Oxford Textbook of Palliative Care for Children (3 edn)

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Previous Edition (2 ed.)

Publisher: Oxford University Press
Print ISBN-13: 9780198821311
DOI: 10.1093/med/9780198821311.001.0001

Print Publication Date: Jul 2021
Published online: Jul 2021

Difficult pain: Adjuvants or co-analgesics

Chapter: Difficult pain: Adjuvants or co-analgesics

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DOI: 10.1093/med/9780198821311.003.0019

Introduction

A common reason that pain is difficult to treat—perhaps the most common—is that its physical components are relatively minor contributors to the patient's 'total' experience of pain. The child's own existential suffering must always be considered in the evaluation of refractory symptoms. The suffering of families can be expressed through frequent requests of breakthrough medications on behalf of the child, and such distressed behaviour may inappropriately influence clinical decision-making, leading to increases in opioid dose that are not indicated and so risk causing unnecessary toxicity (3).

It is nevertheless possible to describe several clusters of clinical symptoms that can characterize a patient's pain and indicate that management is likely to need more than general-purpose analgesics such as opioids. Identifying a patient's pain syndrome by forming a clear understanding of the clinical scenario in combination with careful,

detailed assessment, and measurement of pain is important for both diagnosis and treatment. Establishing the aetiology of pain is important. Pain in children with life-limiting conditions (LLC) is often multifactorial, however, involving a combination of nociceptive and neuropathic features as a result of multiple pathologies. Increasing survivorship from conditions that previously would have proved fatal means the management of pain is now influenced by developments in understanding of genomics, plasticity, and the response to painful stimuli in a preexisting damaged nervous system, all of which can be involved in the individual child's own unique experience of pain. At the same time, concern about rare adverse effects of opioids such as hyperalgesia and central sensitization can contribute to the complexity of pain management in the child.

As biomolecular knowledge and evidence grows to support theories regarding complex neuro-immune mediated inflammatory and neuropathic pain processes it highlights the increasing potential for pain modulation. There remains, however, a substantial gap between such theoretical advances and robust evidence of positive clinical outcomes in analgesic interventions for children (2).

Combination pharmacotherapy

Combinations of medication are often useful in clinical practice, especially where there has been only a partial response to maximum tolerable doses of a single drug (3). The theoretical rationale for drug combinations is often difficult to support empirically because of the difficulty of studies in the small population of children needing palliative care. Pain relief might hypothetically be enhanced through combining pharmacologic interventions to target different receptors along the nociceptive pathway. Opioids, anticonvulsants, non-steroidal anti-inflammatory drugs with local anaesthetic agents can all relieve cancer pain, which may be complex and combine bone, deep tissue, and neuropathic elements. A multimodal approach is effective in relieving difficult pain.

In this chapter, different pain syndromes and associated challenging pain issues are considered in relation to pharmacotherapy and interventional pain management. In the reality of clinical practice, these pain syndromes often coexist in children with LLCs. The interplay offers the clinician diagnostic challenge and illustrates the need for a comprehensive and integrated approach in order to manage pain effectively.

Neuropathic pain

Neuropathic pain may be a symptom of neurological disease, or it may be a distinct disease entity in itself (e.g. post-herpetic neuralgia). Neuropathic pain can be particularly severe and disabling. Adult patients with neuropathic pain seem to have higher pain scores and lower health-related quality of life than patients with other pain syndromes, to require

more medications, and to report less pain relief with treatments (4). Typically, there are limited response rates to medications, with often only a partial reduction in neuropathic pain at tolerable doses.

Neuropathic pain is mechanistically distinct from other pain conditions. Conditions that have driven the research base in adults are peripheral diabetic neuropathy, radiculopathy, and post-herpetic neuralgia. All are rare in children, and the scientific basis of paediatric neuropathic pain is significantly less well understood than that of adults. There are important reasons for believing that children differ from adults when considering neuropathic pain states. Rodent models have highlighted some intriguing aspects of chemotherapy induced neuropathic pain, such as mechanical hypersensitivity that is considerably slow to emerge, in marked contrast to the rapid onset chemotherapy induced adult rodent neuropathic pain profile (5). The brain of the infant or child is specialized for rapid development; it is more 'plastic' than the adult brain and retains the ability to recover after injury. Normal development and central nervous system (CNS) plasticity in children strongly pull towards normalcy, and perhaps merely the passing of time has a strong influence on neuropathic pain behaviour.

Clinical characteristics of neuropathic pain

Central to the definition of neuropathic pain is that it is the nerves themselves that are damaged or functioning abnormally. The International Association for the Study of Pain (ISAP) Special Interest Group on Neuropathic Pain (NeuPSIG) proposed the most widely accepted neuropathic pain definition (6) as '*pain arising as a direct consequence of a lesion or disease affecting the somatosensory system*'. It is one of the normal functions of nerves to mediate pain, so the experience of pain is not in itself evidence that nerve damage is the cause. Neuropathic pain needs to be distinguished, for example, from the pain of muscle spasticity and rigidity (mediated by activation of nociceptive afferents from muscle), or pain from excessive vasoconstriction leading to tissue hypoxia and activation of chemo-sensitive nociceptors. Such pain is mediated by a normally functioning somatosensory system and so would not constitute neuropathic pain according to the NeuPSIG definition. Neuropathic pain needs to be carefully explicated from physiological neuroplasticity; that is, the inherent capacity of the nervous system to adapt in response to strong nociceptive stimulation. That sort of central sensitization too is part of the normal functioning of nerves.

Although if nerve damage is extensive enough there might be some motor dysfunction, it is sensory deficit or other abnormal sensation that provides the hallmark of peripheral neuropathic pain. Maximum pain is typically within, or even coextensive with, the area of sensory deficit. Abnormal sensation (dysaesthesia) ranges from numbness or absence of feeling (hypoaesthesia) to abnormal non-painful sensations such as numbness and tingling (paraesthesia), or burning, tingling, or electrical

shock sensations. Clinically, simple touch can become a painful stimulus (allodynia), painful responses may be magnified (hyperalgesia), and responses to relatively innocuous stimuli are prolonged and exaggerated (hyperpathia). A distinction is often made between positive symptoms of abnormal sensation, and negative symptoms of decreased sensation (see Table 19.1) (7). In the non-communicating child, allodynia may be manifest as obscure changes in behaviour pattern, such as distress whilst brushing hair or wearing socks. It may also be a cause of ‘screaming of unknown origin’ or ‘neuro-irritability’.

Table 19.1 Common features suggestive of neuropathic pain

Term	**Definition**
Symptoms	
Paraesthesias	Non-painful positive sensations (formication —‘ants crawling’, ‘tingling’)
Burning pain	Frequent quality of spontaneous pain sensations
Shooting pain	Spontaneous or evoked intense pain sensation of several seconds’ duration
Signs	
Hypoesthesia	Impaired sensitivity to a stimulus
Tactile hypoesthesia	Impaired sensitivity to tactile stimuli
Cold hypoesthesia	Impaired sensitivity to cold stimuli
Hypoalgesia	Impaired sensitivity to a normally painful stimulus
Hyperalgesia	Increased pain sensitivity (may include a decrease in threshold and an increase in supra-threshold response)
Punctate hyperalgesia	Hyperalgesia to punctate stimuli (e.g. a pinprick)
Static hyperalgesia	Hyperalgesia to blunt pressure

Heat hyperalgesia	Hyperalgesia to heat stimuli
Cold hyperalgesia	Hyperalgesia to cold stimuli
Allodynia	Pain due to a non-nociceptive stimulus

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If available, the patient's own description provides the best indication that the pain may be of neuropathic origin. The child may describe numbness, itching, tingling, or unusual 'crawling', and/or burning sensations. Some may use their own expressions to describe the sensations, such as 'shivering', 'fizzing', 'prickling', 'tickling', and 'pins and needles'.

