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LEADING ARTICLE

Postoperative Pain Management in Pediatric Spinal Fusion Surgery for Idiopathic Scoliosis

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Abstract

This article reviews and summarizes current evidence and knowledge gaps regarding postoperative analgesia after pediatric posterior spine fusion for adolescent idiopathic scoliosis, a common procedure that results in severe acute postoperative pain. Inadequate analgesia may delay recovery, cause patient dissatisfaction, and increase chronic pain risk. Despite significant adverse effects, opioids are the analgesic mainstay after scoliosis surgery. However, growing emphasis on opioid minimization and enhanced recovery has increased adoption of multimodal analgesia (MMA) regimens. While opioid adverse effects remain a concern, MMA protocols must also consider risks and benefits of adjunct medications. We discuss use of opioids via different administration routes and elaborate on the effect of MMA components on opioid/pain and recovery outcomes including upcoming regional analgesia. We also discuss risk for prolonged opioid use after surgery and chronic post-surgical pain risk in this population. Evidence supports use of neuraxial opioids at safe doses, low-dose ketorolac, and methadone for postoperative analgesia. There may be a role for low-dose ketamine in those who are opioid-tolerant or have chronic pain, but the evidence for preoperative gabapentinoids and intravenous lidocaine is currently insufficient. There is a need for further studies to evaluate pediatric-specific optimal MMA dosing regimens after scoliosis surgery. Questions remain regarding how best to prevent acute opioid tolerance, opioid-induced hyperalgesia, and chronic postsurgical pain. We anticipate that this timely update will enable clinicians to develop efficient pain regimens and provide impetus for future research to optimize recovery outcomes after spine fusion.

1 Introduction

Adolescent idiopathic scoliosis (AIS) is the most common spinal deformity in children. Some degree of spinal curvature is present in 1–3% of children 10–16 years of age [1]. Posterior spinal fusion (PSF) accounts for 90% of scoliosis surgery [2] with approximately 38,000 spinal fusion surgeries occurring annually in the United States [3]. Analgesia after PSF is challenging due to extensive dissection, inflammation, and ensuing central and peripheral nerve sensitization. Inadequate analgesia may lead to delays in recovery goals such as oral intake and ambulation, causing patient/

Key Points

Intravenous opioids are still the mainstay of postoperative analgesia but have several adverse effects; in comparison, the neuraxial route may offer advantages

Multimodal analgesia is an important component of opioid minimization and enhanced recovery protocols after spinal fusion.

Non-steroidal anti-inflammatory drugs and methadone are valuable adjuncts in a multimodal analgesic strategy after posterior spinal fusion.

Evidence for efficacy of gabapentinoids, low-dose ketamine, intravenous lidocaine, and regional techniques is currently insufficient.

Acute opioid tolerance, opioid-induced hyperalgesia, and chronic postsurgical pain are significant problems after major surgery. Additional research is needed to identify effective preventative strategies.

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family dissatisfaction and increased risk of chronic postsurgical pain (CPSP) [4–6].

Traditionally, opioids have been the mainstay of analgesia after scoliosis surgery, despite significant adverse effects. Minor adverse effects are common, including vomiting (40%), pruritus (20%), and constipation (15–90%) [7]. Severe adverse events such as respiratory depression are much less frequent (0.0013%) [7]. It is believed that opioid adverse effects are related to the total dose consumed. In addition to adverse effects, development of acute opioid tolerance and opioid-induced hyperalgesia may complicate and delay recovery and discharge. With a goal of decreasing opioid consumption, multimodal analgesia (MMA) has been adopted for pain management. MMA combines different modes/classes of analgesics to treat pain and supports enhanced recovery after surgery (ERAS) [8]. However, there are adverse effects to different medications used for MMA; for example, high-dose ketorolac and non-steroidal anti-inflammatory drugs pose potentially increased risk for non-fusion and bleeding. Therefore, it is necessary to evaluate risks and benefits of the different adjunct medications and safe dosing factors before deciding on the optimal MMA protocol.

This review article aims to summarize currently available evidence and knowledge gaps regarding postoperative analgesia after pediatric posterior spine fusion for adolescent idiopathic scoliosis, including multimodal analgesia and enhanced recovery protocols. With growing literature and several multimodal strategies being used and evaluated, we anticipate this timely topic will aid development of hospital-specific protocols and provide direction for future research.

2 Multimodal Analgesia and Enhanced Recovery After Surgery Protocols

Since their introduction in the 1990s, MMA [9] and ERAS [10] have been widely recognized and promoted by the medical community at large. ERAS is a multidisciplinary perioperative care model that aims to hasten the recovery of patients undergoing surgery without increasing complications or diminishing patient satisfaction. Many surgical subspecialties have developed ERAS protocols to accelerate discharge and improve perioperative care. Similarly, ERAS protocols for AIS patients undergoing PSF have been developed to decrease length of stay (LOS) and cost of care without increasing complication rates.

MMA is a key component of ERAS protocols. It consists of the combined administration of different medications targeting different mechanisms for providing analgesia [11]. This could be preemptive (administered before surgical insult) or preventive (where the timing of administration is not critical). Preventive analgesia is a wider concept and aims to minimize noxious sensations arising intra- or postoperatively. The goal of MMA is to decrease opioid requirements and opioid-related adverse effects, and combined with ERAS, the overall goals are to achieve accelerated recovery goals, including transition from epidural or patient-controlled analgesia (PCA) to enteral analgesia, and ambulation. Since current consensus indicates that use of preemptive analgesia does not result in consistent clinical benefits after surgery [12], we do not classify modalities as preemptive or preventive, but describe when they are used. Regardless of the timing of the intervention (preoperative or intraoperative or postoperative), we will discuss the influence on postoperative analgesia for each analgesic intervention.

In a quality improvement project, Muhly et al. standardized a rapid recovery pathway for AIS patients undergoing PSF. While receiving a standardized MMA regimen, patients were transitioned off PCA to enteral analgesia with intravenous (IV) intermittent opioids for breakthrough pain and ambulated on the first postoperative day (POD). After ERAS protocol initiation, investigators were able to accelerate functional recovery, decrease pain scores, and decrease LOS from 5.7 to 4 days [13]. Most protocols incorporate preoperative education, multimodal analgesia, early mobilization, early transition to oral medications, prompt discontinuation of drains/catheters, and involve multidisciplinary collaborations [14–18]. Salient features of the protocols and outcomes are described in Table 1. Some of the studies evaluated pain outcomes and readmission rates. Fletcher et al. also compared an accelerated pathway at one institution ($N=279$) with a standard discharge pathway at a separate institution ($N=86$), demonstrating that prioritizing early diet, frequent mobilization with physical therapy, and early removal of drains and urinary catheters resulted in shorter LOS (2.9 vs 4.3 days, $p<0.0001$) and no significant increase in complications [19].

According to a national database study ($N=7349$), there is wide variation in adjuvant therapies used and insufficient evidence for the effectiveness of several of the adjuvants [20]. Multimodal therapy may result in additive or synergistic effects and more effective pain relief compared with single-modality interventions [21]. Multimodal analgesia can potentially minimize adverse events by reducing opioid requirements as well [22, 23]. It is recommended that clinicians offer multimodal analgesia for treating postoperative pain in both children and adults. Providers must recognize that multiple potential combinations are possible and appropriate, depending on the type of surgery, patient preference, and individual factors [21]. We present currently available evidence for the different components of MMA regimens after surgeries for AIS, including opioids and opioid adjuvants.

In addition, recent advances in minimally invasive scoliosis (MIS) surgery may suggest need for future refinement

of pain management protocols. Surgical techniques used are direct or extreme lateral interbody fusion, axial lumbar interbody fusion, and transforaminal lumbar interbody fusion [24]. However, there is insufficient literature regarding pain trajectories after MIS surgeries. One retrospective study did not find any differences in PCA opioid use or pain scores on comparing seven patients who underwent MIS with 15 adolescents who underwent standard open surgery [25], while another one found higher pain scores in the MIS group versus PSF [26]. Hence, it is too early to assess if any modifications will be needed. It seems more likely that MMA will be useful for MIS procedures too.

3 Opioids

Although there is a push for opioid-reduced and opioid-free anesthesia, opioids continue to be used for intraoperative and postoperative analgesia [27]. Commonly used opioids for pain management in pediatric spine fusion protocols are discussed below and classified by route of administration.

3.1 Intravenous Opioids

Both ultrashort (remifentanil) and long-acting (methadone) opioids are often used intraoperatively during spine fusion with an impact on postoperative analgesia and pain outcomes. Discussion of these opioids will be followed by commonly used postoperative use of opioids using patient-controlled analgesia modalities.

3.1.1 Methadone

Methadone is a μ-opioid agonist, a potent N-methyl-d-aspartate (NMDA) receptor antagonist [28] and serotonin/norepinephrine reuptake inhibitor, thus it potentially provides mood as well as analgesic benefits [29, 30]. Several studies in adults have shown a beneficial effect of methadone doses of 0.1–0.3 mg/kg or 10–20 mg doses prior to incision for its effects on pain scores and opioid consumption after complex spine surgery [31–33]. However, there are only two studies evaluating use of methadone in children undergoing spine fusion, both showing decreased opioid (hydromorphone) consumption postoperatively (Table 2). One may argue that methadone is also an opioid and total morphine equivalents need to be compared. Methadone is unique given its long elimination half-life (24–36 h) but quick onset (8 min) compared with other commonly used IV opioids [30]. Methadone pharmacokinetic studies have shown a linear increase in blood concentrations with doses; a pharmacokinetic study in adolescents undergoing spine fusion administered methadone 0.25 mg/kg IV before surgical incision found mean concentrations of 58 μg/L by the first hour, which was previously deemed the minimum effective analgesic concentration [34]. The authors in the aforementioned pharmacokinetic study recommend following the bolus (0.25 mg/kg) with an infusion (0.1–0.15 mg/kg/h for 4 h) during spinal surgery to ensure adequate plasma concentrations for 24 h. More pediatric studies are needed to establish appropriate safety parameters for methadone dosing. In adults, the incidence of respiratory depression was not different from controls, except in elderly patients, and although QTc on electrocardiogram was prolonged in 58.8% of patients after surgery, it did not lead to arrhythmias [35]. Additionally, in cases of respiratory depression, it is recommended to consider a naloxone infusion and not a one-time reversal dose due to methadone's long half-life [36].

3.1.2 Remifentanil

Remifentanil, on the other hand, has an extremely short half-life of 1 min and an elimination half-life of 0.5 h. Hence, it is often used in conjunction with propofol for total intravenous anesthesia intraoperatively during spine fusion to facilitate intraoperative neuromonitoring and enable 'wake up' tests when necessary. The intraoperative use of remifentanil may have ramifications for postoperative analgesia. There has been concern that remifentanil could theoretically trigger opioid-induced hyperalgesia (OIH). Its use has been associated with higher morphine consumption during the first 24 h after scoliosis surgery [39]. However, findings of acute opioid tolerance and OIH after intraoperative remifentanil have been inconsistent, as other clinical studies have suggested no difference [40–43]. Co-administration of anesthetics such as propofol, ketamine, and nitrous oxide have been suggested to attenuate development of OIH [44–46].

A retrospective chart review examined the influence of intraoperative remifentanil ($N=37$) and fentanyl infusions ($N=25$) on postoperative morphine equivalents use over 48 h after spine fusion. To their surprise, they found higher postoperative opioid usage in the fentanyl group [47].

Hence, although the effect of intraoperative remifentanil may theoretically have negative effects on postoperative analgesia, current evidence does not condone its use.

3.1.3 Patient-Controlled Analgesia

For severe acute postoperative pain, IV opioid administration via PCA continues to be widely used [48]. Most studies use weight-appropriate initial loading doses followed by morphine 20 μg/kg or hydromorphone 2–4 μg/kg PCA demand doses with lockout intervals of 7–10 min (± basal infusions of 10 or 2 μg/kg/h, respectively) [39, 49–51]. Intermittent as-needed boluses of morphine (0.05–0.1 mg/kg) or hydromorphone (10–20 μg/kg) or fentanyl (0.5–1 μg/kg) are often made available every 4 h for breakthrough severe pain.

Table 1 Multimodal analgesia and enhanced recovery after surgery: protocols from literature

Studies	[a]Muhly 2016 [13]	[a]Gornitzky 2016 [17]	Rao 2016 [18]	Fletcher 2017[14]	Sanders 2017[15]	Chan 2017[16]
Study cohorts	*N* = 134 (CP), 104 (transition population), and 84 (AP); 2011–2015	*N* = 58 (AP) vs 80 (CP)	51 (CP) vs 100 (AP1: 2009–2013) vs 39 (AP2: 2013–2014)	2011–2012 *N* = 105 (AP) vs 45	2013–2014 *N* = 90 (AP) vs 134	*N* = 74 No comparative group
Day 0 preop meds	Gabapentin PO Acetaminophen PO		–	–	–	–
Day 0 Intraop meds	Methadone before incision Acetaminophen IV at closure		–	–	–	SQ bupivacaine prior to closure 2 mg/kg in 25 ml
Day 0 postop meds	Hydromorphone PCA		Acetaminophen Ketorolac PCA or epidural	morphine PCA IV diazepam Ketorolac q6h prn	PCA	PCA morphine IV ondansetron
Day 1	D/C PCA; Hydromorphone rescue q3h prn Ketorolac q6h PO oxycodone prn q4h PO acetaminophen q4h prn Diazepam q6h prn Gabapentin PO evening		Continue	D/C PCA PO narcotics Ketorolac q6h prn Diazepam PO prn	D/C PCA PO opioids	PO oxycodone started when PCA D/C ed. PO Celebrex 200 mg qday q12h PO Acetaminophen 500–1000 mg q6h
Day 2–3	Continue Ketorolac, Acetaminophen PO, Oxycodone PO, gabapentin PO at evening, Diazepam PO q6hr PRN		Prn to ATC oral opioids	Continue	Continue	
PCA	POD0-2		POD0-POD2 Epidural d/c POD3 (AP1); POD2 (AP2)	POD0-1	POD 0-1	POD0; d/c when consumption <5 mg/24 h
PO meds start	POD1		POD2	POD3	POD1	
Regular diet	POD1		POD2-3	POD1	POD1	POD1/2
Mobilization start	POD0-advance POD1		POD1-2	POD1	POD0-1	< 24 h
Foley d/c	POD1		POD1/3	POD4-5	POD1	18-24h
Other	Surgical team involvement; education; dedicated team		Use of epidural	Surgical time/curve different between groups	Education; coordinated effort	Preoperative exercise, counseling, dual attending strategy
LOS/other primary outcomes	4 (AP) vs 5.7 days (CP)	5.0 ± 0.8 (CP) vs 3.5 ± 0.8 days (AP)	98.4 h (CP) 27.8 h (AP1) 84.3 27.2 h (AP2)	2.2 (AP) vs 4.2 days (CP)	3.7 ± 0.9 (AP) vs. 5.0 ± 1.3 days Hospital charges decreased $18,360 (AP) vs. $23,640	3.6 ± 0.6 days
Pain	Improved on POD0 and 1	Improved pain; decreased opioid consumption POD0	Similar pain scores in all groups; higher patient satisfaction in AP1 and AP2 vs CP	–	< 1 point significant increase in pain	–
Readmission rates	No change	No change	–	–	No significant change	–

AP accelerated protocol, *ATC* around the clock, *CP* conventional protocol, *D/C* discontinue, *POD* postoperative day, *PO* per os, *SQ* subcutaneous

[a]Referenced studies followed similar protocols

Table 2 Studies evaluating use of methadone in children undergoing spine fusion

Study	Study design	Methadone dose and groups	Results
Murphy 2017 [31, 37]	DB, RCT $N=115$	Methadone 0.2 mg/kg at start of surgery vs hydromorphone 2 mg at surgical closure	Decrease hydromorphone use POD 1–3 (4.56 vs 9.90 mg; 0.60 vs 3.15 mg; 0 vs 0.4 mg; all $p<0.001$). Decreased pain scores ($p=0.001$ to <0.0001) and higher satisfaction ($p=0.001$ to <0.0001)
Martin 2018 [38]	Prospective, RCT; blinded $N=60$	Remifentanil alone (REMI), remifentanil + methadone (MET) (0.1 mg/kg IV over 15 min), and remifentanil + magnesium (MAG) (50 mg/kg bolus over 30 min followed by 10 mg/kg/h)	Decreased opioid consumption in MET group (95% CI of difference: −0.14 to −0.01; $p=0.035$); no difference in pain scores

CI confidence interval, *DB* double-blinded, *IV* intravenous, *POD* postoperative day, *RCT* randomized controlled trial

In addition, medications for counteracting opioid adverse effects are usually available through pre-designed order sets on most electronic prescribing platforms. These medications include nalbuphine, an opioid agonist–antagonist (0.05 mg/kg) for opioid-induced itching/urinary retention, ondansetron (0.1 mg/kg) for nausea/vomiting, and naloxone, an opioid antagonist (1–2 µg/kg for over-sedation; 10–20 µg/kg for respiratory depression, and sometimes 0.25 µg/kg/h IV infusion for itching).

