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Advances in Paediatric Rheumatology and Translation of Research to Targeted Therapies

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Title:

Overview of neurodevelopment and pain research, possible treatment targets.

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Abstract

Pain is a common presenting and often persistent symptom for children with rheumatological disease. Pain is not clearly related to disease severity in children with inflammatory juvenile idiopathic arthritis, and presentations of non-inflammatory musculoskeletal pain are common but there is limited evidence to guide management. Pain assessment must extend beyond measures of pain severity to more fully evaluate characteristics of pain, functional impact and psychosocial effects, and family interactions. Evaluation of mechanisms of joint pain in adults has identified potential treatment targets, but additional studies are required as the acute and long-term impact of pain and injury change during postnatal development. Genotyping, sensory evaluation and neuroimaging may better characterize chronic musculoskeletal pain, identify high-risk groups, and/or provide additional outcome measures to monitor disease and treatment progress. An integrated approach to management is required to effectively select and target interventions, reduce pain and disability, and improve long-term outcome.

Key words

Pain, nociception, development, children, arthritis, chronic pain, musculoskeletal pain

Introduction

Significant neurodevelopmental changes in nociceptive processing occur from infancy through to adolescence, that impact on the nature and degree of response to pain, and can also influence the pharmacodynamic profile of analgesic agents. Due to the enhanced plasticity of the developing nervous system, there is potential for pain and injury in early life pain to produce long-term changes in sensitivity that are not seen following the same insult at older ages [1-3]. As a result, the ability to extrapolate data obtained from studies in adults may be limited, and the presentation and pathophysiology of diseases associated with chronic pain in paediatric populations differ from those seen in adults. There is a need to increase the quality and quantity of evidence to inform paediatric pain management. Outcome measures that extend beyond isolated measures of pain intensity to more fully characterize pain and its impact are required, with detailed assessment incorporating age- and disease-appropriate measures of activity, sleep and mood, and sensory function. An integrated and inter-disciplinary approach to management of chronic musculoskeletal pain in children is required to effectively select and target interventions, reduce pain and disability, and improve long-term outcomes [4-7]. In this review, data from studies in children and adolescents with inflammatory (eg. juvenile inflammatory arthritis JIA) or non-inflammatory conditions will be used to illustrate the need for more comprehensive understanding of chronic musculoskeletal pain.

Pain Mechanisms

A mechanism-based approach to pain diagnosis and management has been advocated for many years [8, 9], and is also relevant to rheumatological conditions [10]. Laboratory models of inflammatory arthritis and osteoarthritis have been essential for investigating underlying mechanisms and identifying and assessing potential analgesic targets [11-13]. However, it is clear from studies in young animals that acute and long-term

responses to noxious stimuli, peripheral inflammation and nerve or visceral injury change throughout postnatal development [1, 2]. Further evaluation of specific age-dependent effects in developmental models of musculoskeletal pain and joint inflammation is warranted [3].

Peripheral nociceptive pathways and sensitization

Peripheral nociceptive pathways sense and transduce noxious stimuli into electrical signals that are transmitted to the central nervous system and synapse in the spinal dorsal horn (see Table 1 for definitions and taxonomy). The joint capsule, ligaments, synovium, periosteum and subchondral bone are densely innervated with peripheral nociceptors. Nociceptors respond to noxious mechanical, thermal or chemical stimuli via a range of receptors, and depolarization results in action potential generation and propagation in peripheral myelinated A δ fibres and unmyelinated C fibres. In addition, release of neuropeptides (substance P and calcitonin gene-related peptide, CGRP) from peripheral afferent nerves contributes to the inflammatory response (neurogenic inflammation) [14]. In the presence of tissue injury and inflammation, nociceptors in muscle and joint become sensitized, particularly to mechanical stimuli [14]. This state of peripheral sensitization has been specifically identified in electrophysiology recordings of afferent nerves from inflamed joints [13] and is characterized by a reduction in the threshold for activation, an enhanced response to suprathreshold stimuli, and recruitment of previously 'silent' nociceptors [14]. Mediators released from tissue injury and/or the inflamed synovium contribute to sensitization, including pro-inflammatory chemokines and cytokines (eg. tumour necrosis factor-alpha, TNF- α ; interleukin-1, IL-1; IL-6; IL-17), prostaglandins (eg. PGE₂), neuropeptides (eg. vasoactive intestinal peptide (VIP) from inflamed synovium), and growth factors (eg. nerve growth factor (NGF) from articular cartilage, meniscus and synovium) [10, 13-16]. Enhanced sensitivity can occur within minutes via phosphorylation and changes in gating

properties of ion channels, or over more prolonged period (e.g. changes in expression of receptors and ion channels) [14].