Assessment

Pain assessment in children generally is discussed in Chapter 16, 'Introduction to pain' of this book. Although there are well-validated specific tools for assessing neuropathic pain, they are all in adults or children with chemotherapy-induced peripheral neuropathy (8).

It is particularly challenging to confirm somatosensory damage in the infant or child although neurophysiological techniques and quantitative sensory testing (QST) are starting to be explored. A recent European study of thirty cerebral palsy patients (aged 6–20 years without intellectual impairment) suffering from chronic pain, demonstrated, using QST, a combination of mechanical hypoaesthesia, thermal hypoaesthesia, and mechanical hyperalgesia associated with neuronal dysfunction in the thalamic area, likely due to a history of periventricular leukomalcia (9). Furthermore, focus on phenotypic subgrouping of paediatric patients is extremely important as it has the potential to support more relevant, specific clinical trials and lead to personalized pain therapy (Figure **19.1**).

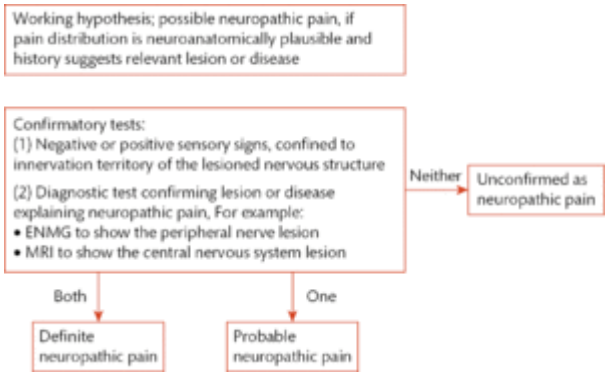

Figure 19.1
Once a careful history and examination have linked the initial damage with the subsequent development of pain, the pain complaint may be termed ‘possible’ neuropathic pain. Increased certainty regarding the ‘definite’ or ‘probable’ presence of neuropathic pain requires confirmatory evidence from a neurological examination or confirmatory tests

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Pathophysiology

Any damage to the somatosensory system presents a potential risk of the development of neuropathic pain. Such damage can range from simple nerve severance to complex genetic disorders that compromise axonal transport due to disordered neuro-processing at the molecular level. Lesions that cause neuropathic pain have a diverse aetiology, and include infection, trauma, surgery, chemotherapy, radiation, neurotoxins, tumour infiltration, and nerve compression. The causal injury may be focal or diffuse, mild or severe, may involve single or multiple distinct processes (inflammatory, metabolic, mechanical, and/or vascular), and may occur at any level of the somatosensory system.

Multiple pathological modalities giving rise to neuropathic pain syndromes may be encountered in paediatric palliative care practice. The physician may need to think laterally when considering this diagnosis (e.g. the child with unstable kyphoscoliosis and vertebral instability compromising the spinal cord and nerve roots, or the population of infants and children with neurometabolic conditions and white matter

anomalies that may cause lesions or disordered processing within the nervous system) (Box 19.1).

Box 19.1 LLCs in children that might be associated with neuropathic pain

- Effects of cancer disease processes and their treatment
- Spinal cord injury
- Hereditary neurodegenerative disorders
- Mitochondrial disorders neuronal migration disorders post-surgery, human immunodeficiency virus /acquired immunodeficiency syndrome (HIV/AIDS).

Treatment

Several professional bodies have proposed guidelines for the treatment of neuropathic pain (10). There have been large numbers of randomized controlled trials (RTCs) in adults, but nevertheless no consensus is well-supported by evidence. Most RCTs have included patients with either painful diabetic neuropathy or post-herpetic neuralgia (peripheral neuropathies), and many RCTs have been of short duration (usually less than 3 months), whereas neuropathic pain in palliative care is typically of long duration. There have been few head-to-head trials comparing different treatments that might offer direct comparison of the efficacy, safety, and tolerability of treatments; and ranking choices of medication is challenging. Furthermore, there is considerable variation in study design, and different outcome measures have been utilized, making it difficult to make valid comparisons between them. Summary estimates of efficacy, such as the number needed to treat (NNT) are generally reliable but may not be accurate if they are derived from pooling of data across patients with different neuropathic pain syndromes and using agents with different mechanisms of action.

Current advice in adults (see Box 19.2) is to base the choice of medication on an individual patient whilst considering other parameters such as adverse effect profile of drug, comorbidities such as depression and sleep disorders, and drug interactions. The assumption is made that these principles and treatment modalities can be extrapolated across differing conditions and that they are appropriate in the paediatric population.

Box 19.2 Stepwise pharmacological management of neuropathic pain in children

Step 1

- Assess pain and establish the diagnosis of NP; consider investigations; if uncertain about the diagnosis, refer to a pain specialist or neurologist.
- Establish and treat the cause of NP; if uncertain about availability of treatments for cause of NP, refer to appropriate specialist
- Identify relevant comorbidities (e.g. cardiac, renal, or hepatic disease, sleep disturbance, seizures, polypharmacy) that might be relieved or exacerbated by NP treatment or that might require dosage adjustment or additional monitoring of therapy
- Explain the diagnosis and treatment plan to the patient and carers; establish realistic expectations

Step 2

- Initiate therapy for the disease causing NP, if applicable
- Initiate symptom treatment with one or more of the following: A TCA (Amitriptyline nortriptyline) (*consider ECG with Amitriptyline usage) or A calcium channel a2-d ligand, either gabapentin or pregabalin
- For patients with localized peripheral NP, topical lidocaine used alone or in combination with one of the other first-line therapies
- For patients with acute NP, neuropathic cancer pain, or episodic exacerbations of severe pain and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or may be used alone or in combination with 1 of the first-line therapies
- Evaluate patient for nonpharmacological treatments and initiate if appropriate

Step 3

- Reassess pain and health-related quality of life frequently
- If substantial pain relief (e.g. average pain reduced to ≤3/10; improved patterns of behaviour and sleep) and tolerable adverse effects continue treatment
- If partial pain relief (e.g. average pain remains ≥4/10; inconsistent behavioural improvement and partial affects) after an adequate trial, add one of the other first-line medications

- If no or inadequate pain relief (e.g. <30% reduction; little or no behavioural improvement; sleep patterns much the same) at target dosage after an adequate trial, switch to an alternative first-line medication

Step 4

- If trials of first-line medications alone and in combination fail, consider second- and third-line medications or referral to a pain specialist or multidisciplinary pain centre
- Second line medication in adolescents and children may include Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)
- Continue monitoring pain behaviours and side effects; consider tapering opioids when first line therapies are titrated, and pain improved. Regular monitoring of medication dosage: weight.

NP = neuropathic pain; TCA = tricyclic antidepressant.

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There is relatively little empirical evidence to inform management of neuropathic pain in the paediatric population (11). The mainstay of pharmacological management of neuropathic pain in children is the use of antidepressants and anticonvulsant drugs. Their effectiveness is variable for reasons that include the broad mechanism of action of first line agents and the multiple pathophysiological mechanisms involved which cannot easily be targeted by a single agent. More recent studies have attempted to identify specific responder profiles using prespecified phenotypic profiling based on questionnaires and/or QST (12). Clinical advances in this field will be determined by the validation of specific clinical assessment tools and identifying the QST paradigms facilitating characterization of these syndromes in children.

Opioids

It is commonly thought that opioids are ineffective in the management of neuropathic pain. That is not true. The analgesic potency of opioids is such that they are powerfully effective in the treatment of neuropathic pain, as they are in most types of physical pain. It is true, however, that neuropathic pain is more likely than other types of pain to be only partially responsive to opioids alone. As always, suitable co-analgesics (adjuvants) should be instituted as soon as a diagnosis of neuropathic pain is made. Those include antidepressants, anticonvulsants, N-methyl

D-Aspartate (NMDA) antagonists, as well as a range of other systemic and topical agents.

