Management of Chronic Pain in Children and Young People

A National Clinical Guideline

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Contents

1. Introduction

Patient View

“From a patient perspective I feel these recommendations should be adhered to, to improve patient experience within paediatric chronic pain services. Highlighting the positive experiences of other patients can have an effect on how willing the patient is to cooperate with the multi-disciplinary team.

Drawing from my own experience, it is important that all professionals are delivering the same advice to the patients and families. At present, many patients feel there are discrepancies amongst the different professionals and the advice they have received.

I personally believe these guidelines will play an important role in the improvement of paediatric pain services, and will be an important resource for those experiencing chronic pain.”

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or perceived tissue damage or described in terms of such damage" [1]. Pain can be described as acute, where it is of recent onset, or chronic, which is commonly defined as longer than three months. However, in reality there is often no clear dividing line between acute and chronic pain. Epidemiological studies indicate a prevalence of chronic and recurrent pain in children of 15-30%, with 8% of children reported as having severe and frequent pain [2-4]. In a systematic review of the epidemiology of chronic pain in children and adolescents the prevalence rates varied. Generally pain prevalence rates were higher in girls and increased with age for the majority of pain types. In addition, lower socioeconomic status was correlated with higher pain prevalence, particularly in headache conditions [5].

Most chronic pain in children can be effectively managed in primary care, with appropriate investigations to exclude treatable causes. There should be an early emphasis on the biopsychosocial nature of pain with

access to reliable information and self-management resources for the child and family. There is a significant minority of children where chronic pain can be severely debilitating, affecting all aspects of the child's life and that of their parents and family members. The impact of pain is wide-ranging affecting school attendance, participation in sports or social activities as well as increased healthcare seeking and medication use. The deleterious effects of untreated pain in children can extend into adulthood [6]. It has also been shown that chronic pain can have a serious negative impact on financial wellbeing. In a cost of illness study in this population, the financial burden of adolescent chronic pain on the UK economy in one year was calculated to be £3840 million [7]. In a study of 149 young adults (aged 10-17) presenting at interdisciplinary pain services in the US it was found that the average cost of care per patient was $11,787 annually [8]. The total cost of moderate to severe chronic pain in the US was estimated to be $19.5 billion a year. The long-term effects of chronic pain on pain processing are not well understood, but it is likely that changes occur leading to excess sensitivity and altered signalling in the nervous system, even without any ongoing tissue damage or injury.

Specialist chronic pain services for children and young people are patchy and have developed through the enthusiasm and commitment of a small number of clinicians. There is very limited access to multidisciplinary pain management and this can be particularly difficult for teenage young people, falling into a gap between children's and adult services or not having an organised transition from one to the other [9, 10]. It is essential that there should be more healthcare professional and public education and resources to effectively manage pain. This is in keeping with the gold standard that care is responsive, and personalised care incorporates a multidimensional pain assessment. Any management plan should address these dimensions of a child or young person's pain experience, taking account of challenges such as geographical limitations to accessing this care.

The Scottish Intercollegiate Guidelines Network (SIGN) guideline on the Management of Chronic Pain in Primary Care (SIGN 136) did not include paediatric pain in remit as the limited evidence base was thought

to be insufficient for a full SIGN Guideline [11]. During the development of SIGN Guideline 136, there was feedback from key stakeholders that there is a need for expert guidance on managing paediatric chronic pain [12]. While recognising that in many areas, there is limited high quality evidence, this working group has drawn together multidisciplinary expertise to review the available evidence, and to reach consensus on areas where evidence is limited. Wider consultation out with this group has also been sought.

Delivery of good quality, timely care underpinned by the best available evidence is important. Moreover, routine and accurate assessments of pain must consider the child's developmental stage, experiences and communication abilities. Thus, this guideline aims to provide a useful practical resource, improving quality of life and reducing the risks of longer term harms for children and young people with chronic pain.

Remit of guideline

The current evidence for the key areas identified has been reviewed with the support of SIGN, using their methodology [13]. Chronic pain was defined as pain lasting longer than three months, or beyond the expected time of wound healing. Neither acute nor cancer pain were included. As chronic pain is caused by many underlying conditions, it was not the focus of this guideline to target specific conditions. The impact of chronic pain is wide-ranging which suggests that the data can be extrapolated to chronic pain as a whole.

The main guideline summarises available evidence, combined with consensus group agreement on key recommendations and suggested patient pathways. We have followed the methodology of SIGN 136 and hope that this guideline will facilitate the transition to adult services. Our aim is that this will ensure all health professionals are delivering a consistent, evidence-based approach. Research gaps have not been specifically listed, as these are clear from the key recommendations and current level of evidence associated with these.

