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Where Will Gabapentin's Bumpy Road Lead us? A Narrative Review of Pediatric Perioperative Gabapentinoids

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Abstract

Purpose of Review Gabapentinoids, including gabapentin and pregabalin, have been commonly administered in the perioperative period since opioid-sparing effects were found in adults in the early 2000s. This review examines the current evidence for and against the perioperative use of gabapentinoids in children and identifies potential future directions for research.

Recent Findings Many factors led to increasing use of gabapentinoids for surgical patients. The national opioid epidemic hastened the move toward the use of multimodal analgesia and early recovery after surgery protocols for both adults and children. However, subsequent adult studies have found less benefit in postoperative pain reduction than once thought, while others have investigated substantial adverse side effects. The most convincing data supporting the use of pediatric perioperative gabapentinoids show reductions in emergence agitation, postoperative nausea and vomiting (PONV), and chronic persistent surgical pain.

Summary As adult trials of perioperative gabapentinoids show decreasing benefits in postoperative pain, opioid consumption, and postoperative nausea and vomiting (PONV) amidst increasing concerns of adverse side effects, benefits for children focus more on reduction in emergence agitation, PONV, and chronic postsurgical pain with more research needed to explore optimal dosing regimens and potential adverse side effects.

Keywords Perioperative gabapentinoids · Gabapentin · Pregabalin · Non-opioid analgesia · Multimodal analgesia · Enhanced recovery after surgery · Emergence delirium · Postoperative nausea and vomiting · Chronic postsurgical pain

Introduction

Pediatric postoperative pain management has evolved over a half century, from near denial of its existence, to an era of focusing on pain as the fifth vital sign, to the recent increased interest in a multimodal approach. Today, perioperative pharmacologic analgesia strategies are primarily based on opioids and nonopioids. Instead of a historic opioid-centric model, multimodal analgesia may include regional anesthesia, nonsteroidal anti-inflammatories, acetaminophen, membrane stabilizers, NMDA antagonists, alpha agonists, local anesthetics, and magnesium. Gabapentin and pregabalin are among a group of nonopioid medications called gabapentinoids that have become more prevalent for perioperative use in children.

Gabapentin was first approved in December 1993 by the US Food and Drug Administration (FDA) as an adjunct medication for the treatment of partial seizures in adults with approval in 2000 for use in children 3–12 years old [1]. This medication gained approval for the treatment of postherpetic neuralgia in 2002 and became available in generic form in 2004 [2]. In adults, these medications were eventually approved for the treatment of specific neuropathic pain conditions, including diabetic neuropathy, fibromyalgia, and pain related to nerve damage such as spinal cord injuries. Gabapentin use tripled between 2002 and 2015, and it was one of the most prescribed medications in the USA [3, 4].

Search Strategy: We used PubMed, Google Scholar, and Scopus as our primary sources for literature review.

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Some estimate that gabapentin is prescribed for off-label use 95% of the time [5].

Synthesized in 2001, pregabalin was the first drug approved by the US FDA in December 2004 for the treatment of pain associated with both diabetic peripheral neuropathy and postherpetic neuralgia in adults [6]. Gabapentinoids prevent hyperalgesia and inhibit pain transmission via selective inhibition at the α2δ-1 subunit of spinal N-type Ca (2 +) channels. These receptors are densely located in the cerebellum and hippocampus, which may explain common side effects of dizziness, somnolence, and abnormal eye movements. Peak plasma concentrations of pregabalin and gabapentin can be found at 1.5 and 2 h, respectively [7]. In healthy individuals, gabapentinoids do not impact spinal cord NMDA receptor activity, and there is minimal interaction between the α2δ-1 subunit and NMDA receptors. However, gabapentinoids prevent interaction of the α2δ-1 subunit and NMDA receptor in the spinal cord of patients with chronic neuropathic pain, because chronic pain causes upregulation of this subunit, which increases NMDA receptor activity. These observations have been proposed as a possible mechanism to explain why gabapentinoids, when administered before surgery, may have limited influence on spinal cord NMDA receptor [8–10].

