Delivering transformative action in paediatric pain: a *Lancet Child & Adolescent Health* Commission

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Executive summary

Every infant, child, and adolescent will experience pain at times throughout their life. Childhood pain ranges from acute to chronic, and includes procedural, disease-related, breakthrough, and other types of pain. Despite its ubiquity, pain is a major challenge for individuals, families, health-care professionals, and societies. As a private mental experience, 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, including continued chronic pain, disability, and distress. This undertreatment of pain should not continue, as there are available tools, expertise, and evidence to provide better treatment for childhood pain.

In this Commission, we present four transformative goals that will improve the lives of children and adolescents with pain and their families. These goals, taken at face value, might 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. We take a developmental perspective that encompasses children from birth to 24 years, and focus on how the provision of paediatric pain treatment and services can be improved.

First, make pain matter. Pain has not mattered enough, as evidenced by common failings to provide adequate or appropriate pain relief in clinical practice, insufficient training among health-care professionals, a lack of investment in research and services, and inequity in access to pain management. Despite some good examples of knowledge translation, investment in a strong social science research base for paediatric pain is needed to catapult us into a new era in which the social and cultural context of pain can be understood and addressed.

Second, make pain understood. There has been excellent progress in our mechanistic understanding of nociception and pain perception for both acute and chronic pain states, but gaps in knowledge remain. Pain research needs to include the whole biopsychosocial model, including its subjective nature and the multiple inputs at different stages of development that affect the pain experience. Advances in developmental biology, genetics, psychology, nosology, and classification will all help to speed up discovery in these areas. Greater investment is also needed in larger international birth cohort studies that incorporate comprehensive pain-related measurements.

Third, make pain visible. Pain can and should be assessed in every child. Methods for pain assessment throughout childhood and in all clinical scenarios need to be optimised. Although 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 have been developments in our understanding of the biological correlates of pain, and in broader patient-reported outcome variables that can provide a more holistic understanding of patients' pain status. Finally, a greater focus should be placed on assessing outcomes that are important to patients, rather than those that are central to researchers and clinicians.

Fourth, make pain better. This goal can be achieved by advancing our knowledge of multiple treatment options in all areas (eg, psychological, pharmacological, and physical interventions). Few randomised controlled trials of pain interventions in children have been done, and the pipeline for innovation and new treatments is running dry. Novel drug discovery studies and trial design (eg, using single-case designs when the randomised controlled trial is not ethical or practical) could advance treatment options. There is innovation in new ways to personalise individual treatments, but greater investment in research and coordinated approaches at all levels are needed.

These four goals are not sequential and must be addressed simultaneously. It is time for change. Paediatric pain should matter to everyone, and cross-sector collaboration is needed to make quick and effective progress. By bringing the issues of paediatric pain into the open, we call for policy makers, funders, and health-care executives, researchers, and clinicians to engage enthusiastically and to deliver both the easy and the difficult changes needed to improve the lives of children and adolescents with pain.

Introduction

Pain is a feature of life that is present across all cultures and ages.[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. Although a primary function

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Panel 1: Jill Lawson's advocacy for pain management in infants

It was a mother, Jill Lawson, who contributed to one of the most radical changes in pain research and pain treatment since Ronald Melzack and Patrick D Wall presented their theory of CNS plasticity in 1965. In 1986, her son, Jeffrey Lawson, was born prematurely and placed in the care of the Children's Hospital National Medical Centre in Washington, DC, USA. Jeffrey underwent extensive surgery without adequate anaesthesia or analgesia because, as recently as 1985, the belief that infants did not have the capability to experience pain was common and prevalent among medical professionals.[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 because of a paucity of scientific evidence for the existence of pain in infants, and because of a fear of possible serious adverse events associated with the available drugs. Infants received surgery using muscle paralytic agents, with a focus on immobilisation to facilitate the procedure rather than the prevention of suffering.[7] Jeffrey Lawson lived for 5 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 to be unnecessary or unsafe. By 1995, practices had changed and a UK-based survey showed that 91% of anaesthetists now provided systemic opioid analgesia to infants for major surgery, whereas in 1988 only 10% adopted this practice.[5] Science is not always enough to change practice; public awareness and policy can translate knowledge into action.[8,9]

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 use, 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 few leaps since Jill Lawson's advocacy in 1986 led to change in the use of anaesthesia in infants (panel 1). In 2020, 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 believe many areas of paediatric pain require change.

In this Commission, we consider four transformative goals that we believe will improve the lives of infants, children, and adolescents—(1) make pain matter, (2) make pain understood, (3) make pain visible, and (4) make pain better. These four goals are not sequential and must be addressed simultaneously. Although our goals look simple, delivering them is complex and needs multidisciplinary attention from policy makers, funders, researchers, clinicians, and the public.

In this Commission, we take a developmental perspective and consider children of all ages, from infants to late adolescents (up to age 24 years). We focus on how middle-income and high-income countries can improve their provision of pain treatment and services, while recognising that the different challenges for low-income settings are beyond the scope here. The best pain management practices need to be adopted when treating children who experience all types of pain—from routine immunisation to cancer pain management, to the provision of complex residential multidisciplinary rehabilitation for idiopathic disabling pain. Beyond the individual, we also show how the interpersonal and social challenges of under-recognised pain-related distress can be better understood. Childhood pain is common, ranging from acute to chronic, and includes procedural, disease-related, breakthrough, and other types of pain (figure 1). We highlight the effects of childhood pain on parents and other family members, and the challenges of explaining pain to others, including other children. As with all illness and adversity, pain also operates on a moral and social plane[10] 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 effects the recognition of pain in others and equity in access to care.

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. Although people can often be highly sensitive to their own pain, a social insensitivity to pain in others is common,[11,12] and when people describe their pain the importance of it can be too easily diminished.[13] In this Commission, we outline a strategy to make children's pain matter to others. To achieve this goal, there needs to be an understanding of the social science of pain. We discuss how the absence of voice can lead to an assumption that there is an absence of need and we 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 consider how ignoring childhood pain can be prevented in children who have a limited verbal repertoire, which can result in them being seen to have fewer needs than those who are better able to articulate their pain. We also consider how best to avoid scenarios in which analgesia is withheld or withdrawn during clinical treatments. Importantly, we appreciate that these goals will only be achieved when a
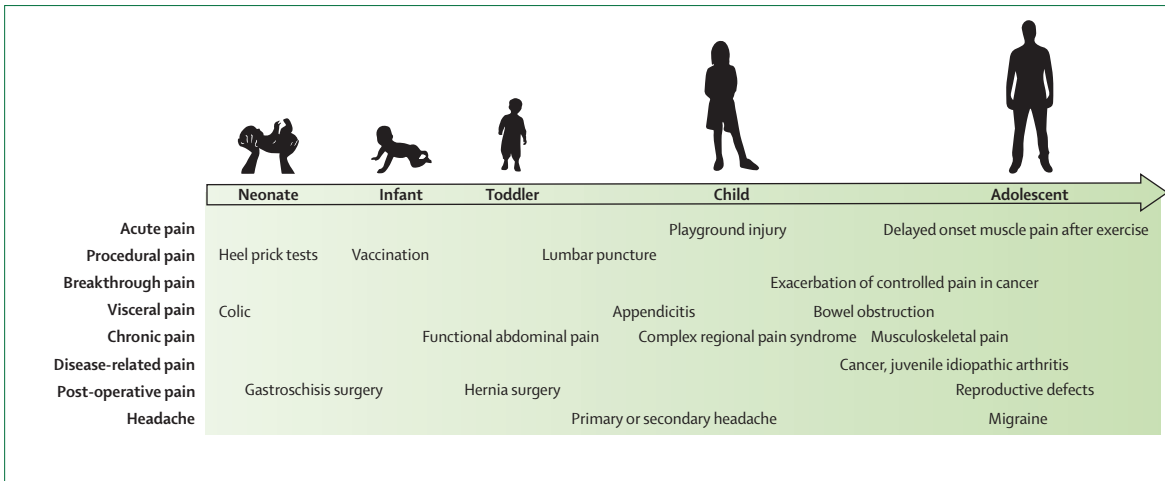
Figure 1: Common types of pain during childhood
Note, this figure is not an exhaustive list of all types of pain experienced by children.

clear organisational strategy is in place. Successful approaches that have been used to improve knowledge, attitudes, and practices in health care and other formal settings frequented by children are also 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, and how others view and respond to people experiencing pain.[18] Children learn how to express and respond to noxious stimuli in keeping with societal norms from their families and the wider 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 (eg, pain following an acute injury) or fairly straightforward to treat, with known underlying causes. 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 belief is not true, and these societal misconceptions of pain can be harmful. The dominant social belief that pain is temporary and should be endured can result in stigmatisation of children and adolescents living with chronic pain.[19] This belief 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 might be a further contributing factor to the 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 (eg, lumbar puncture, bloodwork, and burn dressing changes). Clinicians were more concerned about the adverse consequences of treating pain (eg, administration of opioids) than the consequences of inflicting pain.[23–25] Medical education in pain remains a challenge. In Canada, veterinary students received more formal education on pain (eg, understanding and treating pain) 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 health care is often a product of treatment. For example, vaccinations and other related skin-breaking needle procedures (eg, bloodwork and intravenous cannulas) are routine and represent a substantial number of painful procedures in health-care settings for paediatric patients, yet in many cases pain relief is infrequently given.[20] In the UK, children are usually given 16 separate injections between birth and the age of 14 years, many without any pain management.[28] Although 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, and 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 most commonly reported deterrent in obtaining the influenza vaccine in adults working in a health-care

Panel 2: Pain management during vaccinations

Immunisation is a global priority for preventing infectious disease. Vaccination involving a needle puncture is painful and can cause fear and vaccine hesitancy, resulting in future avoidance of vaccinations, which can have a large negative societal impact. In 2015, the first clinical practice guideline[32] for reducing pain during vaccine injections in children and adults was published, and it suggests the following:

- Aspiration (pulling back on the syringe to ensure it is not in the blood vessel) should not be used during intramuscular injections for people of all ages
- Injecting the most painful vaccine last rather than first during visits with more than one vaccination
- Breastfeeding or formula feeding infants aged ≤2 years during the procedure or giving them a sugar solution before the injection
- Holding children aged ≤3 years in the caregiver's arms during injections to provide them with a sense of comfort
- Adopting an upright position when administering vaccinations in children aged ≥3 years as this position provides a sense of control and decreases fear
- Parents of children aged ≤10 years should be present during vaccine injections to lower their child's distress levels
- Topical analgesics should be applied before injection in children of all ages
- 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. It provides important acknowledgment from 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]

setting, with 8% of clinicians and 27% of hospital employees not receiving their flu vaccine because of 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. In 2015, WHO adopted some of the guideline recommendations, which reviewed the evidence for reducing pain during immunisation in children.[32] The WHO position paper[33] specifically described the importance of reducing pain at the time of vaccination, as well as how to manage such pain (panel 2). The evidence is clear that providing pain management needs to be as essential as any other component of medical procedures and treatments (eg, sterility and explaining the procedure to children and caregivers). Despite international guidelines, even in the most highly resourced medical centres, a culture of assertive pain management is not common.[20,34] Although there are hospitals and health-care centres that implement institution-wide interventions to manage needle pain so that children and adolescents receive better procedural pain care,[35] this practice is not widespread.

An additional consideration is that 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] A study found that, in Denmark, Norway, and Sweden, boys are more likely than girls to be prescribed opioids during ages 0–10 years, but adolescent girls (ages 11–19 years) are more likely to be prescribed opioids than adolescent boys.[37] However, girls are also more likely to report chronic pain during adolescence than boys.

It is not solely pain treatment that can differ by sex. Despite the higher prevalence of reported chronic pain in girls than in boys during adolescence, their chronic pain concerns were dismissed more often by physicians (35%) compared with boys (17%).[38] A similar bias towards pain management differences has been found to persist into adulthood in most but not all studies[39] and are described as an ethical issue in pain care.[40]

Mobilising knowledge: dissemination and implementation

The problems of poor paediatric pain practice might stem from inadequate knowledge or understanding, or from a failure of training. However, this view is at best partial. 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. Knowledge translation is also referred to as knowledge mobilisation or, increasingly, dissemination and implementation of evidence to improve practice.[9] Shortening this gap from knowledge production to implementation[41] is crucial and might now be more achievable given the explosion in new computerised media. Consumers of health care can access this information much more readily, and there is increasing pressure for scientists to consider the dissemination and impact of their research. These additional considerations mean making research understandable for the lay person and seeing how it can change knowledge or behaviour. Of course, there is also a lot of poor-quality, non-evidence-based information on the internet regarding pain, and researchers might be nervous to disseminate information to the public, for good reasons. Strategies to tackle misinformation and provide a trusted accessible place to obtain new evidence-based information could be one way to disseminate knowledge. 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, health-care professionals, and communities (table). Launched in 2019, Solutions for Kids in Pain (SKIP) is a prominent organisation that brings together Canada's paediatric pain specialists, front-line knowledge user organisations, end beneficiaries, and over 100 partners across various sectors (eg, charities, governments, businesses, and health care). It aims to improve children's pain management in Canadian health institutions, beginning with members of Children's Healthcare Canada (Ottawa, ON, Canada).

Good examples also exist of how to collectively capture and benchmark practice. For example, the EUROPAIN

	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 ten centres	Australia	https://www.uow.edu.au/ahsri/eppoc
Improve clinical practice			
ChildKind	Encourage institutional commitment to providing comfort and pain relief	International	http://childkindinternational.org
Increase public awareness			
Solution for Kids in Pain	Confirm the information needed by the user (eg, parents), organise resources and evidence, produce and promote knowledge mobilisation tools, facilitate institutional change, and increase awareness of paediatric pain among the general public	Canada	https://www.kidsinpain.ca
#ItDoesntHaveToHurt	Provide evidence-based information about the management of paediatric pain across social media platforms	Canada	https://itdoesnthavetohurt.ca

Table: **Initiatives to mobilise knowledge in paediatric pain, by aim**

(EUROpean Pain Audit In Neonates) study[42] showed that provision of analgesia is widespread among neonatal intensive care units in 18 European countries, but that there is extensive unexplained variability between sites. In Australia, the Paediatric Electronic Persistent Pain Outcomes Collaboration (PaedePPOC)[43] initiative that introduced common assessment practice for pain management in ten centres has successfully been integrated into practice, providing the means for comparison between populations and different resource settings.

Although some countries have not developed surveillance and benchmarking practices for paediatric pain management,[44] there have been substantial advances. In countries where evidence-based guidance is available, the focus should turn to the implementation of evidence-based guidelines.[45] There is no single correct approach to implementing an organisational change programme to improve pain care.[35,46–48] It is worth stressing that pain management also occurs outside of the hospital, such as in the home,[49] in educational settings,[50] in the community (eg, family practitioners' offices), and in pre-hospital emergency environments.[51] No single strategy works in all settings, and context needs to be considered; thus, the type of institution, leadership, culture, value of research in practice, number and type of health-care professionals, and physical resources[52] are all relevant and need to be considered. A further example at a hospital level is the implementation of the Children's Comfort Promise,[35] which adopted new protocols for nurses to provide options to reduce pain during needle procedures. Developed by the Special Interest Group on Pain in Children of the International Association for the Study of Pain (IASP), ChildKind (the organisation that developed the Children's Comfort Promise) is a prominent international initiative with the unique aim to establish

and maintain practice improvement through certification. To obtain certification, ChildKind requires the institution to have a facility-wide policy on pain prevention, assessment, and treatment that shows clear institutional commitment to pain relief, and ongoing education on pain for staff, trainees, and patients. The institution also needs to show evidence of the sustained use of developmentally appropriate processes for pain assessment, specific evidence-informed protocols for pain prevention and treatment (including pharmacological, psychological, and physical methods), and regular institutional self-monitoring within the framework of continuous quality improvement.

A final example of an approach that helps to mobilise knowledge of paediatric pain is the online initiative #ItDoesntHaveToHurt, a collaboration between paediatric pain researchers, parents, and the YummyMummyClub.ca (an online blogging platform for parents to share advice on issues surrounding motherhood). This initiative provides Canadian parents with evidence-based information about children's pain management across social media platforms (eg, Facebook, YouTube, Instagram, and Twitter) and, in 2016, had more than 72 million content views worldwide in the first 6 months.

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 is, instead, about fair access to unequal resources according to need. There is poor equity in access to pharmacological pain management worldwide[53] and the types of multidisciplinary treatment described in this Commission are not available for all infants, children, and adolescents. Despite the documented international and intranational 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 inequities that are driven by income group, race, and sex and gender. With children, the most extensive study of these inequities has been in sickle cell disease, an inherited chronic disorder of blood cells causing painful crises in patients who are mostly of African heritage and for whom prejudicial inequity in access to pain management is well recognised.[55,56] Other forms of pain management inequity exist among 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 than children and adolescents without disability.[57] This issue is concerning as children with disabilities typically experience high pain intensity.[58] There is a need to better understand the patterns and effect of inequity in pain-relief provision at a societal level. There is also a need to explore the psychological effects of perceived inequity. Human experimental studies are beginning to reveal that perceptions of injustice and inequity can affect pain and disability status. If one believes one is being unfairly treated, this belief can worsen the experience of pain, disability, and treatment effectiveness.[59,60] Little is known 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 the recognition that pain management has become highly politicised in many countries as a result of 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] 80% of the world's supply of opioid medicines are 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] However, paediatric pain medicine 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]

Substance use disorders and pain medication are both conflated in policy and in the media's portrayal of the North American opioid crisis. An analysis of the Canadian media shows 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 misconception has, in turn, influenced policy approaches (eg, criminalisation and large oversights 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 patients,[69] whereby the media depicts opioids as the villain and the underlying reason for substance misuse. Opioids have their place in paediatric pain medicine. In the context of the oversupply of opioids, childhood pain can usefully be considered a risk factor for long-term harmful exposure to opioids.[70]

Overall, there needs to be a new social science of pain, as well as an explicit recognition that at an individual and societal level, the articulation of pain will always have to struggle against forces that would silence it. For some questions, a political science of pain is needed to move beyond description and policy towards understanding how political values shape experience. Other questions will need novel anthropological research to improve the understanding of culturally embedded experience, and modern implementation science is needed to explore the best evidence for organisational change.

Research and clinical priorities to make pain matter

Three areas should be prioritised to achieve the goal of making 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. 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.

First, it is important to know where equity and inequity in pain management exist, as well as to understand where inequity lies within health-care systems. Within chronic pain particularly, much of the research is done in adults who are middle class and white. Similarly, in high-income countries, patients are most likely to be treated by white men. Less is known about how different cultures, races, and socioeconomic groups interpret and communicate pain, or their preferences for pain management. In circumstances in which pain becomes invisible to others, in particular to those with power and control over the allocation of shared resources, inequality and inequity are perhaps inevitable. Such inequities pervade paediatric pain management. And when invisibility and inequity exist, there is the opportunity for unchallenged prejudicial inequality. The issue of whose pain matters least needs to be addressed, as well as the social forces that silence the dissent of, or attempts at, social or political redress.

Second, the optimal methods for managing stigma and ways to mitigate its effects need to be researched. Pain has become reduced to a medical framework, 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 does not seem to matter.[72,73] Medical professionals might not be able to diagnose a specific disease or have immediate tools to provide pain relief. Although it is possible to inform the patient that they do not know what is wrong, this message must be communicated appropriately. When pain is dismissed, families report substantial distress from attempting to talk about something people do not want to hear. However, to not talk about something so fundamental as a child's pain is equally distressing.

Finally, investment in a social science of paediatric pain is needed, starting from the premise that pain is inherently subjective and language resistant. Culturally it is language destroying.[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, and on the ability of the observer to be able to decode the signal,[18] their aptitude for allocentricism, and ultimately empathy.[74] Furthermore, part of how humans cope with life events—with the sometimes staggering social and personal injustice, multiple experiences of loss, and fear of one's own inevitable death—is to have inherent biases towards optimism, avoidance of emotional distress, and systematic diminution of the effect 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] Humans 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, the suffering of others is often ignored and underestimated.

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 they are 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 the physical versus mental dualism

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, the so-called biological drivers, thereby denying the psychological and social elements that affect the experience of all types of pain.[80–85] We judge that it is important to be clear in our thinking when describing models of nociception only, and when attempting to understand or explain pain as a whole. This distinction is particularly pertinent in children's pain, in which both mechanisms and perceptions are also a function of age and developmental stage.

To make pain understood in all its contexts, the use of pain terminology should be consistent. The current clinical and scientific definitions and classifications of pain (panel 3) can seem complex and confusing, not least because they require frequent revision with advancing knowledge and experience. 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, which makes a strict temporal distinction somewhat arbitrary and artificial.

For chronic pain, IASP reported the results of their task force on an updated classification, and the latest version of the of the WHO International Classification of Diseases (ICD-11) also included chronic pain as a discrete entity for the first time.[86,87] 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 might 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.

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 panel 3), showing how they relate to different sources of pain, as well as some of the basic neural circuits and pathways that lead to pain perception in the brain. Clearly, one or more somatosensory mechanisms could be involved in a given clinical pain presentation, and the mechanisms involved might change over time (eg, due to disease progression in a long-term health condition such as arthritis or cancer, or when pain arises or persists although the damage to the 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 (ie, nociceptors), the spinal cord, brainstem, and importantly the brain, which is also integrating multiple other pain-related and non-pain-related inputs, leading to different patterns of activity that characterise an individual's pain. Importantly, during childhood, almost all body systems undergo structural and functional changes, including pain

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Panel 3: Pain definition and classifications

In 2020, a new International Association for the Study of Pain 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",[86] 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".[86] 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 (ie, pain-detecting nerves). Nociceptive pain is the mechanism operating in most everyday painful experiences and, when it results from an injury or a damage, it should resolve when healing has occurred. In infants, children, and throughout later 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, it can generate pain, although it might not respond to a previously painful stimulus. Cellular and molecular mechanisms of neuropathic pain are different from those of nociceptive pain, and are less likely to resolve with the healing process. During development and maturation, the mechanisms and clinical presentations of neuropathic pain differ with age and depend on the 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 shown in some individuals for whom a clear underlying cause is not detectable by currently available methods.