The guideline's definition of 'child' is derived from the UN Convention of the Right of a Child (UNCRC): termed as a person under 18 years of age. At the national level, the Children and Young People (Scotland) Act 2014 similarly define a child as an individual who has not yet attained 18 years of age [14].

Treatment Pathways

Figure 1 overleaf represents a **Paediatric Pain Pathway,** which can be utilised by both clinicians and patients to guide management.

Recommendations

Recommendations (Section 2 and Figure 3) in this guideline are based on:

- a synthesis of the quality of the evidence;

and

- expert consensus opinion of the multidisciplinary guideline development group.

Where there is moderate to high quality evidence, this is highlighted with the recommendations. Due to the limitations in the evidence base, unless otherwise stated, the majority of recommendations are based on expert opinion (4), informed by current evidence.

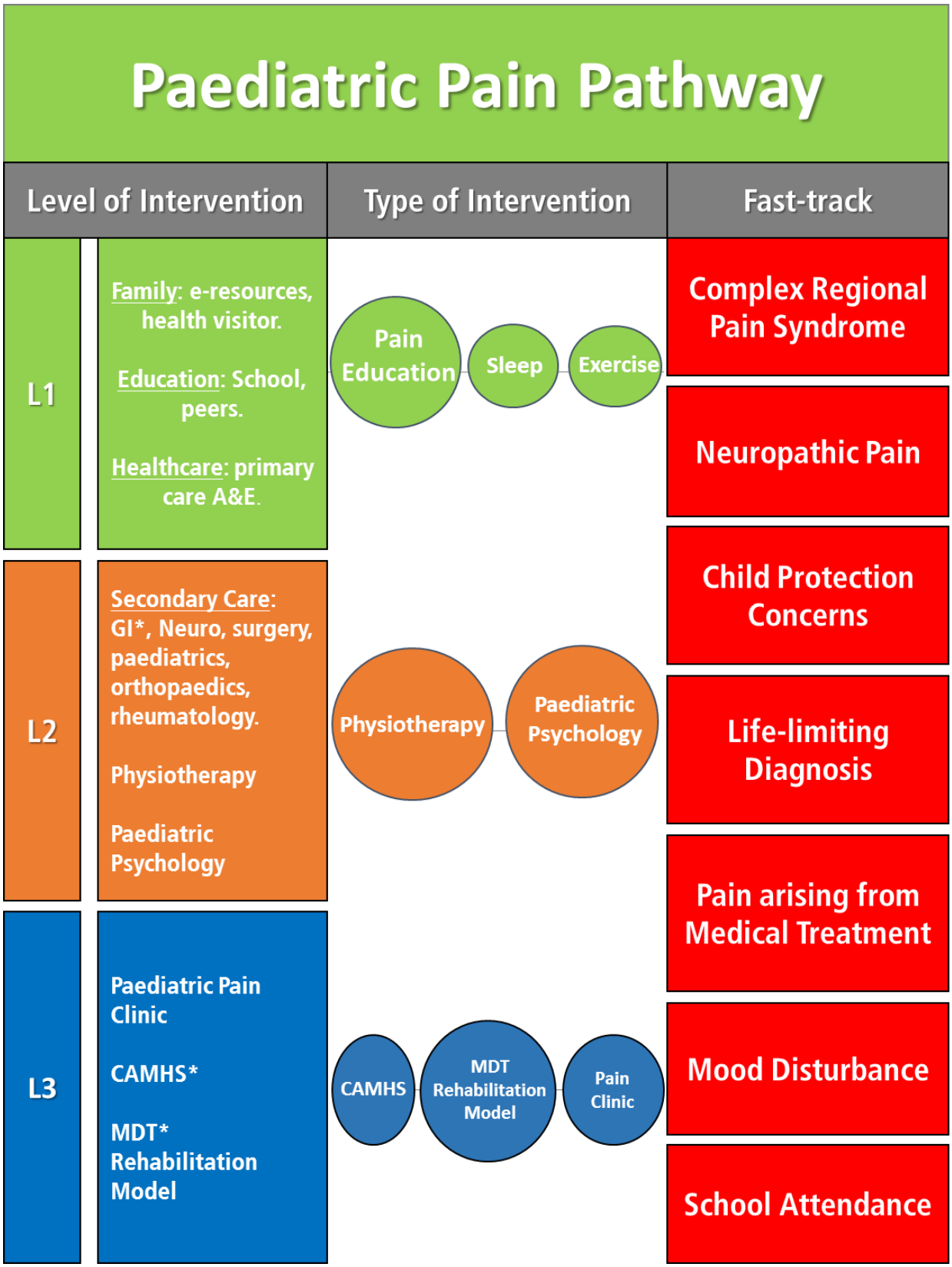
Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (SPC). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers [15].