The perioperative use of gabapentinoids in children emerged as adult studies at the turn of the century described opioid-sparing properties [11]. Over the following decade, perioperative gabapentinoid use became even more prevalent for a variety of reasons: (a) a national crisis in opioid overprescribing with increasing levels of illicit and prescription drug-related fatal overdoses [12]; (b) relatively few alternative nonopioid analgesic medications that could be used perioperatively [13]; (c) a movement of incorporating a multimodal analgesic plan balanced with nonopioid adjuvants to intrinsically decrease opioid consumption [14]; (d) development of early recovery after surgery protocols to decrease opioid consumption and postoperative hospital length of stay [15, 16]; and (e) formal society guidelines that encourage gabapentinoid use in the perioperative arena [17, 18]. In 2019, the Society for Pediatric Anesthesia included gabapentinoids among its recommendations for nonopioid analgesics for children with chronic pain undergoing major surgery [19]. Of note, the French Society of Anesthesia and Intensive Care Medicine does not recommend the systematic use of perioperative gabapentinoids, and the European Society of Regional Anesthesia recommends perioperative gabapentinoids only in laparoscopic gastric sleeve cases when paracetamol and nonsteroidal anti-inflammatory analgesics are impossible [20, 21]. In studies where perioperative gabapentinoids are administered, there is considerable variation in dosing protocols. The most common preoperative dose of gabapentin analyzed was 10 mg/kg given 1 to 2 h before surgery, while the most common postoperative dose was 15 mg/kg daily (divided two or three times per day). While most trials used gabapentin, fewer examined perioperative pregabalin (22 vs six studies, respectively). Pregabalin was administered as a single dose in adults before surgery, two-dose series before surgery (the evening before and 2 h before surgery), and as a two-dose series perioperatively (1 h before and 12 h after). The doses studied were 2–5 mg/kg or 150 mg or 300 mg [22]. While some studies did not find significant analgesia from gabapentinoids, a systematic review in pediatric patients revealed significant reductions in postoperative pain when the gabapentinoid was administered within 6 h of the procedure [23••].

Gabapentinoids may have variable effects on patients at extreme ends of age. Pharmacokinetic models for a single 10 mg/kg dose of gabapentin in healthy, fasted children reveal the need for a 33% larger dose for children between 1 month and 5 years of age compared with those between 5 and 12 years old [24]. Inversely, patients over 65 years of age who started on perioperative gabapentin may be more prone to adverse clinical events. A retrospective cohort study of 967,547 adults over 65 who underwent major surgery (cardiac, gastrointestinal, genitourinary, orthopedic, neurological excluding cases involving the brain, thoracic, and vascular surgery) and were administered perioperative gabapentin were found to have a significantly increased risk of delirium (3.4% vs 2.6%; RR 1.28), pneumonia (1.3% vs 1.2%, RR 1.11), and new antipsychotic use (0.8% vs 0.7%, RR 1.17) compared with those who were not started on perioperative gabapentin. This study also found that, compared with those who did not receive gabapentin, those who were initiated on perioperative gabapentin were more likely to be treated with anxiolytics (71% vs 62%), antidepressants (25% vs 16.7%), and analgesics including opioids (91.9% vs 80.9%), with an increased daily opioid dose (mean [SD] morphine milligram equivalents {MME}, 7.6 [6.1] MME vs 5.8 [5.6] MME). The study's sensitivity analysis revealed that increases in the doses of gabapentin were associated with increases in the risk of diagnoses of delirium (1 to < 600 mg: adjusted odds ratio [AOR] 1.25; 600 to < 1200 mg: AOR 1.3; > 1200 mg: AOR 1.34) and pneumonia (1 to < 600 mg: AOR, 1.05; 600 to < 1200 mg: AOR, 1.16; > 1200 mg: AOR, 1.34) [25]. Conversely, a reduction in anxiety or emergence agitation in children who are administered perioperative gabapentin has been shown in multiple studies.