Receptors involved in peripheral nociception and sensitization following joint inflammation/injury include, but are not limited to, the following:

i) transient receptor protein (TRP) channels comprise a family of non-selective cation channels that transduce thermal and chemical stimuli. The TRPV₁ receptor is expressed by nociceptive fibres in joints and levels increase following inflammation [10]. TRPV₁ is directly activated by capsaicin, noxious heat >43°C, and low pH in inflamed tissue, and indirectly sensitized by inflammatory mediators such as bradykinin, PGE₂, and NGF [12, 14]. TRPA₁ is activated by cold temperatures, bradykinin, and pungent chemicals (eg. mustard oil), and may also contribute to joint inflammatory pain [12] (Table 2).

ii) Acid-sensing ion channels (ASICs) are activated by low extracellular pH during inflammation, and may have a particular role in ischaemic pain in skeletal muscle [14].

iii) Purinergic receptors comprise a P_{2x} family of ionotropic channels and a P_{2y} family of G-protein coupled receptors. ATP opens P_{2x} channels and mediates pain in contracting muscles or inflammatory states [14].

iv) Proteinase activated receptors (PAR2 and PAR4) are expressed on joint primary afferent nerve endings. Rather than being a ligand-gated receptor, proteinases (such as mast cell tryptase) cleave specific PARs and this alters nociceptive signaling and contributes to sensitization [12].

v) Voltage-gated sodium (Na_v) channels are essential for the generation and propagation of action potentials. Sub-types of Na_v channels vary in their structure, kinetics, distribution and sensitivity to tetrodotoxin. Nociceptive neurons express mainly Na_v1.7, Na_v1.8 and Na_v1.9, and these channels modulate excitability ('set the gain') and have important roles in both pain sensitivity and specific disease states [17]. Channel expression and activity is increased

following peripheral tissue inflammation [18], and in joint afferents from Complete Freund's Adjuvant (CFA) inflamed knees [19].

vi) Effects of endogenous cannabinoids are mediated by CB1 and CB2 receptors [13], and atypical receptors such as the orphan receptor GPR55 [12]. In the periphery, a CB1 agonist reduces mechanosensitivity of afferents from control and arthritic knees; whereas a CB2 agonist reduced joint afferent firing in controls, but potentiated firing in OA knee joint mechanoreceptors [13].

Developmental changes: Nociceptors are responsive to noxious mechanical, thermal and chemical stimuli after birth, and peripheral sensitization has been demonstrated from young ages in laboratory and clinical studies [1]. Age-related changes in receptor function and distribution and in firing frequency can alter sensitivity to different stimuli. TRPV₁ mRNA is present in the afferent cell body in the dorsal root ganglion (DRG) and peripheral TRPV₁ receptors are functional in early life [20] although the density of TRPV₁-positive nerve terminals in cutaneous tissue is initially less than in adults [21]. Levels of TRPA₁ mRNA are low in DRG neurons at birth [20], but peripherally applied TRPA₁ agonists (eg. mustard oil) produce peripheral sensitization in neonatal rodents [22]. In early development, a higher proportion of DRG neurons express P2X₃ receptors, and P2X₃ agonists evoke increased behavioural responses [23]. Na_v1.8 and Na_v 1.9 are expressed on C-fibres at birth and reach adult levels by postnatal day 7 (P7) [24]. Hindpaw injection of inflammatory agents such as carrageenan or CFA produce robust acute inflammatory responses in neonatal rodents, and depending on the type and volume of material injected also produce long-term changes in structure and function, including persistent neurotrophin-dependent hyperinnervation in wounded tissue [1, 2, 25].

Spinal cord and ascending pathways

Nociceptive primary afferent neurons synapse in the dorsal horn of the spinal cord, form local circuits with inhibitory and excitatory interneurons, connect to wide dynamic range neurons in deeper laminae, and provide input to a number of ascending projection pathways. Ongoing input in afferent nerves from skin, joint and/or muscle can lead to central sensitization, with a reduction in threshold, spontaneous activity and enlargement of the receptive field of dorsal horn neurons. Changes in the threshold, kinetics and distribution of glutamate (α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA; and N-methyl-D-aspartate, NMDA) receptors increase membrane excitability and produce synaptic facilitation; and disinhibition due to reduced actions of inhibitory gamma-aminobutyric acid (GABA) and glycine further increases sensitivity [26]. Joint inflammation triggers central sensitization via multiple transmitters and signaling pathways, including IL-6 [12], TNF- α [27] and endocannabinoids [13, 28]. Clinically, this is manifest as sensitivity extending beyond the area of injured peripheral tissue [29].

Projection neurons in the spinal dorsal horn are concentrated in lamina I, scattered through deeper laminae, and relay to several brain areas [30]. Briefly, inputs to spinothalamic tracts ascend via the ventral posterolateral thalamus to the primary somatosensory cortex and signal the sensory-discriminative aspects of pain. Ascending spinoparabrachial pathways to the lateral parabrachial area project to forebrain areas such as the amygdala and hypothalamus, and are involved in emotional and autonomic components of pain. Projections to the nucleus of the solitary tract mediate cardio-respiratory responses to pain, and those to the periaqueductal grey (PAG) link to other brainstem areas and descending modulatory pathways [30]. Using neuroimaging techniques, specific patterns of increased brain activity in response to noxious stimulation or different pain states have been identified that include the thalamus, hippocampus and amygdala, in addition to the somatosensory and other cortical regions (insula, anterior cingulate, and posterior parietal) [31].