Key to evidence statements

LEVELS OF EVIDENCE

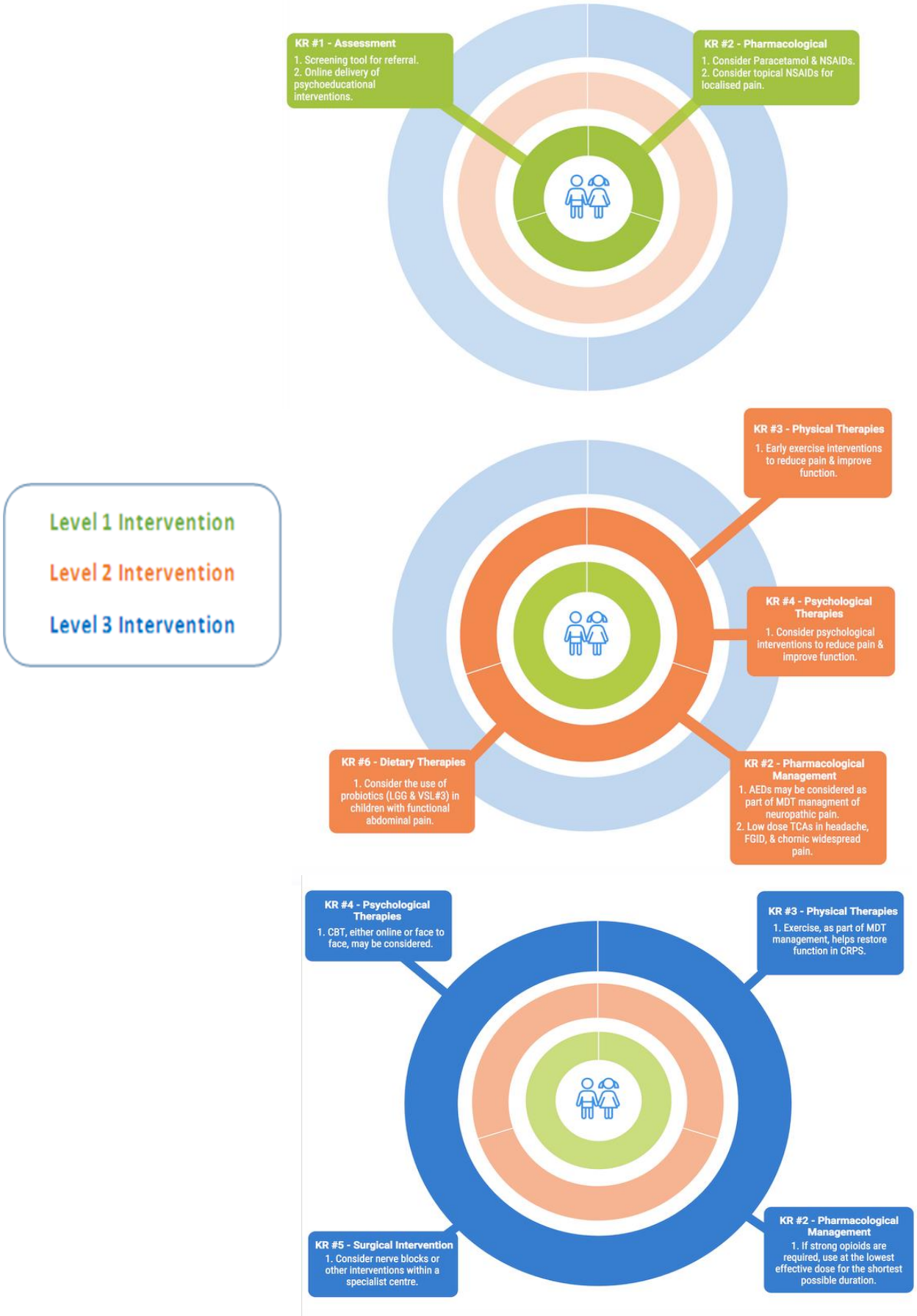
1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Figure 1: Paediatric Pain Pathway[1]



[1] ***GI** = Gastrointestinal, **CAMHS** = Child and Adolescent Mental Health Service, **MDT** = Multidisciplinary Team

Figure 2: Key Recommendations (KR)



2. Summary of Recommendations

2.1 Assessment and Planning of Care

- Use of a screening tool to identify children and young people at risk of adverse outcomes due to chronic pain should be considered to aid in planning intensity and type of intervention.

