT et al (2017) Systematic Review of Self-Report Measures of Pain Intensity in 3- and 4-Year-Old Children: Bridging a Period of Rapid Cognitive Development. *J Pain* **18**(9): 1017-26.
von Baeyer CL & Spagrud LJ (2007) Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. *Pain* **127**(1-2): 140–50.
Vondracek P, Oslejskova H, Kepak T et al (2009) Efficacy of pregabalin in neuropathic pain in paediatric oncological patients. *Eur J Paediatr Neurol* **13**(4): 332-6.
Voronov P, Tobin MJ, Billings K et al (2008) Postoperative pain relief in infants undergoing myringotomy and tube placement: comparison of a novel regional anesthetic block to intranasal fentanyl--a pilot analysis. *Paediatr Anaesth* **18**(12): 1196-201.
Walco GA, Kopecky EA, Weisman SJ et al (2018) Clinical trial designs and models for analgesic medications for acute pain in neonates, infants, toddlers, children, and adolescents: ACTTION recommendations. *Pain* **159**(2): 193-205.
Walker BJ, Flack SH & Bosenberg AT (2011) Predicting lumbar plexus depth in children and adolescents. *Anesth Analg* **112**(3): 661–65.
Walker BJ, Long JB, De Oliveira GS et al (2015a) Peripheral nerve catheters in children: an analysis of safety and practice patterns from the pediatric regional anesthesia network (PRAN). *Br J Anaesth* **115**(3): 457-62.
Walker BJ, Long JB, Sathyamoorthy M et al (2018) Complications in Pediatric Regional Anesthesia: An Analysis of More than 100,000 Blocks from the Pediatric Regional Anesthesia Network. *Anesthesiology* **129**(4): 721-32.
Walker BJ, Noonan KJ & Bosenberg AT (2012a) Evolving compartment syndrome not masked by a continuous peripheral nerve block: evidence-based case management. *Reg Anesth Pain Med* **37**(4): 393–97.
Walker SM (2008) Pain in children: Recent advances and ongoing challenges. *Br J Anaesth* **101**(1): 101–10.
Walker SM (2013) Biological and neurodevelopmental implications of neonatal pain. *Clin Perinatol* **40**(3): 471–91.
Walker SM (2015b) Pain after surgery in children: clinical recommendations. *Current opinion in anaesthesiology* **28**(5): 570-76.
Walker SM, Franck LS, Fitzgerald M et al (2009) Long-term impact of neonatal intensive care and surgery on somatosensory perception in children born extremely preterm. *Pain* **141**(1–2): 79–87.
Walker SM, Grafe M & Yaksh TL (2012b) Intrathecal clonidine in the neonatal rat: dose-dependent analgesia and evaluation of spinal apoptosis and toxicity. *Anesth Analg* **115**(2): 450–60.
Walker SM, Westin BD, Deumens R et al (2010) Effects of intrathecal ketamine in the neonatal rat: evaluation of apoptosis and long-term functional outcome. *Anesthesiology* **113**(1): 147–59.
Walker SM & Yaksh TL (2012c) Neuraxial analgesia in neonates and infants: a review of clinical and preclinical strategies for the development of safety and efficacy data. *Anesth Analg* **115**(3): 638–62.
Walther-Larsen S, Pedersen MT, Friis SM et al (2017) Pain prevalence in hospitalized children: a prospective cross-sectional survey in four Danish university hospitals. *Acta Anaesthesiol Scand* **61**(3): 328-37.
Walther-Larsen S, Petersen T, Friis SM et al (2019) Immersive Virtual Reality for Pediatric Procedural Pain: A Randomized Clinical Trial. *Hosp Pediatr* **9**(7): 501-07.