Developmental changes: Dorsal horn neurons have low thresholds and large peripheral receptive fields, and there is a relative excess of excitatory responses and delayed development of inhibitory mechanisms in developing spinal pathways [1]. Maturation is activity dependent and can be altered by excess nociceptive input during critical periods [2, 32]. Transcription of voltage-gated sodium and potassium channels in the superficial dorsal horn vary in a sub-type specific and age-dependent manner, and can influence efficacy of analgesics targeting these sites [33]. Projections to higher centres are functional following birth, as noxious stimuli produce electroencephalogram (EEG) and blood flow changes indicative of activity in the somatosensory cortex even in preterm born neonates [1].

Descending modulation of pain

Descending pathways that relay in brainstem nuclei, particularly the PAG and rostral ventromedial medulla (RVM), can facilitate or inhibit nociceptive transmission in the spinal cord; with the balance depending on the transmitters and receptors involved, and the type and duration of injury [34]. Descending opioidergic and noradrenergic pathways have inhibitory actions, whereas serotonin (5-HT) has bidirectional effects with inhibition via 5-HT₁ and facilitation via 5-HT₂ and 5-HT₃ receptors. Altered descending modulatory pathways contribute to central sensitization, and may have important roles in chronic pain states, such as fibromyalgia. The anterior cingulate cortex, amygdalae and hypothalamus relay via these brainstem nuclei, providing a neural pathway for the influence of cognitive and emotional factors on pain experience [31, 34, 35].

Developmental changes: Descending pathways in early life are predominantly facilitatory and endogenous inhibitory mechanisms are slow to mature [1, 36]. As a result, endogenous inhibitory mechanisms may be less effective throughout childhood and early adolescence [3]. In addition, the balance of descending control may be influenced by early pain exposure. Using quantitative sensory testing (QST) generalized decreases in pain

sensitivity but increased sensitization with a sustained thermal stimulus have been identified in children born preterm requiring intensive care [37], and threshold changes were more marked in those who also required surgery suggesting that the degree of tissue injury may have an impact [38].

Neuroimmune Interactions

The sensitivity of nociceptive pathways is mediated not only by alterations in neuron-to-neuron signaling, as additional interactions between neurons and glial cells also have a significant impact [39, 40]. In peripheral nervous system sensory ganglia (dorsal root and trigeminal ganglia), neurons, satellite glial cells that surround and communicate with neuronal cell bodies, and macrophages form a network that modulates pain sensitivity [39]. In adult rodents, macrophage infiltration in the DRG following antigen-induced arthritis or surgical destabilization to model osteoarthritis correlated with increased sensitivity and the onset of pain behaviour [10]. In the spinal cord, afferent nerve terminals release not only neurotransmitters that activate receptors on the post-synaptic neuron, but also factors such as ATP and chemokines that increase reactivity of nearby microglia and astrocytes. Subsequent release of inflammatory mediators and signaling molecules from glial cells modulate synaptic transmission, and this feedback loop can further enhance pain sensitivity. Upregulation of microglial and astrocytic markers in the spinal cord that are suggestive of increased reactivity have been documented in a number of pain models, including joint arthritis [39].

Developmental changes: The impact of neuro-glial signaling is influenced by age and type of injury. Spinal microglia can be primed by neonatal surgical injury and contribute to enhanced sensitivity following injury in later life [41]. However, when compared to adult animals, peripheral nerve injury initially produces less glial response and minimal

hyperalgesia in young animals [42-44]. The role of neuroglial signaling following arthritis at different postnatal ages has not been evaluated.

Neuropathic pain

Neuropathic pain is the result of a lesion or disease of the somatosensory nervous system [45]. Although peripheral mechanisms differ from inflammatory pain, spontaneous activity and enhanced sensitivity of damaged afferent nerves can also produce central sensitization. Histological changes in joint afferents and in nerve fibre density have been identified in adult models of osteoarthritis, and neuropathic pain arising from these damaged peripheral nerves may contribute to the overall pain experience [12, 13].

Developmental changes: Laboratory models of peripheral nerve injury produce minimal hyperalgesia in young animals. Similarly, neuropathic pain is less frequently reported when surgery or trauma occur at younger ages (< 6 years), but a number of diseases (eg. erythromelalgia, Fabry's disease) and treatments (eg. chemotherapy) can also produce neuropathic pain in children. The presentation of neuropathic pain differs from inflammatory pain. Pain may be paroxysmal and episodic with no clear precipitating factor. Typical sensory descriptors include stabbing, pins and needles, shooting, piercing, and electric shocks. Altered sensory symptoms and signs can range from sensory loss to marked allodynia. Treatment is largely extrapolated from adult practice to include anti-convulsants and/or low dose anti-depressants with actions on descending noradrenergic mechanisms (see recent reviews for further details) [4, 46]. Nerve damage has not been assessed in developmental joint injury models.

Mechanism-Based Pharmacotherapy : Potential Targets

Improved understanding of nociceptive processing has identified multiple potential analgesic targets, with some examples included below. However, it must be emphasized that many are based on laboratory studies in adult animals and/or clinical studies in adult populations with minimal evidence from age-related laboratory models or clinical use in children. As the efficacy, therapeutic window, and potential toxicity of novel analgesics may differ in early life, further evaluation may be required before these data can be extrapolated to paediatric practice. Due to the complexity of the mediators, ion channels and pathways involved in nociceptive signaling, symptomatic pain management will continue to benefit from a multimodal approach rather than relying on single agents, in parallel with disease-modifying therapy when appropriate.

