British Journal of Anaesthesia **101 (1):** 101–10 (2008)
doi:10.1093/bja/aen097 Advance Access publication April 21, 2008

BJA

Pain in children: recent advances and ongoing challenges

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Significant advances in the assessment and management of acute pain in children have been made, and are supported by an increase in the availability and accessibility of evidence-based data. However, methodological and practical issues in the design and performance of clinical paediatric trials limit the quantity, and may influence the quality, of current data, which lags behind that available for adult practice. Collaborations within research networks, which incorporate both preclinical and clinical studies, may increase the feasibility and specificity of future trials. In early life, the developing nervous system responds differently to pain, analgesia, and injury, resulting in effects not seen in later life and which may have long-term consequences. Translational laboratory studies further our understanding of developmental changes in nociceptor pathway structure and function, analgesic pharmacodynamics, and the impact of different forms of injury. Chronic pain in children has a negative impact on quality of life, resulting in social and emotional consequences for both the child and the family. Despite age-related differences in many chronic pain conditions, such as neuropathic pain, management in children is often empirically based on data from studies in adults. There is a major need for further clinical research, training of health-care providers, and increased resources, to improve management and outcomes for children with chronic pain.

Br J Anaesth 2008; **101**: 101–10

Keywords: children; neonates; pain, acute; pain, chronic

Effective management of pain in children is a major priority for patients, parents, and health-care providers, and has been highlighted as a priority in the Children's National Service Framework from the UK Department of Health (www.dh.gov.uk/en/Healthcare/NationalServiceFrameworks/ChildrenServices). 'Children' encompasses an extremely broad group from premature neonates to adolescents. There are marked age-related changes affecting all aspects of pain management including assessment, physiological and pharmacological responses, and in the importance of different clinical outcomes. Recent advances in paediatric pain management have been reliant on multiple factors including: knowledge of the developmental neurobiology of pain processing and developmental pharmacokinetics of analgesic agents; improved age-appropriate tools for pain assessment; and increased availability and accessibility of current best evidence in clinical practice guidelines. Details for clinical management are available in the referenced reviews and guidelines and are not the focus of this review. Rather, recent research and significant ongoing challenges associated with pain management in children will be highlighted. Methodological and practical difficulties can limit the quantity or quality of data from paediatric clinical trials, and there are insufficient data to guide acute pain management in all clinical settings, particularly during the neonatal period. The immature nervous system can respond very differently to pain and analgesia, and injury in early life may produce long-term changes in sensory processing and/or pain sensitivity. Finally, chronic pain in children, which may be more common than previously recognized, has a significant impact on quality of life, and further research and resources are required to improve management and outcomes.

Evidence-based paediatric acute pain management

Guidelines and practice recommendations

The significant advances in the assessment and management of acute pain in children are supported by an increase in the availability of evidence-based data. In the first edition of *Acute Pain Medicine: Scientific Evidence* in 1999 only 8% of paediatric citations were based on Levels I and II evidence (in contrast to 67% of adult citations), increasing to 50% in the second edition in 2005.[17] A recent update of Level I evidence (meta-analyses and systematic reviews) in December 2007 included 13 new citations relevant to paediatric practice (www.anzca.edu.

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au/resources/books-and-publications). Recommendations and guidance specifically relating to paediatric acute pain management include Statements on the Management of Procedure-related Pain in Neonates and Management of Procedure-related Pain in Children and Adolescents by The Paediatrics and Child Health Division of the Royal Australasian College of Physicians (www.racp.edu.au/index.cfm?objectId=A4268489-2A57-5487-DEF14F15791C4F22), and more recently Good Practice in Postoperative and Procedural Pain by the Association of Paediatric Anaesthetists of Great Britain and Ireland.[18] The aim of evidence-based acute pain guidelines is not to provide global standards or absolute requirements, but to provide current data in an accessible form to assist decision-making about healthcare. As treatment settings vary markedly in size, resources, complexity, and patient populations, there can be no 'one size fits all' recommendation, and the efficacy of any intervention must be assessed and titrated in individual patients.[136]

Evaluating the evidence

Many paediatric treatments are empirically based on data from adults, gaps in knowledge persist, and there are insufficient data to guide treatment in all practice settings.[24 63] Many practical and methodological factors in the design and performance of clinical paediatric trials can limit the quality or quantity of available research data. This not only has an impact on the grading of recommendations in clinical practice guidelines, but also should be considered by individual practitioners when reading and interpreting published data. Factors affecting trial sensitivity include the following:

(i) *Sample size*: The challenge of recruiting paediatric patients into clinical trials often results in small or heterogeneous groups being compared. Inclusion of children across a wide age range may increase sample size but at the cost of increased variability due to age-related changes in analgesic requirement. Additionally, the validity of combining data from varying age-appropriate observational and self-report assessment tools has not been fully established. Younger children in particular may not fully understand the equal interval properties of scales and be more likely to choose the extremes of self-report scales.

