Pediatric pain treatment and prevention for hospitalized children

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\section*{Abstract}

\textbf{Introduction:} Prevention and treatment of pain in pediatric patients compared with adults is often not only inadequate but also less often implemented the younger the children are. Children 0 to 17 years are a vulnerable population.

\textbf{Objectives:} To address the prevention and treatment of acute and chronic pain in children, including pain caused by needles, with recommended analgesic starting doses.

\textbf{Methods:} This Clinical Update elaborates on the 2019 IASP Global Year Against Pain in the Vulnerable “Factsheet Pain in Children: Management” and reviews best evidence and practice.

\textbf{Results:} Multimodal analgesia may include pharmacology (eg, basic analgesics, opioids, and adjuvant analgesia), regional anesthesia, rehabilitation, psychological approaches, spirituality, and integrative modalities, which act synergistically for more effective acute pediatric pain control with fewer side effects than any single analgesic or modality. For chronic pain, an interdisciplinary rehabilitative approach, including physical therapy, psychological treatment, integrative mind–body techniques, and normalizing life, has been shown most effective. For elective needle procedures, such as blood draws, intravenous access, injections, or vaccination, overwhelming evidence now mandates that a bundle of 4 modalities to eliminate or decrease pain should be offered to every child every time: (1) topical anesthesia, eg, lidocaine 4\% cream, (2) comfort positioning, eg, skin-to-skin contact for infants, not restraining children, (3) sucrose or breastfeeding for infants, and (4) age-appropriate distraction. A deferral process (Plan B) may include nitrous gas analgesia and sedation.

\textbf{Conclusion:} Failure to implement evidence-based pain prevention and treatment for children in medical facilities is now considered inadmissible and poor standard of care.

\textbf{Keywords:} Pediatric pain, Pain treatment, Pain prevention, Multimodal analgesia, Topical anesthesia, Comfort positioning, Sucrose, Breastfeeding, Distraction

1. Introduction

Data from children’s hospitals around the world reveal that pain in pediatric patients from infancy to adolescence is common, under-recognized and undertreated.\textsuperscript{6,48,144,148,162,170,179} Compared with adult patients, pediatric patients with the same diagnoses receive less analgesic doses, and the younger the children are, the less likely it is that they receive adequate analgesia in the medical setting.\textsuperscript{5,9,117,137} The pain experienced by children in a hospital, medical facility, or doctor’s office can be disease- and/or treatment-related and may be based on one, several, or all of the following pathophysiologies:

(1) Acute somatic pain (eg, tissue injury), which arises from the activation of peripheral nerve endings (nociceptors) that respond to noxious stimulation [and may be described as localized, sharp, squeezing, stabbing, or throbbing].

(2) Neuropathic pain, resulting from injury to, or dysfunction of, the somatosensory system [burning, shooting, electric, or tingling]. Central pain would be caused by a lesion or disease of the central somatosensory nervous system.

(3) Visceral pain results from the activation of nociceptors of the thoracic, pelvic, or abdominal viscera [poorly localized, dull, crampy, or achy].

(4) Total pain: suffering that encompasses all of a child’s physical, psychological, social, spiritual, and practical struggles.\textsuperscript{134}

(5) Chronic (or persistent) pain; pain beyond expected time of healing

A particularly vulnerable group of patients are infants and neonates. A recent systematic review showed that neonates admitted to intensive care units frequently suffer through an average of 7 to 17 painful procedures per day, with the most frequent procedures being venipuncture, heel lance, and insertion of a peripheral venous catheter.\textsuperscript{5} In most infants no analgesic strategies are used.\textsuperscript{136} In addition, children with serious medical conditions are
Key Points

1. According to the 2010 Declaration of Montreal, access to pain management is a fundamental human right and it is a human rights violation not to treat pain.
2. Evidence-based pain prevention and treatment must become a priority for all medical facilities providing pediatric care.
3. Effective multimodal analgesia for acute pain act synergistically for more effective pediatric pain control with fewer side effects than single analgesic or modality and includes pharmacology (eg, basic analgesia, opioids, and adjuvant analgesia), regional anesthesia, rehabilitation, psychology, spirituality, and integrative (“nonpharmacological”) modalities.
4. For chronic persistent pediatric pain, an interdisciplinary rehabilitative approach including (1) physical therapy, (2) psychological interventions, (3) active integrative mind–body techniques, and (4) normalizing life (eg, school, sleep, social, and sports) has been shown most effective.
5. Opioids are usually not indicated in chronic pain in the absence of new tissue injury.
6. For elective needle procedures, evidence now mandates to consistently offer 4 strategies to every child every time: (1) topical anesthetics, (2) sucrose or breastfeeding for infants 0 to 12 months, (3) comfort positioning (including swaddling, skin-to-skin contact, or facilitated tucking for infants, sitting upright for children), and (4) age-appropriate distraction.

2. Prevention and treatment of acute pain in children

Acute nociceptive pain might be due to tissue injury caused by disease, trauma, surgery, interventions, and/or disease-directed therapy. Untreated acute pain may lead to fear and even avoidance of future medical procedures.

Multimodal analgesia (Fig. 1) is the current recommended approach to address acute pain in hospitalized children. Pharmacology (including basic analgesia, opioids, and adjuvant analgesia) alone might not be sufficient to treat children with acute pain. The addition and integration of modalities such as regional anesthesia, rehabilitation, effective psychosocial interventions, spirituality, and integrative (“nonpharmacological”) modalities acts synergistically for more effective (opioid-sparing) pediatric pain control with fewer side effects than single analgesic or modality.

2.1. Treat underlying disease process

Pain is foremost a symptom and might be a warning sign. After a detailed medical history, clinical examination, and potentially further workup (including imagery or laboratory investigations), an underlying disease process (such as tissue injury including infection, and trauma) needs to be addressed as appropriate in the specific clinical scenario to avoid further harm. As an example, in a child with increasing foot pain after orthopedic surgery, the primary intervention would be to rule out and address a potential compartment syndrome, and not simply to increase the analgesic dose.

2.2. Basic analgesia

Basic (or “simple”) analgesia usually includes acetaminophen (paracetamol) and nonsteroidal anti-inflammatory drugs (NSAIDs). Data have shown that ibuprofen-sodium (available over-the-counter in the United States) compared with standard ibuprofen has a faster analgesic onset (within 10 minutes), only requires 50% of the dose, and has a longer duration of action. If NSAIDs are contraindicated due to their side-effect profile (which includes bleeding risk and gastrointestinal side effects), one may consider a COX-2 inhibitor (eg, celecoxib). The renal toxicity profile may be somewhat better compared with classic NSAIDs. For starting doses, see Table 1. Although in some countries dipyrone (metamizole) is commonly used as a basic analgesic, it is not available in many countries, including the United States.

2.3. Opioids

Opioids are often indicated for medium to severe acute pain due to tissue injury. The World Health Organization (WHO) step 2 suggests opioid use in children with persisting medium–severe pain due to medical illness in addition to basic analgesia (and not waiting for the effect of acetaminophen or an NSAID). Morphine remains the “gold standard,” but other “strong” opioids, such as fentanyl, oxycodone, hydromorphone, and diamorphine (in the United Kingdom only), and methadone are equally effective in their respective analgesic effects. For opioid starting doses, see Table 2; for neonates, Table 3; and for usual patient-controlled analgesia (PCA) pump starting doses, see Table 4.