Most cited advantages of PCA include patients' control over their own analgesia with improved relief, satisfaction, and psychological well-being [52]. While adult literature does not support use of basal infusions due to increased risk of respiratory depression [53], pediatric studies demonstrated that basal infusions had an inconsistent effect on opioid consumption [54–57] and adverse effects [54–59]. A meta-analysis of pediatric PCA use found that basal rates alone have no effect on outcomes, including pain scores, opioid consumption, and adverse effects [60]. Because of this conflicting and insufficient evidence, the Society of Pediatric Anesthesia recommends basal infusions only be used in select patients based on clinical situation, pain severity, and risk factors [61]. Despite widespread use, adverse events related to opioids remain a concern, and minimizing duration of PCA use is a priority [62]. A recent study by Fletcher et al. describes best practice guidelines for discontinuing PCA on postoperative day one and transitioning to oral opioids to facilitate quicker recovery [14].

3.2 Oral Opioids

Oral opioids are initiated when children tolerate oral intake after surgery. With ERAS protocols, there is a push for starting liquids and progressing to regular diet as early as possible. In general, the goal would be to transition from IV to oral opioids on POD1. While there are no studies comparing different oral opioids used after spine fusion, commonly used opioids include oxycodone 0.1 mg/kg/dose, hydromorphone 0.03–0.08 mg/kg/dose and hydrocodone 0.1–0.2 mg/kg/dose every 4 h as needed for pain [13]. We refer readers to the implications of pharmacogenetics for use of oral opioids such as codeine and tramadol, as ultrarapid metabolizers for the *CYP2D6* enzyme may experience higher adverse effects with these oral opioids, which carry black box warnings by the FDA [63]. Of note, patients are often discharged home with prescriptions for oral opioids. Children who underwent spine fusion were among those prescribed on average 44.13 more doses than children who underwent other surgeries (95% CI 34.72–53.54; $p<0.001$) [64]. While one study showed that patients were discharged home with an average of 61 pills (SD 14), of which 90.1% were utilized [65], other studies show that patients were dispensed 113 pills (80–115), of which only 39 pills (20–80) were actually used [64]. Given the risk for higher opioid use with availability and leftover pills, which can subsequently be diverted, these data suggest closer attention is warranted to avoid overprescribing and underline the need for education for proper disposal of leftover opioids.

3.3 Epidural Opioids

Epidural analgesia can be delivered as either continuous infusions, patient-controlled approaches with demand bolus and lockout interval (PCEA) or programmed intermittent boluses (PIB). The modes of delivery used in the studies are described in Table 3, with most of the studies using continuous infusions. Although there are studies showing superior analgesic efficacy of PCEA + PIB over continuous/PCEA in laboring parturients [66], there are no comparative studies in children undergoing scoliosis surgery. Most studies evaluating efficacy and safety of epidural analgesia after spine fusion commonly include mixtures of opioids and local anesthetic solutions for epidural use (Table 3). Only one retrospective study ($N=56$) evaluated the use of an opioid-only regimen with hydromorphone 5 µg/kg (maximum 200 µg) + fentanyl 1 µg/kg (maximum 50 µg) through an epidural catheter before wound closure, followed by epidural infusion of hydromorphone 5 µg/mL at 12–16 mL/h with

2-mL boluses permitted every 30 min [67]. Though not a comparative study, the authors concluded that narcotic-only epidural infusion was a safe and effective mode of analgesia. Some studies use single while others have used double catheters; one study compared their use and found that double epidural catheter had a modest benefit over single catheter for analgesia [68]. One of the studies used epidural analgesia when the epidural space was violated during surgery and showed no negative consequences [69]. Epidural opioid doses range from morphine 30–50 μg/kg, hydromorphone 5–20 μg/kg, and fentanyl 1 μg/kg with or without local anesthetic followed by infusions (of local anesthetic + opioid) via catheter. A Cochrane review of 11 trials (7 trials analyzed, 249 participants) found that there was little evidence that epidural local anesthetic infusion alone accelerates return of gastrointestinal function, time to first mobilization, or hospital discharge [68, 70], and studies have demonstrated epidural failure rates as wide as 8–37% [49, 71]. Yet, the Cochrane Review found moderate- and low-quality evidence that epidural analgesia may have a small advantage in pain reduction in the first 72 h after surgery compared with systemic analgesia with no difference in complication rates (vomiting, respiratory depression, wound infection, epidural abscess, etc.). Hence, epidural analgesia is a potentially safe and effective postoperative modality after spine fusion, and has been used in conjunction with MMA protocols [18]. The comparative efficacy of modes of epidural delivery for spine surgery are yet to be determined.

3.4 Intraoperative Intrathecal Opioids

Intrathecal opioids, mainly morphine—typically after induction of anesthesia and prior to incision—have been evaluated in doses of 2–20 μg/kg for postoperative analgesia after spine surgery [80–85]. Studies demonstrated that this technique reduced intraoperative and postoperative opioid consumption and decreased pain scores (Table 4). The analgesic effect lasts for at least 12 h [86] to 18.8 h [80–83]. There is some compelling evidence that intrathecal opioids may significantly decrease intraoperative blood loss, though the mechanism of the blood-sparing effect remains unclear [80–83]. Some hypothesize that the diminished blood loss may be due to lower mean arterial pressures. Yet, other studies have demonstrated no difference in blood pressures [82]. Effects of sex and race on efficacy and adverse effects of this recommended dose in adolescents undergoing scoliosis surgery ($N = 287$) were evaluated by Son-Hing et al. [84]. They found that analgesic efficacy was similar in females/males (F/M) and White/African American (W/AA) groups. While there was no statistical difference in the incidences of nausea/vomiting and pruritis between females and males (31.7%/25.5%), there was a statistically significant difference between White and African American groups (34.4%/17.5%). However, it is important to note that there was no statistical difference in the incidences of respiratory depression for different sexes (F/M 4.1%/6.4%) or different ethnicities (W/AA 4%/6.3%). Thus, while most studies demonstrated no differences in major adverse effects, a study evaluating different doses concluded that higher doses of intrathecal morphine (≥ 20 μg/kg) may be associated with greater risk of significant respiratory depression and 9–19 μg/kg (mean 14 μg/kg) doses are safe and effective [83].

3.5 Comparison of Opioid Routes for Postoperative Analgesia

One retrospective study compared the efficacy of PCA morphine with single preoperative intrathecal morphine injection (7 μg/kg) and PCA (IT/PCA), and epidural catheter infusion (a bolus dose of hydromorphone [10–20 g/kg] followed by a continuous infusion of hydromorphone [20 g/mL] and bupivacaine 0.1% at an initial rate of 0.1–0.2 mL/kg/h) without PCA (EPI) for postoperative pain control after PSF [87]. They found that while both EPI and IT groups had superior pain control compared with PCA, the EPI group had longer postoperative analgesia due to the infusion, while IT analgesia lasted about 24 h. The difference in analgesia duration allowed for quicker return to diet. Another double-blinded randomized, controlled trial (RCT) compared use of IT morphine (7.5 μg/kg) ($N = 37$) with extended-release epidural morphine (EREM) (150 μg/kg) ($N = 31$) and found no significant differences for 48-h opioid consumption but lower pain scores over 28–36 h post-surgery in the EREM group, which also had lower incidence of pruritis [88]. In summary, regional opioids are superior to PCA for pain control and recovery; IT and epidural opioids are comparable in analgesia for about 24 h, beyond which opioid supplementation will be needed for the IT opioid regimens.

4 Acetaminophen

Acetaminophen (APAP) is a widely used, centrally acting analgesic used as an opioid adjuvant for postoperative pain. Its central analgesic effect is mediated through activation of descending serotonergic pathways [89]. Proposed primary mechanisms of action include COX-3 enzyme inhibition and acting as a cannabinoid agonist and NMDA antagonist in the spinal cord [90]. It has demonstrated opioid-sparing potential across numerous studies [91]. Oral, intravenous, and rectal formulations are available [92]. Since IV APAP was approved for use in the US in 2010, it became an important component of perioperative multimodal analgesia. In a placebo-controlled RCT in 36 adolescents, patients in the IV APAP experienced fewer hours (8.7%) in severe pain

Table 3 Studies evaluating epidural for postoperative analgesia after spine fusion for idiopathic scoliosis

References	Epidural catheters	Analgesia regimen	Comparison group	Outcome
Shaw et al. 1996 [70] Observational	Single	0.1–0.25% bupivacaine 5–10 mL + morphine 30–50 μg/kg then 0.0625–0.125% bupivacaine 4–10 mL/h with hydromorphone 10–50 μg/mL @ 2–10 mL/h	None	Successful analgesia in 64 patients (arousable yet denying pain). 8% Failure rate
Arms et al. 1998 [71] Observational	Single T5–T12 cath tip	Bolus dose of morphine 30–50 μg/kg + 0.1–0.25% bupivacaine 5–10 mL followed by 0.0625–0.125% bupivacaine @ 4–10 mL/h and morphine 5–10 μg/kg/h	None	Satisfactory postoperative analgesia in all patients
Cassady et al. 2000 [72] Randomized Prospective	Single T6–7 entry	0.25% bupivacaine with epinephrine 1:200,000 10 mL bolus, then 0.125% Bupivacaine + fentanyl 25 μg/mL @ 0.35–0.4 mg/kg/h bupivacaine 0.28–0.32 mL/kg/h	Morphine PCA	No difference in analgesic efficacy. Epidural group had a faster return of bowel sounds
Tobias et al. 2001 [73] Observational	Double	Initial dose of hydromorphone 5 μg/kg and fentanyl 1 μg/kg then 0.1% ropivacaine with hydromorphone 10 μg/mL at 0.3 mL/kg/h	None	Adequate analgesia with median daily pain scores of 1.5, 1.6, 1.6, 1.4, and 1.1. (maximum score 10)
Ekatodramis et al. 2002 [74] Observational	Double	Initial bolus with 0.0625% bupivacaine followed by 0.0625% bupivacaine w/ fentanyl 2 μg/mL + clonidine 3 μg/mL @ 10 mL/h via each catheter	None	Complete analgesia at rest in all patients. Adequate analgesia with mobilization and respiratory physiotherapy in 19 of 23 patients. The other 4 required supplemental IV morphine for VAS > 30
O'Hara et al. 2004 [75] Randomized prospective	Single Midthoracic epidural	3 mL bolus followed by 4 mL/h of 0.1% bupivacaine + fentanyl 5 μg/mL or 0.065% bupivacaine + fentanyl 5 μg/mL	Morphine PCA	No consistent difference detected on morphine consumption, VAS, or estimated pain scale over whole follow-up period. No difference was in time to oral intake, ambulation, bowel sounds, or LOS when compared with placebo. Epidural failure in 2 patients
Lavelle 2010 Retrospective [67]	Double catheter	0.1% bupivacaine with fentanyl 2 mcg/mL	Control PCA group (N=26)	Lower mean pain score over 24 h after surgery
Van Boerum 2000; Retrospective [76]	Single catheter	Upon closure, 0.1% bupivacaine with morphine sulfate 0.05 mg/kilogram/h. Additional doses of 0.03 mg/kg per hour with 30-min lockout by patient-controlled demand	PCA (n=20)	Comparable pain control; 0.5 day earlier diet resumption and discharge from hospital in epidural group
Blumenthal et al. 2005 [77] Randomized prospective	Double T1–T4 cath tip L1–L4 cath tip	0.3% Ropivacaine 4–8 mL bolus then 4–10mL/h via each catheter for T2–T12 sensory block	IV remifentanil infusion x 1 day, then IV morphine 50μg/kg/h infusion + morphine bolus PRN	Epidural group consistently had better pain scores, bowel activity, PONV, and pruritis for up to 72 h
Gauger et al. 2009 [47] Randomized prospective	Single T9–T12 entry	Fentanyl 1 μg/kg (max 50 μg) and 5 μg/ kg hydromorphone (max 0.2 mg) then 0.1% Bupivacaine + hydromorphone 10 μg/mL at 8 mL/h + bolus dosing of 2 mL every 30 minutes with PCEA	Hydromorphone PCA with continuous 2 μg/kg/h	Epidural group had significantly better pain compared to PCA group on POD 2–3. Epidural failure rate 37% requiring switch to PCA. Also, 3 epidurals never placed due to bleeding, hypotension, and unable to thread. No difference in adverse effects.

Table 3 (continued)

References	Epidural catheters	Analgesia regimen	Comparison group	Outcome
Klatt et al. 2013 [66] Randomized Prospective	Single T10–T11 entry or double T7–T8 T12–L1	0.1% Bupivacaine + fentanyl 2 µg/mL 0.2 mL/kg (divided in 2 for participants with 2 catheters with max = 12 mL) then Bupivacaine 01% + fentanyl 2 µg/mL at 12 mL/h + 0.1 mL/kg PCEA	Hydromorphone PCA	Double epidural catheter showed modest benefit for decreasing pain scores in comparison to single epidural catheter or PCA, which were statistically equivalent. No differences in adverse effects, time to ambulation, transition to enteral analgesia, LOS
Sucato et al. 2005 [69] Retrospective	Single low thoracic	Hydromorphone 10–20 µg/kg the 0.1% Bupivacaine + 20 µg/mL @ 0.1–0.2mL/kg/h	Morphine or meperidine PCA	Epidural failure in 8% of patients

ASF anterior spinal fusion, *PSF* posterior spinal fusion, *PCA* patient controlled analgesia, *AIS* adolescent idiopathic scoliosis, *POD* postoperative day

(visual analog scale pain score ≥ 6) versus the placebo group (17.8%) within 24 h after surgery [93]. However, there was no difference in cumulative oxycodone dose required during the first 24 postoperative hours. It is notable that the study used higher APAP daily and individual doses (30 vs 15 mg/kg/dose and 90 vs 75 mg/kg/day). The recommended maximum daily dose of APAP is 75 mg/kg/day with hepatotoxicity occurring at 150 mg/kg/day. In a prospective, observational study in adolescents undergoing PSF, Olbrecht and colleagues demonstrated that conventional doses of IV APAP significantly decreased opioid consumption on postoperative days 1 and 2, decreased LOS by 0.6 days and accelerated oral intake by approximately 1 day by mediation of opioid-related adverse effects [94]. However, with the cost of IV APAP increasing in 2014 (from US$14.60 to US$35.05 for a 1-gm bottle), its cost effectiveness over the much cheaper alternative oral acetaminophen has been called into question. Recent adult studies comparing IV and oral APAP for patients demonstrated no significant difference for pain scores and opioid consumption at 12, 24, and 48 h, incidence of nausea/vomiting, or LOS [95], with oral APAP showing more beneficial outcomes [96]. There are currently no prospective RCTs demonstrating clinically significant benefits of IV over oral APAP for pediatric spine fusion or dose-dependent effectiveness for IV APAP. So, while IV APAP may still be a useful adjunct for use in patients who are unable to tolerate oral pain medications, transition to the oral form as early as possible postoperatively may be the prudent option.