- Early biopsychosocial assessment and psychological intervention should be considered, particularly where the risk of disability and distress is high.

- The potential effects (both positive and negative) of children's interactions with family, clinicians, educators and peers on assessment and management of chronic pain should be considered. Regarding the nature of interactions with healthcare providers and clinical interventions, remote or online delivery may be considered as an alternative to face to face.

2.2 Pharmacological Management

- Pharmacological treatment should only be started after careful assessment. If being used, it should be part of a wider approach utilising supported self-management strategies within the context of a multidisciplinary approach.

- If pharmacological therapy is being used, then there should be regular review with planned reassessment of ongoing efficacy and side effects. Treatment should only be continued if benefits outweigh risks, and limited to the shortest possible duration. Review should be a minimum of once per year, to assess continued benefit in terms of pain relief and improvement in function and/or quality of life.

- Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) should be considered in the treatment of chronic non-malignant pain in children and young people. Use should be limited to the shortest possible duration, such as during acute on chronic pain episodes.

- Topical NSAIDs should be considered for treatment of children and young people with localised, non CRPS and non-neuropathic pain.

- 5% lidocaine patches should be considered in the management of children and young people with localised neuropathic pain, particularly when aiming to improve compliance with physiotherapy regimes. They are well accepted, with a low incidence of side effects, restricted to occasional hypersensitivity reactions.

- Antiepileptic drugs should be considered as part of a multi-modal approach in the management of children and young people with neuropathic pain:

    - Gabapentin should be considered as first line anti-convulsant (specialist use only). It should be used in the lowest effective dose, with ongoing monitoring for efficacy and adverse effects.
    - Pregabalin should be considered as a second line anti-convulsant drug if gabapentin is not tolerated or is ineffective (specialist use only).

- Low dose amitriptyline should be considered in the treatment of children and young people with functional gastrointestinal disorders.

- Low dose amitriptyline should be considered in the treatment of children and young people with chronic daily headache, chronic widespread pain and mixed nociceptive/neuropathic back pain.

- If amitriptyline is effective but particularly sedative in an individual, nortriptyline should be considered as a less sedating alternative.

- Bisphosphonates should be considered in the management of children and young people with osteogenesis imperfecta who have bone pain.

- Intrathecal baclofen should be considered for reducing spasticity-related pain in children and young people with cerebral palsy.

- In children and young people with recurrent abdominal pain pizotifen should be considered for abdominal migraine; famotidine for dyspepsia; and peppermint oil for irritable bowel syndrome.

- Opioids and compound analgesics containing opioids are rarely indicated for chronic pain because of their adverse effect profile. Be aware of MHRA advice on codeine. Strong opioids should be used with caution and only with specialist advice or assessment.

- Use of opioids should be for as short a time as possible with regular review and monitoring of efficacy and side effects.

- The use of codeine is not recommended in children under the age of 12 (MHRA), as it can be associated with a risk of opioid toxicity and respiratory side effects. In general it should also be avoided in adolescents, particularly if they have respiratory problems and individuals known to be CYP2D6 rapid metabolisers should also avoid codeine. Caution is also needed with tramadol use due to genetic variability in metabolism, and production of active metabolites.

2.3 Physical Therapies

- Exercise should be considered as a key component of chronic pain management in children and young people.

- There should be consideration of early interventions to increase movement, physical activity and restore function.

- Exercise should be used with the aim of producing functional improvement in children and young people with CRPS. Mirror therapy should be considered.

- Exercise therapy should be considered for children and young people with Patellofemoral Pain Syndrome (PFPS) to enhance long term recovery and reduce pain.

- Relaxation and TENS are low risk interventions that should be considered for the treatment of children and young people with chronic pain.

2.4 Psychological Therapies

- Psychological interventions should be part of a multi-disciplinary approach to managing chronic pain in children and young people.

- Face-to-face psychological interventions should be delivered by suitably trained and supervised practitioners.

- Online or computerised delivery of Cognitive Behavioural Therapy (CBT) interventions should be considered if face-to-face therapy is not suitable or not available.

2.5 Surgical Interventions

- Local anaesthetic blockade or other interventions should be considered on an individual patient basis in specialist centres.