Adult studies of perioperative gabapentinoids focus on decreases in postoperative pain, opioid consumption, postoperative nausea and vomiting (PONV), and shivering with post-subarachnoid block [26•, 27, 28]. Advantages and disadvantages are summarized in Table 1. However, pediatric studies measure postoperative outcomes in (a) acute pain intensity and/or opioid consumption reduction, (b) PONV, (c) inclusion in enhanced recovery after surgery (ERAS) protocols, (d) anxiety and emergence agitation, and (e) chronic

Table 1 Potential pros and cons of perioperative use of gabapentinoids in adults and children

Adults		Children	
Pros	Cons	Pros	Cons
Opioid sparing	Opioid and pain score reduction is clinically insignificant	?	?
Decreased postoperative nausea and vomiting	Side effects including dizziness, ataxia, fall risk, and cognitive impairment		
Multimodal analgesia	Respiratory depression if co-administered with opioids		
	Abuse potential		

postsurgical pain (CPSP) [23••]. A 2020 meta-analysis and systematic review of 24,682 perioperative adults enrolled in 281 trials concluded that gabapentinoids should not be routinely administered based on the lack of a clinically meaningful benefit. The primary outcome was postoperative pain intensity with a clinically significant difference defined as 10/100. Surgeries included spinal/orthopedic cases (27%), non-endoscopic abdominal cases (23%), endoscopic abdominal cases (15%), ophthalmologic and otorhinolaryngologic cases (10%), and plastic/peripheral vascular/breast/miscellaneous cases (7%). There was no reduction in pain with any of the dosing regimens using their definition at 6, 12, 24, and 48 postoperative hours [26•]. In addition to a lack of benefit, adult studies have found a greater risk of postoperative visual disturbances, sedation, and dizziness with use of perioperative gabapentinoids [22, 29]. The relative risk of serious adverse effects for perioperative pregabalin use was 2.9. These serious adverse effects included readmission to the hospital, prolonged hospital stay, postponed operation because of sedation, allergic reaction, stroke, pulmonary embolism, myocardial infarction, acute kidney injury, pneumonia, wound infection, bleeding or hematoma, and death [30]. When combined with remifentanil, pregabalin potentiated ventilatory depression, although analgesia was also enhanced [31]. This meta-analysis has been criticized for clinical and statistical heterogeneity as well as for inclusion of studies that compared gabapentin with non-placebo [26•, 32]. Still, the alarming adult data pointing to increased risk, in addition to the lack of clinically significant benefit, have led pediatric anesthesiologists to reexamine the utility of perioperative gabapentinoid use in children.

Few pediatric studies on perioperative gabapentinoids reported adverse effects as a result of the gabapentinoids, compared with those in the adult literature. Instead, adverse effects, including sedation, in children who received perioperative gabapentinoids were more likely to be suggested as a consequence of opioids or a multimodal regimen. Of note, there is substantially more data in adult trials of perioperative gabapentinoids than in the pediatric literature. A 2023 narrative review of pediatric perioperative gabapentinoid use evaluated 49 references, five of which were available only as abstracts presented at conferences [23••]. All but two of these studies point to a benefit for using perioperative gabapentinoids in children. The strongest evidence for reductions in postoperative pain scores and opioid use is in children undergoing spinal surgery. Proposed advantages of perioperative gabapentinoids in children include incorporation of non-opioid analgesia, decreased PONV, and decreased emergence delirium [23••, 33]. Figure 1 highlights the trend of pediatric studies exploring analgesic potential and instead