Biologics such as anti-TNF agents play an important role in management of rheumatic diseases. Despite the large number of trials and subsequent meta-analyses, there is often limited assessment and discussion of pain in adult [47] and paediatric [48] trials. For example, etanercept reduced disease activity in children with JIA, but pain assessment was limited to a single global assessment of the child's pain by the parent [49, 50]. Despite treatment with anti-TNF agents and lower disease activity, many children with JIA had persistent pain, and pain intensity and functional disability were similar to a retrospective historical standard treatment group [51]. Self-reported intensity and frequency of pain, stiffness, and fatigue, were similar despite biologics in children with JIA [52], thus emphasizing the need to optimize pain and symptom management in parallel with new therapies.

Transient receptor potential-V₁ (TRPV₁) antagonists are potential analgesics, but systemic administration in clinical trials has been associated with hyperthermia [14]. TRPV₁-immunoreactivity is increased in synovium from adults undergoing joint replacement, but co-labeling suggested localization with macrophages rather than afferent terminals. Intra-articular administration of a TRPV₁ antagonist in an adult rodent osteo-arthritis model

improved weight bearing and reduced mechanical sensitivity of joint afferents [53]. Although this route avoided systemic side-effects, its clinical utility is currently unclear.

Cannabinoid analgesic actions have been extensively evaluated, but variation in the distribution and function of CB1 and CB2 receptors, and centrally-mediated side-effects with CB1 agonists, limit clinical utility of many agents. An alternative approach is to enhance endogenous endocannabinoid function by inhibiting cellular re-uptake and hydrolysis. In a laboratory OA model, activation of CB receptors in joints reduced sensitivity, and a peripheral inhibitor of endocannabinoid hydrolysis reduced spontaneous activity of joint afferents to produce analgesia [12]. Increased expression of CB2 receptors by neurons and microglia in the spinal cord contributed to central sensitization, and a CB2 agonist reduced pain behaviour and excitability of spinal neurons [28].

Glial-modulators reduce neuroimmune contributions to pain sensitivity [54]. Inhibitors of astrocyte or microglial reactivity can reduce central sensitization and pain behaviour [39] and attenuate mechanical allodynia and improve weight bearing in OA models [13]. Potential adverse effects of inhibiting the immune response and the normal supportive and protective roles of glia must be considered [39], particularly in paediatric practice as microglia have important structural and functional roles in the developing central nervous system [55]. More specific therapy may be possible by targeting mitogen activated protein kinase (MAPK) signaling pathways (eg. phospho-p38 inhibitors), targeting upstream activators (eg. P₂X₄ receptor antagonists), or enhancing actions of anti-inflammatory and pro-resolution lipid mediators (eg. resolvins, lipoxins)[39].

Local anaesthetics non-selectively block sodium channels and action potential propagation in all nerve fibres, but as the duration of action is relatively short, slow-release formulations are being evaluated. Wound infiltration with bupivacaine loaded in multivesicular liposomes reduces perioperative pain scores and opioid requirements for up to 72 hours in adults, but ongoing evaluation of dose-response and safety is required before

use in children [56, 57]. Co-administration of an impermeable highly charged derivative of lidocaine (lidocaine N-ethyl bromide, QX-314) with an agonist that opens large pore TRPV₁ channels allows the local anaesthetic to enter and selectively block only TRPV₁ expressing nociceptive fibres [58]. Initially, QX-314 was co-administered with capsaicin as the TRPV₁ agonist, however this produces significant initial pain. Co-administration with 2% lidocaine has also been effective, producing an initial brief motor block but prolonged sensory blockade of peripheral nerves (9-hrs vs 1-hr with lidocaine alone) [58]. Slow-release formulations have potential utility for infiltration or peripheral nerve blockade for procedural and postoperative analgesia. However, further evaluation is required as delayed hypersensitivity and neurotoxicity has recently been demonstrated following sciatic block with 2% lidocaine, QX-314 and 0.05% capsaicin in adult rodents [59]. Spinal delivery is precluded as intrathecal QX-314 produces marked irritation. As with all potential intrathecal or epidural analgesic/anaesthetic drugs, where relatively high concentrations are delivered in close proximity to the nervous system, preclinical evaluation of toxicity in adult and developmental models is essential before clinical use [60].

Genetic studies and targets

Mutations of the SCN9A gene which encodes Na_v1.7 result in a range of conditions from channelopathy-associated insensitivity to pain (loss of function mutation) to severe pain conditions (eg. inherited erythromelalgia, painful peripheral neuropathy; gain of function mutations), and specific single nucleotide polymorphisms have been associated with altered pain sensitivity [17]. Selective blockers of Na_v1.7 are currently being developed [61]. Na_v1.8 is also a potential target, as gain of function mutations have been associated with painful peripheral neuropathies clinically [61], and selective blockade of Na_v1.8 reduced mechanical pain in a rodent OA model [62].