2.6 Dietary Therapies

- The use of probiotics (LGG and VSL#3) should be considered in children and young people with functional gastro-intestinal disorders.

2.7 Complementary and Alternative Therapies

- Acupuncture may be considered for managing chronic pain in children and young people, for back pain and headache. If used, efficacy should be formally assessed.

- While evidence is very limited, music therapy may be considered for children and young people with chronic migraine.

3. Assessment

3.1 Impact of timing of referral or treatment on outcomes

A Cochrane review of psychological interventions used in chronic pain found 37 moderate to low quality randomised controlled trials (RCTs). There were no studies identified assessing the effect of the timing of interventions. Site of therapy delivery varied and included clinic (18 studies), home (including internet or computer-based) and school (3 studies). Some benefit was found in treatment delivered in schools [16-18]. **1+**

Another comprehensive review, without critical appraisal of the literature, did look at tools of early identification of development of chronic pain, but did not examine the effect of timing of intervention [19].

A RCT of 321 children aged 8 – 18 years, attending a hospital pain service were administered a Paediatric Pain Screening Tool (PPST). The PPST was adapted from the StartBack screening tool with the goal of identifying children with higher risk of adverse outcomes, and potentially facilitating targeted treatment [20]. The risk groups, as assigned by the PPST, were not affected by pain diagnosis, site, or duration. Of participants displaying high levels of disability and distress at 4 month follow up, only 2-7% had been identified as low risk at baseline assessment.

There is moderate evidence that early-intervention psychological therapy could have a modest impact on pain and disability, but no evidence of an effect on depression or anxiety [21].

There is a lack of good quality evidence that the timing of intervention affects outcomes for chronic pain management in children and young people.

There is also moderate evidence of a potentially predictive screening tool to stratify risk.

Recommendations

- Use of a screening tool to identify children and young people at risk of adverse outcomes, due to chronic pain, should be considered to aid in planning intensity and type of intervention.

- Early biopsychosocial assessment and psychological intervention should be considered, particularly where the risk of disability and distress is high.

3.2 Nature of interaction with healthcare professionals, education system and parents

Expert clinical opinion would support the hypothesis that clinical outcomes for children and young people with chronic pain are mediated, at least in part, by their interactions with others, both in a clinical and a social context. Pain in turn influences cognitive and social functioning and may negatively impact upon interactions with family members, school and peers [22]. Commissioning services in England and Wales have recognised the importance of multidisciplinary input for management of chronic pain in children and young people, although the nature of the interactions have not been defined [23].

A good quality systematic review found that intensive interdisciplinary management (typically delivered in an inpatient or hospital setting, on average 8 hours of treatment a day) had a positive effect on clinical outcomes: while demonstrating significant heterogeneity, in general, at post-treatment there were large improvements for disability, small to moderate improvements for pain intensity and small to moderate improvements for depressive symptoms. Positive effects were maintained at short-term follow-up, including improvement in school functioning. The specific effect of interactions with HCPs, education and parents were not explored [24]. **1+** **2++**

A systematic review identified a beneficial effect for online interventions, however the number of studies were small. A meta-analysis of available data found a modest pooled effect size (-0.41 [range 0.17--0.55]) for reductions in pain intensity after computerised CBT, with a mean odds ratio of 6.03 [confidence interval 2.67, 13.63] for significant reductions in pain intensity **2++**

compared to control [25].

A comprehensive systematic review of parental influences on functional abdominal pain (FAP) could not establish a clear relationship due to an insufficient number of good quality studies. There was some increase in reporting of physical symptoms in parents of children with FAP (effect size d=0.36) compared to parents of typically healthy children [26]. **4**

A narrative review has described emerging evidence suggesting a bidirectional relationship between chronic pain in children and family functioning, e.g. conflict and cohesion. The authors commented that interpreting individual studies is difficult due to the lack of longitudinal data. Children's and parental responses to pain may change over time and responses may vary depending on the developmental stage when the pain first began. Following on from this, it is unclear if the efficacy of interventions aimed at parental responses to children's pain is modified by the duration of pain and developmental stage [22] **4**

Non-verbal children, or children with communication difficulties, are at even greater risk of under-treated pain as carers and clinicians may be unaware of the existence of validated pain assessment tools, such as the FLACC (Faces, Legs, Activity, Cry, and Consolability) and the Paediatric Pain Profile. There is a deficiency in knowledge translation and the implementation of research findings in clinical practice [27, 28].