“Weak” opioids, with an analgesic ceiling effect, include codeine, which cannot be recommended anymore due to pediatric deaths, especially in cytochrome P450 2D6 ultrarapid metabolizers. Tramadol, a multifunctional analgesic, however, seems to continue playing a key role not only in outpatient surgery (eg, more than 6,000 pediatric tramadol scripts were filled at Children’s Minnesota in 2018 in part due to its relative respiratory safety profile), but also in treating episodes of inconsolability in children with progressive neurologic, metabolic, or chromosomally based conditions with impairment of the central nervous system. Surprisingly, and not well based on scientific evidence, the US Food and Drug Administration (FDA) issued a warning against pediatric

exposed to frequent painful diagnostic and therapeutic procedures (eg, bone marrow aspirations, lumbar punctures, and wound dressing changes). Furthermore, even healthy children have to undergo significant amounts of painful medical procedures throughout childhood: Vaccinations are the most commonly performed needle procedure in childhood, and pain is a common reason for vaccine hesitancy.

Exposure to severe pain in infants without adequate pain management has negative long-term consequences, including increased morbidity (eg, intraventricular hemorrhage) and mortality. Exposure to pain in premature infants is associated with higher pain self-ratings during venipuncture by school age and poorer cognition and motor function. Research has also shown that exposure to pain early in life even heightens the risk for increased morbidity (eg, intraventricular hemorrhage) and mortality (eg, intraventricular hemorrhage) and mortality.

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use of tramadol and cited the data of 3 children who have died worldwide in the previous 49 years, therefore actually making it far safer than any other opioid. Unfortunately, this warning may place children at greater risk for unrelieved pain and other distressing symptoms by encouraging clinicians to either use strong opioids in the outpatient setting with a higher risk of respiratory depression or not use opioids at all.54

“By the clock”: when pain is constantly present, both administration of basic analgesia and opioid should usually be scheduled “around the clock” (eg, acetaminophen every 6 hours scheduled and/or morphine every 4 hours scheduled). As-needed prescriptions only (without scheduled analgesia) often do not reach the patient, and “PRN” (“pro re nata” or “as-needed”) is often translated into “patient receives nothing”, with 69 percent of hospitalized pediatric patients for whom analgesics had been ordered “PRN” did not receive a single dose in one study.79

2.4. Adjuvant analgesia

Adjuvant analgesics may improve pain control either in addition to basic analgesia and/or opioids, or they may also act as primary analgesics, especially in neuropathic and visceral pain treatment.41,45

| Table 1 | Basic analgesia for children. |
|---------|-------------------------------|
| Drug    | Route | Age       | Pediatric dose | Maximal dose | Dosing interval |
|         |       |           |                |              |                |
| Ibuprofen | PO    | >3–6 months* | 5–10 mg/kg | 400–600 mg/dose | 6–8 hours |
| Ibuprofen-sodium† | 256-mg tablet = 200-mg Ibuprofen | PO | >6 months | 5–(10) mg/kg | 200–(400) mg/dose | 6–8 hours |
| Acetaminophen (paracetamol) | PO, PR | Neonates 0–30 days | 5–10 mg/kg | 20–40 mg/kg/day | 4–6 hours (maximum 4 doses/day) |
|         | PO, PR | Infants 1–3 months | 10 mg/kg | 40 mg/kg/day | 4–6 hours (maximum 4 doses/day) |
|         | PO, PR | 4 months–2 years | 10–15 mg/kg | 40–60 mg/kg/day | 4–6 hours (maximum 4 doses/day) |
|         | PO, PR | >2 years | 15 mg/kg | 60 mg/kg/day | 6 hours |
|         | PO, PR | <1 year | <10 kg = 7.5 mg/kg | 30 mg/kg/day | 6 hours |
|         | PO, PR | >1 year | >10 kg = 15 mg/kg | 75 mg/kg/day | 6 hours |
|         | PO, PR | >2 years (>50 kg) | 15 mg/kg | 4000 mg/day | 6 hours |
| Ketorolac‡ | IV | 6 months–2 years* | 0.25 mg/kg | 30 mg/dose | 6–8 hours |
|         | IV | >2 years | 0.5 mg/kg | 30 mg/dose | 6–8 hours |
| Celecoxib║ | PO | >6 months | 1–2 mg/kg | 100 mg/dose | 12–24 hours |

* For NSAIDs in infants <3 to 6 months, consult Pediatric Pain Service.
† Fast-acting, compared with standard Ibuprofen: onset of analgesia after 10 minutes, last longer, and only half the dose required.
‡ Due to high cost, only if rectal or oral administration contraindicated, re-evaluate daily.
║ If classical NSAIDs contraindicated, safety and efficacy have been established in children 2 years of age or older for a maximum of 6 months of treatment in JRA.
NSAIDs, nonsteroidal anti-inflammatory drugs.
This heterogeneous group includes gabapentinoids (such as gabapentin and pregabalin), alpha-2-adrenergic agonists (such as clonidine or dexmedetomidine), low-dose tricyclic antidepressants (such as amitriptyline or nortriptyline), N-methyl-D-aspartate (NMDA) channel blockers (such as clonidine or dexmedetomidine), and sodium-channel blockers (such as lidocaine). See Table 5 for dosing recommendations.

Cannabis and medical marijuana (including cannabidiol [CBD] and tetrahydrocannabinol [THC]) lack any evidence to support its use for treatment of acute or chronic pain. The updated American Academy of Pediatrics policy opposes marijuana use, citing lack of research and potential harms including correlation with mental illness, testicular cancer, and increased risk of addiction. In our clinical practice, we do not support the use of marijuana (or medical cannabis) for a child with a primary pain disorder and a normal life expectancy. However, in children with life-limiting conditions, the administration of medical cannabis might be requested by patients and their parents and certainly may be considered on a case-by-case basis. It is important to watch carefully for side effects (including pancreatitis and psychosis).

### 2.5. Integrative medicine

Many integrative medicine (other terms used may include “non-pharmacologic,” “complementary,” or “alternative medicine”)

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### Table 2

| Medication (route of administration) | Starting dose IV | IV/P0 ratio | Starting dose PO (or transdermal) |
|-------------------------------------|------------------|-------------|-----------------------------------|
| Morphine (PO, SC, IM, and IV)†‡     | Bolus dose: 0.05–0.1 mg/kg (max. 5 mg) | 1:3 (ie, 1 mg IV = 3 mg PO) | 0.15–0.3 mg/kg (max. 7.5–15 mg) every 4 hours |
| Fentanyl (SC, IM, and IV)           | Bolus dose: 0.5–1 mcg/kg (max. 25–50 mcg) | 1:1 (IV to transdermal) | 12 mcg/h patch (must be on the equivalent of at least 30-mg oral morphine/24 hours, before switching to patch) |
| Hydromorphone (PO, SC, IM, and IV)  | Bolus dose: 15–20 mcg/kg (max. 1 mg) | 1:5 (ie, 1 mg IV = 5 mg PO) | 60 mcg/kg (max. 2000–3000 mcg or 2–3 mg) every 3–4 hours |
| Oxycodone (PO, SC, IM, and IV)‡     | IV not available in the United States (Bolus dose: 0.05–0.1 mg/kg [max 2.5–5 mg] every 4 hours) | 1:2 (ie, 1 mg IV = 2 mg PO) | 0.1–0.2 mg/kg (max. 5–10 mg) every 4 hours or 0.15–0.3 mg/kg (max. 7.5–15 mg) every 6 hours |
| Tramadol (PO and PR)‡               | IV not available in the United States (Bolus dose: 1 mg/kg every 3–4 hours) | 1:1 | 1–2 mg/kg every 3–4 hours, max. Of 8 mg/kg/day (>50 kg: max. of 400 mg/day) |
| Methadone (PO, PR, SC, and IV)§     | 0.04–0.08 mg/kg (max. 2–4 mg) Q8h | 1:1–1:2 (in adults usually IV usually 50% of PO dose, in pediatrics consider IV = 80% of PO dose) | 0.05–0.1 mg/kg (max. 2.2–5 mg) PO Q8h |