5 Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are analgesics that inhibit cyclooxygenase (COX), which decreases the production of prostaglandins and, in turn, the inflammatory response. The most commonly studied NSAID in children is ketorolac. In a national cohort of children undergoing scoliosis surgery ($N = 7349$), ketorolac was independently associated with significantly lower odds of prolonged LOS and prolonged duration of IV opioid use [20]. Munro et al. [50] showed that conventional use of ketorolac (0.5 mg/kg/dose IV every 6 h for a total of six doses) reduced pain scores, morphine consumption, and improved activity on PODs 1 and 2.

While NSAIDs decrease inflammation and pain via inhibition of COX and prostaglandin synthesis, there has been concern regarding their effects on platelet function and bone formation/healing—critical processes for successful spinal fusion. Concern about bone formation/healing has been fueled by delayed bone healing in animal models and studies performed in certain adult populations [97]. A study in a rabbit arthrodesis model comparing effects of large doses

Table 4 Studies evaluating intrathecal opioids for postoperative analgesia after spine fusion

Study	Study design	Comparative cohorts	Analgesia effects	Side effects
Goodarzi [80]	Prospective comparative study	$N=80$; Group A (intrathecal): morphine 20 μg/kg + sufentanil 50 μg/kg administered L3–L4 after the induction of anesthesia Group B (control): inhalation and intravenous narcotic anesthesia	Blood loss decreased (27% vs 53% of blood volume lost); 14.5-h analgesia (0–38 h); no need for PCA; able to mobilize quicker	Hypotension in Group A; no increased side effects
Gall et al. [81]	Randomized controlled trial	$N=30$; single dose of 0 (saline injection), 2, or 5 μg/kg intrathecal morphine	Improved pain scores and decreased PCA use with morphine Doses of 2 and 5 μg/kg have similar effectiveness	Doses of 2 and 5 μg/kg have similar side-effect profiles; decreased intraoperative bleeding with 5 μg/kg but not 2 μg/kg
Eschertzhuber et al. [82]	Randomized controlled trial	$N=46$; morphine 5 μg/kg (-1) plus sufentanil 1 μg/kg(-1) [low-dose intrathecal opioid (LITO)], morphine 15 μg/kg(-1) plus sufentanil 1 μg/kg(-1) [high-dose intrathecal opioid (HITO)] intrathecally, or no intrathecal opioid	Decreased pain scores, opioid consumption and blood loss in IT opioid groups; low-dose regimen adequate as high dose did not further improve analgesia	No increase in side effects
Tripi et al. [83]	Retrospective	No dose ($n=68$); moderate dose of 9–19 μg/kg, mean 14 μg/kg ($n=293$); and high dose of 20 μg/kg or greater, mean 24 μg/kg ($n=46$)	Mean time to first morphine rescue was 6.6, 16.7, and 22.9 h, respectively	Respiratory depression occurred in 1 (1.5%), 8 (2.7%), and 7 (15.2%) patients
Blackman et al. [85]	Prospective	$N=33$; no control; 10 μg/kg IT morphine in 10 mL before closure	Analgesia 8 to > 40 h (average 18 h)	Respiratory depression in 5 patients

IT intrathecal, *PCA* patient controlled analgesia

of celecoxib, indomethacin, and saline solution found that while indomethacin significantly inhibited the rate of spinal fusion, celecoxib did not. The authors postulated this was because bone healing was inhibited by COX-1 [98]. A systematic review and meta-analysis evaluating effect of postoperative ketorolac administration (dosage, duration of use) on pseudarthrosis in adults following PSF [99] concluded ketorolac (administered for > 2 days and/or at doses ≥ 120 mg/day) was associated with pseudarthrosis. Sucato and colleagues compared AIS patients who received ketorolac and those who did not after PSF. While overall pseudarthrosis rate was 2.5%, ketorolac did not increase probability of pseudarthrosis [100]. Another retrospective study in 434 adults undergoing spine surgery reported the incidence of non-fusion rates after use of perioperative ketorolac (< 110 mg/day) was 6%, high-dose ketorolac (120–240 mg/day) was 29%, celecoxib (200–600 mg/day) was 8.3%, and rofecoxib (50 mg/day) was 7.3% compared with 8.5% in the group that did not receive NSAIDs [101]. Therefore, it appears that short-term exposure to NSAIDs including low-dose ketorolac is not associated with nonunion after spinal fusion [102].

Postoperative ketorolac administration was not associated with bleeding-related adverse events, such as increased likelihood of transfusion or increased reoperation rates [103]. A retrospective study of 208 children undergoing spine surgery found postoperative ketorolac use did not significantly increase complications, including transfusion and reoperation [103]. Ketorolac may cause prolonged bleeding time, but large-scale prospective RCTs and meta-analyses failed to establish an association with increased perioperative blood loss [104].

Given recent evidence that a low dose (10 mg) of IV ketorolac is as effective as higher doses, it is recommended to cap maximum doses of ketorolac at 10 mg for postoperative analgesia after spine fusion [105].

6 Gabapentinoids

Gabapentin and pregabalin are structural analogs of gamma-aminobutyric acid (GABA). Gabapentinoids modulate excitatory neurotransmitter release by binding to voltage-gated calcium channels, and may exert their effect by decreasing spontaneous sensory nerve firing [106].

There are two RCTs evaluating pregabalin within MMA for pediatric scoliosis, with opposite findings [107, 108] (Table 5). Findings vary for gabapentin use depending on timing of use. Only one study evaluated preoperative-only gabapentin and found no analgesic advantage to its use before surgery [109]. Studies where gabapentin was continued for 5 days postoperatively [110], until discharge, or one dose on POD1 in addition to a preoperative dose [111, 112] reported positive findings with respect to opioid consumption. One of the retrospective studies mentioned above also included a group receiving a combination of gabapentin and transdermal clonidine 0.5 mg/day [111]. They found that the addition of clonidine + gabapentin further decreased PCA usage and had faster time to ambulation compared with the gabapentin group. None of the above studies reported an increase in opioid adverse effects from the addition of gabapentin. However, sedation, dizziness, and visual disturbances are reported adverse effects, which have prompted a call for moderating the use of gabapentinoids in general [113]. In fact, current American Pain Society and European Society of Regional Anaesthesia and Pain Therapy guidelines offer conflicting recommendations for the use of gabapentinoids in the perioperative period [21, 114]. It is important to point out that a recent meta-analysis (281 trials, $N = 24{,}682$) did not support the preoperative use of gabapentinoids as they did not find a clinically significant analgesic effect. Although no pediatric studies were included, they did exploratory subgroup analyses by surgery, which showed that gabapentinoids may be favored (summary estimate -8 [-12, -5]) for spine surgeries. In summary, there is insufficient evidence to currently recommend the use of preoperative gabapentinoids for opioid-sparing effects after surgery.

7 Ketamine

Ketamine is an NMDA receptor antagonist that also activates μ-, δ-, and κ-opioid receptors, γ-aminobutyric acid-mediated central nervous system inhibition, and monoaminergic inhibitory pathways [115]. Tissue trauma during major surgery causes central nervous system sensitization by release of excitatory amino acids working through the NMDA receptor [116, 117]. Thus, many have theorized that ketamine *may* decrease central sensitization and perincisional hyperalgesia [118–122].

In children undergoing spine fusion, there have only been five trials evaluating ketamine as an adjunct analgesic (Table 6). Two of these trials utilized low-dose ketamine infusions only during the intraoperative phase of care [123, 124]. However, only one of those two studies found a significant difference in postoperative opioid consumption. The other three RCTs examined the benefits of low-dose ketamine infusions during both the intraoperative and postoperative phases of care [51, 125, 126]. Only one of those three studies found a significant difference in postoperative opioid consumption, and the authors of the one positive study noted that the difference might not be clinically relevant. All these studies had < 50 subjects and followed different protocols with respect to non-opioid analgesia, intraoperative inhalation versus total intravenous anesthesia, etc., which could influence results. While they were not powered to do so,

Table 5 Studies evaluating gabapentinoids for pediatric scoliosis

Study	Study design	Cohorts and doses	Findings
Mayell et al. [109]	RCT; gabapentin vs placebo; $N=18$	600 mg 1 h before surgery	Did not decrease opioid consumption or pain in 72 h following surgery
Rusy et al. [110]	RCT; gabapentin vs placebo; $N=30$	15 mg/kg 25–30 min before being taken to the OR; 5 mg/kg 3 × a day from POD 1 for 5 d	Decreased morphine consumption on POD 1 and POD 2 by 16 and 33%, respectively
Trzcinski et al. [112]	Retrospective; $N=129$	Gabapentin initial loading dose of 10 mg/kg on day of surgery and at least 15 mg/kg/d by POD 1	Significantly lower mean pain scores on POD 1–3 and decreased opioid use POD 1–2
Choudhry et al. [111]	Retrospective; $N=127$ group P, morphine PCA only (42 patients), group G, morphine PCA + gabapentin (45 patients), and group C, morphine PCA + gabapentin + clonidine 0.05 mg/day (40 patients)	Gabapentin dose: 10 mg/kg (max 600 mg) 1 h preoperative; 200 mg twice a day for patients > 50 kg body weight and 100 mg 3 × a day for patients < 50 kg body weight starting on POD 1 until discharge from hospital	Less postoperative opioid consumption, faster return to orals, faster return to ambulation and decreased LOS
Raddaoui et al. [108]	RCT; pragabalin vs placebo; $N=40$	Pregabalin 150 mg orally 1 h before and 12 h after surgery	Decreased postoperative 48-h PCA morphine consumption
Helenius et al. [107]	DB, RCT; prebagalin vs placebo; $N=51$ AIS	Pregabalin (2 mg/kg twice daily) preoperatively and for 5 d after surgery	No difference to opioid consumption postoperatively

AIS adolescent idiopathic scoliosis, *DB* double-blind, *LOS* length of stay, *PCA* patient-controlled analgesia, *POD* postoperative day, *RCT* randomized controlled trial

none of the studies demonstrated a difference in time to oral intake, time to ambulation, LOS, or CPSP. Lastly and most importantly, the optimal regimen for ketamine infusions for children and adolescents remains unknown.

Thus, we will cite some relevant adult literature to support our conclusions. A meta-analysis evaluating the benefits of perioperative low-dose ketamine for postoperative analgesia in adult spine surgery patients showed that ketamine significantly reduced opioid consumption and pain scores for 24 h. However, differences in dosing, infusion protocols (e.g., continuous infusions vs IV PCA), and patient populations (e.g., inclusion or exclusion of patients with chronic pain or opioid tolerance) were theorized to impact the results after the first 24 h [127]. Based on best available evidence for adults, the American Society of Regional Anesthesia and Pain Medicine (ASRA), American Society of Anesthesiologists, and the American Academy of Pain Medicine's recent guideline for the use of ketamine in acute pain management recommends a low-dose IV ketamine bolus with a maximum dose of 0.35 mg/kg followed by a subanesthetic infusion of 0.15–1 mg/kg/h (titrated to the lowest effective dose) [128]. Higher doses of ketamine may be required in pediatric populations to maintain a steady-state concentration due to age-related pharmacokinetics [129]. Analgesic concentrations are deemed to be 70–160 ng/mL [130]. While dissociation and other psychoactive effects are adverse effects of ketamine infusions, little to no psychoactive effects were observed at the dose of 0.1 mg/kg IV (resulting in ~ 25–50 ng/mL concentrations) in adults [131].

Although current evidence for the routine use of ketamine to reduce pain and opioid consumption for children and adolescents undergoing AIS surgery is not strong, there may be a role for low-dose ketamine postoperatively in patients who are opioid tolerant, have chronic pain, or are at high risk from adverse events due to high-dose opioids (ASRA guideline) [128]. Future studies are needed to determine effective and safe dosing regimens and duration of ketamine infusions to decrease opioid consumption, pain intensity, recovery, and LOS as well as CPSP and chronic opioid use after AIS surgeries.

8 Local Anesthetics

Local anesthetics act by blocking voltage-gated sodium channels of afferent neurons. For AIS surgery, local anesthetics have primarily been used as part of epidural analgesia regimens, usually together with opioids, as discussed in the epidural opioid section. However, recently, other modes of local anesthetic delivery have been explored, including IV continuous infusion, local wound infiltration, and, most recently, erector spinae blocks.

Table 6 Studies evaluating ketamine for AIS PSF in pediatric subjects: randomized controlled trials

Study	Anesthetic	Ketamine dosing	Pre-op/post-op additions	Primary outcome measure	Secondary outcomes
Engelhardt et al. [123]	Propofol + remifentanil	Intra-op: 0.5 mg/kg followed by 4 μg/kg/min Discontinued at end of surgery	Post-op: Morphine IV PCA with continuous infusion (20 μg/kg/dose, 6-min lockout, 10 μg/kg/h) Scheduled acetaminophen 20 mg PO q6h	1st 24-h opioid consumption – No significant difference	Pain scores—no difference Adverse effects—no difference
Moustafa et al. [124]	Propofol + remifentanil	Intra-op: 1 μg/kg/min Discontinued at end of surgery when flipped supine	Pre-op: Midazolam 0.25 mg/kg PO Post-op: Morphine IV PCA without continuous infusion (0.5 mg/dose, 6-min lockout) Acetaminophen 20 mg PO q6h scheduled	First 4-h opioid consumption – Ketamine group significantly less opioid consumption	Pain scores—significantly lower Recovery room score—no difference Time to first PCA demand—significantly longer
Pestieau et al. [51]	Desflurane + remifentanil	Intra-op: 0.5 mg/kg followed by 0.25 mg/kg/h Post-op: 0.1 mg/kg/h (= 1.67 μg/kg/min) Discontinued at 72 h	Pre-op: Midazolam 0.5 mg/kg PO (max 20 mg) or midazolam 0.05–0.1 mg/kg IV Postop: Morphine IV PCA with continuous infusion (0.02 mg/kg/dose, 8-min lockout, 0.02 mg/kg/h) PCA adjusted by Pain Service Scheduled oxycodone and diazepam Acetaminophen as needed for fever	Daily opioid consumption – No difference	Pain scores—no difference Adverse effects—no difference
Minoshima et al. [126]	Propofol + remifentanil	Intra-op: 0.5 mg/kg followed by 2 μg/kg/min Post-op: 2 μg/kg/min (= 0.12 mg/kg/h) Discontinued at 48 h	Post-op: Morphine IV PCA with continuous infusion (20 μg/kg/dose, 10-min lockout, 10 μg/kg/h) Scheduled diclofenac 25 mg PR q6h	1st 48-h opioid consumption – Significant difference, but perhaps not clinically relevant	Pain scores—no difference Adverse effects—no difference Anti-emetics—less Time to ambulation—no difference LOS—no difference CPSP—no difference
Perelló et al. [125]	Propofol + remifentanil	Intra-op: 0.5 mg/kg followed by 2 μg/kg/min Post-op: 2 μg/kg/min (= 0.12 mg/kg/h) Discontinued at 72 h	Post-op: Morphine IV PCA with continuous infusion (20 μg/kg/dose, 5-min lockout, 5 μg/kg/h) Scheduled paracetamol IV + naproxen	Morphine consumption during hospital stay – No difference	Pain scores—no difference Adverse effects—no difference Time to PO intake—no difference Time to ambulation—no difference LOS—no difference Peri-incisional hyperalgesia—no difference CPSP—no difference

AIS adolescent idiopathic scoliosis, *CPSP* chronic postsurgical pain, *IV* intravenous, *LOS* length of stay, *PCA* patient-controlled analgesia, *PO per os* (orally), PSF posterior spinal fusion, *PR* Per rectum, *qxh* every *x* hours

8.1 IV Lidocaine Infusions

The theoretical analgesic effects of lidocaine are diverse with peripheral and central actions including altered conduction in the dorsal horn and dorsal root ganglion, decreased firing of sodium channels after increased expression of sodium channels with peripheral nerve injury, reduced neurogenic inflammation at the site of injury, anti-hyperalgesia with NMDA receptor inhibition, and glycinergic system modulation. A study compared lidocaine versus control groups for proinflammatory mediators before, immediately after, 6 h after, and 12–15 h after spine surgery in children [132]. They observed reduced pain intensity until 6 h after surgery as well as negative correlations between pro-inflammatory mediators (neuron growth factor [NGF], high mobility group box 1 [HMGB1], interleukin 6 [IL-6]) and lidocaine concentrations after surgery.