(ii) *Ethical issues*: In addition to parental consent, child assent should be gained if possible,[121] and all efforts should be made to ensure clarity of consent documents.[122] In children, comparison with another active treatment rather than a placebo is usually employed, necessitating a larger sample size to ensure the study is adequately powered. Increasingly, regulatory or legislative requirements, such as directives from the European Union medicines regulatory regime[93] (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev10.htm) and the UK Medicines and Healthcare products Regulatory Agency (MHRA; www.mhra.gov.uk), must be incorporated in the design and conduct of clinical trials.

(iii) *Outcome measures*: Outcome measures with limited sensitivity or specificity reduce the power of clinical studies and increase the likelihood of a Type II error (i.e. failure to find a difference when a difference does exist).

Outcomes commonly used in analgesic trials include the following:

(i) *Pain intensity*: Recent systematic reviews have evaluated the validity, utility, and reliability of assessment tools for children aged 3 yr and above. Recommended observer-based behavioural scales include: FLACC and CHEOPS for acute procedural and postoperative pain; the COMFORT scale for children in intensive care; and the Parents Postoperative Pain Measure (PPPM) for postoperative pain managed by parents at home.[126] Recommended self-report tools include: pieces of Hurt tool for children aged 3–4 yr; Faces Pain Scale-Revised for 4–12 yr; and visual analogue scale for children more than 8–10 yr.[118] Uniform adoption of fewer assessment tools would aid comparison across trials and the combination of data in future meta-analyses.[58] In clinical practice, regular and consistent use of an assessment tool within a hospital may be more important than which tool is chosen.

(ii) *Time to first analgesia*: This measure requires the return of pain before analgesia, and the trigger for analgesic administration will influence the results. In a meta-analysis examining addition of clonidine to caudal local anaesthetic, the use of different criteria from a range of scales (e.g. VAS >4/10 or 6/10; CHEOPS >6 or >9) limited the ability to combine the raw data.[16]

(iii) *Analgesic consumption*: If rescue analgesia is being effectively titrated in a clinical study, all subjects should achieve similar pain scores and therefore a difference in analgesic consumption rather than pain score should be seen. However, inter-individual variability in analgesic requirements and in pharmacokinetics will reduce the sensitivity of this measure, particularly if patients from a range of ages are included. Differences in metabolism due to age-related changes in enzyme activity or genetic polymorphism will have an impact with studies using codeine[139] or tramadol.[3] As noted above, criteria or triggers for administration of analgesia must be standardized, and in studies after day case surgery, this will be influenced by parental assessment and administration of analgesia.[45]

Suggestions for improved study design have been outlined with the aim of stimulating further research,[4] and

areas requiring additional research are highlighted by current guidelines. Collaborative research networks (such as the Medicines for Children Research Network in the UK; www.mcrn.org.uk) and initiatives to increase paediatric trials and licensing (e.g. from the US Food and Drugs Agency and within the European Union) may increase the number of future paediatric analgesic trials.[93]

Pain in early life

Effective management of pain in early life can be challenging, and this is becoming increasingly relevant as the rate of premature birth is increasing and infants are surviving from earlier gestational ages.[79] Repeated procedural interventions are essential for monitoring and intensive care management,[116] and major surgery may be required to treat complications of prematurity or correct congenital anomalies. Although significant advances have been made in perioperative pain management,[24 123] effective control of responses to procedural interventions in neonatal intensive care units (NICUs) remains problematic.[130] Analgesia may be less likely to be used for procedural *vs* postoperative pain, and there is marked variability in practice across different units.[74] It is difficult to effectively block the relatively brief but intense nociceptive stimulus associated with some procedures; for example, topical local anaesthetic preparations are more effective against venepuncture than heel lance, presumably due to differences in the depth of penetration and intensity of the stimulus.[120] Non-pharmacological treatments reduce procedure-related distress[18] and further research is required to evaluate the efficacy of both pharmacological and non-pharmacological methods, given alone and in combination, for procedural pain in neonates.

