Purpose of review
Many children with cancer suffer from neuropathic pain. However, there are no published pediatric randomized controlled trials (RCTs), nor agreed upon pediatric treatment recommendations. Pediatric neuropathic pain in patients with malignancies is often underassessed and undertreated with ineffective therapies.

Recent findings
This article describes main themes in the literature and commonly used treatment strategies.

Summary
A combination of integrative, rehabilitative, and supportive therapies with pharmacotherapy, including first line medications such as NSAIDs, opioids, low-dose tricyclics, and gabapentinoids, appear to be successful treatment strategies. There is a dearth of evidence regarding the management of neuropathic pain in children with cancer; studies, especially RCTs, are desperately needed.

Keywords
cancer, neuropathic, pain, pediatric

INTRODUCTION
Despite increasing awareness about the causes and treatment of pain in children with malignancies, the majority of children with cancer still experience pain [1]. A meta-analysis demonstrated the prevalence of neuropathic mechanisms in patients with cancer pain older than 12 years between 19 and 39% [2]. This article reviews management options of neuropathic pain in children with cancer.

DEFINITION
The International Association for the Study of Pain defines neuropathic pain as ‘...pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [3].’ However, the definition also states ‘...but, not all lesions in the somatosensory system lead to neuropathic pain.’

CAUSE
In pediatric cancer patients, there are multiple causes for neuropathic pain. Chemotherapeutic agents such as vincristine, cisplatin, and paclitaxel may cause neuropathic pain that can persist for months or even years after therapy [4,5]. A lesion of the spinal cord may cause pain arising as a direct consequence of affecting the somatosensory system. For children with malignancy, tumor-related pain as a result of direct tissue and nerve injury can cause significant neuropathic pain. Although this may be transient postoperative pain, it can persist and display clinical signs, in which we can suspect neuropathic components. This situation is especially true for children with advanced unresectable solid tumors, in which nerve entrapment may pose a major problem, such as at sciatic nerve or brachial plexus. Approximately 60–80% of adult patients with an amputation experience phantom sensations in their amputated limb, and most sensations are painful [6]. Data for children have not been published. Phantom limb pain is a complex phenomenon that includes a wide variety of
symptoms ranging from tingling and itching to burning and aching [7].

PAIN ASSESSMENT

Specific pain intensity scales for neuropathic pain are currently only validated for adults and examples include the Neuropathic Pain Scale [8,9] and the Pain Quality Assessment Scale [10]. As a result, neuropathic pain assessment in children often involves tools validated for acute pain, such as Likert-type visual analog scales (VAS), which have been used as primary outcome measures in pediatric neuropathic pain trials. Age-appropriate tools include one-dimensional self-report measures (e.g., VAS, numerical rating scales-11, or faces scales) due to their ease of use in alert and responsive children who are able to communicate. For infants and children under 4 years of age, there are several validated proxy pain assessment tools available for measuring the frequency of physical behaviors. Other well validated tools, including COMFORT, CRIES, FLACC, and NIPS, are recommended and comprehensive reviews comparing these assessment tools have been published [11–16].

A symptom leading to the diagnosis of neuropathic pain on examination is often dysesthesia, such as allodynia and/or hyperalgesia. However, some children may only report paresthesia (e.g. tingling, numbness, or ‘ants crawling on my skin’) as their leading distressing symptom of neuropathic dysfunction.

TREATMENT

There are no published randomized controlled trials (RCTs) about the management of neuropathic pain in children. In order to weigh benefits and burdens of treatment strategies for children with acute and neuropathic pain, therapies should usually be administered along a continuum from least invasive to most invasive (i.e. from integrative/nonpharmacological/supportive/rehabilitative, to topical, to enteral and parenteral administration of medications, and finally to invasive procedures if necessary). (See Table 1).

IDENTIFY AND TREAT THE UNDERLYING DISEASE PROCESS

A medical examination and history is paramount when caring for a child in neuropathic pain. For instance, consider radiation and/or corticosteroids if appropriate, and as always, when a child presents with a distressing symptom, the clinician must try to identify a possible underlying disease process. The underlying cause should then be treated, if this is feasible and within the goals of care for the child and family.