The utility of perioperative lidocaine for children and adolescents undergoing major spine surgery has not been studied extensively. Batko et al. evaluated the efficacy of an addition of lidocaine to a standardized multimodal analgesia regimen (preoperative gabapentin; intraoperative acetaminophen, dexamethasone, sevoflurane, metimazole, and morphine; postoperative morphine IV-PCA, scheduled non-opioids—acetaminophen, metimazole, and gabapentin) [133]. Lidocaine was administered as a 1.5-mg/kg bolus over 30 min prior to incision followed by a 1 mg/kg/h infusion intraoperatively and then postoperatively up to 6 h after surgery finished. The control group received an equal volume and rate of a placebo. They demonstrated decreased morphine consumption at 24 h, 48 h (> 30% reduction), and the entire hospitalization, compared with the control group. Additionally, first oral intake, sitting, and walking were all positively influenced. Also, they conducted 2-month and 4-year follow-ups to determine if the two groups experienced any significant difference in quality of life but found no difference. Another recent retrospective study demonstrated in a small cohort of 50 pediatric patients that IV lidocaine infusions were generally well tolerated [134]. The mean ± SD infusion dose was 15 ± 6.3 μg/kg/min with 24% of infusions associated with adverse effects, primarily neurologic ones, including paresthesias (10%) and visual disturbances (4%).

Due to the paucity of pediatric literature in spine surgery, we mention relevant adult literature regarding perioperative IV lidocaine infusions. The most recent Cochrane review in 2019 included 68 clinical trials (two involving spine surgery) with over 4500 participants and found no significant effect on postoperative pain intensity, opioid consumption, return to bowel function, or postoperative nausea [135]. Since then, there have been two RCTs exploring the use of perioperative lidocaine infusions for adult patients undergoing multilevel spine surgery, both of which found no benefit with regard to pain intensity or opioid consumption [136, 137]. Of these, Dewinter et al. enrolled 70 patients (of which 28 were adolescent idiopathic scoliosis patients undergoing posterior spine fusion) in a prospective, double-blind RCT in which patients received either a lidocaine bolus of 1.5 mg/kg at induction of a standardized total intravenous anesthetic followed by an infusion of 1.5 mg/kg/h intraoperatively and continued until 6 h after arrival in the post-anesthesia care unit, or placebo. There was no difference between groups with respect to pain intensity, opioid consumption at 48 h and 72 h after surgery, incidence of postoperative nausea and vomiting, recovery of bowel function, LOS, or quality of life [136].

In short, while the evidence for perioperative IV lidocaine infusions (with a loading dose of 1.5 mg/kg followed by an infusion of 1–2 mg/kg/h) is compelling, it is not consistent enough to warrant routine use in a multimodal analgesia regimen at this time. Future studies should examine the dosing, duration, pain intensity reduction, and opioid consumption.

8.2 Local Wound Infiltration

Some adult studies show that continuous infusion of local anesthetics via wound catheters with an elastomeric pain pump significantly improves pain, including after spine surgeries in adults [138]. However, the available evidence for the use of wound catheters for PSF in AIS is limited. Two retrospective studies evaluated bupivacaine infusions through bilateral wound catheters [139, 140] (Table 7). Overall, the group of patients that received the wound catheters consumed 28–38% less opioids than the control group over 24 h postoperatively. Both the studies reported no differences in frequency of adverse effects, although possible additional risks include infection, dislodgement, etc. However, there were many uncontrolled variables that depended on the individual care teams, such as the analgesia regimens the patients received. In short, there is at most weak evidence that continuous local anesthetic infusions via wound catheters may lower postoperative opioid requirements but more prospective studies are needed.

8.3 Erector Spinae Blocks

A recent case report demonstrated proof-of-concept in two healthy AIS patients that pre-incisional bilateral erector spinae (ES) single shot blocks at two levels (T4 and T10) with 0.25% bupivacaine and epinephrine 5 μg/mL for PSF could enhance a multimodal perioperative anesthesia/analgesia regimen. The MMA regimen also included acetaminophen, dexamethasone, dexmedetomidine, and ketamine infusions. The first patient received minimal to no opioids intraoperatively and importantly they were then successfully transitioned to oral analgesia on POD1. Further research is needed to determine if this proof of concept may be

translated to a larger population of AIS patients undergoing PSF [141]. In a letter to the editor, Tsui et al. described use of percutaneously placed ES catheters (bilaterally above incision site with tips above T6 transverse processes) for a T4–T12 PSF [142]. They used 0.5% lidocaine 20 mL boluses through ES catheters every 60 min via an automated pump (increased to 22 mL on POD1). They removed the catheters on POD2. They measured lidocaine concentrations in serum (0.9–1.1 μg/mL). Although the patient experienced peak pain (5/10 pain score) the first night, they conclude that ES catheters may aid mobilization. While these anecdotal reports suggest ES catheters may present a novel analgesic modality for postoperative pain management after spine fusion, optimal local anesthetic (LA) dosages and efficacy are yet to be elucidated.

9 Muscle Relaxants

Since scoliosis is a musculoskeletal condition, correction of the deformity is associated with muscle tightness. Diazepam (benzodiazepine and GABA agonist), methocarbamol (a centrally acting muscle relaxant), baclofen (possibly GABA-B agonist), and tizanidine (α2 adrenergic agonist) are often used to treat muscle spasm after spine fusion (see Table 1 for MMA protocols). Diazepam is often used in doses of 0.05–0.1 mg/kg every 4–6 h as needed IV and methocarbamol in doses of 15 mg/kg (maximum 1000 mg) every 8 h IV and then transitioned to oral formulations at similar doses for diazepam and 500–1000 mg every 8 h for methocarbamol. However, there are not many systematic studies assessing these adjuvants on pain relief. A double-blinded RCT comparing chlorzoxazone, a centrally acting muscle relaxant, demonstrated no immediate analgesic effects compared with

Table 7 Studies evaluating bupivacaine infusions through bilateral wound catheters

Study	Anesthetic	Intervention	Pre-op/post-op management	Primary outcome measure	Secondary outcomes
Ross et al. [140]	IT Morphine: Pre-incision or by surgeon prior to dura mater exposure Anesthesiologist discretion: - Balanced opioids + inhalational vs TIVA (no details) - IV opioids - Muscle relaxation and reversal	Wound catheter × 0, 1, or 2 (surgeon discretion) Wound catheter location: paraspinal muscle, subfascial, subcutaneous (surgeon discretion) 0.5% bupivacaine at 4 mL/h (2 mL/h for each catheter) over approximately 100 h	Pre-operative: no details Post-operative: - PCA opioid (all) - Scheduled diazepam (added during time of the study) Care team discretion - PCA continuous infusion - NSAIDs	Total ICU opioid consumption over first 24 postoperative hours: Wound catheter group—28% reduction Wound catheter group more likely to receive intraoperative IV opioids and postoperative diazepam, but less likely to get postoperative ketorolac No significant difference in intraoperative IV opioid dose between two groups	6, 12, and 24-h postoperative pain scores: no difference Opioid consumption based on wound catheter location: no difference Frequency of treatment of adverse effects: no difference
Reynolds et al. [139]	Induction: - IV fentanyl Maintenance: - IV propofol infusion - IV fentanyl or remifentanil infusion - 0.5 MAC isoflurane - IT morphine 5–8 μg/kg (max: 0.6 mg, mean: 4.8 μg/kg)	Wound catheter × 2 0.25% bupivacaine at 4 mL/h (2 mL/h for each catheter) over approximately 100 h	Pre-operative: no details Post-operative: PCA morphine - No standardization - No details given Additional opioid and non-opioid analgesics - IV morphine - IV hydromorphone - Oral hydrocodone - Oral codeine - IV meperidine - IV fentanyl - NSAIDs - No details given	Opioid consumption over first 24 postoperative hours Wound catheter group—38% reduction	Immediate post-operative VAS: Wound catheter group—38% reduction Mean 24-h VAS: no difference (wound catheter group trended lower, but not statistically or clinically significant) Adverse effects over 3 postoperative days: no significant difference Low incidence for both groups

ICU intensive care unit, *IT* intrathecal, *IV* intravenous, *MAC* minimum alveolar concentration, *NSAID* non-steroidal anti-inflammatory drug, *PCA* patient-controlled analgesia, *TIVA* total intravenous anesthesia, *VAS* visual analog scale

placebo in patients experiencing moderate-to-severe acute post-operative pain following spine surgery [143]. In a randomized prospective study of 50 consecutive patients comparing an opioid only (meperidine hydrochloride) with adjunctive use of diazepam/baclofen, the regimens with muscle relaxants successfully relieved postoperative spasm, but did not change pain severity or opioid requirement [144]. It is important to note the adverse effects of this adjunctive group of medications, which include drowsiness and withdrawal after prolonged use [145]. Although there is evidence for their benefits in chronic low back pain and other surgeries including joint surgery and Chiari decompression, further studies are warranted to understand their efficacy after spine fusion [145].

10 Dexmedetomidine

Dexmedetomidine's action is mediated via postsynaptic α2 adrenergic receptors. It has been shown to have analgesic and opioid-sparing properties, but the literature in pediatric scoliosis is limited. One retrospective study compared use of PCA with opioids ± dexmedetomidine infusion 0.4 μg/kg/h (over 24 h postoperatively) and concluded that it may have opioid-sparing effects, as opioid use increased after discontinuing dexmedetomidine ($N=37$) compared with the PCA opioid-only group ($N=94$) [146]. Another similar study using fentanyl PCA recommends use of dexmedetomidine (0.25 μg/kg/h with fentanyl 0.5 μg/kg/h to decrease opioid consumption after surgery [147]. In comparison, retrospective chart review of 106 children receiving PCA + dexmedetomidine, and 57 who received PCA opioids only, failed to demonstrate any difference in opioid use on any postoperative day [148]. There are only conference abstracts studying the effect of intraoperative dexmedetomidine on postoperative analgesia following scoliosis surgery. Thus, further research is warranted to study dose, timing, and opioid-sparing effects of dexmedetomidine for spine fusion.

11 Non-Pharmacological Methods

Anxiety and pain catastrophizing enhances pain perception after surgery in children [149, 150]. Several non-pharmacological methods that target anxiety have been shown to decrease post-surgical pain [151]. These include education (setting expectations preoperatively), psychological methods (guided imagery, hypnosis, distraction, cognitive behavioral therapy/counseling, mindfulness), physical methods (cold, heat, massage, acupuncture, transcutaneous electrical nerve stimulation), and distraction (virtual reality, play, videos). Some of these may be helpful both before and after surgery to help children cope with pain [152]. In one RCT, children were taught hypnosis with guided imagery at 1 week before admission, lasting no longer than 30 min ($N=26$). Imagery interventions decreased self-reported pain after major surgery (including scoliosis surgery) compared with usual care ($N=26$) [153]. However, very few studies evaluate non-pharmacological therapies perioperatively for spine fusion surgeries, and this is an emerging field of research that may hold a lot of promise, to enable ERAS and minimize opioids after surgery.

12 Chronic Postsurgical Pain (CPSP)

CPSP is defined as pain of at least 3–6 months duration, that develops after a surgical procedure, increases in intensity or has different characteristics after the surgical procedure, and significantly affects function. Other conditions like infection and malignancy should be excluded before a diagnosis of CPSP is made [154, 155]. CPSP is a significant clinical as well as socioeconomic problem in children, with a prevalence of ≈ 20% at 12 months after surgery, and important negative behavioral and physical consequences [156]. Spine fusion for AIS has been studied in several pediatric cohorts, with differences in CPSP incidence ranging from 11% to 53.6%, depending on the definition of CPSP used (Table 8).

12.1 Factors Affecting CPSP after Spine Fusion

Occurrence of CPSP after spine fusion in children is multifactorial. Psychosocial, perioperative, and genomic factors have been proposed. In addition, several preventive perioperative measures have been evaluated, mostly in adult cohorts, with conflicting results [165–168].

12.1.1 Psychosocial Factors and CPSP

The psychosocial factors that have been identified to be associated with risk of CPSP are anxiety sensitivity, self-image perception, pain unpleasantness, and pain catastrophizing [3, 156, 158, 160]. A longitudinal, prospective study identified that membership in a high symptom cluster including higher depression, fatigue, pain interference, catastrophizing, and painDETECT scores, predicted pain interference at 1 year after spine fusion [169]. In addition, parental factors including parent pain catastrophizing as well as anxiety has also been shown to influence child's risk of CPSP [161, 170]. Understanding psychological risk is crucial to developing interventional treatments preoperatively. A recent systematic review provided preliminary evidence that cognitive behavioral therapy-based psychological interventions reduce CPSP intensity and disability in adults, which will also likely be true for children [151].

12.1.2 Perioperative Factors and CPSP

Preoperative as well as acute postoperative pain, and higher postoperative opioid consumption, have been found to be associated with higher pain trajectories after spine surgery [3, 159, 171]. Similarly, higher surgical duration, but not scoliosis curve or number of vertebral levels to be fused, has been predictive of CPSP [3].

12.1.3 Perioperative Medications and CPSP

While intraoperative remifentanil has been suspected to cause OIH, there are no studies implicating use of remifentanil in CPSP. Interestingly, intraoperative intrathecal morphine was found to predict membership in high opioid use trajectories after spine fusion, which was hypothesized to be due to innate genetic resistance to opioid actions [172]. There is evidence that higher opioid use in the postoperative period may lead to CPSP after spine fusion in adolescents [3] as well as after other surgeries [173, 174]. While this might be a proxy for intense postoperative pain, OIH and acute opioid tolerance (AOT) may also play a role [175, 176]. Thus, minimizing opioid use in the perioperative period using MMA is expected to decrease the incidence of CPSP. However, a meta-analysis evaluating MMA and CPSP in adults showed that available evidence does not support the efficacy of gabapentin, pregabalin, NSAIDs, intravenous steroids, oral NMDA blockers, oral mexiletine, intravenous fentanyl, intravenous lidocaine, oral venlafaxine, or inhaled nitrous oxide for the prevention of CPSP [177]. They did find that that IV ketamine (bolus doses in the range of 0.2–0.75 mg/kg, followed by infusions of 2–7 μg/kg/min) may decrease incidence of CPSP. Recent meta-analysis using limited data supported use of IV lidocaine infusions to prevent CPSP, though the difference in pain intensity was not significantly decreased [178].