NGF sensitizes nociceptors, and loss of function mutations in the gene for the Trk-A receptor which binds NGF are associated with congenital insensitivity to pain with anhidrosis

[35]. Monoclonal antibodies against NGF produced analgesia and initial functional improvement in adults with OA [63], but the balance between therapeutic and adverse effects requires further evaluation [14].

The degree to which pain sensitivity, risk of persistent pain, and analgesic response is genetically determined is an area of increasing interest [10, 35, 64]. Single nucleotide polymorphisms (SNPs) or haplotypes of a number of genes have been associated with an altered risk of chronic pain, with the potential for identification of high-risk groups and/or targeted therapies in the future. However results can be variable, the underlying mechanism is not always clear, and other confounding factors that could modulate pain (such as mood) are not always taken into account [35]. Some examples related to musculoskeletal pain include:

1. Catechol-O-methyltransferase (COMT) regulates extracellular catecholamine concentrations and SNPs with low COMT activity have been associated with increased pain sensitivity. A meta-analysis of 8 studies reported the Met allele of rs4680 SNP as a risk allele for fibromyalgia or widespread pain [65].
2. GTP cyclohydrolase (GCH1) is a rate-limiting enzyme for tetrahydrobiopterin (BH4) synthesis, an essential co-factor for catecholamine, serotonin and nitric oxide production. Reduced GCH1 transcription and low BH4 levels has been associated with less pain following discectomy for radicular low back pain [66]. The prevalence of different GCH1 haplotypes differs in adults with fibromyalgia [67]. Sulfasalazine may have an analgesic action by inhibiting sepiapterin reductase in the BH4 synthesis cascade and reducing BH4 levels [68].
3. The potassium channel alpha subunit KCNS1, involved in neuronal excitability, is constitutively expressed in sensory neurons and markedly downregulated following nerve injury. A 'valine risk allele' has been associated with higher pain scores and an increased risk of neuropathic pain in patients with disc herniation [69].

4. Variation in the gene encoding the P₂X₇ receptor has been associated with lower pain intensity in a cohort with osteoarthritis, and related laboratory studies identified a related change in channel structure and function that may have therapeutic potential [70].

Epigenetic mechanisms influence gene activity without altering the DNA sequence. Chemical modifications to chromatin, such as DNA methylation and histone modifications, alter the accessibility of DNA to the transcription machinery, and can underlie developmental and environmental effects on gene activity [71, 72]. Epigenetic mechanisms have been implicated in the pathogenesis of rheumatoid arthritis [71] and also influence pain processing [72], and therefore represent potential treatment targets.

Assessing New Therapies : Pain And Related Outcomes

Confirming efficacy with any current or new therapy or intervention requires appropriate outcome measures that are sensitive and specific, and relevant to the needs of clinicians, patients and families. The lack of appropriate outcome tools poses particular challenges in paediatric musculoskeletal pain research [73]. Children with JIA continue to report significant levels of pain despite new therapies, and disease-related factors explain only a small proportion of the variance in pain scores [52, 74]. In addition, non-inflammatory musculoskeletal pain is common in childhood and adolescence [75, 76], comprises an increasing proportion of presentations to paediatric rheumatology clinics, and can be associated with significant negative impacts on physical, emotional and social well-being [77-79].

Pain is a complex sensory and emotional experience but assessment in clinical trials is often limited, and a more detailed and standardized approach in research and clinical rheumatology practice has been recommended [80]. This consensus statement was

developed from core outcome domains for pediatric acute and chronic/recurrent pain clinical trials (Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; PedIMMPACT) [81]. Characteristics of pain, impact on function, and factors that modify pain experience should be evaluated.

Pain Assessment

Assessment of pain requires a detailed pain history that includes, but extends beyond, measurement of pain intensity. Observer [82] and self-report [83] tools have been developed to measure pain intensity in children of different ages and in different clinical settings, but most have been validated for acute procedural or postoperative pain [84]. Single measures of pain intensity (such as parental global assessment of child pain on a 10cm visual analogue scale) [49] do not reflect the distribution, frequency and duration of pain episodes in children with chronic pain; and variance is often seen between patient, parent and physician report. Specific descriptors and the pattern of pain (eg. paroxysmal shooting pains unrelated to activity and with associated allodynia) may suggest a neuropathic pain component that warrants specific evaluation and different pharmacotherapy [4, 46]. Retrospective measures such as average pain in the last week can be inaccurate or provide limited information [85]. Prospective diaries with real-time collection of data (usually for one week) reduce problems associated with retrospective recall and summarization of events, and artificial contexts or settings [86]. Electronic formats have higher rates of compliance than paper-based pain diaries [87]. Additional details of pain experience (degree and distribution, duration, pain unpleasantness) and the temporal relationship to functional limitations, stiffness and fatigue can be collected, and have confirmed significant levels of pain and disability in children with JIA [52, 88]. Detailed pain assessment has the potential to more accurately guide management, generate quality

improvement indices, evaluate predictors of persistent symptoms, and provide more informative outcome measures for clinical trials [80, 89].

Functional Impact And Pain Modifiers

Evaluation of health-related quality of life (HRQOL) is an established component of care, and tools such as the Pediatric Quality of Life Inventory (PEDsQL) are widely used in rheumatology research and clinical practice [90]. Pain is a strong determinant of overall HRQOL, particularly psychosocial well-being, in both inflammatory [88, 91, 92] and non-inflammatory [78] musculoskeletal conditions.