Table 1. Step-by-Step recommendations for neuropathic pain management in children with cancer^a

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Identify and treat underlying disease process, and consider radiation and/or corticosteroids when CNS compression appears evident.</th>
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<tr>
<td>Step 2</td>
<td>Start integrative (nonpharmacological) therapies to help manage comorbidities, such as anxiety and sleep disturbance.</td>
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<td>Step 3</td>
<td>Administer an opioid (plus NSAID/celecoxib, if no contraindications). Consider tramadol (for mild-medium pain) or methadone (for medium-severe pain); however, there are no clear data that these two medications are superior to morphine, fentanyl, hydromorphone or oxycodone.</td>
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<tr>
<td>Step 4</td>
<td>Add a low-dose TCA, such as amitriptyline or nortriptyline (or gabapentinoid if QTc-prolongation). These medications may take days to start working, so consider starting low-dose ketamine as a ‘bridge’ in severe cases.</td>
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<tr>
<td>Step 5</td>
<td>Combine a low-dose TCA and gabapentinoid.</td>
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<tr>
<td>Step 6</td>
<td>If pain is localized, consider the addition of a lidocaine 5% patch (can be cut to fit).</td>
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<td>Step 7</td>
<td>Begin an NMDA-receptor-channel blocker such as ketamine and or methadone, if not already administered. Depending on the clinical picture, consider the step-wise addition of a low-dose benzodiazepine, α-agonist such as dexmedetomidine or clonidine, and/or intravenous lidocaine.</td>
</tr>
<tr>
<td>Step 8</td>
<td>Consider regional anesthesia and referral to a pediatric pain specialist, if this has not already happened.</td>
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</table>

^aThere are no pediatric evidence-based recommendations. The approach suggested in this table may be considered. However, it should be altered depending on the age, underlying condition, pathophysiology, and treatment goals for the individual patient.
INTEGRATIVE AND REHABILITATIVE THERAPIES

State of the art pain management in the 21st century demands that pharmacological management be combined with supportive measures, rehabilitative therapies, and integrative, nonpharmacological treatment modalities. Common comorbidities that are likely to worsen the neuropathic pain experience include insomnia and/or anxiety and these comorbidities should be addressed.

Integrative, supportive, and rehabilitative therapies are an expected part of the treatment protocol. Age-appropriate modalities include: physical (massage, transcutaneous nerve stimulation, comfort positioning, allowing family for close contact/touch), rehabilitation (physical therapy, occupational therapy), behavioral (deep breathing, imagery, hypnosis, smart-phone/tablet ‘apps’), acupressure, acupuncture, and aromatherapy [17].

PHARMACOLOGIC MANAGEMENT

The following section is an overview of current pediatric pharmaceutical pain management options, including suggested dosing and potential side effects.

Nonsteroidal anti-inflammatory drugs

Barring obvious contraindications for NSAIDs, clinical experience has shown that this group of medications can be quite effective in the management of pediatric neuropathic pain. Scheduled NSAIDs play an important role in the pharmacological approach to neuropathic pain. One might consider a COX-2 inhibitor, such as celecoxib, if there is a risk of bleeding-related side effects.

Ibuprofen (5–10 mg/kg PO every 6 h; dose limit 2400 mg/day) is associated with the fewest gastrointestinal side effects among the NSAIDs. It should be used with caution with hepatic or renal impairment, history of gastrointestinal bleeding or ulcers, and it may inhibit platelet aggregation.

Ketorolac has the advantage of intravenous administration, but should be rotated to oral ibuprofen as soon as it is tolerable (<2 years = 0.25 mg/kg every 6 h; >2 years = 0.5 mg/kg every 6 h; maximum 30 mg/dose; recommended dosing no longer than 3–5 days).

Celecoxib (a COX-2 inhibitor) may be considered if classical NSAIDs are contraindicated (e.g., due to bleeding risk or gastrointestinal side effects). Safety and efficacy has been established only in children 2 years of age or older and for a maximum of 6 months of treatment in juvenile rheumatoid arthritis (1–2 mg/dose; maximum 100 mg every 12–24 h).