Given current evidence, the most promising strategies to prevent CPSP in children undergoing surgery would be preoperative setting of expectations, psychological optimization to help with pain coping, and close monitoring of those who have high risk factors for CPSP. Besides, there are other individual genomic factors that may be involved that are

Table 8 Studies describing chronic post-surgical pain incidence and predisposing factors after scoliosis surgery in children

Study	Procedures	Study type	Incidence	Predisposing factors
Fortier et al. [157]	Orthopedic procedures	Cross-sectional retrospective study	13%	
Landman et al. [158]	Scoliosis	Retrospective 1–2 years	1 years 53.6% non-zero pain in past month 2 years 29.5%	Self-image perception of deformity
Sieberg et al. [159]	Scoliosis	Longitudinal prospective study over 5 years	1 years 11% 2 years 15% 5 years 15%	
Page et al. [160, 161]	Orthopedic and general surgery	6–12 months after surgery	1 years 22% NRS > 3/10 at 10 week—3 × OR pain at 6 months—2 × OR pain at 1 years	Pain unpleasantness predicted initial transition, whereas anxiety sensitivity predicted maintenance; parent pain catastrophizing
Connelly et al. [162]	Scoliosis	6 months, prospective	22%	Higher preoperative levels of pain and anxiety
Rabbitts et al. [163]	Heterogenous surgical population	1 months follow up with HRQOL Prospective	23% had decline of HRQOL	Parental pain catastrophizing
Chidambaran et al. [3]	Scoliosis	Prospective	42% at 1 year	Childhood anxiety sensitivity index, acute postsurgical pain and surgical duration
Rosenbloom et al. [164]	Major orthopedic	Prospective	35.5% of children had moderate-to-severe pain (i.e. pain rated at a 4 or more out of 10) 6 months after surgery and 38.73% ($n = 86$) had moderate-to-severe pain at 12 months	Pre-surgical functional disability

HRQOL health-related quality of life, *NRS* numerical rating scale

beyond the scope of this manuscript. We refer to the following reviews for further reading on this topic [165–168].

13 Prolonged Opioid Use After Surgery

Importantly, spine fusion and CPSP may also pose a risk for prolonged opioid use. In fact, one of the surgeries predictive of higher opioid use after hospital discharge was spine fusion, with 25.42 (95% CI 19.16–31.68; $p < 0.001$) more doses than those who underwent other types of surgery [64]. A search of a large insurance database revealed that prolonged opioid use (receiving new prescriptions for an opioid medication > 6 weeks following the date of surgery, up to 8 months postoperatively) after PSF for AIS was 9.78% [179]. Besides preoperative opioid use (odds ratio, 2.93; $p < 0.001$), which was the most significant predictor, female sex, obesity, preoperative anxiety, and preoperative muscle relaxer use were also significant risk factors for prolonged postoperative opioid use. Fewer total fusion levels and preoperative anxiolytic and antidepressant use decreased risk for prolonged opioid use after PSF. Thus, use of behavioral non-pharmacological and pharmacological therapies may be useful in decreasing opioid use after surgery. However, we would caution against routine use of pharmacologic agents as there are potential safety concerns with their use. A meta-analysis of antidepressants for acute and chronic postoperative pain evaluated several studies using amitriptyline, bicifadine, desipramine, duloxetine, fluoxetine, fluradoline, tryptophan, and venlafaxine but concluded that the evidence was insufficient to recommend use of these medications routinely in adults [180].

14 Conclusion

The goal of perioperative analgesic regimens is to enhance recovery while minimizing opioid use. While MMA is a critical component of rapid recovery, an optimal regimen for scoliosis surgery has not been established. We present a menu of MMA/ERAS components, suggested dosing regimens, and recovery pathways based on our literature review (Tables 9 and 10). Studies have evaluated other medications including magnesium, dexmedetomidine, dexamethasone, and esmolol as opioid-sparing adjuncts [181– 184]. However, these interventions have not been evaluated systematically in children undergoing spine fusion.

Large-scale, multi-institutional studies are required to establish optimal regimens as spinal fusion is associated with considerable healthcare charges (estimated at US$1.1 billion in 2012), mostly determined by the cost of the implant and partly by in-patient hospital stay) [185, 186]. This is especially relevant given that health care providers are incentivized to deliver more efficient and cost-effective care with outcome driven goals [187]. PCA and epidural analgesia provide excellent pain relief, but additional research is needed to determine best practices for each and to decrease the incidence of adverse effects. NSAIDs have proven to be excellent adjuvants that decrease opioid-related adverse effects, accelerate mobilization, and shorten LOS without introducing additional risk. The addition of IV APAP to an opioid-only strategy with or without ketorolac saves at least US$510 per spine surgery patient and decreases opioid adverse effects [188]. However, the optimal cost-effective IV versus oral APAP dosage regimens have not been determined. Although implementation of an accelerated discharge program for the surgical treatment of AIS significantly reduced average LOS by 21%, this accounted for only a 9% decrease in the average cost per episode of care [186]. It is important to factor in cost savings associated with CPSP and prolonged opioid use, which are expensive problems. Additional research is needed for individualization of analgesia to prevent CPSP. Improved screening for at-risk patients, preoperative targeted risk optimization (based on psychosocial factors, setting of expectations, genetic and epigenetic factors) [165, 189], individualized multimodal regimens guided by pharmacogenomics [190, 191], early mobilization, and targeted follow-up for opioid tapering and functional rehabilitation is essential [192]. This is imperative in light of the present opioid crisis as the risk for new persistent opioid use after discharge is higher in children undergoing spine surgery [64, 193] and increases to 30% with continued need for opioids at 30 days [194].

Table 9 Evidence based postoperative enhanced recovery pathway after spine fusion for idiopathic scoliosis

Modality	Components	
Preoperative		
Non-pharmacologic	**Education; setting preoperative positive and realistic expectations; Behavioral modifications (coping)**	
Intraoperative		
Preemptive/preventive analgesia	**Methadone 0.1–0.2 mg/kg (max 10 mg)** **Ketorolac 0.5 mg/kg/dose (max 10-15 mg)** **IV acetaminophen 15 mg/kg/dose (max 1000 mg)** **± Epidural 0.1–0.25% bupivacaine 5-10 mL + morphine 30–50 µg/kg OR Intrathecal morphine 9–15 mcg/kg** **± Ketamine dose of 0.35 mg/kg followed by infusion of 0.15–1 mg/kg/h (if history of chronic pain)**	
POD 0	Pain service follows patient	
Activity	Early mobilization and involvement with physical/occupational therapy; Spirometer 10×/h while awake	
Diet	Clears and advance as tolerated	
Pain control	**PCA hydromorphone 5 mcg/kg demand doses/7-min lockout interval/no continuous infusion/10 mcg/kg PRN breakthrough pain loading dose q4h** ***OR PCA Morphine 20 mcg/kg demand doses/7-min lockout interval/ no continuous infusion/50 mcg/kg PRN breakthrough pain loading dose q4h*** ***OR Epidural 0.0625–0.125% bupivacaine 4–10 mL/h with hydromorphone/morphine*** **+ Acetaminophen 15 mg/kg IV (max 1000 mg) or PO 15 mg/kg (max 650 mg) q6h Max dose 75 mg/kg/day or 3g/day** **+ Ketorolac 0.5 mg/kg (max 10-15 mg) IV q6h for 8 doses alternating with acetaminophen Q3H** **+ Diazepam 0.05 mg/kg (max 5 mg) IV q4h PRN muscle spasms** **+ Methocarbamol 15 mg/kg (max 1000 mg) q8h IV**	
Integrative care	**Ice packs or warm packs** **Integrative care relaxation and breathing techniques/massage**	
Opioid side effect management	**PRN nausea/vomiting** **PRN pruritis** **PRN respiratory depression/oversedation**	**Ondansetron 4 mg IV q6h** **Nalbuphine 0.05 mg/kg or Naloxone 0.25 mcg/kg/h** **Naloxone 1-2 mcg/kg (for over-sedation); 10–20 mcg/kg (for life threatening respiratory depression);**

Table 9 (continued)

Modality	**Components**	
POD 1		
Pain control	**If PCA/Intrathecal**	**Start Oxycodone 0.1 mg/kg PO q4h scheduled (round to 5mg or 7.5 mg/dose)** **Discontinue PCA if tolerating PO meds**
	If Epidural	**Continue epidural**
	When tolerating PO	**Switch IV to acetaminophen PO 650 mg q6h (max 75 mg/kg/day or 3 g/day)** **Continue ketorolac IV (alternatively, start Celebrex PO 100 mg twice a day)** **Switch IV to PO diazepam 0.05-0.075 mg/kg (max 5 mg) q4h PRN muscle spasm** **Switch methocarbamol IV to PO 15 mg/kg (500–1000 mg) q8h**
Integrative care	Continue non-pharmacologic modalities	
Diet	Regular	Start bowel regimen (stool softener/Senna)
Activity	Walk 3×/day with nursing assistance; physical therapy; out of bed to chair; Spirometer 10×/h while awake	
Drains/Foley	Discontinue (unless epidural)	
POD 2		
Pain control	**Continue oral pain medications (oxycodone q4h, valium q4h PRN, methocarbamol q8h, acetaminophen q6h)** **If Epidural, Discontinue epidural catheter**	
Activity	Walk 3×/day with nursing assistance; physical therapy; out of bed to chair; Spirometer 10x/h while awake	
Bowel regimen	Continue	
Disposition	Home if excellent mobilization and pain control with PO meds	
Discharge orders by Surgery	**Oxycodone 0.1 mg/kg PO q4h PRN pain** **Acetaminophen q6h**	
POD 3 and beyond	Continue activity; continue incentive spirometry; continue bowel regimen and diet; pain medication as per discharge orders above	

Bolded areas are the multimodal analgesia components of the enhanced recovery pathway

APS acute pain service, *PRN* pro re nata, or when necessary, *IV* intravenous, *PO* Per os/oral, *POD* postoperative day

Table 10 Summary of evidence based recommendations for use of multimodal analgesia components

Modality	Components and dose	Recommendations	Comments
Non-pharmacologic	Education and setting preoperative positive and realistic expectations Cognitive behavioral therapy Mindfulness Virtual reality based immersion	Recommended though weak evidence of decreased post-operative pain	Potential benefit far outweighs any risks Prospective clinical trials needed to determine efficacy
Premedication	Gabapentin 10 mg/kg (max 600 mg) OR Pregabalin 50–75 mg 1 h before surgery	Not recommended at this time	Weak evidence for minimal opioid-sparing effects; Effect on CPSP remains uncertain Increasing reports of gabapentioid abuse
Anesthesia	Propofol + remifentanil	Most commonly used	Theoretical concerns of opioid hyperalgesia
Preemptive /preventive analgesia	Methadone 0.1–0.2 mg/kg (max 10 mg)	Recommended, but pediatric dosing studies are needed	Decreases postoperative opioid consumption; Prolong QTc but no evidence of significant adverse events
	Ketorolac 0.5 mg/kg/dose (max 10–15 mg)	Low dose ketorolac is safe and effective	Bleeding and non-fusion not a concern at this dose
	IV acetaminophen 15 mg/kg/dose (max 1000 mg)	Likely effective for patients unable to PO	Comparative cost-effectiveness of IV vs. oral APAP not established
	Epidural 0.1–0.25% bupivacaine 5–10 mL + morphine 30–50 µg/kg OR Intrathecal morphine 9–15 mcg/kg	Safe and effective alternative to PCA	Optimal dosing regimens need to be determined
Others	Ketamine maximum dose of 0.35 mg/kg followed by a subanesthetic infusion of 0.15 to 1 mg/kg/h	Routine use not recommended. May be appropriate for specific sub-populations (opioid-tolerant, chronic pain, high-risk for adverse events)	Weak evidence of opioid-sparing effect
	Continuous wound catheters/erector spinae catheters	Insufficient evidence	More studies needed to evaluate efficacy/dosing/duration
	IV Lidocaine 1.5 mg/kg followed by 1.5 mg/kg/h	Weak evidence; Routine use not recommended yet	Additional studies needed to determine efficacy and optimal duration/dosing

APAP acetaminophen

Declarations

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References

1. Lonstein JE. Adolescent idiopathic scoliosis. Lancet. 1994;344(8934):1407–12. https://doi.org/10.1016/s0140-6736(94)90572-x.
2. Kesling KL, Reinker KA. Scoliosis in twins. A meta-analysis of the literature and report of six cases. Spine (Phila Pa 1976). 1997;22(17):2009–14. https://doi.org/10.1097/00007632-199709010-00014.
3. Chidambaran V, Ding L, Moore DL, Spruance K, Cudilo EM, Pilipenko V, et al. Predicting the pain continuum after adolescent idiopathic scoliosis surgery: a prospective cohort study. Eur J Pain. 2017;21(7):1252–65. https://doi.org/10.1002/ejp.1025.
4. Fletcher D, Stamer UM, Pogatzki-Zahn E, Zaslansky R, Tanase NV, Perruchoud C, et al. Chronic postsurgical pain in Europe: an observational study. Eur J Anaesthesiol. 2015;32(10):725–34. https://doi.org/10.1097/EJA.0000000000000319.
5. Rabbitts JA, Palermo TM, Zhou C, Mangione-Smith R. Pain and health-related quality of life after pediatric inpatient surgery. J Pain. 2015;16(12):1334–41. https://doi.org/10.1016/j.jpain.2015.09.005.
6. Haller G, Laroche T, Clergue F. Morbidity in anaesthesia: today and tomorrow. Best Pract Res Clin Anaesthesiol. 2011;25(2):123–32. https://doi.org/10.1016/j.bpa.2011.02.008.
7. Jitpakdee T, Mandee S. Strategies for preventing side effects of systemic opioid in postoperative pediatric patients. Paediatr Anaesth. 2014;24(6):561–8. https://doi.org/10.1111/pan.12420.
8. Tanious MK, Ljungqvist O, Urman RD. Enhanced recovery after surgery: history, evolution, guidelines, and future directions. Int Anesthesiol Clin. 2017;55(4):1–11. https://doi.org/10.1097/AIA.0000000000000167.
9. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg.