By time
- Acute pain: pain that lasts ≤3 months (eg, acute postoperative pain and vaccination pain). Mechanisms of acute pain are mostly nociceptive and resolution is normally expected when healing occurs.
- Chronic pain: pain that lasts or recurs for ≥3 months (eg, chronic musculoskeletal pain and chronic disease-related pain). Chronic pain can involve nociceptive, neuropathic, and nociplastic mechanisms.
- In clinical situations, pain might also be described as continuous (ie, background pain) or intermittent (ie, episodic pain), or as either predictable (ie, incident) or unpredictable (ie, spontaneous).

By context or location
- Disease-related pain: pain that is associated with specific diagnoses or conditions (eg, juvenile inflammatory arthritis and cancer pain).
- Tissue or organ-dependent pain: pain arising from specific tissues or organs (eg, visceral, musculoskeletal [associated with bone, joint, and muscle], headaches, and pelvic pain).
- Iatrogenic pain: pain associated with or following medical treatments (eg, procedure pain including vaccination, surgical, or medical [eg, chemotherapy-induced neuropathy] interventions).
- Idiopathic pain (also known as functional or primary pain): pain for which there is no clear identified cause (eg, chronic primary abdominal pain)

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

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processing mechanisms themselves, potentially influencing nearly every aspect of the experience of pain at different ages with ongoing consequences for later life (figure 2).

Nociceptive pain occurs within an intact and normally functioning somatosensory nervous system and can therefore be regarded to an extent as so-called normal pain because it is the mechanism of the common everyday pain experienced after injury. This type of pain 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. Nociceptive pain has different physiology, pharmacology, and psychology at different ages, and its relationship to other pain mechanisms and states needs to be fully appreciated 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 are 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—ie, peripheral and central sensitisation leading to lower pain thresholds (also known as allodynia) and increased sensitivity to previously painful stimuli (also known as 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
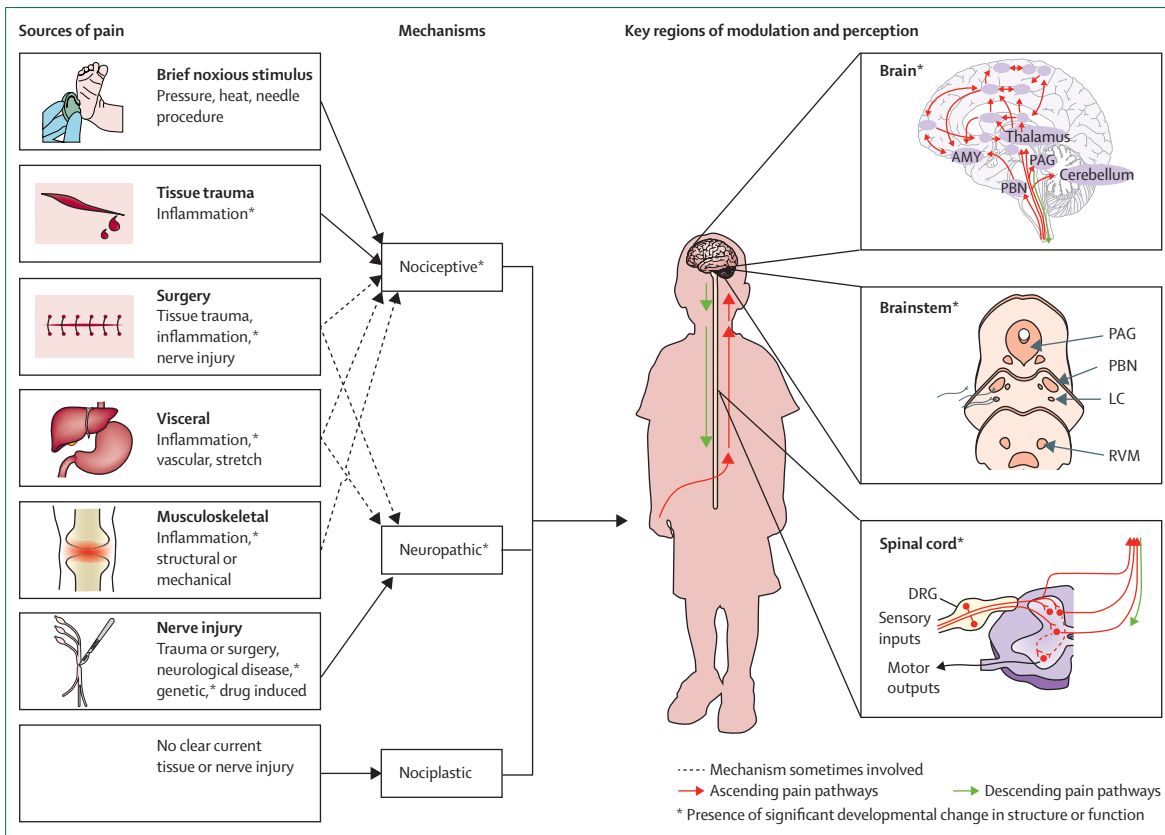
Figure 2: Pain mechanisms and sources of pain
Pain can be broadly classified as being nociceptive, neuropathic, or nociplastic, with combinations of these mechanisms present in different forms of injury or illness (dashed arrows indicate mechanisms that are sometimes involved). Afferent activity in the peripheral nervous system can be generated by different sources of pain and is transmitted to the spinal cord where modulation occurs. Ascending pain pathways reach the brainstem and brain (where pain is perceived), and descending pathways also modulate (ie, inhibit or facilitate) sensitivity in the spinal cord. AMY=amygdala. DRG=dorsal root ganglion. LC=locus coruleus. PAG=periaqueductal grey matter. PBN=parabrachial nucleus. RVM=rostroventral medulla.

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 a complex network of neurons, glia, and immune cells in the peripheral nervous system and CNS. Pain perception, rather than being confined to a discrete single brain area (as with many senses, such as hearing or vision), is the result of activating a distributed network of brain regions that signal and modulate the sensory, affective, motivational, and cognitive aspects of pain (figure 2, 3A). 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, which characterises pain by recruiting multiple brain regions to produce a constantly adjusting signature of pain.[92–94] This pain signature is currently not well characterised during different stages of development. Nevertheless, even newborn infants, who are only a few days old, show adult-like patterns of noxious-evoked brain activity following nociceptive events that adults have described as being mildly painful.[95,96]

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 chemical stimuli and transduce signals into action potentials transmitted by primary afferent fibres to the spinal cord; the first CNS 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 that subserve different aspects of pain perception (including stimulus location, intensity, and modality), those involved in modulation, and the regions associated with physiological and behavioural responses to pain. Descending pathways from the brainstem have a bimodal function and can inhibit or facilitate spinal cord signalling (figure 3).

Following birth, noxious-evoked brain activity can be evaluated using electroencephalography (EEG) or inferred from blood flow changes using near-infrared
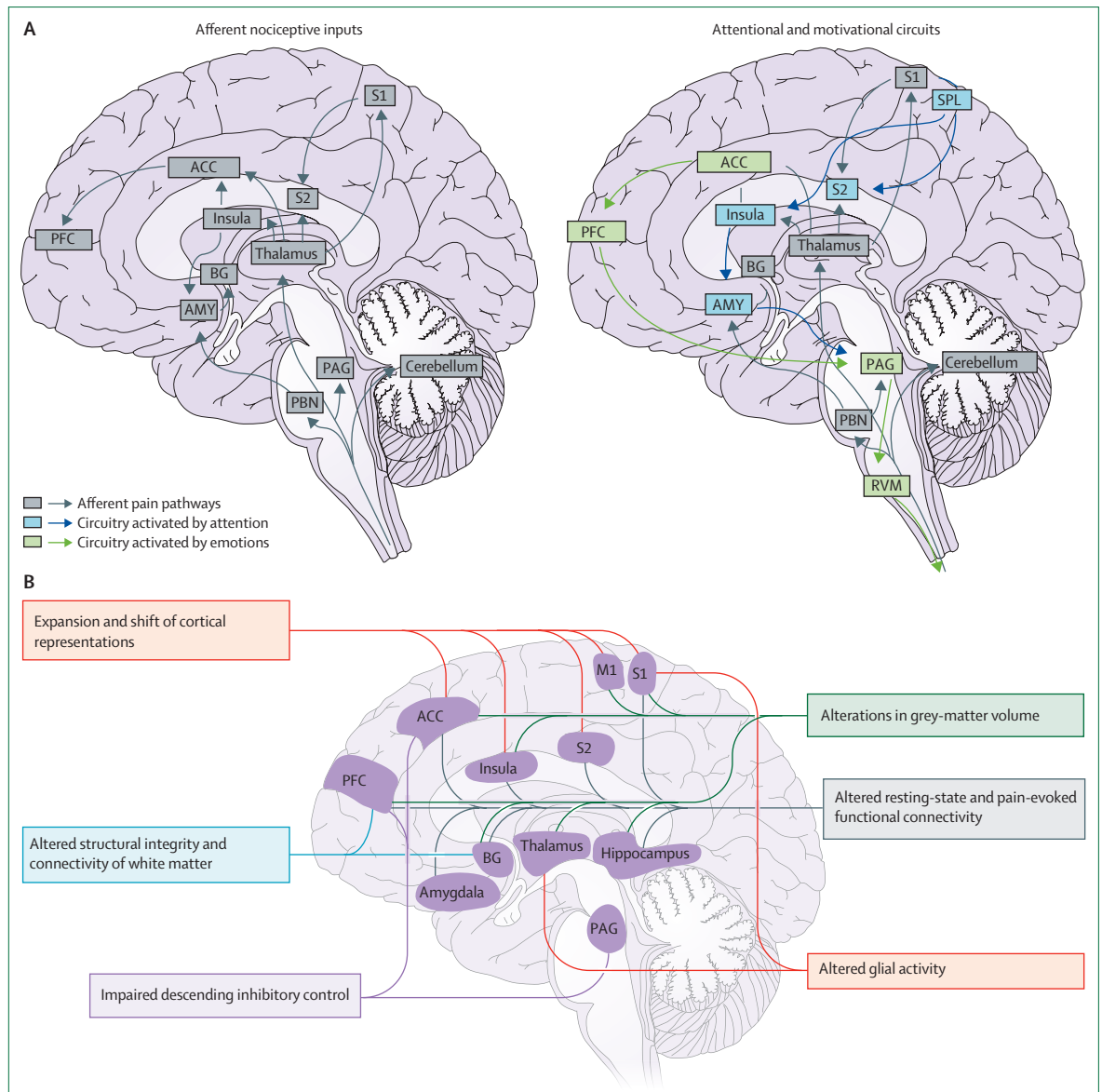
***Figure 3:* Brain networks in nociceptive (acute) and chronic pain**
(A) Pain activates a variety of brain regions that subserve both the sensory (ie, major ascending afferent nociceptive pathways) aspects and the emotional aspects of the pain experience.[90,91] (B) Chronic pain is associated with structural and functional changes in the brain. ACC=anterior cingulate cortex. AMY=amygdala. BG=basal ganglia. M1=primary motor cortex. PAG=periaqueductal grey matter. PBN=parabrachial nucleus. PFC=prefrontal cortex. RVM=rostroventral medulla. SPL= superior parietal lobule. S1=primary somatosensory cortex. S2=secondary somatosensory cortex. Part A reproduced from Bushnell et al[90] and part B Kuner and Flor,[91] by permission of Springer Nature.

spectroscopy and functional MRI (fMRI). Cortical responses are evoked by noxious events, such as heel lance in preterm (from 25 weeks after conception) and term neonates,[97,98] immunisation 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 has shown activation of brain regions known to be involved in both sensory and affective components of pain response[96] and variation with stimulus modality and intensity.[101] These data show the influence of painful inputs on responses in developing central nociceptive pathways and highlight the potential for proxy measures of the effects of analgesics.[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 influence the sensitivity of the system.[102,103] Myelination affects the latency of response. These differences, among others, result in a marked change in the relationship between stimulus intensity and response that vary with age (eg, mechanical nociceptive thresholds have been shown to be lower in early development).[104] Mechanical thresholds for nociceptive reflex responses, such as hind-limb withdrawal[105] and abdominal musculature contraction,[106] 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 children, cross-sectional[107] and longitudinal[108,109] psychophysical studies have shown that increases in (modality-specific) pain thresholds continue throughout adolescence, with sex-dependent differences emerging for some modalities. Similar to adults,[110] responses to standardised experimental stimuli also show substantial variability between individuals. 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 contributes to the lower thresholds and more generalised reflex responses seen in children of younger ages.[111,112] Low-threshold sensory input (eg, touch) and spontaneous movements contribute to activity-dependent normal maturation of sensorimotor 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.[94,115]

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 can develop after tissue injury at all ages, including neonates and infants. Such sensitisation is shown by reduced mechanical thresholds for the hind-limb withdrawal reflex following repeated heel lance;[116] similarly, reductions in the force of mechanical stimulus required to evoke contraction of abdominal muscles (ie, abdominal skin reflex) has quantified changes in wound sensitivity following abdominal surgery[117] and referred visceral hyperalgesia in infants with unilateral hydronephrosis of the kidney.[106] However, different forms of tissue damage (eg, inflammation, surgical injury, visceral stimuli, nerve injury, and chemotherapy) also have age-dependent mechanisms that influence the patterns of behavioural sensitivity observed.[118–121] In normal circumstances, these changes in pain modulation leading to sensitisation of the system resolve with healing, but in some patients such changes do 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 factors that initiate and maintain sensitisation during development will help to clarify why some pain is more refractory to treatment and could open pathways to potential 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), which strongly reinforces the assertion that children are not merely 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 care,[42] with uncertainty regarding subtle long-term effects of treatment. The importance of pharmacogenomic influences in neonates is little studied. However, genetic variations that affect drug clearance (eg, uridine 5′-diphospho-glucuronosyl-transferase [UGT1A9]) or response (eg, catechol-o-methyltransferase [COMT]) can result in greater morphine exposure in the brain. Pharmacogenomics, together with neonatal clinical factors, are differentially related to anxiety and depressive symptoms (ie, internalising) and to acting out (ie, externalising) behaviours at 18 months postmenstrual age in children born very preterm.[125] Aside from these genetic influences, responses to analgesic interventions (as well as pain and injury) can differ between males and females throughout the lifespan. 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 susceptible to injury-induced changes in structure and function that can alter future development and therefore responses, including those to reinjury 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 following preterm birth, and with subsequent cognitive, behavioural, and somatosensory outcomes in later life.[109,129,130] Alterations in somatosensory function in adolescents who had neonatal intensive care early in life have also been clearly shown, but precise changes can vary, depending on initial exposure (eg, gestational age at birth, need for surgery, and duration of intensive care), type and intensity of experimental stimulus, and age at follow-up.[131]

The extent 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 reinjury following neonatal incision[127] 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 more 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 the transition from acute to chronic pain (figure 3B). Such changes 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 finding is consistent 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 these observed changes could be implicated in both the cause and effect of ongoing pain; it is 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 evidence that it too is a serious global health and economic problem, the full impact of which is 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 scarce, 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 in adulthood.[141,142]

There are substantial gaps in our 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. Emerging data show the importance of psychosocial and pre-morbid risk factors (eg, psychiatric conditions, depression, anxiety, coping, threat appraisal, and parental coping) for several chronic pain conditions, including post-surgical pain, with biological factors (eg, female sex and nociceptive function) clearly also relevant.[143–145] Many different factors are likely to contribute to the development and maintenance of chronic pain, and these are modelled and summarised in figure 4.[147] Key to this model is 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. Although many of the potentially important contributors to the development and maintenance of chronic pain are common to patients of all ages, the superimposition of developmental processes on these factors will determine the differences seen at different ages.

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 the integration of key regulatory centres (eg, the thalamus)[149] and the structure, function, and connections of regions for more advanced processing mature at older ages.[93] Developmental processes—such as neurogenesis and apoptosis, the migration of neurons to appropriate targets, the 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 might be disrupted by abnormal stimulus exposures (eg, persistent pain input during critical periods). Prolonged exposure to acute nociceptive pain and episodes of high pain intensity could trigger adverse neuroplastic changes—eg, in neonates who had received intensive care. Psychophysical evaluation of somatosensory function with quantitative sensory testing has identified persistent changes associated with previous experience (including pain) or chronic disease in children that had been poorly recognised.[128] Diabetic neuropathy causing neuropathic pain was previously thought to be rare in children, but one study found that almost half of teenagers with type 1 diabetes had detectable subclinical changes in small-fibre function.[150] Following childhood acute lymphoblastic leukaemia, deficits in vibration and mechanical detection thresholds possibly reflect persistent chemotherapy-induced neuropathy.[151] Persistent sensory loss (ie, anaesthesia) and sensory gain (ie, allodynia) have been identified adjacent to scars even after many years following surgery in the neonatal period[109] and in 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
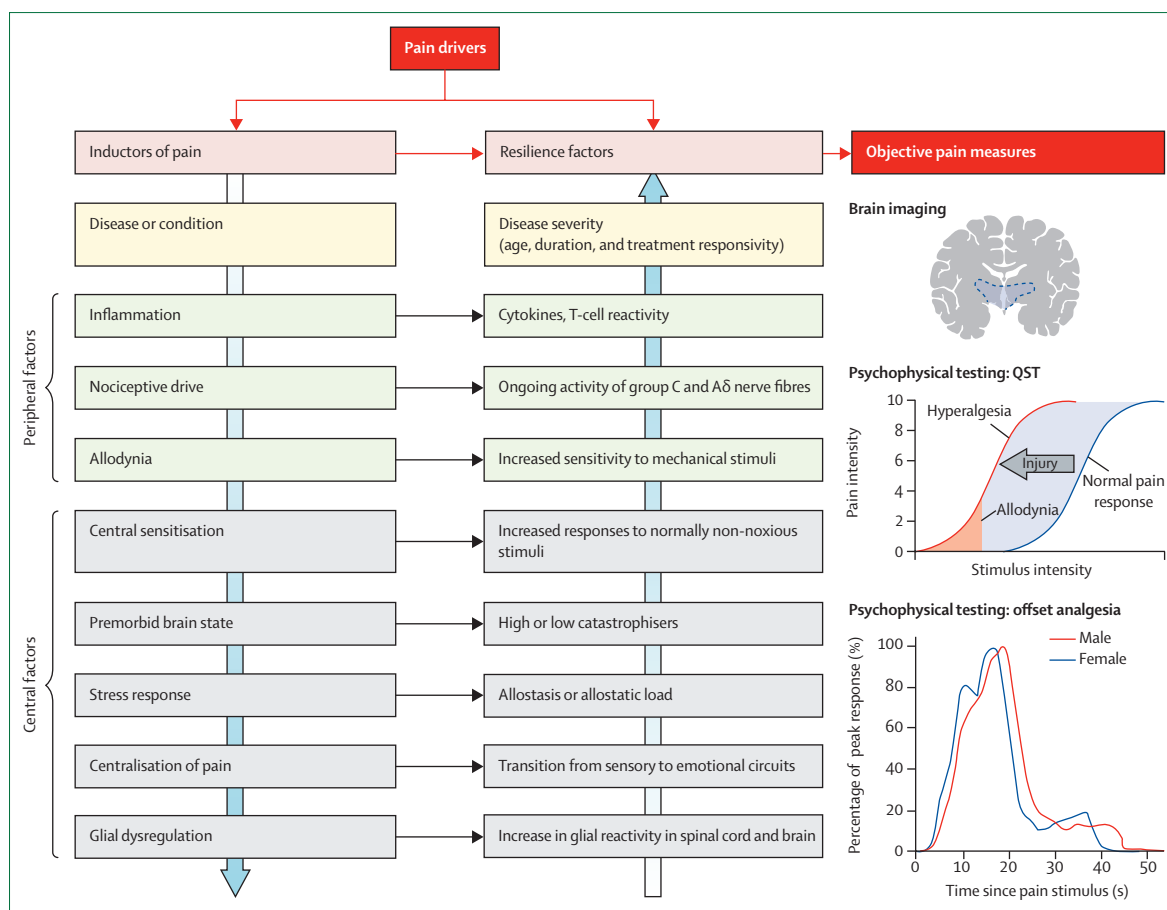
Figure 4: Potential mechanisms contributing to susceptibility to paediatric chronic pain

Pain drivers, including inductors of pain and resiliency factors, affect and predict objective pain measures. Factors that affect disease severity are influenced by both peripheral factors (eg, nociceptive drive, and allodynia) and central factors (eg, central sensitisation, premorbid brain state, stress response, centralisation of pain, and glial dysregulation), which can be inductors of pain or protective against the development of chronic pain. Imaging can be used to assess functional and structural changes in the brain. Quantitative sensory testing (QST) can be used to produce measures of ongoing peripheral nervous system and CNS sensitisation. Offset analgesia can be used to measure of CNS modulatory responsivity, such as normal or intact offset analgesia.[146] Examples of QST and offset analgesia are shown. Adapted from Sieberg et al.[147]

models (eg, rodents) pain might emerge in later life, long after any injury has taken place and was thought to have healed.[118] This observation highlights the potential for clinical presentations in childhood to differ from that seen at older ages, despite the same initial insult, and the potential for subtle changes, possibly predisposing to long-term pain, to go undetected.