*Above doses represent stating doses, which then need to be titrated to effect and may be significantly higher.†Maximum per kg dose capped at 50-kg body weight.‡Calculated rescue (breakthrough) dose: 10% to 16% of 24-hour opioid dose to be given every 2 hours as needed. Depending on the clinical scenario a breakthrough dose may given every 1-4 hours as needed.) Inform prescribing clinician, if requiring more than 3 breakthrough doses in less than 24 hours.§Methadone should not be prescribed without proper training about dosing and potential side effects. Prescribing clinicians should closely observe the child for potential side effects from the time he or she receives the first dose and following medication changes such as tapering, titration, or adding other potentially sedating medications.

### Table 3

| Opioids | PO/PR/SL |
|---------|----------|
| Morphine | 0.075–0.15 mg (neonates 0–30 days) | 6 hours |
|         | 0.08–0.2 mg (infants 1–6 months)   | 4–6 hours |
| Morphine† | IV/SC‡ | 0.025–0.05 mg/kg (neonates 0–30 days) | 6 hours |
|         |         | 0.1 mg/kg (infants 1–6 months)      | 6 hours |
|         |         | Infusion (with PCA bolus of same dose): 0.005–0.01 mg/kg/h (neonates 0–30 days) | 2–4 hours |
|         |         | 0.01–0.03 mg/kg/h (infants 1–6 months) | 2–4 hours |
| Fentanyl† | IV/SC‡ | 1–2 mcg/kg (neonates and infants 0–12 months) | 2–4 hours |
|         |         | Infusion (with PCA bolus of same dose): 0.5–1 mcg/kg (neonates and infants 0–6 months) | 2–4 hours |

*World Health Organization. WHO—Principles of Acute Pain Management for Children http://whqlibdoc.who.int/publications/2012/9789241548120_Guidelines.pdf. 2012.
†Administer IV slowly over at least 5 minutes.
‡Calculated rescue (breakthrough) dose: 10% to 16% of 24-hour opioid dose to be given every 2 hours as needed. Depending on the clinical scenario a breakthrough dose may given every 1-4 hours as needed.) Inform prescribing clinician, if requiring more than 3 breakthrough doses in less than 24 hours.§Methadone should not be prescribed without proper training about dosing and potential side effects. Prescribing clinicians should closely observe the child for potential side effects from the time he or she receives the first dose and following medication changes such as tapering, titration, or adding other potentially sedating medications.

PO dose, in pediatrics consider IV.
modalities seem very effective in treating and preventing pediatric acute pain. In infants, these modalities include breastfeeding, non-nutritive sucking with sucrose 24%, and skin-to-skin contact. In toddlers, school children's and young adults' age-appropriate effective integrative modalities include distraction, deep breathing, biofeedback, self-hypnosis, yoga, acupuncture, transcutaneous electrical nerve stimulation and massage. Many active mind-body techniques, such as guided imagery, hypnosis, biofeedback, yoga, and distraction may result in pain reduction through involvement of several mechanisms simultaneously within the analgesic neuraxis.

### 2.6. Psychological interventions

Anxiety, depression, catastrophizing thoughts about pain, and behavioral disorders represent risk factors for the development of acute to chronic pain in children and adolescents. A recent meta-analysis of clinical trials involving adolescents and adults undergoing orthopedic surgery demonstrated that preoperative psychological interventions, such as cognitive-behavioral therapy (CBT), hypnosis, relaxation, emotional counselling, and mixed psychotherapies, are effective to reduce acute post-operative anxiety and to improve longer term quality of life, with no effects found on postoperative pain.

2.7. Physical therapy, exercise, and rehabilitation

Physical therapy and exercise are key modalities in the treatment of children with acute and other pain conditions, including pediatric patients with serious illness. Independent from pain treatment, increasing physical activity levels has also shown to decrease levels of depression. Graded Motor Imagery, including mirror therapy, is the process of thinking about moving without actually moving and has been shown especially effective in children when moving the injured body part is too painful.

### 2.8. Spirituality

A correlation between spiritual coping and the quality of life in pediatric patients with chronic illness has been described.

### Table 4

| Class                  | Medication          | Dose          | Route of administration | Comments/side effects (see text for further details) |
|------------------------|---------------------|---------------|-------------------------|---------------------------------------------------|
| Continuous infusion    | Morphine            | 10–20 (max. 1000) mcg/h | PO                      | Tertiary amine TCA; stronger anticholinergic side effects (including sedation) than nortriptyline Secondary amine TCA; anticholinergic side effects |
|                        | Hydromorphone       | 2–5 (max. 100–250) mcg/h | Transdermal patch      | Not for severe hepatic dysfunction                 |
|                        | Fentanyl            | 0.5–1 (max. 25–50) mcg/h | PO Transdermal patch   | Not for severe hepatic dysfunction                 |

| PCA bolus (mcg)        | Lock-out time (minutes) | Maximum number of boluses/hour |
|------------------------|-------------------------|-------------------------------|
| Morphine               | 5–10                    | 4–6                           |
| Hydromorphone          | 5–10                    | 4–6                           |
| Fentanyl               | 5                      | 4–6                           |

Dose escalation usually in 50% increments both for continuous and PCA bolus dose (Department of Pain Medicine, Palliative Care & Integrative Medicine, Children’s Hospitals and Clinics of Minnesota, USA). Doses for children >6 months of age and are capped at 50-kg body weight.

