Delivering transformative change in paediatric pain: A Lancet Child & Adolescent Health Commission

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Executive Summary

Every baby, child and adolescent will experience pain at times throughout their life. Despite its ubiquity, pain is a major challenge for individuals, families, healthcare professionals, and societies. Pain is often hidden and can go undiscussed or ignored. Undertreated, unrecognised, or poorly managed pain in childhood leads to important and long-lasting negative consequences that continue into adulthood. This undertreatment should not continue. We have the tools, expertise, and evidence to provide better treatment for childhood pain.

In this Commission we present four transformative goals that will, if achieved, transform the lives of children with pain and their families. These goals, taken at face value, may seem simple and obvious. However, if the goals were easy to achieve there would be few, if any, young people reporting poorly managed acute pain, pain after surgery or procedures, or ongoing chronic pain. Pain is multifactorial, and influenced by biological, psychological and social factors, making it complex and difficult to treat effectively, especially in infants, children and adolescents. This Commission focusses on children from birth through to 24 years of age in developed countries.

The first transformative goal is to 'make pain matter'. Here we argue that pain has not mattered enough, as evidenced by common failings in clinical practice, low levels of training and investment, and a lack of concern for issues of equity and equality. Despite some good examples of knowledge translation, we highlight that investment in a strong social science research base for paediatric pain will catapult us into a new era in which we can address the social and cultural context of pain.

The second is to 'make pain understood' at a fundamental biological and psychological level. There has been excellent progress in mechanistic understandings of nociception and pain perception for

both acute and chronic pain states but gaps in knowledge remain. Advances in developmental biology, in genetics, in psychology, and in nosology and classification will all help speed up the discovery in these areas. There is also a need for greater investment in larger international birth cohort studies that incorporate comprehensive pain-related measurement incorporated.

The third is to 'make pain visible'. Pain can and should be assessed. We need to help improve understanding of optimal methods for pain assessment at throughout childhood and in all clinical scenarios. While subjective pain report is the primary and desirable method when this is possible, many of the methods and measures that are in common use can and should be improved. There has been development in understanding the biological correlates of pain, and in broader patient reported outcome variables that can expand our horizons. Finally, we should be more focussed on assessing outcomes that are important to patients, rather than those that are central to researchers and clinicians.

The fourth is to 'make pain better' by advancing our knowledge of multiple treatment options in all areas. There is a very small number of randomised controlled trials of pain interventions in children. The pipeline for innovation and novel treatments is running dry. Novel drug discovery studies using single case designs could advance treatment options. There is innovation in new ways to personalise individual treatments, but there is a need for greater investment in research and coordinated approaches at all levels.

This Commission is a call for researchers, clinicians, policy makers, funders, and healthcare executives to engage enthusiastically and deliver both the easy and the difficult changes needed to improve the lives of children with pain.

Introduction

Pain is a feature of life that is present across cultures and age.1-3 It is often associated with acute injury or is a symptom of disease, but it can also be evoked by physical activities or social interactions: from play and sport to body adornment and religious ritual. Regardless of its origin, pain is typically experienced as unpleasant, negative, and threatening. While a primary function of acute pain is to protect an organism from potential damage, at a biological, psychological and social level it also functions to promote recovery, to facilitate escape from immediate harm, to avoid future harm, and to warn others of potential danger. 4 Nevertheless, pain can often extend past its functional utility, and can exist only as a negative experience. Despite the ubiquity of pain, it remains poorly understood in infants, children and adolescents, and has made relatively few leaps since Jill Lawson's advocacy in 1986 led to change in the use of anaesthesia in infants (Box 1). Approaching 40 years later, we consider how much of what we do (or fail to do) now for children in pain will come to be seen as unwise, unacceptable or unethical in another 40 years? Indeed, how much of our common practice and received wisdom should policy makers, funders, researchers or clinicians challenge? How much of what is being done can and should be built upon and strengthened? We think in many

areas of paediatric pain that it is time for change. In this commission we considered four transformative goals that we believe will improve the treatment of paediatric pain. Our goals are simple, but delivering them is complex and needs multidisciplinary attention from researchers, clinicians, policy makers, funders and the public. Our goals are not sequential, but the aim of this commission is to (1) make pain matter, (2) make pain understood, (3) make pain visible, and (4) make pain better.

Box 1. Jeffrey and Jill Lawson and advocacy for pain management

Here, we consider children of all ages, from infants to late adolescents, and focus this Commission on how middle to high income countries can improve their provision of pain treatment. We need to adopt the best pain management practices when we treat children who experience all types of pain, from routine inoculation to cancer pain management, to the provision of complex residential multidisciplinary rehabilitation for idiopathic disabling pain. Beyond the individual we also demonstrate how we can better understand the interpersonal and social challenges of under-recognised pain-related distress. Childhood pain is common, ranging from acute to chronic, and includes procedural, disease-related, and breakthrough pain amongst others (see Figure 1). We highlight the effects of childhood pain on parents and other significant family members, and the challenge of explaining pain to those around us, including other children. As with all illness, disease and distress, pain also operates on a moral and social plane10 and any attempt to improve paediatric pain management would be incomplete without consideration of the linguistic construction of the meaning of pain, and how this impacts the recognition of pain in others and equity in access to care.

Figure 1. Common types of pain during childhood

Goal 1: Make pain matter

When one is in severe pain, nothing is as important as finding relief. But pain in others evokes a less urgent response. Pain is often expected to be transitory, diagnostically useful, bearable and easily forgotten, but when this is not the case it is more difficult to tolerate. While people can often be highly sensitive to their own pain, a social insensitivity to pain in others is common11, 12, and when people describe their pain the importance of it can be too easily diminished.13 Here, we outline a strategy to make children's pain matter to others. To achieve this there needs to be an understanding of the social science of pain. We will discuss how the absence of voice can lead to an assumption that there is an absence of need and we will give examples of how pain can be inadvertently dismissed as being unimportant, and how our language can suggest to children that pain should be stoically and quietly endured 14-16. We will consider how ignoring childhood pain can be prevented in children who have a more limited verbal repertoire and how that can result in them being seen to have fewer rather than greater needs. We will also consider how best to avoid scenarios where analgesia is withheld or withdrawn during clinical treatments. Importantly, we appreciate that these goals will only be achieved when a clear organisational strategy is in place. Successful approaches which have been used to improve knowledge, attitudes and practices in health care and other formal settings frequented by children will be discussed.

Social organisation

Access to pain relief should be a basic human right, but navigating policy and governmental responses to uphold that right has not been easy and is arguably in retreat.17 Pain is not immediately thought to be a social phenomenon, but more often considered to be a physical and cognitive experience. Nevertheless, culture influences our behavioural expression of pain, how others view people experiencing pain and one's response to someone in pain.18 We learn how to express and respond to noxious stimuli in keeping with societal norms from our families and those around us in society, and phrases such as 'big boys don't cry', and 'no pain no gain' are common. For many, the experience of pain is short and self-limiting (e.g. pain following an acute injury) or relatively straightforward to treat, with a known underlying aetiology. Therefore, for many in society, pain that does not follow an acute trajectory can be dismissed and perceived as unimportant because of the belief that all pain is similar to the acute pain that most people experience. However, this is not true, and these societal misconceptions of pain can be harmful. Dominant social beliefs that pain is temporary and should be endured can result in stigmatization of children and adolescents living with chronic pain.19 It can also predispose infants, children, and adolescents to endure repeated procedural pain,20 and can then lead to a culture of poor pain management practice.21, 22 Variability in the experience and expression of pain may be a further contributing factor to dominant misconceptions and myths held in society that inhibit access to pain management.

Traditionally nurses and physicians were not formally taught about pain, nor how to provide adequate pain care to treat infants, children and adolescents who had to undergo painful procedures and treatments (e.g. lumbar puncture, bloodwork, burn dressing changes). In fact, clinicians were more concerned about the adverse consequences of treating pain (e.g. administration of opioids) than the consequences of inflicting pain.23-25 Medical education in pain remains a challenge. Veterinary students receive more formal education on pain (e.g. understanding pain, pain treatment) than nursing and medical students.26 Improvements in education are needed but alone are inadequate as even when individual clinicians are interested in improving their own practice, systematic barriers exist.27

The experience of pain within healthcare is often a product of treatment. For example, vaccinations and other related skin-breaking needle procedures (e.g. bloodwork, intravenous cannulas) are routine and represent a substantial number of painful procedures in healthcare settings for paediatric patients, yet in many cases pain relief is infrequently given.20 For example, in the UK, children are usually given 16 separate injections between birth and 14 years, many without any pain management 28. While the short-term pain associated with these procedures could be considered fleeting or inconsequential, they are known to cause considerable distress when repeated in children or infants over weeks, months or years, when each momentary experience is compounded and can be traumatic.29 Untreated pain has multiple consequences. For example, the establishment or exacerbation of needle fear is common during childhood, where 20-50% of adolescents report fear of needles.30 This consequence matters: it can delay or prevent important vaccinations and blood tests that are necessary for the prevention or diagnosis of illness. For example, needle fear and phobias were found to be the deterrent in obtaining the influenza vaccine as adults working in a healthcare setting with 8% of clinicians and 27% of hospital employees not receiving their flu vaccine due to

needle fear.30 What is often presented as ‘just one poke’ has long lasting effects.31 Moreover, not actively treating procedural pain is not defendable as there is high-quality evidence on how to reduce pain during procedures including needle skin puncture for children of all ages. The World Health Organisation adopted some of the guideline recommendations, which reviewed the evidence for reducing pain during immunization in children.32 The WHO guideline specifically described the importance of, and how to, reduce pain at the time of vaccination (Box 2). The evidence is clear that providing pain management needs to be as essential as any other component of medical procedures and treatments (e.g. sterility, explaining the procedure to children and caregivers).

Box 2: Vaccination pain management: from clinical practice guideline to WHO

Despite international guidelines, even in the most highly resourced medical centres, a culture of assertive pain management is not always common.20, 34 Whilst there are places that implement institutional wide interventions to manage needle pain, so children and adolescents receive better procedural pain care35, this practice is not widespread. Interestingly, pain management can differ between sexes. For example, pain management is more commonly offered to infant boys than girls, and parental presence influences its provision.36 In early childhood, boys are more likely to be prescribed opioids, but in adolescence girls are more likely to be prescribed opioids37. However, girls are also more likely to report chronic pain during adolescence compared to boys.

It is not solely pain treatment that can differ by sex. Despite girls being more likely to report chronic pain during adolescence, their chronic pain concerns were dismissed significantly more often by physicians (35%) compared to boys (17%) 38. Similar bias towards pain management differences has been found to persist into adulthood in most but not all studies 39 and describe as an ethical issue in pain care 40.

Mobilising knowledge; Dissemination and implementation

The problems of poor paediatric pain practice may stem from lack of knowledge or understanding, or from a failure of training. However, this is at best a partial view. The problem in many cases is not one of knowledge but of knowledge translation, which refers to the uptake and application of knowledge in practice with a focus on overcoming barriers. This is also often referred to as knowledge mobilization, or increasingly, dissemination and implementation of evidence to improve practice.9 Shortening this gap from knowledge production to implementation 41 is critical and might now be more achievable given the explosion in new computerised media. Consumers of healthcare can access this information much more readily, and there is increasing pressure for scientists to consider the translation and impact of their research. This means, making their research understandable for the lay person and seeing how it can change knowledge or behaviour. Of course, there is also a flood of poor-quality, non-evidence-based information on the Internet regarding pain, and researchers can be nervous to disseminate to the public, for good reasons. Strategies to tackle misinformation and provide a trusted accessible place to access new evidence-based information could be one way to disseminate. Because of the need for reliable information and support, and now the technological possibility to provide it there are a growing number of initiatives to disseminate science more quickly to parents, healthcare professionals, and communities.

One such prominent organisation – Solutions for Kids in Pain (SKIP), launched in 2019 brings together Canada's paediatric pain knowledge producers, front-line knowledge user organizations, end beneficiaries, and over 100 partners from across sectors. SKIP's four goals to support its mission and vision are: 1) Confirm knowledge user needs (including patients, caregivers, health professionals, administrators, policy makers) and organize current resources and evidence; 2) Produce and promote knowledge mobilization tools to address diverse knowledge user needs; 3) Facilitate institutional change by assisting knowledge users to access, adapt, and implement evidence; and 4) Increase awareness and foster a sense of urgency amongst the general public to prevent and treat pain in children. SKIP's long-term outcome is improved children's pain management in Canadian health institutions, beginning with Children's Healthcare Canada members.

Good examples also exist of how to collectively capture and benchmark practice. The 'EUROPAIN' (EUROpean Pain Audit In Neonates) study is one example in neonatal care showing widespread analgesic practice but with extensive unexplained variability between sites.42 With older children there are also examples; in Australia the Paediatric Electronic Persistent Pain Outcomes Collaboration (PaedePPOC) initiative introducing common assessment practice for pain management in 10 centres has successfully been integrated into practice, providing the means for comparison between populations and different resource settings.43

Although some countries have not developed surveillance and benchmarking practices for paediatric pain management,44 there have been substantial advances. Where evidence-based guidance is available, the focus should turn to its implementation, where successful attempts at translating knowledge into practice have been demonstrated.45 There is no single correct approach to implementing an organisation change programme to improve pain care. 35, 46-48 It is worth stressing that pain management also often occurs outside of the hospital, in the home 49 in educational settings,50 in the community (e.g., family practitioners offices), and in pre-hospital emergency environments.51 No single strategy works in all settings, and context needs to be considered; thus type of institution, leadership, culture, value of research in practice, number and type of healthcare professionals, and physical resources52 are all relevant and need to be considered. A further example at a hospital level is the implementation of the "Children's Comfort Promise" which executed new protocols for nurses to provide options to reduce pain during needle procedures.35 One prominent international initiative called ChildKind (http://childkindinternational.org/). Uniquely, ChildKind is an attempt to establish and maintain practice improvement through certification, developed by the Special Interest Group on Pain in Children of the International Association for the Study of Pain. The core principles include 1) Presence of a facility wide policy on pain prevention, assessment, and treatment which demonstrates clear institutional commitment to pain relief; 2) Ongoing education on pain for staff, trainees, and patients; 3) Evidence of the sustained use of developmentally appropriate process for pain assessment; 4) Specific evidence informed protocols for pain prevention and treatment including pharmacological, psychological, and physical methods; 5) Regular institutional self-monitoring within the framework of continuous quality improvement.

Finally, a final example is the online initiative '#ItDoesn'tHaveToHurt' which involved a collaboration between paediatric pain researchers, parents, and 'YummyMummyClub.ca', a digital platform for Canadian parents to provide evidence-based information about children's pain management across social media platforms (e.g., Facebook, YouTube, Instagram, Twitter). This initiative had more than 72 million content views worldwide in just one year.9 (https://cihr-irsc.gc.ca/e/49821.html). Examples are summarised in Table 1.

Table 1. Recent and ongoing initiatives to mobilise knowledge in paediatric pain

Equity

Focus on the delivery and provision of care should come with a focus on equity. Equity is not about equal access to shared resource, but rather fair access to unequal resources according to need. Worldwide there is poor equity in access to pharmacological pain management,53 and the types of multidisciplinary treatment described in this Commission are not available for all infants, children, and adolescents. Despite the documented inter- and intra-national inequalities, there is little formal study of equity and inequity in the context of pain, with some exceptions,54 but very few in paediatrics. In research there has traditionally been an interest in income, racial and gender driven inequities. With children the most extensive study of this has been in sickle cell disease, an inherited chronic disorder of blood cells causing painful 'crises' in sufferers who are mostly of African heritage and in whom prejudicial inequity in access to pain management is well recognised.55, 56 Other forms of pain management inequity exist amongst children with disability. For example, children and adolescents with disabilities have their postoperative pain assessed less often and receive fewer opioids and fewer days of opioid pain management for the same surgery as children and adolescents without disability.57 It is concerning that children with disabilities receive less pain management but also experience the most pain.58 There is a need to better understand the patterns and impact of inequity in pain provision at a societal level. There is also a need to explore the psychological effects of perceived inequity. In human experimental studies, for example, we are beginning to understand that perceptions of injustice and inequity can affect pain and disability status. If one believes they are being unfairly treated this can worsen both the experience of pain, disability and treatment effectiveness.59, 60 We know so little about how young people and their parents perceive inequity and injustice, and there are few studies attempting to implement change in perception, reality, or both.

An examination of the social science of paediatric pain treatment would be incomplete without recognition that pain management has become highly politicised in many countries due to the changes in patterns of opioid prescribing and use for chronic pain, and the subsequent increase in substance use disorders and related harms.61 This debate has also been extended to the appropriate use of opioids in acute pain and in paediatric anaesthesia 62. Eighty percent of the world's supply of opioid medicines is distributed to less than 10% of the world's population with the highest supply being in the USA and Canada, followed by Austria and Germany.63, 64 Paediatric pain medicine, however, has not been explicitly addressed in most of the national responses to the different 'opioid crises' leading to a concern that measures to control opioid use in adult pain management will be inappropriately applied to young people.65, 66 In policy and in the media portrayal of the North American opioid crisis conflates substance use disorders and pain medication. An analysis of the

Canadian media reports that the negative sequela of opioids is frequently reported whereas an understanding of how to treat acute and chronic pain is not.67 Through this media, public views have been influenced to consider opioids as drugs of addiction rather than pain medicine. This has in turn, influenced policy approaches (e.g. criminalization, significant oversight of physician prescribing behaviour), which risk distancing physicians from treating those who need their care.68 Health care professionals, young people and parents continue to hold misconceptions and believe myths about opioid use in paediatric patients69 in which the media paints the opioids themselves as the villain and underlying reason for substance misuse. Opioids have their place in paediatric pain medicine. In a context of the oversupply of opioids, childhood pain can usefully be considered a risk factor for long-term harmful exposure to opioids.70

Overall, we need a new social science of pain and explicit recognition that at an individual and societal level, articulation of pain will always have to struggle against forces that would silence it. For some questions we need a political science of pain to take us beyond description and policy toward understanding how political values shape experience. Other questions will need novel anthropology to help understand culturally embedded experience, and we need modern implementation science to explore the best evidence for organisational change.