Antidepressants

In adults, there is good evidence that antidepressants such as tricyclic antidepressants (TCAs) and the serotonin and noradrenaline reuptake inhibitors (SNRIs) are effective in a range of neuropathic pain states. Their pain-relieving effects are independent of any antidepressant effect and they are effective in the absence of depression.

Tricyclic antidepressants (TCAs)

TCAs have been shown to relieve various neuropathic symptoms, although a Cochrane review of antidepressants for chronic non-cancer pain in children and adolescents found insufficient evidence to support or refute their use in non-malignant chronic pain (14).

The most commonly used and most widely studied agent is amitriptyline, which is a tertiary amine TCA. Other tertiary agents in use include imipramine and doxepin, while secondary amines include desipramine and nortriptyline. These drugs are generally well-absorbed from the gastrointestinal tract, reach peak plasma levels after 2–8 hours, and have long half-lives. This makes them ideal for once daily dosing at night in order to accommodate or even to exploit their sedative side effect. They are lipophilic, strongly protein bound, and widely distributed to the brain and other organs.

The mechanism of action of TCAs is not fully understood, but is likely to involve their multimodal activity, particularly inhibition of pre-synaptic reuptake of noradrenaline and serotonin, and an inhibitory action on sodium-channel activity. Blockage of the reuptake of serotonin and noradrenaline augments endogenous analgesia—suppressing pathways descending from the brainstem. In addition, these drugs block voltage-dependent calcium channels and NMDA receptors, which may also contribute to their analgesic effect. Blockade of postsynaptic adrenergic, histaminergic, and muscarinic cholinergic receptors causes the well-known side effects of the TCAs.

Adverse dose-limiting side effects are common during therapy and there is genetic polymorphism of the enzymes that metabolize TCAs, which can result in significant pharmacokinetic variability. TCAs are contraindicated in patients with epilepsy (these agents lower seizure threshold), heart failure, or cardiac conduction block. An ECG is recommended, particularly if long-term use is anticipated. Initiation of treatment is best done slowly, titrating the dose upwards every 3–7 days while monitoring effect and tolerability.

Selective serotinin reuptake inhibitors (SSRI) and serotonin and noradrenaline reuptake inhibitors (SNRI)

SSRI and SNRI inhibit serotonin and noradrenaline reuptake. SSNRIs are not usually considered first-line treatment for paediatric pain syndromes, although RCTs in adults suggest that duloxetine and venlafaxine are effective in adult patients with painful peripheral neuropathy. They are generally well-tolerated, although reported adverse effects include nausea (common), dry mouth, headache, dizziness, reduced appetite, somnolence, and insomnia. There is little information about their use in children and a reason for caution is that when used to treat anxiety and depression in young adults their use is associated with an increased risk of suicidal thoughts.

Anticonvulsants

The CNS exists in a state of equilibrium that represents a balance between excitability and inhibition. Excessive neuronal activity, such as with damage to the somatosensory system, may result in a shift of this equilibrium. Although different mechanisms result in neuropathic pain, the latter is generally considered to be a consequence of excessive or inappropriate neuronal activity. Epileptic medications have several pharmacological actions that either decrease excitatory transmission or increase inhibitory transmission, thereby resulting in an overall depressant effect. It is thought that these effects underpin the analgesic properties shown by some anticonvulsant medications in neuropathic pain states (Box 19.3).

Box 19.3 Hypothetical mechanisms for anticonvulsants in neuropathic pain

- Calcium-channel modulation (gabapentinoids)
- Prolonged inactivation of the sodium channel (carbamazepine, phenytoin, lamotrigine, topirimate, valproic acid)
- Prolonged activation of the chloride channel through the γ-aminobutyric acid (GABA) receptor (vigabatrin, topirimate, valproate)
- Prolonged activation of the chloride channel as a direct effect on the channel (barbiturates, benzodiazepines).

Gabapentinoids

Gabapentin and pregabalin are structurally related compounds that have been shown in some (though not all) RCTs to be efficacious in a range of neuropathic pain conditions. Pregabalin is an analogue of gabapentin and

has the same mechanism of action. Both drugs bind to the pre-synaptic α2-δ subunit of voltage-gated calcium channels in the dorsal horn, reducing the release of neuroexcitatory transmitters. Kinetics of the two compounds are different, however, in ways that might be clinically relevant. Gabapentin enteral absorption is limited to the small bowel while pregabalin is absorbed in the small bowel and ascending colon. The absorption of gabapentin is saturable, so that the relationship between oral dose and serum concentration is less predictable than that of pregabalin. The bioavailability of pregabalin is higher than that of gabapentin. Pregabalin has a higher affinity for the pre-synaptic calcium channel. It is more potent, has a shorter titration period, and in adults appears to provide analgesia more rapidly than gabapentin.

Although there is relatively little evidence in children, several published reviews and case reports indicate that gabapentin is effective in neuropathic pain in children and neonates. Gabapentinoids show few drug interactions but the dose should be reduced in patients with renal insufficiency. In general, gabapentinoids are well-tolerated by children. They have, however, been associated with a number of adverse effects including somnolence, nausea and vomiting, and behavioural or neuropsychiatric adverse effects that include emotional labiality, hostility or aggression, restlessness or hyperactivity, and thought disorders such as difficulty in concentrating and poor school performance. The behavioural effects are mild to moderate in severity and a reduction in dose produces resolution of symptoms in most patients. Children with pre-existing attention deficit disorder, developmental delays, or other learning disabilities are more likely to experience these adverse effects.

Both gabapentin and pregabalin require titration (both up and down) to find the optimal dose that is effective but tolerable. Starting and discontinuation of therapy can both be associated with unpleasant symptoms. There is no overall evidence for the superiority of either drug in the management of neuropathic pain, although the lower cost of and familiarity with gabapentin, particularly in paediatric patients, may lead clinicians to prefer it.

Carbamazepine

Although carbamazepine is effective in the treatment of trigeminal neuralgia, randomized controlled trials performed in other neuropathic pain states have been of variable quality and produced mixed results. Guidelines state that carbamazepine is no longer recommended for the treatment of neuropathic pain.

N-methyl-D-aspartate (NMDA) receptor antagonists

NMDA receptor antagonists have a potential role in the management of diverse neuropathic pain syndromes, including central and peripheral neuropathic pain, inflammatory pain, phantom limb pain, and peripheral vascular disease.

Methadone

Methadone is an opioid analgesic with additional multimodal pharmacological action. Methadone is a synthetic opioid with NMDA antagonist activity whose activity is mediated by acting as a mu receptor agonist, with additional activity against kappa and delta opioid receptors. Its pharmacokinetic complexity has led to methadone being '*underused misunderstood, and feared by many professionals including palliative care providers*' (14). Providing it is commenced carefully and with appropriate precautions, however, methadone is a safe and effective medication with unique characteristics that give it an important place in management of difficult pain.

Methadone possesses a long and unpredictable duration of action as a result of its high lipid solubility and its long half-life. An unusual feature of methadone pharmacokinetics is the 'secondary peak' phenomenon. When methadone is given occasionally or at low doses it distributes into fat as well as into serum. After a few days of repeated or high doses, however, the fat becomes saturated and methadone suddenly distributes only into serum. At that point, the relationship between the dose of methadone that the patient takes, and the serum concentration that results, becomes unpredictably quite different.

As a result, there is no consistent conversion ratio between morphine and methadone and, unlike most opioids, the potency of methadone cannot easily be expressed as an equivalent to oral morphine. A high pre-switch opioid dose, in particular, does not necessarily warrant a high dose of methadone. Rotation to regular methadone from other opioids is complex and unpredictable. In view of the real (though small) risk of sudden death from toxic serum concentrations, starting regular methadone ideally requires in-patient admission or extremely close supervision in the community. The same is not true of methadone given 'as needed' because under those circumstances the patient takes methadone only when serum concentrations have fallen to a level that is sub-therapeutic and, by the same token, to a level that is safe.