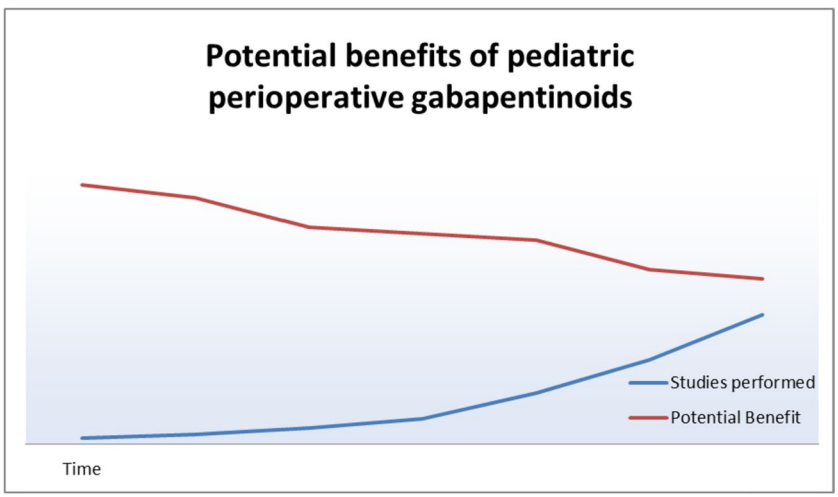

Fig. 1 Benefit potential of perioperative gabapentinoids in children over time

finding potential benefits in secondary indices. Table 2 outlines the literature that has evaluated the use of perioperative pediatric gabapentinoids. Studies evaluating these outcomes are reviewed, and suggestions for future research directions have been identified.

A 2023 multihospital retrospective review evaluated length of stay, opioid use, and patient-reported pain scores after the addition of gabapentin into five distinct pain protocols for posterior spinal fusion in adolescent idiopathic scoliosis. Among 682 hospitalizations, 49% received gabapentin at doses ranging from 3.6 to 13.4 mg/kg/day on postoperative days (POD) 0–3. Compared to patients who did not receive gabapentin, addition of gabapentin to pain protocols decreased average opioid use percentage from immediately after surgery until POD 3 (4.2 vs 4.8 morphine milligram equivalents, $p < 0.001$). No effect was seen on average pain or average length of stay [34••]. A 2022 single-center, randomized, blinded, placebo-controlled study investigated analgesic effects of perioperative gabapentin in children aged 9–17 undergoing Ravitch procedure for anterior chest wall deformity. The dosing regimen consisted of the following: 15 mg/kg preoperatively, 7.5 mg/kg postoperatively, and twice per day for 3 days. When compared against placebo, gabapentin reduced POD 1 morphine and metamizole demand (median 0.016 vs. 0.019 mg/kg/h, $p = 0.03$; median 1 vs 2, $p = 0.04$, respectively) and improved patient satisfaction (median 10 vs 9, $p = 0.018$), while no change was found in anxiety and postoperative side effects [35••]. A 2019 prospective, double-blinded, randomized controlled trial of 84 children aged 3–16 years undergoing lower extremity surgery revealed that those receiving gabapentin 10 mg/kg 1–2 h prior to surgery experienced more sedation prior to induction of anesthesia ($p < 0.01$), exhibited an attenuated autonomic response to intubation despite similar opioid consumption, presented with less agitation in the first postoperative hour (12.5% vs 36.3%, $p < 0.05$), and significantly reduced pain at postoperative hours four and eight ($p < 0.05$) [36]. Previous studies showed that repeated perioperative doses of gabapentin, but not a single preoperative dose, reduced opioid requirements following spinal fusion for idiopathic scoliosis [37]. A 2014 randomized controlled trial failed to show that a single 600 mg preoperative dose of gabapentin resulted in a significant difference in opioid consumption or pain scores by adolescents undergoing scoliosis surgery [38]. Another factor to consider for adolescents with idiopathic scoliosis preparing for surgical correction is the likelihood of intrinsic deformity-related anxiety and depression as well as the importance of psychological well-being to decrease postoperative pain and opioid requirements [39, 40]. Variation both in the analgesic efficacy of gabapentinoids and in the above studies' dosing protocols point to two areas where more gabapentinoid research in the perioperative pediatric population is still needed.