Research and clinical priorities to make pain matter

Three areas should be prioritised that will enable us to achieve our goal to make pain matter to everyone; 1) Improve equity; 2) mitigate stigma, and 3) understand the social science of pain, including sociology, social psychology, political science, and anthropology (Box 3). A final area on improving accountability in all sectors of society, increasing awareness, urgency, and responsibility for all children's pain needs to be addressed by funders and policy makers (see Box 10).

Box 3: Research and clinical priorities to make pain matter

First, we need to understand equity and inequity in pain management, and where inequity lies within our healthcare systems. Within chronic pain particularly, much of the research is conducted in middle class, Caucasian adults. Similarly, within Western medicines, patients are most likely to be treated by Caucasian males. Less is known about how different cultures, races, and socioeconomic groups interpret and communicate pain, or their preferences for pain management. When pain becomes invisible to others, in particular to those with power and control over the allocation of shared resource then inequality and inequity are perhaps inevitable. Such inequities pervade paediatric pain management. And where there is invisibility and inequity, there is the opportunity for unchallenged prejudicial inequality. We need to address whose pain matters least, and the social forces that silence the dissent or attempts at social or political redress.

Second we need to research the optimal methods for managing stigma and mitigate its effects. Pain has become a means to enable the medical gaze in modern medicine, relevant only insofar as it is diagnostically useful.71 Pain that is without diagnostic meaning becomes 'idiopathic', 'medically unexplained', 'functional', or 'psychological'. Patients and families often report these labels as

unhelpful or insulting but socially they function to silence complaint; pain doesn't seem to 'matter'.72, 73 Medical professionals may not be able to diagnose a specific disease or have immediate tools to provide pain relief. Whilst it is possible to inform the patient that they 'don't know' what is wrong, this must be communicated appropriately. When pain is dismissed, families report significant distress from attempting to talk about something people do not want to hear. But to not talk about something so fundamental as your child's pain is equally distressing.

Finally, we need to invest in a social science of paediatric pain. Starting from the idea that pain is inherently subjective, and that culturally "it lends itself to invisibility and is language resistant".14 Like all private mental events each person has a privileged position from which to observe one's own experience, meaning that others' experience of one's pain is always secondary, always dependent on the clarity and force of the signal; upon the ability of the observer to be able to decode the signal,18 and their aptitude for allocentricism, and ultimately empathy.74 Further, part of how humans cope with life events, with the sometimes staggering levels of social and personal injustice, multiple experiences of loss, and fear of one's own inevitable death, is to have inherent biases toward optimism, avoidance of emotional distress, and systematic diminution of the impact of problems that are difficult or impossible to solve.75 For the pain of others these self-protection biases translate into the systematic underestimation of the pain children experience. Pain underestimation is not mitigated by familiarity, it is not a stranger effect: mothers underestimate the pain of their children and nurses of their patients.76 We have the capacity to experientially avoid distress, including the distress caused by witnessing other's unalterable suffering.77 Socially and psychologically, every day and in multiple ways, we turn away from the suffering of others.

Goal 2. Make pain understood

Improvements in the care of children with pain, including better recognition, valid explanation, reliable assessment and the development of safe and effective treatments, will only emerge in a safe and sustainable way if informed by a full scientific understanding of pain. Our second goal is to make childhood pain understood by improving our fundamental knowledge of the developmental aspects of nociception and pain systems.

Moving on from Descartes

Central to the challenge of explaining mechanisms in pain is the stubborn persistence of a longstanding Cartesian 'dualism' regarding the relationship between physical and mental events that can hamper more modern scientific inquiry.78, 79 Particularly damaging is the stubborn belief that an individual's pain can only be objectively investigated by, and even reduced to its purely 'biological' drivers thereby denying the psychological and social elements that impact the experience of all types of pain.80-85 We judge that it is important to be clear in our thinking when we are describing models of nociception only, and when we are attempting to understand or explain pain as a whole. This is particularly pertinent in children's pain where both mechanisms and perceptions are also a function of age and state of development.

To make pain understood, in all its contexts, we should be consistent in our use of pain terminology, which can seem complex and confusing, not least because it requires frequent revision with advancing knowledge and experience. Some of the current most widely used clinical and scientific definitions and classifications of pain are described in Box 5. In this discussion of mechanisms we have used the general clinical terms acute and chronic pain, as defined, nevertheless acknowledging that each encompasses an overlapping range of causes and mechanisms making a strict temporal distinction somewhat arbitrary and artificial.

For chronic pain the International Association for the Study of Pain (IASP) reported the results of their task force on an updated classification in 2020, and following the latest version of the WHO International Classification of Diseases (ICD-11) included chronic pain as a discrete entity for the first time.86 Although the appearance of a new classification and nomenclature for chronic pain is itself a major success story, bringing increasing awareness and clarity to a complex area, it may not best represent all types of chronic pain in children: both acute and chronic pain in paediatric practice should also always be considered in a developmental context.

Box 4. Pain definition and classifications

Nociception, and somatosensory pain transmission

Figure 2 presents a schematic of current knowledge regarding the different mechanisms for nociceptive, neuropathic and nociplastic pain (defined in Box 4) illustrating how they relate to different sources of pain, and showing some of the basic neural circuits and pathways that lead to pain perception in the brain. Clearly, one or more somatosensory mechanism may be involved in a given clinical pain presentation, and this may change over time. For example, due to disease progression in a long-term health condition such as arthritis or cancer, or when pain arises or persists although damage to tissue cannot be identified. A common characteristic of pain transmission by any mechanism is that modulation of pain signalling can potentially occur at multiple sites along pain pathways including peripheral pain receptors (nociceptors), the spinal cord, brainstem and importantly the brain, which is also integrating multiple other pain and non-pain related inputs, leading to different patterns of activity that characterise an individual's pain. Importantly, during childhood virtually all body systems are changing structurally and functionally, including pain processing mechanisms themselves, potentially influencing almost every aspect of the experience of pain at different ages with ongoing consequences for later life.

Figure 2 Pain mechanisms and sources of pain

Nociceptive pain occurs within an intact and normally functioning somatosensory nervous system and can therefore be regarded to an extent as 'normal pain' because it is the mechanism of the common everyday pain we experience after injury. It is often predictable in duration and intensity and is by far the most common and frequent experience reported. Therefore, but often erroneously, nociceptive pain is assumed to be the 'model' for all pain. The physiology, pharmacology and psychology of nociceptive pain differs at different ages. This, and its relationship to other pain

mechanisms and states needs to be fully appreciated in order to understand the mechanisms of aberrant or refractory pain presentations; including those underlying the intensity, quality, persistence and consequence of pain.

Developmental aspects of nociception and analgesia

Nociceptive pain mechanisms have been studied in children but there remain considerable and important gaps in our knowledge. Nociceptive pain involves temporary structural and functional changes in the system in response to tissue injury that resolve over time with healing (i.e., peripheral and central sensitisation leading to lower pain thresholds (allodynia) and increased sensitivity to previously painful stimuli (hyperalgesia) at the site of inflammation or trauma, and changes affecting more distant sites). This neuroplasticity determines the adaptive ability of the somatosensory nervous system, and the mechanisms that initiate and control it have proven important for our understanding of the changes in nociception throughout development and the changes in normal and pathological pain states in children and adults.88, 89

Nociceptive signals are known to be processed through complex networks of neurons, glia and immune cells in the peripheral and central nervous system. Pain perception, rather than being confined to a discreet single brain area (as with many senses such as hearing or vision), is the result of activation of a distributed network of brain regions that signal and modulate the sensory, affective, motivational and cognitive aspects of pain (Figure 2). Activity in this distributed network, sometimes described as the pain 'neuromatrix', gives rise to spatial and temporal patterns of activity in the brain known as the 'dynamic pain connectome' that characterise pain by recruiting multiple brain regions to produce a constantly adjusting signature of pain that is currently not well characterised during different stages of development.90-92 Nevertheless, even newborn infants, who are just a few days old, show adult-like patterns of noxious-evoked brain activity following nociceptive events that adults would describe as mildly painful.93, 94

Central and peripheral nervous system responses to nociceptive stimuli are clearly evident after birth. However, the rate of functional maturation varies in different regions of the nervous system and so there are marked differences in the response to pain at different ages. In the mature somatosensory nervous system nociceptors respond to mechanical, thermal and/or chemical stimuli and transduce signals into action potentials transmitted by primary afferent fibres to the spinal cord; the first central nervous system site for modulation and integration of noxious and other incoming sensory information (Figure 2). Ascending pathways from spinal laminae I and V project to brain regions sub-serving the different aspects of pain perception including stimulus location, intensity and modality, and those involved in modulation, and the regions associated with physiological and behavioural responses to pain (Figure 3). Descending pathways from the brainstem have a bimodal function and can inhibit or facilitate spinal cord signalling.

Figure 3 Brain networks in nociceptive (acute) and chronic pain

Following birth, noxious-evoked brain activity can be evaluated using electroencephalography (EEG), or inferred from blood flow changes using near-infrared spectroscopy, and functional magnetic resonance imaging (fMRI). Cortical responses are evoked by noxious events such as heel lance in preterm (from 25 weeks post-conception) and term neonates,97, 98 immunization in infants,99 and venous cannulation in young children.100 The pattern and distribution of EEG response and relationship to stimulus intensity differs according to postnatal age and sex, and is influenced by stress, illness and previous experience even at this young age. In neonates and adults, fMRI shows activation of brain regions known to be involved in both sensory and affective components of pain response94 and variation with stimulus modality and intensity.101 These data highlight the potential for developing central nociceptive pathways to be influenced by pain inputs, and can provide a proxy for measuring effects of analgesia.97 Laboratory and clinical studies have already identified many age-dependent changes in these nociceptive processing pathways that influence responses to noxious stimuli, tissue injury and analgesia. For example, alterations in the function, distribution and density of key receptors involved in the detection and transmission of nociceptive signals influences the sensitivity of the system.102, 103 Myelination influences the latency of response. These, and other differences, result in a marked change in the relationship between stimulus intensity and response that vary with age (e.g., mechanical nociceptive thresholds being lower in early development.104) Mechanical thresholds for nociceptive reflex responses such as hind-limb withdrawal105 and abdominal musculature contraction106 are very low in preterm neonates and increase with postnatal age. In addition, responses are initially more generalised and less discriminate, with specificity for a nociceptive stimulus improving with increasing postnatal age.105

In healthy populations of children, cross-sectional107 and longitudinal108, 109 psychophysical studies have shown that increases in (modality specific) pain thresholds continue throughout adolescence, also with differences between males and females emerging for some. Similar to adults,110 responses to standardized experimental stimuli also show significant between-subject variability. The balance between excitatory and inhibitory descending modulation of incoming pain signals is known to differ in immature nociceptive circuits; reduced endogenous inhibitory control also contributing to the lower thresholds and more generalised reflex responses at younger ages.111, 112 Low threshold sensory input (such as touch), and spontaneous movements, contribute to activity-dependent normal maturation of sensori-motor circuits in the spinal cord.113, 114 In the brain, spontaneous and evoked patterns of activity in the somatosensory cortex are also influenced by postnatal age and type of injury.92, 115

Sensitisation and long-term effects

Alongside lower nociceptive thresholds at younger ages, tissue injury is known to induce sensitisation, familiar to us as the tissue sensitivity that develops for some time after a significant injury, at all ages including neonates and infants. This is demonstrated by reduced mechanical thresholds for the hind-limb withdrawal reflex following repeated heel lance116 and similarly, reductions in the force of mechanical stimulus required to evoke contraction of abdominal muscles (i.e. abdominal skin reflex) has quantified changes in wound sensitivity following abdominal surgery117 and referred visceral hyperalgesia in infants with unilateral hydronephrosis of the kidney.106 However, different forms of tissue damage (e.g. inflammation, surgical injury, visceral stimuli, nerve injury, chemotherapy) also have age-dependent mechanisms that influence the patterns of behavioural sensitivity that are observed.118-121 In normal circumstances, these

changes in pain modulation leading to sensitisation of the system resolve with healing, but in a proportion of patients this does not happen for reasons that are less clear but are starting to be investigated. Persistence of sensitisation is thought to be a key feature of many types of chronic pain. A better understanding of the initiating and maintaining factors for sensitisation during development will shed further light on why some pain is more refractory to treatment may open pathways to potentially new therapies.

Therefore, how an individual responds to and experiences pain is different throughout infancy, childhood and adolescence, and this difference is also influenced by the cause of the pain, and related psychological, environmental and other factors including pain duration, intensity, and age first experienced; strongly reinforcing the assertion that children are not just little adults.

Perhaps unsurprisingly, reflecting the differences in underlying mechanisms, the developmental pharmacodynamic profile of analgesic interventions, such as opioids, can also be influenced by age, sex, genetics and the type of tissue injury.122-124 Morphine, for example, is widely used to manage distress and pain during mechanical ventilation of very preterm infants in neonatal intensive care42, with uncertainty regarding subtle long-term effects of treatment. The importance of pharmacogenomic influences in neonates is relatively unexplored, however, genetic variations that affect drug clearance (e.g., uridine 5'-diphospho-glucuronosyltransferase enzyme, UGT1A9) or response (e.g., catechol-o-methyl transferase, COMT) can result in greater morphine exposure in the brain. This, together with neonatal clinical factors, are differentially related to anxiety and depressive symptoms (internalizing) and to acting out (externalizing) behaviours at 18 months postmenstrual age in children born very preterm.125 Aside from these genetic influences it is also clear that throughout the lifespan responses to analgesic interventions (as well as pain and injury) can differ between males and females; for this reason laboratory studies increasingly include sex as a biological variable,123, 126, 127 but these potentially important factors are rarely addressed in clinical studies.

Long-term consequences of acute pain

Activity-dependent regulation renders the developing nervous system vulnerable to injury-induced changes in structure and function that can alter future development and therefore responses including those to re-injury throughout the lifespan.111, 127, 128 In infants and children, neuroimaging studies have identified long-term changes in structure and connectivity that correlate with the degree of acute pain exposure during neonatal intensive care unit (NICU) management following preterm birth, and with subsequent cognitive, behavioural and somatosensory outcomes in later life.109, 129, 130 Alterations in somatosensory function in adolescents who experienced neonatal intensive care early in life have also been clearly demonstrated; but precise changes can vary, depending on initial exposure (e.g. gestational age at birth, need for surgery, duration of intensive care), type and intensity of experimental stimulus, and age at follow-up.131

The degree to which persistent changes in somatosensory function correlate with altered response to future injury as shown in laboratory studies 127 or risk of chronic pain in later life is far from fully understood and requires further clinical evaluation. Complex age-dependent differences in communication between multiple physiological systems are likely to be relevant, for example, in

juvenile rodent pain models spinal neuro-glial interactions have been associated with enhanced response to re-injury following neonatal incision127 and also with delayed emergence of allodynia, a marker of sensitisation, following traumatic nerve injury.118

Chronic pain

Pain that persists is sometimes challenging to explain mechanistically and can be very difficult to manage clinically.132 Chronic pain lasting for longer than 3 months, or beyond the expected time of healing following an injury, encompasses a wide range of potential antecedents, symptoms, mechanisms, and diagnoses. The biopsychosocial model of pain is helpful to fully appreciate and understand antecedents to chronic pain, the mechanisms involved and how to best assess and treat pain.133 Data from adult neuroimaging and other studies have shown changes in brain structure, function and neurochemistry associated with transition from acute to chronic pain that include a general shift away from brain regions encoding the sensory components of pain towards those such as the subcortical limbic system, amygdala and hippocampus that encode motivational and emotional aspects; this maps well with features seen in clinical presentations of both adults and children with chronic pain (Figure 3).134, 135 Comparisons with healthy individuals, and some evidence of reversal of brain changes with effective treatment of chronic pain, also imply that the observed changes could be implicated in both the cause and effect of on-going pain; it's important to note that data do not support any attempt to dichotomise chronic pain to either 'physical' or 'psychological' in its origins, and to do so is both inaccurate and unhelpful.135, 136 The study of chronic pain in children lags woefully behind that in the adult despite data suggesting that it too is a serious global health and economic problem the full impact of which is likely yet to be fully uncovered.137-139

Although the incidence of chronic pain in childhood has been documented,140 integrative research examining mechanisms contributing to pain remains limited, and even less examined is the role of childhood chronic pain on later biological development and health. Acute pain in children can progress to chronic pain, potentially leading or predisposing to chronic pain and other chronic health problems as adults.141, 142

There are substantial gaps in our current understanding of the transition from acute to chronic pain in children and the maintenance of pain; initial data imply that multiple antecedents, mechanisms and other factors are likely to be interacting. Data on the importance of psychosocial and pre-morbid risk factors such as psychiatric conditions, depression, anxiety, coping and threat appraisal, and parental coping, is emerging for several chronic pain conditions including postsurgical pain, with biological factors, including female sex and nociceptive function clearly also relevant 143-145. Using the example of adolescent endometriosis-related pelvic pain, Figure 4 attempts to model and summarise some of the many different factors that likely contribute to the development and maintenance of chronic pain 146. The concept of groups of 'inductors' of pain and 'resilience' factors (due to disease and an individual's predisposition) that will interact to determine the clinical features and measurable changes in psychophysical and brain structural and functional parameters are key. Although many of the potentially important contributors are common to patients of all ages, the superimposition of developmental processes on these factors will determine differences seen at different ages: some examples are discussed below.