Methadone is an effective opioid in its own right, but its unpredictability when used regularly means that in practice it is usually reserved for 'breakthrough' pain (especially when neuropathic) alongside background treatment with more conventional opioids such fentanyl or morphine. Methadone is also sometimes used as an alternative to fentanyl or buprenorphine in patients who have end stage renal failure.

A recent study of intravenous (IV) methadone use in sickle cell disease suggested that children may metabolize methadone slightly quicker than adult counterparts (17). Compared with other opioid agonists a unique side effect of methadone is that it can cause prolongation of the interval seen in an electrocardiogram, (QT) interval, with theoretical risk of sudden death. A small retrospective paediatric study demonstrated

prolonged QT in 16% of patients but this was only significant in one patient with pre-existing comorbidities (18).

Ketamine

Ketamine is a phencyclidine derivative that binds with high affinity (and therefore non-competitively) to the NMDA receptor in the CNS. It is often used in dissociative anaesthesia, during which ketamine acts by activating the limbic system and depressing the cerebral cortex. At sub-anaesthetic ketamine is analgesic without reduction in consciousness, although cognition can sometimes be affected and psychomimetic adverse effects such as hallucinations are relatively common.

Oral and intravenous ketamine are used for cancer pain management in adult and paediatric patients, often by administering the intravenous preparation or specially prepared syrup by mouth. Ketamine is frequently used as an analgesic alongside opioids in patient and nurse-controlled analgesia pumps in infants and children and is associated with lower scores in post-operative pain. Conversion of ketamine dosage from parenteral to enteral is complicated. Analgesic effects following oral administration are seen after 30 minutes, with a half-life of 1–3 hours. Usual recommendations are that oral doses should be the same or, paradoxically, less than parenteral doses. The explanation may be that there is significant enterohepatic circulation of ketamine and that its main metabolite, norketamine, has inherent analgesic activity. Ketamine is highly lipid soluble and so its access to the CNS is largely unimpeded.

A recent meta-analysis found moderate evidence favoring the use of ketamine in chronic intractable (non-cancer) pain in adults but made no clear recommendations concerning indications and dosages as studies need to be undertaken with more precisely defined target populations and management regimes (19).

Ketamine a homologue of phencyclidine and shares with it the risk of unpleasant psychomimetic effects, such as vivid dreams, hallucinations, confusion, delirium, and feelings of detachment from the body. Those are easy for clinicians to miss, particularly in young and nonverbal children. These side effects are, however, less likely in lower ketamine doses, in children under the age of 16 years, and if ketamine is administered slowly. If they do occur, ketamine should ideally be discontinued, but if it is thought to be essential its unpleasant side effects can often be countered with additional medications such as benzodiazepines or haloperidol.

Other systemic co-analgesics (adjuvants)

Corticosteroids

Endogenous steroid is known to control the development, growth, maturation, differentiation, and plasticity of the nervous system. Clinical evidence suggests that corticosteroids may be effective co-analgesics in

neuropathic pain. The theoretical basis for this remains unclear. Steroids are, however, known to inhibit the expression of collagenase and pro-inflammatory cytokines, thereby inducing anti-inflammatory actions in damaged peripheral or central tissues.

The efficacy of corticosteroids is reported in reflex sympathetic dystrophy, arthralgia, and diverse types of cancer pain, including bone pain, neuropathic pain from tumour infiltration, or compression of neurological structures, headaches due to raised intracranial pressure, and bowel obstruction. Despite being commonly used in cancer pain there is little data supporting efficacy and a recent systematic review concluded that evidence for pain control in cancer patients is weak however data sources were variable.

Various corticosteroids are available, but those with minimal salt-retaining properties, such as prednisolone and dexamethasone, are preferable for clinical use. Dexamethasone has a relative potency twenty-five times that of cortisone, and a biological half-life of 36–54 hours, suggesting that once or at most twice daily dosing is required. A second dose in the early afternoon may reduce the neuropsychiatric side effects and poor sleep patterns observed with night-time dosing.

The adverse effects of corticosteroids are well-recognized and include gastrointestinal disturbance, hyperglycaemia, myopathy, immunosuppression, and cushingoid habitus. In children, neuropsychological effects can be particularly distressing, ranging from changes in mood and behaviour to impaired cognitive function, hyperactivity, and frank psychosis. This does not seem to be a predictable linear dose response. The progressive distortion of a child’s physical appearance and low, irritable mood should not be underestimated by clinicians; it can have a significant negative effect, especially on the body-image-conscious adolescent or young child, and cautious prescribing is necessary.

There is no published evidence to inform the optimum way to use steroids for this indication. Current clinical practice is usually to use the lowest-dose of steroid that will be effective for the shortest duration. Steroids are given as a brief intense 3–5-day course, repeated as symptoms dictate. A large single dose can often help to relieve a severe pain crisis.

Clonidine

Clonidine is an α2-adrenoceptor agonist that has sedative, anxiolytic, and analgesic sparing effects. It is approved for treatment of hypertension but is also a useful medication for treatment of intractable pain and pain secondary to muscle spasm. Clonidine is available as a transcutaneous patch, making it a useful co-analgesic (adjuvant) when gastrointestinal function is compromised, or the enteral route is not available.

Dexmedetomidine

Dexmedetomidine is a highly selective α2 adrenergic receptor antagonist with sedative, anxiolytic, and analgesic properties used in children in the intensive and peri-operative care setting as a sedative that does not cause respiratory depression. Dexmedetomidine is administered via the intravenous or intranasal routes. In recent case series dexmedetomidine reduced pain scores and opioid requirement in children and adolescents with difficult cancer pain and as a co-analgesic during painful immunotherapy treatment in children with neuroblastoma (20). Although dexmedetomidine can cause bradycardia and hypotension, it is likely to play an important role in paediatric pain management in the future.

Baclofen

Baclofen is an agonist at the γ-aminobutyric acid type B (GABAB) receptor. It is effective in the treatment of trigeminal neuralgia in the adult population and is considered a third-line co-analgesic (adjuvant) in neuropathic pain. Titration from a low dose is necessary until positive effects occur or side effects prevail. In children, tolerability can be limited by excess sedation, central hypotonia, constipation, and drooling. Serious withdrawal syndrome on abrupt discontinuation (including delirium and seizures) can be avoided by adopting a slow tapering protocol.

Botulinum toxin type A

There is good evidence for use the use of Botulinum toxin in treating specific chronic neuropathic pain conditions through reduction in hyperalgesia (23). As botulinum toxin type A already has a good safety profile in children for the treatment of spasticity, this is an interesting area of development for the paediatric patient. When adult patients with neuropathic pain received intradermal injections once in the affected area, it was found that subsequent analgesia lasted for 12 weeks. However, large-scale trials are required to assess the value of botulinum toxin type A for clinical practice.

Cannabinoids

Cannabinoids have been shown to reduce central pain in multiple sclerosis and human immunodeficiency virus (HIV) encephalopathy. As evidence for their effectiveness as accumulated, many legislatures have begun to permit some cannabinoids to be prescribed for a range of indications that includes some forms of pain. The psychoactive component of medical cannabinoids is tetrahydrocannabinol (THC) which is a partial agonist at endogenous cannabinoid receptors. A second pharmacologically active component is cannabidiol (CBD), which is not thought to be significantly psychoactive and has little or no action at cannabinoid receptors. Its effect appears to be mediated through other receptors or by inhibiting breakdown of endogenous cannabinoids.

Cannabinoids, particularly CBD, hold out some promise that in the future the medical benefits of naturally occurring cannabinoids could be offered without their psychoactive adverse effects. A recent systematic review of medical cannabinoids in children and adolescents, however, concluded that there is currently insufficient data to support their use in neuropathic pain (24). Cannabinoids interact powerfully and potentially dangerously with a wide range of medications that children with LLCs are likely to be taking. As enthusiasm for the possible benefits of cannabinoids continues to outstrip available evidence for their safety and efficacy, many families are choosing to self-medicate with cannabinoid products. Clinicians should be aware of the potential toxicity of drug-to-drug interaction between cannabinoids and opioids.