Recommendations

- The potential effects (both positive and negative) of children's interactions with family, clinicians, educators and peers on assessment and management of chronic pain should be considered. Regarding the nature of interactions with healthcare providers and clinical interventions, remote or online delivery may be considered as an alternative to face to face.

4. Pharmacological management

4.1 Background

Pharmacological management in children forms a small part of a multidisciplinary strategy (Section 10: Paediatric Pain Pathway). It should be recognised that pharmacological management alone is unlikely to provide the best outcome for patients. In the course of developing this guideline it was apparent that, in contrast to the adult population, there is little high quality evidence of efficacy in the paediatric population. There may be several reasons for this, including the ethical challenges of carrying out randomised controlled trials in this population [29]. As a result, many of the treatments used are out with their marketing authorisation ("off label use"). Such use should be supported by appropriate evidence and experience. "Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability" [30].

The General Medical Council (GMC) [31] recommends that when prescribing a medicine off label, doctors should:

- Be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists).
- Be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources.
- Record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice.
- Take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the

legislative framework and their own professional prescribing standards.

Although many of the medications used in the management of chronic pain are used off label – information regarding adverse effects and dosing can be obtained from the British National Formulary for Children (BNFC)[32].

Table 1: Suggested approach to using pharmacological treatment children

Step 1	Assess suitability for pharmacological therapy
Step 2	Start trial of analgesic medication (including dose titration if required)
Step 3	Monitor outcome of trial – continue if benefit; stop if unacceptable side effects or limited pain relief
Step 4	Planned reassessment; at least annually, more frequently if dose changes +/- adverse effects

4.2 Non-opioid analgesics

4.2.1 Simple analgesics

There is paucity of evidence specifically related to the use of simple analgesics in children with chronic non-malignant pain. Aspirin is not recommended for use in children, because of the risk of Reye's Syndrome [33-35]. Other long term side effects of NSAIDs in children have limited evidence, despite extensive study in adults [11].

A Cochrane review found 4 studies of NSAIDs, only one of which was of high quality. This demonstrated short term pain reduction using naproxen in patellofemoral pain syndrome [35, 36]. In a review of the management of children with sickle cell disease piroxicam was found to be superior to aspirin for treatment of pain, although this study was of low quality [37] (see also previous paragraph about the use of aspirin). **1+** **1-**

A meta-analysis of 18 RCTs compared ibuprofen to acetaminophen (paracetamol) for treatment of pain (mainly acute pain, with a small number of chronic pain conditions) in children [38]. Ibuprofen was **1-**

superior to acetaminophen for short term treatment of pain (i.e. immediately after surgery, but not the days following).

4.2.2 Topical analgesics

There is no high quality evidence relating to either lidocaine patches or capsaicin in the management of chronic pain in children. There are a small number of case series where lidocaine patches have been used, and were found to be a safe, effective method for improving patient functionality [39-41]. **3**

There is limited experience of capsaicin therapy in children, as it can cause localised pain during treatment. There is a single case report of the efficacy of capsaicin in the treatment of a case of erythromelalgia [42]. **3**

4.2.3 Anti-convulsants

There was no high quality evidence to support the use of anti-convulsant drugs in children and young people with chronic pain.

One RCT compared the effectiveness of amitriptyline with gabapentin in the treatment of neuropathic pain in children [43]. This was a well-designed study, but only limited conclusions could be drawn in view of the small number of patients studied. 34 patients with neuropathic pain aged between 8 and 17 years were randomised to receive either gabapentin 300mg tds or amitriptyline 10mg at night. Both groups received physiotherapy and psychological therapy. At 6 weeks, the reduction in pain score (MID, a decrease in pain of 1 or more) in the amitriptyline group was 6 (46.2%) and 9 (60%) for the gabapentin group. Although there was no statistically significant difference between the two drugs (p= 0.71 for complete cases and p= 0.73 for all cases). **1-** **3**

In reported case series the most frequently used anticonvulsant drug is gabapentin – which has been used as part of a multi-modal approach to treat Complex Regional Pain Syndrome (CRPS), neuropathic pain in Fabry disease, orchialgia, and distress behaviours in children with severe neurological impairment [44-46]. In children with CRPS, 70% required adjuvant medications (amitriptyline and/or gabapentin) for pain relief and to enable them to participate in physiotherapy. A high percentage of children (92%)

had complete resolution of symptoms using this treatment regime (mean=15.4 weeks [range, 3 days to 64 weeks]), but 40% required treatment as a hospital inpatient and 20% had a relapse episode [47]. In the study of children with refractory orchialgia, eight children (57%) treated had resolution of pain, with 50% of those treated with medications alone responding (two to gabapentin and a tricyclic antidepressant, one to gabapentin alone); and five out of eight (63%) treated with medications and then nerve block (ilioinguinal-iliohypogastric block) responding [44]. Of the 22 children with severe impairment of the central nervous system that were treated with gabapentin 21 (91%) had a significant decrease in symptoms [45]. The mean gabapentin dose for children five years of age or less (n=11) was 50 mg/kg/day (95% CI 45-56) compared to children older than 11 years (n=11) with a mean dose of 36 mg/kg/day (95% CI 34-38). No serious adverse events were reported.