Opioids

Children with cancer with medium to severe neuropathic pain often require opioids. A review of adult RCTs regarding drug approaches to neuropathic pain revealed that the number needed to treat (NNT) was 2.5 [18–20]. The NNT for tricyclic antidepressants (TCAs) was 3.6, 4.4 for lidocaine patch, 2.9–3.9 for gabapentinoids, and 6.8 for selective serotonin reuptake inhibitors (SSRI) [16,18,21,22]. Traditional teaching that neuropathic pain is unresponsive to opioids cannot be upheld.

There is a subset of children with neuropathic cancer pain for whom the administration of opioids might not be indicated: children who display only mild to medium neuropathic pain or whose pain is well controlled alone with simple analgesia (e.g., an NSAID/COX-2 inhibitor and an adjuvant such as amitriptyline or gabapentin).

‘Weak’ Opioids

In some pediatric patients with neuropathic pain, particularly those with neurologic dysfunction, tramadol might be helpful. It is a weak μ-receptor agonist, a serotonin and norepinephrine reuptake inhibitor, and is also likely to be an α-2 agonist. Recommended dosing is 1–2 mg/kg every 4–6 h, maximum 8 mg/kg per day (adult 50–100 mg every 4–6 h, maximum 400 mg/day). Tramadol has been trialed in neonates and children (mainly postoperative) and it was shown to be well tolerated and effective [23,24]. Common adverse effects include nausea, vomiting, dizziness, constipation, and sedation. A rare but severe side effect is serotonergic syndrome. Tramadol does not appear to increase the risk of idiopathic seizures, but patients with seizure tendency or medication that lowers seizure threshold (TCAs, SSRI, MAOI, antipsychotics), may be at increased risk.

‘Strong’ Opioids

The usual starting dose for morphine in opioid-naive children older than 6 months is 0.05–0.1 mg/kg intravenous or 0.15–0.3 mg/kg PO every 4 h titrated to effect. If dose-limiting side effects occur, experience has shown that opioid rotation at equianalgesic doses of fentanyl, hydromorphone, oxycodone, diamorphine, or methadone may improve analgesia and decrease side effects. Methadone may be a useful opioid for the management of neuropathic pain, with its combined activity as a μ-receptor agonist, N-methyl-D-aspartate (NMDA)-
receptor antagonist, and serotonin/norepinephrine reuptake inhibitor (see below). However, methadone should not be prescribed by clinicians unfamiliar with its use.

Although methadone and tramadol yield theoretical benefit through their complementary action in the management of neuropathic and nociceptive pain, there are no data to support that they are more effective than other opioids such as morphine, fentanyl, hydromorphone, and oxycodone.

**Corticosteroids**

Corticosteroids are potent anti-inflammatory agents useful in both nociceptive and neuropathic pain. Reducing inflammation and peritumor edema can relieve pressure on a nerve or the spinal cord, decrease intracranial pressure from a brain tumor, or decrease obstruction of a hollow viscus.

Most of the complications of steroid use (i.e., proximal muscle weakness, osteoporosis, and immunosuppression) are long-term sequelae and need to be carefully watched. Steroid psychosis is a potential side effect that requires either rotation to another corticosteroid, cessation of the drug, or treatment with neuroleptics. Dexamethasone has a long half-life requiring only once or twice daily dosing. Typical doses start at 0.1–1.5 mg/kg (maximum 4–10 mg) per day.

**Adjuvant analgesia**

Adjuvant analgesics are medications that, when added to primary analgesics, further improve pain control. Occasionally they may also be primary analgesics. For a significant number of children with malignancies suffering from severe neuropathic pain, applying the World Health Organization pain ladder (i.e., administering scheduled opioids +/− NSAIDs/celecoxib) may not provide adequate neuropathic pain relief, and the addition of adjuvant analgesics may be indicated.