Pain cannot be adequately assessed or managed as an isolated symptom. Tools such as the Bath Adolescent Pain Questionnaire include mood and functional subscales, and psychosocial variables (depression and pain-specific anxiety) were found to be as important as condition-related variables when assessing physical function in adolescents with rheumatological conditions [89]. Children with chronic musculoskeletal pain report increased anxiety and depression [93], and cognitive and affective variables influence physical and emotional function and pain experience [79]. Maladaptive cognitions with catastrophizing about pain, and fear of pain and movement, can lead to activity avoidance, and increasing musculoskeletal symptoms [94]. Pain coping style and self-efficacy impact on HRQOL in newly diagnosed JIA [95], correlate with sensitivity to acute experimental stimuli [96], and also contribute to the variance in long-term pain report [97]. A bidirectional relationship has also been reported between sleep and pain: pain worsens sleep and poor sleep quality is predictive of increased pain the following day [98, 99].

Parental perceptions and responses are important contributors to pain-related disability in children and adolescents with chronic pain [100]. Parent emotional distress influences proxy-reported HRQOL in children with newly-diagnosed JIA [95]. Family involvement can encourage adherence to home exercise programs, particularly in older

adolescents [101], and parental education and involvement is essential if progress is to be maintained when managing children with chronic musculoskeletal pain [5].

Neurosensory Evaluation: Quantitative Sensory Testing

Quantitative sensory testing (QST) protocols encompass multiple mechanical and thermal sensory domains relevant to the perception of pain; whereas clinical nerve conduction studies do not adequately assess the function of small unmyelinated and C-fibre pathways. QST has been used in adults with musculoskeletal pain to: assess normal and pathological sensory function and pain perception; aid in phenotyping and differential diagnosis; identify and quantify central sensitization; and monitor disease progression or treatment response [102, 103]. In paediatric populations, QST has also been used to: identify age-related changes in sensory function; evaluate effects of prior injury; quantify sensitivity in chronic pain states; characterize disease progress and/or monitor response to treatment [37, 38, 104-107].

Peripheral sensitization with localized changes in thermal, tactile and pressure sensitivity has been identified in adults with joint disease [103, 108, 109]. In addition, widespread changes in threshold and increased temporal summation suggest central sensitization of pain pathways, and thus provide additional diagnostic information and can inform management [102, 103]. Generalized reductions in pressure pain thresholds have been reported in fibromyalgia [110] and in children with joint hypermobility and musculoskeletal pain [111]. Compared to healthy controls, children with JIA had significantly lower pressure pain thresholds over involved joints, but also at distant sites (eg. inflamed knee and ankle as well as distant paraspinal muscles [112] and over inflamed joints as well as negative control bony sites on the forehead and anteromedial aspect of the tibia [29]). Sensitivity persisted beyond the period of active inflammation [113] and neither disease duration nor disease activity correlated with the total mean pressure threshold [29].

Pain sensitivity and tolerance can be assessed with the Cold Pressor Task, in which pain intensity and/or duration of immersion is measured following placement of the hand in cold water (0 to 15°C) [114]. In a small group of 16 children with JIA, pain tolerance (ie. immersion duration) was reduced, but pain threshold and intensity were not significantly different from controls [96]. Cold pressor tasks are often included as the conditioning stimulus in tests of endogenous pain control, termed conditioned pain modulation (CPM) or diffuse-noxious inhibitory control (DNIC). A test stimulus (eg. pressure or heat) is delivered before, during, and after a conditioning stimulus is applied to a different body region, and the degree of inhibition is assessed by changes in the reported intensity or threshold of the test stimulus. In accordance with laboratory studies demonstrating late maturation of endogenous inhibitory mechanisms, CPM became more effective in older children (12-17yrs vs 8-11yrs) [115].

Neuroimaging

Specialised neuroimaging techniques have identified structural changes and altered patterns of brain activity and connectivity in association with different pain conditions; and have also been used to assess modulation by analgesia, cognitive and emotional factors [116-118]. Increased exposure to procedural pain in neonatal intensive care has been associated with impaired brain structure and connectivity [119]. Relatively few have studied children with chronic pain, but fMRI identified alterations in connectivity and stimulus-evoked brain activation in children with Complex Regional Pain Syndrome [120, 121].

Management Approach : Beyond Pharmacology

Mechanisms underlying pain in non-inflammatory musculoskeletal conditions are often unclear, and reported pain does not directly correlate with disease activity in

inflammatory conditions such as JIA. In addition, there are complex interactions between pain, disability, and psychosocial variables that impact on overall well-being and HRQOL. As a result, development of a more comprehensive 'biopsychosocial model' for the assessment of children with chronic pain, including those with musculoskeletal pain, has been advocated [4, 79, 80, 89]. Management occurs within a multidisciplinary framework that incorporates pain education, targeted psychological and physical interventions, self-management and pharmacotherapy [4, 5, 77, 79].