Efficacy of pregabalin is described in a case series of children with neuropathic pain secondary to chemotherapy and one small case series of children with Complex Regional Pain Syndrome (CRPS) [48]. Following their diagnosis of CRPS, 5 patients were administered gabapentin at a dose of 30mg/kg/day, and 2 patients were administered pregabalin at a dose of 150-300mg/day. Pharmacological treatment lasted between 3 and 6 months. All patients participated in physiotherapy, first with passive mobilisation and then with active mobilisation. The authors noted that the 5 patients responded well to both pregabalin and gabapentin. **3**

There is limited evidence regarding the adverse effects arising from the use of antiepileptic drugs in children and young people with chronic pain, however there is extensive published evidence arising from their use in the management of epilepsy [49]. The commonest side effects of gabapentinoids (including pregabalin) are sedation, nausea and an increase in appetite in children and young people.

In the face of limited evidence of efficacy, the incidence of adverse effects plays a major role in the decision to use anti-convulsant drugs and in the choice of drug. Of the commonly used anti-convulsant drugs gabapentin and pregabalin have the most favourable adverse effect profile [50].

It should be noted that anti-convulsants are not licensed for the management of neuropathic pain in children, however there is a wide body of experience in using these drugs for both epilepsy and pain in children.

4.2.4 Anti-depressants

There is one good quality systematic review of the use of anti-depressants for chronic pain in children [51], which found a lack of high quality studies in this area. Two RCTs were identified, using between 10-30mg of amitriptyline for a maximum of 8 weeks for children with functional gastrointestinal disorders. Amitriptyline did improve quality of life scores by 15% (p=0.007). There are no long term trials evaluating the effectiveness of amitriptyline for pain in children. **1+**

There is no evidence supporting the use of other antidepressant medications in children and/or young people for the treatment of pain including selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) [52].

Based on clinical experience, amitriptyline can have a favourable risk benefit profile when used in low dose in children and young people with a range of chronic pain conditions. The dose should be titrated up to a maximum of 0.5 mg/kg/day over a two to three week period and to benefit, assessed up to six weeks after starting.

Adverse effects using this regimen are usually cognitive behavioural interference and occasionally weight gain. It is advisable to perform a routine electrocardiogram (ECG) before commencing treatment, and to withhold treatment if an abnormal corrected QT (QTc) interval is present.

4.2.5 Non-standard analgesics

There have been several systematic reviews identifying small studies with limited power [53-55]. Specific interventions in the literature search were ketamine, cannabinoids, baclofen, diazepam and clonidine.

There is limited evidence (three RCTs of two small populations) of benefit of intrathecal baclofen with pain reduction as a primary outcome in children with cerebral palsy [53]. **2+**

Pain management was measured as a secondary outcome in children with cerebral palsy treated with botulinum toxin. There was no evidence of any benefit of this treatment on pain. **2+**

There is limited evidence of effectiveness of oral alendronate in management of bone pain in osteogenesis imperfecta, but not other bisphosphonates. **2+**

One systematic review on analgesia for functional abdominal pain showed low grade effect of famotidine, cyproheptadine and peppermint oil [54]. Famotidine may only be of benefit in dyspepsia. This was probably the least robust systematic review, as a number of issues related to search strategies were not mentioned. **2-**

Another systematic review on recurrent abdominal pain suggests: pizotifen may be of particular benefit in the treatment of abdominal migraine; famotidine in dyspepsia; peppermint oil in irritable bowel syndrome [55]. **2-**

There is no good quality evidence of effect of ketamine, cannabinoids, oral baclofen, diazepam or clonidine in managing chronic pain in children.

4.3 Opioids

In the management of chronic pain in adults, the use of opioids has increased significantly over the last 10-20 years, with increasing concerns about harm from long term use [56]. There is a considerable body of published evidence on using opioids in chronic pain in adults, but this needs to be balanced with concerns that approaches to study design may overestimate the treatment effect [57-59], and an absence of studies examining the effectiveness of long term use. Potential harms include misuse, overdose, endocrine dysfunction, poorly understood effects on the immune system, and fracture [56].