### Table 5

| Class                  | Medication          | Dose          | Route of administration | Comments/side effects (see text for further details) |
|------------------------|---------------------|---------------|-------------------------|---------------------------------------------------|
| Tricyclic antidepressants (TCA) | Amitriptyline      | Starting dose 0.1 mg/kg QHS, usually slowly titrated up to 0.5 mg/kg (max. 20–25 mg) | PO                      | Tertiary amine TCA; stronger anticholinergic side effects (including sedation) than nortriptyline Secondary amine TCA; anticholinergic side effects |
|                        | Nortriptyline       | Starting dose 0.1 mg/kg QHS, usually titrated up to 0.5 mg/kg (max. 20–25 mg) | PO                      | Tertiary amine TCA; stronger anticholinergic side effects (including sedation) than nortriptyline Secondary amine TCA; anticholinergic side effects |
| Gabapentinoids         | Gabapentin          | Starting dose 2 mg/kg QHS, usually slowly titrated up to initial target dose of 6 mg/kg/ dose TID (max. 300 mg/dose TID), Max. dose escalation to 24 mg/kg/dose TID (max. 1200 mg/dose TID) Infants <1 year: 4.5 mg/kg/dose Q6h, titrated to max. 18 mg/kg/dose Q6h; Starting dose 0.3 mg/kg QHS, usually slowly titrated up to initial target dose of 1.5 mg/kg/ dose BID (max. 75 mg/kg/dose BID), Max. dose escalation to 6 mg/kg/dose BID (max. 300 mg/dose BID) | PO                      | Slow dose increase required; side effects: Ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, and peripheral edema Switch from gabapentin, if distressing side effects or inadequate analgesia. Side effects: Ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, and peripheral edema, associated with weight gain |
|                        | Pregabalin          | Starting dose 2 mg/kg QHS, usually slowly titrated up to initial target dose of 6 mg/kg/ dose TID (max. 300 mg/dose TID), Max. dose escalation to 24 mg/kg/dose TID (max. 1200 mg/dose TID) Infants <1 year: 4.5 mg/kg/dose Q6h, titrated to max. 18 mg/kg/dose Q6h; Starting dose 0.3 mg/kg QHS, usually slowly titrated up to initial target dose of 1.5 mg/kg/ dose BID (max. 75 mg/kg/dose BID), Max. dose escalation to 6 mg/kg/dose BID (max. 300 mg/dose BID) | PO                      | Slow dose increase required; side effects: Ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, and peripheral edema Switch from gabapentin, if distressing side effects or inadequate analgesia. Side effects: Ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, and peripheral edema, associated with weight gain |
| Sodium channel blocker/local anesthetic | Lidocaine 5%        | Max. of 4 patches (in patients >50 kg) 12 hours on/12 hours off | Transdermal patch      | Not for severe hepatic dysfunction                 |
| Alpha agonist          | Clonidine           | 1–3 mcg/kg (max 150 mcg) QHS to Q6h Infusion: 0.3 mcg/kg/h; titrate to max. 2 mcg/kg/h | PO Transdermal IV       | For sleep induction; use extended-release, if interrupted sleep, possible analgesic effect |
| Horseine               | Melatonin           | 0.06–0.2 mg/kg (max. 3–10 mg) QHS | PO                      | For sleep induction; use extended-release, if interrupted sleep, possible analgesic effect |

*Friedrichsdorf SJ. Prevention and treatment of pain in hospitalized infants, children, and teenagers: from myths and morphine to multimodal analgesia. In: Pain 2016. Refresher Courses. 16th World Congress on Pain Washington, DC: International Association for the Study of Pain, IASP Press; 2016:309–319.

BID, bis in die, twice a day; IV, intravenous administration; PO, per os, oral administration; Q6h, every 6 hours; QHS, every night at bedtime; TID, ter in die, 3 times a day.
Parents of children with serious illness described religion, spirituality, and/or life philosophy playing an important role in their life and of the affected child. Most children’s hospitals encourage the inclusion of spiritual aspects of life into health care, for instance, by making hospital chaplains available.

2.9. Regional anesthesia

One of the most effective analgesic modalities in children with tissue injury represents regional or neuraxial anesthesia. Nociceptive pathways may be blocked using central neuraxial infusions, peripheral nerve, and plexus blocks or infusions, or neurolytic blocks. Benefits of regional anesthesia include reduced (or no) need for opioid analgesics, absence of systemic side effects such as sedation or nausea, improved gastrointestinal motility, reduced incidence of delirium, and the opportunity for the patient to be awake and able to remember conversations with clinicians and family. In addition to motor weakness, less common potential side effects with epidural infusion of local anesthetic or opioids include pruritus, urinary retention, and hypotension.

3. Management of chronic pediatric pain

Pediatric chronic pain is a significant problem with conservative estimates that posit 20% to 35% of children and adolescents affected by it worldwide. Pain experienced by patients in children’s hospitals is known to be common, with more than 10% of hospitalized children showing features of chronic pain. Although the majority of children reporting chronic pain are not greatly disabled by it, about 3% of pediatric chronic pain patients require intensive rehabilitation.

The 2012 American Pain Society Position Statement, “Assessment and Management of Children with Chronic Pain,” indicates that chronic pain in children is the result of a dynamic integration of biological processes, psychological factors, and sociocultural variables, considered within a developmental trajectory. Unlike in adult medicine, chronic pain in children is not necessarily defined by using arbitrary temporal parameters (eg, 3 months) but rather uses a more functional definition such as “pain that extends beyond the expected period of healing” and “hence lacks the acute warning function of physiological nociception.”

3.1. Interdisciplinary management of chronic pediatric pain

An interdisciplinary approach combining (1) rehabilitation, (2) integrative medicine/active mind–body techniques, (3) psychological interventions, and (4) normalizing daily school attendance, sports, social life, and sleep seem to be most effective. As a result of restored function, pain improves and commonly resolves. Opioids are not indicated for primary pain disorders (including centrally mediated abdominal pain syndrome, primary headaches [tension headaches/migraines], and widespread musculoskeletal pain) and other medications, with few exceptions, are usually not first-line therapy.

A recent Cochrane review concluded that face-to-face psychological treatments might be effective in reducing pain outcomes for children and adolescents with headache and other types of chronic pain. Psychological treatments have also been found to be effective for reducing pain-related disability in children and adolescents with mixed chronic pain conditions at post-treatment and follow-up and for children with headache at follow-up. The most commonly used psychological therapy, CBT, has been shown to reduce pain severity in children and adolescents with widespread musculoskeletal/joint pain, headaches, abdominal pain, and headaches.

As proposed by Palermo’s conceptual framework for understanding chronic pain in children and adolescents and the Interpersonal Fear-Avoidance Model, a child’s social environment and especially parents play a key role in understanding childhood chronic pain. Increasing evidence suggests that it is important to target parental catastrophizing thoughts, parental distress, and parental behaviors with regard to child pain (eg, protective behaviors), which has led to recommendations to incorporate parents within the multidisciplinary treatment. A recent Cochrane review indeed indicated a beneficial effect of psychological therapies for parents of children with chronic pain conditions on parenting behavior (eg, reduction of protective behaviors) at post-treatment and follow-up. Furthermore, this review also showed that psychological therapies can improve parent mental health in this population. When considering children’s treatment outcomes, a small beneficial effect was found on children’s behavior and disability at post-treatment and follow-up. Furthermore, a moderate beneficial effect was found on children’s pain at post-treatment, but no effects on child mental health at post-treatment or follow-up.

With regard to the specific effects of CBT, the available evidence shows that CBT is effective in decreasing parents’ protective responses in children with chronic (or persistent) abdominal pain. Furthermore, a recent randomized controlled trial examining the effects of family-based CBT delivered through the internet demonstrated greater reductions in activity limitations from baseline to 6-month follow-up for internet-delivered CBT compared with an educational intervention. Additional beneficial effects of CBT were found on sleep quality, reduction of parents’ protective behaviors, and treatment satisfaction. Secondary longitudinal analyses further showed that child disability, parent protective behavior, and parent distress improved over the 12-month study period. Indeed, a recent systematic review on the effects of internet-delivered CBT in youth with chronic pain and their parents showed that, compared with pretreatment, internet-delivered CBT had medium to large benefits on child pain intensity, activity limitations, and parental protective behaviors immediately after treatment. Furthermore, small to medium positive effects were found for child depressive symptoms, anxiety, and sleep quality. However, still limited evidence is available, and more trials are needed.