Endogenous modulation

Disruption of normal endogenous descending controls from the brain is considered an important factor in adults with many persistent pain states. Improved knowledge of the development of inhibitory modulation, the alterations induced by different pain conditions, and the interactions with psychological factors at different ages might improve our 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 protocols can help to evaluate the degree and directionality (ie, 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 conditioned pain modulation has been reported in children aged between 12 and 17 years compared with children aged between 8 and 11 years.[156] This finding parallels the predicted normal delayed emergence of descending inhibition as seen in juvenile rodent studies;[128] but results are also influenced by the testing protocol.[157,158] In children with functional abdominal pain, both decreased descending inhibition and generalised increased pressure sensitivity on testing suggested centrally driven changes that led to enhanced responses to nociceptive inputs.[159] Similarly, children with a high degree of pain and dysfunction related to functional abdominal pain continued to have persistent

pain and increased central sensitisation (ie, temporal summation to heat stimulus) years later into adulthood.[160] Impaired conditioned pain modulation predicted persistent post-surgical pain in adults,[161] and although 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 protocols, in which endogenous inhibition of pain is induced (figure 4), also potentially allow exploration of pain inhibitory mechanisms that, although conceptually related to conditioned pain modulation, possibly act via different pain pathways and have rarely been 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 (ie, sensory phenotyping) using quantitative sensory testing.[165,166] Sensory abnormalities appear in different combinations in individuals who have similar pain symptoms, which suggests 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 (ie, sensory loss, mechanical hyperalgesia, and thermal hyperalgesia) that could 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 fully characterise somatosensory alterations associated with chronic pain and to evaluate the potential use of sensory profiling as biomarkers for prediction of persistent pain, indicators of mechanism, or response to treatment. In addition, evaluations of the interplay between psychosocial variables (eg, fear of pain, anxiety, depression, and worry associated with pain) and nociceptive function (assessed with quantitative sensory testing) could also be helpful to predict pain outcomes in young people who are at risk of developing chronic pain.[169,170]

The brain and non-neural CNS structures

Compared with adult studies, relatively few studies for paediatric chronic pain have included neuroimaging. Those available have predominantly included adolescents with complex regional pain syndrome, a poorly understood but common presentation in paediatric chronic pain clinics. Nevertheless, such studies found alterations in brain structure and connectivity[171] that might differ in acute versus chronic states, and from adults with complex regional pain syndrome.[172] They also revealed different patterns and degrees of brain activation in response to sensory stimuli applied to affected and unaffected limbs,[136] reduced grey matter density in the thalamic reticular nucleus associated with increased pain intensity,[172] and altered brain connectivity

within the amygdala, salience default mode, and sensorimotor networks.[173] Studies have also found that functional outcomes (eg, fear of pain)[174] and improvement in symptoms are associated with, at least partial, reversal of brain changes following intensive rehabilitation.[171,175,176]

There is no doubt that technical developments of bespoke brain imaging methods that are specifically designed for neonatal and paediatric populations will advance our understanding of the cerebral processes that underlie the development of paediatric pain.[177,178] Alterations in thalamic function and thalamocortical dysrhythmia, which might influence the intensity and perception of persistent pain, have been observed in adults.[179,180] Shifts from sensorimotor to emotion-related circuitry,[134] 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, are risk factors for persistence of back pain in adults.[181] Neuroimaging has not yet been used to assess risk factors for the chronification of pain in paediatric populations.

The roles of non-neural glial cells in the nervous system extend well beyond homoeostasis, the formation of myelin, and support for neurons, and non-neural glial cells have been implicated in the maintenance and modulation of chronic neuropathic pain (panel 3, figure 2) throughout postnatal development and into adulthood. Microglia affect neurogenesis, synaptic pruning, and synaptic plasticity.[182,183] The normal age-dependent 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 disorders[186–189] or, more specifically, can influence injury response and analgesic efficacy.[122,127]

Stress and environment

Popular targets 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 (eg, changes in temporal summation, reduced inhibitory conditioned pain modulation, and hyperalgesia), increases anxiety, and might be variably associated with changes in other physiological parameters (eg, differences in blood pressure or cortisol).[171,192–194] By contrast, chronic stress is highly comorbid with chronic pain.[195] Chronic stress has been categorised as a "worldwide epidemic" by WHO, is associated with increased rates of mental illness and suicide, and costs over US$300 billion 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 who had higher concentrations of cortisol.[198] However, 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 (eg, thermal and pressure tolerance) in children who had previously had severe burn injury as neonates, unlike healthy control children.[199]

The experience of adverse and stressful life events in childhood might also be related to the maintenance and exacerbation of chronic pain in later life. However, 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 might have a higher risk of cognitive, emotional, and health problems,[203,204] but the timing, severity, and type of stress needed to induce this cycle, and how it might contribute to chronic pain, is unclear. For example, negative life events in early childhood have been variably reported to be predictive,[205] or have no association,[206] with functional abdominal pain in adolescents.

Conversely, the biological reactivity model posits that stress could be protective for some, although the required amount of stress is unknown.[207] Nevertheless, translational models of deprivation, threat, stress, drug exposure, and injury during early life show significant adverse and persistent effects on brain structure, behavioural outcomes, hypothalamic–pituitary–adrenal axis function, response to reinjury, and risk of medical and psychiatric disorders in later life.[97,208–212] By contrast, positive experiences (eg, environmental enrichment, parental care, and a healthy diet) can improve outcome in laboratory models of early life stress; effects vary with age and sex and further show the complexity and overlap of mechanisms involved in the stress response, pain perception, and mood.[209]

Numerous environmental factors might be important for the regulation of 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 colonise the gut from birth, with variability increasing during adolescence.[214] Preclinical models report inter-actions 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 could facilitate the study of stress responses, resilience, and susceptibility in both human and animal studies across the life course.

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 several different chronic pain conditions.[216,217] Pharmacogenomic differences might be relevant as they can also influence response to current analgesic medications[218] and potentially new analgesic targets based on genetically determined differences in molecular signalling in individuals with chronic pain.[219]

Genetic disorders can also result in neuropathic pain. Mutations affecting voltage-gated sodium channels (Nav) on sensory nerves that can influence pain sensitivity or be associated with specific pain disorders are increasingly recognised in children.[220] Erythromelalgia (a rare disease related to mutations of the SCN9A gene that alter excitability of Nav1.7 channels and is characterised by neuropathic pain that typically affects the hands and feet) 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, an X-linked lysosomal storage disease, and tends to occur earlier and can be more severe in boys than girls; enzyme replace-ment therapy can 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 can be transmitted across generations.[225] Interactions between genes and the environment have been associated with early life (perinatal and postnatal) events that adversely[210,226] or positively[227] influence neurodevelopment, and account for a large proportion of individual variance in risk for chronic disease over the lifespan.[227] Epigenetic mechanisms also have roles in the development or maintenance of persistent pain[228,229] and could 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 study. Additionally, the investigation of intergenerational pain transmission[231–233] will be a valuable contribution to the field. Advances in genetic testing and more detailed phenotyping of clinical pain conditions could improve individualised therapy.[219]

Research and clinical priorities to make pain understood

Progress in our understanding of how the maturing pain system determines and influences both current and future pain states has been slow. Several areas requiring further investigation and changes in research and clinical practice should be prioritised to make childhood pain better 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 for chronic and recurrent pain estimated at approximately 28% in paediatric populations,[140] it is tempting to reclassify pain as a normal part of life. But when it comes to child

pain, common does not mean trivial. However, such high prevalence does beg an explanation and should give us pause to ask whether the same types and severities of pain are being discussed when talking about pain. The effects of the new ICD-11 classifications in changing the science and clinical practice in chronic pain have yet to be seen, but its application is expected in the next decade. Masked behind the high prevalence 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. This work should be managed by a task force of IASP who published the latest definition of pain in 2020.[86] Moreover, 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 that 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, mind and body, and physiology and psychology is not easy. These distinctions between the inside (ie, hidden) and the outside (ie, observable) are coded in language, structure much of how the world is experienced,[234] and are useful in many areas of science and practice. However, they are not useful in the study of pain and they hold us back.

Third, perhaps one of the biggest advances in paediatric pain has been in developmental biology. Having an 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 to understanding the effect of developmental factors on nociception, pain, child anxiety, and their clinical assessment and treatment.

Fourth, further methods are needed 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, in which a better understanding is needed. By focusing on mechanisms, pathology in the central and peripheral nervous system can be better described. 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, the importance of persistent peripheral sensitisation for the onset and persistence of chronic pain is not known. 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 CNS vulnerabilities, which project into adulthood.[131] Depressive symptoms, 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 periods of development is imperative. Advances in human neuroimaging techniques will undoubtedly help,[172] as will investment in the development of biomarkers and better phenotyping. This science is still in its infancy and improvements in measurement, identification, and 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 crucial 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, show how transformational these registries can be. Although lifelong epidemiological studies will help, such as the HUNT study[235] or the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort in the UK (also called the Children of the 90s study),[236,237] investment in clinical cohorts of well described painful diseases is also needed. These registries can be helpful in phenotyping and understanding the effect of the 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, but rather general developmental databases assessing a wide range of data for 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 of disease. Assessing pain in these databases is crucial for fully understanding its advancement and effect 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 evaluate whether a treatment is efficacious.

Nevertheless, there are challenges, especially in the youngest patients, and in patients with intellectual, communication, or motor limitations. However, assessment methods are available and should be used. Pain should be made visible by doing 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 assessment is not an easy endeavour as pain is, by definition, a private mental experience. Although the gold standard is self-report, whereby the child directly describes their experiences, doing so is not always possible and other indirect measures including facial expression, behavioural observations, physiological responses (eg, changes in heart rate or respiratory rate), and neuroimaging approaches can also be used to examine this private experience. Nevertheless, in most instances, human language provides a rich channel by which subtle sensory and affective experiences can be communicated, and early in development children learn to verbalise their experiences. This facility for communication 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 make a judgment about their pain intensity and label that judgment with a number, usually between 0–10.

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 summarise their experiences across various episodes. For example, asking a child the question "In the past 7 days, how would you rate your pain on average?" needs to be a developmentally informed assessment. For guidance, self-reported measures of pain, such as numerical rating scales, can be used from age 6 years onwards.[238] There might be difficulties in applying this approach to all children due to the cognitive demands of such explicit judgment. It can also be difficult to appreciate the influence of other individual, interpersonal, and contextual factors that affect the child's communication or expression of pain, and methods to assess pain should be developmentally appropriate (panel 4).

Using proxies of pain

In the absence of, or in addition to, self-report, reports of the child's pain by others could be used. Researchers or clinical professionals can ask parents or others to make judgments about the pain or related experiences of the child when the child is not able to do so themselves, 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 others' reports of the child's pain because they might be

> **Panel 4: Developmentally appropriate methods to assess pain intensity for children aged ≥6 years**
>
> A wide range of methods are available to researchers and clinicians who are interested in assessing pain intensity in children across the developmental lifespan. In a 2019 systematic review,[238] 60 separate pain intensity assessments were identified. Not only were there many different measures, but there were also different anchors for the scales used to measure pain, such as the numerical rating scale and the visual analogue scale. The systematic review also showed that researchers and clinicians must understand whether the participants and patients can understand and interpret the scale to provide a reliable response.
>
> The systematic review also provides recommendations (strong or weak) for and against the scales used to measure pain.[238] For children aged ≥6 years with acute pain, there is a strong recommendation for the use of the numerical rating scale with an 11-point scale from 0 (no hurt) to 10 (the worst hurt you could ever imagine). The Faces Pain Scale-Revised was strongly recommended for children aged ≥7 years, and the Colour Analogue Scale was strongly recommended in children aged ≥8 years. No other strong recommendations were provided for other pain intensity scales for acute, post-operative, or chronic pain. However, there is a week recommendation for using the visual analogue and numerical rating scales in children aged ≥6 years to assess post-operative and chronic pain, provided that the child could show numerical competency.

biased or influenced by factors other than pain.[240,241] Disagreements between the child and parent do not necessarily reflect inaccuracies in judgment, but rather different perspectives on pain or the health problem.[242] As such, such discrepancies should not be considered as error obscuring a true score, but as valuable information.

For children younger than 6 years or for those who are unable to verbally report, behavioural scales can provide a valuable alternative to assess pain in clinical settings.[243] For example, it could 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 structures for pain perception[95,96] and manifest behaviours (eg, facial grimacing or crying) that are analogous to the pain responses of adults or older children.[244] The behaviour of children is typically coded by trained observers.[245] Numerous neonatal pain scales have been created; 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 has meant that clinicians and researchers have adapted and tweaked them without the necessary validation steps to make them more appropriate for use in their specific settings. This inconsistency 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
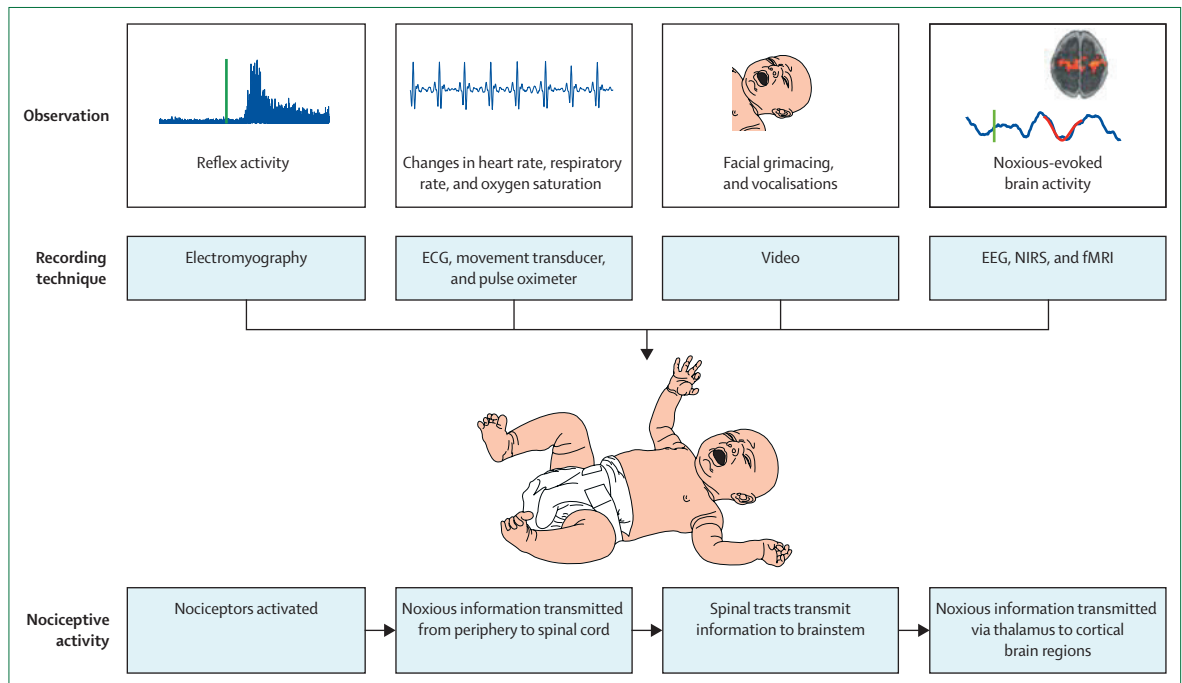
Figure 5: Assessing pain in infants
Available infant pain assessment techniques and nociceptive activity when an infant experiences pain. ECG=electrocardiogram. EEG=electroencephalogram. fMRI=functional MRI. NIRS=near-infrared spectroscopy. Reproduced from ref 251, by permission of Moultrie and colleagues.[251]

to noxious and innocuous events,[248–250] for example, by using fMRI, near-infrared spectroscopy, and 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 infants, and could also prove useful in other paediatric populations who are non-verbal or not able to self-report their pain experience.

The identification of robust and developmentally-sensitive pain indicators should continue to be a priority, so that there are better tools for use in both clinical practice and research. Accuracy is a challenge when using proxies and, when used, the possibilities of accurate detections of pain or false positives (ie, infant indicates they are in pain when they are not) should be considered. 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, in which 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 infants,[253,254] and infants who are at high risk of neurological impairment can exhibit decreased facial grimacing following clinical procedures compared with infants 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
Making future pain visible, or at least understanding the risks that influence whether pain might emerge in the future, is important. Moreover, being able to predict which children are likely to experience pain later on can create windows of opportunities for early interventions and allow the prioritisation of resources (ie, time, personnel, and treatment intensity) for those who have a high risk of having a poor outcome. The growing interest in predicting the transition from acute to chronic pain has spurred efforts to identify the 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,[145] and these could 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-reported instruments and usually 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 at predicting the future adverse effects of pain.[257] The field of clinical prediction is rapidly evolving, and guidelines and standards are available to help researchers and clinicians to develop and validate such screening tools.[258,259] There are few screening tools for use in paediatric settings. A notable exception is the Paediatric Pain Screening Tool (PPST),[260] which is based on the nine-item STarT Musculoskeletal Screening Tool in adults.[261] The content of the items in the PPST has been thoughtfully selected and adapted for use in children (aged between 8–18 years) presenting with pain problems. The instrument can be used to rapidly identify treatment targets (eg, sleep disruption and pain-related fear) and to stratify young people into low-risk, medium-risk, and high-risk groups to inform referral to appropriate interventions. The initial results are promising, and further studies show its potential usefulness for specific pain populations.[262,263]

Going beyond pain and measuring its wider effects

Importantly, the field of pain measurement has not focused solely on pain intensity. Indeed, progress has been made in making pain visible through the development of tools to assess both pain characteristics (eg, location, frequency, and duration) and its effects on multiple domains of life. There are many validated tools available to assess pain, as well as physical, emotional, and social role functioning, and health outcomes in children and adolescents. Systematic reviews of measures of pain effect,[264] pain-related anxiety,[265] sleep disturbances,[266] observational and behavioural measures of pain,[243] and self-reported measures of pain for very young children[267] and specific patient populations (eg, patients with abdominal pain)[268] are available. Despite the efforts of many to go beyond pain and to measure the effects 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. to make pain and its effects immediately visible (panel 5).

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 two stage Delphi process and a subsequent consensus meeting to identify core outcome domains and measures that might 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 six outcome domains: pain

> **Panel 5: Routine assessment questions to help make child pain and its effect visible**
>
> - What are your concerns and 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?

intensity, global judgment of satisfaction with treatment, symptoms and adverse events, physical recovery, emotional response, and economic factors. Chronic pain trials should include eight outcome domains: pain intensity, physical functioning, emotional functioning, role functioning, symptoms and adverse events, global judgment 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. However, the actual uptake of the recommendations was suboptimal. Of 337 randomised controlled trials of paediatric postoperative pain management, only two outcome domains of the PedIMMPACT recommendations were commonly included: pain intensity (included in 93% of trials) and symptoms and adverse events (included in 83% of trials).[270] Fewer than 30% of these trials included outcomes in any of the other four PedIMMPACT domains. Similarly, a systematic review of reporting practices in 107 randomised controlled trials of paediatric chronic pain interventions[271] found that 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 pharmacological treatments. Sleep and economic factors were rarely assessed across any intervention for paediatric chronic pain.[272] Overall, these findings indicated that trials of interventions for acute and chronic paediatric pain had insufficiently used the PedIMMPACT recommended core outcome sets.

Uptake of the PedIMMPACT core outcome set will increase when the following concerns are addressed. First, it is essential to have 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 (eg, adverse events, global judgment of satisfaction with treatment, and economic factors),

which hinder their inclusion in trials. Understandably, there are challenges in standardising 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 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. OMERACT originally published a recommendation for four core outcomes: life impact, pathophysiological 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 juvenile idiopathic arthritis core outcome set, which included several strategies to obtain broader input, including literature reviews, qualitative surveys, and online discussion boards with patients and parents.[274] A Delphi process was used to edit the domain list and to achieve consensus on domains. Notably, this process led to the inclusion of new domains, and the juvenile idiopathic arthritis core outcome set now consists of five domains: pain, joint inflammatory signs, activity limitation and physical function, patients' perception of disease activity (overall wellbeing), 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 standardisation of patient-reported outcomes through the Patient Reported Outcomes Measurement Information System (PROMIS),[276] developed by the US National Institutes of Health. Since 2012, considerable work has been 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 (eg, pain interference, emotional distress, and physical mobility),[276] and are recommended by various initiatives. Because PROMIS measures are available for adults, an important advantage is the consistency in measurement at the upper end of the adolescent and young adult age range and in assessing the opinions of parents and caregivers as proxy measures. Work is underway to validate the PROMIS measures in children and adolescents in a variety of painful conditions.[277,278] For example, one study validated that all seven PROMIS domains showed treatment responsiveness in children

and adolescents with chronic musculoskeletal pain conditions.[278] 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 are publicly available and include domains that span different diseases and settings (eg, physical function and depressive symptoms). There are now more than 20 multidimensional item banks of physical, mental, and social health for children and adolescents aged between 1 and 17 years. These item banks include short forms (comprised of 4–10 items), computer adaptive tests, and profiles normed to the US general population and validated in clinical subgroups. Versions are available in Dutch, English, German, and Spanish, among other languages. Moreover, PROMIS can be expanded for use in clinical practice, population health (eg, large epidemiological studies), and internationally to improve measurement consistency.