Currently, there is insufficient high-quality evidence to guide management, particularly of non-inflammatory musculoskeletal pain [94]. Physiotherapy is the most commonly recommended treatment, but it is difficult to perform controlled trials of physical interventions, and supporting evidence is limited for some conditions. A 12-week exercise program improved lower limb muscle strength in children with JIA "without negative consequences on pain", but assessment and reporting of pain outcomes was limited [122]. Three recent systematic reviews could not identify many high quality studies of physiotherapy for pain associated with generalized joint hypermobility [77, 123, 124], and only one trial conducted specifically in children had a low risk of bias [73]. Evaluating physiotherapy for management of CRPS was also hampered by the methodological quality of reported trials, and often the impact of physiotherapy could not be separated from concurrent medial and/or psychological interventions [125]. As lower physical activity levels (Physical Activity Questionnaire) were associated with increased pain (intensity and distribution) and increased interference due to pain (Child Activity Limitations Interview-21) in children with JIA, exercise therapy interventions were postulated to have a role for pain management [126].

A systematic review of psychological interventions reported improvements in pain and disability in children with chronic pain, and included trials conducted in fibromyalgia and JIA [127]. Involvement of parents in management was also shown to be beneficial [128].

Greater benefit from a psychological intervention was found in children with JIA who had high pain scores and low HRQOL [129], suggesting it may be advantageous to target specific patient groups.

Further research is required to evaluate the impact of multidisciplinary management, using sensitive and relevant outcome measures. There is also a need to understand which components of management programs are best-suited to which patients, and how they can be better implemented to improve adherence [101] and ensure sustained benefit. Treatment expectations and willingness to accept a biopsychosocial formulation can vary, and adolescents were less likely than their parents to appreciate the role of emotional and psychological factors in pain experience [130]. Pain beliefs and “readiness to change” influence acceptance of a self-management approach to pain [131], but the ability of specific questionnaires to assess this and/or predict outcome of multidisciplinary care requires further validation in paediatric populations. The potential for long-term effects of childhood chronic pain on mood, function and future employment also highlights the importance of transitional care from paediatric to adult services [132, 133].

Summary

Increased quality and quantity of evidence is required to inform management of chronic musculoskeletal pain in children and adolescents. Pain and pain-related disability represent complex interactions that encompass: peripheral and central sensitization of nociceptive pathways; genetic susceptibility to persistent pain; effects on sleep, activity, and quality of life; and modulation by mood and family factors. Research is identifying potential targets for mechanism-based interventions which require evaluation within an integrated plan for assessment and management.

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Conflicts of Interest

The author has no conflict of interest to declare.

Practice Points

- pain assessment encompasses a detailed pain history, effects on function and quality of life, and consideration of the role of psychosocial and family factors
- an integrated and inter-disciplinary approach to management of chronic musculoskeletal pain in children is required to more effectively select and target interventions, reduce pain and disability, and improve long-term outcomes

Research Agenda

- as nociceptive processing and the impact of different forms of injury vary during postnatal development, further evaluation of age-related changes in laboratory models relevant to musculoskeletal pain is required to inform mechanism-based treatment
- improved assessment of pain and associated disability, with more sensitive and inclusive outcomes, is required to evaluate current and potential interventions and inform evidence-based practice
- specialized techniques for sensory evaluation and neuroimaging will better characterize chronic musculoskeletal pain in association with different conditions
- determining predictors of persistent pain and identifying high-risk groups will enhance our ability to target treatments for different patients, and select the best timing and type of intervention

FIGURE LEGEND

Figure 1. Simplified schematic of major nociceptive pathways. Maturation varies at different points in the central nervous system, and the textboxes highlight developmental differences. Afferent nerve inputs from joint and muscle reach the sensory dorsal horn, where sensitivity is influenced by local excitatory and inhibitory mechanisms, descending pathways from the brainstem (green), and neuroimmune interactions. Pain projections include ascending spinoparabrachial pathways (red) and spinothalamic (blue) pathways. *Legend:* DRG, dorsal root ganglion; PB, parabrachial nucleus; PAG, periaqueductal grey; RVM, rostral ventral medulla. *Adapted from* Fig. 6.1. Walker SM, Baccei M. In: McGrath PJ, Stevens BJ, Walker SM, Zempsky WT (Eds). Oxford Textbook of Paediatric Pain, Oxford University Press, 2014