3.2. Early screening of children’s risk profile to tailor clinical care

To ensure optimal clinical care and treatment for children and adolescents who present with chronic pain complaints at the hospital, early identification of risk factors for adverse outcomes may be warranted. Recently, a 9-item Pediatric Pain Screening Tool (PPST) has been developed, to rapidly assess risk factors associated with adverse outcomes, such as sleep problems, catastrophizing thoughts, pain-related fear, and depression. Early identification of risk factors that may maintain chronic pain allows optimal stratified care and may improve recovery rates. Importantly, evidence supports the generalizability of the PPST across pain complaints. Based on this brief scale, a risk profile of the child can be calculated, which provides indications for the type of care needed, ie, conservative treatment including education/advice, for instance, regarding sleep hygiene (low-risk profile), referral to physiotherapy (medium-risk profile), or...
Box 1. Treatment of chronic pain and primary pain disorders.50

(1) Rehabilitation (eg, physical therapy, graded motor imagery,131 and occupational therapy)
(2) Integrative (“nonpharmacological”) modalities (eg, mind–body techniques such as diaphragmatic breathing, bubble blowing, self-hypnosis, progressive muscle relaxation, and biofeedback plus modalities such as massage, aromatherapy, acupressure, and acupuncture)
(3) Education (eg, cognitive behavioral therapy, acceptance and commitment therapy)
(4) Normalizing life (usually life gets back to normal first, then pain goes down—not the other way around)

(5) Medications (may or may not be required)

- Basic analgesia (eg, paracetamol/acetaminophen, NSAIDs, and COX-2 inhibitor)
- Adjuvant analgesics (eg, gabapentin, clonidine, and/or amitriptyline)
- Of note: Opioids in the absence of new tissue injury, eg, epidermolysis bullosa and osteogenesis imperfecta, are usually not indicated

referral for multidisciplinary treatment, for instance, including psychological treatment and physical therapy for elevated pain-related fear (high-risk profile).70,145

Given the major role of parents in influencing a child’s pain experience and functioning,60,62 Simons et al. also developed a brief 12-item self-report screening tool (Parent Risk and Impact Screening Measure [PRISM]145) to assess parents’ psychosocial functioning (ie, parents’ distress and health), behavioral responses to their child’s pain, and the impact of the child’s pain on the family. Similar to the PPST, risk profiles of parents can be calculated, identifying parents at low, medium, or high risk and informing the clinician, which parents would benefit from a referral for parent-focused treatment or targeted pain-related interventions for parents (eg, to reduce protective behaviors).

3.3. Strengthening resilience mechanisms

Next to identifying and targeting risk factors for adverse outcomes, it has increasingly been acknowledged that it is also important to identify and promote factors or strengths that can improve adaptive or resilient functioning.25,61 Resilient functioning can be best defined as the ability to restore and sustain living a fulfilling life in the presence of pain.61 (eg, is the child able to engage in activities he/she finds important despite the pain; can he/she keep high levels of well-being despite the pain)? When a child presents with pain complaints at the hospital, attention should not only be paid to malfunctioning but also to what goes well in the child’s life, and how this resilient functioning can be further improved. This can be performed by strengthening resilience mechanisms such as positive affect, psychological flexibility, acceptance of pain, gratitude, and availability of family support over and above targeting/reducing risk factors such as pain-related fear.51 Although empirical evidence is still in its infancy, studies in adults show promising results of resilience-based treatment approaches such as positive psychology interventions128 and acceptance-based approaches.174 Although more empirical research is needed which interventions are most effective for whom, interventions promoting resilience mechanisms may be particularly valuable in early stages of treatment, to support adaptive domains of functioning and to prevent adverse outcomes in the long run. In children with high-risk profiles, it may be an important component of a multimodal approach to treatment.

Research on Acceptance and Commitment Therapy (ACT)68,129 a third generation behavior therapy that aims to promote resilient functioning by fostering psychological flexibility and acceptance of pain, is growing, and there is accumulating evidence that it can promote better functioning in adolescents with chronic pain, better pain acceptance, better school attendance, and reduced catastrophizing and anxiety and reduced use of health care facilities.57,129 Furthermore, a recent nonrandomized clinical trial in adolescents with chronic pain and their parents69 showed that acceptance and commitment therapy had positive effects not only on adolescents’ functioning but also on parents. Specifically, it was found to lead to significant improvements in parents’ depressive symptoms and psychological flexibility. Moreover, this study showed that improvements in parents’ psychological flexibility were associated with better adolescent pain acceptance over time.

4. Management of needle pain in children

Untreated needle pain, caused by procedures such as vaccinations, blood draws, injections, and venous cannulation can have long-term consequences including needle phobia, procedural anxiety, hyperalgesia, and avoidance of health care, resulting in increased morbidity and mortality.153,154 Current evidence,154,158,159 supported by guidelines from the Canadian Paediatric Society,18,82 HELPinKids,72,111,112,157 and recently brought forward by science-to-social media campaigns (“Be Sweet to Baby”21 and especially “It Doesn’t Have to Hurt” by Chambers et al.20), strongly suggests that 4 bundled modalities could be offered.

Box 2. Prevention and treatment of needle pain.

Offer a bundle of these 4 (or 3 for >12 months) evidence-based modalities to all children all the time:

(1) Topical anesthesia “Numb the skin” eg, 4% lidocaine cream (administered 30 minutes prior procedure), EMLA (lidocaine 2.5% and prilocaine 2.5%) cream (60 minutes prior), amethocaine [tetracaine] 4% gel (30–60 minutes prior) or needleless lidocaine application using pressurized gas to propel medication through the skin (1 minutes prior) eg J-Tip®
(2) Sucrose or breastfeeding for infants 0 to 12 months.
(3) Comfort positioning “Do not hold children down.” For infants, consider parent-infant skin-to-skin (kangaroo care) contact. If not feasible, consider swaddling, warmth, facilitated tucking, and/or cobedding for twins. For children 6 months and older, offer sitting upright with parents holding them on their lap or sitting nearby.
(4) Age-appropriate distraction,9,137,171 such as toys, books, blowing bubbles or pinwheels, stress balls, and using apps, videos, or games on electronic devices. Of note: If above ineffective or not feasible, consider nitrous gas analgesia/ sedation. For needle phobia, in addition, consider referral to pediatric psychologist.
should be offered for elective needle procedures to reduce or eliminate pain and anxiety experienced by children (Box 2). Failure to prevent or minimize treatable procedural pain in children is now considered both inappropriate and unethical. (1) Topical anesthesia needs to be offered (and unless verbal children decline for themselves), administered to all children 36 weeks’ corrected gestational age and older for every elective needle procedure. Topical anesthetics include 4% lidosomal lidocaine cream (of note, currently, all 4% lidocaine cream available over-the-counter in the United States and Canada is lidosomal), EMLA (lidocaine 2.5% and prilocaine 2.5%) cream, or needle-less lidocaine application through a J-tip (sterile, single-use, disposable injector that uses pressurized gas to propel medication through the skin).

EMLA cream may be on the skin for up to 4 hours and provides maximum analgesia after at least 60 minutes compared with 4% lidocaine cream, which is already effective after 30 minutes and may be on skin up to 2 hours. In comparison with EMLA cream, amethocaine (tetracaine) 4% gel is superior in preventing pain associated with needle procedures. Only topical anesthesia, such as lidocaine provided consistent analgesia within an additive pain intervention regimen during vaccinations in infants. Dispelling a common myth, topical anesthetics do not constrict veins and do not decrease the chance of venous cannulation. Not surprisingly, topical anesthesia even works for kids under general anesthesia and should therefore be considered.