Topical agents

Topical therapeutic approaches in the management of neuropathic pain produce a clinically useful concentration of drug at the site of application without systemic administration. Few agents have reached a sufficient level of evidence to support systematic use as treatment options. Localized treatments are based on the pharmacological characteristics and pharmacodynamics profile of each agent.

Capsaicin

Capsaicin is a natural vanilloid derived from the capsicum plant. It selectively binds to the transient potential vanilloid receptor (TRPV1) a well-characterized calcium receptor expressed on A and C nerve fibers. A single application of a high-concentration capsaicin dermal patch produces substantial analgesia in some models of neuropathic pain but use in children is limited by tolerability. Many find the application painful and require a local anaesthetic prior to the procedure, but the treatment seems to have a long-term effect of up to 12 weeks with no systemic side effects.

Olvanil is a new potentially superior topical analgesic agent, a synthetic analogue of capsaicin, with laboratory data showing a higher analgesic effect via direct desensitization of TRPV1 channels with fewer side effects (21).

Lidocaine

Lidocaine is a sodium-channel blocker. As a topical treatment without substantial systemic absorption, the 5% lidocaine patch has shown efficacy and excellent tolerability in many different types of peripheral neuropathic pain, although its clinical impact is less consistently clear. On the basis of available evidence, lidocaine 5% patches are not recommended as first-line treatment in localized neuropathic pain. One recent prospective multicentre single arm study in children, however, demonstrated benefit in 69% (of 115 patients) with minimal adverse effects (22).

Central (thalamic) pain

Central, or thalamic, pain is a specific example of neuropathic pain arising from damage to the CNS itself. The term ‘thalamic pain’ originated in an early case series of adults with a lesion in the thalamus and internal capsule causing ‘*severe, persistent, paroxysmal, and often intolerable pain not yielding to any analgesic treatment*’ (25). It is perhaps misleading, as central neuropathic pain can be caused by damage to any of that part of the CNS that is specialized for pain perception.

Such damage results in disordered nociceptive processing at the molecular, cellular, and circuit level, leading to system-wide changes in neuroexcitability that ultimately lead to an amplified pain experience. In adults, causes of central neuropathic pain include multiple sclerosis and stroke. These conditions are rare in children however, parallel pathology exists in LLCs in childhood and may potentially cause central pain. Thalamic MRI anomalies have been reported in neurometabolic and genetic conditions (Leigh syndrome, Krabbe disease, leukodystrophies, gangliosidoses), and as a consequence of infectious, hypoxic, or traumatic brain injury. Many of these diseases result in damage to the CNS, including disordered infrastructure, abnormal neuronal migration, and myelination, and/or abnormalities of normal neurological systems at the molecular level. The clinical picture can be one of persistent, intense screaming and distress. Central pain is an important differential diagnosis when considering causes of distress in the non-verbal children, alongside cerebral irritability and visceral hyperalgesia.

Visceral hyperalgesia

Visceral hypersensitivity or hyperalgesia is an altered response to stimulation in the gastrointestinal tract, which results in a distorted threshold to pain. As such a normal stimulus, such as distension and pressure within the gastrointestinal (GI) tract results in significant pain. Visceral hyperalgesia is characterized by motor abnormalities of the gut, raised intraluminal pressures, and a reduced threshold for nociceptor stimulation. Visceral hyperalgesia is also known as visceral dysaesthesia (indicating an unpleasant sensation) or gastrointestinal dystonia.

Gastrointestinal pain and symptoms are common in children with severe neurological impairment. Distress is often temporally related to gastrointestinal symptoms and signs, including pain, feed intolerance, flatus, retching, and vomiting. Pain appears to be localized to the gastrointestinal tract and associated with digestion, despite adequate treatment of constipation and gastro-oesophageal reflux. It has been suggested that visceral hypersensitivity may be a result of neuronal plasticity following experiences of recurrent gastrointestinal pain in early life (e.g. due to prolonged neonatal care, gastro-oesophageal reflux, constipation, or gastrostomy feeding) resulting in amplification of pain signals and sensitization of the GI tract. In effect, it is the gastrointestinal

equivalent of heel hyperalgesia following multiple heel pricks during neonatal intensive care (26).

Given the difficulty in defining the syndrome, it is not surprising that there is little published evidence regarding visceral hyperalgesia. The clinical picture is, however, well-recognized by practitioners caring for medically fragile children who are surviving for longer than previously experienced and among whom these symptoms seem increasingly prevalent. Medication used to treat neuropathic pain has resulted in improved symptoms, including a reduction in retching, vomiting, and feed tolerance. Anti-neuropathic co-analgesic agents such as TCAs and anticonvulsants, particularly the gabapentiniods, are used for treatment, but it is becoming clear that this is a multidimensional phenomenon that demands a multimodal approach. Combining a pharmacological approach with manipulation of feeding regimen appears to improve the outcome.

Complete gastrointestinal failure associated with severe pain may progress into an end-of-life episode in some children. Analgesic management in this group can be extremely challenging and in some instances it may be impossible to reintroduce feed even with maximum therapeutic management. Severe, distressing GI pain can occur spontaneously this cohort often without a trigger.

Bone pain

Bone pain is a common problem in children in the palliative care setting. Its association with malignant LLCs is well-known, but it is also a significant problem for many children with non-malignant conditions. Although the management approaches overlap, their mechanisms are different and the range of aetiologies in non-malignant conditions is wide (see Box 19.4). Management of bone pain in non-malignant LLCs is often correction of the underlying condition where that is possible.

Box 19.4 Causes of bone pain in non-malignant LLCs

- Non-ambulatory children with chronic neurological conditions—contributing factors include:
  - immobility
  - feeding difficulties
  - use of anticonvulsants
  - poor exposure to sunlight (1)
- Inherited metabolic disorders involving
  - primary defects of structural bone proteins—e.g. osteogenesis imperfecta

— pathological involvement of bone from systemic disease—e.g. mucopolysaccharidosis

• Secondary distortion of the normal skeletal structures during periods of growth

— effect of systemic treatment e.g. prolonged steroid use

— result of skeletal abnormality (dislocation or fracture)

Source: data from Beecham E. et al. (2015). Pharmacological interventions for pain in children and adolescents with life-limiting conditions. *Cochrane Database Syst Rev.*13(3):CD010750. DOI: 10.1002/14651858.CD010750.pub2.

In children and young people with cancer, bone pain is associated with primary bone tumours (i.e. osteosarcomas and Ewing's sarcoma), metastatic tumour (particularly neuroblastoma and rhabdomyosarcoma), haematological malignancy, and results from chemotherapy treatment itself.

The relationship between bone damage and pain in patients with cancer has been clarified in recent years. Animal studies have shown that although the periosteum is more densely innervated, it is the bone marrow space that receives the highest number of sensory and sympathetic nerve fibres. The natural immune response to tumour and infiltrate is the release of a multitude of factors, including interleukins, growth factors, and cytokines. Cancer cells themselves release inflammatory infiltrate, including macrophages, T-lymphocytes and neutrophils, prostaglandins, and tumour necrosis factor. These mediators increase the sensitivity of peripheral nociceptors and activate osteoclast activity. Experimental models have revealed complex interactions between local factors at the site of bone cancer, and the resulting inflammatory and neuropathic response in the CNS. Evidence is accumulating which suggests that this pain response is unique to cancer-induced bone pain. Furthermore, altered regulation of the normal bone micro-environment is lost, with disruption of the balance between osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells) resulting in disordered and abnormal bone matrix formation. A role for glutamate is suggested by the observation that gabapentinoids are effective in animal models of cancer-induced bone pain (27).

Treatment of bone cancer pain can involve multidisciplinary therapies, such as radiotherapy together with systemic treatment (hormone therapy or chemotherapy), and supportive care (analgesic therapy and bisphosphonates). In some selected cases, use of radioisotopes and other non-invasive or minimally invasive techniques may be useful. Treatment

should be individualized according to the patient's clinical condition, life expectancy, and quality of life (Box 19.4).