Figure 4. Potential Mechanisms Contributing to susceptibility to Paediatric Chronic Pain

Developmental nociceptive plasticity

Importantly, throughout development, there are 'critical periods' when neurobiological factors and a wide range of experiences interact to shape normal brain development and long-term behaviour.113, 148 Areas for simpler stimulus-dependent responses develop early, while integration of key regulatory centres such as the thalamus149 and the structure, function and connections of regions for more advanced evaluation mature at older ages.91 Developmental processes such as neurogenesis and apoptosis, migration of neurons to appropriate targets, formation of synapses, gliogenesis and myelination occur throughout the late prenatal period but continue after birth, with activity-dependent processes further refining synaptic function and neural circuit formation in the postnatal period and beyond. However, this normal developmental trajectory may be disrupted by abnormal stimulus exposures (e.g., persistent pain input at critical times). Prolonged exposure to acute nociceptive pain and episodes of high pain intensity may trigger adverse neuroplastic changes as previously mentioned in neonates who experienced admission to a NICU. Psychophysical evaluation of somatosensory function with quantitative sensory testing (QST) has identified persistent changes associated with prior experience or chronic disease in children that were previously poorly recognised.(128) Diabetic neuropathy causing neuropathic pain is thought to be rare in children, but it was found that almost half of teenagers with Type 1 diabetes had detectable subclinical changes in small-fibre function.150 Following childhood acute lymphatic leukaemia, deficits in vibration and mechanical detection thresholds likely reflect persistent chemotherapy-induced neuropathy.151 Persistent sensory loss (anaesthesia) and/or sensory gain (allodynia) has been identified adjacent to scars many years following surgery in the neonatal period109 and later childhood.152, 153 Nerve injury in early life does not result in neuropathic pain as frequently in younger children as if a similar injury occurred in an adult, but in laboratory models pain may emerge in later life, long after any injury has taken place and thought to heal.118 This highlights the potential for clinical presentations in childhood to differ from that seen at older ages, despite the same initial insult and for subtle changes, possibly predisposing to long term pain, to go undetected.

Endogenous modulation

Disruption in normal endogenous descending controls from the brain is considered a factor important in adults with many persistent pain states. Further understanding of the development of inhibitory modulation, alterations induced by different pain conditions, and interactions with psychological factors at different ages may improve understanding of the transition to chronic pain in children, provide targets for therapy, and help to monitor progress.154 Psychophysical testing using conditioned pain modulation (CPM) protocols evaluate the degree and directionality (facilitatory or inhibitory) of descending modulation from the brainstem by measuring changes in sensitivity to a test stimulus before and after a conditioning stimulus at a distant body site: decreased sensitivity to the test stimulus indicates descending inhibition, whereas increased sensitivity indicates descending facilitation.155 An increased degree of inhibitory CPM has been reported in older children aged 12-17 years versus those 8-11 years.156 This parallels the predicted normal delayed emergence of descending inhibition as seen in juvenile rodent studies (128); but results are also influenced by CPM protocol.157, 158 In children with functional abdominal pain, both decreased descending inhibition

and generalized increased pressure sensitivity on testing suggest centrally driven changes leading to enhanced responses to nociceptive inputs 159. Similarly, children with high levels of pain and dysfunction related to functional abdominal pain continued with persistent pain and increased central sensitization (temporal summation to heat stimulus) years later into adulthood.160 Impaired CPM predicts persistent post-surgical pain in adults,161 and while impaired inhibition was identified in 49% of adolescents with chronic pain associated with idiopathic scoliosis,162 more research is needed in paediatric populations to clarify its significance. However, reduced inhibition did predict the transition from acute to persistent musculoskeletal pain in children.145 Similarly, offset analgesia (OA) protocols in which endogenous inhibition of pain is induced (Figure 4) also potentially allow exploration of pain inhibitory mechanisms that, although conceptually related to CPM, likely act via different pain pathways and have been little used so far in children 163, 164.

Phenotypical sensory profiling

One of the major advances in adult chronic pain has been in the exploration of individual somatosensory function (sensory phenotyping) again using QST.165, 166 Sensory abnormalities appear in different combinations in different patients who have similar pain symptoms suggesting that no single biological mechanism readily explains the various patterns of sensory dysfunctions observed.(166) In adults, patterns of increased or decreased sensitivity have identified specific sensory profiles (sensory loss, mechanical hyperalgesia, thermal hyperalgesia) that may provide greater mechanistic insight than disease-based classifications.167, 168 In children with chronic pain further standardised evaluation in much larger samples will be required to both fully characterise somatosensory alterations associated with chronic pain, and evaluate the potential use of sensory profiling as biomarkers for prediction of persistent pain, indicators of mechanism or the response to treatment. In addition, evaluations of the interplay between psychosocial variables (e.g., fear of pain, anxiety, depression, and worry associated with pain) and QST-assessed nociceptive function may also be helpful to predict pain outcomes in youth at-risk for the development of chronic pain.169, 170

The brain and non-neural CNS structures

Compared with literature in adults, relatively few paediatric chronic pain studies have included neuroimaging. Those available have predominantly included adolescents with complex regional pain syndrome (CRPS), a poorly understood but relatively common presentation in children's chronic pain clinics. Nevertheless, findings have included: i) alterations in brain structure and connectivity171 that may differ in acute versus chronic states, and from adults with CRPS172 ii) different patterns and degrees of brain activation in response to sensory stimuli applied to affected and unaffected CRPS limbs136 iii) reduced gray matter density in thalamic reticular nucleus associated with increased pain intensity,172 and altered brain connectivity within the amygdala, salience default mode and sensorimotor networks173 iv) associations with functional outcome (e.g. fear of pain 174, and v) improvement in symptoms and at least partial reversal of brain changes following intensive physical rehabilitation.171, 175, 176

There is no doubt that recent technical developments of bespoke brain imaging methodologies that are specifically designed for the neonatal and paediatric population will advance understanding of the cerebral processes that underlie the development of paediatric pain.177, 178 Alterations in

thalamic function and thalamocortical dysrhythmia, that may influence the intensity and perception of persistent pain have been observed in adults179, 180 and shifts from sensorimotor to emotion-related circuitry134 as previously indicated have been associated with the transition from acute to chronic pain. Connectivity changes within the dorsal medial prefrontal cortex-amygdala-accumbens circuit as well as smaller amygdala volume were risk factors for persistence of back pain in adults.181 Neuroimaging has not yet been utilised to assess risk factors for chronification of pain in paediatric populations.

The roles of non-neural glial cells in the nervous system extend well beyond homeostasis, formation of myelin, and support for neurones and have been implicated in the maintenance and modulation of chronic neuropathic pain (Box 4; Figure 2) throughout postnatal development and into adulthood. Microglia have critical effects on neurogenesis, synaptic pruning and synaptic plasticity.182, 183 The normal age- and sex-dependent developmental trajectories of microglial distribution and function can be influenced by afferent input and environmental factors.111, 183-185 Subsequent immune or environmental challenges, and physical or psychological stressors can influence susceptibility to neurological and psychological disorders186-189 or more specifically influence injury response and analgesic efficacy.122, 127

Stress and environment

A popular target for exploring potential mechanisms underlying pathophysiological recovery and environmental factors contributing to chronic pain are those that relate to stress responses in the context of threat, and their relationship with measures of resilience.190, 191 Acute stress alters modulation of experimental nociceptive pain sensitivity in healthy adults (e.g. changes in temporal summation, reduced inhibitory CPM and hyperalgesia), increases anxiety, and may be variably associated with changes in other physiological parameters (e.g. differences in blood pressure or cortisol).171, 192-194 Chronic stress, on the other hand, is highly comorbid with chronic pain populations.195 Interestingly, chronic stress has been categorized as a “worldwide epidemic” by the World Health Organization: it has been associated with increased rates of mental illness and suicide, and costs over 300 billion US dollars annually.196, 197

Physiological stress can alter nociceptive responses from very early life. Noxious-evoked brain activity recorded using EEG in response to heel lance was increased in term-born neonates with higher cortisol.198 Whereas, in an investigation of the long-term effect of severe stress exposure in the neonatal period, acute performance-related stress did not reduce sensitivity to experimental stimuli (e.g., thermal and pressure tolerance) in children who had previously experienced severe burn injury as neonates unlike healthy control children.199

The experience of adverse and stressful life events in childhood may also be related to the maintenance and exacerbation of chronic pain in later life; but identifying stress as a causal factor is complicated by variable results in different studies and populations.200-202 Children exposed to environmental stressors or early adverse life events may have higher risk for cognitive, emotional, and health problems,203, 204 but the timing, severity, and type of stress needed to induce this cycle and how it may contribute to chronic pain is unclear. For example, negative life events in early

childhood have been variably reported to be predictive205 or have no association206 with functional abdominal pain in adolescents.

Conversely, the Biological Reactivity Model posits that stress may be protective for some, although the required level is unknown.207 Nevertheless, translational models of deprivation, threat/stress, drug exposure and injury during early life demonstrate significant adverse and persistent effects on brain structure, behavioural outcome, hypothalamic-pituitary-adrenal (HPA) axis function, response to re-injury and risk of medical and psychiatric disorders in later life.97, 208-212 In contrast, 'positive experiences' (environmental enrichment/parental care/healthy diet) can improve outcome in laboratory models of early life stress; effects vary with age and sex and further demonstrate the complexity and overlap of mechanisms involved in stress response, pain perception, and mood.209

Numerous environmental factors may be important in regulating long-term pain responses. The gut microbiome, for example, influences visceral sensitivity, either directly or via alterations in stress response and has been implicated in chronic gastrointestinal disorders in both children and adults.213, 214 A range of organisms colonize the gut from birth, with variability increasing during adolescence.214 Preclinical models report interactions of the microbiota-gut-brain axis with immune, neural, endocrine and metabolic pathways that alter neurodevelopmental and behavioural outcomes such as anxiety and fear learning.209 Approaches to studying multiple, interacting physiological systems and molecular pathways are needed for the development of translatable biomarkers that would facilitate the study of stress responses, resilience, and vulnerability across both human and animal studies across the age spectrum.

Genetic influences

Genetic factors are estimated to account for 20-55% of reported variability in experimental pain sensitivity,215 and influence the risk of transition from acute to chronic pain.132 Single nucleotide polymorphisms in multiple genes have been associated with a number of different chronic pain conditions.216, 217 As previously mentioned, pharmacogenomic differences may be relevant as they can also influence response to current analgesic medications218 and potentially new analgesic targets based on genetically determined differences in molecular signalling in individuals with chronic pain have been identified.219

Genetic disorders can also more directly result in neuropathic pain. Mutations affecting voltage-gated sodium (Nav) channels on sensory nerves that can influence pain sensitivity and/or be associated with specific pain disorders are increasingly recognised in children.220 Erythromelalgia (a rare disease characterised by neuropathic pain typically experienced in the hands and feet) related to mutations of the SCN9A gene that alter excitability of Nav1.7 channels, produces severe pain and the genotype influences both the age of onset and the pharmacological response to potential analgesic interventions.221 Neuropathic pain is often the first presentation of Fabry disease, a lysosomal storage disease, and as this is an X-linked disorder, pain tends to occur earlier and can be more severe in boys than girls; enzyme replacement therapy may reduce the pain and improve long-term outcome.222-224

Epigenetic modifications in DNA structure and chromatin formation regulate gene expression in early development, and in response to environmental cues, and may be transmitted across generations.225 Interactions between genes and the environment have been associated with early life (perinatal and postnatal) events that adversely210, 226 or positively227 influence neurodevelopment, and account for a large proportion of individual variance in risk for chronic disease over the lifespan 227. Epigenetic mechanisms also play roles in the development or maintenance of persistent pain228, 229 and may offer potential analgesic targets if more specific agents are developed.230. How pain risk genes manifest phenotypically in differing environments will be an important area of inquiry. Additionally, investigation of intergenerational pain transmission231-233 will be a valuable contribution to the field. Advances in genetic testing and more detailed phenotyping of clinical pain conditions may improve individualised therapy.219

We are making slow progress understanding how the maturing pain system determines and influences both current and future pain states. In Box 5 we summarise the main priorities for further investigation in this area and changes in research and clinical practice that should be employed to make childhood pain more understood.

Box 5: Research and clinical priorities to make pain understood

Research and clinical priorities to make pain understood.

First, for pain to matter, it must be correctly understood. When an experience is ubiquitous it can be misinterpreted as unimportant. With procedural pain being common, and prevalence estimates for chronic and recurrent pain estimated at approximately 28%,140 it is tempting to re-classify pain as a normal part of life. But when it comes to child pain: common does not mean trivial. Such high prevalence rates, however, do beg an explanation, should give us pause to ask whether we are always talking about the same thing when we talk about pain. We have yet to see the impact of the new ICD-11 classifications in changing both the science and clinical practice in chronic pain, but expect its application in the next decade. Masked behind high prevalence rates reported in epidemiology is a complex network of inter-related functions and dysfunctions of the pain system. Making that system understood is a primary goal. We encourage further debate on the definition of pain. In some fields, constant redefinition is considered indecision, but in pain we believe that this definition needs to be regularly questioned, work managed by a task force of the International Association for the Study of Pain who published the latest definition of pain in 2020 87. Further, classification of disease states characterised by pain should be further developed.

Second, a major challenge in making pain understood is to escape the shadow of a pervasive dualism that diverts and misdirects science. An example is the search for an objective measure of pain as a goal in itself which inappropriately relegates private experience as inaccurate or of less value than a biological correlate.83, 84 It is possible to better define biological correlates and surrogates which will be helpful, but pain should also be defined within a psychological and social context, as well as a developmental context. A related example is the practice of representing pain as only a sensory

phenomenon, measuring intensity and ignoring affect, cognition, motivation, or behaviour. Escaping dualistic notions of subjective and objective, of mind and body, of physiology and psychology is not easy. These inside (hidden) – outside (observable) distinctions are coded in language, structure much of how we experience the world,234 and are useful in many areas of science and practice. However, they are not useful in the study of pain science and they hold us back.

Third, perhaps the biggest advance in paediatric pain science in the last 20 years has been in developmental biology. Early experience of pain matters and has a lasting effect on nervous system development and subsequent pain behaviour. However, there is still a long way to go in understanding the impact of developmental factors on nociception, pain, child anxiety, and their clinical assessment and treatment.

Fourth, further methods are needed in order to facilitate pain assessment in neonates that are rigorous, valid, and reliable. It is unacceptable to be ignorant of anyone's pain in the 21st Century, particularly those who are most vulnerable.

Fifth, mechanisms underlying the development of chronic pain is an important area of study where better understanding is needed. First, focussing on mechanism we can now better describe pathology in peripheral and central nervous system function. Tissue damage can invoke peripheral sensitisation, but different forms of damage have age-specific responses. For some types of chronic pain repeated peripheral sensitisation is thought to be a key feature. However, we do not know how important persistent peripheral sensitisation is for the onset and persistence of chronic pain. Indeed, a major turning point in this field will be to understand and treat the risk factors of developing chronic pain after an acute injury. Multiple mechanisms are implicated in the development of different chronic pain presentations, including central nervous system vulnerabilities which project into adulthood.131 Higher depressive symptomology, anxiety, and adverse life events are implicated in the transition between acute and chronic pain. Understanding the long-term effects of often short exposures to physical insult at critical stages of development is imperative. Advances in human neuroimaging techniques will undoubtedly help172 as will investment in the development of biomarkers and better phenotyping. This science is still in its infancy and improvements in measurement, in identification, and in replication are all necessary to better understand pain and its mechanisms.

Finally, investment in longitudinal datasets must continue and be developed, as these provide unique and critical information over the course of childhood and adolescence. There are very few registries of children with pain. The advances in other areas of paediatrics, from rare disease to trauma registries show how transformational these can be. Although life-long epidemiological studies will help, such as the HUNT study235 or the "Children of the 90s", Avon Longitudinal Study of Parents and Children (ALSPAC) cohort in the UK,236, 237 we also need to invest in clinical cohorts of well described painful diseases. These registries can be helpful in phenotyping and understanding the impact of indirect influences of environmental stress and of family context. However, these databases are rare, and their absence is setting us back in our understanding. Although there are some databases, these are not specifically medical or pain-related databases, but rather general

developmental databases assessing a wide range of data on everything from road safety to diet. Pain researchers and clinicians should have a more prominent role when setting up these databases, as pain is a common feature not only of a healthy childhood, but also disease. Assessing pain in these databases is critical for properly understanding its advancement and impact on childhood.

Goal 3: Make pain visible.

Childhood pain can be assessed, no matter the age or clinical status of the child. Children need the opportunity to communicate their pain to clinicians, parents, and caregivers to drive decision making regarding treatment options and to assess whether a treatment is efficacious. Nevertheless, there are challenges, especially in the youngest patients, and in patients with intellectual, communication, or motor limitations. However, methods are available and should be used. Pain should be made visible by performing a developmentally appropriate valid pain assessment in every child.

Pain assessment in children is an inferential process in which all available information about the child should be considered. This is not an easy endeavour as, by definition, pain is a private mental experience. While the gold standard is self-report, whereby the child directly describes their experiences, this is not always possible and other indirect measures including facial expression, behavioural observations, physiological responses, such as changes in heart rate or respiratory rate, and neuroimaging approaches can also be used to examine this private experience. Nevertheless, in most cases human language provides a rich channel by which subtle sensory and affective experiences can be communicated, and early in development children learn to verbalize their experiences. This is not different for pain, and expressions such as “ouch” are used to describe and communicate pain to others.

Assessing pain

In clinical practice, the most commonly used pain assessment is a numerical rating scale.238 This approach requires children to attend internally, make a judgment, and label that judgement. Hence, to use a numerical rating scale, children need to have acquired the capacity to assign a number to an experience and have the ability to summarize their experiences across various episodes. For example, if you ask a child “In the past 7 days, how would you rate your pain on average?”, it needs to be a developmentally informed assessment. For guidance, self-report measures of pain such as numerical rating scales can be used from the age of 6 years onwards.238 There may be difficulties in applying this approach to all children due to the cognitive demands of such explicit judgement. It can also be difficult to appreciate the influence of other individual, interpersonal, and contextual factors that impact the child’s communication or expression of pain. In Box 6 we have captured how pain intensity assessment changes with child developmental level.