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

With ongoing technological innovations, 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 (eg, depression and 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 that

For more on **PROMIS** see www.healthmeasures.net

could lower the burden in observers who code pain expression or behaviours.[245,284] 3D 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 instruments for self-reporting 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. To make pain visible, a better understanding of whether outcome measures show that pain treatments are effective and safe is needed. Standardisation of outcome domains and measurement tools for clinical trials 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 to make evidence-based treatment decisions for this patient population. Further research should study commonly used paediatric pain outcome measures to understand clinically meaningful change, and should gather child and family input to learn what information they use to determine whether a treatment is working (eg, attaining particular goals or 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] Regulatory agencies are now using longitudinal daily experience data in clinical trials to better understand how an intervention makes a difference in patients' daily life.

Research and clinical priorities to make pain visible

We are dragging paediatric pain out of the shadows, although we acknowledge 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 aberrant experiences is crucial to the diagnosis of pathology. In neurology, descriptions of internal state, cognitive testing, and interview responses can be as important to tailoring treatment as brain imaging. In physical medicine, there is now a recognition that patient-reported outcomes are the missing piece of the patient experience that can guide more effective intervention, with growing interest in patient-related outcome measures and core outcome sets.[269,277] Moreover, there is movement towards values-based health care, 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. Several areas of clinical practice and research need to be prioritised.

First, pain characteristics should be assessed in every child. It is important for everyone, from parents to clinicians, to be comfortable with assessing internal processes by self-reporting where possible. Of course, self-reporting is influenced by factors such as social demand (ie, the obedient desire to please), but this factor should not discredit attempts to capture private experience or be a reason to leave pain unassessed. Child pain assessment is an inferential process and is drawn from multiple sources of evidence. For neonatal pain, researchers and clinicians can capture observer judgments of a range of behaviours that are relevant to pain, from facial expression and bodily expression, to non-verbal utterances, including crying. Health-care professionals need to guard against over-interpretation and under-interpretation of these behavioural signals, and context can be crucial. For older children who are verbal and are able to form concrete operations and manage metaphor and temporal abstraction, one can use measures that assign numbers to experience, or require a judgment about time. As a child's ability to introspect develops, they can learn to compartmentalise experience. Researchers and clinicians rarely go beyond intensity when measuring pain, 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 effects associated with pain is not only the experience itself. Pain negatively affects a child's physical, emotional, and social functioning, and health-care professionals must understand all the consequences 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 trials of novel interventions in chronic pain, it would now be considered poor science to ignore multiple domains of the child's experience. A consequence of this measurement translation of concepts and assessments is that factors that are most important to children and their caregivers (eg, consequences on friendships, career, finance, and marital

relationships) are not assessed. Siblings are also ignored. Due to the multitude of measures assessing the same concept, measurement development in some areas needs to be stopped; it is time that outcomes that are important to patients are explored, invested in, and developed.

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

Fourth, as we have highlighted throughout this Commission, people are complex. There is a need for a person-centred approach to assessment of pain in infants, children, and adolescents. This approach 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.

Lastly, 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, large amounts of data can now be captured. The near ubiquitous adoption of mobile telephones means that the passive capture of geolocation and movement sensing data is now easy. So-called near-time assessment of behaviour linked to a specific antecedent target is also possible, meaning that the context of specific behaviours and experiences can be assessed. 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 the environmental influences of pain.

Goal 4: make pain better

Every child should have access to evidence-based pain assessment and subsequent treatment using the most effective methods and means available. A growing number of high-quality systematic reviews, meta-analyses, and clinical practice guidelines show that some psychological, pharmacological, physical, and integrative treatment modalities are efficacious in reducing pain and improving function.[32,291–295] These treatment strategies are crucial for care to move beyond 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 might 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, particularly in older children.[272] Effective psychological treatments are predominantly based on cognitive and behavioural therapies and target cognitions, emotions, and behaviours, most notably cognitive-behavioural therapy (CBT).[296–299] The therapeutic aims of psychological treatments include the prevention of episodic pain (eg, headache or recurrent abdominal pain), the mitigation of severe or unavoidable pain, and the management of the aversive consequences of persistent pain. Psychological interventions with robust evidence for procedural pain include distraction, hypnosis, combined CBT, and breathing exercises.[297] 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 reframing,[303] among others. However, data for the possible harms from these approaches is rarely collected and is largely unavailable.[304]

Physical interventions are commonly used to address both acute and chronic pain but the literature supporting them is not as robust as the frequency of their use would suggest. The investigation of physical interventions for paediatric pain has largely focused on those available for preterm infants, term infants, and young children during medical procedures. Evidence-supported interventions include non-nutritive sucking (eg, by using a pacifier), breastfeeding (for babies experiencing acute pain),[305] swaddling or facilitated tucking (flexed positioning of the infant's arms and legs in supine, prone, or side position), skin-to-skin contact, rocking, and holding (eg, comfort positioning).[306–308] Other contextually relevant strategies to effectively reduce acute pain and distress are to direct how procedures are done (eg, simultaneous injections) or alterations to the environment (eg, low noise and lighting, and soothing smells).[306,307] Evidence for physical interventions for paediatric chronic pain is less common,[272] although neuromuscular exercise training[309] and aerobic exercise are promising strategies.[310] The scarce adult literature on other physiotherapeutic techniques (eg, transcutaneous electrical nerve stimulation) has been extrapolated to children and this modality is commonly used in children and young adults.[311,312]

Reviews of integrative therapies highlight the interest in acupuncture, creative arts, herbal therapy, homoeopathy, and massage therapy for different pain conditions.[313,314] However, the evidence supporting these therapies is scarce. Evidence suggests that improving patient or family understanding of pain and its mechanisms through the provision of pain education could also provide some therapeutic benefit.[315] 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 and procedural pain,[35] perioperative pain,[293] and chronic[316] pain management from infancy to late adolescence.[317]

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,[318] topical anaesthetics,[319] sweet-tasting solutions,[320] non-steroidal anti-inflammatory drugs,[321,322] antiepileptic drugs,[323,324] antidepressants[325] and opioids.[326–328] However, despite the common use, ubiquity, and clinical utility of pharmacotherapy, there is very little research on existing or new agents, particularly in the area of chronic pain management. In a 2019 overview of systematic reviews, only six randomised controlled trials of analgesic pharmacological interventions for paediatric chronic non-cancer pain were identified and there were no trials for chronic cancer-related pain,[329] meaning that the evidence base for the most common treatments used in children with chronic pain was formed on the basis of few trials with few patients (ie, <400 patients). Similarly, the use of interventional procedures (eg, nerve blocks and neurostimulation) for paediatric chronic pain is supported primarily by case reports with few randomised trials.[330] Although there are more randomised trials for paediatric perioperative care, evidence from adults is often extrapolated to paediatric populations,[329] mirroring a shortage of clinical drug trials across other areas of paediatrics.[293] A more substantive indirect evidence base will support the use of 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] Therefore, we should ask why there is no concerted effort to capture data for 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 is the provision of analgesia for infants and children after surgery. Analgesic medications are not licensed for pain management in newborn infants, so the choice of treatment is left to clinical judgment. Therefore, the choices of drug, dose, and route of administration are selected on the basis of expert consensus and individual experience, which might not be supported by strong evidence. Consequently, off-label analgesics are commonly administered to infants in unsuitable formulations, with little know-ledge of the pharmacokinetic properties, drug efficacy, or safety. Furthermore, despite being developmentally distinct, children are frequently grouped together using broad age ranges, and in the absence of adequate data due to the paucity of studies, regulatory decisions that are 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 is the regulatory response to reports of respiratory depression following codeine use,[334–337] which had effectively led to analgesic compounds (eg, 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, and patients and parents are essential for improving 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, for whom it can be unclear as to whether the infant is experiencing pain. This problem is also true for many children with communication impairments, leading to ethical questions related to how best to treat pain, whereby the reduction or avoidance of pain is not a goal without costs and favourable analgesic effects can seem inseparable from unfavourable adverse effects.[29] As an example, considerable uncertainty exists regarding whether preterm infants should receive medication before they receive 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 if it was applied using positive pressure in a non-breathing infant. However, it is not known how distressing laryngoscopy without sedation or analgesia is for extremely preterm infants, although it seems reasonable to assume that it is unpleasant. The provision of sedation or analgesia presumably reduces the infant's discomfort (although this is difficult to evaluate); however, studies have shown 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 one, but also 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 high-lights the way that decisions about pain management are often posited, in which it is necessary to weigh different values. Attaining more clarity about the adverse effects of

early life pain compared with increased physiological instability might be possible as more evidence is acquired. However, there will still be a need to decide which, and whose, values to prioritise. Considering these balanced ethical considerations, a recommendation based on the precautionary principle is made. Care providers should, when possible, make all efforts to reduce pain exposure by avoiding pain-causing procedures. In scenarios in which 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 is an unknown balance between the potential benefits and harms associated with these decisions, and this uncertainty 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 that they administer, recognise their potential complications so that they are better able to inform parents and patients, and to have the skills and strategies to resolve these complications when 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 with older children who can communicate complex needs, there is an absence of primary studies, and little translation from theory to preclinical studies to clinical intervention research. For example, one of the most examined areas of paediatric pain management is in child-focused psychological treatments. However, there are important areas that are missing. First, few studies included parents, siblings, and peers, although these studies 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 pain,[344] and in chronic primary pain, treatments have not been developed and risk factors are only starting to be identified.[143,145]

Promoting evidence-based paediatric pain management

Adoption of such a meta-scientific approach could appear unduly and unhelpfully critical. In dwelling on the practically, ethically, and clinically complex aspects of pain, 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. The pain community is at an important 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 advanced enough to quickly improve this field. For example, randomised controlled trials, the gold standard trial design, are in many instances unethical, impractical, or both,[345] such as in the example of testing the effectiveness of pharmacological interventions in a palliative or end-of-life setting in which randomisation without a viable rescue medication would be unethical and difficult to justify. The blinded randomised 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 method should not be thoughtlessly applied 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 reintroduced.[348,349] As an example, most of the studies included in a review of interdisciplinary chronic pain care used a single-group, pre-post design.[316] This review found significant differences after treatment on most outcomes, including pain intensity, physical and emotional functioning, and school attendance. In this instance, a focus on methods for describing complex interventions was needed, including the content of the intervention, using criteria such as available templates for intervention description and replication,[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 method to evaluate the efficacy of interventions, as well as implementation strategies, which are needed 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 fundamental shift in the thinking of the pain community, policy makers, and research funders. When 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 manages 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. When asking how to design a study to evaluate the efficacy and safety of any intervention, either clinically for the individual or in a trial on a sample population, 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. Primary or secondary outcome measures that differ between the online trial registry (eg, ClinicalTrials.gov) and publication, or important prespecified outcome measures that

are missing at publication, might lead to suspicion unless addressed adequately.[352] Other key considerations when interpreting evidence for the treatment of paediatric pain include managing and interpreting risk of biases, size, and quality of evidence. Depending on trial design, trialists should reduce bias and fully report methods whenever possible. Full and transparent reporting will increase confidence around the estimate of effect and improve the evidence base, rather than adding more uncertainty.[353] In regard to size, many research papers strongly argue that size matters when analysing and interpreting evidence from pain trials.[354] Trials with fewer than 50 participants overestimated the treatment effect around 50% of the time.[355] This inflated effect size found in smaller studies was also seen in a 2018 review of psychological interventions for children with chronic pain,[298] which found that small trials produced a large beneficial treatment effect for reducing pain compared with larger trials, which found no beneficial effect. Therefore, larger trials will also help to increase certainty, as smaller trials typically overestimate the effects of interventions.

Finally, it is important to interpret the quality of evidence with the effect of treatment, such as by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[356,357] In GRADE, outcomes are rated from very low (ie, there is very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect) to high (ie, there is high confidence 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 done.

Improving available treatments

Another way to make pain better is by working with what is already known. 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 the optimal dose, timing, and route of administration. Although they might be aware that the dose should be reduced in children who are 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 pharmacokinetics (commonly defined by clearance [CL] and volume of distribution [V]) combined with a pharmacodynamic effect (often defined by maximum effect [efficacy or E_{MAX}]) and the concentration at which half that maximum effect is achieved [C_{50}]). These parameters are associated with variability. Quantifying and sourcing this variability and how it relates to dose in
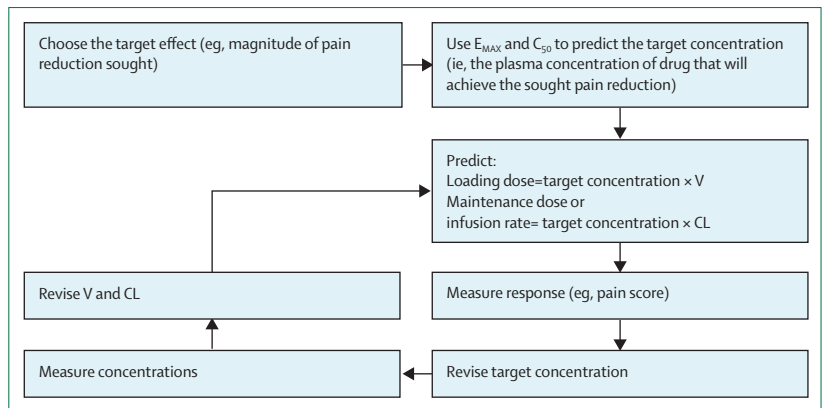

Figure 6: **Strategy to determine the correct dose of pharmacological treatment**
C_{50}=concentration at 50% of maximum response. CL=clearance. E_{MAX}=maximum effect. V=volume of distribution.

individual children helps clinicians to personalise drug use. This method avoids the concept that one dose fits all, regardless of age, maturation, or disease process. It also sidesteps the concept that pain relief only has merit if it decreases by a predetermined value (eg, by 50%). Determining the right dose can be achieved by the use of target concentration strategy (figure 6).

Population pharmacokinetic–pharmacodynamic modelling can be used to determine key parameters such as CL, V, E_{MAX}, and C_{50}. 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 integrating physiological parameters into the equations. The Hill equation, used originally to describe oxygen dissociation,[358] has proven popular and versatile to describe drug response, although other descriptors are equally valid. This method involves determination of a desired target effect, which in turn requires a robust pain measure or measures. Description of a concentration–pain response relationship allows for the assessment of pain relief on a concentration continuum (figure 7). Such 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 to determine the optimal dose.

Population pharmacokinetic–pharmacodynamic modelling uses mixed effects to study variability in drug responses in individuals who represent those for 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 individual patient.[362] Variability is associated with all parameters used in pharmacokinetic and pharmacodynamic equations. Covariate information (eg, weight, age, pathology, drug interactions, and pharmacogenomics) can be used to help predict the
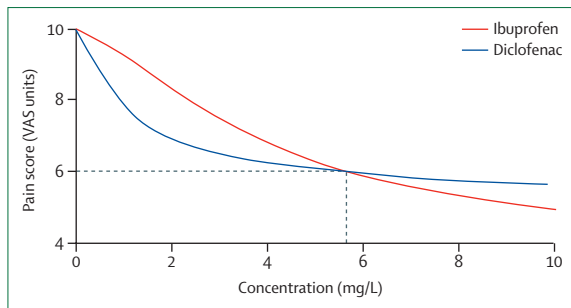
Figure 7: A concentration–response relationship for ibuprofen and diclofenac, determined for acute pain after tonsillectomy
The response curve is described using the Hill equation. The maximum effect (E_{MAX}) is similar for both drugs.[359,360] A target reduction of 4 pain units on the VAS (range 0–10; a score above 4 is usually considered as pain) correlates with a target concentration of 5·8 mg/L for both diclofenac and ibuprofen. VAS=visual analogue scale.

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 approximately 10% of white individuals) has been shown to be beneficial in adults.[363] Single polymorphisms that control the hepatic enzyme CYP2D6 influence the metabolism of drugs commonly used for pain management, such as codeine, tramadol, and amitriptyline. Consequently, this enzyme contributes to observed effects and adverse effects. It is possible to do bedside testing to assess genotype and this information can be used to review dose. Although genotype does not always equate with phenotype,[364] such information can be used as a guide for initial dosing.

Genetic influences are complex and could prove difficult to unravel. The importance of pharmacogenomics in dose individualisation is still uncertain. If a single genetic variant was responsible for major pharmacokinetic or pharmacodynamic differences, then dose individualisation would be easier. However, there appears to be a multiplicity of genetic influences on both morphine pharmacokinetics and pharmacodynamics, and the effects from interaction of these variants are not fully understood. Pain response is further complicated by numerous other factors (eg, psychosocial, race, environment, underlying pathology, and age).[365] An understanding of these complexities is needed before they can be used to individualise therapy.

We present this argument in full as 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 use 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. Although assessing the pharmacokinetic and pharmacodynamic properties of drugs can help to optimise pharmacological interventions, other strategies can be used (eg, 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 insomnia. Therefore, trialists have started trying to combine treatment modalities and test the efficacy of delivering CBT for pain and insomnia together,[282] or for anxiety and pain concurrently,[366] and initial results seem promising. In addition, researchers are also investigating which patients report the greatest gains in treatment in completed randomised trials. Studies have found that parental factors at the beginning of treatment could predict which children will benefit most from treatment.[367,368] For example, parents with higher distress before treatment predicted less improvement in their children's disability 12 months following treatment, compared with parents who reported lower distress.[368] This finding indicates that for caregivers with high distress, it could be important to target their own distress early in treatment to effect change on child disability. This information is crucial for refining psychological therapies and providing more individualised treatment.

Improving access and scale
An additional 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 (table). Researchers have risen to the challenge of improving access to evidence-supported treatments in the use of computing technology to deliver psychological, educational, or nurse-led treatments that have behaviour as a core target of the intervention. In the same way as technology has started to be used for assessment, investigators have begun exploring the use of computing technology for treatment. There is a long history of attempts at using technology to increase access (eg, the telephone)[369] and at automating instruction or therapeutic direction.[370] Often these attempts expanded as computing technology became ubiquitous. The dominance of mobile phones and the growth of computing in smartphones have led investigators to transfer face-to-face approaches onto these platforms, and to attempt innovation in new treatments that can only be delivered remotely.[371–373] One systematic review[372] identified ten randomised controlled trials that tested the efficacy of remotely delivered treatments for children

with chronic pain, and found small effects for reducing pain intensity and disability after treatment. However, the long-term effects of these approaches are unknown.

Despite the large number of mobile applications for pain education and treatment, very few are supported by evidence or are based on a theoretical framework. There are some very good examples of how technology has been successfully used to improve access to treatments,[374] but attempts at increasing the scale of access to treatments have been less successful. Applications 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 an average of $300 000 of grant funds for each application.[375] Scalability and sustainability remain challenging and could involve a reassessment of how treatments are developed, as well as changing the relationships between researchers, commercial providers, health-care planners, insurers, and government agencies to improve funding and regulatory 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 at Macquarie University (Sydney, NSW, Australia) has developed over 15 interventions for mental and physical health conditions in children and adults, including panic attacks, depression, social anxiety, post-traumatic stress, chronic pain (solely in adults), diabetes, and epilepsy. 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 in the research studies. The eCentre Clinic has done over 40 trials, with more than 4000 Australians testing these interventions to establish efficacy and safety.

Embracing complexity

Finally, to fulfil the ambition of improving the effectiveness, safety, quality, access, and scalability of available treatments, there should be a focus on the context in which these treatments will be delivered. Much of the evidence is based on single studies or the amalgamation of those studies in research syntheses. There are three specific challenges associated with the translation from the research to the clinical setting: comorbidity, 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 managed in the context of disease or after immunological challenge, as in surgery. In neonates, as described earlier,

fast developing systems (often at a crucial stage of development) need to be understood in any analgesic strategy. In children with neurodisability, pain from multiple sources (eg, muscle spasms) and complex comorbid conditions (eg, sleep apnoea) is frequent. In adolescents with chronic pain, comorbid mental health problems are common and should be considered in any management plan.[372,377] Trials in this area often exclude patients with more complex diagnoses and aim to improve physical functioning. Despite the comorbidities often seen in child and adolescent populations, randomised controlled trials of pain management provide little treatment to manage anxiety and depression and, therefore, there is little change in their symptoms 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 that are felt most acutely when faced with variety in patients who present 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 have been several studies in populations that are typically excluded from trials, such as children from low-income communities[378] or children with complex comorbidities.[366] More needs to be done to reach these groups and those who do not present with manageable disease due to assessment difficulties, stigma, fear of social exclusion, or a coping strategy of minimising 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 influence 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 parental distress[368] 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. Achieving this goal will mean understanding not only the evidence but the strengths and weaknesses of our habits of evidence production.

Research and clinical priorities to make pain better

Researchers and care providers have to get smarter about how to make pain better; in trial design, treatments, what is delivered, and to whom. There are currently serious shortcomings in treatment plans for children throughout the developmental age-span that need to be addressed.

First, there are fundamental gaps in the ambition to make pain better for all children and innovative solutions are needed to overcome current shortcomings. There is 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 scarcity 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 do randomised controlled trials in children, and include paediatric formulations when feasible. Unfortunately, these strategies, although welcome, have had little success in the field of pain. The absence of suitable data has driven calls for newer and different approaches and for the modification of trial designs, although the perception persists that these kinds of studies are difficult and impractical to do.[385,386] Nevertheless, alternative approaches are needed to generate evidence to guide clinical practice that go beyond the pharmacological randomised controlled trial. Although randomised controlled trials can manage some of the biases affecting study outcomes, they are expensive, time consuming, often inconclusive, and difficult to translate into clinical practice. Randomised controlled trials also incur opportunity costs for alternative ways of exploring efficacy and harm for the individual patient. Nevertheless, large, multi-site trials that minimise 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, there is an urgent need for 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. Health-care professionals often use older analgesics (eg, 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 individual children can help clinicians to personalise 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 doing single case designs when prescribing and switching drugs in children 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 (eg, age, sex, weight, height, and diagnosis), prescription (eg, drug, dose, and route), and outcomes (eg, pain intensity and interference, adverse events, and 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 psychology,[387]

their application in paediatric pain is rare,[349] but examples exist in adult pain research.[388] Paradoxically, focusing on the individual might allow us to imagine ways to increase access to evidence-supported treatments and to scale up the production of these treatments.