Pain assessment in neonates

Systematic evaluation of pain in NICU has been shown to improve awareness of treating pain and to increase the use of analgesics.[1] Many assessment tools are available, but as yet have not been systematically evaluated (in comparison with tools for older children, see previous section). No single scale provides a 'gold standard' or has been universally adopted. The behaviour of infants having a large number of procedures may become habituated or sensitized depending on the temporal proximity of repeated procedures, motor development, and previous handling.[62] Overlap with manifestations of other states of distress (such as hunger) and confounding clinical factors (such as medications, sepsis, and heart disease) can further reduce the specificity of behavioural and physiological responses.[126] The sensitivity and specificity of assessment tools can have a major impact on the interpretation of research studies.[130] For example, marked variability in observer pain scores at baseline and after procedural interventions can reduce the sensitivity of a study.[32] Behavioural responses of neonates with neurological impairment differ and signs of irritability may reduce the specificity of 'pain' assessment tools.[117] The clinical utility of different analgesic and sedative regimes for ventilated neonates, including associated side-effects and impacts on acute and long-term outcomes, requires further evaluation.

Developmental neurobiology

Nociceptive processing in early life is not simply a scaled down version of that in the adult; acute behavioural, neurophysiological and molecular nociceptive processes undergo important post-natal changes.[46] Nociceptive pathways are functional after birth, but post-natal structural and functional changes in transmitter levels, receptor distribution, and function can alter responses to noxious stimuli and influence the response to analgesia and injury. Translational laboratory studies are essential for the investigation and understanding of: (i) changes in nociceptor pathway structure and function;[19 92 137] (ii) analgesic pharmacodynamics;[64 89 135] and (iii) the acute and long-term impact of different forms of injury.[65 132 134]

Peripheral nociceptors respond to chemical, mechanical, and thermal stimuli after birth,[46] and persistent stimuli produce peripheral sensitization; for example, local sensitivity after repeated heel lances in neonates.[48] In the spinal cord, post-natal changes in structure and function have a significant impact on the modulation of nociceptive inputs. Initially, there is a relative excess of excitatory mechanisms and delayed maturation of inhibition.[92] This is reflected in developmental changes in reflex responses: (i) mechanical thresholds are initially low and increase with age;[13 15] (ii) generalized responses involving multiple muscle groups gradually become more focused;[11 14] and (iii) poorly directed responses may result in inappropriate movement towards rather than away from the stimulus in early development.[13] However, even in premature neonates, the amplitude of the reflex is matched to the intensity of the stimulus.[12] Changes in reflex thresholds may prove useful as a surrogate measure of sensitivity after surgery or in quantifying the effects of analgesia.[14 15 49]

Using near-infrared spectroscopy (NIRS), changes in cerebral oxygenation over the contralateral somatosensory cortex were demonstrated after blood sampling from 25 weeks post-menstrual age.[20 112] Changes were not produced by less intense stimuli, suggesting that noxious peripheral stimuli specifically produce functional cortical activation in even the most premature neonate. The degree to which these effects can be modulated by analgesia warrants further investigation.

Developmental pharmacology

Dose requirements for analgesic agents vary throughout post-natal development. Pharmacokinetic variables change rapidly after birth and will be influenced by: (i) organ maturation (e.g. renal tubular function and change in

glomerular filtration rate); (ii) body composition (e.g. total body water approximates 85% in preterm neonates, 75% at term, and 60% by 5 months of age); (iii) changes in protein concentration and binding (affecting the volume of distribution); and (iv) changes in drug elimination pathways.[2 6] In preterm neonates, post-conceptional age and not just post-natal age requires consideration in pharmacokinetic models.[6 8] Understanding age-related changes in pharmacokinetics has allowed refinement of dose recommendations for acetaminophen[2 9 10] and i.v. morphine[29 71 77] in preterm and term neonates and infants. There is a poor correlation between pain score and plasma concentration that may be related to discrepancies between plasma and effect-site concentrations or large inter-individual variability in kinetics.[51 108 123] This emphasizes the need for regular assessment and titration of doses against response in the clinical setting. Further details of analgesic use in neonates can be found in reviews and practice guidelines.[7 18 24 57 123 129]