**TRICYCLIC ANTIDEPRESSANTS**

There are no data that TCAs provide better analgesia than gabapentinoids. The reason that TCAs are often the first adjuvant include once at night dosing options [versus three times per day (TID) for gabapentin] and the significant sedative effect at night, often improving insomnia. It may take days or weeks for TCAs and/or gabapentinoids to show their analgesic effect, so in select cases this time period might be bridged by (or combined with) low-dose ketamine (see below).

TCAs are the best-studied antidepressant class that show efficacy in treating neuropathic pain. Amitriptyline and nortriptyline, which have been extensively studied, block reuptake of serotonin and norepinephrine which possibly stimulates descending inhibiting pathways stemming from the periaqueductal grey, and they may also block the NMDA receptor. In addition, opioid analgesia might be improved with concurrent TCA administration via a serotoninergic mechanism at the brainstem. Adverse effects of all TCAs include arrhythmia and anticholinergic/antihistamine effects, such as dry mouth, constipation, urinary retention, blurred vision, and sedation. Nortriptyline (a secondary amine) may be better tolerated than amitriptyline (a tertiary amine) because it has fewer anticholinergic side effects.

Dose recommendations are the same for both amitriptyline and nortriptyline. Both are available in liquid form and are usually started at 0.1 mg/kg by mouth at bedtime (adult dose 5 mg) and increased to a maximum of 0.4–0.5 mg (maximum 20–25 mg once at night). Experience has shown that increasing beyond that dose does not appear to result in increased analgesic effect. It may take 1–2 weeks to titrate up to an effective dose and to determine if the analgesic therapy is working; however, the induction of sleep will start much sooner. An electrocardiogram to rule out QTc-prolongation/Wolff–Parkinson–White syndrome prior to initiation is recommended.

**GABAPENTINOIDS**

Gabapentin, and to a lesser degree, pregabalin, are commonly used in pediatric neuropathic pain management. There have been no pediatric RCTs and only a few case reports published. In adults, a recent meta-analysis showed gabapentinoids to be efficacious in the control of neuropathic pain of various etiologies with a NNT of 2.9–3.9 [25]. Gabapentinoids are α-2-δ ligands, locking on a voltage-gated calcium-channel at the presynaptic nerve terminal (first neuron) at the level of the dorsal horn, resulting in decreased release of pain transmitters, such as glutamate, norepinephrine, and substance P. Adult data and pediatric experience suggest that a significant number of patients who experience inadequate analgesia from pregabalin benefit from gabapentin, and vice versa.

**GABAPENTIN**

An initial low starting dose is 2 mg/kg per dose (maximum 100 mg/dose) once at night titrated to 6 mg/kg per dose (maximum 300 mg/dose) TID. For
mild to medium neuropathic pain, the titration may take up to 2 weeks to avoid side effects. For severe pain, the titration may be significantly faster (1–3 days), if there is no onset of distressing side effects. If analgesia is inadequate, the dose may be titrated in steps up to 12 mg/kg per dose (maximum 600 mg/dose) TID, then up to 18 mg/kg per dose (maximum 900 mg/dose) TID, and finally up to 24 mg/kg per dose (maximum 1200 mg/dose) TID. Gabapentin (as oppose to pregabalin) has a non-linear bioavailability, meaning dose increases close to the maximum dose may have less of an effect. Side effects include lethargy, ataxia, nystagmus, dizziness, thought disorder, hallucinations, headache, peripheral edema, and myalgia; these side effects appear to be mitigated by slow dose escalation.

**PREGABALIN**

Pregabalin is approved for the treatment of neuropathic pain in adults [26]. It can be used when gabapentin is not effective or has intolerable side effects. Safety and efficacy are not established in pediatric patients and there is no accepted pediatric dosing. Experience and anecdotal evidence suggests the following for older children and teenagers: initial starting dose 0.5 mg/kg per dose (maximum 50 mg/dose) every HS slowly titrated to 1.5 mg/kg per dose (maximum 75 mg/dose) BID. For mild to medium neuropathic pain the titration may take up to 2 weeks to avoid side effects. For severe pain the titration may be significantly faster (2–3 days). If analgesia is inadequate, the dose may be titrated in steps up to 3 mg/kg per dose (maximum 150 mg/dose) BID, then up to 4.5 mg/kg per dose (maximum 225 mg/dose) BID, and finally up to 6 mg/kg per dose (maximum 300 mg/dose) BID.