In studies investigating gabapentin for postoperative pain, a secondary finding of decreased PONV was seen in children, who suffer from this twice as frequently as adults. It is uncertain if the reduction in PONV is an intrinsic benefit of the gabapentinoid or is due to its opioid-sparing properties. In one prospective randomized controlled trial, investigators compared a single 20 mg/kg dose of gabapentin given 2 h before surgery with placebo in children 4–8 years old presenting for adenotonsillectomy and found a significant reduction in PONV incidence (28% vs 43%, respectively, $p = 0.007$) as well as lower likelihood of requiring any rescue analgesia [41]. As mentioned earlier, there have been numerous studies evaluating PONV as a secondary outcome, including two studies that included gabapentin as part of multimodal ERAS regimens, alluding to gabapentinoid-related conclusions of questionable significance [42, 43]. Other studies that investigated gabapentin at lower preoperative doses (< 15 mg/kg) showed no impact on PONV.

In addition to PONV prevention, the sedative properties of gabapentinoids have made them a natural choice to prevent emergence delirium, which is also seen at higher rates in children than in adults. Often occurring within 30 min after anesthesia, emergence delirium can cause harm to the patient and disruption of the recovery area, making the preventive effect of gabapentinoids of great interest to clinicians. Five studies evaluated gabapentin at doses of 5–30 mg/kg 1–2 h before anesthesia, and three studies evaluated pregabalin at doses of 75 mg fixed dose, 1.5 mg/kg, and 5 mg/kg [33, 36, 44–49]. A reduction in anxiety or emergence agitation was observed in all but one study [23••]. This study compared children undergoing same-day surgery who received preoperative oral midazolam (0.75 mg/kg) with those who received oral pregabalin (5 mg/kg). Although significant reductions in perioperative anesthetic and analgesic requirements, pediatric acute care unit stay duration, and time to eye-opening and extubation were observed in those who received pregabalin compared with those who received preoperative midazolam, no significant reduction in emergence delirium or postoperative vomiting was found [49].

The ERAS group was established in 2001 in Europe to develop a protocol that would avoid postoperative complications, expedite postoperative recovery, and shorten hospital stay during the acute perioperative setting [50]. The adoption of multimodal analgesia aims to improve postoperative pain control, reduce surgical stress, and facilitate early oral diet and mobilization [51]. Though early emphasis focused on non-steroidal anti-inflammatory drugs (NSAID), concerns over adverse influence of NSAIDs on anastomotic integrity led to a renewed interest in gabapentinoids. Analysis of the efficacy of the evolving ERAS protocols may prove challenging, given the dynamic variables. Considerable variation exists not only in the dosing, but in the use of gabapentinoids

Table 2 Summary of gabapentinoid use for analgesia and decreasing opioid consumption in postoperative pediatric patients