Wang C, Allegaert K, Tibboel D et al (2014) Population pharmacokinetics of paracetamol across the human age-range from (pre)term neonates, infants, children to adults. *J Clin Pharmacol* **54**(6): 619–29.
Wang CY, Ihmsen H, Hu ZY et al (2019a) Pharmacokinetics of Intranasally Administered Dexmedetomidine in Chinese Children. *Front Pharmacol* **10**: 756.
Wang F, Wang Q, Li C et al (2017) The role of Celsr3 in the development of central somatosensory projections from dorsal root ganglia. *Neuroscience* **359**: 267-76.
Wang H, Liu G, Fu W et al (2015) The effect of infraorbital nerve block on emergence agitation in children undergoing cleft lip surgery under general anesthesia with sevoflurane. *Paediatr Anaesth* **25**(9): 906-10.
Wang HL, Zhang GY, Dai WX et al (2019b) Dose-dependent neurotoxicity caused by the addition of perineural dexmedetomidine to ropivacaine for continuous femoral nerve block in rabbits. *J Int Med Res* **47**(6): 2562-70.
Wang X, Yi Y, Tang D et al (2018) Gabapentin as an Adjuvant Therapy for Prevention of Acute Phantom-Limb Pain in Pediatric Patients Undergoing Amputation for Malignant Bone Tumors: A Prospective Double-Blind Randomized Controlled Trial. *J Pain Symptom Manage* **55**(3): 721-27.
Wani T, Beltran R, Veneziano G et al (2018) Dura to spinal cord distance at different vertebral levels in children and its implications on epidural analgesia: A retrospective MRI-based study. *Paediatr Anaesth* **28**(4): 338-41.
Ward RM, Drover DR, Hammer GB et al (2014) The pharmacokinetics of methadone and its metabolites in neonates, infants, and children. *Paediatr Anaesth* **24**(6): 591-601.
Wasiak J, Cleland H, Campbell F et al (2013) Dressings for superficial and partial thickness burns. *Cochrane Database Syst Rev* **3**: CD002106.
Waterhouse MR, Liu DR & Wang VJ (2013) Cryotherapeutic topical analgesics for pediatric intravenous catheter placement: ice versus vapocoolant spray. *Pediatr Emerg Care* **29**(1): 8–12.
Wathen JE, Gao D, Merritt G et al (2007) A randomized controlled trial comparing a fascia iliaca compartment nerve block to a traditional systemic analgesic for femur fractures in a pediatric emergency department. *Ann Emerg Med* **50**(2): 162-71, 71.e1.
Watkins N (2006) Paediatric prehospital analgesia in Auckland. *Emerg Med Australas* **18**(1): 51–56.
Weber F, Wulf H, Gruber M et al (2004) S-ketamine and s-norketamine plasma concentrations after nasal and i.v. administration in anesthetized children. *Paediatr Anaesth* **14**(12): 983–88.
Weerink MAS, Struys M, Hannivoort LN et al (2017) Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. *Clin Pharmacokinet* **56**(8): 893-913.