Other modalities, including vapocoolants, ice, cool/cold packs, and vibrating devices might be helpful but currently have insufficient evidence for or against their use to reduce pain at time of injection and therefore should be considered in addition to topical anesthetics, but not instead of numbing cream. In comparison with EMLA cream, amethocaine (tetracaine) 4% gel is superior in preventing pain associated with needle procedures. Only topical anesthesia, such as lidocaine provided consistent analgesia within an additive pain intervention regimen during vaccinations in infants. Dispelling a common myth, topical anesthetics do not constrict veins and do not decrease the chance of venous cannulation. Not surprisingly, topical anesthesia even works for kids under general anesthesia and should therefore be considered.

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skin-to-skin contact for infants or not restraining children; (3) sucrose or breastfeeding for infants; and (4) age-appropriate distraction. A deferral process for children where this bundle is ineffective may include nitrous gas analgesia and sedation.

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References
[1] American Society of Anesthesiologists Task Force on S, Analgesia by N-A. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004–17.
[2] Anand KJ, Barton BA, McIntosh N, Lagercrantz H, Pelausa E, Young TE, Vasa R. 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 1999;153:331–8.
[3] Baeumler PI, Fleckner KS, Biedert F, Bader J, Imich D. Acupuncture-induced changes of pressure pain threshold are mediated by segmental inhibition—a randomized controlled trial. PAIN 2015;150:2245–52.
[4] Benoit B, Campbell-Yeo M, Johnston C, Latimer M, Caddell K, Orr T. Staff nurse utilization of kangaroo care as an intervention for procedural pain in preterm infants. Adv Neonatal Care 2016;16:229–38.
[5] Beyer JE, DeGood DE, Ashley LC, Russell GA. Patterns of postoperative analgesic use with adults and children following cardiac surgery. Pain 1983;17:71–81.
[6] Birnie KA, Grinbergs CT, Fernandes CV, Forgeron PA, Latimer MA, McGrath PJ, Cummings EA, Finlay GA. Hospitalized children continue to report undertreated and preventable pain. Pain Res Manag 2014;19:198–204.
[7] Birnie KA, Noel M, Chambers CT, Uman LS, Barker JA. Psychological interventions for needle-related procedural pain and distress in children and adolescents. Cochrane Database Syst Rev 2018;10:CD005179.
[8] Brattberg G. Do pain problems in young school children persist into early adulthood? A 13-year follow-up. Eur J Pain 2004;8:187–99.
[9] Broome ME, Richtsmeier A, Maliker V, Alexander M. Pediatric pain practices: a national survey of health professionals. J Pain Symptom Manage 1996;1:312–20.
[10] Burns J, Jackson K, Sheehy KA, Finkel JC, Quezado ZM. The use of dexmedetomidine in pediatric palliative care: a preliminary study. J Palliat Med 2017;20:779–83.
[11] Burns DA, Using regional anesthesia to manage pediatric acute pain. 11th Pediatric Pain Management’s Conference (Conference), Minneapolis, MN, USA. 2018.
[12] Bussing A, Ostermann T, Ludtke R, Michalsen A. Effects of yoga interventions on pain and pain-associated disability: a meta-analysis. J Pain Symptom Manage 2010;39:904–13.
[13] Chrysostomou C, Schulman SP, Herrera Castellanos M, Cofer BE, Mitra S, da Rocha MG, Wiseman WA, Gramlich L. A phase II/III, multicenter, safety, efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. J Pediatr 2014;164:276–82, e271–273.
[14] Ciszowska C, Madadi P, Phillips MS, Lauwers AE, Koren G, Codeine, ultrapid-metabolism genotype, and postoperative death. N Engl J Med 2009;361:827–8.
[15] Cousins LA, Kalaparakakel S, Coken LL, Simons LE. Topical review: resilience resources and mechanisms in pediatric chronic pain. J Pediatr Psychol 2015;40:840–5.
[16] Cussins N, Boughrouph J, Duvile E. The efficacy of continuous fascia iliaca compartment block for pain management in burn patients undergoing skin-grafting procedures. Anesth Analg 2004;98:1077–81, table of contents.
[17] Daling JR, Doody DR, Sun X, Trabert BL, Weiss NS, Chen C, Biggs ML, Sturr JR, Day SK, Schwartz SM. Association of marijuana use and the incidence of testicular germ cell tumors. Cancer 2009;11:1215–23.
[18] Desphande A, MAILIS-GAGNON A, ZOHEYNI N, LAKHA SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: systematic review of randomized controlled trials. Can Fam Physician 2015;61:e372–381.
[19] Eccleston C, Malpass PN, Clinic J, Connell H, Sourbut C. Chronic pain in adolescents: evaluation of a programme of interdisciplinary cognitive behaviour therapy. Arch Dis Child 2003;88:881–5.
[20] Eccleston C, Palermo TM, Williams AC, Lezard HW, Holley A, Morley S, Fisher E, Law E. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev 2014;5:CD003960.
[21] Edwards KM, Hackell JM; Committee on Infectious Diseases TCOP, Ambulatory M. Countering vaccine hesitancy. Pediatrics 2016;138:e20162146.
[22] Edwards L, DeMeeo S, Homik CD, Cotten CM, Smith PB, Pizoli C, Hauer JM, Bidelman G. Gabapentin use in the neonatal intensive care unit. J Pediatr 2013;162:10–15.
[23] Evans S, Tsao JC, Zeltzer LC. Complementary and alternative medicine for acute procedural pain in children. Ambulatory M. Countering vaccine hesitancy. Pediatrics 2016;138:e20162146.
[24] Edwards L, DeMeeo S, Hornik CD, Cotten CM, Smith PB, Pizoli C, Hauer JM, Biedelan G. Gabapentin use in the neonatal intensive care unit. J Pediatr 2013;162:10–15.
[25] Evans S, Tsao JC, Zeltzer LC. Paediatric pain management: using complementary and alternative medicine. Rev Pain 2006;2:14–20.
[26] Evans S, Moieni M, Taub R, Subramanian SK, Tsao JC, Stemble J, Zeltzer LC. Ivy yoga for young adults with rheumatoid arthritis: results from a mixed-methods pilot study. J Pain Symptom Manage 2015;49:994–102.
[27] FDA (Food and Drug Administration). Codeine and tramadol medications: drug safety communication—restricting use in children, recommending against use in breastfeeding women. 2017. Available at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ ucm554029.htm?source=govdelivery&utm_medium=email&utm_ source=govdelivery&Accessed September 3, 2019.
[28] Ferrini R, Paice JA. How to initiate and monitor infusional lidocaine for severe and/or neuropathic pain. J Support Oncol 2004;2:90–4.
[29] Finchel J, Pestieau S, Quezado Z. Ketamine as an adjuvant for treatment of cancer pain in children and adolescents. J Pain 2007;8:515–21.
[30] Finnerup NB, Atilal N, Haroutousian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haapamaa M, Hansson P, Jensen TS, Kameran FR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Senna E, Sirdjel P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73.
Kemani MK, Kanstrup M, Jordan A, Caes L, Gauntlett-Gilbert J. Evaluation of an intensive interdisciplinary pain treatment based on acceptance and commitment therapy for adolescents with chronic pain and their parents: a nonrandomized clinical trial. J Pediatr Psychol 2018; 43:981–94.

Kennedy A, Baskett M, Sheedy K. Vaccine attitudes, concerns, and information sources reported by parents of young children: results from the 2009 HealthStyles survey. Pediatrics 2011;127(suppl 1):S92–99.

King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, McDonald AJ. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. PAIN 2011;152:2729–38.