Third, there is a need to intervene earlier to prevent the onset of chronic pain. Identification of risk factors and the 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 so far has focused 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 substantially reduce the number of children transitioning from acute to chronic pain after injury, surgery, or other events.

Fourth, there is a need to stop some trials in fields for which there is sufficient evidence, or for which further evidence is unlikely to change our confidence in the estimate of effect. Examples include psychological interventions for chronic pain, and distraction for children undergoing procedural pain. It is unlikely that more randomised controlled trials of psychological interventions, however well done, will reduce the overall uncertainties around effect estimates. The next steps in psychological treatment research should be to establish an evidence base for interventions to reduce distress and improve function in children with comorbidities or complex needs, and interventions that target parents. There is also a need for further evidence for interventions to improve social outcomes and to prevent 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 and dissect the roles of the specific techniques, general conditioning, and the ongoing relationship with the therapist. However, when trials are reported, so should data for adverse events be, which are frequently missing in psychological interventions.[298]

Finally, a benefit of an idiographic approach to research, by focusing on the individual, is that complexity ceases to be a problem and instead becomes the solution. Researchers and care providers should recognise that complexity is the norm, and focus on what works for individual patients. For some, that complexity will possibly involve comorbidity and polypharmacy, and will also include a personal learning history and a specific environmental and learning context. Complexity science could be helpful in determining novel individualised treatments; for example, pain-related data (big and small) can be made visible by the pervasive personal sensing and computing and begin to inform treatment.

Transformative action for policy makers and funders

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

The WHO–UNICEF–Lancet Commission[389] on securing a future for children argued that children should be put at the centre of action to meet the sustainable development goals and that a focus on the health and wellbeing of children is essential to population survival. In this Commission, we focused on paediatric pain in middle-income and high-income 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. Among health-care 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 important goals that, if achieved, will transform paediatric pain—making children's and adolescents' pain matter, understood, visible, and better for future generations. These goals might seem obvious and many people might 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 problem, 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.

In the Introduction of this 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? While we have set out the clinical and research priorities needed to achieve the four goals (panel 6), it is only by cross-sector collaboration between researchers, clinicians, policy makers, funders, patients, and parents that progress can be made quickly and effectively. A coordinated approach is needed on all fronts, from all disciplines and agencies, and policy makers and funders should focus on several priority areas (panel 7).

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

As evidence for understanding, assessing, and treating pain continually evolves, so should the education of health-care professionals. Specialist knowledge to treating pain is often centralised, and greater efforts are needed to educate those in community settings to be able to manage neonates, children, and adolescents with pain. Curricula for all health-care professionals should include information on pain assessment and management, so that the health-care professionals are better equipped to manage pain and not perceive it as a by-product of a procedure or disease. In addition, curriculum revision is needed for medical nursing and allied health students treating future children with pain, who receive insufficient information about assessing and managing pain across the childhood lifespan, as well as regular retraining for front-line staff treating neonates, children, and adolescents.

Knowledge mobilisation is another strategy that could be key in reducing inequity in health-care 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, and several initiatives are ongoing to mobilise knowledge in paediatric pain (table). 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 increasingly digitalised world where health-care information is often only a click away.

Panel 6: Priorities for research and clinical practice

Make pain matter
- Improve equity—pain care should not be determined by non-personal determinants of health (eg, socioeconomic status, age, sex, disability, and ethnicity).
- Study factors that contribute to inequity in pain management, the consequences of inequality in pain management, and strategies to mitigate inequity.
- Develop effective strategies to make the latest pain management research accessible and understandable for patients (eg, older children and adolescents) and their caregivers.
- Ensure that all clinicians involved in the care of a child or adolescent are competent to provide pain care within their scope of practice.
- Mitigate stigma—consider labels given to pain that cannot be diagnosed with a known condition, and determine the best communication strategies when talking to children and families with pain to communicate understanding, empathy, and treatment course.
- Improve macro-understanding of the societal forces (eg, cultural, political, and health-care institutions) that influence paediatric pain experiences and management (eg, research funding allocation, political agendas that shape policy and narratives, and an understanding of culturally embedded experiences), and micro-understanding of mechanisms and interventions that leverage social factors (eg, family, friends, peers, and teachers) to improve the experiences of those living with pain (eg, by decreasing stigma and improving social health).

Make pain understood
- Promote a 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
- Abandon concepts that negate the explicit integration of biological, psychological, and social elements that comprise all forms of pain.
- Research and clinical understanding of pain should include the whole biopsychosocial model, eliminating suggestions of dualism between subjective and objective, mind and body, and physiology and psychology.
- Improve understanding of the early experience of pain on later development and behaviour.
- Improve understanding of the factors that contribute 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.
- Make use of existing longitudinal studies, and design and do additional longitudinal studies that track individual

development and the biological, environmental, psychological, and social factors that affect normal developmental trajectories, including effects on sensory and affective components of the pain response and risk of chronic pain in later life.

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 effect 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 when determining relevant outcome measures and whether pain treatments are achieving 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 in paediatric pain.
- Further develop methods to provide robust surrogate pain measures in immature or non-verbal populations.

Make pain better
- Establish a systematic evidence base for pharmacological interventions in children with chronic pain, and innovative solutions in trial design when the randomised controlled trial is not ethical or practical.
- Develop ways to improve existing treatments, such as through understanding the pharmacokinetic and pharmacodynamic properties of analgesics. These improvements could include tailoring treatments for individual children with pain and also attempt to personalise treatments on the basis of known covariates that include pharmacogenomics.
- Establish evidence on how and when to treat children with acute pain to prevent transition to chronic pain, and develop interventions that are effective at providing coping skills to prevent the onset of long-term pain.
- Stop trials in areas where there is sufficient evidence and where further evidence will not change the quality or confidence in the estimate of effect. Start trials for children with complex needs to prevent the onset of long-term pain and address comorbitities.
- Recognise that complexity is the norm and should always be considered when developing and testing treatments to meet the needs of patients.

Inequities in the provision of services need to be addressed. Clinically, there has been growing provision of dedicated child pain centres and many countries have successfully attempted 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 and staffed with specialists, yet it would be naive 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 specialist centres. When children reach treatment centres, their pain should be managed by health-care professionals who have up-to-date knowledge, such as through regular training, practice reflection, supervision, and resources (eg, time and facilities).

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

There needs to be a shift to make leadership of both health-care professionals and organisations take charge of patient care and increase accountability. As we have advocated, all pain should be assessed and treated. When that does not happen, a failure of care has occurred. When 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 goal includes making pain visible by targeting funding and policy to children who have been ignored or who have received inequity in pain management. We are not talking about equal access to all resources, but equitable access to shared resource base on need. Research funding is needed to illuminate inequity within health-care and community settings to help rectify this issue.

Diverse leadership at an organisational level is crucial for dealing with local child pain challenges that present within an institution or a region. Patient-partners are important to include in these leadership teams as they provide a different perspective to other professionals, as well as a voice to those who are subject to assessments and interventions. Increasing 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, the so-called small data innovation (ie, the collection of day-to-day data traces) has yet to be seen and used.[395] As more sensors are put in clothing, homes, vehicles, and in almost every object, it is possible to capture data for all behaviour. When these

novel data are combined with data captured actively as children volunteer information about their personal experience on social media, then what was once painstakingly and expensively done in the laboratory is now accessible as part of the daily life of children in this data revolution.[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. Despite having sufficient engineering capability, there are marked deficiencies in our understanding of behavioural science that can help us to look for the right patterns of data and interpret behaviour as meaningful. However, children and adolescents are generally positive about the use of technology in health care and expect such care 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.[397] Clinically, in paediatric pain, our current thinking about technology deployment (which focuses on establishing concordance with conventional methods) could be leapfrogged, and instead the assessment could be adapted to match what is being freely given, using
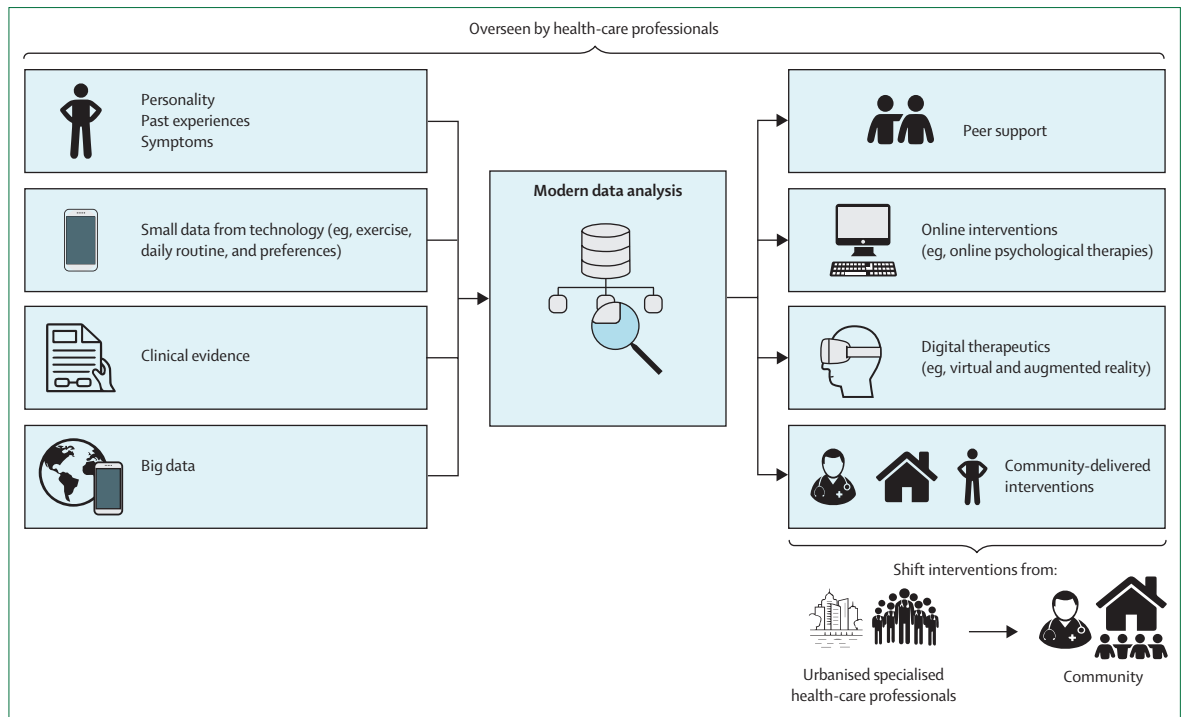
Panel 7: Priorities for policy makers and funders

- Introduce national-level initiatives to measure pain and its effects in large-scale monitors or surveys (each country has their own health survey, but pain does not have a prominent place). Ideally, the same measures should be used across countries to allow international comparisons.
- Pain service provision and specialism should not only be available in urbanised locations. A greater emphasis should be given to providing community health-care professionals with remote access to centralised services and knowledge to treat children with pain.
- Develop strategies and interventions to increase the accountability for improved pain curriculum to prepare health-care students for clinical practice (eg, accreditation bodies and universities) and to increase care providers' knowledge and competences about paediatric pain. Training and resources should be prioritised and provided for frontline staff to prevent unnecessary pain in patients.
- Implement knowledge mobilisation initiatives to reduce the gap between evidence and practice.
- Plan and provide funding for multidisciplinary and multi-professional pain management services for children in a way that is similar to services already in place for adults
- Develop leadership—including partners from diverse sectors (eg, policy, medicine, research, and industry)—to come together to raise awareness and develop solutions to improve treatment of paediatric pain.
- Introduce institutional commitment initiatives concerning prevention, diagnostics, and treatment of pain in children in all hospitals.
- Incorporate strategies and interventions to increase the accountability of health-care administrators and clinicians in providing pain care to infants, children, and adolescents (eg, professional regulators, hospital accreditation associations, and making inadequate pain management a patient safety issue).
- Ensure the creation of systems that allow for the full participation of patient partners in institutional policy and decision making on paediatric pain.

***Figure 8:* Redesigning pain services**

A redesigned pain service involves a system of knowledge overseen by pain specialists. Data from individual patients (including symptoms, experiences, and small data collected via technology), clinical evidence, and big data contribute to knowledge generation (potentially aided by machine learning), which enables peer support, access to online interventions, and other interventions delivered in community settings. In doing so, pain services that are currently delivered by specialists in centralised, urban settings can be shifted to the community setting and be delivered by local workers with appropriate training and supervision from peers or experts.

media to capture experience (eg, location and movement data).

Beyond assessment, patients cannot wait for the establishment of evidence bases, which are likely to take a generation to be funded, created, accumulated, and disseminated. Many 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, more pain clinics are needed, and they should be focused on the patient, with personalised management that recognises complexity. 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 redesign should be considered. Rather than considering the expert as the intelligence of the system, the means of production, and the quality control process, these functions can be separated. First, the expert should be allowed 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, and knowledge should be moved from the individual to an integrated computerised knowledge system (ie, machine learning). Second, collection of small data

from individual patients can potentially be matched with insights from big data on the experience of others and with evidence from clinical studies to improve management. Third, by providing multiple local health-care providers in the community with appropriate training to deliver the specific intervention under supervision from peers or experts, specialists can be relieved of these duties. 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 it can be currently managed (figure 8).

Conclusion

This Commission has covered four important goals that 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 focused on high-income and middle-income countries but recognise that there are different challenges for low-income settings. We also have not focused much on the importance of experimental research, theoretical development, and the need for their closer union.

It is time for change. To achieve our first goal of making pain matter, the social and personal forces that traditionally silence pain complaints, put them out of sight, and allow pain management to be ignored need to be exposed. There is a long way to go in the study of pain mechanisms to achieve our second goal of making pain understood, and investment and support for multi-disciplinary collaboration will be key to successful and rapid progression. For our third goal, to make pain visible, we advocate for the need to develop an intolerance for the absence of assessment and to equip everyone working with children in pain with the ability to navigate the inferential process of determining a patient's pain status. Lastly, to make pain better, better treatments and better access to these treatments are needed for more people by making optimal use of technological innovation and by creating new treatment models built around individual contextualised experience.

References
1 Walco GA, Krane EJ, Schmader KE, Weiner DK. Applying a lifespan developmental perspective to chronic pain: pediatrics to geriatrics. *J Pain* 2016; **17** (suppl): T108–17.

2 Lau JYF, Heathcote LC, Beale S, et al. Cognitive biases in children and adolescents with chronic pain: a review of findings and a call for developmental research. *J Pain* 2018; **19:** 589–98.

3 McGrath PJ, Craig KD. Developmental and psychological factors in children's pain. *Pediatr Clin North Am* 1989; **36:** 823–36.

4 Melzack R, Wall PD. The challenge of pain. London: Penguin London, 1988.

5 de Lima J, Lloyd-Thomas AR, Howard RF, Sumner E, Quinn TM. Infant and neonatal pain: anaesthetists' perceptions and prescribing patterns. *BMJ* 1996; **313:** 787.

6 Schechter NL, Allen D. Physicians' attitudes toward pain in children. *J Dev Behav Pediatr* 1986; **7:** 350–54.

7 Wesson SC. Ligation of the ductus arteriosus: anesthesia management of the tiny premature infant. *AANA J* 1982; **50:** 579–82.

8 McGrath PJ. Science is not enough: the modern history of pediatric pain. *Pain* 2011; **152:** 2457–59.

9 Chambers CT. From evidence to influence: dissemination and implementation of scientific knowledge for improved pain research and management. *Pain* 2018; **159** (suppl 1): S56–64.

10 Brandt AM, Rozin P. Morality and health. London: Routledge, 2013.

11 De Ruddere L, Goubert L, Stevens M, de C Williams AC, Crombez G. Discounting pain in the absence of medical evidence is explained by negative evaluation of the patient. *Pain* 2013; **154:** 669–76.

12 De Ruddere L, Bosmans M, Crombez G, Goubert L. Patients are socially excluded when their pain has no medical explanation. *J Pain* 2016; **17:** 1028–35.

13 De Ruddere L, Craig KD. Understanding stigma and chronic pain: a-state-of-the-art review. *Pain* 2016; **157:** 1607–10.

14 Scarry E. The body in pain: the making and unmaking of the world. NY, USA: Oxford University Press, 1985.

15 Morris DB. The culture of pain. Oakland: University of California Press, 1991.

16 Bourke J. The story of pain: from prayer to painkillers. Oxford: Springer, 2017.

17 Brennan F, Lohman D, Gwyther L. Access to pain management as a human right. *Am J Public Health* 2019; **109:** 61–65.

18 Craig KD. The social communication model of pain. *Can Psychol* 2009; **50:** 22–32.

19 Martin SR, Cohen LL, Mougianis I, Griffin A, Sil S, Dampier C. Stigma and pain in adolescents hospitalized for sickle cell vasoocclusive pain episodes. *Clin J Pain* 2018; **34:** 438–44.

20 Stevens BJ, Abbott LK, Yamada J, et al. Epidemiology and management of painful procedures in children in Canadian hospitals. *CMAJ* 2011; **183:** E403–10.

21 Twycross A, Forgeron P, Chorne J, Backman C, Finley GA. Pain as the neglected patient safety concern: five years on. *J Child Health Care* 2016; **20:** 537–41.

22 Chorney JM, McGrath P, Finley GA. Pain as the neglected adverse event. *CMAJ* 2010; **182:** 732.

23 McGrath PJ, Finley GA. Attitudes and beliefs about medication and pain management in children. *J Palliat Care* 1996; **12:** 46–50.

24 Purcell-Jones G, Dormon F, Sumner E. Paediatric anaesthetists' perceptions of neonatal and infant pain. *Pain* 1988; **33:** 181–87.

25 Anand KJ, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* 1987; **1:** 243–48.

26 Watt-Watson J, McGillion M, Hunter J, et al. A survey of prelicensure pain curricula in health science faculties in Canadian universities. *Pain Res Manag* 2009; **14:** 439–44.

27 Dorkham MC, Chalkiadis GA, von Ungern Sternberg BS, Davidson AJ. Effective postoperative pain management in children after ambulatory surgery, with a focus on tonsillectomy: barriers and possible solutions. *Paediatr Anaesth* 2014; **24:** 239–48.

28 Public Health England. UK immunisation schedule: the green book. 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/855727/Greenbook_chapter_11_UK_Immunisation_schedule.pdf (accessed Sept 15, 2020).

29 Moultrie F, Shriver A, Hartley C, et al. A universal right to pain relief: balancing the risks in a vulnerable patient population. *Lancet Child Adolesc Health* 2019; **3:** 62–64.

30 McLenon J, Rogers MAM. The fear of needles: a systematic review and meta-analysis. *J Adv Nurs* 2019; **75:** 30–42.

31 McMurtry CM, Pillai Riddell R, Taddio A, et al. Far from "just a poke": common painful needle procedures and the development of needle fear. *Clin J Pain* 2015; **31** (suppl)**:** S3–11.

32 Taddio A, McMurtry CM, Shah V, et al. Reducing pain during vaccine injections: clinical practice guideline. *CMAJ* 2015; **187:** 975–82.

33 WHO. Reducing pain at the time of vaccination: WHO position paper, September 2015-recommendations. *Vaccine* 2016; **34:** 3629–30.

34 Shomaker K, Dutton S, Mark M. Pain prevalence and treatment patterns in a US children's hospital. *Hosp Pediatr* 2015; **5:** 363–70.

35 Friedrichsdorf SJ, Eull D, Weidner C, Postier A. A hospital-wide initiative to eliminate or reduce needle pain in children using lean methodology. *Pain Rep* 2018; **3** (suppl 1): e671.

36 Courtois E, Droutman S, Magny J-F, et al. Epidemiology and neonatal pain management of heelsticks in intensive care units: EPIPPAIN 2, a prospective observational study. *Int J Nurs Stud* 2016; **59:** 79–88.

37 Mahic M, Fredheim OM, Borchgrevink PC, Skurtveit S. Use of prescribed opioids by children and adolescents: differences between Denmark, Norway and Sweden. *Eur J Pain* 2015; **19:** 1095–100.

38 Igler EC, Defenderfer EK, Lang AC, Bauer K, Uihlein J, Davies WH. Gender differences in the experience of pain dismissal in adolescence. *J Child Health Care* 2017; **21:** 381–91.

39 Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth* 2013; **111:** 52–58.

40 Hoffmann DE, Tarzian AJ. The girl who cried pain: a bias against women in the treatment of pain. *J Law Med Ethics* 2001; **29:** 13–27.

41 Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. *J R Soc Med* 2011; **104:** 510–20.

42 Carbajal R, Eriksson M, Courtois E, et al. Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study. *Lancet Respir Med* 2015; **3:** 796–812.

43 Lord SM, Tardif HP, Kepreotes EA, Blanchard M, Eagar K. The Paediatric electronic Persistent Pain Outcomes Collaboration (PaedePPOC): establishment of a binational system for benchmarking children's persistent pain services. *Pain* 2019; **160:** 1572–85.