Weiner DL, Hibberd PL, Betit P et al (2003) Preliminary assessment of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients with sickle cell disease. *Jama* **289**(9): 1136–42.
Weintraub Y, Rabinowicz N, Hanuka P et al (2014) Medical clowns facilitate nitrous oxide sedation during intra-articular corticosteroid injection for juvenile idiopathic arthritis. *Isr Med Assoc J* **16**(12): 771-3.
Weintraud M, Lundblad M, Kettner SC et al (2009) Ultrasound versus landmark-based technique for ilioinguinal-iliohypogastric nerve blockade in children: the implications on plasma levels of ropivacaine. *Anesth Analg* **108**(5): 1488-92.
Weintraud M, Marhofer P, Bosenberg A et al (2008) Ilioinguinal/iliohypogastric blocks in children: where do we administer the local anesthetic without direct visualization? *Anesth Analg* **106**(1): 89–93.
Weiser G, Cohen D, Krauss B et al (2014) Premedication with midazolam for urethral catheterization of febrile infants. *Eur J Emerg Med* **21**(4): 314-8.
Weisman S, Bernstein B & Schechter N (1998) Consequences of inadequate analgesia during painful procedures in children. *Arch Pediatr Adolesc Med* **152**(2): 147–49.
Weiss JE, Haines KA, Chalom EC et al (2015) A randomized study of local anesthesia for pain control during intra-articular corticosteroid injection in children with arthritis. *Pediatr Rheumatol Online J* **13**: 36.
Weisz K, Bajaj L, Deakyne SJ et al (2017) Adverse Events During a Randomized Trial of Ketamine Versus Co-Administration of Ketamine and Propofol for Procedural Sedation in a Pediatric Emergency Department. *J Emerg Med* **53**(1): 1-9.
Weksler N, Nash M, Rozentsveig V et al (2001) Vocal cord paralysis as a consequence of peritonsillar infiltration with bupivacaine. *Acta Anaesthesiol Scand* **45**(8): 1042-4.
Weldon BC, Connor M & White PF (1993) Pediatric PCA: the role of concurrent opioid infusions and nurse-controlled analgesia. *Clin J Pain* **9**(1): 26–33.
Weng YM, Chang YC & Lin YJ (2010) Triage pain scales cannot predict analgesia provision to pediatric patients with long-bone fracture. *Am J Emerg Med* **28**(4): 412–7.
Wente SJ (2013) Nonpharmacologic pediatric pain management in emergency departments: a systematic review of the literature. *J Emerg Nurs* **39**(2): 140-50.
Werdehausen R, Braun S, Hermanns H et al (2011) The influence of adjuvants used in regional anesthesia on lidocaine-induced neurotoxicity in vitro. *Reg Anesth Pain Med* **36**(5): 436–43.
West N, Ansermino JM, Carr RR et al (2015) A naloxone admixture to prevent opioid-induced pruritus in children: a randomized controlled trial. *Can J Anaesth* **62**(8): 891-900.
Wheatley BM, Nappo KE, Christensen DL et al (2019) Effect of NSAIDs on Bone Healing Rates: A Meta-analysis. *J Am Acad Orthop Surg* **27**(7): e330-e36.