Box 6: Developmentally appropriate pain intensity assessment methods for children six years and older

Using proxies of pain

In the absence of, or in addition to, self-report, report of the child's pain by others may be used. Researchers or clinical professionals may ask parents or others to make judgments about the pain or related experiences of the child when the child is not able to, or to complement the child's report.239 Parents can provide valuable information about their child's pain experience. Nevertheless, one should be cautious about relying solely on other-reports of the child's pain because they may be biased or influenced by factors other than pain.240, 241 Disagreements between child and parent do not necessarily reflect inaccuracies in judgment, but rather different perspectives on pain or the health problem.242 As such, discrepancies between child and parent should not be considered as error obscuring a true score, but as valuable information.

For children younger than 6 years or children who are unable to verbally report, behavioural scales may provide a valuable alternative to assess pain in clinical settings.243 In infants, these may be the first alternative. For example, it may be inferred that a newborn infant expresses pain when they are subjected to a procedure that would be painful to adults. Such inference is reasonable, given that infants have the basic neurological structures93, 94 and manifest behaviours - such as facial grimacing or crying244 - that are analogous to pain responses of adults or older children. Currently, the behaviour of children is coded by (trained) observers.245 Numerous neonatal pain scales have been created, which each calculate pain scores that are based primarily on behavioural and physiological observations following clinical procedures.246 These scales are not substantially different from each other, and most often the pain scales prescribe a value to a set of observed behaviours and physiological activity.247 Nevertheless, general dissatisfaction with these scales means clinicians and researchers adapt and tweak them without the necessary validation steps to make them more appropriate for use in their specific settings. This makes it difficult to combine and synthesise evidence about how much pain infants are experiencing and whether interventions to prevent or alleviate pain are efficacious.

Substantial research efforts are also being targeted towards identifying developmentally sensitive surrogate pain measures that can discriminate between responses to noxious and innocuous events.248-250 In recent years this has included the use of functional magnetic resonance imaging (fMRI), near-infrared spectroscopy (NIRS) and electroencephalography (EEG) to quantify changes in brain activity that are evoked by noxious input (Figure 5). These brain-derived measures will aid our understanding of the underlying neurological activity associated with pain in nonverbal infants. These types of brain-derived measures may also prove useful in other paediatric populations who are nonverbal or not able to self-report their pain experience.

Figure 5. Assessing pain in infants

We should continue to focus on the identification of robust developmentally-sensitive pain indicators so that there are better tools for use in both clinical practice and research. When using proxies of pain, it will be important to carefully weigh the costs of false positives or false alarms against the accurate detections of pain. Accuracy is a challenge when using proxies as the following examples illustrate. Consider that false positive inferences can arise when newborn infants display pain-related behaviours in response to non-painful events. For example, infant crying has evolved as a non-

specific protective mechanism to elicit response from caregivers,252 and can be used to signal other experiences, such as tiredness, hunger, or discomfort at handling. False negative inferences are also possible, where a newborn infant experiences pain, but fails to manifest the usual external signs of pain. For example, extremely premature infants can display reduced facial grimacing compared with term-born infants253, 254 and infants at high risk of neurological impairment can exhibit decreased facial grimacing following clinical procedures compared to those who have a low risk of neurological complications.255 Notwithstanding these shortcomings, for many patients, such as those who are non-verbal, other-reported measures of their pain is the only option. Our confidence in their use will increase when there is a strong evidence base documenting the sensitivity and specificity of behavioural markers and alternative pain biomarkers.

Screening for future pain problems

Frequently we are interested in making future pain visible, or at least in understanding the risks that pain might emerge in the future. Being able to predict which children are likely to suffer from pain later on, has advantages. It creates windows of opportunities for early interventions, and allows the prioritisation of resources (time, personnel, treatment intensity) for those with a high risk for a poor outcome. The growing interest in predicting the transition from acute to chronic pain has spurred efforts at identifying risk factors of chronic pain. The challenge is to identify the characteristics with predictive value and then to validly measure them, as briefly as possible. Research is uncovering neurobiological, social, emotional, and behavioural risk factors that are associated with the transition from acute to chronic pain in children and adolescents (e.g.,145), and these may form the basis of screening tools. In adults several screening tools for predicting chronic pain problems have been developed and validated.256, 257 These tools are brief self-report instruments, most often items cover domains such as pain and other somatic symptoms, disability, low mood and anxiety, pain-related worrying, and expectancies about future pain or disability. Overall, these screening instruments are good to excellent in predicting future adverse impact of pain.257 The field of clinical prediction is a rapidly evolving field, and guidelines and standards are available to help researchers and clinicians to develop and validate such screening tools.258, 259 As yet, there are not many screening tools for use in paediatric settings. A notable exception is the Paediatric Pain Screening Tool (PPST)260 which is based on the 9 item STarT Musculoskeletal Screening Tool in adults.261 The content of the items of the PPST has been thoughtfully selected and adapted for use in children presenting with pain problems. The instrument can be used to rapidly identify treatment targets (e.g. sleep disruption, pain-related fear) and to stratify youth into low, medium and high-risk groups to inform referral to appropriate interventions. The initial results are promising, and further studies reveal its potential usefulness for specific pain populations.262, 263

Going beyond pain and measuring its wider impact.

Critically, the field of pain measurement has not focussed solely on pain intensity. Indeed, progress has been made on making pain visible through the development of measurement tools to assess both pain characteristics (e.g., location, frequency, duration) and its impact on multiple domains of life. There are many validated tools available to assess pain, physical, emotional and social role functioning, and health outcomes in children and adolescents. Systematic reviews of measures of pain impact,264 pain-related anxiety,265 sleep disturbances,266 observational/behavioural measures of pain,243 and self-report measures of pain for very young children,267 and for specific patient populations, such as abdominal pain268 are available. Despite the efforts of many to go

beyond pain and to measure the impact of pain on daily life, patient experience is often unexamined. Even in resource challenged environments or where routine assessment is frustrated by structural or attitudinal barriers there are simple questions one can ask of every child. In Box 7 we suggest a short series of questions that can make pain and its impact immediately visible.

Box 7: Routine assessment questions to help make child pain and its impact visible

Core Outcome Sets

Several notable efforts have been made to develop core outcome sets in paediatric pain. In 2006, a paediatric working group of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (Ped-IMMPACT) gathered 26 professionals from academia, governmental agencies, and the pharmaceutical industry to participate in a 2-stage Delphi poll and a subsequent consensus meeting to identify core outcome domains and measures that may be considered in clinical trials of treatments for acute and chronic pain in children and adolescents.269 According to the Ped-IMMPACT recommendations, acute pain trials should include outcome domains of pain intensity, global judgement of satisfaction with treatment, symptoms and adverse events, physical recovery, emotional response, and economic factors. Chronic pain trials should include outcomes pertaining to the domains of pain intensity, physical functioning, emotional functioning, role functioning, symptoms and adverse events, global judgement of satisfaction with treatment, sleep, and economic factors.

These recommendations are highly cited as a guide for choosing outcome domains in clinical trials and clinical registries. The actual uptake of the recommendations however remains suboptimal. Of 337 randomized controlled trials of postoperative pain management, only 2 outcome domains of the PedIMMPACT recommendations were commonly included; pain intensity (93% of trials) and symptoms and adverse events (83% of trials).270 Fewer than 30% of these postoperative pain trials included outcomes in any of the other four PedIMMPACT domains. In a similar effort, Connelly et al. (2019) recently published a systematic review of reporting practices in 107 randomized controlled trials of paediatric chronic pain interventions.271 Nearly all trials included pain intensity as an outcome domain but fewer than 35% of trials included outcomes in the other PedIMMPACT domains. Trials of behavioural interventions were more likely to include outcome domains of quality of life, emotional functioning, and physical functioning than trials of pharmacologic treatments. Sleep and economic factors are rarely assessed across any intervention for paediatric chronic pain 272. Overall, these findings indicate that trials of interventions for acute and chronic paediatric pain have insufficiently used the PedIMMPACT recommended core outcome sets.

Uptake of the PedIMMPACT core outcome set will increase when the following concerns are addressed. First, essential is the systematic involvement of children and parents as stakeholders in the entire process. Second, further specificity is needed in recommendations or criteria for selecting instruments. For example, multiple outcome instruments are recommended rather than one instrument for each domain. Third, there are gaps in available measures of several outcome domains (e.g., adverse events, global judgment of satisfaction with treatment, and economic factors) hindering their inclusion in trials. Understandably, there are challenges in standardizing

recommendations because of the large number of pain conditions, disciplines, and treatment modalities involved in children's pain management.

Another well-established core outcome set is the Juvenile idiopathic arthritis (JIA) core outcome set, developed in 2014 by Outcome Measures in Rheumatology (OMERACT),273 an international group of health professionals, methodologists, and patient research partners focused on outcome measures in rheumatology. They originally published a recommendation for four core outcomes: life impact, pathophysiologic manifestations, resource use, and adverse events. However, because the original set did not include the perspective of children and parents, the OMERACT group updated the JIA Core Outcome Set. Morgan and colleagues274 reported on this process, which included several strategies to obtain broader input including literature review, qualitative surveys, and online discussion boards with children with JIA and parents. A Delphi process was used to edit the domain list and achieve consensus on domains. Notably, this process led to the inclusion of new domains, and the JIA Core Outcome Set now consists of 5 domains: pain, joint inflammatory signs, activity limitation/physical function, patients' perception of disease activity (overall well-being) and adverse events.274 Using the rigorous criteria of the 'COnsensus-based Standards for the selection of health Measurement Instruments' (COSMIN) initiative,275 this group is identifying and evaluating the best outcome measures for these domains.

Innovations in pain assessment

Several innovations in assessment are ongoing, and more are to be expected. A first area of innovation is the standardization of patient-reported outcomes through the Patient Reported Outcomes Measurement Information System (PROMIS)276 developed by the US National Institutes of Health. Over the past decade, considerable work was invested in the development of these measures, including use of Item Response Theory and Computer Adaptive Testing, and they are now freely available for both clinical and research use. Paediatric PROMIS measures include assessments in the domains of mental health, physical health, and social health, e.g., pain interference, emotional distress, physical mobility,276 and are recommended by various initiatives. Because PROMIS measures are available in adults, an important advantage is consistency in measurement at the upper end of the adolescent/young adult age range and in assessing parents/caregivers of youth. Work is underway to validate the PROMIS measures in children and adolescents with a variety of painful conditions.277, 278 For example, Kashikar-Zuck and colleagues 278 validated PROMIS measures demonstrating treatment responsiveness in youth with chronic musculoskeletal pain conditions. Widespread use of validated PROMIS measures have been integrated into registries that track patient-reported information as part of standard clinical practice in paediatric chronic pain, such as the Pediatric-Collaborative Health Outcomes Information Registry (Peds-CHOIR).279

PROMIS measures include domains that cut across different diseases and settings (e.g., physical function, depressive symptoms). There are now > 20 item banks of physical, mental and social health for children ages 1-17 years. This includes short forms (4-10 items), computer adaptive tests (CATs), and profiles normed to the US general population and validated in clinical subgroups. Dutch, English, German, Spanish, and other language versions are available. Expanded to clinical practice, quality measurement, population health, and international adoption. The measures are publicly-available on www.healthmeasures.net

A further development is the frequent capture of information in the contexts that matter for children or their parents. Typically, self-report instruments require children or parents to report on their experience over/across a particular time period (e.g., a week or a month). Such recalls are affected by memory biases or heuristics, such as the peak (or saliency) heuristic.280 Recent technological advances make the real-time capture of information within reach of research and practice. Children may be prompted by smartphone notifications to report on their experience during randomly selected times during the day (time sampling), or to report on their experience when particular events occur (event sampling). Also possible is the passive capture of information (e.g., geolocation, physical activity, physiological measurement, bodily position, etc). These innovations allow a real-time recording of experience of the dynamics of pain and its impact across time and daily contexts. This will provide invaluable information for the initial phase of diagnosis, and for the evaluation of interventions using designs that capture within-day changes. Ultimately, we could evolve such work into the delivery of just in time adaptive interventions, where health behaviour interventions are adapted to an individual's changing internal and contextual state as has been done in other paediatric populations (e.g., diabetes 281).

The update of technological innovations is ongoing. There is an increasing use of electronic daily diaries in paediatric chronic pain trials, in particular for the real-time measurements of pain, physical functioning, sleep, and emotional functioning (e.g., depression, anxiety).282, 283 Technological advances are abundant in many areas and already profoundly affect research and clinical practice. Computerised automated systems for the recognition of pain expression and behaviour are being developed, which may lower the burden in observers who code pain expression or behaviours.245, 284 3-D motion capture and analysis allow us to evaluate gait mechanics, balance, and other functional movements.285 All in all, these technological advances occur at an incredibly fast pace, and initial results are promising. Notwithstanding the pace of development, research documenting the reliability and validity of these innovations is lagging behind. This research is essential because the same criteria for the reliability and validity of self-report instruments apply to these technological innovations as they do to standard measurement practice.

Clinical relevance and use

The real test of measurement technology is not its popularity, or how researchers use the tools in studies, but whether the routine measurements in paediatric pain produce useful outcomes for patients, families and their clinicians. In order to make pain visible, we need to better understand whether outcome measures show that pain treatments are effective and safe. This will require further research on commonly used paediatric pain outcome measures to understand clinically meaningful change, and research gathering child and family input to learn what information they use to determine whether a treatment is working (e.g., attaining certain goals, having fewer high pain days). Novel ways of characterising pain and treatment effects are on the horizon. Intensive longitudinal data analyses of the daily pain experience will allow researchers and clinicians to identify alterations in the child's typical pain experience, through new analytics, such as dynamic structural equation modelling 286. In fact, regulatory agencies are now using longitudinal daily experience data in clinical trials to better understand how an intervention makes a difference in daily life for patients.

Standardization of outcome domains and measurement tools for clinical trials of treatments for paediatric pain would enhance the quality of the evidence for treatments of pain in childhood, strengthen and simplify systematic reviews of paediatric pain interventions, and help clinicians make evidence-based treatment decisions for this patient population. In Box 8 we summarise the main priorities for further investigation and changes in research and clinical practice that should be employed to make every child's pain more visible.

Box 8: Research and clinical priorities to make pain visible

Research and clinical priorities to make pain visible

We are dragging paediatric pain out of the shadows. We are, however, realistic and know that this exposure is confronting for many people. Witnessing others' distress can be discomforting. However, the self-report of internal states is not new. People want to communicate and share their experience.287 Accurately capturing private experience and improving its communication has been the subject of over 100 years of measurement science.288 In mental health studies knowing the structure of the aberrant experience is crucial to the diagnosis of pathology. In neurology the description of internal state, cognitive testing, and response to interview can be as important in tailoring treatment as brain imaging. In physical medicine there is now a recognition that patient-reported outcomes are the missing piece of patient experience that can guide more effective intervention, with the growth of interest in patient-related outcome measures and core outcome sets.269, 277 And going even further, there is movement toward values based healthcare, in which shared decision making by patient, family, and health care professionals becomes the norm.289 All rely on the communication of private personal experience.

First, pain characteristics should be assessed in every child. It is important to be comfortable with assessing internal processes by self-report where possible. Of course, self-report is influenced by factors such as social demand (the obedient desire to please), but this should not discredit attempts to capture private experience or provide reason to leave pain unassessed. Child pain assessment is an inferential process; we draw from multiple sources of evidence. For neonatal pain, researchers and clinicians can capture observer judgements of a range of pain relevant observable behaviours, from facial expression and bodily expression, and non-verbal utterances including crying. Healthcare professionals need to guard against over and under-interpretation, and context can be crucial. For older verbal children who are able to form concrete operations and manage metaphor and temporal abstraction, one can use measures that assign numbers to experience, or require a judgement about time. As introspection develops one can learn to compartmentalise experience. Researchers and clinicians rarely go beyond intensity in our measurement practice. But Carl von Baeyer, an international expert in pain measurement, reminded us that to describe pain by its intensity is like describing music by its volume only.290 Going beyond intensity, at least to quality, duration, affect, and interference, and even to its meaning, is possible and desirable.

Second, the impact of pain is not just the experience itself. Pain negatively impacts a child's physical, emotional, and social functioning and healthcare professionals must understand the impact of pain on daily life. There are multiple measures to assess domains within these areas of functioning. For

example, within pain anxiety, fear of pain, and pain catastrophising which are conceptually similar areas, a systematic review found seven separate measures.265 In chronic pain the measurement of multiple domains of experience should be routine. In randomised controlled trials of novel interventions in chronic pain it would now be considered poor science to ignore multiple domains of child experience. A consequence of this measurement translation of concepts and assessments is that we do not assess concepts that are most important to children and their caregivers. For example, friendships, impact on career, financial impact, and impact of pain on marital relationships are rarely assessed or discussed. Siblings are also ignored. Whilst we need to stop measurement development in some areas, it is time that patient-important outcomes are explored, invested in, and developed.

Third, most measures where created in a top-down manner, a worrying trend observable across the field. Assessments first created and tested in adults, are then 'simplified' for children, assuming that children have the same worries and fears as adults. Very few measures are created 'bottom-up'. Consolidation of measures out there and careful thinking about their developmental validity is important before integrating into a research study or practice.

Fourth, as we have highlighted throughout this commission, people are complex. There is a need for person-centred approach to assessment of pain in infants, children, and adolescents. This will help when allocating patients to optimal treatments to reduce symptoms. In particular, children with chronic pain often present with comorbidities, and therefore assessing multiple domains of functioning are important to inform which treatments to provide.

Fifth, the next frontier in the measurement of child pain is partly technological and partly intellectual. Computing technology has radically altered all biomedical science. Whatever the domain of experience we can now capture large amounts of data. Consider that the near ubiquitous adoption of mobile telephony means that the passive capture of geolocation and movement sensing data is now easy. 'Near-time' assessment of behaviour linked to a specific antecedent target is also possible, so we can assess the context of specific behaviours and experiences. So called 'big' data creates the possibility for machine learning to identify population patterns of data, which has been used to follow patterns of disease and its alteration, and could be used in pain to assess environmental influences of pain.