Possible side effects of pregabalin include blurred vision, life-threatening angioedema (take precautions if prescribing angiotensin-converting enzyme inhibitors concurrently), dizziness, somnolence, and weight gain.

There is no overall evidence of superior efficacy for either gabapentin or pregabalin in a meta-analysis, although the lower cost may favor gabapentin. Conversion from gabapentin to pregabalin is around 6:1, meaning 300 mg gabapentin TID (= 900 mg/day) equals pregabalin 75 mg BID (=150 mg/day) [19]. To avoid pain or precipitating seizures, these anticonvulsants should be weaned over a period of 1–2 weeks.

As mentioned above, the efficacy of TCAs and gabapentinoids appears equal. If a single adjuvant appears ineffective and there are no contra indications in the individual child, a combination of a medication from each group is recommended as their mechanism of action is completely different.

**TOPICAL LIDOCAINE**

Experience has shown that the administration of a lidocaine 5% patch can be beneficial, especially if the neuropathic pain is localized. Lidocaine is a nonselective inhibitor of sodium channels, which have also been utilized to treat neuropathic pain. The lidocaine 5% patch appears effective in the management of adult neuropathic pain, including postherpetic neuralgia, painful diabetic neuropathy, painful idiopathic sensory polyneuropathy, non-postherpetic peripheral neuropathies, as well as osteoarthritis, and lower back pain. There are no pediatric RCTs and the data are conflicting in a recent adult meta-analysis [19]. The patch can be cut to fit, and worn for approximately 12 h on/12 h off. A contraindication would be severe hepatic dysfunction. Side effects include skin problems, such as irritation and redness.

**N-METHYL-D-ASPARTATE-CHANNEL BLOCKER**

NMDA channels might commonly be involved in the spinal neural circuitry that leads to a neuropathic pain state. At a normal resting level the NMDA-channel is blocked by magnesium. Increased excitation, including strong pain stimuli, may open the NMDA channel, producing hyper excitability of dorsal root neurons, leading to central sensitization (i.e., amplification of neural signaling within the CNS that elicits pain hypersensitivity), wind-up phenomenon, and memory of pain. NMDA-receptor antagonists, such as ketamine, methadone, and levophanol (possibly dextromethorphan and amantadine) – which block the channel – can help prevent this phenomenon, leading to decreased opioid resistance, improved hyperalgesia, and improved allodynia.

Ketamine is an NMDA-receptor antagonist, but it possesses other actions that may contribute to its analgesic effect, including a μ-opioid, δ-opioid and κ-opioid like effect, interactions with calcium and sodium channels, cholinergic transmission, and noradrenergic and serotonergic reuptake inhibition. Clinical experience has shown that ketamine is effective for pediatric neuropathic pain in low (i.e., sub-anesthetic) doses, either alone or, more commonly, in combination with opioids. Ketamine is unique among anesthetic agents in that it does not depress respiratory and cardiovascular systems. In low analgesic doses, the typical anesthetic-dose side effects of ketamine (nystagmus, lacrimation,
tachycardia, and altered sensorium) are not usually seen, though pediatric data are limited. Most pediatric centers schedule a low-dose benzo-diazepine during the ketamine administration to avoid psychomimetic side effects. There is evidence of significant opioid reduction in end-of-life pediatric cancer care after the initiation of low-dose ketamine [24,27]. The advantage of ketamine in comparison to other frequently used adjuvant analgesia, such as anticonvulsants or antidepressants, is its immediate onset of action.