Wheeler MA, Heffner DL, Kim S et al (2014) TNF-alpha/TNFR1 signaling is required for the development and function of primary nociceptors. *Neuron* **82**(3): 587–602.
Whelan KT, Heckmann MK, Lincoln PA et al (2015) Pediatric Withdrawal Identification and Management. *J Pediatr Intensive Care* **4**(2): 73-78.
Whiston C, Ali S, Wright B et al (2018) Is caregiver refusal of analgesics a barrier to pediatric emergency pain management? A cross-sectional study in two Canadian centres. *Cjem* **20**(6): 892-902.
White MC, Hommers C, Parry S et al (2011) Pain management in 100 episodes of severe mucositis in children. *Paediatr Anaesth* **21**(4): 411–16.
White MC & Karsli C (2007) Long-term use of an intravenous ketamine infusion in a child with significant burns. *Paediatr Anaesth* **17**(11): 1102-4.
Whiteside LK, Russo J, Wang J et al (2016) Predictors of Sustained Prescription Opioid Use After Admission for Trauma in Adolescents. *Journal of Adolescent Health* **58**(1): 92-97.
Whitley DE, Li T, Jones CMC et al (2017) An Assessment of Newly Identified Barriers to and Enablers for Prehospital Pediatric Pain Management. *Pediatr Emerg Care* **33**(6): 381-87.
Whitlow PG, Saboda K, Roe DJ et al (2015) Topical analgesia treats pain and decreases propofol use during lumbar punctures in a randomized pediatric leukemia trial. *Pediatr Blood Cancer* **62**(1): 85-90.
WHO (2012) *WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses*. Geneva, World Health Organisation.
WHO (2015) *Reducing pain at the time of vaccination: WHO position paper - September 2015.* https://www.who.int/we/2015/wer9039.pdf?ua=1 Accessed 23 May 2020
Wiffen PJ, Cooper TE, Anderson AK et al (2017a) Opioids for cancer-related pain in children and adolescents. *Cochrane Database Syst Rev* **7**: Cd012564.
Wiffen PJ, Derry S, Moore RA et al (2017b) Oral paracetamol (acetaminophen) for cancer pain. *Cochrane Database Syst Rev* **7**: CD012637.
Wilkinson DG (2001) Multiple roles of EPH receptors and ephrins in neural development. *Nat Rev Neurosci* **2**(3): 155–64.
Willaschek C, Wolter E & Buchhorn R (2009) Tramadol withdrawal in a neonate after long-term analgesic treatment of the mother. *Eur J Clin Pharmacol* **65**(4): 429–30.
Wille-Ledon C, Chappuy H, Giraud C et al (2011) Comparison of a morphine and midazolam combination with morphine alone for paediatric displaced fractures: a randomized study. *Acta Paediatr* **100**(11): e203–07.
Williams DG, Hatch DJ & Howard RF (2001) Codeine phosphate in paediatric medicine. *Br J Anaesth* **86**(3): 413–21.
Williams DG & Howard RF (2003) Epidural analgesia in children. A survey of current opinions and practices amongst UK paediatric anaesthetists. *Paediatr Anaesth* **13**(9): 769–76.
Williams DG, Patel A & Howard RF (2002) Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* **89**(6): 839–45.
Williams DM, Rindal KE, Cushman JT et al (2012) Barriers to and enablers for prehospital analgesia for pediatric patients. *Prehosp Emerg Care* **16**(4): 519-26.
Williams G, Fabrizi L, Meek J et al (2015) Functional magnetic resonance imaging can be used to explore tactile and nociceptive processing in the infant brain. *Acta Paediatr* **104**(2): 158-66.
Williams S, Keogh S & Douglas C (2019) Improving paediatric pain management in the emergency department: An integrative literature review. *Int J Nurs Stud* **94**: 9-20.
Willschke H, Marhofer P, Bosenberg A et al (2005) Ultrasonography for ilioinguinal/iliohypogastric nerve blocks in children. *Br J Anaesth* **95**(2): 226–30.
Willschke H, Marhofer P, Bosenberg A et al (2006) Epidural catheter placement in children: comparing a novel approach using ultrasound guidance and a standard loss-of-resistance technique. *Br J Anaesth* **97**(2): 200–07.
Windsor RB, Tham SW, Adams TL et al (2019) The Use of Opioids for Treatment of Pediatric Neuropathic Pain: A Literature Review. *Clin J Pain* **35**(6): 509-14.
Winner P, Farkas V, Stillova H et al (2016) Efficacy and tolerability of zolmitriptan nasal spray for the treatment of acute migraine in adolescents: Results of a randomized, double-blind, multi-center, parallel-group study (TEENZ). *Headache* **56**(7): 1107-19.
Winner P, Linder S & Hershey AD (2015) Consistency of response to sumatriptan/naproxen sodium in a randomized placebo-controlled, cross-over study for the acute treatment of migraine in adolescence. *Headache* **55**(4): 519-28.
Winton P, Whyte E, Reimer EJ et al (2011) Dexmedetomidine for co-analgesia in chemotherapy-induced severe enterocolitis. *Paediatr Anaesth* **21**(9): 980–81.
Wober-Bingol C (2013) Epidemiology of migraine and headache in children and adolescents. *Curr Pain Headache Rep* **17**(6): 341.
Wolf AR, Doyle E & Thomas E (1998) Modifying infant stress responses to major surgery: spinal vs extradural vs opioid analgesia. *Paediatr Anaesth* **8**(4): 305–11.
Wolf AR & Hughes D (1993) Pain relief for infants undergoing abdominal surgery: comparison of infusions of i.v. morphine and extradural bupivacaine. *Br J Anaesth* **70**(1): 10–16.