44 Velazquez Cardona C, Rajah C, Mzoneli YN, et al. An audit of paediatric pain prevalence, intensity, and treatment at a South African tertiary hospital. *Pain Rep* 2019; **4:** e789.

45 Gagnon MM, Hadjistavropoulos T, Hampton AJ, Stinson J. A systematic review of knowledge translation (KT) in pediatric pain. *Clin J Pain* 2016; **32:** 972–90.

46 Stevens BJ, Yamada J, Promislow S, Stinson J, Harrison D, Victor JC. Implementation of multidimensional knowledge translation strategies to improve procedural pain in hospitalized children. *Implement Sci* 2014; **9:** 120.

47 Schechter NL. From the ouchless place to comfort central: the evolution of a concept. *Pediatrics* 2008; **122** (suppl 3): S154–60.

48 Johnston CC, Gagnon A, Rennick J, et al. One-on-one coaching to improve pain assessment and management practices of pediatric nurses. *J Pediatr Nurs* 2007; **22:** 467–78.

49 Rabbitts JA, Aaron RV, Fisher E, et al. Long-term pain and recovery after major pediatric surgery: a qualitative study with teens, parents, and perioperative care providers. *J Pain* 2017; **18:** 778–86.

50 Logan DE, Gray LS, Iversen CN, Kim S. School self-concept in adolescents with chronic pain. *J Pediatr Psychol* 2017; **42:** 892–901.

51 Friesgaard KD, Riddervold IS, Kirkegaard H, Christensen EF, Nikolajsen L. Acute pain in the prehospital setting: a register-based study of 41.241 patients. *Scand J Trauma Resusc Emerg Med* 2018; **26:** 53.

52 Harvey G, Kitson A. PARIHS revisited: from heuristic to integrated framework for the successful implementation of knowledge into practice. *Implement Sci* 2016; **11:** 33.

53 Knaul FM, Farmer PE, Bhadelia A, Berman P, Horton R. Closing the divide: the Harvard Global Equity Initiative-Lancet Commission on global access to pain control and palliative care. *Lancet* 2015; **386:** 722–24.

54 Crowley-Matoka M, Saha S, Dobscha SK, Burgess DJ. Problems of quality and equity in pain management: exploring the role of biomedical culture. *Pain Med* 2009; **10:** 1312–24.

55 Ezenwa MO, Patil C, Shi K, Molokie RE. Healthcare injustice in patients with sickle cell disease. *Int J Hum Rights Healthc* 2016; **9:** 109–19.

56 Fleegler EW, Schechter NL. Pain and prejudice. *JAMA Pediatr* 2015; **169:** 991–93.

57 Malviya S, Voepel-Lewis T, Tait AR, et al. Pain management in children with and without cognitive impairment following spine fusion surgery. *Paediatr Anaesth* 2001; **11:** 453–58.

58 Breau LM, Camfield CS, McGrath PJ, Finley GA. The incidence of pain in children with severe cognitive impairments. *Arch Pediatr Adolesc Med* 2003; **157:** 1219–26.

59 Miller MM, Scott EL, Trost Z, Hirsh AT. Perceived injustice is associated with pain and functional outcomes in children and adolescents with chronic pain: a preliminary examination. *J Pain* 2016; **17:** 1217–26.

60 Zhang H, Wang H, Sun J, Xie X. Adding insult to injury: perceived inequity modulates pain perception. *J Health Psychol* 2018; published online Oct 8. https://doi.org/10.1177/1359105318802936.

61 Ballantyne JC. Opioids for the treatment of chronic pain: mistakes made, lessons learned, and future directions. *Anesth Analg* 2017; **125:** 1769–78.

62 Chalkiadis G, Goobie S, Walker S. Are opioids pediatric anesthesiologists' sword of Damocles? With great power comes great responsibility and risk. *Paediatr Anaesth* 2019; **29:** 544–46.

63 Manjiani D, Paul DB, Kunnumpurath S, Kaye AD, Vadivelu N. Availability and utilization of opioids for pain management: global issues. *Ochsner J* 2014; **14:** 208–15.

64 Stannard C. Opioids for pain in Europe: differing problems and differing solutions. In: Eccleston C, Wells C, Morlion B, eds. European Pain Management. Oxford: Oxford University Press, 2017: 225–42.

65 Martin SR, Zeltzer LK. Prioritizing pediatric chronic pain and comprehensive pain treatment in the context of the opioid epidemic. *Pain Manag* 2018; **8:** 67–70.

66 Schechter NL, Walco GA. The potential impact on children of the CDC guideline for prescribing opioids for chronic pain: above all, do no harm. *JAMA Pediatr* 2016; **170:** 425–26.

67 Webster F, Rice K, Sud A. A critical content analysis of media reporting on opioids: the social construction of an epidemic. *Soc Sci Med* 2020; **244:** 112642.

68 Webster F, Rice K, Katz J, Bhattacharyya O, Dale C, Upshur R. An ethnography of chronic pain management in primary care: the social organization of physicians' work in the midst of the opioid crisis. *PLoS One* 2019; **14:** e0215148.

69 Vagnoli L, Mammucari M, Graziani D, Messeri A. Doctors and nurses' knowledge and attitudes towards pediatric pain management: an exploratory survey in a children's hospital. *J Pain Palliat Care Pharmacother* 2019; **33:** 107–19.

70 Groenewald CB, Law EF, Fisher E, Beals-Erickson SE, Palermo TM. Associations between adolescent chronic pain and prescription opioid misuse in adulthood. *J Pain* 2019; **20:** 28–37.

71 Foucault N. The birth of the clinic. London: Routledge, 2012.

72 Pincus T, Noel M, Jordan A, Serbic D. Perceived diagnostic uncertainty in pediatric chronic pain. *Pain* 2018; **159:** 1198–201.

73 Neville A, Jordan A, Beveridge JK, Pincus T, Noel M. Diagnostic uncertainty in youth with chronic pain and their parents. *J Pain* 2019; **20:** 1080–90.

74 Goubert L, Craig KD, Vervoort T, et al. Facing others in pain: the effects of empathy. *Pain* 2005; **118:** 285–88.

75 Nes LS, Segerstrom SC. Dispositional optimism and coping: a meta-analytic review. *Pers Soc Psychol Rev* 2006; **10:** 235–51.

76 Rajasagaram U, Taylor DM, Braitberg G, Pearsell JP, Capp BA. Paediatric pain assessment: differences between triage nurse, child and parent. *J Paediatr Child Health* 2009; **45:** 199–203.

77 Hayes-Skelton SA, Eustis EH. Experiential avoidance. In: Abramowitz JS, Blakey SM, eds. Clinical handbook of fear and anxiety: maintenance processes and treatment mechanisms. Washington, DC: American Psychological Association, 2020: 115–31.

78 Hatfield G. René Descartes: the Stanford encyclopedia of philosophy. 2018. https://plato.stanford.edu/archives/sum2018/entries/descartes (accessed March 1, 2020).

79   Bechtel W. Mental mechanisms: philosophical perspectives on cognitive neuroscience. New York: Taylor & Francis, 2008.

80   Chalmers DJ. Facing up to the problem of consciousness. *J Conscious Stud* 1995; **2:** 200–19.

81   Chalmers DJ. Moving forward on the problem of consciousness. *J Conscious Stud* 1997; **4:** 3–46.

82   Nagel T. What is it like to be a bat? *Philos Rev* 1974; **83:** 435–50.

83   Robinson ME, Staud R, Price DD. Pain measurement and brain activity: will neuroimages replace pain ratings? *J Pain* 2013; **14:** 323–27.

84   Davis KD. Legal and ethical issues of using brain imaging to diagnose pain. *Pain Reports* 2016; **1:** e577.

85   Miller GA. Mistreating psychology in the decades of the brain. *Perspect Psychol Sci* 2010; **5:** 716–43.

86   Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain* 2020; published online May 23. https://doi.org/10.1097/j.pain.0000000000001939.

87   Treede R-D, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the: international classification of diseases. *Pain* 2019; **160:** 19–27.

88   Fitzgerald M. Development of nociception. In: Binder MD, Hirokawa N, Windhorst U, eds. Encyclopedia of neuroscience. Berlin, Germany: Springer, 2008.

89   Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science* 2000; **288:** 1765–69.

90   Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci* 2013; **14:** 502–11.

91   Kuner R, Flor H. Structural plasticity and reorganisation in chronic pain. *Nat Rev Neurosci* 2016; **18:** 20–30.

92   Kucyi A, Davis KD. The neural code for pain: from single-cell electrophysiology to the dynamic pain connectome. *Neuroscientist* 2017; **23:** 397–414.

93   Cao M, Huang H, He Y. Developmental connectomics from infancy through early childhood. *Trends Neurosci* 2017; **40:** 494–506.

94   Verriotis M, Chang P, Fitzgerald M, Fabrizi L. The development of the nociceptive brain. *Neuroscience* 2016; **338:** 207–19.

95   Goksan S, Baxter L, Moultrie F, et al. The influence of the descending pain modulatory system on infant pain-related brain activity. *eLife* 2018; **7:** e37125.

96   Goksan S, Hartley C, Emery F, et al. fMRI reveals neural activity overlap between adult and infant pain. *eLife* 2015; **4:** e06356.

97   Gursul D, Hartley C, Slater R. Nociception and the neonatal brain. *Semin Fetal Neonatal Med* 2019; **24:** 101016.

98   Slater R, Cantarella A, Gallella S, et al. Cortical pain responses in human infants. *J Neurosci* 2006; **26:** 3662–66.

99   Verriotis M, Fabrizi L, Lee A, Ledwidge S, Meek J, Fitzgerald M. Cortical activity evoked by inoculation needle prick in infants up to one-year old. *Pain* 2015; **156:** 222–30.

100   Poorun R, Hartley C, Goksan S, et al. Electroencephalography during general anaesthesia differs between term-born and premature-born children. *Clin Neurophysiol* 2016; **127:** 1216–22.

101   Williams G, Fabrizi L, Meek J, et al. Functional magnetic resonance imaging can be used to explore tactile and nociceptive processing in the infant brain. *Acta Paediatr* 2015; **104:** 158–66.

102   Fitzgerald M, Walker SM. Infant pain management: a developmental neurobiological approach. *Nat Clin Pract Neurol* 2009; **5:** 35–50.

103   Hjerling-Leffler J, Alqatari M, Ernfors P, Koltzenburg M. Emergence of functional sensory subtypes as defined by transient receptor potential channel expression. *J Neurosci* 2007; **27:** 2435–43.

104   Walker SM, Tochiki KK, Fitzgerald M. Hindpaw incision in early life increases the hyperalgesic response to repeat surgical injury: critical period and dependence on initial afferent activity. *Pain* 2009; **147:** 99–106.

105   Cornelissen L, Fabrizi L, Patten D, et al. Postnatal temporal, spatial and modality tuning of nociceptive cutaneous flexion reflexes in human infants. *PLoS One* 2013; **8:** e76470.

106   Andrews KA, Desai D, Dhillon HK, Wilcox DT, Fitzgerald M. Abdominal sensitivity in the first year of life: comparison of infants with and without prenatally diagnosed unilateral hydronephrosis. *Pain* 2002; **100:** 35–46.

107   Blankenburg M, Meyer D, Hirschfeld G, et al. Developmental and sex differences in somatosensory perception—a systematic comparison of 7- versus 14-year-olds using quantitative sensory testing. *Pain* 2011; **152:** 2625–31.

108   Hirschfeld G, Zernikow B, Kraemer N, et al. Development of somatosensory perception in children: a longitudinal QST-study. *Neuropediatrics* 2012; **43:** 10–16.

109   Walker SM, Melbourne A, O'Reilly H, et al. Somatosensory function and pain in extremely preterm young adults from the UK EPICure cohort: sex-dependent differences and impact of neonatal surgery. *Br J Anaesth* 2018; **121:** 623–35.

110   Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. *Pain* 2017; **158** (suppl 1): S11–18.

111   Brewer CL, Baccei ML. The development of pain circuits and unique effects of neonatal injury. *J Neural Transm* 2019; **127:** 467–79.

112   Fitzgerald M. The development of nociceptive circuits. *Nat Rev Neurosci* 2005; **6:** 507–20.

113   Khazipov R, Milh M. Early patterns of activity in the developing cortex: focus on the sensorimotor system. *Semin Cell Dev Biol* 2018; **76:** 120–29.

114   Koch SC, Fitzgerald M. Activity-dependent development of tactile and nociceptive spinal cord circuits. *Ann N Y Acad Sci* 2013; **1279:** 97–102.

115   Chang P, Fabrizi L, Olhede S, Fitzgerald M. The development of nociceptive network activity in the somatosensory cortex of freely moving rat pups. *Cereb Cortex* 2016; **26:** 4513–23.

116   Fitzgerald M, Millard C, McIntosh N. Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anaesthesia. *Pain* 1989; **39:** 31–36.

117   Andrews K, Fitzgerald M. Wound sensitivity as a measure of analgesic effects following surgery in human neonates and infants. *Pain* 2002; **99:** 185–95.

118   Fitzgerald M, McKelvey R. Nerve injury and neuropathic pain—a question of age. *Exp Neurol* 2016; **275:** 296–302.

119   Hathway GJ, Murphy E, Lloyd J, Greenspon C, Hulse RP. Cancer chemotherapy in early life significantly alters the maturation of pain processing. *Neuroscience* 2018; **387:** 214–29.

120   Schappacher KA, Xie W, Zhang JM, Baccei ML. Neonatal vincristine administration modulates intrinsic neuronal excitability in the rat dorsal root ganglion and spinal dorsal horn during adolescence. *Pain* 2019; **160:** 645–57.

121   Walker SM, Beggs S, Baccei ML. Persistent changes in peripheral and spinal nociceptive processing after early tissue injury. *Exp Neurol* 2016; **275:** 253–60.

122   Averitt DL, Eidson LN, Doyle HH, Murphy AZ. Neuronal and glial factors contributing to sex differences in opioid modulation of pain. *Neuropsychopharmacology* 2019; **44:** 155–65.

123   Fullerton EF, Doyle HH, Murphy AZ. Impact of sex on pain and opioid analgesia: a review. *Curr Opin Behav Sci* 2018; **23:** 183–90.

124   van den Hoogen NJ, de Kort AR, Allegaert KM, et al. Developmental neurobiology as a guide for pharmacological management of pain in neonates. *Semin Fetal Neonatal Med* 2019; **24:** 101012.

125   Chau CMY, Ross CJD, Chau V, et al. Morphine biotransformation genes and neonatal clinical factors predicted behaviour problems in very preterm children at 18 months. *EBioMedicine* 2019; **40:** 655–62.

126   Sorge RE, Strath LJ. Sex differences in pain response. *Curr Opin Physiol* 2018; **6:** 75–81.

127   Walker SM. Early life pain—effects in the adult. *Curr Opin Physiol* 2019; **11:** 16–24.

128   Ganguly K, Poo MM. Activity-dependent neural plasticity from bench to bedside. *Neuron* 2013; **80:** 729–41.

129   Chau CMY, Ranger M, Bichin M, et al. Hippocampus, amygdala, and thalamus volumes in very preterm children at 8 years: neonatal pain and genetic variation. *Front Behav Neurosci* 2019; **13:** 51.

130   Loh WY, Anderson PJ, Cheong JLY, et al. Longitudinal growth of the basal ganglia and thalamus in very preterm children. *Brain Imaging Behav* 2019; **14:** 998–1011.

131   Walker SM. Long-term effects of neonatal pain. *Semin Fetal Neonatal Med* 2019; **24:** 101005.

132   Borsook D, Youssef AM, Simons L, Elman I, Eccleston C. When pain gets stuck: the evolution of pain chronification and treatment resistance. *Pain* 2018; **159:** 2421–36.

133 Turk DC, Wilson H, Swanson KS, Ebert M, Kerns R.
The biopsychosocial model of pain and pain management.
Cambridge: Cambridge University Press, 2011.

134 Apkarian AV, Baliki MN, Farmer MA. Predicting transition
to chronic pain. *Curr Opin Neurol* 2013; **26**: 360–67.

135 Liossi C, Howard RF. Pediatric chronic pain: biopsychosocial
assessment and formulation. *Pediatrics* 2016; **138**: e20160331.

136 Lebel A, Becerra L, Wallin D, et al. fMRI reveals distinct CNS
processing during symptomatic and recovered complex regional
pain syndrome in children. *Brain* 2008; **131**: 1854–79.

137 Groenewald CB, Essner BS, Wright D, Fesinmeyer MD, Palermo TM.
The economic costs of chronic pain among a cohort of treatment-
seeking adolescents in the United States. *J Pain* 2014; **15**: 925–33.

138 Sleed M, Eccleston C, Beecham J, Knapp M, Jordan A.
The economic impact of chronic pain in adolescence:
methodological considerations and a preliminary costs-of-illness
study. *Pain* 2005; **119**: 183–90.

139 Walters CB, Kynes JM, Sobey J, Chimhundu-Sithole T,
McQueen KAK. Chronic pediatric pain in low- and middle-income
countries. *Children (Basel)* 2018; **5**: 113.

140 King S, Chambers CT, Huguet A, et al. The epidemiology of chronic
pain in children and adolescents revisited: a systematic review. *Pain*
2011; **152**: 2729–38.

141 Brattberg G. Do pain problems in young school children persist into
early adulthood? A 13-year follow-up. *Eur J Pain* 2004; **8**: 187–99.

142 Simon L. Relieving pain in America: a blueprint for transforming
prevention, care, education, and research. *Mil Med* 2016;
181: 397–99.

143 Huguet A, Tougas ME, Hayden J, McGrath PJ, Stinson JN,
Chambers CT. Systematic review with meta-analysis of childhood
and adolescent risk and prognostic factors for musculoskeletal pain.
Pain 2016; **157**: 2640–56.

144 Rabbitts JA, Groenewald CB, Tai GG, Palermo TM. Presurgical
psychosocial predictors of acute postsurgical pain and quality of life
in children undergoing major surgery. *J Pain* 2015; **16**: 226–34.

145 Holley AL, Wilson AC, Palermo TM. Predictors of the transition
from acute to persistent musculoskeletal pain in children and
adolescents: a prospective study. *Pain* 2017; **158**: 794–801.

146 Niesters M, Hoitsma E, Sarton E, Aarts L, Dahan A. Offset
analgesia in neuropathic pain patients and effect of treatment with
morphine and ketamine. *Anesthesiology* 2011; **115**: 1063–71.

147 Sieberg CB, Lunde CE, Borsook D. Endometriosis and pain in the
adolescent-striking early to limit suffering: a narrative review.
Neurosci Biobehav Rev 2020; **108**: 866–76.

148 Kolb B, Harker A, Gibb R. Principles of plasticity in the developing
brain. *Dev Med Child Neurol* 2017; **59**: 1218–23.

149 Nakagawa Y. Development of the thalamus: from early patterning
to regulation of cortical functions. *Wiley Interdiscip Rev Dev Biol*
2019; **8**: e345.

150 Blankenburg M, Kraemer N, Hirschfeld G, et al. Childhood diabetic
neuropathy: functional impairment and non-invasive screening
assessment. *Diabet Med* 2012; **29**: 1425–32.

151 Lieber S, Blankenburg M, Apel K, Hirschfeld G, Hernáiz Driever P,
Reindl T. Small-fiber neuropathy and pain sensitization in survivors
of pediatric acute lymphoblastic leukemia. *Eur J Paediatr Neurol*
2018; **22**: 457–69.

152 Kristensen AD, Ahlburg P, Lauridsen MC, Jensen TS, Nikolajsen L.
Chronic pain after inguinal hernia repair in children. *Br J Anaesth*
2012; **109**: 603–08.

153 Kristensen AD, Pedersen TA, Hjortdal VE, Jensen TS, Nikolajsen L.
Chronic pain in adults after thoracotomy in childhood or youth.
Br J Anaesth 2010; **104**: 75–79.

154 Hwang PS, Ma ML, Spiegelberg N, Ferland CE. Current
methodological approaches in conditioned pain modulation
assessment in pediatrics. *J Pain Res* 2017; **10**: 2797–802.

155 Yarnitsky D. Role of endogenous pain modulation in chronic pain
mechanisms and treatment. *Pain* 2015; **156** (suppl 1): S24–31.

156 Tsao JC, Seidman LC, Evans S, Lung KC, Zeltzer LK, Naliboff BD.
Conditioned pain modulation in children and adolescents: effects
of sex and age. *J Pain* 2013; **14**: 558–67.

157 Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice AS. Reliability
of conditioned pain modulation: a systematic review. *Pain* 2016;
157: 2410–19.

158 Nahman-Averbuch H, Leon E, Hunter BM, et al. Increased pain
sensitivity but normal pain modulation in adolescents with
migraine. *Pain* 2019; **160**: 1019–28.

159 Pas R, Rheel E, Van Oosterwijck S, et al. Endogenous pain
modulation in children with functional abdominal pain disorders.
Pain 2019; **160**: 1883–90.

160 Walker LS, Sherman AL, Bruehl S, Garber J, Smith CA. Functional
abdominal pain patient subtypes in childhood predict functional
gastrointestinal disorders with chronic pain and psychiatric
comorbidities in adolescence and adulthood. *Pain* 2012;
153: 1798–806.

161 Petersen KK, Graven-Nielsen T, Simonsen O, Laursen MB,
Arendt-Nielsen L. Preoperative pain mechanisms assessed by cuff
algometry are associated with chronic postoperative pain relief after
total knee replacement. *Pain* 2016; **157**: 1400–06.

162 Teles AR, Ocay DD, Bin Shebreen A, et al. Evidence of impaired
pain modulation in adolescents with idiopathic scoliosis and
chronic back pain. *Spine J* 2019; **19**: 677–86.