In addition to changes in pharmacokinetics, post-natal age can influence the pharmacodynamic profile of analgesic drugs, but this can be difficult to investigate clinically. Data from preclinical investigations can inform, and improve the design of, clinical studies[22] by providing additional information regarding the following:

(i) *Analgesic efficacy*: Evaluation of dose-related effects at a range of post-natal ages in the rat pup has provided data about the efficacy and sensitivity to side-effects for a number of systemic and regionally administered analgesics, including local anaesthetics,[64] opioids,[81 140] NSAIDs,[54] and alpha$_2$-adrenergic agonists.[132]

(ii) *Changes in receptor expression and distribution*: Developmental alterations in opioid receptor distribution are likely to contribute to the age-related differences in dose requirements observed in clinical studies.[28 89] During the first post-natal week, functional opioid receptors are expressed by both small (C-fibre) and large (A-fibre) cell bodies in the dorsal root ganglia, but by post-natal day (P) 21 the adult pattern of expression in predominantly small diameter neurons is seen.[25 90] In the spinal cord, mu opioid receptor binding sites are initially spread diffusely through the dorsal horn, with a peak in overall binding at P7, reducing by P21 and becoming more localized to the superficial dorsal horn.[101]

(iii) *Changes in transmitter function*: The neurotransmitter noradrenaline has a trophic role in the developing nervous system, and alpha$_2$-adrenergic receptors are highly expressed in the brainstem during the early post-natal period.[59] These changes may underlie the increased susceptibility to centrally mediated sedative and cardiovascular effects of the alpha$_2$-agonist dexmedetomidine seen in younger rat pups.[107 132 135]

(iv) *Developmental toxicity*: The nervous system may be susceptible to unexpected age-related effects, as shown by recent data linking general anaesthetics, including ketamine, with apoptosis (programmed cell death) in the developing brain.[84] This occurs in the absence of hypoxia,[143 144] hypoglycaemia,[69] or reductions in cerebral blood flow.[143] Additionally, this effect is limited to specific susceptible developmental periods (which differ across species), is dose-related, is worse when combinations of GABA agonists and NMDA antagonists are given, and can produce long-term structural and functional consequences.[50 68 91 114 144] The significance of these findings has been debated,[115] but further clinical research is warranted.[36]

Long-term effects of early injury

There are well-established critical periods in early post-natal life when the normal development of sensory neuronal circuits is activity-dependent and shaped by experience.[60] Experimental *reductions* in activity in nociceptive pathways during the early post-natal period produce persistent functional and structural changes in the spinal cord,[21] and *increased* nociceptive activity is likely to underlie alterations after early injury.[47] The pattern of long-term response is critically dependent on the type, severity, and duration of early injury: chronic neonatal inflammation produces structural alterations in the distribution of primary afferent fibres in the dorsal horn which persist until adulthood;[105] whereas acute inflammation produces a reversible change that is not seen after the same injury in adults.[134] In rodents, acute hindpaw inflammation during the first post-natal week (a developmental period which has some correlations with the preterm human)[46] produces generalized baseline *hypo*algesia, but greater localized *hyper*algesia when the previously injured paw is reinflamed.[102] It is hypothesized that enhanced descending inhibitory mechanisms compensate for segmental hyperalgesia, which is then unmasked by further injury.[103] Plantar hindpaw incision in the first post-natal week, but not at older ages, is also associated with an enhanced response to subsequent incision.[133] This provides a model to evaluate the ability of analgesic interventions at the time of initial surgery to modify or prevent long-term changes in sensory processing.

Clinical studies of long-term effects after neonatal intensive care and/or surgery have utilized a range of methodologies, including the following:

(i) *Alteration in behavioural responses*: Differences in pain reactivity have been reported after intensive care in extremely low birth weight infants, but differences from full-term infants are subtle and change with follow-up at different ages.[53] In addition, the cognitive and behavioural impairments reported in large cohorts of ex-premature infants[26 80] may

confound the interpretation of alterations in pain behaviour.[53 100] It is difficult to attribute changes specifically to pain experienced in the neonatal unit as multiple factors related to the intensive care environment, repeated handling, immune challenges associated with infection, or alterations in generalized stress systems may all have an impact.

(ii) *Change in baseline sensory function*: More specific evaluation of changes in sensory function is possible using quantitative sensory testing (QST) which provides objective, quantifiable, and reliable measures of sensory thresholds in children.[83] Generalized decreases in thermal sensitivity and alterations in thermal perception have been demonstrated many years after neonatal intensive care[61] or thoractomy.[110] A recent study suggests that surgery has an additional impact on the degree of change in thermal sensitivity in extremely premature children, which is independent of cognitive function or current pain experience (Walker and colleagues, in preparation).