Wolfe J, Grier HE, Klar N et al (2000) Symptoms and suffering at the end of life in children with cancer. *N Engl J Med* **342**(5): 326-33.
Wolfe J, Orellana L, Cook EF et al (2014) Improving the care of children with advanced cancer by using an electronic patient-reported feedback intervention: results from the PediQUEST randomized controlled trial. *J Clin Oncol* **32**(11): 1119-26.
Wolfe J, Orellana L, Ullrich C et al (2015) Symptoms and Distress in Children With Advanced Cancer: Prospective Patient-Reported Outcomes From the PediQUEST Study. *J Clin Oncol* **33**(17): 1928-35.
Wollgarten-Hadamek I, Hohmeister J, Demirakca S et al (2009) Do burn injuries during infancy affect pain and sensory sensitivity in later childhood? *Pain* **141**(1-2): 165-72.
Wong DL & Baker CM (1988) Pain in children: comparison of assessment scales. *Pediatr Nurs* **14**(1): 9–17.
Wong GK, Arab AA, Chew SC et al (2013a) Major complications related to epidural analgesia in children: a 15-year audit of 3,152 epidurals. *Can J Anaesth* **60**(4): 355–63.
Wong GK, Joo DT & McDonnell C (2010) Lipid resuscitation in a carnitine deficient child following intravascular migration of an epidural catheter. *Anaesthesia* **65**(2): 192–95.
Wong I, St John-Green C & Walker SM (2013b) Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children. *Paediatr Anaesth* **23**(6): 475–95.
Woo KJ, Kang BY, Min JJ et al (2016) Postoperative pain control by preventive intercostal nerve block under direct vision followed by catheter-based infusion of local analgesics in rib cartilage harvest for auricular reconstruction in children with microtia: A randomized controlled trial. *J Plast Reconstr Aesthet Surg* **69**(9): 1203-10.
Worley A, Fabrizi L, Boyd S et al (2012) Multi-modal pain measurements in infants. *J Neurosci Methods* **205**(2): 252–57.
Wossner S, Weber K, Steinbeck AC et al (2017) Pregabalin as adjunct in a multimodal pain therapy after traumatic foot amputation - A case report of a 4-year-old girl. *Scand J Pain* **17**: 146-49.
Wright J, Adams D & Vohra S (2013) Complementary, holistic, and integrative medicine: music for procedural pain. *Pediatr Rev* **34**(11): e42–46.
Wrona S, Chisolm DJ, Powers M et al (2007) Improving processes of care in patient-controlled analgesia: the impact of computerized order sets and acute pain service patient management. *Paediatr Anaesth* **17**(11): 1083–89.
Wu S, Sapru A, Stewart MA et al (2009) Using acupuncture for acute pain in hospitalized children. *Pediatric Critical Care Medicine* **10 (3)**: 291–96.
Wurzer P, Forbes AA, Hundeshagen G et al (2017) Two-year follow-up of outcomes related to scarring and distress in children with severe burns. *Disabil Rehabil* **39**(16): 1639-43.
Xiang K, Cai H & Song Z (2014) Comparison of analgesic effects of remifentanil and fentanyl NCA after pediatric cardiac surgery. *J Invest Surg* **27**(4): 214-8.
Xie M, Li XK & Peng Y (2017a) Magnesium sulfate for postoperative complications in children undergoing tonsillectomies: a systematic review and meta-analysis. *J Evid Based Med* **10**(1): 16-25.
Xie Z, Shen W, Lin J et al (2017b) Sedation effects of intranasal dexmedetomidine delivered as sprays versus drops on pediatric response to venous cannulation. *Am J Emerg Med* **35**(8): 1126-30.
Xing F, An LX, Xue FS et al (2019) Postoperative analgesia for pediatric craniotomy patients: a randomized controlled trial. *BMC Anesthesiol* **19**(1): 53.
Xu H, Zhao B, She Y et al (2018a) Dexmedetomidine ameliorates lidocaine-induced spinal neurotoxicity via inhibiting glutamate release and the PKC pathway. *Neurotoxicology* **69**: 77-83.
Xu X, Craig KD, Diaz D et al (2018b) Automated Pain Detection in Facial Videos of Children using Human-Assisted Transfer Learning. *CEUR Workshop Proc* **2142**: 10-21.
Yackey KJ & Rominger AH (2018) Are We Adequately Treating Pain in Children Who Present to US Emergency Departments?: Factors That Contribute to Pain Treatment in Pediatric Patients. *Pediatr Emerg Care* **34**(1): 42-46.
Yamamoto-Hanada K, Futamura M, Kitazawa H et al (2015) Relieving pain and distress during venipuncture: Pilot study of the Japan Environment and Children's Study (JECS). *Pediatr Int* **57**(5): 1044-7.
Yaman A, Demir B, Belen FB et al (2016) Paracetamol infusion-related severe hypotension and cardiac arrest in a child. *Turk J Pediatr* **58**(5): 550-53.
Yanagihara Y, Ohtani M, Kariya S et al (2003) Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. *Biopharm Drug Dispos* **24**(1): 37–43.
Yang C, Gong G, Jin E et al (2019) Topical application of honey in the management of chemo/radiotherapy-induced oral mucositis: A systematic review and network meta-analysis. *Int J Nurs Stud* **89**: 80-87.
Yang J & Cooper MG (2010) Compartment syndrome and patient-controlled analgesia in children--analgesic complication or early warning system? *Anaesth Intensive Care* **38**(2): 359–63.
Yang W, Ming YC, Kau YC et al (2015) A comparison of parecoxib and thoracic epidural analgesia for postoperative analgesia following Nuss procedure. *J Pediatr Surg* **50**(12): 2032-4.
Yao Y, Yu C, Zhang X et al (2018) Caudal and intravenous dexmedetomidine similarly prolong the duration of caudal analgesia in children: A randomized controlled trial. *Paediatr Anaesth* **28**(10): 888-96.
Yao YS, Qian B, Chen BZ et al (2009) The optimum concentration of levobupivacaine for intra-operative caudal analgesia in children undergoing inguinal hernia repair at equal volumes of injectate. *Anaesthesia* **64**(1): 23–26.