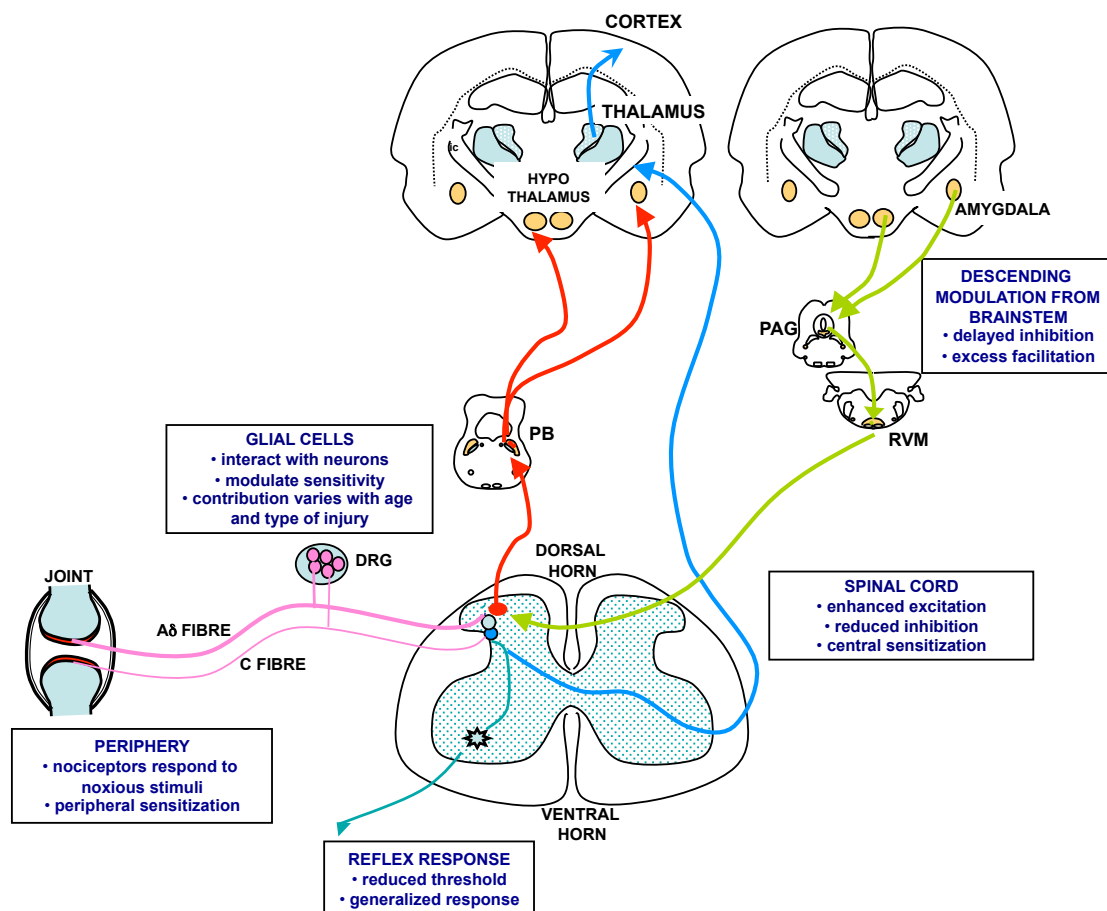


Table 1. Definitions and Taxonomy

Term	Definition	Note
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.	<i>The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. In pre-verbal children, composite scales incorporating behavioural and physiological responses may be viewed as a form of pain 'report'.</i>
Nociception	The neural process of encoding noxious stimuli.	<i>Consequences of encoding may be autonomic (e. g. elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior).</i>
Nociceptor	A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli.	
Peripheral sensitization	Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields.	<i>Sensitization can include a drop in threshold and an increase in suprathreshold response. Spontaneous discharges and increases in receptive field size may also occur. This is a neurophysiological term.</i>
Central sensitization	Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.	<i>Clinically, sensitization may only be indirectly inferred from phenomena such as hyperalgesia or allodynia.</i>
Hyperalgesia	Increased pain from a stimulus that normally provokes pain.	<i>This may be the consequence of peripheral or central sensitization, or both.</i>
Allodynia	Pain due to a stimulus that does not normally provoke pain.	<i>Touch, light pressure, or moderate cold or warmth evoke pain when applied to apparently normal skin.</i>
Nociceptive pain	Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.	<i>Pain is occurring with a normally functioning somatosensory nervous system</i>
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system.	<i>Neuropathic pain is a clinical description (and not a diagnosis) which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria.</i>

Source: International Association for the Study of Pain (IASP) Taxonomy. <http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&navItemNumber=576>

Table 2. Examples of Nociceptor Receptors and Channels

Receptor/ Channel	Activation	Arthritic pain
TRPV1	<ul style="list-style-type: none">• noxious heat• low pH• capsaicin	<ul style="list-style-type: none">• sensitized by BK, PGE2, NGF• increased expression• contributes to thermal hyperalgesia
TRPA1	<ul style="list-style-type: none">• mechanical stimuli• cold and chemicals	<ul style="list-style-type: none">• contributes to mechanical hyperalgesia
ASICs	<ul style="list-style-type: none">• hydrogen ions: low pH in inflamed tissue	<ul style="list-style-type: none">• contributes to peripheral sensitization
PAR2, PAR 4	<ul style="list-style-type: none">• enzymatic cleavage of receptor by proteinases	<ul style="list-style-type: none">• elevated proteinases in synovial fluid• contribute to peripheral sensitization
Na _v 1.7, Na _v 1.8	<ul style="list-style-type: none">• voltage gated sodium channels	<ul style="list-style-type: none">• increased expression• increased excitability
CB2	<ul style="list-style-type: none">• endogenous cannabinoids	<ul style="list-style-type: none">• increased expression in synovium and spinal cord• agonist reduces pro-inflammatory cytokine release and reduces pain

TRP, transient receptor potential; ASIC, acid sensing ion channel; PAR, protease activated receptor; Na_v, voltage-gated sodium channel; CB, cannabinoid

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