Analgesic (subanesthetic) ketamine dosing includes the following: intravenous: 1–5 mcg/kg per min (= 0.06–0.3 mg/kg per hour); PO: 0.2–0.5 mg/kg TID–QID and PRN (as needed). Ketamine may also be administered subcutaneously, sublingually, intranasally, or per rectum or spinally. In the USA, ketamine is only available as a racemic mixture [S(+)-enantiomer (providing analgesia, general anesthesia); R(−)-enantiomer (causing bronchodilatation, nightmares)]. In most other countries, ketamine-S [S(+)-enantiomer] is also available, reducing the required dose by 40–50%.

OTHER ADJUVANTS

Groups of medications, which might be considered for refractory neuropathic pain in children with cancer, include the following.

Benzodiazepines such as diazepam, midazolam, and lorazepam can aid in the treatment of pain of multiple causes; particularly when the pain is worsened by anxiety or difficulty in sleeping.

A sodium-channel blocker that is effective for neuropathic pain includes intravenous lidocaine. There is limited pediatric experience in the use of intravenous lidocaine. A case series showed it was effective after anti-GD2 antibody therapy in children with neuroblastoma, at a dose of 1 mg/kg per hour [28,29]. Published dose recommendation for lidocaine for neuropathic pain includes 1 mg/kg over 5 min or 2 mg/kg over 30 min, then 1 mg/h - target: 2–5 mcg/ml [28,30]. Side effects of intravenous lidocaine include allergic reaction (serious, but rare), and dose-related numbness around the mouth, dizziness, slurring of speech, hallucinations, muscle twitches, and seizures [31].

α-2-Adrenergic agonists such as clonidine or dexmedetomidine can be effective adjuvant analgesics for both nociceptive and neuropathic pain in our experience. They act at the spinal cord in two ways. First, they act on the same neurons in the cord and lead to the same intracellular events as opioids, but act through a different receptor; 2-adrenergic and opioid receptors activate the same potassium channel via inhibitory G proteins. Thus, it is likely that they enhance the antinociceptive effects of opioids. Second, α-2-adrenergic agonists decrease sympathetic outflow involved with neuropathic pain and hyper arousal. Clonidine can be given orally, transdermally, or intraspinally. Side effects include sedation, dry mouth, and hypotension. Dexmedetomidine can also be an effective adjuvant, leading to opioid-sparing. It carries the advantage of not affecting respiration. However, potential side effects include hypotension and bradycardia. Dose recommendations: dexmedetomidine (0.3–2 mcg/kg per hour intravenous); Clonidine (starting dose 1–3 mcg/kg dose QHS (once a night) to every 6 h titrated to effect PO or transdermal).

SELECTIVE SEROTONIN REUPTAKE INHIBITORS/SELECTIVE NOREPINEPHRINE RE-UPTAKE INHIBITORS

Newer atypical antidepressants (e.g., selective nor-epinephrine re-uptake inhibitors such as venlafaxine and duloxetine) show some evidence of efficacy for treating neuropathic pain but they have not been well studied. In addition, there is little evidence to support their efficacy in treating pediatric depression. Studies have shown SSRIIs to be much less effective in treating pain and are not recommended for the treatment of neuropathic pain: Finnerup et al. [19] (2010) stated that the ‘clinical relevance of these compounds is questionable’.

CANNABIS

Activation of the endocannabinoid system suppresses behavioral responses to acute and persistent noxious stimulation through central and peripheral mechanisms [32,33]. Cannabinoid receptors exist in the periaqueductal gray area, rostral ventromedial medulla, and dorsal horn of the spinal cord. In animal experiments, cannabinoids produce analgesia and potentiate opioids, particularly in neuropathic pain [34–36]. There are over 60 active compounds extracted from cannabis. Delta-9-tetrahydrocannabinol (THC) (dronabinol, nabilone) does not fully replicate the effect of total cannabis preparation [37]. Cannabis sativa extract (oromucosal pump spray) is composed of both D-9-THC and cannabidiol in a 1 : 1 ratio. Cannabis sativa extract is approved for use in Canada for multiple sclerosis patients with neuropathic pain [38]. Adult meta-analytic data show there is a modest effect on central pain in multiple sclerosis (two RCTs), pain relief for peripheral neuropathic pain (three RCTs), lack of pain relief for polyneuropathy (one small RCT), and superiority of smoked cannabis compared with
placebo in HIV neuropathy (three RCTs) [19]. There are no published pediatric studies. Persistent cannabis users show neuropsychological decline from childhood to midlife [39] and in our clinical practice we do not support the use of marijuana for pain control in children and teenagers with neuropathic cancer pain, mostly because the above mentioned pharmacological and nonpharmacological strategies seem to be effective, combined with our clinical experience that usually teenagers with a history of nonadherence to medical recommendations tend to request marijuana.