Yawn BP & John-Sowah J (2015) Management of Sickle Cell Disease: Recommendations from the 2014 Expert Panel Report. *Am Fam Physician* **92**(12): 1069-76.

Ydemann M, Nielsen BN, Henneberg S et al (2018) Intraoperative clonidine for prevention of postoperative agitation in children anaesthetised with sevoflurane (PREVENT AGITATION): a randomised, placebo-controlled, double-blind trial. *Lancet Child Adolesc Health* **2**(1): 15-24.

Ye ZJ, Zhang Z, Liang MZ et al (2019) Symptoms and management of children with incurable cancer in mainland China. *Eur J Oncol Nurs* **38**: 42-49.

Yeaman F, Oakley E, Meek R et al (2013) Sub-dissociative dose intranasal ketamine for limb injury pain in children in the emergency department: a pilot study. *Emerg Med Australas* **25**(2): 161-7.

Yee MM, Josephson C, Hill CE et al (2013) Cytochrome P450 2D6 polymorphisms and predicted opioid metabolism in African American children with sickle cell disease. *J Pediatr Hematol Oncol* **35**(7): e301–05.

Yenigun A, Et T, Aytac S et al (2015) Comparison of different administration of ketamine and intravenous tramadol hydrochloride for postoperative pain relief and sedation after pediatric tonsillectomy. *J Craniofac Surg* **26**(1): e21-4.

Yenigun A, Yilmaz S, Dogan R et al (2018) Demonstration of analgesic effect of intranasal ketamine and intranasal fentanyl for postoperative pain after pediatric tonsillectomy. *Int J Pediatr Otorhinolaryngol* **104**: 182-85.

Yildirim M, Koroglu E, Yucel C et al (2019) The effect of hospital clown nurse on children's compliance to burn dressing change. *Burns* **45**(1): 190-98.

Yilmaz G & Alemdar DK (2019) Using Buzzy, Shotblocker, and Bubble Blowing in a Pediatric Emergency Department to Reduce the Pain and Fear Caused by Intramuscular Injection: A Randomized Controlled Trial. *J Emerg Nurs* **45**(5): 502-11.

Yin HC, Cheng SW, Yang CY et al (2017) Comparative Survey of Holding Positions for Reducing Vaccination Pain in Young Infants. *Pain Res Manag* **2017**: 3273171.

Yinger OS (2016) Music Therapy as Procedural Support for Young Children Undergoing Immunizations: A Randomized Controlled Study. *J Music Ther* **53**(4): 336-63.

Yiu Y, Mahida JB, Cooper JN et al (2017) The effect of perioperative dexamethasone dosing on post-tonsillectomy hemorrhage risk. *Int J Pediatr Otorhinolaryngol* **98**: 19-24.

Young KD (2005) Pediatric procedural pain. *Ann Emerg Med* **45**(2): 160-71.

Ystrom E, Gustavson K, Brandlistuen RE et al (2017) Prenatal Exposure to Acetaminophen and Risk of ADHD. *Pediatrics* **140**(5).

Yue Z, Jiang P, Sun H et al (2014) Association between an excess risk of acute kidney injury and concomitant use of ibuprofen and acetaminophen in children, retrospective analysis of a spontaneous reporting system. *Eur J Clin Pharmacol* **70**(4): 479–82.

Zafar MS, Stewart AM, Toupin DN et al (2018) Continuous Intravenous Valproate as Abortive Therapy for Pediatric Status Migrainosus. *Neurologist* **23**(2): 43-46.