Clinical features of bone pain

Bone pain is characterized by a focal, deep-seated, intense background pain described as 'boring' or 'like a drill'. Background pain can initially be intermittent in nature, but often escalates to become constant and unremitting. It is frequently complicated by spontaneous pain at rest and/or movement-related incident pain.

Management of bone pain

The effective management of bone pain relies upon upon individualized response tailored to the identified cause(s) and the child's clinical condition, life expectancy, and quality of life. These can include non-pharmacological methods, particularly appropriate orthopaedic management, a multimodal pharmacological approach, and sometimes more invasive pain interventions.

Non-pharmacological interventions

Radiotherapy

Radiotherapy offers effective pain control for focal cancer and is probably the treatment of choice for localized bone metastasis disease. Palliative radiotherapy is typically administered as a single fraction or short course and generally provides pain relief in a median of 2–3 weeks for 60% patients with few adverse effects. Acute toxicity may include local erythema, pain and itching at the site, and the occurrence of nausea, vomiting, and tiredness. Where pain recurs retreatment can be considered after at least 4 weeks to allow a response. Many patients will require reduction in analgesia; in some cases, this will need to be particularly rapid to avoid narcotization (that is, opioid toxicity occurring as a result of reduction in pain, rather than increase in opioid dosage).

Stereotactic radiotherapy is an advanced technique that offers targeted radiotherapy, matching treatment to tumour shape and accurately delivering it to disease sites with the aid of computed tomography. High-dose stereotactic treatments can potentially improve symptom management and quality of life in patients with metastatic disease.

Radiopharmaceuticals

Radionucleides are 'radioactive bone-seeking agents', either radiolabelled molecules or monoclonal antibodies, that are preferentially absorbed at areas where there is a high rate of bone turnover, such as metastatic sites.

Strontium-89 and samarium-153 are commonly used radionuclides that are approved for the treatment of painful bone metastases. In adults, radionucleides are effective in reducing pain and analgesic requirements

and improving quality of life. Evidence in children with metastatic bone pain is lacking, however, and further studies are required to evaluate their safety and efficacy.

Pharmacological management

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs possess clear analgesic activity and have a specific role in the management of bone pain. NSAIDs inhibit cyclooxygenase and thus prostaglandin synthesis. Prostaglandins have a key role in the production of inflammatory and pain mediators and the pain response, both locally and in the CNS. There are two distinct isoforms of cyclooxygenase which produce specific prostaglandins: COX-1 is *constitutive* (i.e. part of the body's normal constitution), expression of COX-1 produces prostaglandins responsible for gastric protection, endothelial integrity, kidney function, and platelet function; COX-2 expression is generally much lower, but is *inducible* (i.e. produced by inflammation) resulting in the production of prostaglandins specifically responsible for inflammation, fever, and pain.

There is little evidence that selective NSAIDs are any more effective or less toxic in clinical practice. Furthermore, COX-2-specific NSAIDs have been associated with an increased risk of thrombotic events in adults, resulting in the withdrawal of several of these drugs from the market. Small-scale studies in children have shown acceptable effectiveness and tolerability. Nevertheless, given concerns about their use in adult palliative care, this is probably insufficient evidence to justify their use. Administration of COX-2 selective NSAID in children is now uncommon.

There is good evidence that NSAIDs are effective in the management of cancer pain. However, the evidence that they are specifically effective in bone pain is weak. Concerns about a deleterious effect of NSAIDs on bone healing should be borne in mind but are probably unfounded (28).

Bisphosphonates

Osteoporosis is an under-recognized complication of chronic illness in childhood, characterized by low bone mineral density and impaired micro architecture leading to reduced bone strength and fractures. Bisphosphonates are the mainstay of treatment for this condition and have been used extensively on an 'off label' basis in paediatrics for a variety of indications, including pain and hypercalcaemia, caused by primary and secondary, osteopenia, including cancer and associated therapies, epidermolysis bullosa, and non-ambulatory children with cerebral palsy and neuromuscular disorders. Bisphosphonates are analogues of inorganic pyrophosphate that inhibit osteoclast activity and directly reduce bone resorption.

Controversies persist about the optimal agent, dose and duration of drug use because of a lack of disease specific RCTs. Intravenous agents appear to be more effective than oral agents in reducing fractures. Pamidronate

is the most extensively used agent. The more potent zoledronic acid is sometimes preferred because it can be infused more rapidly and less frequently and so reduces the need for hospital admission during the last few weeks and months of life (29).

Common side effects of bisphosphonate infusions include transient flu-like symptoms and injection site reactions following the first dose. Ocular inflammation and osteonecrosis of the jaw are recognized risks but are rare in children.

Deep tissue pain

Muscle, joints, and viscera are major sources of pain. Little is known about the mechanism involved in deep tissue nociceptive signalling, as historically pain research has focused on cutaneous pain. As such, despite its prevalence, we have limited knowledge about deep somatic pain from the musculoskeletal system and viscera.

Deep tissue pain is particularly prevalent and problematic in children with non-malignant LLCs. It can arise from a variety of conditions including dystonia, cerebral palsy, surgery, scoliosis, and any form of muscle damage. Furthermore, visceral pain, another frequent cause of deep pain, can be associated with any internal organ for example gastrointestinal failure, bladder conditions, ischaemic heart disease (or secondary ischaemia in the bowel), and pancreatitis among others.

Deep tissue pain can present as a more diffuse entity distributed over large areas, and in some cases may have whole body manifestation. This widespread manifestation can be associated with chronification of the pain state and is perhaps what is observed in the child with severe neurological impairment and pain associated with one or more of spasticity, post-surgical pain, and visceral pain (30). Although modulation of the chronic deep pain state is still poorly understood, there is some evidence that abnormal peripheral and central sensory neurotransmission (sensitization) can contribute to the maintenance of persisting pain. It can be postulated that the ‘neuroplastic’ child with neurological impairment may be more vulnerable to developing an abnormal pain state.

As with all pain entities, the pharmacological approach to deep tissue pain requires careful consideration of the causative pathology and the profile of analgesic medication that may be suitable for use in these cases. The pharmacological management of pain is dependent upon the correct identification and categorization of pain and the use of multiple medications with different mechanisms of action. Caution should always be taken with the longer-term use of opioids in those with persisting pain in non-malignant LLCs.

Factors contributing to difficult pain states

Central and peripheral sensitization and the wind-up phenomenon

‘Plasticity’ is the ability of the nervous system to alter in response to injury. It is this plasticity of the nervous system that underlies the adaptive, non-dependable, relationship between the intensity of noxious (pain) stimuli and the perception of pain (31).

It is well-known, that peripheral tissue damage and subsequent local inflammation cause the release of a variety of chemical factors that can sensitize the primary afferent fibers to amplify the intensity of a painful stimulus.

There are also central mechanisms that can excite or inhibit pain transmission in the brain and spinal cord. These include local excitatory or inhibitory interneurons and NMDA receptors. After nerve injury, changes in these mechanisms can result in the heightened response of the dorsal neuron to incoming afferent nerve signals, and thereby increased spinal output to the brain. This is known as central sensitization. After prolonged peripheral nerve stimulation or ‘drive’, increased release of the presynaptic neurotransmitters (glutamate and substance P) causes post-synaptic membrane depolarization and, through the NMDA receptor, results in increased post-synaptic excitability. The NMDA receptor allows the CNS to amplify perception of pain. That is the phenomenon known as ‘wind-up’. If the right conditions exist, this can mean that prolonged pain states are generated despite the fact that input into the spinal cord is unchanged.