Koh JL, Harrison D, Myers R, Dembinski R, Turner H, McGraw T. A randomized, double-blind comparison study of EMLA and EMA-Lax for the relief of refractory malignant pain in a terminally ill pediatric cancer patient. J Pediatr Hematol Oncol 2002;24:566–8.

Koren G, Caims J, Chitayat D, Gaedigk A, Leeder SJ. Differential changes in functional disability and pain intensity after surgery. Acad Pediatr 2018;18:376–83.

Kovacic K, Hainsworth K, Sood M, Chelinsky G, Unteutsch R, Nugent M, Simpson P, Miranda A. Neurostimulation for abdominal pain-related functional gastrointestinal disorders in adolescents: a randomised, double-blind, sham-controlled trial. Lancet Gastroenterol Hepatol 2017;2:727–34.

Kutner L, Friedrichsdorf SJ. Hypnosis and palliative care. Therapeutic hypnosis with children and adolescents. Bethel: Crown House Publishing Limited, 2013. p. 491–509.

Lacson JC, Tuzon CD, Tuazon E, Castelao EJ, Bernstein L, Cortessis VK. Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. Cancer 2012;118:3574–85.

Lander JA, Weltman BJ, Soo SS. WITHDRAWN: EMLA and amethocaine injected lidocaine to reduce venipuncture pain for young children. Ann Emerg Med 2015;66:466–74.

Lee BH, Scharff L, Sethna NF, McCarthy CF, Scott-Sutherland J, Shea Law E, Fisher E, Eccleston C, Palermo TM. Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database Syst Rev 2019;3:CD009660.

Lee BH, Schaff R, Senthin NA, McCarthy CF, Scott-Sutherland J, Soria AM, Sullivan P, Meier P, Zurakowski D, Masek BJ, Berde CB. Physical therapy and cognitive-behavioral treatment for complex regional pain syndromes. J Pediatr 2002;141:135–40.

Levy RL, Langer SL, Walker LS, Romano JM, Christie DL, Yousuff N, DuPen MM, Feliz AD, Ballard SA, Welsh EM, Jeffery RW, Young M, Coffey MJ, Whitehead WE. Cognitive-behavioral therapy for children with functional abdominal pain and their parents decreases pain and other symptoms over time. J Pediatr Gastroenterol Nutr 2010;50:946–56.

Lilland BE, Mangione-Smith R, Palermo TM, Rabbitts JA. Agreement between parent proxy report and child self-report of pain intensity and health-related quality of life after surgery. Acad Pediatr 2018;13:376–83.

Livingston M, Lawell M, McAllister N. Successful use of nitrous oxide for the relief of refractory malignant pain in a terminally ill pediatric cancer patient. J Pediatr Hematol Oncol 2002;24:566–8.

Maynard CS, Amari A, Wieczorek B, Christensen JR, Sifter KJ. Interdisciplinary behavioral rehabilitation of pediatric pain-associated disability: retrospective review of an inpatient treatment protocol. J Pediatr Psychol 2010;35:128–37.

McMurtry CM, Pillai Riddell R, Taddia A, Racine N, Asmundson GJ, Noel M, Chambers CT, Shah V; HelpinKids, Adults T. Far from "just a poke": common painful needle procedures and the development of needle fear. Cijn J Pain 2015;31(10 suppl):S3–11.

McMurtry CM, Taddia A, Noel M, Antony MM, Chambers CT, Asmundson GJ, Pillai Riddell R, Shah V, MacDonald NE, Rogers J, Bucci LM, Mousmanis P, Lang E, Halperin S, Bowles S, Halpert C, Iyp M, Rieder MJ, Robson K, Uleyk E, Volta Bleecker E, Dubey V, Hanrahan A, Lockett D, Scott J. 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 2016;45:217–55.

Meier MH, Caspi A, Ambler A, Harrington H, Kouts R, Keefe RS, McDonald K, Ward A, Poullon R, Moffit TE. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A 2012;109:26267–2664.

Meier MH, Hall W, Caspi A, Belisky DW, Cerda M, Harrington HL, Houts R, Poullon R, Moffit TE. Which adolescents develop persistent substance dependence in adulthood? Using population-representative longitudinal data to inform universal risk assessment. Psychol Med 2016;46:877–89.

Moffit TE, Meier MH, Caspi A, Poullon R. Reply to Rogeberg and Daly: no evidence that socioeconomic status or personality differences confound the association between cannabis use and IQ decline. Proc Natl Acad Sci U S A 2013;110:E980–982.

Moore RA, Derry S, Straube S, Treanor-Paine J, Wiljen PJ. Faster, higher, stronger? Evidence for formulation and efficacy for ibuprofen in acute pain. PAIN 2014;155:14–21.

Nissen NE, Yeomans ND, Solomon DH, Luscher TF, Libby P, Husni ME, Graham D, Borer J, Wissel, Wolski KE, Wang Q, Menon V, Ruschitzka F, Gaffney M, Beckerman B, Berger MF, Bao W, Lincoff AM, Investigators P. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med 2005;352:1985–97.

Odel S, Logan DE. Pediatric pain management: the multidisciplinary approach. J Pain Res 2013;6:785–90.

Palermo TM, Scher MS. Treatment of functional impairment in severe somatoform pain disorder: a case example. J Pediatr Psychol 2001;26:429–34.

Palermo TM, Eccleston C, Lewandowski AS, Williams AC, Morley S. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: an updated meta-analytic review. PAIN 2010;148:387–97.

Palermo TM, Valrie OR, Karlson CW. Family and parent influences on pediatric chronic pain: a developmental perspective. Am Psychol 2014;69:550–62.

Palermo TM, Law EF, Fales J, Bromberg MH, Jessen-Fiddick T, Tai G. Internet-delivered cognitive-behavioral treatment for adolescents with chronic pain and their parents: a randomized controlled multicenter trial. PAIN 2016;157:174–85.

Palermo T, Cognitive-behavioral therapy for chronic pain in children and adolescents. New York: Oxford University Press, 2012.

Pedersen BS, Bayat A, Steen NP, Jacobsen ML. Nitrous oxide provides safe and effective analgesia for minor paediatric procedures—a systematic review. Dan Med J 2013;60:A4627.

Pediatrics, American Academy of Updated AAP policy opposes marijuana use, citing potential harms, lack of research. 2015. Available at: http://www.aapd.org/pubs/aapnews/2015/1/26/aapnews150126-1 Accessed September 3, 2019.

Peixoto RD, Hawley P. Intravenous lidocaine for cancer pain without electrocardiographic monitoring: a retrospective review. J Palliat Med 2015;18:373–7.

Peters M, Smeeets E, Feigje M, van Breukelen G, Andersson G, Buhrman M, Linton SJ. Happy despite pain: a randomized controlled trial of an 8-week internet-delivered positive psychology intervention for enhancing well-being in patients with chronic pain. Clin J Pain 2017;33:962–75.

Piechow M, Vowell KE, Wickless R. Acceptance and commitment therapy for pediatric chronic pain: theory and application. Children (Basel) 2017;4:E10.

Postier AC, Eull D, Schulz C, Fitzgerald M, Synamal B, Watson D, Georgerness L, Friedrichsdorf SJ. Pain experience in a US children’s hospital: a point prevalence survey undertaken after the implementation of a system-wide protocol to eliminate or decrease pain caused by needles. Hosp Pediatr 2018;8:515–23.
Ramsey LH, Carlson CW, Collier AB. Mirror therapy for phantom limb pain in a 7-year-old male with osteosarcoma. J Pain Symptom Manage 2017;53:65–7.