(iii) *Enhanced responses to future pain*: Using QST, increased perceptual sensitization after a prolonged thermal stimulus was demonstrated in ex-NICU children.[61] The behavioural response after routine immunization at 4–6 months was increased in infants who had undergone neonatal circumcision without analgesia. This was partially modified when topical local anaesthetic was applied before the initial surgery.[119] Intraoperative fentanyl and postoperative morphine requirements were increased when subsequent surgery was performed in the same dermatome as neonatal surgery.[99]

Chronic pain in children

Chronic pain in children has a negative impact on quality of life, resulting in social and emotional consequences for both the child and the family. Recognition and management of chronic pain may be delayed due to limited access to appropriate resources.[34 94] There is a major need for further clinical research, and increased training of healthcare providers, to improve management and outcomes for children with chronic pain.[23 63]

Aetiology and prevalence

Chronic pain in children may result from multiple aetiologies including: (i) recurrent pain syndromes (e.g. headache and recurrent abdominal pain); (ii) medical illnesses (e.g. juvenile arthritis and sickle cell disease); (iii) neuropathic pain (including CRPS); and (iv) cancer and/or its treatment.

The reported prevalence of chronic pain in children varies depending on research design and focus. Chronic recurrent pain syndromes are relatively common, but have a variable impact on function. In a survey of 495 Canadian school children aged 9–13 yr, 57% reported at least one recurrent pain, and 6% reported chronic pain.[124] 'Pain existing recurrently or continuously for more than 3 months' was reported by 25% of respondents in a survey of more than 5000 Dutch school children, and in 8% pain was frequent and severe.[95] Gender differences have been noted in pain prevalence and intensity (higher in girls) and site of pain (increased headache and abdominal pain in girls, increased back and limb pain in boys).[85 95] Suggested data for prevalence of some other painful conditions include: arthritis, 3–460 per 100 000; sickle cell disease, 28–120 per 100 000; limb pain, 4.2–33.6%; recurrent abdominal pain, 6–15%; migraine, 4–27%; and non-migraine headache, 6.3–29%.[56 82]

Assessment and impact of chronic pain

As in adults, the interaction between biological processes, psychological factors, and social/environmental factors will influence the overall experience and impact of chronic pain in children. In addition, the pattern of pain experience, level of reporting, and types of coping strategies vary significantly throughout childhood and adolescence.[67] Therefore, appropriate age-specific outcome measures are required to determine the overall impact of chronic pain on physical and social function, assess the efficacy of different treatments, and develop evidence-based practice. Although many instruments have been used in different clinical settings,[131] relatively few have been specifically evaluated for adolescents with chronic pain.[40] To fully assess the impact of chronic pain in children, evaluation should include the following:

(i) *Effects on the child*: The Bath Adolescent Pain Questionnaire (BAPQ) incorporates multiple domains including physical disability, mood, social and family functioning, and school attendance.[39] Regardless of the aetiology, chronic pain has a major impact on quality of life in children and adolescents,[66 85] including negative effects on school attendance and social function.[42 43] The intensity of chronic pain has been shown to be a significant predictor of functional disability and depression (but not anxiety).[43]

(ii) *Family effects*: The evaluation and management of chronic pain in children must incorporate effects and interactions within the family. Parents and guardians have essential roles in: assessing and reporting the child's pain (which can be assessed with the BAPQ-Parent report; BAPQ-P);[41] presenting him/her for medical care; and compliance with subsequent treatment. Changes in levels of stress, mood, parenting behaviour, marital adjustment, and general functioning may occur in parents of adolescents with chronic pain.[70] Conversely, parental response can also have an impact on the child's pain experience. Parental attention may reinforce symptoms in girls with functional abdominal pain,[128] and maternal

psychological symptoms may also influence the use of health-care services.[76]

(iii) *Economic impact*: Chronic pain in children may incur direct costs related to health-care utilization, and indirect costs such as loss of work as parents care for their child. Of children with chronic recurrent pain, 39% had used medication and over half had consulted a physician[96] or other health-care provider.[97] Families of children who consult medical practitioners for chronic benign pain report a higher financial burden.[97] The economic impact of chronic pain has been estimated at £8000 per adolescent per year, and £3840 million per year in the UK.[113]