Goal 4: Make pain better.

Every child should have access to evidence-based pain assessment and subsequent treatment using the currently most effective methods and means. A growing number of high quality systematic reviews, meta-analyses, and clinical practice guidelines demonstrate efficacy for at least some psychological, pharmacological, physical, and/or integrative treatment modalities to reduce pain and improve function.32, 291-295 These treatment strategies are critical for care to move beyond the historical and harmful practices that can still easily be found.

Treatment approaches

We will not provide an exhaustive review of all possible treatments here. Physical, psychological and pharmacological treatment have their own relevance to paediatric pain management, as different approaches may work for different children of different ages, at different times, and in different circumstances. In chronic and episodic pain, psychological treatments have the most robust evidence base of all treatment modalities, having been the most studied, in particular with older children 272. Effective psychological treatments are predominantly based on cognitive and/or behavioural therapies and target cognitions, emotions, and behaviours, most notably cognitive-behavioural therapy (CBT).296-299 The therapeutic aim includes prevention of episodic pain such as headache or recurrent abdominal pain, the mitigation of severe or unavoidable pain, or the management of the aversive consequences of persistent pain. Equally, the evidence of psychological interventions is robust for procedural pain, including distraction, hypnosis, combined CBT, and breathing interventions297. There are many primary studies and evidence syntheses of psychological therapies delivered to children and adolescents with pain, including hypnosis,297 problem-solving therapy,300 acceptance commitment therapy,301 mindfulness,302 and memory reframing303 amongst others. Data on possible harms from these approaches is rarely collected and so unavailable.304

Physical interventions are commonly used to address both acute and chronic pain but the literature supporting them is not as robust as their use would suggest. Investigation of physical interventions for paediatric pain has largely focused on those available for preterm and term infants and young children during medical procedures. Evidence supported interventions include non-nutritive sucking (such as using a pacifier), swaddling/facilitated tucking, skin-to-skin contact, rocking, and holding (such as comfort positioning).305-307 Other contextually relevant strategies to effectively reduce acute pain and distress direct how procedures are conducted (such as simultaneous injections) or alterations to the environment (such as low noise and lighting, and soothing smells).305, 306 Evidence for physical interventions for paediatric chronic pain is less common 272, although neuromuscular exercise training 308 and aerobic exercise appear promising.309 The limited adult literature on other physiotherapeutic techniques such as transcutaneous electrical nerve stimulation has been extrapolated to children and this modality is in common usage in children and young adults 310, 311.

Reviews of integrative therapies highlight the interest in acupuncture, creative arts, herbal therapy, homeopathy, and massage therapy for different pain conditions,312, 313 however, the evidence is scarce. Evidence suggests that improving patient or family understanding of pain and its mechanisms through the provision of pain education may also provide some therapeutic benefit.314 Furthermore, given the complex biopsychosocial nature of all pain experience, efforts to consolidate scientific evidence to inform multi-modal paediatric pain care are noted in clinical practice guidelines to address acute/procedural,35 perioperative,293 and chronic315 pain management from infancy to late adolescence.316

Although there is a growing research interest in physical, psychological and surgical interventions, by far the most commonly used treatments are pharmacological. Pharmacotherapy for pain, both acute and chronic, includes paracetamol,317 topical anaesthetics,318 sweet-tasting solutions,319 non-steroidal anti-inflammatory drugs,320, 321 antiepileptic drugs,322, 323 antidepressants324, and opioids.325-327 However, despite the common use of pharmacotherapy, its ubiquity, and clinical utility, there is very little research on existing or new agents, particularly in the area of chronic pain

management. Although not pharmacological, there is also evidence for the efficacy of breastfeeding for babies experiencing acute pain.328 In a recent overview of systematic reviews only six randomised controlled trials of analgesic pharmacological interventions for paediatric chronic non-cancer pain were identified and no trials for chronic cancer-related pain,329 meaning that the evidence base for the most common treatments used in children with chronic pain is based on few trials with few patients. Similarly, the use of interventional procedures (such as nerve blocks and neurostimulation) for paediatric chronic pain is supported primarily by case reports with few randomised controlled trials (RCTs).330 Although there are more RCTs for paediatric perioperative care, evidence from adults is often extrapolated to paediatric populations.329 This mirrors a lack of clinical drug trials across other areas of paediatric health.293 A more substantive indirect evidence base supports pharmacological treatments and regional nerve blocks for paediatric acute, postoperative, and procedural pain 331.

An absence of evidence is not the same as evidence of an absence of effect, and there is a growing need for new treatments.332, 333 This should lead us to ask why there is no concerted effort to capture data on the efficacy and safety of existing medicines, or to develop new medicines for children and adolescents.

Practices of analgesic decision making

Analgesic provision for both acute and chronic pain is often guided by local culture or attitudes. A good example of this is in analgesic provision for infants and children post-operatively. Analgesic medications are not licensed for pain management in newborn infants, so the choice of treatment is left to clinical judgement. Therefore, the choices of drug, dose and route of administration are selected based on expert consensus and individual experience, which may not be supported by strong evidence. Consequently, so called 'off-label' analgesics are commonly administered to infants, in unsuitable formulations, with limited knowledge of the pharmacokinetic properties, drug efficacy or safety. Furthermore, as developmentally very distinct, children are frequently grouped together across a broad age range, and in the absence of adequate data due to the paucity of studies, regulatory decisions designed to protect some children can have unintended effects on access to analgesia for a greater number of children who are at low risk. An example of this has been the regulatory response to cases of respiratory depression following codeine 334-337, that have effectively led to analgesic compounds such as codeine and tramadol 334, 338 becoming unavailable to increasingly large numbers of children after surgery. There is an urgent need for analgesic drugs to be studied and licensed in children, especially infants, and stronger links between academia, industry, regulatory bodies, parents and their children is essential if we are to improve the treatment of pain. A clear pathway from identifying optimal endpoints to measuring drug efficacy and safety through to licensing should be forged. International collaborations need to lead the way and be supported in their efforts to provide safe and effective treatments for the neonatal population.

Of course, many treatments do not lend themselves easily to randomised controlled trials and the right course of action is not immediately clear. For example, there are considerable uncertainties in how to manage pain in newborn or preterm infants, where it can at times be unclear as to whether or not the infant is experiencing pain, this is also true for many children with communication impairments. This leads to ethical questions related to how best to treat pain, as the reduction or

avoidance of pain is not a goal without costs, where favourable analgesic effects can seem inseparable from unfavourable adverse effects.29 As an example, considerable uncertainty exists regarding whether preterm infants should receive pre-medication when they are receiving surfactant by so-called “minimally invasive” techniques.339, 340 These techniques involve laryngoscopy and passing a fine bore catheter into the larynx to administer surfactant to the spontaneously breathing infant. In part, the proposed benefit of this technique is attributed to the belief that the infant’s spontaneous breathing distributes surfactant more effectively than would be the case if it was applied using positive pressure in a non-breathing infant. However, we do not know how distressing laryngoscopy without sedation or analgesia is for extremely preterm infants, although it seems safe to assume that it is unpleasant. The provision of sedation or analgesia presumably reduces the infant’s discomfort (though this is difficult to evaluate); however, it also appears that even low dose sedation is associated with increases in episodes of blood oxygen desaturation and the need for manual ventilation during the procedure.341

This question is not only a clinical question, but an ethical one: how should these risks be balanced? Is it worse for the infant to have a more unpleasant procedure, or to have more episodes of oxygen desaturation and increased likelihood for the need for ventilation and consequent increased morbidity? This example highlights the way that decisions about pain management are often posited where it is necessary to weigh different values. Greater clarity about the adverse effects of early life pain compared to increased physiological instability may be possible as more evidence is acquired. However, there will still be a need to decide which, and whose, values to prioritise. In light of these balanced ethical considerations, a recommendation based on the precautionary principle is made. We should, where possible, make all efforts to limit pain exposure by avoiding pain-causing procedures. Where these procedures are unavoidable, interventions to alleviate pain should be used that have been carefully evaluated and are least likely to be associated with long-term harm. There remains an unknown balance between the potential benefits and harms associated with these decisions, and this is likely to vary. Parents should be involved in decisions relating to pain management in their infants and children so that their views and values are considered. Medical care providers need to be aware of the drugs they are administering, recognise their potential complications to inform parents, and also possess the skills and strategies to resolve these complications as they arise. It is important to see more involvement of clinical ethicists, or perhaps the public recognition of the involvement of clinical ethicists in the questions surrounding paediatric pain management, especially in infants and children who cannot verbally communicate.

Even in working with older children who can communicate complex needs, there is absence of primary study, and a lack of pull through from theory to pre-clinical study to clinical intervention research. For example, one of the most examined areas of paediatric pain management is child-focussed psychological treatments. However, there are important areas that are missing. First, there are few studies that include parents, siblings, and peers, although they are starting to emerge.300, 342, 343 Second, there is a distinct missing focus on prevention of pain, its exacerbation, or its maintenance in both post-surgical and chronic primary pain conditions. In post-surgical pain up to 20% of children and adolescents go on to report long-term pain344 and in chronic primary pain, treatments have not been developed, and risk factors are just starting to be identified.143, 145

Promoting evidence based paediatric pain management

In adopting a meta-scientific approach we could appear unduly and unhelpfully critical. In dwelling on the practically, ethically, and clinically complex we are not promoting a nihilistic abandonment of scientific endeavour. Complexity is the starting point, not the destination. To make pain better, there needs to be more creative and far-reaching methods to evaluate new and emerging health technologies. As a community, we are at a critical turning point in the production of evidence. If we do the same as we have done before we will get the same results. Further, the common methods and study designs might not be up to the advances needed to quickly advance in this field. For example, the gold standard trial design is commonly presented as the randomised controlled trial. However, in many cases the randomised controlled trial is unethical, impractical or both 345, such as in testing the effectiveness of pharmacological interventions in a palliative or end of life setting when randomisation without a viable rescue medication would be unethical and difficult to justify. The blinded randomized controlled trial is a gold standard in clinical evidence production because it evolved as a method to control for known biases in evidence production (see Cochrane Risk of Bias tool),346 but this methodology should not be thoughtlessly evaluated when reviewing evidence.

Increasingly common are practical designs such as stepped-wedged design in which centres or individuals can act as their own control for varying amounts of time before beginning treatment.347 Similarly, the use of single case series, in which an individual can act as their own control are being re-introduced.348, 349 For a second example, consider that most of the studies included in a recent review of interdisciplinary chronic pain care were single-group, pre-post design.315 This review found significant differences from after treatment on most outcomes, including pain intensity, physical and emotional functioning, and school attendance. Needed in this case is a focus on methods for describing complex interventions, including the content of the intervention, using criteria such as available templates for intervention description and replication (TiDieR),350 and open availability of manuals with full treatment descriptions to allow for an analysis of active components. Hybrid effectiveness-intervention designs also provide a methodology to evaluate efficacy of interventions as well as implementation to determine how the intervention can be integrated within clinical settings.351

One way to improve the quality and quantity of evidence for how to help children in pain is to create a critical shift in the thinking of the pain community, policy makers, and research funders. Where appropriate, there should be a move away from the adoption of non-bespoke research methods from another field of study, or from another time or population, and go back to basics. The reason the randomised controlled trial and its constituent parts is popular is because it successfully introduced ways to manage bias. The methods and associated statistics were created, however, to support agriculture not medicine,288 only later being transferred across to the study of humans. In asking how to design a study to evaluate the efficacy and safety of any intervention, either clinically for the individual you are trying to help, or as trial on a sample of population with need, one needs to understand how to manage bias.

One must always be critical when reviewing evidence in any field, and paediatric pain is no exception. Most funders and many journals require trials to register aims, hypotheses, and assessments a-priori on online registries (e.g., clinicaltrials.gov). If primary or secondary outcomes measures differ from registration to publication, or if important outcome measures are missing at publication that were registered, this may lead to suspicion unless addressed adequately.352 There are other key

considerations when interpreting evidence for the treatment of paediatric pain, including managing and interpreting risk of biases, size, and quality of evidence. Depending on trial design, trialists should reduce bias and fully report methods wherever possible. Biases that are important in randomised controlled trials are outlined in the Cochrane Risk of Bias tool.346 Full and transparent reporting will increase confidence around the estimate of effect and improve our evidence-base, rather than adding more uncertainty.353 In regard to size, there is a large body of literature that strongly argues that size matters when analysing and interpreting evidence from pain trials.354 Trials with fewer than 50 participants overestimate the treatment effect around 50% of the time.355 This can also be seen in a recent review of psychological interventions for children with chronic pain298 which found small trials produced a large beneficial treatment effect for reducing pain, compared to larger trials which found no beneficial effect. Therefore, larger trials will also help increase certainty, as smaller trials typically over-estimate effects of interventions.

Finally, it is important to interpret the quality of evidence with the effect of treatment. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) is most commonly used in healthcare evidence.356, 357 Using this system, outcomes are rated from very low (we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect) to high (we are very confident that the true effect lies close to that of the estimate of effect). Therefore, even when interventions show a very large beneficial effect, or a null effect, the quality of evidence is important to interpret what will guide clinicians, researchers, and policy makers on how reliable that evidence is, and how likely it would be to change if new trials were conducted.

Improving available treatments

Another way to make pain better is by working with what is known already. A good example is in the application of the pharmacokinetic and pharmacodynamic properties of analgesics in the developing child. Medical practitioners caring for children in pain want to know how effective a drug is likely to be and to know the optimal dose, timing and route of administration. While they may be aware that the dose should be reduced in the very young, there are often uncertainties about how much the dose is reduced or what reduction is required for a loading dose as opposed to a maintenance dose. Dose reduction could be attributable to either pharmacokinetic (commonly defined by clearance (CL) and volume of distribution (V)) combined with a pharmacodynamic effect (often defined by maximum effect (efficacy or EMAX) and the concentration at which half that maximum effect is achieved (C50)). These parameters are associated with variability. Quantifying and sourcing this variability and how it relates to dose in the individual child helps clinicians to personalize drug use. This method avoids the concept that one dose fits all, regardless of age, maturation, or disease process. It also sidesteps the approach where pain relief only has merit if it decreases by a predetermined value (e.g., 50%). Determining the ‘right’ dose is achieved by the use of target concentration strategy, the simplistic method is shown in Figure 6.

Figure 6. Determining correct dose in a target concentration analgesic strategy

Population pharmacokinetic-pharmacodynamic (PKPD) modelling can be used to determine key parameters such as CL, V, EMAX and C50. This modelling is a Bayesian statistical method in which mathematical equations are used to describe the typical (or population) time-concentration and concentration-response relationships observed after drug administration. Compartment models are usually used to describe drug disposition. This approach has been extended by integration of physiological parameters into the equations. The Hill equation, used originally to describe oxygen dissociation358 has proven popular and versatile to describe drug response, although other descriptors are equally valid. This methodology involves determination of a desired target effect and that in turn requires a robust pain measure or measures. Description of a concentration-pain response relationship allows assessment of pain relief on a concentration continuum. Simple relationships for ibuprofen359 and diclofenac360 determined for acute pain after tonsillectomy using a visual analogue scale (0-10) are shown in Figure 7.

Figure 7: A concentration-response relationship for ibuprofen and diclofenac, determined for acute pain after tonsillectomy

Population PKPD modelling uses mixed effects to study variability in drug responses in individuals who represent those in whom the drug will be used. If the variability between patients is modelled, then it is possible to predict the magnitude of the difference between predictions and the observations in the next subject.362 Variability is associated with all parameters used in PK and PD equations. Covariate information (e.g. weight, age, pathology, drug interactions, pharmacogenomics) can be used to help predict the typical dose in a specific patient, reducing population parameter variability. This type of modelling aims to personalise medicine.

Pharmacogenomics is one area that can provide information to individualise treatment. The drug irinotecan, used to treat cancer, has an active metabolite that is metabolised by a glucuronide (UGT1A1); a pathway similar to that involved in morphine clearance (UGT2B7). A variant allele UGT1A1*28 has been identified that is associated with severe neutropenia and diarrhoea. Genetic testing in patients to identify this allele (present in 10% Caucasians) has been shown to be beneficial in adults.363 Single polymorphisms that control the hepatic enzyme CYP2D6 influence metabolism of drugs such as codeine, tramadol and amitriptyline, drugs commonly used in pain management. Consequently, this enzyme contributes to observed effects and adverse effects. It is possible to perform bedside testing to assess genotype and that information can be used to review dose. Although genotype dose not always equate with phenotype,364 such information can be used as a guide for initial dosing.

We accept that genetic influences are complex and may prove difficult to unravel. It remains uncertain how much an understanding of pharmacogenomics will play in dose individualisation. If a single genetic variant was responsible for major PK or PD differences, then dose individualisation would be easier. However, there appears a multiplicity of genetic influences on both morphine PK and PD and the impact from interaction of these variants are not fully understood. Pain response is further complicated by numerous other factors (e.g. psychosocial, race, environment, underlying

pathology, age).365 We need to understand these complexities before they can be used to individualise therapy.

We present this in full as an example of an approach to optimise drug management that is rarely used for children with chronic pain but could be an effective way to radically improve the utility of existing treatments. One way to improve the management of pain is through better education around the pharmacokinetic and pharmacodynamic properties of analgesics in children.

This approach to personalisation could have merit across many of the existing treatments. Whilst assessing the pharmacokinetic and pharmacodynamic properties of drugs can help to optimise pharmacological interventions, other strategies can be used, for example, with psychological treatments. Within research of children with chronic pain, researchers are starting to stratify children and provide more targeted treatment modalities. Children with chronic pain often have comorbidities, such as anxiety, depression, post-traumatic stress, or higher levels of insomnia. Therefore, trialists have started trying to combine treatment modalities and test efficacy of delivering pain and insomnia CBT together282 or deliver anxiety and pain CBT366 with promising effects. In addition, from the RCTs already conducted, researchers are also investigating who reports the greatest gains in treatment. For example, studies have found that parent factors at the beginning of treatment could predict children who make the most gains after treatment.367, 368 For example, parents with higher distress pre-treatment predicted less improvement in child disability 12 months following treatment, compared to parents who reported lower distress.368 This indicates that for those caregivers with high distress, it may be important to target their own distress early in treatment, to effect change on child disability. This is critical information for refining psychological therapies and providing more individualised treatment.