Reference, year; number of patients receiving gabapentinoid	Study design	Population demographics	Gabapentinoid dosing	Outcome measures for analgesia/opioid consumption[a]	Comparator group(s)	Perioperative and postoperative analgesia outcomes	Opioid consumption outcomes
Badawy 2018; *n*=33 [33]	RCT	3.7 ± 1.4 yo (mean ± SD), strabismus repair	Gabapentin 5 mg/kg 1 h pre-op	Number of patients requiring meperidine post-op (secondary outcome)	Placebo (*n*=34)	Not reported	Significantly fewer patients required post-op meperidine in gabapentin group
Fenikowski 2022; n=28 [35]	RCT	14 (mean; SD not provided), Ravitch	Gabapentin 15 mg/kg 1 h pre-op, then 7.5 mg/kg bid on pod1-pod3	Average daily pain (NRS 0-10) on pod0 through pod3; morphine consumption; total number of metamizole rescue doses	Placebo (n=28)	Significantly lower pain scores on average on day of surgery and lower max pain scores on day of surgery and pod2 at rest	Significantly lower median amt of morphine in gabapentin group on pod1 only; Significantly lower number of total rescue metamizole doses in gabapentin group
Helenius 2020; *n*=32 [62]	RCT	15.8 ± 2.3 yo (mean ± SD), PSF for spinal deformities	Pregabalin 2 mg/kg (rounded up to nearest 25 mg) evening (12 h) and 2 h pre-op	Pain (NRS) at 2, 4, 6, 8, 12, 16, 20, 24, 36, and 48 h post-op; opioid consumption over 8 h intervals until 48 h post-op; cumulative daily opioid consumption until discharge	Placebo (n=31)	No difference in pain scores at rest at any point post-op	No difference in opioid consumption at any point post-op
Mayell 2014; *n*=18 [38]	RCT	14.7 ± 1.8 yo (mean ± SD), PSF for scoliosis	Gabapentin 600 mg 1 h pre-op	Morphine consumption between 0 and 24 h post-op; time to first rescue analgesia; pain (NRS) at rest and movement; cumulative opioid consumption at 1, 4, 8, 12, 24, 48, and 72 h post-op	Placebo (n=17)	No significant difference in NRS score at rest or with movement at any point within 72 h post-op	No significant differences between groups in morphine consumption at any point 72 h post-op; no differences between groups in time to first rescue analgesia
Mohamed 2014; *n*=72 [41]	RCT	5.4 ± 2.3 yo (mean ± SD), adenotonsillectomy	Gabapentin 20 mg/kg 1 h pre-op	Number of patients requiring analgesic within 6 h post-op (secondary outcome)	Placebo (n=72)	Significantly higher frequency of requiring analgesic in placebo group	Not reported
Pinto Filho 2019; *n*=40 [36]	RCT	62.8 ± 59.2 months old (mean ± SD), unilateral inferior limb surgery	Gabapentin 10 mg/kg 1–2 h pre-op	Pain (CRIES, CHIPPS, or Wong- Baker FACES) intensity defined as mild, moderate, or severe at 1, 4, 8, 12, 18, and 24 h post-op; time to first use of morphine and frequency of morphine use	Placebo (n=44)	Significantly lower pain intensity observed at 4 and 8 h post-op in gabapentin group	No significant differences in time to first morphine dose nor frequency of use
Pinto Filho 2019; *n*=90 [44]	RCT with 2 levels of gabapentin dosing	3.29 ± 1.42 (15 mg/kg dose group) and 3.42 ± 1.39 (30 mg/kg dose group) yo (mean ± SD), LP or myelogram	Gabapentin 15 mg/kg (*n* = 44) or 30 mg/kg (*n* = 46) 1–2 h pre-op	Pain (CHIPPS) at 0 and 30 min post-op	Placebo (n=45)	Significantly lower pain at 30 min post-op for both gabapentin dose groups	Not reported
Rusy 2010; *n*=29 [37]	RCT	14.8 ± 2.1 yo (mean ± SD), PSF for AIS	Gabapentin 15 mg/kg 25–30 min pre-op, then 5 mg/kg tid for 5 days	Total daily morphine consumption on POD0, POD1, POD2, POD3, and POD4; pain scores (NRS) in PACU and bid on POD1, POD2, POD3, and POD4	Placebo (n=30)	Significantly lower pain in gabapentin group in PACU and on morning of POD1	Significantly lower morphine consumption in gabapentin group on POD0, POD1, and POD2
Talaat 2021; *n*=30 [49]	RCT	23.5 (median) and 14–43 (IQR) months old, day-case surgery[b]	Pregabalin 5 mg/kg 30 min pre-op	Intra-op fentanyl consumption; intra-op meperidine consumption; time to first analgesic; pain (FLACC) at PACU arrival and discharge, and at 2, 4, 6, 8, 10, 12 h post-op	Midazolam 0.75 mg/ kg PO 30 min pre-op (*n*= 30)	Significantly lower pain with pregabalin at PACU discharge and at 2, 4, 6, and 8 h post-op	Significantly less fentanyl and meperidine consumption intra-op in pregabalin group; significantly longer time to first analgesic requirement in pregabalin group
Tomaszek 2020; *n*=20 [45]	RCT	13 (10–15) yo (median and IQR), Ravitch procedure	Gabapentin 15 mg/ kg 1 h pre-op, then 7.5 mg/kg bid for 3 days	Pain intensity (NRS) as daily mean scores on POD0, POD1, POD2, and POD3; total fentanyl consumption	Placebo (n=20)	No significant difference in mean pain scores on POD0, POD1, POD2, or POD3	No significant difference in total opioid consumption
Wang 2018; *n*=23 [61]	RCT	14.3 ± 2.8 yo (mean ± SD), amputation for bone tumor	Gabapentin 300 mg once 4 days pre-op, 300 mg bid 3 days pre-op, then 300 mg tid until 30 days post-op	Daily pain scores (VAS) on POD0–14	Placebo (n=22)	No significant difference in pain scores seen until POD4	Not reported
Zhang 2023; n=336 [34]	Retrospective, multi-center, observational	14.7 (mean; SD not provided), PSF for AIS	Gabapentin load 0 - 10.6 mg/kg/day, 5.3-10.3 mg/kg/day on pod1, 5.2-13.4 mg/kg/day on pod2, 0-12.4 mg/kg/day on pod3	Average daily pain (NIRS 0-10) on pod0 through pod3; mean daily opioid use (oral MME/kg) on pod0 through pod3	Standard of care without gabapentin	No difference in pain scores on any day	Significantly lower mean opioid consumption in gabapentin group on pod0 to pod3