Central sensitization is an example of spinal events that enhance pain signaling resulting in altered activity in the brainstem. Functional magnetic resonance imaging results have identified increased activity in the spinal cord as well as multiple brainstem areas during so called ‘wind up’ of dorsal horn neurons (32). Numerous systems within the CNS act to either increase or decrease incoming pain messages. Endogenous descending inhibitory and facilitatory (excitatory) control pathways (‘top-down’ processing) originate in the brain stem and higher brain areas, project to and terminate in the dorsal horn of the spinal cord, altering spinal output and pain levels. These ‘top-down’ processing pathways exert powerful control of the spinal cord through the actions of norepinephrine (NE) (inhibitory) and 5-hydroxytryptamine (5-HT-3) (excitatory). There is now sound evidence that there is a function failure of the NE inhibitory control in persisting pain states in the animal models of neuropathy. Pathological alteration in descending control pathways are seen in animal models with differing peripheral mechanisms of pain of both nociceptive and neuropathic origin. Changes in 5-HT3 receptor descending facilitations have been described in pain states ranging from acute to persistent inflammation, neuropathy, and opioid-induced hyperalgesia. Thus, dysfunctional central descending modulation seems common to many pain states and it is postulated that a loss of central

control of descending modulation and a shift to either facilitation or a loss of inhibition could produce a diffuse pain state (33).

Opioid-induced hyperalgesia (OIH)

Morphine remains the ‘gold-standard’ analgesic in the treatment of moderate to severe pain in children, particularly with respect to cancer pain. Rarely, however, opioids themselves can be associated with making pain worse. Opioid-induced hyperalgesia (OIH) describes a situation in which breakthrough opioids paradoxically exacerbate a patient’s pain rather than relieving it. It is unrelated to tolerance, which describes a reduction in the degree of analgesia the same dose of opioids (34). OIH typically occurs where the dose of opioid has been escalated rapidly and out of proportion to the rate at which the patient’s pain is worsening, and where there is too great a reliance on opioids alone rather than in combination with appropriate co-analgesics (adjuvants).

The mechanism of OIH is not clear. Early studies showed an association with unusually high ratios of neurotoxic morphine 3-glucuronide (M3G) to morphine 6-glucuronide, especially in the CSF (1). M3G has no affinity for the opioid receptor and naloxone does not reverse hyperalgesia in healthy volunteers exposed to remifentanil, so, if accumulation of M3G is the cause, it must be mediated through other, non-opioid, mechanisms. Data from animal studies have implicated the central glutaminergic system, spinal dynorphin content and descending serotoninergic excitatory circuits at spinal level.

The risk of OIH can be reduced by appropriate use of co-analgesics (adjuvants) and carefully measured opioid titration in which increases background opioid are made firmly in line with increasing requirements. Where OIH occurs, opioid rotation (switching or substitution) is the simplest solution. Judicious opioid rotation allows a reduction in total opioid dose without the risk of losing control of pain relief. The more distinct the structure of the destination opioid is from the previous one the more likely the manoeuvre is to succeed. If the original opioid is morphine, then hydromorphone or oxycodone are only moderately good destination opioids because they are structurally similar to morphine and are metabolized in a similar way. Fentanyl and methadone, on the other hand, are ideal destinations from morphine because they are structurally quite different. Methadone seems particularly effective in reversing paradoxical pain, perhaps because, in addition to avoiding an accumulation of neurotoxic M3G, methadone has additional actions that are not mediated through opioid mechanisms at all.

Interventional approaches for refractory pain in paediatric palliative care

The term ‘interventional approaches’ encompasses a range of treatments including regional anaesthetic blocks and infusions, implanted ports and pumps, neurolytic procedures, and neurostimulation.

For the great majority of children and adolescents with refractory pain associated with life-limiting illnesses, it is feasible to provide adequate pain relief using systemic analgesic approaches. There remains a small subset of children and adolescents for whom adequate analgesia is difficult to achieve, or for whom side-effects of treatment are intolerable.

Publications in this area are largely limited to case reports and case series (35, 36, 37). Regional anaesthesia refers to the infusion of local anaesthetics and other medications to provide pain relief in a specific area of the body. These are usually applied via indwelling catheters placed near specific peripheral nerves, a plexus, in the epidural space, or in the subarachnoid space. Perioperative use of regional anaesthesia in paediatrics has expanded greatly in the past two decades. Ultrasound guidance has been a major factor in improving the technical success and clinical efficacy in paediatric perioperative regional anaesthesia. In the discussion that follows, the term ‘neuraxial’ means in the spinal canal, in either the epidural or subarachnoid space, and ‘spinal’ means specifically subarachnoid, not epidural. For peripheral and plexus infusions, the primary medications are local anaesthetics. For neuraxial infusions, local anaesthetics are often combined with analgesics with specific actions in the spinal dorsal horn, including opioids and clonidine. Table 19.2 summarizes some of these approaches.

Table 19.2 Regional anaesthetic approaches for refractory cancer pain

Technique	Advantages	Limitations or disadvantages	Example
Peripheral nerve and plexus	• Very localized effect, ideal when pain generators are within territory of a just one or two peripheral nerves or a single plexus • Low risks for infection, bleeding, and other complications	• As tumour progresses, pain generators may expand beyond the covered nerve territories	• Femoral nerve catheter for unresectable osteosarcoma of the femur with pathologic fracture and movement-related pain

Epidural	• Ideal for pain from upper thoracic dermatomes • Feasible to direct unilaterally via fluoroscopy to get predominantly one-sided effect • Avoids need for dural puncture	• Less range for local anaesthetic dose escalation compared to subarachnoid • Epidural fibrosis can occur with infusions over more than 3–4 months	• Thoracic epidural port with catheter directed to left side at T5 • For pain arising from left chest wall tumour
Subarachnoid	• Strongest and most versatile approach for pain in wide territories from mid thoracic to sacral dermatomes • Most durable pain relief for long time periods (e.g. >4 months) • Can adjust mixtures of opioids and local anaesthetics to balance analgesia versus side-effects	• Gives bilateral effect, which may not always be desirable • Hard to control spread of local anaesthetic effect for pain arising above around T6 • Depending on the location of pain and the drug combinations used, may cause partial sensory and motor block in the lower extremities and may	• Intrathecal port with catheter tip at T9 for pain from widespread abdominal and pelvic tumour

		impact bowel or bladder function	

In the setting of palliative care, the intent is usually to maintain catheters for regional anaesthetic infusions over periods of weeks to months, or occasionally more than a year. Three general options are used to facilitate longer term use: subcutaneously tunnelled catheters, subcutaneous ports, and implanted pumps. For tunnelled catheters and ports, a small external infusion pump is used, permitting continuous infusion and intermittent boluses. Advantages and disadvantages of each technique are summarized in Table 19.3

Table 19.3 Tunnelled catheters, ports, and pumps

Technique	Advantages	Disadvantages
Tunnelled catheter	• Simplest to place • Feasible even in infants	• Some chance of dislodgment with long-term use. Requires careful attention to skin care
Implanted port	• Port prevents dislodgment of internal system, facilitates skin care • Feasible from around age 2 and older	• Requires connection to external pump and continuous access via Huber needle
Implanted pump	• Convenient • No external connection or home infusion is required • Easiest for skin care	• Pump and implantation are expensive. • Too large for most children ages <7 years or weight <30 kg • Most practical for potent and water-soluble drugs given via intrathecal route • Depending the situation, reservoir

		refills may be inconvenient • ‘Bridging’ while changing solutions can be cumbersome and requires close observation

Implanted pumps contain a reservoir with a volume of 20 or 40 ml that is accessed intermittently via injection of the medication percutaneously through a septum. These pumps are controlled by external magnetic programming devices, and the pumps infuse medications into the cerebrospinal fluid at low rates, typically less than 0.1 ml/hr. Implanted pumps are used almost entirely for intrathecal medications of high potency and high aqueous solubility. Their use in adult palliative care and cancer pain management began with infusion of intrathecal morphine. In many centres, this has extended to use of mixtures of opioids with local anaesthetics, clonidine, or other additives. Higher dosing of local anaesthetics in implanted pumps is limited by additional technical and clinical considerations.