1993;77(5):1048–56. https://doi.org/10.1213/00000539-199311000-00030.
10. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth. 1997;78(5):606–17. https://doi.org/10.1093/bja/78.5.606.
11. Rosero EB, Joshi GP. Preemptive, preventive, multimodal analgesia: what do they really mean? Plast Reconstr Surg. 2014;134(4 Suppl 2):85s–93s. https://doi.org/10.1097/prs.0000000000000671.
12. Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiol J Am Soc Anesthesiol. 2002;96(3):725–41.
13. Muhly WT, Sankar WN, Ryan K, Norton A, Maxwell LG, Di Maggio T, et al. Rapid recovery pathway after spinal fusion for idiopathic scoliosis. Pediatrics. 2016;137:4. https://doi.org/10.1542/peds.2015-1568.
14. Fletcher ND, Andras LM, Lazarus DE, Owen RJ, Geddes BJ, Cao J, et al. Use of a novel pathway for early discharge was associated with a 48% shorter length of stay after posterior spinal fusion for adolescent idiopathic scoliosis. J Pediatr Orthop. 2017;37(2):92–7. https://doi.org/10.1097/BPO.0000000000000601.
15. Sanders AE, Andras LM, Sousa T, Kissinger C, Cucchiaro G, Skaggs DL. Accelerated discharge protocol for posterior spinal fusion patients with adolescent idiopathic scoliosis decreases hospital postoperative charges 22. Spine (Phila Pa 1976). 2017;42(2):92–7. https://doi.org/10.1097/BRS.0000000000001666.
16. Chan CYW, Loo SF, Ong JY, Lisitha KA, Hasan MS, Lee CK, et al. Feasibility and outcome of an accelerated recovery protocol in Asian adolescent idiopathic scoliosis patients. Spine (Phila Pa 1976). 2017;42(24):E1415–22. https://doi.org/10.1097/BRS.0000000000002206.
17. Gornitzky AL, Flynn JM, Muhly WT, Sankar WN. A rapid recovery pathway for adolescent idiopathic scoliosis that improves pain control and reduces time to inpatient recovery after posterior spinal fusion. Spine Deformity. 2016;4(4):288–95. https://doi.org/10.1016/j.jspd.2016.01.001.
18. Rao R, Hayes M, Lewis C, Hensinger R, Farley F, Li Y. Mapping the road to recovery: shorter stays and satisfied patients in posterior spinal fusion. J Pediatr Orthop. 2017;37:e536–42. https://doi.org/10.1097/bpo.0000000000000773.
19. Fletcher ND, Shourbaji N, Mitchell PM, Oswald TS, Devito DP, Bruce RW. Clinical and economic implications of early discharge following posterior spinal fusion for adolescent idiopathic scoliosis. J Child Orthop. 2014;8(3):257–63. https://doi.org/10.1007/s11832-014-0587-y.
20. Rosenberg RE, Trzcinski S, Cohen M, Erickson M, Errico T, McLeod L. The association between adjuvant pain medication use and outcomes following pediatric spinal fusion. Spine (Phila Pa 1976). 2017;42(10):E602–8. https://doi.org/10.1097/BRS.0000000000001892.
21. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016;17(2):131–57. https://doi.org/10.1016/j.jpain.2015.12.008.
22. McDaid C, Maund E, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review. Health Technol Assess. 2010;14(17):1–153. https://doi.org/10.3310/hta14170.
23. Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology. 2005;103(6):1296–304. https://doi.org/10.1097/00000542-200512000-00025.
24. Liu G, Liu S, Zuo Y-Z, Li Q-Y, Wu Z-H, Wu N, et al. Recent Advances in technique and clinical outcomes of minimally invasive spine surgery in adult scoliosis. Chin Med J (Engl). 2017;130(21):2608–15. https://doi.org/10.4103/0366-6999.212688.
25. Sarwahi V, Horn JJ, Kulkarni PM, Wollowick AL, Lo Y, Gambassi M, et al. Minimally invasive surgery in patients with adolescent idiopathic scoliosis: is it better than the standard approach? A 2-year follow-up study. Clin Spine Surg. 2016;29:8.
26. Minimally invasive scoliosis surgery assisted by O-arm navigation for Lenke Type 5C adolescent idiopathic scoliosis: a comparison with standard open approach spinal instrumentation. Journal of neurosurgery Pediatrics. 2017;19(4):472–8. https://doi.org/10.3171/2016.11.peds16412.
27. Kim DJ, Bengali R, Anderson TA. Opioid-free anesthesia using continuous dexmedetomidine and lidocaine infusions in spine surgery. Korean J Anesthesiol. 2017;70(6):652–3. https://doi.org/10.4097/kjae.2017.70.6.652.
28. Davis AM, Inturrisi CE. d-Methadone blocks morphine tolerance and N-methyl-D-aspartate-induced hyperalgesia. J Pharmacol Exp Ther. 1999;289(2):1048–53.
29. Sharma A, Tallchief D, Blood J, Kim T, London A, Kharasch ED. Perioperative pharmacokinetics of methadone in adolescents. Anesthesiology. 2011;115(6):1153–61. https://doi.org/10.1097/ALN.0b013e318238fec5.
30. Kharasch ED. Intraoperative methadone: rediscovery, reappraisal, and reinvigoration? Anesth Analg. 2011;112(1):13–6. https://doi.org/10.1213/ANE.0b013e3181fec9a3.
31. Murphy GS, Szokol JW. Intraoperative methadone in surgical patients: a review of clinical investigations. Anesthesiology. 2019;131(3):678–92. https://doi.org/10.1097/aln.0000000000002755.
32. Gottschalk A, Durieux ME, Nemergut EC. Intraoperative methadone improves postoperative pain control in patients undergoing complex spine surgery. Anesth Analg. 2011;112(1):218–23. https://doi.org/10.1213/ANE.0b013e3181d8a095.
33. Gourlay GK, Willis RJ, Wilson PR. Postoperative pain control with methadone: influence of supplementary methadone doses and blood concentration–response relationships. Anesthesiology. 1984;61(1):19–26.
34. Stemland CJ, Witte J, Colquhoun DA, Durieux ME, Langman LJ, Balireddy R, et al. The pharmacokinetics of methadone in adolescents undergoing posterior spinal fusion. Paediatr Anaesth. 2013;23(1):51–7. https://doi.org/10.1111/pan.12021.
35. Dunn LK, Yerra S, Fang S, Hanak MF, Leibowitz MK, Alpert SB, et al. Safety profile of intraoperative methadone for analgesia after major spine surgery: An observational study of 1,478 patients. J Opioid Manag. 2018;14(2):83–7. https://doi.org/10.5055/jom.2018.0435.
36. Norris JV, Don HF. Prolonged depression of respiratory rate following methadone analgesia. Anesthesiology. 1976;45(3):361–2. https://doi.org/10.1097/00000542-197609000-00022.
37. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear TD, Deshur MA, et al. Clinical effectiveness and safety of intraoperative methadone in patients undergoing posterior spinal fusion surgery: a randomized, double-blinded. Controlled Trial Anesthesiology. 2017;126(5):822–33. https://doi.org/10.1097/aln.0000000000001609.

38. Martin DP, Samora WP 3rd, Beebe AC, Klamar J, Gill L, Bhalla T, et al. Analgesic effects of methadone and magnesium following posterior spinal fusion for idiopathic scoliosis in adolescents: a randomized controlled trial. J Anesthesia. 2018;32(5):702–8. https://doi.org/10.1007/s00540-018-2541-5.
39. Crawford MW, Hickey C, Zaarour C, Howard A, Naser B. Development of acute opioid tolerance during infusion of remifentanil for pediatric scoliosis surgery. Anesth Analg. 2006;102(6):1662–7. https://doi.org/10.1213/01.ane.0000216036.95705.c2.
40. Angst MS, Chu LF, Tingle MS, Shafer SL, Clark JD, Drover DR. No evidence for the development of acute tolerance to analgesic, respiratory depressant and sedative opioid effects in humans. Pain. 2009;142(1–2):17–26. https://doi.org/10.1016/j.pain.2008.11.001.
41. Cortinez LI, Brandes V, Munoz HR, Guerrero ME, Mur M. No clinical evidence of acute opioid tolerance after remifentanil-based anaesthesia. Br J Anaesth. 2001;87(6):866–9. https://doi.org/10.1093/bja/87.6.866.
42. Hansen EG, Duedahl TH, Romsing J, Hilsted KL, Dahl JB. Intraoperative remifentanil might influence pain levels in the immediate post-operative period after major abdominal surgery. Acta Anaesthesiol Scand. 2005;49(10):1464–70. https://doi.org/10.1111/j.1399-6576.2005.00861.x.
43. Lahtinen P, Kokki H, Hynynen M. Remifentanil infusion does not induce opioid tolerance after cardiac surgery. J Cardiothorac Vasc Anesth. 2008;22(2):225–9. https://doi.org/10.1053/j.jvca.2007.07.004.
44. Shin SW, Cho AR, Lee HJ, Kim HJ, Byeon GJ, Yoon JW, et al. Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery. Br J Anaesth. 2010;105(5):661–7. https://doi.org/10.1093/bja/aeq257.
45. Echevarria G, Elgueta F, Fierro C, Bugedo D, Faba G, Iniguez-Cuadra R, et al. Nitrous oxide (N(2)O) reduces postoperative opioid-induced hyperalgesia after remifentanil-propofol anaesthesia in humans. Br J Anaesth. 2011;107(6):959–65. https://doi.org/10.1093/bja/aer323.
46. Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain. 2003;106(1–2):49–57. https://doi.org/10.1016/s0304-3959(03)00276-8.
47. Kars MS, Villacres Mori B, Ahn S, Merwin S, Wendolowski S, Gecelter R, et al. Fentanyl versus remifentanil-based TIVA for pediatric scoliosis repair: does it matter? Reg Anesth Pain Med. 2019;44(6):627–31. https://doi.org/10.1136/rapm-2018-100217.
48. Berde CB, Lehn BM, Yee JD, Sethna NF, Russo D. Patient-controlled analgesia in children and adolescents: a randomized, prospective comparison with intramuscular administration of morphine for postoperative analgesia. J Pediatr. 1991;118(3):460–6. https://doi.org/10.1016/s0022-3476(05)82169-9.
49. Gauger VT, Voepel-Lewis TD, Burke CN, Kostrzewa AJ, Caird MS, Wagner DS, et al. Epidural analgesia compared with intravenous analgesia after pediatric posterior spinal fusion. J Pediatr Orthop. 2009;29(6):588–93. https://doi.org/10.1097/BPO.0b013e3181b2ba08.
50. Munro HM, Walton SR, Malviya S, Merkel S, Voepel-Lewis T, Loder RT, et al. Low-dose ketorolac improves analgesia and reduces morphine requirements following posterior spinal fusion in adolescents. Can J Anaesth. 2002;49(5):461–6. https://doi.org/10.1007/BF03017921.
51. Pestieau SR, Finkel JC, Junqueira MM, Cheng Y, Lovejoy JF, Wang J, et al. Prolonged perioperative infusion of low-dose ketamine does not alter opioid use after pediatric scoliosis surgery. Paediatr Anaesth. 2014;24(6):582–90. https://doi.org/10.1111/pan.12417.
52. McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. Cochrane Database Syst Rev. 2015;6:CD003348. https://doi.org/10.1002/14651858.CD003348.pub3.
53. George JA, Lin EE, Hanna MN, Murphy JD, Kumar K, Ko PS, et al. The effect of intravenous opioid patient-controlled analgesia with and without background infusion on respiratory depression: a meta-analysis. J Opioid Manag. 2010;6(1):47–54. https://doi.org/10.5055/jom.2010.0004.
54. McNeely JK, Trentadue NC. Comparison of patient-controlled analgesia with and without nighttime morphine infusion following lower extremity surgery in children. J Pain Symptom Manage. 1997;13(5):268–73. https://doi.org/10.1016/s0885-3924(96)00324-7.
55. Doyle E, Robinson D, Morton NS. Comparison of patient-controlled analgesia with and without a background infusion after lower abdominal surgery in children. Br J Anaesth. 1993;71(5):670–3. https://doi.org/10.1093/bja/71.5.670.
56. Yildiz K, Tercan E, Dogru K, Ozkan U, Boyaci A. Comparison of patient-controlled analgesia with and without a background infusion after appendicectomy in children. Paediatr Anaesth. 2003;13(5):427–31. https://doi.org/10.1046/j.1460-9592.2003.01061.x.
57. Weldon BC, Connor M, White PF. Pediatric PCA: the role of concurrent opioid infusions and nurse-controlled analgesia. Clin J Pain. 1993;9(1):26–33.
58. Doyle E, Harper I, Morton NS. Patient-controlled analgesia with low dose background infusions after lower abdominal surgery in children. Br J Anaesth. 1993;71(6):818–22. https://doi.org/10.1093/bja/71.6.818.
59. Kelly JJ, Donath S, Jamsen K, Chalkiadis GA. Postoperative sleep disturbance in pediatric patients using patient-controlled devices (PCA). Paediatr Anaesth. 2006;16(10):1051–6. https://doi.org/10.1111/j.1460-9592.2006.01932.x.
60. Hayes J, Dowling JJ, Peliowski A, Crawford MW, Johnston B. Patient-controlled analgesia plus background opioid infusion for postoperative pain in children: a systematic review and meta-analysis of randomized trials. Anesth Analg. 2016;123(4):991–1003. https://doi.org/10.1213/ANE.0000000000001244.
61. Cravero JP, Agarwal R, Berde C, Birmingham P, Cote CJ, Galinkin J, et al. The Society for Pediatric Anesthesia recommendations for the use of opioids in children during the perioperative period. Paediatr Anaesth. 2019;29(6):547–71. https://doi.org/10.1111/pan.13639.
62. Son HJ, Kim SH, Ryu JO, Kang MR, Kim MH, Suh JH, et al. Device-related error in patient-controlled analgesia: analysis of 82,698 patients in a tertiary hospital. Anesth Analg. 2019;129(3):720–5. https://doi.org/10.1213/ANE.0000000000003397.
63. Chidambaran V, Sadhasivam S, Mahmoud M. Codeine and opioid metabolism: implications and alternatives for pediatric pain management. Curr Opin Anaesthesiol. 2017;30(3):349–56. https://doi.org/10.1097/ACO.0000000000000455.
64. Monitto CL, Hsu A, Gao S, Vozzo PT, Park PS, Roter D, et al. Opioid prescribing for the treatment of acute pain in children on hospital discharge. Anesth Analg. 2017;125(6):2113–22. https://doi.org/10.1213/ANE.0000000000002586.
65. Feinberg AE, Chesney TR, Srikandarajah S, Acuna SA, McLeod RS, on behalf of the Best Practice in Surgery G. Opioid use after discharge in postoperative patients: a systematic review. Ann Surg. 2018;267:6.
66. Xu J, Zhou J, Xiao H, Pan S, Liu J, Shang Y, et al. A systematic review and meta-analysis comparing programmed intermittent bolus and continuous infusion as the background infusion for parturient-controlled epidural analgesia. Sci Rep. 2019;9(1):2583. https://doi.org/10.1038/s41598-019-39248-5.