AIS, Adolescent Idiopathic Scoliosis; *bid*, twice daily; *CHIPPS*, Children and Infants Postoperative Pain Scale; *FLACC*, Faces, Legs, Activity, Cry, Consolability; *intra-op*, intraoperatively; *IQR*, *I*nterquartile Range; *IV*, intravenous; *LP*, lumbar puncture; *MME*, morphine milligram equivalents; *NRS*, numeric rating scale; *PACU*, post-analgesia care unit; *PO*, by mouth; *POD*, postoperative day; *post-op*, postoperatively; *preop*, preoperatively; *PSF*, posterior spinal fusion; *RCT*, randomized controlled trial; *SD*, standard deviation; *tid*, three times daily; *VAS*, visual analog scale; *yo*, years old

[a]First outcome listed in table is primary outcome unless otherwise indicated

[b]Outpatient day surgeries — hernia repair, adenotonsillectomy, adenoidectomy, hydrocelectomy, and orchiopexy

Modified from Hall EA, et al. Perioperative Indications for Gabapentinoids in Pediatrics: A Narrative Review. *Pediatr Drugs*. 2023 Jan;25(1):43–66. Permission requested from *Pediatric Drugs*

in some but not all protocols [52•]. The inclusion of gabapentinoids as part of ERAS protocols also makes for a dizzying array of adverse side effects that may not be reliably attributed to the gabapentinoids, particularly if other sedating medications are administered, such as ketamine, clonidine, or dexmedetomidine. Somnolence is a known side effect of gabapentin, which can make blinding challenging if it were the only known variable in perioperative studies compared with placebo. Nonpharmacologic interventions included in ERAS protocols, such as preoperative fasting minimization, postoperative early physical therapy, and early removal of urinary catheters and surgical drains, can obscure the specific effect of perioperative gabapentinoids, although they share the ultimate goal of shortening hospital stay and minimizing complications. The use of a postoperative cooling brace for children after idiopathic scoliosis surgery has been found to decrease opioid consumption (1.7 mg/kg vs 1.2 mg/kg, $p=0.02$) on postoperative day 1 as well as reduce length of hospital stay (4 vs 3 days, $p=0.004$) [53]. Given that ERAS protocols are constantly evolving and occasional circumstances that may lead to electively choosing to adhere to only some portions of the protocol, many studies evaluating the efficacy of gabapentinoids revealed variation in protocol compliance of up to 80% [54] Conversely, efficacy of ERAS protocols as manifested by decreased length of hospital stay has been explained by the teaming concept seen in the multidisciplinary approach of all stakeholders, including patients and their families [55, 56].