Reynolds N, Mrug S, Guion K. Spiritual coping and psychosocial adjustment of adolescents with chronic illness: the role of cognitive attributions, age, and disease group. J Adolesc Health 2013;52:556–65.

Richardson J, Smith JE, McCall G, Pilkington K. Hypnosis for procedure-related pain and distress in pediatric cancer patients: a systematic review of effectiveness and methodology related to hypnosis interventions. J Pain Symptom Manage 2006;31:70–84.

Richmond C. Dame cicely saunders. BMJ 2003;331:238.

Robertson DW, 2010;12:85–93.

Rother A, Parikh C, Yuen EW, Sgro M, Singh H, Halbert E, Ipp M, Thivakaran S, Jamal A, Parikh C, Smart S, Sovran J, Stephens D, Katz J. Survey of the prevalence of immunization non-compliance due to needle fears in children and adults. Vaccine 2012;30: 4807–12.

Taddio A, McMurtry CM, Shah V, Riddell RP, Chambers CT, Noel M, MacDonald NE, Rodgers J, Buacci LM, Mousmannis P, Lang E, Halperin SA, Bowles S, Halpert C, Ipp M, Asmundson GJ, Rieder MJ, Robson K, Uleryk E, Antony MM, Dubey V, Hannah A, Lockett D, Scott J, Votta Bleeker E; HelpinKids, Adults. Reducing pain during vaccine injections: clinical practice guideline. CMAJ 2015;187:975–82.

Taddio A, Parikh C, Yuen EW, Sgro M, Singh H, Halbert E, Ipp M, Affili AR, Pillai, Riddell R, Shah V. Impact of parent-directed education on parental use of pain treatments during routine infant vaccinations: a cluster randomized trial. PAIN 2015;156:185–91.

Taddio A, Shah V, McMurtry CM, MacDonald NE, Ipp M, Riddell RP, Noel M, Chambers CT; HelpinKids, Adults T. Procedural and physical interventions for vaccine injections: systematic review of randomized controlled trials and quasi-randomized controlled trials. Clin J Pain 2015;31(10 suppl):S20–37.

Taddio A, Pillai Riddell R, Ipp M, Moss S, Baker S, Tolkin J, Malini D, Feerasta S, Govan P, Fletcher E, Wong H, McNair C, Mithal P, Stephens D. Relative effectiveness of addictive pain interventions during Cochrane Database Syst Rev 2017;19:EC0007–E254.

Tang WX, Zhang LF, Ai YQ, Li ZS. Efficacy of Internet-delivered cognitive-behavioral therapy for the management of chronic pain in children and adolescents: a systematic review and meta-analysis. Medicine (Baltimore) 2018;97:e12061.

Taylor EM, Boyer K, Campbell FA. Pain in hospitalized children: a prospective cross-sectional survey of pain prevalence, intensity, assessment and management in a Canadian pediatric teaching hospital. Pain Res Manag 2008;13:25–32.

Teerawattanachot C, Tantayakom P, Suwanaviboon B, Kachtamath W. Risk of perioperative bleeding related to highly selective cyclooxygenase-2 inhibitors: a systematic review and meta-analysis. J Arthritis Rheum 2017;46:520–9.

Tegsengborff M, Belardi A, Meistrich B, Meistrich G. Comorbidity of mental disorders and chronic pain: chronology of onset in adolescents of a National Representative Cohort. J Pain 2015;16:1054–64.

Tobias JD. Applications of nitrous oxide for procedural sedation in the pediatric population. Pediatr Emerg Care 2013;29:245–65.

Tong F, Dannaway J, Enke O, Essig L. Effect of preoperative psychological interventions on elective orthopaedic surgery outcomes: a systematic review and meta-analysis. ANZ J Surg 2019, doi: 10.1111/ans.15332. [Epub ahead of print].

Trabert B, Sigurdison AJ, Sweeney AM, Strom SS, McQuay K. Marijuana use and testicular germ cell tumors. Cancer 2011;117:348–53.

Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Kosek E, Lavand’homme P, Nicholas M, Perrot S, Schug S, Smith BH, Svensson P, Vaesen JW, Wang SJ A. A classification of chronic pain for ICD-11. PAIN 2015;116:1003–7.

Turk D, Okifuji A. Pain terms and taxonomies of pain. In: J Bonica, J Loeser, C Chapman, D Turk, S Butler, editors. Bonica’s management of pain. Lippincott Williams & Wilkins, Philadelphia, 2001.

Tweedy CR, Collins SF. How well is acute pain in children managed? A snapshot in one English hospital. Pain Manag Nurs 2013;14:e204–215.

Twycross A, Collis S. How well is acute pain in children managed? A 7-year follow-up: a snapshot in one English hospital. Pain Manag Nurs 2013;14:e204–215.

Urban LS, Birnie KA, Noel M, Parker JA, Chambers CT, McGrath PJ, Twycross A, Collis S. How well is acute pain in children managed? A prospective cross-sectional survey of pain prevalence, intensity, assessment and management in a Canadian pediatric teaching hospital. Pain Res Manag 2008;13:25–32.

Vase J, Santos-Rey K, Navarro-Pablo R, Modesto M, Aguilar I, Campos Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KM. Acceptance–commitment therapy for chronic musculoskeletal pain: a randomized controlled trial. PAIN Reports 2015;1:ans15332. [Epub ahead of print].

Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. Cogn Behav Ther 2016;45:55–31.

Verkamp EK, Flowers SR, Lynch-Jordan AM, Taylor J, Ting TV, Kashkar-Zuck S. A survey of conventional and complementary therapies used by youth with juvenile-onset fibromyalgia. Pain Manag Nurs 2013;14:e244–250.

Vervoort T, Logan DE, Goubert L, De Clercq B, Hublet A. Severity of pediatric pain in relation to school-related functioning and teacher instruction.
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support: an epidemiological study among school-aged children and adolescents. PAIN 2014;155:1118–27.

[177] Victoria NC, Murphy AZ. Exposure to early life pain: long term consequences and contributing mechanisms. Curr Opin Behav Sci 2016;7:61–8.

[178] Wallace MS, Lee J, Sorkin L, Dunn JS, Yaksh T, Yu A. Intravenous lidocaine: effects on controlling pain after anti-GD2 antibody therapy in children with neuroblastoma—a report of a series. Anesth Analg 1997; 85:794–6.

[179] Walther-Larsen S, Pedersen MT, Friis SM, Aagaard GB, Romsing J, Jeppesen EM, Friedrichsdorf SJ. Pain prevalence in hospitalized children: a prospective cross-sectional survey in four Danish university hospitals. Acta Anaesthesiol Scand 2016;61:328–37.

[180] World Health Organization. WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. Geneva: WHO Press, 2012.

[181] Xiang A, Cheng K, Shen X, Xu P, Liu S. The immediate analgesic effect of acupuncture for pain: a systematic review and meta-analysis. Evid Based Complement Altern Med 2017;2017:3837194.

[182] Zhu LM, Stinson J, Palozzi L, Weingarten K, Hogan ME, Duong S, Carbajal R, Campbell FA, Taddio A. Improvements in pain outcomes in a Canadian pediatric teaching hospital following implementation of a multifaceted knowledge translation initiative. Pain Res Manag 2012;17:173–9.

[183] Zier JL, Liu M. Safety of high-concentration nitrous oxide by nasal mask for pediatric procedural sedation: experience with 7802 cases. Pediatr Emerg Care 2011;27:1107–12.