(iv) *Chronic pain in adulthood*: It has been suggested that chronic pain in childhood predisposes to pain and disability in adulthood, and early intervention may facilitate learning of adaptive rather than maladaptive coping strategies.[109] However, this hypothesis has not been investigated in controlled longitudinal studies, and the duration of follow-up in case series is variable and often limited. In children with chronic benign pain, 48% still experienced chronic pain at 1 yr follow-up, and 30% at 2 yr.[98] Higher levels of functional disability, school or work absence, and clinic visits have been reported at 5 yr follow-up of children with recurrent abdominal pain,[88 127] and associations have been found between recurrent abdominal pain and increased anxiety and medication use in adulthood.[31] Other childhood experiences, such as abuse or neglect, have been associated with an increased risk of experiencing chronic pain in adulthood.[37]

Neuropathic pain in children

Neuropathic pain and Complex Regional Pain Syndromes (CRPS) can account for up to 40% of referrals to a paediatric chronic pain clinic, but the overall incidence in children and adolescents is unknown.[23 34] Neuropathic pain may be related to traumatic or surgical injury, and is increasingly recognized in children with cancer (due to effects of the tumour, surgery, radiotherapy, or chemotherapy).[30]

The presentation of neuropathic pain and CRPS differ in children when compared with adults, but treatment is often empirically based on data from adult trials. CRPS has a peak incidence in early adolescence. In contrast to adults, there is a marked female preponderance (4–6 times), and the lower limb is 6–8 times more likely to be involved than the upper limb.[78 138] Diagnosis is based on the clinical history of pain and autonomic symptoms, and examination. Sensory changes, most commonly cold allodynia, have been documented using QST,[111] and the main role of radiological investigations is to rule out other underlying pathology.[138]

There are significant age-related changes in the susceptibility to neuropathic pain after nerve injury. Good restoration of sensory function *without* persistent pain has been documented after subsequent surgical repair of brachial plexus palsy during birth.[5 27 44] In contrast, neuropathic pain *has* been reported after traumatic brachial plexus palsy in older children and adolescents.[33 44] Phantom limb pain occurs in paediatric patients,[72 73 142] but is more likely to occur in association with traumatic injury than congential absence of a limb,[86] and in older children.[141] In a survey of primary care records in the UK, the incidence of phantom limb pain, trigeminal neuralgia, and post-herpetic neuralgia was lowest in the 0–14 yr group and subsequently increased with age, and there were no reports of diabetic neuropathy in children under 14 yr.[55] Laboratory studies also demonstrate age-related differences, as peripheral nerve injury produces allodynia in adult but not in young animals.[65 104] This provides a model for investigating mechanisms, such as neural–immune interactions,[87 125] which may contribute to differences in susceptibility to neuropathic pain.

Evidence for paediatric chronic pain management?

There is limited evidence to guide management of chronic pain in children, many pharmacological treatments are extrapolated from adult studies, and there are relatively few controlled trials evaluating the safety and efficacy of treatment in paediatric patients.

A systematic review of controlled trials of medications for headache and migraine reported efficacy for acetaminophen, ibuprofen, and sumatriptan; but also recognized the need for further high-quality studies which incorporate other outcomes, such as quality of life, school attendance, parent and/or child satisfaction.[35] Psychological therapies reduce the severity and frequency of chronic headache in children aged 7–18 yr, with a number needed to treat of 2.32.[38]

Gabapentin has been reported to improve neuropathic pain in children,[106] but there are no controlled trials and insufficient evidence to guide recommendations for the use of anti-convulsants for paediatric pain.[52] In children with CRPS, management focuses on non-invasive therapies[138] and reductions in pain and improved function have been reported in case series and in a prospective trial of cognitive behavioural therapy and physiotherapy.[75] However, it has been noted that the 'choice among therapies often seems to depend more on what type of clinician sees the patient, rather than on evidence from prospective controlled clinical trials'.[23]

Conclusion

Significant advances in the assessment and management of pain in children are supported by an increase in the availability and accessibility of evidence-based data. However, the evidence for paediatric acute pain lags behind that available for adults and very few controlled

trials have evaluated chronic pain interventions in children. There is a need for improved critical evaluation of assessment tools and outcome measures in clinical studies. Additionally, it is important to understand developmental changes in nociceptive processing and analgesic action via the study of preclinical models that may help to direct treatment in the future.

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