Improving access and scale

One further way to make pain better is by working to increase access to the available treatments, and by extension increase their scale of production. We have already highlighted the important contribution of knowledge translation and provided examples in Table 1. Researchers have risen to the challenge of improving access to evidence supported treatments in the use of computing technology to deliver psychological, educational or nursing led treatments that have behaviour as a core target of the intervention. Just as technology has started to be used for assessment, investigators began exploring the use of computing technology for treatment. There is a relatively long history of attempts at using technology to increase access (e.g., the telephone)369 and at the automation of instruction or therapeutic direction.370 Often these attempts have expanded as computing technology became ubiquitous. For example, as we write the number of mobile data connections runs at more than the population in most countries, meaning that per population people have more than one device connected (https://ourworldindata.org/grapher/mobile-cellular-subscriptions-per-100-people). The dominance of the phone and the growth of computing in ‘smart’ phones has led investigators to both transfer face-to-face technologies onto these platforms, and to attempt innovation in new treatments that can only be delivered remotely.371-373 One systematic review identified ten randomised controlled trials testing the efficacy of remotely-delivered treatments for children with chronic pain, and found small effects for reducing pain intensity and disability after treatment.372 However, the long-term effects of these are currently unknown.

Despite the large number of apps delivering pain education and treatment, very few that have been developed are supported by evidence or based on a theoretical framework. There are some very good examples of how technology has been successfully used to improve access to treatments (e.g., 374) Less successful have been attempts at increasing the scale of access to treatments. Those that have been developed by scientists and tested for efficacy, often in University settings, are typically difficult to commercialise.375 For example, fewer than 30% of researcher-led applications for paediatric pain assessment and management became available to users, accounting for on average $300,000 of grant funds for each application.375 Scalability and sustainability remains a challenge and may actually involve reassessment of how to develop treatments, and our relationships with commercial providers, health care planners, insurers, and governmental agencies in funding and regulating access to treatments.376

One country that has made online, evidence-based psychological therapies for mental and physical health freely available is Australia. The eCentre Clinic (https://ecentreclinic.org) at Macquarie University has developed over 15 interventions for mental and physical health conditions, including panic attacks, depression, social anxiety, post-traumatic stress, chronic pain (in adults), diabetes, epilepsy, amongst others, in both children and adults. Once an intervention has been determined to be efficacious, it is made freely available to Australians. Often, participants accessing the interventions agree to be included into the research studies. The eCentre Clinic have conducted over 40 trials of over 4000 Australians testing these interventions to establish efficacy and safety.

Embracing complexity

Finally, in delivering the ambition of how to improve the effectiveness, safety, quality, access and scalability of the available treatments, there should be a focus on the context in which these treatments are to be delivered. Much of the evidence is based on single studies or the amalgamation of those studies in research synthesis. On translation from the research to the clinical setting there are three specific challenges: co-morbidity, ecological validity, and specificity.

Very few patients present with a single condition.377 Although medicine has arguably become fragmented through specialisation and super-specialisation, and there is a general tendency to see a patient through the lens of an individual's specific or specialist training, the skills and experience of the more general practitioner or child health worker are equally important. Pain is often being managed in the context of disease or after immunological challenge, as in surgery. In the neonate, as described earlier, fast developing systems often at a critical stage of shaping, need to be understood in any analgesic strategy. In children with neurodisability pain from multiple sources, for example muscle spasms, and complex co-morbid conditions such as sleep-apnoea syndrome are frequent. In the adolescent with chronic pain, comorbid mental health problems are common and should be considered in any plan.372, 377 Trials in this area often exclude those with more complex diagnoses and aim to improve physical functioning. Despite the comorbidities often seen in child and adolescent populations, RCTs in this field provide little treatment to manage anxiety and depression, and therefore, there is little change in their symptomology after pain treatment.

Our habit of excluding complexity in clinical trials and other research designs by excluding patients with multiple needs has led to gaps in our knowledge which are felt most acutely when faced with variety in patients presenting for help. Attempts have and are being made across paediatric pain to address problems in the ecological validity of trials used to guide practice. For example, there are recent studies in populations that are typically excluded from trials such as those from low income communities 378 or those with complex co-morbidities366. More needs to be done to reach these groups and those failing to present with manageable disease due to assessment difficulties, stigma, fear of social exclusion, or a coping strategy of minimizing adverse health concerns.

One size does not and should not fit all. Not all treatments work for everyone,379 exemplified by a desire to individualise and personalise pharmacotherapy. Sex and gender influences treatment outcome,380 as do genetic factors in later development of pain sensitivity or drug metabolism.381 Many factors beyond the individual child are also relevant, such as parent distress368 and the social context surrounding the child. A challenge for us will be to use what is known about what makes pain better as a foundation on which to build. That will mean understanding not only the evidence but the strengths and weaknesses of our habits of evidence production.

Box 9: Research and clinical priorities to make pain matter

We have to get smarter with how we make pain better; in trial design, treatments, what we deliver and to whom. There are currently serious shortcomings in treatment plans for children throughout the developmental age-span which need to be addressed (Box 9).

First, there are some fundamental gaps in the ambition to make pain better for all children and we need to innovate solutions to overcome our shortcomings. We have very little evidence for or against most pharmacological treatments commonly used in pain with needs being greatest for acute pain indications in the youngest children, and chronic and long- term pain for all age groups.251, 329 This situation is far from new, and in recognition of the widespread lack of data for medications in children the Best Pharmaceuticals for Children Act (2002)382 and the Pediatric Research Equity Act (2003),383 in the USA and the Paediatric Rule (2007),384 in Europe, were introduced. This legislation was designed to incentivise or require pharmaceutical companies to conduct RCTs with children, and include paediatric formulations where feasible; unfortunately, these strategies, although welcome, have clearly had limited success in the field of pain. The lack of suitable data has driven calls for newer and different approaches and modification of trial designs although the perception persists that these kinds of studies are difficult and impractical to conduct.385, 386 Nevertheless, we do need to consider alternative approaches to providing evidence to guide clinical practice that goes beyond the pharmacological RCT. The RCT was introduced to manage specific human influences which are known to bias outcomes of studies, masking any true effect of a novel health technology, and it manages some of these biases well. However, the RCT is expensive, time consuming, often inconclusive, and difficult to translate into clinical practice. They incur opportunity costs for alternative ways of exploring efficacy and harm for the individual patient. Nevertheless, large, multi-site trials that are free from bias will increase the confidence in the estimate of effects and provide clinicians with confidence when treating patients.

Second, there is a pressing need for novel drug discovery, in particular, medications that do not stimulate the reward system especially in this era of concern about opioid misuse. We encourage variety in clinical studies, especially in studies of efficacy. The analysis of a close investigation of pharmacokinetic-pharmacodynamic profiling was one such example. Often, healthcare professionals are dealing with older analgesics (e.g., morphine), the properties of which are well documented and understood at a population level and in multiple clinical samples. Quantifying and determining the source of variability in response, and how the variability relates to dose, route of administration, and scheduling in the individual child can help clinicians to personalize their analgesic strategy. One size does not fit all. Optimal drug management can be done at an individual level. Often individual hospitals and individual physicians treat patients by essentially conducting single case designs when prescribing and switching drugs in children in order to manage their pain. However, these procedures are not systematically and fully reported in an accessible way. Creating a shared national or international database of essential participant characteristics (age, sex, weight, height, diagnosis), prescription (drug, dose, route), and outcomes (pain intensity and interference, adverse events, functioning) that can be systematically recorded and shared will further our understanding of which drugs work for children with different pain conditions. Although there is a strong tradition of single case studies in clinical psychology387 their application in paediatric pain is rare,349 but examples exist in adult pain research.388 Paradoxically, focussing on the individual might allow us to imagine ways to increase access to evidence supported treatments and to scale up the production of those treatments.

Third, there is a need to intervene earlier to prevent onset of chronic pain. Identification of risk factors and tailoring of treatments could accelerate progress in this field. Early prevention is likely to reduce personal and societal effects of developing chronic pain, particularly in childhood. Psychological and physical interventions could be particularly useful in this domain, providing children and their parents with skills and understanding of pain management. Much of the trial evidence to date has focussed on managing chronic or procedural pain, but understanding who is most likely to develop pain and how to reduce this risk, through interventions delivered at community level, could dramatically reduce the numbers of children transitioning from acute to chronic pain after injury, surgery, or other.

Fourth, there is a need to stop some trials in the field where we have sufficient evidence, or further evidence is unlikely to change our confidence in the estimate of effect. One example is for psychological interventions for chronic pain, although there are other examples we could present such as distraction for children undergoing procedural pain. It is unlikely that more RCTs of psychological interventions, however well conducted, will reduce the overall uncertainties around effect estimates. The next steps in psychological treatment research should be to establish an evidence base for 1) complex participants with comorbidities, aimed at reducing distress as well as improving function, including parents, and improving social outcomes for participants, and 2) for prevention of long-term pain in children and adolescents. Although commonly used in practice, physical interventions for chronic pain would benefit from rigorous evaluation to better understand the role of the specific techniques versus general conditioning versus the ongoing relationship with the therapist. However, wherever trials are being reported, so should adverse event data. These are frequently missing in psychological the interventions.298

Finally, a benefit of an idiographic approach to research, in focusing on the single case, on the person, is that complexity ceases to be a problem and becomes the solution. We are interested in the peculiar, the unusual, as every case is ordinary in relation to itself. Our focus is on what works for the person, and complexity is the norm. For some, that complexity will likely involve co-morbidity, and polypharmacy, and will include a personal learning history and a specific environmental and learning context. Complexity science could be helpful in determining novel individualised treatments. If we can use the pain related data (big and small) made visible by the pervasive personal sensing and computing, we can start to use it for treatment.

Meaningful and lasting change: Action for policy makers and funders

Child pain matters. But not, it seems, to everyone, not for every child, and not for every pain. We have to work harder to make child pain matter to all, be understood and be visible; to make it important enough to bring out into the open and to act upon. Only then can pain be made better. However, these goals are not sequential, each must be addressed simultaneously to improve the well-being of infants, children, adolescents, and the adults they become.

The WHO–UNICEF–Lancet special commission on securing a future for children recently argued that children should be put at the centre of action to meet the sustainable development goals, that a focus on the health and wellbeing of children is essential to population survival.389 Here we focussed on pain within developed countries. We welcome a focus on child thriving, on the promotion of cognitive, emotional, and motivational resource, and on positioning children as central to political action. Children's ability to drive sustainable change should not be underestimated, nor should the degree to which young people care about a positive future for all.

Consensus on the importance of child health and wellbeing is an important start. Amongst healthcare professionals it is easy to agree that no child should experience pain if that pain can and should be prevented, avoided, or successfully treated. In practice, however, there is ample evidence that children frequently experience preventable pain, and that in high income settings with advanced health care systems, and highly educated and regulated health professionals, children, from newborns to emerging adults, experience pain that goes unnoticed, unreported, or is not responded to.390 Asserting a voice in pain can lead to social rejection, marginalisation, and stigma. Advocating individually for a child in pain can bring similar dangers of being labelled at best as unhelpful, and at worst as criminally interfering.391

In this commission we set out four critical goals, that if achieved, will transform paediatric pain; making children's pain matter, understood, visible and better for future generations. As we described at the start of this commission, these goals may seem obvious and many people may believe that they have confidence in successfully actioning them every day. However, we challenge everyone to step back and reconsider how they can further improve their clinical and research practice based on these goals. We sought to understand the reasons for the discordance between a belief in the importance of a goal, in what is thought correct and morally defensible, and the collective inaction in

organised attempts to deliver that goal. Casting the problem as a social science, one in addition to a psychological or medical one, can help reframe our future investigations. We do not suggest that individuals deliberately hurt or harm children by their actions or inaction. It is the individuals working to improve the lives of children and family who advocate for children in pain and deliver the solutions needed.

Here we focus on priorities for policy makers and funders that will enable healthcare professionals, researchers, patients and families to be able to achieve these goals (Box 16). At the beginning of the commission we asked how much of what we do (or fail to do) now for children in pain will come to be seen as unwise, unacceptable or unethical in the next 40 years? It is only by cross-sector collaboration between researchers, clinicians, policy makers, and funders that progress can be made quickly and effectively. We need a coordinated approach on all fronts, from all disciplines and agencies.

Box 10. Priorities for policy makers and funders

On a national level, longitudinal data are needed to fully understand the impact of pain experienced during childhood on later development and achievement. Although there are a number of databases which exist, pain often does not play a central role in such databases, despite it being a primary symptom of many diseases and illnesses. Children who experience pain during childhood are likely to go on to report pain in adulthood, so understanding the impact from inception is critical to understanding the later impact. A coordinated approach between countries is essential so researchers are able to compare the prevalence and impact of pain across cultures.

As evidence for understanding, assessing and treating pain continually evolves, so should the education of the healthcare professionals involved in this domain of care. As highlighted in the inequity of care, specialist knowledge to treating pain is often centralised. Greater efforts are needed to educate those in community settings to be able to treat neonates, children, and adolescents with pain. Improving curricula for all healthcare professionals is critically needed to include information on pain assessment and management, so that the healthcare professionals are better equipped to manage pain and not perceive it as a bi-product of a procedure or disease. In addition to this, curriculum revision is needed for medical nursing and allied health students treating future children with pain, who receive relatively little information about assessing and managing pain across the childhood lifespan, as well as regular re-training for front-line staff treating neonates, children, and adolescents.

Knowledge mobilisation is another strategy that could be key in reducing inequity in healthcare knowledge. There is now an active discussion about the importance of bridging the gaps between knowledge and its use, between science and clinical practice, and between patient experience and the design of services. We highlighted examples (Table 1). There is a need for other countries or international efforts to develop similar knowledge mobilisation networks to promote awareness of the problems of pain. There is also a need for countries or international efforts to develop knowledge

mobilisation networks to promote awareness of the problems of pain, particularly in an ever-increasing digitalised world where healthcare information is often just a click away.

Inequities in the provision of services need to be addressed. Clinically, there has been a growth in provision of dedicated child pain centres (e.g., https://www.iasp-pain.org/About/Content.aspx?ItemNumber=7916) and in many countries there have been successful attempts to audit and benchmark practice against a standard. However, there is still a long way to go. Most of these treatment centres are in urbanised areas under specialist professionals, yet it would be naïve to think that children only experience pain in these settings. There is benefit in gathering such knowledge and specialism in centres, but it can be to the detriment of children experiencing pain elsewhere, and to those who cannot always access these healthcare centres. When children reach treatment centres, their pain should be managed by healthcare professionals who have up-to-date knowledge. This means regular training, practice reflection, supervision, and resource.

Multidisciplinary treatments are considered the gold standard of care in this area, but despite the prevalence of pain in children, the services available to them often lack behind those of adults. There is evidence that pain experienced during childhood is reported in adulthood 392, and children do not spontaneously recover from chronic pain once it is reported 393, and symptoms deteriorate whilst awaiting interventions or clinic appointments 394. Therefore, funding for sustainable multidisciplinary services are critical for managing pain in these children and adolescents.

There needs to be a shift to make healthcare individuals and organisation leadership take charge of patient care and increase accountability. As we have advocated, all pain should be assessed and treated. Where that does not happen, a failure of care is occurring. Where pain is unassessed or untreated, intolerance needs to replace tolerance. Children are in pain now, across the world and more should be done to manage that pain. This includes making pain visible by targeting funding and policy to those who have been ignored or received inequity in pain management. As we discussed earlier, we are not talking about equal access to all resources, but fair access to unequal resources. Research funding is need to illuminate inequity within healthcare and community settings, so this can be rectified.

Diverse leadership at an organisational level is critical to dealing with local child pain challenges that present within the institution or region. Patient-partners are important to include in these leadership teams, providing a different perspective to other professionals and providing a voice of those who are subject to assessments and interventions. Driving the awareness of pain across the developmental lifespan and developing solutions at local levels is important.

With leadership will come novel innovation including new models of care. For example, we have yet to see ‘small data’ innovation 395, where by small data we mean the collection of data traces we shed as we go about our business. As more sensors are put in clothing, homes, vehicles, in fact in almost every object, it is possible to capture data on all behaviour. Combine that with data captured

actively as children volunteer information about their personal experience on social media, then one can begin to see that we are in the middle of a data revolution. What was once painstakingly and expensively done in the laboratory is now accessible as part of the daily life of children.396

Information does not guarantee knowledge. The intellectual task is to explore how both passive and actively captured data can be combined in statistical models to predict personal outcomes. We have the engineering capability, but we lack the behavioural science that can help us look for the right patterns of data and interpret behaviour as meaningful. Children and adolescents are, however, generally positive about the use of technology in healthcare and expect healthcare to be personalised and relevant. There are ethical considerations to the collection, storage, and use of such personal data which needs to be thoughtfully managed (e.g.,397. Clinically, in paediatric pain, we might usefully leapfrog current thinking about technology deployment which is focussed on establishing concordance with established paper and pencil methods, and instead adapt our assessment to match what is being freely given, using media which is capturing experience.

Beyond assessment patients cannot wait for the establishment of evidence bases, likely to take a generation to be funded, created, accumulated, and disseminated. Children, throughout the developmental spectrum, are in pain now. The evidence-based research that is available should be implemented in practice more frequently. To achieve our ambitions in accessibility and scale we need more pain clinics that start by being patient focussed, understanding the complex, idiosyncratic, and peculiar, personalising pain medicine for each patient. However, these centres should aim to be geographically diverse and not consolidate the centralisation of specialist pain knowledge identified in Goal 1. Use of technology in this revolution will be essential.