67. Hong R, Gauger V, Caird MS, Burke C. Narcotic-only epidural infusion for posterior spinal fusion patients: a single-center, retrospective review. J Pediatric Orthopaedics. 2016;36:5.
68. Klatt JW, Mickelson J, Hung M, Durcan S, Miller C, Smith JT. A randomized prospective evaluation of 3 techniques of postoperative pain management after posterior spinal instrumentation and fusion. Spine (Phila Pa 1976). 2013;38(19):1626–31. https://doi.org/10.1097/BRS.0b013e31829cab0b.
69. Lavelle ED, Lavelle WF, Goodwin R, Gurd D, Kuivila T, Youssef G, et al. Epidural analgesia for postoperative pain control after adolescent spinal fusion procedures which violated the epidural space. Clin Spine Surg. 2010;23:5.
70. Guay J, Suresh S, Kopp S, Johnson RL. Postoperative epidural analgesia versus systemic analgesia for thoraco-lumbar spine surgery in children. Cochrane Database Syst Rev. 2019;1:CD012819. https://doi.org/10.1002/14651858.CD012819.pub2.
71. Sucato DJ, Duey-Holtz A, Elerson E, Safavi F. Postoperative analgesia following surgical correction for adolescent idiopathic scoliosis: a comparison of continuous epidural analgesia and patient-controlled analgesia. Spine (Phila Pa 1976). 2005;30(2):211–7. https://doi.org/10.1097/01.brs.0000150832.53604.64.
72. Shaw BA, Watson TC, Merzel DI, Gerardi JA, Birek A. The safety of continuous epidural infusion for postoperative analgesia in pediatric spine surgery. J Pediatr Orthop. 1996;16(3):374–7. https://doi.org/10.1097/00004694-199605000-00016.
73. Arms DM, Smith JT, Osteyee J, Gartrell A. Postoperative epidural analgesia for pediatric spine surgery. Orthopedics. 1998;21(5):539–44.
74. Cassady JF Jr, Lederhaas G, Cancel DD, Cummings RJ, Loveless EA. A randomized comparison of the effects of continuous thoracic epidural analgesia and intravenous patient-controlled analgesia after posterior spinal fusion in adolescents. Reg Anesth Pain Med. 2000;25(3):246–53. https://doi.org/10.1016/s1098-7339(00)90006-3.
75. Tobias JD, Gaines RW, Lowry KJ, Kittle D, Bildner C. A dual epidural catheter technique to provide analgesia following posterior spinal fusion for scoliosis in children and adolescents. Paediatr Anaesth. 2001;11(2):199–203. https://doi.org/10.1046/j.1460-9592.2001.00632.x.
76. Ekatodramis G, Min K, Cathrein P, Borgeat A. Use of a double epidural catheter provides effective postoperative analgesia after spine deformity surgery. Can J Anaesth. 2002;49(2):173–7. https://doi.org/10.1007/BF03020491.
77. O'Hara JF Jr, Cywinski JB, Tetzlaff JE, Xu M, Gurd AR, Andrish JT. The effect of epidural vs intravenous analgesia for posterior spinal fusion surgery. Paediatr Anaesth. 2004;14(12):1009–15. https://doi.org/10.1111/j.1460-9592.2004.01387.x.
78. Van Boerum DH, Smith JT, Curtin MJ. A comparison of the effects of patient-controlled analgesia with intravenous opioids versus Epidural analgesia on recovery after surgery for idiopathic scoliosis. Spine (Phila Pa 1976). 2000;25(18):2355–7.
79. Blumenthal S, Min K, Nadig M, Borgeat A. Double epidural catheter with ropivacaine versus intravenous morphine: a comparison for postoperative analgesia after scoliosis correction surgery. Anesthesiology. 2005;102(1):175–80. https://doi.org/10.1097/00000542-200501000-00026.
80. Goodarzi M. The advantages of intrathecal opioids for spinal fusion in children. Paediatr Anaesth. 1998;8(2):131–4. https://doi.org/10.1046/j.1460-9592.1998.00737.x.
81. Gall O, Aubineau JV, Berniere J, Desjeux L, Murat I. Analgesic effect of low-dose intrathecal morphine after spinal fusion in children. Anesthesiology. 2001;94(3):447–52. https://doi.org/10.1097/00000542-200103000-00014.
82. Eschertzhuber S, Hohlrieder M, Keller C, Oswald E, Kuehbacher G, Innerhofer P. Comparison of high- and low-dose intrathecal morphine for spinal fusion in children. Br J Anaesth. 2008;100(4):538–43. https://doi.org/10.1093/bja/aen025.
83. Tripi PA, Poe-Kochert C, Potzman J, Son-Hing JP, Thompson GH. Intrathecal morphine for postoperative analgesia in patients with idiopathic scoliosis undergoing posterior spinal fusion. Spine (Phila Pa 1976). 2008;33(20):2248–51. https://doi.org/10.1097/BRS.0b013e31817bd8be.
84. Son-Hing JP, Poe-Kochert C, Thompson GH, Potzman J, Tripi PA. Intrathecal morphine analgesia in idiopathic scoliosis surgery: does sex or racial group affect optimal dosing? J Pediatr Orthop. 2011;31(5):489–95. https://doi.org/10.1097/BPO.0b013e3182203988.
85. Blackman RG, Reynolds J, Shively J. Intrathecal morphine: dosage and efficacy in younger patients for control of postoperative pain following spinal fusion. Orthopedics. 1991;14(5):555–7.
86. Ibach BW, Loeber C, Shukry M, Hagemann TM, Harrison D, Johnson PN. Duration of intrathecal morphine effect in children with idiopathic scoliosis undergoing posterior spinal fusion. J Opioid Manag. 2015;11(4):295–303. https://doi.org/10.5055/jom.2015.0278.
87. Milbrandt TA, Singhal M, Minter C, McClung A, Talwalkar VR, Iwinski HJ, et al. A comparison of three methods of pain control for posterior spinal fusions in adolescent idiopathic scoliosis. Spine. 2009;34:14.
88. Cohen M, Zuk J, McKay N, Erickson M, Pan Z, Galinkin J. Intrathecal morphine versus extended-release epidural morphine for postoperative pain control in pediatric patients undergoing posterior spinal fusion. Anesth Analg. 2017;124(6):2030–7. https://doi.org/10.1213/ane.0000000000002061.
89. Anderson BJ. Paracetamol (acetaminophen): mechanisms of action. Paediatr Anaesth. 2008;18(10):915–21. https://doi.org/10.1111/j.1460-9592.2008.02764.x.
90. Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, Leone S. Paracetamol: new vistas of an old drug. CNS Drug Rev. 2006;12(3–4):250–75. https://doi.org/10.1111/j.1527-3458.2006.00250.x.
91. Wong I, St John-Green C, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children. Paediatr Anaesth. 2013;23(6):475–95. https://doi.org/10.1111/pan.12163.
92. Zuppa AF, Hammer GB, Barrett JS, Kenney BF, Kassir N, Mouksassi S, et al. Safety and population pharmacokinetic analysis of intravenous acetaminophen in neonates, infants, children, and adolescents with pain or Fever. J Pediatr Pharmacol Ther. 2011;16(4):246–61. https://doi.org/10.5863/1551-6776-16.4.246.
93. Hiller A, Helenius I, Nurmi E, Neuvonen PJ, Kaukonen M, Hartikainen T, et al. Acetaminophen improves analgesia but does not reduce opioid requirement after major spine surgery in children and adolescents. Spine (Phila Pa 1976). 2012;37(20):E1225–31. https://doi.org/10.1097/BRS.0b013e318263165c.
94. Olbrecht VA, Ding L, Spruance K, Hossain M, Sadhasivam S, Chidambaran V. Intravenous acetaminophen reduces length of stay via mediation of postoperative opioid consumption after posterior spinal fusion in a pediatric cohort. Clin J Pain. 2018;34(7):593–9. https://doi.org/10.1097/ajp.0000000000000576.
95. Sun L, Zhu X, Zou J, Li Y, Han W. Comparison of intravenous and oral acetaminophen for pain control after total knee and hip arthroplasty: a systematic review and meta-analysis. Med (Baltim). 2018;97(6):e9751. https://doi.org/10.1097/MD.0000000000009751.
96. Stundner O, Poeran J, Ladenhauf HN, Berger MM, Levy SB, Zubizarreta N, et al. Effectiveness of intravenous acetaminophen for postoperative pain management in hip and knee

arthroplasties: a population-based study. Reg Anesth Pain Med. 2019;44(5):565–72. https://doi.org/10.1136/rapm-2018-100145.
97. Glassman SD, Rose SM, Dimar JR, Puno RM, Campbell MJ, Johnson JR. The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. Spine (Phila Pa 1976). 1998;23(7):834–8. https://doi.org/10.1097/00007632-199804010-00020.
98. Long J, Lewis S, Kuklo T, Zhu Y, Riew KD. The effect of cyclooxygenase-2 inhibitors on spinal fusion. J Bone Joint Surg Am. 2002;84(10):1763–8. https://doi.org/10.2106/00004623-200210000-00004.
99. Li J, Ajiboye RM, Orden MH, Sharma A, Drysch A, Pourtaheri S. The effect of ketorolac on thoracolumbar posterolateral fusion: a systematic review and meta-analysis. Clin Spine Surg. 2018;31(2):65–72. https://doi.org/10.1097/BSD.0000000000000613.
100. Sucato DJ, Lovejoy JF, Agrawal S, Elerson E, Nelson T, McClung A. Postoperative ketorolac does not predispose to pseudoarthrosis following posterior spinal fusion and instrumentation for adolescent idiopathic scoliosis. Spine (Phila Pa 1976). 2008;33(10):1119–24. https://doi.org/10.1097/BRS.0b013e31816f6a2a.
101. Reuben SS, Ablett D, Kaye R. High dose nonsteroidal anti-inflammatory drugs compromise spinal fusion. Can J Anesthesia. 2005a;52(5):506–12. https://doi.org/10.1007/BF03016531.
102. Reuben SS, Ablett D, Kaye R. High dose nonsteroidal anti-inflammatory drugs compromise spinal fusion. Can J Anaesth. 2005b;52(5):506–12. https://doi.org/10.1007/bf03016531.
103. Vitale MG, Choe JC, Hwang MW, Bauer RM, Hyman JE, Lee FY, et al. Use of ketorolac tromethamine in children undergoing scoliosis surgery. An analysis of complications. Spine J. 2003;3(1):55–62. https://doi.org/10.1016/s1529-9430(02)00446-1.
104. Maslin B, Lipana L, Roth B, Kodumudi G, Vadivelu N. Safety considerations in the use of ketorolac for postoperative pain. Curr Drug Saf. 2017;12(1):67–73. https://doi.org/10.2174/1574886312666160719154420.
105. Lyon C, Claus LW. Less is more when it comes to ketorolac for pain. J Fam Pract. 2019;68(1):41–2.
106. Patel R, Dickenson AH. Mechanisms of the gabapentinoids and α2δ-1 calcium channel subunit in neuropathic pain. Pharmacol Res Perspect. 2016;4:2.
107. Helenius L, Puhakka A, Manner T, Pajulo O, Helenius I. Preoperative pregabalin has no effect on intraoperative neurophysiological monitoring in adolescents undergoing posterior spinal fusion for spinal deformities: a double-blind, randomized, placebo-controlled clinical trial. Eur Spine J. 2018;27(2):298–304. https://doi.org/10.1007/s00586-017-5396-9.
108. Raddaoui KRM, Bhar M, Trigui E, Zoghlami K, Nasri A, OaK O. Pregabalin for postoperative analgesia after idiopathic scoliosis surgery. Ann Pediatrics Child Health. 2018;6:4.
109. Mayell A, Srinivasan I, Campbell F, Peliowski A. Analgesic effects of gabapentin after scoliosis surgery in children: a randomized controlled trial. Pediatric Anesthesia. 2014;24(12):1239–44.
110. Rusy LM, Hainsworth KR, Nelson TJ, Czarnecki ML, Tassone JC, Thometz JG, et al. Gabapentin use in pediatric spinal fusion patients: a randomized, double-blind, controlled trial. Anesth Analg. 2010;110(5):1393–8.
111. Choudhry DK, Brenn BR, Sacks K, Shah S. Evaluation of gabapentin and clonidine use in children following spinal fusion surgery for idiopathic scoliosis: a retrospective review. J Pediatr Orthop. 2019;39(9):e687–93. https://doi.org/10.1097/BPO.0000000000000989.
112. Trzcinski S, Rosenberg RE, Vasquez Montes D, Sure A, Zhou P, Tishelman J, et al. Use of gabapentin in posterior spinal fusion is associated with decreased postoperative pain and opioid use in children and adolescents. Clin Spine Surg. 2019;32(5):210–4. https://doi.org/10.1097/bsd.0000000000000783.
113. Martinez V, Carles M, Marret E, Beloeil H. Perioperative use of gabapentinoids in France. Mismatch between clinical practice and scientific evidence. Anaesthesia Crit Care Pain Med. 2018;37(1):43–7. https://doi.org/10.1016/j.accpm.2017.01.010.
114. Verret M, Lauzier F, Zarychanski R, Savard X, Cossi MJ, Pinard AM, et al. Perioperative use of gabapentinoids for the management of postoperative acute pain: protocol of a systematic review and meta-analysis. Syst Rev. 2019;8(1):24. https://doi.org/10.1186/s13643-018-0906-3.
115. Maher DP, Chen L, Mao J. Intravenous ketamine infusions for neuropathic pain management: a promising therapy in need of optimization. Anesth Analg. 2017;124(2):661–74. https://doi.org/10.1213/ANE.0000000000001787.
116. Wilder-Smith OH, Arendt-Nielsen L. Postoperative hyperalgesia: its clinical importance and relevance. Anesthesiology. 2006;104:601–7.
117. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science. 2000;288(5472):1765–9. https://doi.org/10.1126/science.288.5472.1765.
118. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg. 2004;99(2):482–95.
119. Javery KB, Ussery TW, Steger HG, Colclough GW. Comparison of morphine and morphine with ketamine for postoperative analgesia. Can J Anaesth. 1996;43(3):212–5.
120. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand. 1997;41(9):1124–32. https://doi.org/10.1111/j.1399-6576.1997.tb04854.x.
121. De Kock M, Lavand'homme P, Waterloos H. "Balanced analgesia" in the perioperative period: is there a place for ketamine? Pain. 2001;92(3):373–80. https://doi.org/10.1016/s0304-3959(01)00278-0.
122. Burstal R, Danjoux G, Hayes C, Lantry G. PCA ketamine and morphine after abdominal hysterectomy. Anaesth Intensive Care. 2001;29(3):246–51. https://doi.org/10.1177/0310057X0102900304.
123. Engelhardt T, Zaarour C, Naser B, Pehora C, de Ruiter J, Howard A, et al. Intraoperative low-dose ketamine does not prevent a remifentanil-induced increase in morphine requirement after pediatric scoliosis surgery. Anesth Analg. 2008;107(4):1170–5. https://doi.org/10.1213/ane.0b013e318183919e.
124. Moustafa AM, Negmi HH, Rabie ME. The combined effect of ketamine and remifentanil infusions as total intravenous anesthesia for scoliosis surgery in children. Middle East J Anaesthesiol. 2008;19(5):1151–68.
125. Perelló M, Artés D, Pascuets C, Esteban E, Ey-Batlle AM. Prolonged perioperative low-dose ketamine does not improve short and long-term outcomes after pediatric idiopathic scoliosis surgery. Spine (Phila Pa 1976). 2017;42(5):E304–12. https://doi.org/10.1097/brs.0000000000001772.
126. Minoshima R, Kosugi S, Nishimura D, Ihara N, Seki H, Yamada T, et al. Intra- and postoperative low-dose ketamine for adolescent idiopathic scoliosis surgery: a randomized controlled trial. Acta Anaesthesiol Scand. 2015;59(10):1260–8. https://doi.org/10.1111/aas.12571.
127. Pendi A, Field R, Farhan S-D, Eichler M, Bederman SS. Perioperative ketamine for analgesia in spine surgery: a meta-analysis of randomized controlled trials. Spine. 2018;43(5):E299–307. https://doi.org/10.1097/BRS.0000000000002318.