Neuraxial infusions of opioid/local anaesthetic combinations are generally favoured for providing additive or supra-additive analgesia while limiting side-effects. Compared with adults, paediatric infusions tend to be more ‘local anaesthetic-heavy’. Infusions often require changes in drug concentrations, and bolus options seem essential for optimal dose titration, especially for movement-related pain. For infants and children under age 7, the size of an implanted pump may be too large for comfortable implantation in the abdomen. The needle and catheter diameters used for implanted pumps are also larger than those used for tunnelled catheters or implanted ports. Based on all of these considerations, children and adolescents with refractory pain due to advanced cancer are generally treated with ports and tunnelled catheters with external pumps rather than implanted pumps.

Implanted programmable pumps are also widely used in adults and children for long-term intrathecal administration of baclofen, a GABA-B receptor agonist, for management of spasticity of cerebral or spinal origin. In paediatric palliative care, there is a small number of children and adolescents with progressive neurologic disorders for whom refractory spasticity, dystonia, or other movements can generate distress and suffering despite aggressive management using systemic medications. In these situations, an implanted pump for infusion of intrathecal baclofen can be helpful. Examples in clinical practice have included children and adolescents with metachromatic leukodystrophy, infantile ascending hereditary spastic paralysis, Friedrich’s ataxia, and severe strokes involving basal ganglia or thalamus.

Neurolytic procedures

Neurolysis refers to the partial inactivation or destruction of nerves. Neurolysis is most commonly achieved by surgery, chemicals (e.g. phenol, alcohol), or thermal injury (cryotherapy, radiofrequency ablation).

Neurolysis is used infrequently in paediatric palliative care. In most situations, neurolysis sufficient to deafferent the area of pain would lead to unwanted deficits.

Case history

> A patient presented with severe pain due to unresectable pelvic tumour that filled the pelvis and eroded through the pelvic floor. Radiation did not achieve local control, and tumour growth continued despite traditional and investigational chemotherapy. She had previously undergone placement of a colostomy and suprapubic cystostomy. She required deep sedation/general anaesthesia twice weekly for care of her necrotic and chronically infected perineal wounds. Superior hypogastric block was achieved with image guidance. Intrathecal neurolysis was achieved by placing a temporary image-guided caudally directed intrathecal catheter. Once the patient awoke after this procedure, she was positioning in a sitting position. Phenol was made hyperbaric by additional of dextrose to make the solution more dense than cerebrospinal fluid, so that incremental doses would settle to the caudad end of the thecal sac, to achieve a neurolytic ‘saddle block’ of the lower sacral roots innervating the pelvic floor. This combined procedure achieved durable pain relief.

Coeliac plexus neurolysis can be achieved using alcohol, phenol, or radiofrequency ablation. This approach was classically described for adults with pancreatic cancer. It may have a limited role for children with upper abdominal visceral malignancy. It can be helpful when the predominant source of distress is refractory retching or pain due to hepatic capsular stretch where there are contraindications to either a thoracic epidural or intrathecal infusion. Overall, neuraxial approaches are more reliable than Coeliac blockade in a majority of settings, because of the need to cover pain arising from beyond Coeliac/splanchnic afferents.

In adult chronic pain management, there is growing use of several types of radiofrequency ablation and cryotherapy. There is growing understanding of how to apply and control these techniques. There might be future roles for these approaches in selected situations in paediatric care. There is increasing use of spinal cord stimulation in adult chronic

pain management, but little information on whether it might have any role in paediatric palliative care. Deep brain stimulation is used increasingly for refractory dystonia and other movement disorders in both children and adults.

Interventional approaches should not be undertaken lightly and should involve a broad consideration of patient and family wishes, feasibility of ongoing care in the home or hospice setting and balancing of risks and potential benefits. Usually, they are considered after trials of opioid rotation (especially to methadone), trials of neuropathic medications, and a trial of ketamine. Since these procedures are performed infrequently, in most centres, it will be appropriate to enlist collaboration of several local experts (e.g. paediatric anaesthetists, neurosurgeons, interventional radiologists, adult pain specialists) for conduct of the procedure and co-management. Image guidance (via ultrasound, fluoroscopy, Dyna-CT, or other techniques, as indicated) should be encouraged to ensure optimal anatomic location of catheter tips. For example, epidural catheters are much more effective when guided to the proper dermatomal level and to the side of the epidural space ipsilateral to the sites of greatest pain. Management at home requires close collaboration with home/hospice nurses, local paediatricians, and hospital-based palliative care teams. Logistics and feasibility of home management should be evaluated at the time of initial consideration of these approaches. It is crucial to have anticipatory planning and contingency plans to ensure extra supplies and stocks of medications and infusion bags, in order to prevent failures of delivery or inability to escalate regional or systemic medications in the event of rapidly increasing requirements. Interventional approaches are labour- and resource-intensive, but in selected situations they can greatly add to a patient’s comfort, quality of life, and ability to be alert and interactive for a longer period during the course of advanced illness.

Refractory pain and palliative sedation

Failure to achieve adequate pain control with traditional pharmacotherapy, despite rapid dose escalation, use of co-analgesics (adjuvants), opioid rotation, and interventional pain techniques is thankfully rare in practice. The use of interventional pain management in combination with co-analgesics and opioid escalation, often with mobile patient/proxy controlled analgesia—delivering intravenous analgesia (usually an opioid +/- ketamine) in a chosen location has facilitated challenging pain management (38), and as such, refractory pain is extremely unusual. However, there is a subset of patients for whom standard approaches provide insufficient pain relief or are associated with intolerable side effects, even despite surgical decompression or interventional pain and/or radiological management. Options include high-dose or ‘burst’ ketamine, clonidine, dexmedetomidine, and lidocaine infusions all of which have been described in case series as being effective for refractory pain. The safety and efficacy of these agents in children is not clear and risk must be assessed on an individual basis (39).

Many of the analgesics and co-analgesics (adjuvants) used to treat difficult pain carry the risk of drowsiness or somnolence, and the aim of pain management in palliative care is always to minimize such adverse effects as far as possible. It is never appropriate to use sedation as an alternative to analgesia. For most patients, however, it is more important to be out of pain and drowsy than to be awake and in pain. If the nature of pain makes it difficult to treat, it can become clear that the only way to avoid sedation would be to leave a patient in unnecessary pain. Under those circumstances it will often be appropriate to increase the doses of analgesic and co-analgesic medications, even to a point where a degree of sedation becomes inevitable. That is referred to as ‘palliative sedation’, a term that is sometimes contentious because it is mistakenly taken to mean a form of euthanasia. The European Association for Palliative Care defines palliative sedation as ‘the monitored use of medications intended to induce a state of decreased or absent awareness in order to relieve the burden of otherwise intractable suffering in an ethically acceptable manner’. That definition wrongly implies that sedation itself is the therapeutic goal, rather than the inevitable result of maximizing the effectiveness of a multi-modal approach to pain relief. Nevertheless, the outcome of palliative sedation is the same whether the physician intends to reduce a patient’s consciousness or merely knows it is likely to happen.

Reports of intractable pain and suffering at the end of life are rare (though not as rare as is often thought) and are mainly described in children with end stage cancer. There is no evidence to inform effective palliative sedation in children. If there is any doubt about the indications for sedation in a child near the end of life a consensus should be sought, and a clinical ethics consultation considered.

Summary

During the last decade there has been much interest and scientific progress in relation to the mechanisms and treatment of difficult pain ‘syndromes’ or states. Improvements in the modelling of pain in animals, phenotyping, and classification of differing pain states and response to treatment will continue to improve scientific knowledge. Progress in pain imaging and a rapid expansion in pain genomics, will no doubt lead to an even greater understanding of this complex phenomenon. In the meantime, rigorous assessment and a considered, systematic, and analytical approach that is based on sound clinical expertise and informed by empirical evidence where it is available, is likely to remain the most effective challenging pain for some time to come.

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