### REVIEW OF RECENT LITERATURE

A MEDLINE search of recent publications (January 2011 to February 2013) on the topic of neuropathic pediatric cancer pain revealed six articles; none was an RCT.

In a retrospective analysis of 99 pediatric neuroblastoma patients with spinal cord compression, neuropathic pain—among other distressing symptoms—was present in 56% of the cases. After a median observation time of 8 years, 17% of the initial group still reported impaired cutaneous sensitivity and 5% reported neuropathic pain without any clear demonstrated advantage of either first-line neurosurgery or chemotherapy [40**].

A retrospective, single-institution review of pediatric cancer patients over 5 years ($n = 41$) reported that methadone (39% for neuropathic pain) was effective in treating both neuropathic and nociceptive pain that was unresponsive to other opioids [41].

A case report of a 5-year-old girl who was diagnosed with meningitis caused by malignant T-cell lymphoma and difficult to treat neuropathic pain reported that her pain was not relieved by low doses of a fentanyl infusion (0.8 mcg/kg per hour). Intravenous administration of lidocaine (9.3–14 mcg/kg per minute), followed later by ketamine (2 mcg/kg per minute) in combination with fentanyl, provided good analgesia without significant side effects for the last 20 days of her life [42].

A case report of a 3-year-old child with intractable trigeminal neuropathic pain caused by a malignant glioma that was treated with resection, followed by radiotherapy and chemotherapy, discussed successful use of motor cortex stimulation, which provided a 75% reduction in the child’s pain 48 h postoperatively, continuing until the child was pain-free [43].

A retrospective, single-institution review of pediatric patients during a 26-year window revealed a complex pain syndrome of mixed nociceptive and neuropathic pain following limb-sparing surgery for bone cancer ($n = 151$). Therapies included opioids, NSAIDs, acetaminophen-opioid combinations, postoperative continuous epidural infusion, anticonvulsants, and TCAs for neuropathic pain, local anesthetic wound catheters, and continuous peripheral nerve block catheters [44].

A retrospective, single-institution review of pediatric patients who presented with acute lymphoblastic leukemia during a 20-year timeframe ($n = 498$) revealed that 35% of the sample experienced vincristine-associated neuropathic pain. No statistically significant relation between the severity of the neuropathic episode and the cumulative dose of vincristine was found. There was no evidence gabapentin prevented recurrence of neuropathic pain at a mean dose of 15.5 mg/kg per day. However, as the usual maximum dose is 50–70 mg/kg per day, that dose may have been too low to show effect [45].

### CONCLUSION

There is a high prevalence of neuropathic pain in children with cancer. Neuropathic pain is often underassessed and undertreated with ineffective therapies. Although there are few studies in children to guide practice, neuropathic pain in children with cancer can be managed through the application of careful assessment combined with pharmacologic and nonpharmacologic strategies. NSAIDs, opioids, as well as gabapentin and amitriptyline/nortriptyline, are often reliable first-line agents. Integrative and rehabilitative therapies are an essential part of a successful treatment protocol.

### Acknowledgements

None.

### Conflicts of interest

The authors declare no conflicts of interest.

### REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 229–230).

41. The authors retrospectively analyzed the long-term effects of symptoms associated with spinal cord compression in clinical trial patients with neuroblastoma. Long-term residual neurological effects are described for patients who underwent first-line neurosurgery or chemotherapy.
43. The authors of this retrospective chart review describe the effectiveness and side effects associated with methadone use for treating children with cancer-related neuropathic and nociceptive pain.