128. Schwenk ES, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, Narouze S, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43(5):456–66. https://doi.org/10.1097/AAP.0000000000000806.
129. Dallimore D, Anderson BJ, Short TG, Herd DW. Ketamine anesthesia in children—exploring infusion regimens. Pediatric Anesthesia. 2008;18(8):708–14. https://doi.org/10.1111/j.1460-9592.2008.02665.x.
130. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, et al. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. Pharmacol Rev. 2018;70(3):621–60. https://doi.org/10.1124/pr.117.015198.
131. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch General Psychiatry. 1994;51(3):199–214. https://doi.org/10.1001/archpsyc.1994.03950030035004.
132. Kościelniak-Merak B, Batko I, Kobylarz K, Sztefko K, Tomasik PJ. Intravenous, perioperatively administered lidocaine regulates serum pain modulators' concentrations in children undergoing spinal surgery. Pain Med. 2019;21(7):1464–73. https://doi.org/10.1093/pm/pnz212.
133. Batko I, Kościelniak-Merak B, Tomasik PJ, Kobylarz K, Wordliczek J. Lidocaine as an element of multimodal analgesic therapy in major spine surgical procedures in children: a prospective, randomized, double-blind study. Pharmacol Rep. 2020;72(3):744–55. https://doi.org/10.1007/s43440-020-00100-7.
134. Lemming K, Fang G, Buck ML. Safety and tolerability of lidocaine infusions as a component of multimodal postoperative analgesia in children. J Pediatric Pharmacol Therapeutics. 2019;24(1):34–8. https://doi.org/10.5863/1551-6776-24.1.34.
135. Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LH, Hahnenkamp K, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev. 2018;6(6):CD009642. https://doi.org/10.1002/14651858.CD009642.pub3.
136. Dewinter G, Moens P, Fieuws S, Vanaudenaerde B, Van de Velde M, Rex S. Systemic lidocaine fails to improve postoperative morphine consumption, postoperative recovery and quality of life in patients undergoing posterior spinal arthrodesis. A double-blind, randomized, placebo-controlled trial. Br J Anaesth. 2017;118(4):576–85. https://doi.org/10.1093/bja/aex038.
137. Maheshwari K, Avitsian R, Sessler DI, Makarova N, Tanios M, Raza S, et al. Multimodal analgesic regimen for spine surgery: a randomized placebo-controlled trial. Anesthesiol J Am Soc Anesthesiol. 2020;132(5):992–1002. https://doi.org/10.1097/aln.0000000000003143.
138. Liu SS, Richman JM, Thirlby RC, Wu CL. Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. J Am Coll Surg. 2006;203(6):914–32. https://doi.org/10.1016/j.jamcollsurg.2006.08.007.
139. Reynolds RAK, Legakis JE, Tweedie J, Chung Y, Ren EJ, BeVier PA, et al. Postoperative pain management after spinal fusion surgery: an analysis of the efficacy of continuous infusion of local anesthetics. Glob Spine J. 2013;3(1):7–13. https://doi.org/10.1055/s-0033-1337119.
140. Ross PA, Smith BM, Tolo VT, Khemani RG. Continuous infusion of bupivacaine reduces postoperative morphine use in adolescent idiopathic scoliosis after posterior spine fusion. Spine (Phila Pa 1976). 2011;36(18):1478–83. https://doi.org/10.1097/BRS.0b013e3181f352d1.
141. Chin KJ, Dinsmore MJ, Lewis S, Chan V. Opioid-sparing multimodal analgesia with bilateral bi-level erector spinae plane blocks in scoliosis surgery: a case report of two patients. Eur Spine J. 2019. https://doi.org/10.1007/s00586-019-06133-8.
142. Tsui BCH, Esfahanian M, Lin C, Policy J, Vorhies J. Moving toward patients being pain- and spasm-free after pediatric scoliosis surgery by using bilateral surgically-placed erector spinae plane catheters. Can J Anesthesia. 2020;67(5):621–2. https://doi.org/10.1007/s12630-019-01543-0.
143. Nielsen RV, Fomsgaard JS, Siegel H, Martusevicius R, Mathiesen O, Dahl JB. The effect of chlorzoxazone on acute pain after spine surgery. A randomized, blinded trial. Acta Anaesthesiol Scand. 2016;60(8):1152–60. https://doi.org/10.1111/aas.12754.
144. Blumenkopf B. Combination analgesic-antispasmodic therapy in postoperative pain. Spine. 1987;12:4.
145. Witenko C, Moorman-Li R, Motycka C, Duane K, Hincapie-Castillo J, Leonard P, et al. Considerations for the appropriate use of skeletal muscle relaxants for the management of acute low back pain. Pharm Therapeut. 2014;39(6):427–35.
146. Sadhasivam S, Boat A, Mahmoud M. Comparison of patient-controlled analgesia with and without dexmedetomidine following spine surgery in children. J Clin Anesth. 2009;21(7):493–501. https://doi.org/10.1016/j.jclinane.2008.12.017.
147. Yamazaki K, Kaneda T, Suzuki T. Usefulness of additional dexmedetomidine administration in postoperative pain management after the scoliosis surgery. Masui Jpn J Anesthesiol. 2014;63(7):783–8.
148. Jones JS, Cotugno RE, Singhal NR, Soares N, Semenova J, Nebar S, et al. Evaluation of dexmedetomidine and postoperative pain management in patients with adolescent idiopathic scoliosis: conclusions based on a retrospective study at a tertiary pediatric hospital. Pediatric Crit Care Med. 2014;15:6.
149. Kotzer AM. Factors predicting postoperative pain in children and adolescents following spine fusion. Issues Compr Pediatr Nurs. 2000;23(2):83–102. https://doi.org/10.1080/01460860050121411.
150. Rabbitts JA, Groenewald CB, Tai GG, Palermo TM. Presurgical psychosocial predictors of acute postsurgical pain and quality of life in children undergoing major surgery. J Pain. 2015;16(3):226–34. https://doi.org/10.1016/j.jpain.2014.11.015.
151. Nicholls JL, Azam MA, Burns LC, Englesakis M, Sutherland AM, Weinrib AZ, et al. Psychological treatments for the management of postsurgical pain: a systematic review of randomized controlled trials. Patient Relat Outcome Meas. 2018;9:49–64. https://doi.org/10.2147/PROM.S121251.
152. Woragidpoonpol P, Yenbut J, Picheansathian W, Klunklin P. Effectiveness of non-pharmacological interventions in relieving children's postoperative pain: a systematic review. JBI Datab Syst Rev Implement Rep. 2013;11(10):117–56.
153. Lambert SA. The effects of hypnosis/guided imagery on the postoperative course of children. J Dev Behav Pediatr. 1996;17(5):307–10. https://doi.org/10.1097/00004703-199610000-00003.
154. Werner MU, Mjobo HN, Nielsen PR, Rudin A. Prediction of postoperative pain: a systematic review of predictive experimental pain studies. Anesthesiology. 2010;112(6):1494–502. https://doi.org/10.1097/ALN.0b013e3181dcd5a0.
155. Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth. 2008;101(1):77–86. https://doi.org/10.1093/bja/aen099.
156. Rabbitts JA, Fisher E, Rosenbloom BN, Palermo TM. Prevalence and predictors of chronic postsurgical pain in children: a systematic review and meta-analysis. J Pain. 2017;18(6):605–14. https://doi.org/10.1016/j.jpain.2017.03.007.
157. Fortier MA, Chou J, Maurer EL, Kain ZN. Acute to chronic postoperative pain in children: preliminary findings. J

Pediatr Surg. 2011;46(9):1700–5. https://doi.org/10.1016/j.jpedsurg.2011.03.074.
158. Landman Z, Oswald T, Sanders J, Diab M. Prevalence and predictors of pain in surgical treatment of adolescent idiopathic scoliosis. Spine (Phila Pa 1976). 2011;36(10):825–9. https://doi.org/10.1097/BRS.0b013e3181de8c2b.
159. Sieberg CB, Simons LE, Edelstein MR, DeAngelis MR, Pielech M, Sethna N, et al. Pain prevalence and trajectories following pediatric spinal fusion surgery. J Pain. 2013;14(12):1694–702. https://doi.org/10.1016/j.jpain.2013.09.005.
160. Page MG, Stinson J, Campbell F, Isaac L, Katz J. Identification of pain-related psychological risk factors for the development and maintenance of pediatric chronic postsurgical pain. J Pain Res. 2013;6:167–80. https://doi.org/10.2147/JPR.S40846.
161. Page MG, Campbell F, Isaac L, Stinson J, Katz J. Parental risk factors for the development of pediatric acute and chronic postsurgical pain: a longitudinal study. J Pain Res. 2013;6:727–41. https://doi.org/10.2147/JPR.S51055.
162. Connelly M, Fulmer RD, Prohaska J, Anson L, Dryer L, Thomas V, et al. Predictors of postoperative pain trajectories in adolescent idiopathic scoliosis. Spine (Phila Pa 1976). 2014;39(3):E174–81. https://doi.org/10.1097/BRS.0000000000000099.
163. Rabbitts JA, Zhou C, Groenewald CB, Durkin L, Palermo TM. Trajectories of postsurgical pain in children: risk factors and impact of late pain recovery on long-term health outcomes after major surgery. Pain. 2015;156(11):2383–9. https://doi.org/10.1097/j.pain.0000000000000281.
164. Rosenbloom BN, Page MG, Isaac L, Campbell F, Stinson JN, Wright JG, et al. Pediatric chronic postsurgical pain and functional disability: a prospective study of risk factors up to one year after major surgery. J Pain Res. 2019;12:3079–98. https://doi.org/10.2147/JPR.S210594.
165. Chidambaran V, Gang Y, Pilipenko V, Ashton M, Ding L. Systematic review and meta-analysis of genetic risk of developing chronic postsurgical pain. J Pain. 2019. https://doi.org/10.1016/j.jpain.2019.05.008.
166. James SK. Chronic postsurgical pain: is there a possible genetic link? Br J Pain. 2017;11(4):178–85. https://doi.org/10.1177/2049463717723222.
167. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother. 2009;9(5):723–44. https://doi.org/10.1586/ern.09.20.
168. Steyaert A, Lavand'homme P. Prevention and treatment of chronic postsurgical pain: a narrative review. Drugs. 2018;78(3):339–54. https://doi.org/10.1007/s40265-018-0866-x.
169. Voepel-Lewis T, Caird MS, Tait AR, Farley FA, Li Y, Malviya S, et al. A cluster of high psychological and somatic symptoms in children with idiopathic scoliosis predicts persistent pain and analgesic use 1 year after spine fusion. Paediatr Anaesth. 2018;28(10):873–80. https://doi.org/10.1111/pan.13467.
170. Rabbitts JA, Aaron RV, Fisher E, Lang EA, Bridgwater C, Tai GG, et al. Long-term pain and recovery after major pediatric surgery: a qualitative study with teens, parents, and perioperative care providers. J Pain. 2017;18(7):778–86. https://doi.org/10.1016/j.jpain.2017.02.423.
171. Batoz H, Semjen F, Bordes-Demolis M, Bénard A, Nouette-Gaulain K. Chronic postsurgical pain in children: prevalence and risk factors A prospective observational study. Br J Anaesth. 2016;117(4):489–96. https://doi.org/10.1093/bja/aew260.
172. Li MM, Ocay DD, Teles AR, Ingelmo PM, Ouellet JA, Page MG, et al. Acute postoperative opioid consumption trajectories and long-term outcomes in pediatric patients after spine surgery. J Pain Res. 2019;12:1673–84. https://doi.org/10.2147/JPR.S191183.
173. Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. Acta Anaesthesiol Scand. 1999;43(5):563–7.
174. Katz J, Weinrib AZ, Clarke H. Chronic postsurgical pain: from risk factor identification to multidisciplinary management at the toronto general hospital transitional pain service. Can J Pain. 2019;3(2):49–58. https://doi.org/10.1080/24740527.2019.1574537.
175. Yi P, Pryzbylkowski P. Opioid induced hyperalgesia. Pain Med. 2015;16(Suppl 1):S32–6. https://doi.org/10.1111/pme.12914.
176. Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia. Lancet. 2019;393(10180):1558–68. https://doi.org/10.1016/S0140-6736(19)30430-1.
177. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Datab Syst Rev. 2013;2013(7):CD008307. https://doi.org/10.1002/14651858.CD008307.pub2.
178. Bailey M, Corcoran T, Schug S, Toner A. Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of efficacy and safety. Pain. 2018;159(9):1696–704. https://doi.org/10.1097/j.pain.0000000000001273.
179. Yang S, Werner BC. Risk factors for prolonged postoperative opioid use after spinal fusion for adolescent idiopathic scoliosis. J Pediatr Orthop. 2019;39(10):500–4. https://doi.org/10.1097/bpo.0000000000001139.
180. Wong K, Phelan R, Kalso E, Galvin I, Goldstein D, Raja S, et al. Antidepressant drugs for prevention of acute and chronic postsurgical pain: early evidence and recommended future directions. Anesthesiol J Am Soc Anesthesiol. 2014;121(3):591–608. https://doi.org/10.1097/aln.0000000000000307.
181. Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2013;110(2):191–200. https://doi.org/10.1093/bja/aes431.
182. Gelineau AM, King MR, Ladha KS, Burns SM, Houle T, Anderson TA. Intraoperative Esmolol as an adjunct for perioperative opioid and postoperative pain reduction: a systematic review, meta-analysis, and meta-regression. Anesth Analg. 2018;126(3):1035–49. https://doi.org/10.1213/ane.0000000000002469.
183. Gandhi KA, Panda NB, Vellaichamy A, Mathew PJ, Sahni N, Batra YK. Intraoperative and postoperative administration of dexmedetomidine reduces anesthetic and postoperative analgesic requirements in patients undergoing cervical spine surgeries. J Neurosurg Anesthesiol. 2017;29(3):258–63. https://doi.org/10.1097/ana.0000000000000301.
184. De Oliveira GS, Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2013;119(1):178–90. https://doi.org/10.1097/ALN.0b013e318297630d.
185. Kamerlink JR, Quirno M, Auerbach JD, Milby AH, Windsor L, Dean L, et al. Hospital cost analysis of adolescent idiopathic scoliosis correction surgery in 125 consecutive cases. J Bone Joint Surg Am. 2010;92(5):1097–104. https://doi.org/10.2106/JBJS.I.00879.
186. Raudenbush BL, Gurd DP, Goodwin RC, Kuivila TE, Ballock RT. Cost analysis of adolescent idiopathic scoliosis surgery: early discharge decreases hospital costs much less than intraoperative variables under the control of the surgeon. J Spine Surg. 2017;3(1):50–7. https://doi.org/10.21037/jss.2017.03.11.
187. Sood N, Huckfeldt PJ, Escarce JJ, Grabowski DC, Newhouse JP. Medicare's bundled payment pilot for acute and postacute care: analysis and recommendations on where to begin. Health Aff

(Millwood). 2011;30(9):1708–17. https://doi.org/10.1377/hlthaff.2010.0394.
188. Chidambaran V, Subramanyam R, Ding L, Sadhasivam S, Geisler K, Stubbeman B, et al. Cost-effectiveness of intravenous acetaminophen and ketorolac in adolescents undergoing idiopathic scoliosis surgery. Paediatr Anaesth. 2018;28(3):237–48. https://doi.org/10.1111/pan.13329.
189. Chidambaran V, Zhang X, Geisler K, Stubbeman BL, Chen X, Weirauch MT, et al. Enrichment of genomic pathways based on differential dna methylation associated with chronic postsurgical pain and anxiety in children: a prospective, Pilot study. J Pain. 2019;20(7):771–85. https://doi.org/10.1016/j.jpain.2018.12.008.
190. Parikh JM, Amolenda P, Rutledge J, Szabova A, Chidambaran V. An update on the safety of prescribing opioids in pediatrics. Expert Opin Drug Saf. 2019. https://doi.org/10.1080/14740338.2019.1571037.
191. Sadhasivam S, Chidambaran V. Pharmacogenomics of opioids and perioperative pain management. Pharmacogenomics. 2012;13(15):1719–40. https://doi.org/10.2217/pgs.12.152.
192. Brummett CM, Myles PS. Opioid discontinuation after surgery. Br J Anaesth. 2020. https://doi.org/10.1016/j.bja.2020.01.009.
193. Harbaugh CM, Lee JS, Hu HM, McCabe SE, Voepel-Lewis T, Englesbe MJ, et al. Persistent opioid use among pediatric patients after surgery. Pediatrics. 2018;141:1. https://doi.org/10.1542/peds.2017-2439.
194. Shah A, Hayes CJ, Martin BC. Characteristics of initial prescription episodes and likelihood of long-term opioid use—United States, 2006–2015. MMWR Morb Mortal Wkly Rep. 2017;66(10):265–9. https://doi.org/10.15585/mmwr.mm6610a1.