163 Honigman L, Yarnitsky D, Sprecher E, Weissman-Fogel I.
Psychophysical testing of spatial and temporal dimensions of
endogenous analgesia: conditioned pain modulation and offset
analgesia. *Exp Brain Res* 2013; **228**: 493–501.

164 Nahman-Averbuch H, Martucci KT, Granovsky Y, Weissman-Fogel I,
Yarnitsky D, Coghill RC. Distinct brain mechanisms support spatial
vs temporal filtering of nociceptive information. *Pain* 2014;
155: 2491–501.

165 Treede RD. The role of quantitative sensory testing in the prediction
of chronic pain. *Pain* 2019; **160** (suppl 1): S66–69.

166 Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory
testing: a comprehensive protocol for clinical trials. *Eur J Pain* 2006;
10: 77–88.

167 Baron R, Maier C, Attal N, et al. Peripheral neuropathic pain:
a mechanism-related organizing principle based on sensory
profiles. *Pain* 2017; **158**: 261–72.

168 Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain.
Nat Rev Dis Primers 2017; **3**: 17002.

169 Heathcote LC, Timmers I, Kronman CA, et al. Brain signatures of
threat-safety discrimination in adolescent chronic pain. *Pain* 2020;
161: 630–40.

170 Timmers I, Quaedflieg CWEM, Hsu C, Heathcote LC,
Rovnaghi CR, Simons LE. The interaction between stress and
chronic pain through the lens of threat learning.
Neurosci Biobehav Rev 2019; **107**: 641–55.

171 Erpelding N, Simons L, Lebel A, et al. Rapid treatment-induced
brain changes in pediatric CRPS. *Brain Struct Funct* 2016;
221: 1095–111.

172 Youssef AM, Azqueta-Gavaldon M, Silva KE, et al. Shifting brain
circuits in pain chronicity. *Hum Brain Mapp* 2019; **40**: 4381–96.

173 Simons LE, Pielech M, Erpelding N, et al. The responsive
amygdala: treatment-induced alterations in functional connectivity
in pediatric complex regional pain syndrome. *Pain* 2014;
155: 1727–42.

174 Simons LE, Erpelding N, Hernandez JM, et al. Fear and reward
circuit alterations in pediatric CRPS. *Front Hum Neurosci* 2016; **9**: 703.

175 Becerra L, Sava S, Simons LE, et al. Intrinsic brain networks
normalize with treatment in pediatric complex regional pain
syndrome. *Neuroimage Clin* 2014; **6**: 347–69.

176 Erpelding N, Sava S, Simons LE, et al. Habenula functional resting-
state connectivity in pediatric CRPS. *J Neurophysiol* 2014; **111**: 239–47.

177 Hill RM, Boto E, Holmes N, et al. A tool for functional brain imaging
with lifespan compliance. *Nat Commun* 2019; **10**: 4785.

178 Baxter L, Fitzgibbon S, Moultrie F, et al. Optimising neonatal fMRI
data analysis: design and validation of an extended dHCP
preprocessing pipeline to characterise noxious-evoked brain
activity in infants. *Neuroimage* 2019; **186**: 286–300.

179 Alshelh Z, Di Pietro F, Youssef AM, et al. Chronic neuropathic pain:
it's about the rhythm. *J Neurosci* 2016; **36**: 1008–18.

180 Walton KD, Dubois M, Llinás RR. Abnormal thalamocortical activity
in patients with Complex Regional Pain Syndrome (CRPS) type I.
Pain 2010; **150**: 41–51.

181 Vachon-Presseau E, Tétreault P, Petre B, et al. Corticolimbic
anatomical characteristics predetermine risk for chronic pain. *Brain*
2016; **139**: 1958–70.

182 Kettenmann H, Kirchhoff F, Verkhratsky A. Microglia: new roles for the synaptic stripper. *Neuron* 2013; **77:** 10–18.

183 Salter MW, Stevens B. Microglia emerge as central players in brain disease. *Nat Med* 2017; **23:** 1018–27.

184 Hanamsagar R, Alter MD, Block CS, Sullivan H, Bolton JL, Bilbo SD. Generation of a microglial developmental index in mice and in humans reveals a sex difference in maturation and immune reactivity. *Glia* 2017; **65:** 1504–20.

185 Zouikr I, Karshikoff B. Lifetime modulation of the pain system via neuroimmune and neuroendocrine interactions. *Front Immunol* 2017; **8:** 276.

186 Burke NN, Fan CY, Trang T. Microglia in health and pain: impact of noxious early life events. *Exp Physiol* 2016; **101:** 1003–21.

187 Hanamsagar R, Bilbo SD. Environment matters: microglia function and dysfunction in a changing world. *Curr Opin Neurobiol* 2017; **47:** 146–55.

188 Nelson LH, Saulsbery AI, Lenz KM. Small cells with big implications: microglia and sex differences in brain development, plasticity and behavioral health. *Prog Neurobiol* 2019; **176:** 103–19.

189 Perry VH, Holmes C. Microglial priming in neurodegenerative disease. *Nat Rev Neurol* 2014; **10:** 217–24.

190 Riggenbach A, Goubert L, Van Petegem S, Amouroux R. Topical review: basic psychological needs in adolescents with chronic pain-a self-determination perspective. *Pain Res Manag* 2019; **2019:** 8629581.

191 Casale R, Sarzi-Puttini P, Botto R, et al. Fibromyalgia and the concept of resilience. *Clin Exp Rheumatol* 2019; **37** (suppl 116)**:** 105–13.

192 Daviu N, Bruchas MR, Moghaddam B, Sandi C, Beyeler A. Neurobiological links between stress and anxiety. *Neurobiol Stress* 2019; **11:** 100191.

193 Jennings EM, Okine BN, Roche M, Finn DP. Stress-induced hyperalgesia. *Prog Neurobiol* 2014; **121:** 1–18.

194 Doria V, Beckmann CF, Arichi T, et al. Emergence of resting state networks in the preterm human brain. *Proc Natl Acad Sci USA* 2010; **107:** 20015–20.

195 Rizvi SJ, Iskric A, Calati R, Courtet P. Psychological and physical pain as predictors of suicide risk: evidence from clinical and neuroimaging findings. *Curr Opin Psychiatry* 2017; **30:** 159–67.

196 Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018; **67:** 1001–06.

197 Davis MT, Holmes SE, Pietrzak RH, Esterlis I. Neurobiology of chronic stress-related psychiatric disorders: evidence from molecular imaging studies. *Chronic Stress (Thousand Oaks)* 2017; **1:** 2470547017710916.

198 Jones L, Fabrizi L, Laudiano-Dray M, et al. Nociceptive cortical activity is dissociated from nociceptive behavior in newborn human infants under stress. *Curr Biol* 2017; **27:** 3846–51.

199 Wollgarten-Hadamek I, Hohmeister J, Zohsel K, Flor H, Hermann C. Do school-aged children with burn injuries during infancy show stress-induced activation of pain inhibitory mechanisms? *Eur J Pain* 2011; **15:** 423.e1–10.

200 Nemeroff CB. Paradise lost: the neurobiological and clinical consequences of child abuse and neglect. *Neuron* 2016; **89:** 892–909.

201 Burke NN, Finn DP, McGuire BE, Roche M. Psychological stress in early life as a predisposing factor for the development of chronic pain: clinical and preclinical evidence and neurobiological mechanisms. *J Neurosci Res* 2017; **95:** 1257–70.

202 McKillop HN, Banez GA. A broad consideration of risk factors in pediatric chronic pain: where to go from here? *Children (Basel)* 2016; **3:** 38.

203 McLoyd VC. Socioeconomic disadvantage and child development. *Am Psychol* 1998; **53:** 185–204.

204 Oral R, Ramirez M, Coohey C, et al. Adverse childhood experiences and trauma informed care: the future of health care. *Pediatr Res* 2016; **79:** 227–33.

205 Mulvaney S, Lambert EW, Garber J, Walker LS. Trajectories of symptoms and impairment for pediatric patients with functional abdominal pain: a 5-year longitudinal study. *J Am Acad Child Adolesc Psychiatry* 2006; **45:** 737–44.

206 Helgeland H, Sandvik L, Mathiesen KS, Kristensen H. Childhood predictors of recurrent abdominal pain in adolescence: a 13-year population-based prospective study. *J Psychosom Res* 2010; **68:** 359–67.

207 Boyce WT, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Dev Psychopathol* 2005; **17:** 271–301.

208 Harder HJ, Murphy AZ. Early life opioid exposure and potential long-term effects. *Neurobiol Stress* 2019; **10:** 100156.

209 Kentner AC, Cryan JF, Brummelte S. Resilience priming: translational models for understanding resiliency and adaptation to early life adversity. *Dev Psychobiol* 2019; **61:** 350–75.

210 Targum SD, Nemeroff CB. The effect of early life stress on adult psychiatric disorders. *Innov Clin Neurosci* 2019; **16:** 35–37.

211 Walker SM. Translational studies identify long-term impact of prior neonatal pain experience. *Pain* 2017; **158** (suppl 1)**:** S29–42.

212 Sieberg CB, Taras C, Gomaa A, et al. Neuropathic pain drives anxiety behavior in mice, results consistent with anxiety levels in diabetic neuropathy patients. *Pain Rep* 2018; **3:** e651.

213 Shin A, Preidis GA, Shulman R, Kashyap PC. The gut microbiome in adult and pediatric functional gastrointestinal disorders. *Clin Gastroenterol Hepatol* 2019; **17:** 256–74.

214 O' Mahony SM, Dinan TG, Cryan JF. The gut microbiota as a key regulator of visceral pain. *Pain* 2017; **158** (suppl 1)**:** S19–28.

215 Norbury TA, MacGregor AJ, Urwin J, Spector TD, McMahon SB. Heritability of responses to painful stimuli in women: a classical twin study. *Brain* 2007; **130:** 3041–49.

216 Kerr JI, Burri A. Genetic and epigenetic epidemiology of chronic widespread pain. *J Pain Res* 2017; **10:** 2021–29.

217 Zorina-Lichtenwalter K, Meloto CB, Khoury S, Diatchenko L. Genetic predictors of human chronic pain conditions. *Neuroscience* 2016; **338:** 36–62.

218 Packiasabapathy S, Horn N, Sadhasivam S. Genetics of perioperative pain management. *Curr Opin Anaesthesiol* 2018; **31:** 749–55.

219 Bullock D, Jesuthasan A, González-Cano R, Costigan M. Reading and writing: the evolution of molecular pain genetics. *Pain* 2019; **160:** 2177–85.

220 Bennett DL, Clark AJ, Huang J, Waxman SG, Dib-Hajj SD. The role of voltage-gated sodium channels in pain signaling. *Physiol Rev* 2019; **99:** 1079–151.

221 Arthur L, Keen K, Verriotis M, et al. Pediatric erythromelalgia and SCN9A mutations: systematic review and single-center case series. *J Pediatr* 2019; **206:** 217–24 e9.

222 Germain DP, Fouilhoux A, Decramer S, et al. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. *Clin Genet* 2019; **96:** 107–17.

223 Spada M, Baron R, Elliott PM, et al. The effect of enzyme replacement therapy on clinical outcomes in paediatric patients with Fabry disease—a systematic literature review by a European panel of experts. *Mol Genet Metab* 2019; **126:** 212–23.

224 Howard RF, Wiener S, Walker SM. Neuropathic pain in children. *Arch Dis Child* 2014; **99:** 84–89.

225 Tuscher JJ, Day JJ. Multigenerational epigenetic inheritance: one step forward, two generations back. *Neurobiol Dis* 2019; **132:** 104591.

226 Provenzi L, Guida E, Montirosso R. Preterm behavioral epigenetics: a systematic review. *Neurosci Biobehav Rev* 2018; **84:** 262–71.

227 Miguel PM, Pereira LO, Silveira PP, Meaney MJ. Early environmental influences on the development of children's brain structure and function. *Dev Med Child Neurol* 2019; **61:** 1127–33.

228 Bai G, Ren K, Dubner R. Epigenetic regulation of persistent pain. *Transl Res* 2015; **165:** 177–99.

229 Chidambaran V, Zhang X, Geisler K, et al. Enrichment of genomic pathways based on differential DNA methylation associated with chronic postsurgical pain and anxiety in children: a prospective, pilot study. *J Pain* 2019; **20:** 771–85.

230 Niederberger E, Resch E, Parnham MJ, Geisslinger G. Drugging the pain epigenome. *Nat Rev Neurol* 2017; **13:** 434–47.

231 Dennis CH, Clohessy DS, Stone AL, Darnall BD, Wilson AC. Adverse childhood experiences in mothers with chronic pain and intergenerational impact on children. *J Pain* 2019; **20:** 1209–17.

232 Beveridge JK, Neville A, Wilson AC, Noel M. Intergenerational examination of pain and posttraumatic stress disorder symptoms among youth with chronic pain and their parents. *Pain Reports* 2018; **3** (suppl 1)**:** e667.

233 Stone AL, Wilson AC. Transmission of risk from parents with chronic pain to offspring: an integrative conceptual model. *Pain* 2016; **157:** 2628–39.

234 Lakoff G, Johnson M. Metaphors we live by. Chicago: University of Chicago Press, 2008.

235 Hoftun GB, Romundstad PR, Rygg M. Association of parental chronic pain with chronic pain in the adolescent and young adult: family linkage data from the HUNT Study. *JAMA Pediatr* 2013; **167:** 61–69.

236 Fisher E, Caes L, Clinch J, Tobias JH, Eccleston C. Anxiety at 13 and its effect on pain, pain-related anxiety, and pain-related disability at 17: an ALSPAC cohort longitudinal analysis. *Psychol Health Med* 2016; **21:** 1–9.

237 Golding J, Pembrey M, Jones R. The ALSPAC Study Team ALSPAC–the avon longitudinal study of parents and children. *Paediatr Perinat Epidemiol* 2001; **15:** 74–87.

238 Birnie KA, Hundert AS, Lalloo C, Nguyen C, Stinson JN. Recommendations for selection of self-report pain intensity measures in children and adolescents: a systematic review and quality assessment of measurement properties. *Pain* 2019; **160:** 5–18.

239 Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001; **39:** 800–12.

240 Earp BD, Monrad JT, LaFrance M, Bargh JA, Cohen LL, Richeson JA. Featured article: gender bias in pediatric pain assessment. *J Pediatr Psychol* 2019; **44:** 403–14.

241 Vlaeyen JW, Hanssen M, Goubert L, et al. Threat of pain influences social context effects on verbal pain report and facial expression. *Behav Res Ther* 2009; **47:** 774–82.

242 Hemmingsson H, Ólafsdóttir LB, Egilson ST. Agreements and disagreements between children and their parents in health-related assessments. *Disabil Rehabil* 2017; **39:** 1059–72.

243 von Baeyer CL, Spagrud LJ. Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. *Pain* 2007; **127:** 140–50.

244 Bellieni CV. Pain assessment in human fetus and infants. *AAPS J* 2012; **14:** 456–61.

245 Beltramini A, Milojevic K, Pateron D. Pain assessment in newborns, infants, and children. *Pediatr Ann* 2017; **46:** e387–95.

246 Srouji R, Ratnapalan S, Schneeweiss S. Pain in children: assessment and nonpharmacological management. *Int J Pediat* 2010; **2010:** 474838.

247 Mathew PJ, Mathew JL. Assessment and management of pain in infants. *Postgrad Med J* 2003; **79:** 438–43.

248 Meesters N, Dilles T, Simons S, van Dijk M. Do pain measurement instruments detect the effect of pain-reducing interventions in neonates? A systematic review on responsiveness. *J Pain* 2019; **20:** 760–70.

249 Roué J-M, Rioualen S, Gendras J, Misery L, Gouillou M, Sizun J. Multi-modal pain assessment: are near-infrared spectroscopy, skin conductance, salivary cortisol, physiologic parameters, and neonatal facial coding system interrelated during venepuncture in healthy, term neonates? *J Pain Res* 2018; **11:** 2257–67.

250 van der Vaart M, Duff E, Raafat N, Rogers R, Hartley C, Slater R. Multimodal pain assessment improves discrimination between noxious and non-noxious stimuli in infants. *Paediatr Neonatal Pain* 2019; **1:** 21–30.

251 Moultrie F, Slater R, Hartley C. Improving the treatment of infant pain. *Curr Opin Support Palliat Care* 2017; **11:** 112–17.

252 Pillai Riddell R, Racine N. Assessing pain in infancy: the caregiver context. *Pain Res Manag* 2009; **14:** 27–32.

253 Slater R, Cantarella A, Yoxen J, et al. Latency to facial expression change following noxious stimulation in infants is dependent on postmenstrual age. *Pain* 2009; **146:** 177–82.

254 Gibbins S, Stevens B, McGrath PJ, et al. Comparison of pain responses in infants of different gestational ages. *Neonatology* 2008; **93:** 10–18.

255 Stevens B, McGrath P, Gibbins S, et al. Determining behavioural and physiological responses to pain in infants at risk for neurological impairment. *Pain* 2007; **127:** 94–102.

256 Veirman E, Van Ryckeghem DML, De Paepe A, Kirtley OJ, Crombez G. Multidimensional screening for predicting pain problems in adults: a systematic review of screening tools and validation studies. *Pain Rep* 2019; **4:** e775.

257 Karran EL, McAuley JH, Traeger AC, et al. Can screening instruments accurately determine poor outcome risk in adults with recent onset low back pain? A systematic review and meta-analysis. *BMC Med* 2017; **15:** 13.

258 Steyerberg E. Clinical prediction models: a practical approach to development, validation, and updating (statistics for biology and health). New York: Springer, 2009.

259 Steyerberg EW, Moons KG, van der Windt DA, et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med* 2013; **10:** e1001381.

260 Simons LE, Smith A, Ibagon C, et al. Pediatric pain screening tool: rapid identification of risk in youth with pain complaints. *Pain* 2015; **156:** 1511–18.

261 Hay EM, Dunn KM, Hill JC, et al. A randomised clinical trial of subgrouping and targeted treatment for low back pain compared with best current care. The STarT Back Trial Study Protocol. *BMC Musculoskelet Disord* 2008; **9:** 58.

262 Heathcote LC, Rabner J, Lebel A, Hernandez JM, Simons LE. Rapid screening of risk in pediatric headache: application of the pediatric pain screening tool. *J Pediatr Psychol* 2018; **43:** 243–51.

263 Sil S, Cohen LL, Dampier C. Pediatric pain screening identifies youth at risk of chronic pain in sickle cell disease. *Pediatr Blood Cancer* 2019; **66:** e27538.

264 Eccleston C, Jordan AL, Crombez G. The impact of chronic pain on adolescents: a review of previously used measures. *J Pediatr Psychol* 2006; **31:** 684–97.

265 Fisher E, Heathcote LC, Eccleston C, Simons LE, Palermo TM. Assessment of pain anxiety, pain catastrophizing, and fear of pain in children and adolescents with chronic pain: a systematic review and meta-analysis. *J Pediatr Psychol* 2018; **43:** 314–25.

266 Lewandowski AS, Toliver-Sokol M, Palermo TM. Evidence-based review of subjective pediatric sleep measures. *J Pediatr Psychol* 2011; **36:** 780–93.

267 von Baeyer CL, Jaaniste T, Vo HLT, Brunsdon G, Lao H-C, Champion GD. Systematic review of self-report measures of pain intensity in 3-and 4-year-old children: bridging a period of rapid cognitive development. *J Pain* 2017; **18:** 1017–26.

268 Zeevenhooven J, Timp ML, Singendonk MM, Benninga MA, Tabbers MM. Definitions of pediatric functional abdominal pain disorders and outcome measures: a systematic review. *J Pediatr* 2019; **212:** 52–59.

269 McGrath PJ, Walco GA, Turk DC, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. *J Pain* 2008; **9:** 771–83.

270 Boric K, Jelicic Kadic A, Boric M, et al. Outcome domains and pain outcome measures in randomized controlled trials of interventions for postoperative pain in children and adolescents. *Eur J Pain* 2019; **23:** 389–96.

271 Connelly M, Schanberg LE, Ardoin S, et al. Multisite randomized clinical trial evaluating an online self-management program for adolescents with juvenile idiopathic arthritis. *J Pediatr Psychol* 2019; **44:** 363–74.

272 Birnie KA, Ouellette C, Do Amaral T, Stinson JN. Mapping the evidence and gaps of interventions for pediatric chronic pain to inform policy, research, and practice: a systematic review and quality assessment of systematic reviews. *Can J Pain* 2020; **4:** 129–48.

273 Boers M, Kirwan JR, Wells G, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014; **67:** 745–53.

274 Morgan EM, Munro JE, Horonjeff J, et al. Establishing an updated core domain set for studies in juvenile idiopathic arthritis: a report from the OMERACT 2018 JIA Workshop. *J Rheumatol* 2019; **46:** 1006–13.

275 Prinsen CA, Vohra S, Rose MR, et al. How to select outcome measurement instruments for outcomes included in a "core outcome set"—a practical guideline. *Trials* 2016; **17:** 449.

276 Broderick JE, DeWitt EM, Rothrock N, Crane PK, Forrest CB. Advances in patient-reported outcomes: the NIH PROMIS® measures. *EGEMS* 2013; **1:** 1015.

277 Cunningham NR, Kashikar-Zuck S, Mara C, et al. Development and validation of the self-reported PROMIS pediatric pain behavior item bank and short form scale. *Pain* 2017; **158:** 1323–31.