Chronic postsurgical pain (CPSP) of three months' duration or longer can follow acute postoperative pain and last for months or years after painful surgeries such as thoracic, limb amputation, breast, or groin hernia operations in adults or limb-sparing surgeries, amputations, scoliosis repair, or thoracotomies in children [57, 58]. In children, the 12-month prevalence is estimated to be 20%, which is comparable with adult figures. Pediatric risk factors for CPSP include baseline pain, anxiety, pain self-efficacy (one's confidence in own ability to complete a task despite their pain), and parental pain catastrophizing. However, the amount of immediate postoperative opioid exposure, such as a 0.5 mg/kg MME requirement or more on postoperative day 1, is an independent predictive factor for CPSP in adolescents after scoliosis repair [59]. Opioid-reducing perioperative strategies, such as those incorporating gabapentinoids, decrease postoperative morphine consumption in children undergoing scoliosis surgery and were associated with decreased incidence of persistent postoperative pain at 1 year [60]. In children undergoing amputation for malignant bone tumors, starting gabapentin 4 days prior to surgery and continuing for 30 postoperative days was found to significantly decrease pain intensity in the first 14 postoperative days and the rate of phantom limb pain on the 60th postoperative day [61]. This prospective double-blinded randomized controlled trial revealed that the most significant difference in pain scores (43% vs 77%, $p<0.05$) between those on gabapentin and controls was evident starting at postoperative day 4. However, perioperative pregabalin in children undergoing posterior spinal fusion for scoliosis was not found to impact the postoperative opioid requirement at 48 h or pain domain scores on the Scoliosis Research Society Questionnaire at 2 years after surgery [62]. The SRS-24 is a 7-domain outcome questionnaire measuring pain, satisfaction, general self-image, postoperative self-image, function from back condition, postoperative function, and general level of activity. A 2013 Cochrane systematic review did not find statistically significant decreases in pain at 3 or 6 months with perioperative gabapentinoids in adults compared with placebo, although there was substantial variation in dosing regimens [63]. Another 2012 systematic review combined gabapentin and pregabalin studies over various time points and pain assessment measures to conclude that perioperative gabapentinoids may be effective in reducing the incidence of CPSP [64]. More recent data have continued the trend of mixed support in the ability of perioperative gabapentinoids to prevent CPSP in adults.

Much of the effects of perioperative gabapentinoids have been studied in subjects undergoing general anesthesia. However, there are potential uses of perioperative gabapentinoids without general anesthesia, such as in cases with only regional anesthesia or in conjunction with mild or moderate IV sedation. A randomized, double-blinded, placebo-controlled trial of a single preoperative 600 mg dose of gabapentin administered to adults undergoing first-trimester uterine aspiration under paracervical block found a significant reduction in pain on a 100 mm visual analog scale at 10 min after surgery (mean difference − 13.0; $p=0.01$) and at 30 min (mean difference -10.8; $p=0.03$) [65•]. These findings may have more grounded implications than other studies in which perioperative gabapentinoids are included in an ERAS protocol with other confounding variables because all 111 patients received a paracervical block with either placebo or gabapentin. Patients in the trial who were administered gabapentin did not report significantly lower levels of intraoperative pain than their counterparts who received placebo. With the exception of 800 mg ibuprofen administered in the recovery room, none of the subjects received any other systemic medication for anxiety or pain. Although this was an adult trial, the implications may be profound for adolescents who must consider pregnancy termination.

Conclusion

This review reveals that while clinical experience with perioperative gabapentinoids in the pediatric population spans a wide range, there is a substantial need for further research, especially with evolving implications in

adult-based literature. With most data coming from children undergoing scoliosis and tonsil surgery, studies suggest that perioperative gabapentinoids may offer a reduction of acute pain, opioid consumption, PONV, and development of CPSP. However, more formal research must be conducted to help develop a consensus on how perioperative gabapentinoids are best administered in the pediatric population. Clinical research often lags behind in this population, as evidenced by the numerous abstracts and poster presentations included in a recent literature review. Determining optimal dosage and dosing regimens (scheduled vs as needed) can help develop protocols to evaluate the analgesic efficacy of gabapentinoids when administered alone and in conjunction with other interventions and/or anesthetic techniques that may employ regional anesthesia as part of an ERAS protocol. Aside from opioid-sparing analgesia, other beneficial outcomes such as reduction in PONV must be more clearly examined. Lastly, these benefits must be analyzed against its side effects, which themselves must be further characterized.

Declarations

Conflict of Interest Galaxy Li and Pulsar Li declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies of human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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