In expanding how pain management services are delivered, knowledge re-design should be considered. Rather than considering the expert as both the intelligence of the system, the means of production, and the quality control process, these functions can be separated. First, we can allow the expert to manage a system of knowledge, including access to technology, current evidence, peer support, and technical skills, instead of each individual attempting to hold all of the expertise; moving knowledge from the individual to an integrated computerised knowledge system. Second, we can enable access to rich curated ‘small’ data on the individual, potentially matched with insights from big data on the experience of others, supported with evidence from clinical studies. Third, we can liberate the expert from delivery by providing multiple local agents in the community with appropriate training to deliver the specific intervention under supervision from peers or experts. Ultimately the goal would be to shift the location of production, the delivery of assessment and treatment, and the timing of the treatment to where and when the patient needs it, rather than where and when we can currently manage it (Figure 8).

Figure 8. Redesigning pain services

Conclusion

This Commission has covered four important goals we believe will advance the field of paediatric pain over the next 10 years. We have set out goals and priorities to improve research and practice, but it will take the entire research and clinical community, in collaboration with funders and policy makers to achieve these goals. It was not possible to cover everything in this commission, we have focussed on westernised, economically developed countries but recognise that there are different challenges for lower income countries (see commentary on lower income countries in this issue). We have not focussed much on the importance of experimental research, theoretical development, and the need for their closer union.

It is time for change. We want to 'make pain matter' by exposing the social and personal forces that traditionally silence pain complaints, put them out of sight, and allow pain management to be ignored. There is a long way to go in our study of mechanism(s), to 'make pain understood' and this will take investment to progress quickly; and support for multidisciplinary collaboration will be key to its success. We know how to 'make pain visible' so we need to develop an intolerance for the absence of assessment and help educate everyone working with the child in pain on how to navigate the inferential process of determining patient pain status. And ultimately, we need better treatments and better access for more people, by making optimal use of technological innovation, and by creating new treatment models built around and for individual contextualised experience.

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Author contributions

All authors agreed to the submitted version of the commission and are accountable for all aspects of the work. CE oversaw the design, writing, and editing of the commission. CE was involved in the conceptualisation of the commission, drafting and editing the manuscript. EF, RH, and RS formed part of the core author team that conceptualised the commission and scope. They contributed and edited the manuscript. EF co-led goal 4, RH led goal 2, and RS contributed to all goals. PF led goal 1, SW and CS heavily contributed to goal 2, TP led goal 3, and KB co-led goal 4. All authors contributed to the conceptualisation of the commission and edited other sections. BA, CC, GC, GL, ZJ, IJ, CR, NS, DT, DW, CW all contributed to the conceptualisation of the commission and contributed content to specific goals. All authors edited the full draft version of the commission.

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Please note – figures are currently being redrawn by the Lancet team and are not included in this version.

Box 1. Jeffrey and Jill Lawson and advocacy for pain management

It was a mother, Jill Lawson, who contributed to one of the most radical changes in pain research and pain treatment since Melzack and Wall presented their theory of central nervous system plasticity. Her son, Jeffrey Lawson, was born prematurely and placed in the care of the Children's Hospital National Medical Centre in Washington DC in the US. Jeffrey underwent extensive surgery without adequate anaesthesia or analgesia, because as recent as 1985 the professional belief that infants lacked the capability to experience pain was common and prevalent. 5, 6 Although parents, like Jill Lawson, often assumed that their infants would be given pain relief during surgeries, the medical community were reluctant to provide analgesic and anaesthetic agents due to a lack of scientific evidence of the existence of pain in infants, and feared adverse effects of the available drugs. Surgery was performed using muscle paralytic agents, with a focus on immobilisation to practically facilitate the procedures rather than the prevention of suffering.7 Jeffrey lived for five weeks. Jill Lawson's advocacy brought together a combination of science and education to challenge the practice of withholding anaesthesia and analgesia in infants because it was thought unnecessary or unsafe. By 1995 practices had changed and a UK-based survey of anaesthetists demonstrated that 91% now provided systemic opioid analgesia to infants for major surgery, whereas in 1988 only 10% of anaesthetists adopted this practice.5 Science is not always enough to change practice; public awareness, and policy can take us from knowledge to action.8, 9

Box 2: Vaccination pain management: from clinical practice guideline to WHO

Immunization is a global priority to prevent infectious disease. Vaccination involving a needle puncture is painful and the pain experienced from vaccinations can cause fear and vaccine hesitancy, resulting in future avoidance of vaccinations, which can have a huge negative societal impact.

The guideline suggests:

- that for people of all ages, aspiration (pulling back on the syringe to ensure it is not in the blood vessel) should not be used during intramuscular injections.32
- injecting the most painful vaccine last rather than first during visits with more than one vaccination.
- when vaccinating infants and toddlers, breast or formula feeding infants less than two years of age or giving them a sugar solution prior to the injection.
- holding children in one's arms under the age of three during injections to provide them with a sense of comfort.
- when administering a vaccination to children over the age of three, an upright position is recommended as it provides a sense of control and decreases fear.
- parents of children aged 10 years and under should be present during vaccine injections to lower their child's distress levels, and topical analgesics should be applied before injection in children. And,
- educating parents, older children and adults about what to expect with a vaccination and methods to manage any pain.

The guideline culminated in a WHO position paper in 2015 on "Reducing pain at the time of vaccination".33 The position paper was the first policy paper on pain mitigation at the time of vaccination, integrating information pertaining to the reduction of pain, distress and fear across all age groups. The paper provides important acknowledgment from the WHO that:

"pain during vaccination sessions is manageable and managing pain does not decrease the efficacy of the vaccine. There are effective, feasible, non-costly, culturally acceptable, and age-specific evidence-based strategies to mitigate pain at the time of vaccination." 33 (p.3629)

Table 1: Recent and ongoing initiatives to mobilise knowledge in paediatric pain

	Goal	Countries or regions involved	Weblink
Benchmark practice			
EUROPAIN' (EUROpean Pain Audit In Neonates)	Document analgesic practice in neonatal care	Europe	
Paediatric Electronic Persistent Pain Outcomes Collaboration (PaedePPOC)	Introduce common assessment practice for pain management in 10 centres	Australia	https://www.uow.edu.au/ahsri/eppoc/
Improve clinical practice			
Child Kind International	Encourage institutional commitment to providing comfort and pain relief		http://childkindinternational.org
Increase public awareness			
Solution for Kids in Pain	Confirm knowledge user needs, organize current resources and evidence; Produce and promote knowledge mobilization tools; Facilitate institutional change; and Increase awareness amongst the general public	Canada	https://www.kidsinpain.ca
#ItDoesn'tHaveToHurt	Provide evidence-based information about children's pain management across social media platforms	Canada	

Box 3: Research and clinical priorities to make pain matter

To make pain experienced by infants, children, and adolescents matter, to make it visible, and a response to pain expected and required we believe that research should focus on:

1. Improve equity

a. A person's pain care should not be determined by non-personal determinants of health (e.g. socioeconomic status, age, sex, disability, ethnicity). Studies that expose the factors that contribute to inequity in pain management, consequences of inequality in pain management, and strategies to mitigate inequity are needed.

b. Effective strategies to make the latest pain management research accessible and understandable for patients (e.g. older children and adolescents) and their caregivers.

c. Strategies that ensure that all clinicians involved in the healthcare of a child/adolescent are competent to provide pain care within their scope of practice.

2. Mitigate Stigma

a. Consider labels given to pain that cannot be diagnosed with a known condition.

b. Determine best communication strategies when talking to children and families with pain to communicate understanding, empathy, and treatment course.

3. Social Science of Pain. The lives of children, adolescents and their caregivers, and thus pain and pain care, are contextually situated within their social environment that has both macro and micro levels.

a. Macro understanding of the societal (e.g. cultural, political, healthcare institutions) forces that influence paediatric pain experiences and management (e.g. research funding allocation, political agendas that shape policy and narratives, understanding of culturally embedded experiences).

b. Micro understanding of mechanisms and interventions that leverage social factors (e.g. family, friends/peers, teachers) to improve the experience of those living with pain (e.g. decreasing stigma, improving social health)

Box 4. Pain definition and classifications

In 2019, a new IASP task force proposed an updated definition of pain as: “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”, (p.2) 87 with added text to recognise that in many circumstances pain could not be verbally mediated: “Verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a non-human animal experiences pain.” 87.

Pain can be classified or described in multiple ways, some of the most frequently used include:

By somatosensory mechanism:

- Nociceptive pain: Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors (pain-detecting nerves). It is the mechanism operating in most everyday painful experiences, and when it is the result of an injury or damage, it should resolve when healing has occurred. In infants, children and throughout development the mechanisms of nociceptive pain change with age.

- Neuropathic pain: Pain caused by a lesion or disease of the somatosensory nervous system. When the system that detects pain is itself damaged although it may not respond to a previously painful stimulus (anaesthesia), it may also generate pain. Cellular and molecular mechanisms operating when there is neuropathic pain are different from nociceptive pain and less likely to resolve with the healing process. During development and maturation the mechanisms and clinical presentations of neuropathic pain differ with age and underlying cause of damage.

- Nociplastic pain: Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. Changes in nociceptive processing mechanisms can be demonstrated in some individuals where a clear underlying cause is not detectable by currently available methods.

By time

- Acute pain: duration less than 3 months

e.g. acute postoperative pain, vaccination pain.

Mechanisms operating in acute pain are mostly nociceptive and resolution is normally expected when healing occurs.

- Chronic pain: pain that lasts or recurs for longer than 3 months.

e.g. chronic musculoskeletal pain, chronic disease-related pain. Chronic pain may involve nociceptive, neuropathic and/or nociplastic mechanisms.

In clinical situations pain may also be described as continuous (background pain), or intermittent (episodic pain) that is either predictable (incident), or unpredictable (spontaneous).

By context or location

- Disease-related: pain in association with specific diagnoses or conditions

o e.g.: juvenile inflammatory arthritis (JIA); cancer pain

- Tissue or organ-dependent: pain arising from specific tissues or organs

o e.g.: visceral; musculoskeletal (bone and/or joint and/or muscle); headache; pelvic pain

- Iatrogenic: pain associated with or following medical treatments

o e.g.: procedure pain including vaccination, surgical or medical (e.g. chemotherapy-induced neuropathy) interventions

- Idiopathic (or sometimes ‘Functional’ or ‘Primary’): no clear cause identified

o e.g. chronic primary abdominal pain (see Panel 2 for ICD-11 terminology).

When pain is described in terms of context mechanisms may be nociceptive, neuropathic or nociplastic, and may also be acute or chronic.

Box 5. Research and clinical priorities to make pain understood

i) Promotion of greater understanding of the subjective nature of pain and the multiple and varied inputs at different stages of development that influence nociception and the pain response with abandonment of concepts that negate the explicit integration of biological, psychological, and social elements that comprise all forms of pain.

ii) Research and clinical understanding of pain to include the whole biopsychosocial model, eliminating suggestions of dualism.

iii) Greater understanding of the early experience of pain on later development and behaviour.

iv) Further development of methodologies to provide robust surrogate pain measures in immature and/or non-verbal populations.

v) Clearer understanding of the factors contributing to and mechanisms playing a role in individual variability in pain perception, somatosensory function, development and persistence of sensitisation processes, transition to chronic pain and responses to treatments.

vi) Longitudinal studies tracking individual development and how biological, environmental, psychological and social factors affect normal developmental trajectories, including effects on sensory and affective components of pain response and risk of chronic pain in later life.

Box 6. Developmentally appropriate pain intensity assessment methods for children six years and older

There are a wide range of pain assessments available to researchers and clinicians alike, interested in assessing pain intensity in children across the developmental lifespan. In a recent systematic review,238 60 separate pain intensity assessments were identified. Not only are there many different measures, but there are also different anchors for scales such as the numerical rating scale (NRS) and visual analogue scale (VAS). There must also be an understanding of whether the participant or patient can understand and interpret the scale, providing a reliable response.

In the latest review of the evidence for pain intensity scales, recommendations for and against scales were provided.238 Recommendations were either strong or weak, for or against measures. For children with acute pain, strong recommendations for the use of the NRS using an 11-point scale from 0 (no hurt) to 10 (the worst hurt you could ever imagine), in children 6 years and older. The Faces Pain Scale-Revised was strongly recommended for children aged 7 and older, and the Colour Analogue Scale was strongly recommended in children 8 years and older. No other strong recommendations were provided for other pain intensity scales for acute, post-operative, or chronic

pain. However, VAS and NRS scales are recommended (weak recommendation) for children six years or older for post-operative and chronic pain, providing the child can show numerical competency.

Box 7: Routine assessment questions to help make child pain and its impact visible

- What are your concerns/worries about your pain?
- What is a typical day like for you when you have pain?
- What are the things you do that make your pain better, and things you do that make your pain worse?
- What would you be doing differently if your pain was lessened?
- How would you know that a pain treatment was working for you? What would be a meaningful change to you?
- What impact does pain have on your life?

Box 8: Research and clinical priorities to make pain visible

- Assess pain in every child with an acute or chronic condition that is causing pain regardless of age, ability, or sex.
- Ask all children and parents about the impact of pain on their daily lives. Integrate the context of pain measurement by expanding research on social and environmental factors that influence pain assessment.
- Develop measures from a 'bottom-up' manner and provide children and parents a voice in determining relevant outcome measures and whether pain treatment achieves a clinically meaningful change.
- Use person-centred approaches in pain assessment to help match patients with the level of care needed to optimally address pain and comorbidities.
- Expand the potential of daily life assessments and wearable sensors for both clinical practice and research investigations in paediatric pain.

Box 9: Research and clinical priorities to make pain better

- Establish a systematic evidence base for pharmacological interventions in children with chronic pain, in a creative way. Creative solutions in trial design when the randomised controlled trial is not ethical or practical.
- Develop ways to improve treatments we have, such as through the pharmacokinetic and pharmacodynamic properties of analgesics. This could include tailoring treatments for other children with pain and also attempt to personalise treatments based on known covariates that includes pharmacogenomics
- Establish evidence on how and when to treat children with acute pain to prevent transition to chronic pain. Development of interventions that are effective in providing coping skills to prevent the onset of long-term pain are critical.

- Stop trials in areas where there is sufficient evidence, and further evidence will not change the quality or confidence in the estimate of effect. Start trials for complex patients and to prevent onset of long-term pain.
- Address complexity boldly and create and test treatments to meet the needs of those patients.

Box 10: Priorities for policy makers and funders

- National level initiatives should be taken to measure pain and its impact in large-scale monitors or survey (each country has their own health survey, but pain does not have a prominent place). Ideally, same measures across countries, to allow cross-national comparisons.
- Pain service provision and specialism should not only be available in urbanised locations. Greater emphasis should be given to providing community healthcare professionals with remote access to centralised services and knowledge to treat children with pain.
- Strategies/intervention to increase the accountability for improved pain curriculum to prepare healthcare students for clinical practice (e.g. accreditation bodies, universities) and plan to increase knowledge and competences about pain in children in care providers. Ensure that training and resources are prioritised and provided for frontline staff in order to prevent unnecessary pain.
- Knowledge mobilisations initiatives to reduce the gap between evidence to practice.
- Plan and provide funding for multidisciplinary and multi-professional pain management services for children in a way similar to what is already the case for adults.
- Develop leadership including partners from diverse sectors (policy, medicine, research, pharma, etc) come together to raise awareness and develop solutions to address treating paediatric pain. Policy makers, clinicians and researchers must unite in a formal way.
- Introduce institutional commitment initiatives concerning prevention, diagnostics and treatment of pain in children in all hospitals.
- Strategies and interventions to increase the accountability of healthcare administrators and clinicians in providing pain care to infants, children, and adolescents (e.g. professional regulators, hospital accreditation associations, inadequate pain management as a patient safety issue).
- Ensure the creation of systems that allow for the full participation of patient partners in institutional policy and decision making around paediatric pain.

Figure legends

Figure 1. Common types of pain during childhood

Figure 2 Pain mechanisms and sources of pain

Pain can be broadly classified as due to nociceptive, neuropathic or nociplastic, with combinations of these mechanisms present in association with different forms of injury or illness. Afferent activity in the peripheral nervous system can be generated by different sources of pain and is transmitted to the spinal cord where significant modulation occurs. Ascending pain pathways reach the brainstem and brain-where pain is perceived, and descending pathways also modulate (inhibit or facilitate) sensitivity in the spinal cord.

Key:

* presence of significant developmental changes in structure and/or function

--- mechanism sometimes involved

Abbreviations: PAG, periaqueductal grey; PBN, parabrachial nucleus; LC, locus coruleus; RVM, rostroventral medulla

Figure 3 Brain networks in nociceptive (acute) and chronic pain

Upper images: Pain activates a variety of brain regions that subserve both the sensory (i.e. major ascending afferent nociceptive pathways) aspects of pain, and the emotional aspects of pain experience.95, 96

Lower image: a- f, structural and functional changes associated with chronic pain.

Abbreviations: ACC, anterior cingulate cortex; AMY, amygdala; BG, basal ganglia; M1,

primary motor cortex; PAG, periaqueductal grey; PFC, prefrontal cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex

Figure 4. Potential Mechanisms Contributing to susceptibility to Paediatric Chronic Pain

A. Pain Drivers including inductors of pain A1 and resiliency factors A2 impact and predict objective pain measures (red).

B. Disease & C. Disease Severity factors are influenced by both peripheral factors (B1-B3) and central factors (B4-B8) that can be either inductors of pain or protective against the development of chronic pain.

D. Brain Changes, which can include assessment of (1) functional – using resting state measures (RSN) (D1) and structural (D2) – gray matter volume (unpublished data from our group).

E. Psychophysical Changes- Quantitative Sensory Testing (QST) can be used to produce measures of ongoing Peripheral Nervous System (PNS) and Central Nervous System (CNS) Sensitization (E1-E2).