278 Kashikar-Zuck S, Carle A, Barnett K, et al. Longitudinal evaluation of patient-reported outcomes measurement information systems measures in pediatric chronic pain. *Pain* 2016; **157:** 339–47.

279 Bhandari RP, Feinstein AB, Huestis SE, et al. Pediatric-Collaborative Health Outcomes Information Registry (Peds-CHOIR): a learning health system to guide pediatric pain research and treatment. *Pain* 2016; **157:** 2033–44.

280 Stone AA, Schwartz JE, Broderick JE, Shiffman SS. Variability of momentary pain predicts recall of weekly pain: a consequence of the peak (or salience) memory heuristic. *Pers Soc Psychol Bull* 2005; **31:** 1340–46.

281 Mulvaney SA, Vaala SE, Carroll RB, et al. A mobile app identifies momentary psychosocial and contextual factors related to mealtime self-management in adolescents with type 1 diabetes. *J Am Med Inform Assoc* 2019; **26:** 1627–31.

282 Law EF, Wan Tham S, Aaron RV, Dudeney J, Palermo TM. Hybrid cognitive-behavioral therapy intervention for adolescents with co-occurring migraine and insomnia: a single-arm pilot trial. *Headache* 2018; **58:** 1060–73.

283 Palermo TM, Law EF, Fales J, Bromberg MH, Jessen-Fiddick T, Tai G. Internet-delivered cognitive-behavioral treatment for adolescents with chronic pain and their parents: a randomized controlled multicenter trial. *Pain* 2016; **157:** 174–85.

284 Xu X, Craig KD, Diaz D, et al. Automated pain detection in facial videos of children using human-assisted transfer learning. *CEUR Workshop Proc* 2018; **2142:** 10–21.

285 Tran ST, Thomas S, DiCesare C, et al. A pilot study of biomechanical assessment before and after an integrative training program for adolescents with juvenile fibromyalgia. *Pediatr Rheumatol Online J* 2016; **14:** 43.

286 Asparouhov T, Hamaker EL, Muthén B. Dynamic structural equation models. *Struct Equ Modeling* 2018; **25:** 359–88.

287 Rimé B, Bouchat P, Paquot L, Giglio L. Intrapersonal, interpersonal, and social outcomes of the social sharing of emotion. *Curr Opin Psychol* 2020; **31:** 127–34.

288 Salsburg D. The lady tasting tea: how statistics revolutionized science in the twentieth century. New York: Macmillan, 2001.

289 Park ES, Cho IY. Shared decision-making in the paediatric field: a literature review and concept analysis. *Scand J Caring Sci* 2018; **32:** 478–89.

290 von Baeyer CL. Children's self-reports of pain intensity: scale selection, limitations and interpretation. *Pain Res Manag* 2006; **11:** 157–62.

291 Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA* 2014; **312:** 1033–48.

292 Di Lorenzo C, Colletti RB, Lehmann HP, Boyle JT, Gerson WT. Chronic abdominal pain in children. *Pediatrics* 2005; **115:** 812–15.

293 Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American pain society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' committee on regional anesthesia, executive committee, and administrative council. *J Pain* 2016; **17:** 131–57.

294 Howard R, Carter B, Curry J, et al. Good practice in postoperative and procedural pain management. *Paediatr Anaesth* 2008; **18** (suppl 1): 1–3.

295 Schug S, Palmer G, Scott D, Halliwell R, Trinca J. Acute pain management: scientific evidence, 4th edn. Melbourne: Australian and New Zealand College of Anaesthetists, 2015.

296 Abbott RA, Martin AE, Newlove-Delgado TV, et al. Psychosocial interventions for recurrent abdominal pain in childhood. *Cochrane Database Syst Rev* 2017; **1:** CD010971.

297 Birnie KA, Noel M, Chambers CT, Uman LS, Parker JA. Psychological interventions for needle-related procedural pain and distress in children and adolescents. *Cochrane Database Syst Rev* 2018; **10:** CD005179.

298 Fisher E, Law E, Dudeney J, Palermo TM, Stewart G, Eccleston C. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database Syst Rev* 2018; **9:** CD003968.

299 Lalloo C, Shah U, Birnie KA, et al. Commercially available smartphone apps to support postoperative pain self-management: scoping review. *JMIR Mhealth Uhealth* 2017; **5:** e162.

300 Palermo TM, Law EF, Bromberg M, Fales J, Eccleston C, Wilson AC. Problem-solving skills training for parents of children with chronic pain: a pilot randomized controlled trial. *Pain* 2016; **157:** 1213–23.

301 Wicksell RK, Kanstrup M, Kemani MK, Holmström L, Olsson GL. Acceptance and commitment therapy for children and adolescents with physical health concerns. *Curr Opin Psychol* 2015; **2:** 1–5.

302 Abujaradeh H, Safadi R, Sereika SM, Kahle CT, Cohen SM. Mindfulness-based interventions among adolescents with chronic diseases in clinical settings: a systematic review. *J Pediatr Health Care* 2018; **32:** 455–72.

303 Noel M, McMurtry CM, Pavlova M, Taddio A. Brief clinical Report: a systematic review and meta-analysis of pain memory-reframing interventions for children's needle procedures. *Pain Pract* 2018; **18:** 123–29.

304 Palermo TM, Slack K, Loren D, Eccleston C, Jamison RN. Measuring and reporting adverse events in clinical trials of psychological treatments for chronic pain. *Pain* 2019; **161:** 713–17.

305 Harrison D, Reszel J, Bueno M, et al. Breastfeeding for procedural pain in infants beyond the neonatal period. *Cochrane Database Syst Rev* 2016; **10:** CD011248.

306 Taddio A, Shah V, McMurtry CM, et al. Procedural and physical interventions for vaccine injections: systematic review of randomized controlled trials and quasi-randomized controlled trials. *Clin J Pain* 2015; **31** (suppl): S20–37.

307 Pillai Riddell RR, Racine NM, Gennis HG, et al. Non-pharmacological management of infant and young child procedural pain. *Cochrane Database Syst Rev* 2015; **12:** CD006275.

308 Johnston C, Campbell-Yeo M, Disher T, et al. Skin-to-skin care for procedural pain in neonates. *Cochrane Database Syst Rev* 2017; **2:** CD008435.

309 Kashikar-Zuck S, Black WR, Pfeiffer M, et al. Pilot randomized trial of integrated cognitive-behavioral therapy and neuromuscular training for juvenile fibromyalgia: the FIT teens program. *J Pain* 2018; **19:** 1049–62.

310 Kichline T, Cushing CC. A systematic review and quantitative analysis on the impact of aerobic exercise on pain intensity in children with chronic pain. *Child Health Care* 2019; **48:** 244–61.

311 Vance CG, Dailey DL, Rakel BA, Sluka KA. Using TENS for pain control: the state of the evidence. *Pain Manag* 2014; **4:** 197–209.

312 Gibson W, Wand BM, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults. *Cochrane Database Syst Rev* 2017; **9:** CD011976.

313 Ferro MA, Speechley KN. Complementary and alternative medicine use in juvenile idiopathic arthritis: a systematic review of prevalence and evidence. *J Complement Integr Med* 2008; **5:** 33.

314 Tsao JC, Zeltzer LK. Complementary and alternative medicine approaches for pediatric pain: a review of the state-of-the-science. *Evid Based Complement Alternat Med* 2005; **2:** 149–59.

315 Robins H, Perron V, Heathcote LC, Simons LE. Pain neuroscience education: state of the art and application in pediatrics. *Children (Basel)* 2016; **3:** E43.

316 Liossi C, Johnstone L, Lilley S, Caes L, Williams G, Schoth DE. Effectiveness of interdisciplinary interventions in paediatric chronic pain management: a systematic review and subset meta-analysis. *Br J Anaesth* 2019; **123:** e359–71.

317 Scottish Intercollegiate Guidelines Network. Guideline management of chronic pain in children and young people: a national clinical guideline. Edinburgh, UK: Scottish Intercollegiate Guidelines Network, 2018.

318 Cooper TE, Fisher E, Anderson B, Wilkinson NM, Williams DG, Eccleston C. Paracetamol (acetaminophen) for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev* 2017; **8:** CD012539.

319 Shah V, Taddio A, McMurtry CM, et al. Pharmacological and combined interventions to reduce vaccine injection pain in children and adults: systematic review and meta-analysis. *Clin J Pain* 2015; **31** (suppl): S38–63.

320 Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev* 2016; **7:** CD001069.

321 Cooper TE, Heathcote LC, Anderson B, Grégoire MC, Ljungman G, Eccleston C. Non-steroidal anti-inflammatory drugs (NSAIDs) for cancer-related pain in children and adolescents. *Cochrane Database Syst Rev* 2017; **7:** CD012563.

322 Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NM. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev* 2017; **8:** CD012537.

323 Cooper TE, Wiffen PJ, Heathcote LC, et al. Antiepileptic drugs for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev* 2017; **8:** CD012536.

324 Egunsola O, Wylie CE, Chitty KM, Buckley NA. Systematic review of the efficacy and safety of gabapentin and pregabalin for pain in children and adolescents. *Anesth Analg* 2019; **128:** 811–19.

325 Cooper TE, Heathcote LC, Clinch J, et al. Antidepressants for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev* 2017; **8:** CD012535.

326 Cooper TE, Fisher E, Gray AL, et al. Opioids for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev* 2017; **7:** CD012538.

327 Cravero JP, Agarwal R, Berde C, et al. The Society for Pediatric Anesthesia recommendations for the use of opioids in children during the perioperative period. *Paediatr Anaesth* 2019; **29:** 547–71.

328 Wiffen PJ, Cooper TE, Anderson AK, et al. Opioids for cancer-related pain in children and adolescents. *Cochrane Database Syst Rev* 2017; **7:** CD012564.

329 Eccleston C, Fisher E, Cooper TE, et al. Pharmacological interventions for chronic pain in children: an overview of systematic reviews. *Pain* 2019; **160:** 1698–707.

330 Shah RD, Cappiello D, Suresh S. Interventional procedures for chronic pain in children and adolescents: a review of the current evidence. *Pain Pract* 2016; **16:** 359–69.

331 Berde CB, Sethna NF. Analgesics for the treatment of pain in children. *N Engl J Med* 2002; **347:** 1094–103.

332 Birnie KA, Dib K, Ouellette C, et al. Partnering for pain: a priority setting partnership to identify patient-oriented research priorities for pediatric chronic pain in Canada. *CMAJ* 2019; **7:** E654.

333 Liossi C, Anderson AK, Howard RF. Development of research priorities in paediatric pain and palliative care. *Br J Pain* 2017; **11:** 9–15.

334 Anderson BJ, Thomas J, Ottaway K, Chalkiadis GA. Tramadol: keep calm and carry on. *Paediatr Anaesth* 2017; **27:** 785–88.

335 Palmer GM, Anderson BJ, Linscott DK, Paech MJ, Allegaert K. Tramadol, breast feeding and safety in the newborn. *Arch Dis Child* 2018; **103:** 1110–13.

336 Racoosin JA, Roberson DW, Pacanowski MA, Nielsen DR. New evidence about an old drug—risk with codeine after adenotonsillectomy. *N Engl J Med* 2013; **368:** 2155–57.

337 Voelker R. Children's deaths linked with postsurgical codeine. *JAMA* 2012; **308:** 963.

338 US Food and Drug Administration. FDA drug safety communication: FDA requires labeling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older. 2018. https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-drug-safety-podcast-fda-requires-labeling-changes-prescription-opioid-cough-and-cold-medicines#:~:text=On%20January%2011%2C%202018%2C%20FDA,in%20children%20younger%20than%2018 (accessed Sept 15, 2020).

339 Herting E, Härtel C, Göpel W. Less invasive surfactant administration (LISA): chances and limitations. *Arch Dis Child Fetal Neonatal Ed* 2019; **104:** F655–59.

340 De Luca D, Shankar-Aguilera S, Centorrino R, Fortas F, Yousef N, Carnielli VP. Less invasive surfactant administration: a word of caution. *Lancet Child Adolesc Health* 2020; **4:** 331–40.

341 Dekker J, Lopriore E, van Zanten HA, Tan RNGB, Hooper SB, Te Pas AB. Sedation during minimal invasive surfactant therapy: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2019; **104:** F378–83.

342 Stinson J, Ahola Kohut S, Forgeron P, et al. The iPeer2Peer Program: a pilot randomized controlled trial in adolescents with juvenile idiopathic arthritis. *Pediatr Rheumatol Online J* 2016; **14:** 48.

343 Barrera M. Brief clinical report: procedural pain and anxiety management with mother and sibling as co-therapists. *J Pediatr Psychol* 2000; **25:** 117–21.

344 Rabbitts JA, Fisher E, Rosenbloom BN, Palermo TM. Prevalence and predictors of chronic postsurgical pain in children: a systematic review and meta-analysis. *J Pain* 2017; **18:** 605–14.

345 Kossowsky J, Donado C, Berde CB. Immediate rescue designs in pediatric analgesic trials: a systematic review and meta-analysis. *Anesthesiology* 2015; **122:** 150–71.

346 Higgins JP, Altman DG. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. London, UK: Cochrane, 2011: 1–73.

347 Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ* 2015; **350:** h391.

348 Lobo MA, Moeyaert M, Baraldi Cunha A, Babik I. Single-case design, analysis, and quality assessment for intervention research. *J Neurol Phys Ther* 2017; **41:** 187–97.

349 Simons LE, Vlaeyen JWS, Declercq L, et al. Avoid or engage? Outcomes of graded exposure in youth with chronic pain using a sequential replicated single-case randomized design. *Pain* 2020; **161:** 520–31.

350 Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014; **348:** g1687.

351 Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care* 2012; **50:** 217–26.

352 Boutron I, Ravaud P. Misrepresentation and distortion of research in biomedical literature. *Proc Natl Acad Sci USA* 2018; **115:** 2613–19.

353 Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343:** d5928.

354 Moore RA, Gavaghan D, Tramèr MR, Collins SL, McQuay HJ. Size is everything—large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998; **78:** 209–16.

355 Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ* 2013; **346:** f2304.

356 Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; **64:** 383–94.

357 Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; **64:** 401–06.

358 Hill AV. The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. *J Physiol* 1910; **40:** 4–7.

359 Hannam JA, Anderson BJ, Potts A. Acetaminophen, ibuprofen, and tramadol analgesic interactions after adenotonsillectomy. *Paediatr Anaesth* 2018; **28:** 841–51.

360 Hannam JA, Anderson BJ, Mahadevan M, Holford NH. Postoperative analgesia using diclofenac and acetaminophen in children. *Paediatr Anaesth* 2014; **24:** 953–61.

361 Holford NH. The target concentration approach to clinical drug development. *Clin Pharmacokinet* 1995; **29:** 287–91.

362 Ceelie I, de Wildt SN, van Dijk M, et al. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. *JAMA* 2013; **309:** 149–54.

363 Palomaki GE, Bradley LA, Douglas MP, Kolor K, Dotson WD. Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review. *Genet Med* 2009; **11:** 21–34.

364 Allegaert K, Holford N, Anderson BJ, et al. Tramadol and o-desmethyl tramadol clearance maturation and disposition in humans: a pooled pharmacokinetic study. *Clin Pharmacokinet* 2015; **54:** 167–78.

365 Anderson BJ, van den Anker J. Why is there no morphine concentration-response curve for acute pain? *Paediatr Anaesth* 2014; **24:** 233–38.

366 Cunningham NR, Nelson S, Jagpal A, et al. Development of the Aim to Decrease Anxiety and Pain Treatment (ADAPT) for pediatric functional abdominal pain disorders. *J Pediatr Gastroenterol Nutr* 2018; **66:** 16–20.

367 Chow ET, Otis JD, Simons LE. The longitudinal impact of parent distress and behavior on functional outcomes among youth with chronic pain. *J Pain* 2016; **17:** 729–38.

368 Law EF, Fisher E, Howard WJ, Levy R, Ritterband L, Palermo TM. Longitudinal change in parent and child functioning after internet-delivered cognitive-behavioral therapy for chronic pain. *Pain* 2017; **158:** 1992–2000.

369 Levy RL, Langer SL, van Tilburg MA, et al. Brief telephone-delivered cognitive behavioral therapy targeted to parents of children with functional abdominal pain: a randomized controlled trial. *Pain* 2017; **158:** 618–28.

370 Rini C, Porter LS, Somers TJ, et al. Automated Internet-based pain coping skills training to manage osteoarthritis pain: a randomized controlled trial. *Pain* 2015; **156:** 837–48.

371 Won AS, Bailey J, Bailenson J, Tataru C, Yoon IA, Golianu B. Immersive virtual reality for pediatric pain. *Children (Basel)* 2017; **4:** 52.

372 Fisher E, Law E, Dudeney J, Eccleston C, Palermo TM. Psychological therapies (remotely delivered) for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database Syst Rev* 2019; **4:** CD011118.

373 Keogh E, Rosser BA, Eccleston C. e-Health and chronic pain management: current status and developments. *Pain* 2010; **151:** 18–21.

374 Dear BF, Titov N, Perry KN, et al. The pain course: a randomised controlled trial of a clinician-guided internet-delivered cognitive behaviour therapy program for managing chronic pain and emotional well-being. *Pain* 2013; **154:** 942–50.

375 Higgins KS, Tutelman PR, Chambers CT, et al. Availability of researcher-led eHealth tools for pain assessment and management: barriers, facilitators, costs, and design. *Pain Reports* 2018; **3** (suppl 1): 686.

376 Wu YP, Steele RG, Connelly MA, Palermo TM, Ritterband LM. Commentary: pediatric eHealth interventions: common challenges during development, implementation, and dissemination. *J Pediatr Psychol* 2014; **39:** 612–23.

377 Vinall J, Pavlova M, Asmundson GJ, Rasic N, Noel M. Mental health comorbidities in pediatric chronic pain: a narrative review of epidemiology, models, neurobiological mechanisms and treatment. *Children (Basel)* 2016; **3:** 40.

378 Cohen LL, Blount RL, Cohen RJ, Ball CM, McClellan CB, Bernard RS. Children's expectations and memories of acute distress: short- and long-term efficacy of pain management interventions. *J Pediatr Psychol* 2001; **26:** 367–74.

379 Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. *BMJ* 2013; **346:** f2690.

380 Boerner KE, Eccleston C, Chambers CT, Keogh E. Sex differences in the efficacy of psychological therapies for the management of chronic and recurrent pain in children and adolescents: a systematic review and meta-analysis. *Pain* 2017; **258:** 569–82.

381 Packiasabapathy S, Sadhasivam S. Gender, genetics, and analgesia: understanding the differences in response to pain relief. *J Pain Res* 2018; **11:** 2729–39.

382 US National Institutes of Health. Best Pharmaceuticals for Children Act (BPCA). 2002. https://www.nichd.nih.gov/research/supported/bpca#:~:text=The%20Best%20Pharmaceuticals%20for%20Children,under%20the%20FDA%20Reauthorization%20Act (accessed Sept 15, 2020)

383 US Government. Public Law 108–155, 108th Congress, 2003. Pediatric Research Equity Act of 2003. Dec 3, 2003. https://www.congress.gov/108/plaws/publ155/PLAW-108publ155.pdf (accessed Sept 15, 2020).

384 European Medicines Agency. Peadiatric regulations. 2007. https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation (accessed Sept 15, 2020).

385 Berde CB, Walco GA, Krane EJ, et al. Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. *Pediatrics* 2012; **129:** 354–64.

386 Eerdekens M, Beuter C, Lefeber C, van den Anker J. The challenge of developing pain medications for children: therapeutic needs and future perspectives. *J Pain Res* 2019; **12:** 1649–64.

387 Morley S. Single case methods in clinical psychology: a practical guide. Oxford: Routledge, 2017.

388 Hollander MD, de Jong J, Onghena P, Vlaeyen JWS. Generalization of exposure in vivo in complex regional pain syndrome type I. *Behav Res Ther* 2020; **124:** 103511.

389 Clark H, Coll-Seck AM, Banerjee A, et al. A future for the world's children? A WHO-UNICEF—Lancet Commission. *Lancet* 2020; **395:** 605–58.

390 Rodkey EN, Pillai Riddell R. The infancy of infant pain research: the experimental origins of infant pain denial. *J Pain* 2013; **14:** 338–50.

391 Eccleston C. Managing chronic pain in children: the challenge of delivering chronic care in a "modernising" healthcare system. *Arch Dis Child* 2005; **90:** 332–33.

392 Walker LS, Dengler-Crish CM, Rippel S, Bruehl S. Functional abdominal pain in childhood and adolescence increases risk for chronic pain in adulthood. *Pain* 2010; **150:** 568–72.

393 Palermo TM, Slack M, Zhou C, Aaron R, Fisher E, Rodriguez S. Waiting for a pediatric chronic pain clinic evaluation: a prospective study characterizing waiting times and symptom trajectories. *J Pain* 2019; **20:** 339–47.

394 Lynch ME, Campbell F, Clark AJ, et al. A systematic review of the effect of waiting for treatment for chronic pain. *Pain* 2008; **136:** 97–116.

395 Estrin D. Small data, where n= me. *Commun ACM* 2014; **57:** 32–34.

396 Eccleston C, Tabor A, Keogh E. Using advanced technologies to improve access to treatment, to improve treatment, and to directly alter experience. Psychological approaches to pain management (3rd edn). NY, USA: Guildford Press, 2018: 289–302.

397 Henderson EM, Law EF, Palermo TM, Eccleston C. Case study: ethical guidance for pediatric e-health research using examples from pain research with adolescents. *J Pediatr Psychol* 2012; **37:** 1116–26.