Zaidi RH, Casanova NF, Haydar B et al (2015) Urethrocutaneous fistula following hypospadias repair: regional anesthesia and other factors. *Paediatr Anaesth* **25**(11): 1144-50.

Zamzmi G, Kasturi R, Goldgof D et al (2018) A Review of Automated Pain Assessment in Infants: Features, Classification Tasks, and Databases. *IEEE Rev Biomed Eng* **11**: 77-96.

Zanaty OM & El Metainy SA (2015) A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. *Anesth Analg* **121**(1): 167-71.

Zekavat OR, Karimi MY, Amanat A et al (2015) A randomised controlled trial of oral zinc sulphate for primary dysmenorrhoea in adolescent females. *Aust N Z J Obstet Gynaecol* **55**(4): 369-73.

Zempsky WT (2008) Pharmacologic approaches for reducing venous access pain in children. *Pediatrics* **122 Suppl 3**: S140–53.

Zempsky WT, Loiselle KA, Corsi JM et al (2010) Use of low-dose ketamine infusion for pediatric patients with sickle cell disease-related pain: a case series. *Clin J Pain* **26**(2): 163–67.

Zhang C, Hu J, Liu X et al (2014) Effects of intravenous dexmedetomidine on emergence agitation in children under sevoflurane anesthesia: a meta-analysis of randomized controlled trials. *PLoS One* **9**(6): e99718.

Zhang Q, Guo Q, Gui M et al (2018) Henoch-Schonlein purpura with acute pancreatitis: analysis of 13 cases. *BMC Pediatr* **18**(1): 159.

Zhi R, Zamzmi GZD, Goldgof D et al (2018) Automatic Infants' Pain Assessment by Dynamic Facial Representation: Effects of Profile View, Gestational Age, Gender, and Race. *J Clin Med* **7**(7): 173.

Zhou W, Li J, Birmingham B et al (2017) Population Pharmacokinetic Analysis of Zolmitriptan and Its Metabolite in Adults and Adolescents to Support Dose Selection in Children With Migraine. *J Clin Pharmacol* **57**(10): 1258-67.

Zhu A, Benzon HA & Anderson TA (2017) Evidence for the Efficacy of Systemic Opioid-Sparing Analgesics in Pediatric Surgical Populations: A Systematic Review. *Anesth Analg* **125**(5): 1569-87.

Zhu C, Zhang S, Gu Z et al (2018a) Caudal and intravenous dexamethasone as an adjuvant to pediatric caudal block: A systematic review and meta-analysis. *Paediatr Anaesth* **28**(3): 195-203.

Zhu Y, Peng X, Wang S et al (2018b) Vapocoolant spray versus placebo spray/no treatment for reducing pain from intravenous cannulation: A meta-analysis of randomized controlled trials. *Am J Emerg Med* **36**(11): 2085-92.

Zier JL, Rivard PF, Krach LE et al (2008) Effectiveness of sedation using nitrous oxide compared with enteral midazolam for botulinum toxin A injections in children. *Dev Med Child Neurol* **50**(11): 854–58.
Ziesenitz VC, Vaughns JD, Koch G et al (2018) Correction to: Pharmacokinetics of Fentanyl and Its Derivatives in Children: A Comprehensive Review. *Clin Pharmacokinet* **57**(3): 393-417.
Ziesenitz VC, Zutter A, Erb TO et al (2017) Efficacy and Safety of Ibuprofen in Infants Aged Between 3 and 6 Months. *Paediatr Drugs* **19**(4): 277-90.
Zisk RY, Grey M, Medoff-Cooper B et al (2008) The squeaky wheel gets the grease: parental pain management of children treated for bone fractures. *Pediatr Emerg Care* **24**(2): 89-96.
Zwaveling J, Bubbers S, van Meurs AH et al (2004) Pharmacokinetics of rectal tramadol in postoperative paediatric patients. *Br J Anaesth* **93**(2): 224–27.
Zwicker JG, Grunau RE, Adams E et al (2013) Score for neonatal acute physiology-II and neonatal pain predict corticospinal tract development in premature newborns. *Pediatr Neurol* **48**(2): 123–29 e1.