Offset Analgesia (OA) (E3) can be used for measures of CNS Modulatory Responsivity such as normal or intact OA (E3A- in male vs female volunteers ages 6-19 years; including rapid and large decrease in pain levels with a small decrease in pain stimulus, and Disrupted OA (E3B in males vs. female volunteers ages 20-80 years), including minimal decrease in pain levels with a small decrease in pain stimulus). Responses for both E3A & E3B are percentage of peak response. 147

Acknowledgement: Figure adapted from a figure conceptualized by David Borsook and Christine Sieberg.146

Figure 5. Assessing pain in infants

Figure taken from 251.

Figure 6. Determining correct dose in a target concentration analgesic strategy

Figure 7: A concentration-response relationship for ibuprofen and diclofenac, determined for acute pain after tonsillectomy

The response curve is described using the Hill equation. Maximum effect (EMAX) is similar for both drugs. A reduction of 4 pain units correlates with a concentration of 6 mg/L for both drugs.

A target effect of 4 pain units (VAS 0-10) in which a score above 4 is usually considered as pain correlates with a target concentration of 5.8 mg/L for both diclofenac and ibuprofen. Pharmacokinetic knowledge can then be used to estimate the dose that will achieve that target concentration in an individual361 and be used as the starting point of in vitro trial design determining the optimal dosage beforehand.

Figure 8. Redesigning pain services

Additional material

Box 1. Jeffrey and Jill Lawson and advocacy for pain management

It was a mother, Jill Lawson, who contributed to one of the most radical changes in pain research and pain treatment since Melzack and Wall presented their theory of central nervous system plasticity. Her son, Jeffrey Lawson, was born prematurely and placed in the care of the Children's Hospital National Medical Centre in Washington DC in the US. Jeffrey underwent extensive surgery without adequate anaesthesia or analgesia, because as recent as 1985 the professional belief that infants lacked the capability to experience pain was common and prevalent. [5, 6] Although parents, like Jill Lawson, often assumed that their infants would be given pain relief during surgeries, the medical community were reluctant to provide analgesic and anaesthetic agents due to a lack of scientific evidence of the existence of pain in infants, and feared adverse effects of the available drugs. Surgery was performed using muscle paralytic agents, with a focus on immobilisation to practically facilitate the procedures rather than the prevention of suffering.[7] Jeffrey lived for five weeks. Jill Lawson's advocacy brought together a combination of science and education to challenge the practice of withholding anaesthesia and analgesia in infants because it was thought unnecessary or unsafe. By 1995 practices had changed and a UK-based survey of anaesthetists demonstrated that 91% now provided systemic opioid analgesia to infants for major surgery, whereas in 1988 only 10% of anaesthetists adopted this practice.[5] Science is not always enough to change practice; public awareness, and policy can take us from knowledge to action.[8, 9]

Box 2: Vaccination pain management: from clinical practice guideline to WHO

Immunization is a global priority to prevent infectious disease. Vaccination involving a needle puncture is painful and the pain experienced from vaccinations can cause fear and vaccine hesitancy, resulting in future avoidance of vaccinations, which can have a huge negative societal impact.

The guideline suggests:

- that for people of all ages, aspiration (pulling back on the syringe to ensure it is not in the blood vessel) should not be used during intramuscular injections.[32]
- injecting the most painful vaccine last rather than first during visits with more than one vaccination.
- when vaccinating infants and toddlers, breast or formula feeding infants less than two years of age or giving them a sugar solution prior to the injection.
- holding children in one's arms under the age of three during injections to provide them with a sense of comfort.
- when administering a vaccination to children over the age of three, an upright position is recommended as it provides a sense of control and decreases fear.
- parents of children aged 10 years and under should be present during vaccine injections to lower their child's distress levels, and topical analgesics should be applied before injection in children. And,
- educating parents, older children and adults about what to expect with a vaccination and methods to manage any pain.

The guideline culminated in a WHO position paper in 2015 on "Reducing pain at the time of vaccination".[33] The position paper was the first policy paper on pain mitigation at the time of vaccination, integrating information pertaining to the reduction of pain, distress and fear across all age groups. The paper provides important acknowledgment from the WHO that:

"pain during vaccination sessions is manageable and managing pain does not decrease the efficacy of the vaccine. There are effective, feasible, non-costly, culturally acceptable, and age-specific evidence-based strategies to mitigate pain at the time of vaccination." [33] *(p.3629)*

Table 1: Recent and ongoing initiatives to mobilise knowledge in paediatric pain

	Goal	**Countries or regions involved**	**Weblink**
Benchmark practice			
EUROPAIN' (EUROpean Pain Audit In Neonates)	Document analgesic practice in neonatal care	Europe	
Paediatric Electronic Persistent Pain Outcomes Collaboration (PaedePPOC)	Introduce common assessment practice for pain management in 10 centres	Australia	https://www.uow.edu.au/ahsri/eppoc/
Improve clinical practice			
Child Kind	Encourage institutional commitment to providing comfort and pain relief	International	http://childkindinternational.org
Increase public awareness			
Solution for Kids in Pain	Confirm knowledge user needs, organize current resources and evidence; Produce and promote knowledge mobilization tools; Facilitate institutional change; and Increase awareness amongst the general public	Canada	https://www.kidsinpain.ca
#ItDoesn'tHaveToHurt	Provide evidence-based information about children's pain management across social media platforms	Canada	

Box 3: Research and clinical priorities to make pain matter

To make pain experienced by infants, children, and adolescents matter, to make it visible, and a response to pain expected and required we believe that research should focus on:

1. **Improve equity**
    a. A person's pain care should not be determined by non-personal determinants of health (e.g. socioeconomic status, age, sex, disability, ethnicity). Studies that expose the factors that contribute to inequity in pain management, consequences of inequality in pain management, and strategies to mitigate inequity are needed.
    b. Effective strategies to make the latest pain management research accessible and understandable for patients (e.g. older children and adolescents) and their caregivers.
    c. Strategies that ensure that all clinicians involved in the healthcare of a child/adolescent are competent to provide pain care within their scope of practice.

2. **Mitigate Stigma**
    a. Consider labels given to pain that cannot be diagnosed with a known condition.
    b. Determine best communication strategies when talking to children and families with pain to communicate understanding, empathy, and treatment course.

3. **Social Science of Pain.** The lives of children, adolescents and their caregivers, and thus pain and pain care, are contextually situated within their social environment that has both macro and micro levels.
    a. Macro understanding of the societal (e.g. cultural, political, healthcare institutions) forces that influence paediatric pain experiences and management (e.g. research funding allocation, political agendas that shape policy and narratives, understanding of culturally embedded experiences).
    b. Micro understanding of mechanisms and interventions that leverage social factors (e.g. family, friends/peers, teachers) to improve the experience of those living with pain (e.g. decreasing stigma, improving social health)

Box 4. Pain definition and classifications

In 2019, a new IASP task force proposed an updated definition of pain as: *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage", (p.2)* [87] with added text to recognise that in many circumstances pain could not be verbally mediated: *"Verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a non-human animal experiences pain."* [87].

Pain can be classified or described in multiple ways, some of the most frequently used include:

By somatosensory mechanism:

- **Nociceptive pain**: *Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors (pain-detecting nerves). It is the mechanism operating in most everyday painful experiences, and when it is the result of an injury or damage, it should resolve when healing has occurred. In infants, children and throughout development the mechanisms of nociceptive pain change with age.*
- **Neuropathic pain**: *Pain caused by a lesion or disease of the somatosensory nervous system. When the system that detects pain is itself damaged although it may not respond to a previously painful stimulus (anaesthesia), it may also generate pain. Cellular and molecular mechanisms operating when there is neuropathic pain are different from nociceptive pain and less likely to resolve with the healing process. During development and maturation the mechanisms and clinical presentations of neuropathic pain differ with age and underlying cause of damage.*
- **Nociplastic pain**: *Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. Changes in nociceptive processing mechanisms can be demonstrated in some individuals where a clear underlying cause is not detectable by currently available methods.*

By time

- **Acute pain:** duration less than 3 months
  e.g. acute postoperative pain, vaccination pain.
  Mechanisms operating in acute pain are mostly nociceptive and resolution is normally expected when healing occurs.
- **Chronic pain**: pain that lasts or recurs for longer than 3 months.
  e.g. chronic musculoskeletal pain, chronic disease-related pain. Chronic pain may involve nociceptive, neuropathic and/or nociplastic mechanisms.

In clinical situations pain may also be described as continuous (background pain), or intermittent (episodic pain) that is either predictable (incident), or unpredictable (spontaneous).

By context or location

- **Disease-related:** *pain in association with specific diagnoses or conditions*

    - e.g.: juvenile inflammatory arthritis (JIA); cancer pain
- **Tissue or organ-dependent:** *pain arising from specific tissues or organs*
    - e.g.: visceral; musculoskeletal (bone and/or joint and/or muscle); headache; pelvic pain
- **Iatrogenic:** pain associated with or following medical treatments
    - e.g.: procedure pain including vaccination, surgical or medical (e.g. chemotherapy-induced neuropathy) interventions
- **Idiopathic (**or sometimes **'Functional' or 'Primary'):** no clear cause identified
    - e.g. chronic primary abdominal pain (see Panel 2 for ICD-11 terminology).

When pain is described in terms of context mechanisms may be nociceptive, neuropathic or nociplastic, and may also be acute or chronic.

Box 5. Research and clinical priorities to make pain understood

1. Promotion of greater understanding of the subjective nature of pain and the multiple and varied inputs at different stages of development that influence nociception and the pain response with abandonment of concepts that negate the explicit integration of biological, psychological, and social elements that comprise all forms of pain.
2. Research and clinical understanding of pain to include the whole biopsychosocial model, eliminating suggestions of dualism.
3. Greater understanding of the early experience of pain on later development and behaviour.
4. Further development of methodologies to provide robust surrogate pain measures in immature and/or non-verbal populations.
5. Clearer understanding of the factors contributing to and mechanisms playing a role in individual variability in pain perception, somatosensory function, development and persistence of sensitisation processes, transition to chronic pain and responses to treatments.
6. Longitudinal studies tracking individual development and how biological, environmental, psychological and social factors affect normal developmental trajectories, including effects on sensory and affective components of pain response and risk of chronic pain in later life.

Box 6. Developmentally appropriate pain intensity assessment methods for children six years and older

There are a wide range of pain assessments available to researchers and clinicians alike, interested in assessing pain intensity in children across the developmental lifespan. In a recent systematic review,[238] 60 separate pain intensity assessments were identified. Not only are there many different measures, but there are also different anchors for scales such as the numerical rating scale (NRS) and visual analogue scale (VAS). There must also be an understanding of whether the participant or patient can understand and interpret the scale, providing a reliable response.

In the latest review of the evidence for pain intensity scales, recommendations for and against scales were provided.[238] Recommendations were either strong or weak, for or against measures. For children with acute pain, strong recommendations for the use of the NRS using an 11-point scale from 0 (no hurt) to 10 (the worst hurt you could ever imagine), in children 6 years and older. The Faces Pain Scale-Revised was strongly recommended for children aged 7 and older, and the Colour Analogue Scale was strongly recommended in children 8 years and older. No other strong recommendations were provided for other pain intensity scales for acute, post-operative, or chronic pain. However, VAS and NRS scales are recommended (weak recommendation) for children six years or older for post-operative and chronic pain, providing the child can show numerical competency.

Box 7: Routine assessment questions to help make child pain and its impact visible

- *What are your concerns/worries about your pain?*
- *What is a typical day like for you when you have pain?*
- *What are the things you do that make your pain better, and things you do that make your pain worse?*
- *What would you be doing differently if your pain was lessened?*
- *How would you know that a pain treatment was working for you? What would be a meaningful change to you?*
- *What impact does pain have on your life?*

Box 8: Research and clinical priorities to make pain visible

- Assess pain in every child with an acute or chronic condition that is causing pain regardless of age, ability, or sex.
- Ask all children and parents about the impact of pain on their daily lives. Integrate the context of pain measurement by expanding research on social and environmental factors that influence pain assessment.
- Develop measures from a ‘bottom-up’ manner and provide children and parents a voice in determining relevant outcome measures and whether pain treatment achieves a clinically meaningful change.
- Use person-centred approaches in pain assessment to help match patients with the level of care needed to optimally address pain and comorbidities.
- Expand the potential of daily life assessments and wearable sensors for both clinical practice and research investigations in paediatric pain.

Box 9: Research and clinical priorities to make pain better

- Establish a systematic evidence base for pharmacological interventions in children with chronic pain, in a creative way. Creative solutions in trial design when the randomised controlled trial is not ethical or practical.
- Develop ways to improve treatments we have, such as through the pharmacokinetic and pharmacodynamic properties of analgesics. This could include tailoring treatments for other children with pain and also attempt to personalise treatments based on known covariates that includes pharmacogenomics
- Establish evidence on how and when to treat children with acute pain to prevent transition to chronic pain. Development of interventions that are effective in providing coping skills to prevent the onset of long-term pain are critical.
- Stop trials in areas where there is sufficient evidence, and further evidence will not change the quality or confidence in the estimate of effect. Start trials for complex patients and to prevent onset of long-term pain.
- Address complexity boldly and create and test treatments to meet the needs of those patients.

Box 10: Priorities for policy makers and funders

- National level initiatives should be taken to measure pain and its impact in large-scale monitors or survey (each country has their own health survey, but pain does not have a prominent place). Ideally, same measures across countries, to allow cross-national comparisons.
- Pain service provision and specialism should not only be available in urbanised locations. Greater emphasis should be given to providing community healthcare professionals with remote access to centralised services and knowledge to treat children with pain.
- Strategies/intervention to increase the accountability for improved pain curriculum to prepare healthcare students for clinical practice (e.g. accreditation bodies, universities) and plan to increase knowledge and competences about pain in children in care providers. Ensure that training and resources are prioritised and provided for frontline staff in order to prevent unnecessary pain.
- Knowledge mobilisations initiatives to reduce the gap between evidence to practice.
- Plan and provide funding for multidisciplinary and multi-professional pain management services for children in a way similar to what is already the case for adults.
- Develop leadership including partners from diverse sectors (policy, medicine, research, pharma, etc) come together to raise awareness and develop solutions to address treating paediatric pain. Policy makers, clinicians and researchers must unite in a formal way.
- Introduce institutional commitment initiatives concerning prevention, diagnostics and treatment of pain in children in all hospitals.
- Strategies and interventions to increase the accountability of healthcare administrators and clinicians in providing pain care to infants, children, and adolescents (e.g. professional regulators, hospital accreditation associations, inadequate pain management as a patient safety issue).
- Ensure the creation of systems that allow for the full participation of patient partners in institutional policy and decision making around paediatric pain.

Figure legends

Figure 1. Common types of pain during childhood

Figure 2 Pain mechanisms and sources of pain

Pain can be broadly classified as due to nociceptive, neuropathic or nociplastic, with combinations of these mechanisms present in association with different forms of injury or illness. Afferent activity in the peripheral nervous system can be generated by different sources of pain and is transmitted to the spinal cord where significant modulation occurs. Ascending pain pathways reach the brainstem and brain-where pain is perceived, and descending pathways also modulate (inhibit or facilitate) sensitivity in the spinal cord.

Key:

* presence of significant developmental changes in structure and/or function

--- mechanism sometimes involved

Abbreviations: PAG, periaqueductal grey; PBN, parabrachial nucleus; LC, locus coruleus; RVM, rostroventral medulla

Figure 3 Brain networks in nociceptive (acute) and chronic pain

Upper images: Pain activates a variety of brain regions that subserve both the sensory (i.e. major ascending afferent nociceptive pathways) aspects of pain, and the emotional aspects of pain experience.[95, 96]

Lower image: a- f, structural and functional changes associated with chronic pain.

Abbreviations: ACC, anterior cingulate cortex; AMY, amygdala; BG, basal ganglia; M1,

primary motor cortex; PAG, periaqueductal grey; PFC, prefrontal cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex

Figure 4. Potential Mechanisms Contributing to susceptibility to Paediatric Chronic Pain

A. <u>Pain Drivers</u> including inductors of pain A1 and resiliency factors A2 impact and predict objective pain measures (red).

B. Disease & C. Disease Severity factors are influenced by both peripheral factors (B1-B3) and central factors (B4-B8) that can be either inductors of pain or protective against the development of chronic pain.

D. Brain Changes, which can include assessment of (1) functional – using resting state measures (RSN) (D1) and structural (D2) – gray matter volume (unpublished data from our group).

E. Psychophysical Changes- Quantitative Sensory Testing (QST) can be used to produce measures of ongoing Peripheral Nervous System (PNS) and Central Nervous System (CNS) Sensitization (E1-E2).

Offset Analgesia (OA) (E3) can be used for measures of CNS Modulatory Responsivity such as normal or intact OA (E3A- in male vs female volunteers ages 6-19 years; including rapid and large decrease in pain levels with a small decrease in pain stimulus, and Disrupted OA (E3B in males vs. female volunteers ages 20-80 years), including minimal decrease in pain levels with a small decrease in pain stimulus). Responses for both E3A & E3B are percentage of peak response. [147]

Acknowledgement: Figure adapted from a figure conceptualized by David Borsook and Christine Sieberg.[146]

Figure 5. Assessing pain in infants

Figure taken from [251].

Figure 6. Determining correct dose in a target concentration analgesic strategy

Figure 7: A concentration-response relationship for ibuprofen and diclofenac, determined for acute pain after tonsillectomy

The response curve is described using the Hill equation. Maximum effect (EMAX) is similar for both drugs. A reduction of 4 pain units correlates with a concentration of 6 mg/L for both drugs.

A target effect of 4 pain units (VAS 0-10) in which a score above 4 is usually considered as pain correlates with a target concentration of 5.8 mg/L for both diclofenac and ibuprofen. Pharmacokinetic knowledge can then be used to estimate the dose that will achieve that target concentration in an individual[361] and be used as the starting point of in vitro trial design determining the optimal dosage beforehand.

Figure 8. Redesigning pain services