In the paediatric literature, there is very limited evidence for the use of opioids in chronic pain. Identified problems include lack of control groups and small sample sizes [60].

A systematic review, with a somewhat limited search of available databases, of pharmacological management of chronic abdominal pain in children found no studies using strong opioids [51]. **1+**

An extensive literature search of published case reports, found a few studies related to chronic opioid use, and is of limited value [61] for this guideline. While the Cochrane review, of opioid switching, used high quality methodology and did include searches for paediatric use, only 2 studies including a paediatric population were identified (from 1965 and 1988) [62]. One of those only had 2 participants <18 and one focussed on acute use in the management of burns.

A recent comprehensive review of the management of sickle cell disease in children did include the use of opioids for chronic pain management. No good quality studies were identified, and the recommendations were based on expert opinion [63]. **1+**

There have been no studies on the use of compound analgesics in children. MHRA guidance is not to use codeine in children below the age of 13. It should only be used in older children and young people, and only if other analgesics are ineffective.

Pharmacological Management Recommendations

As noted at the start of this section, there was a paucity of high quality evidence in this area. Unless otherwise stated, these recommendations are based on the consensus opinion of the expert group.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (SPC). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers [15].

- Pharmacological treatment should only be started after careful assessment. If being used, it should be part of a wider approach utilising supported self-management strategies within the context of a multidisciplinary approach.

- If pharmacological therapy is being used, then there should

be regular review; There should be planned reassessment of ongoing efficacy and side effects. Treatment should only be continued if benefits outweigh risks. From a pragmatic perspective this should be a minimum of once per year, to assess continued benefit in terms of pain relief and improvement in function and/or quality of life.

- Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) should be considered in the treatment of chronic non-malignant pain in children and young people. Use should be limited to the shortest possible duration, such as during acute or chronic pain episodes.

- Topical NSAIDs should be considered for treatment of children and young people with localised, non CRPS and non-neuropathic pain.
- 5% lidocaine patches should be considered in the management of children and young people with localised neuropathic pain, particularly when aiming to improve compliance with physiotherapy regimes. They are well accepted, with a low incidence of side effects, restricted to occasional hypersensitivity reactions. **3**

- Antiepileptic drugs could be considered as part of a multi-modal approach in the management of children and young people with neuropathic pain:

- Gabapentin should be considered as first line anti-convulsant (specialist use only). It should be used in the lowest effective dose, with ongoing monitoring for efficacy and adverse effects.

- Pregabalin could be considered as a second line anti-convulsant drug if gabapentin is not tolerated or is ineffective (specialist use only).

- Low dose amitriptyline should be considered in the treatment of children and young people with functional gastrointestinal disorders. **1-**

- Low dose amitriptyline should be considered in the treatment of children and young people with chronic daily headache, chronic widespread pain and mixed nociceptive/neuropathic back pain. **3**

- If amitriptyline is effective but particularly sedative in an individual, nortriptyline should be considered as a less sedating alternative.

- Bisphosphonates should be considered in the management of children and young people with osteogenesis imperfecta who have bone pain.

- Intrathecal baclofen should be considered for reducing spasticity related pain in children and young people with cerebral palsy.
- In children and young people with recurrent abdominal pain pizotifen should be considered for abdominal migraine; famotidine for dyspepsia; and peppermint oil forirritable bowel syndrome.

- Opioids and compound analgesics containing opioids are rarely indicated for chronic pain because of their adverse effect profile. Be aware of MHRA advice on codeine. Strong opioids should be used with caution and only with specialist advice or assessment.

- Use of opioids should be for as short a time as possible with regular review and monitoring of efficacy and side effects.

- The use of codeine is not recommended in children under the age of 12 (MHRA), as it can be associated with a risk of opioid toxicity and respiratory side effects. In general it should also be avoided in adolescents, particularly if they have respiratory problems and individuals known to be CYP2D6 rapid metabolisers should also avoid codeine. Caution is also needed with tramadol use due to genetic variability in metabolism, and production of active metabolites.

5. Physical therapies for children and young people

5.1 Exercise Therapy

For the purpose of this guideline, studies were included if they encompassed an intervention that could be described as exercise therapy or an exercise programme.

One systematic review appraised studies, including RCTs and case series, of a variety of combinations of graded exercise therapy including weight-bearing, aerobic, resistance activities, hydrotherapy and facilitated movement, in children with CRPS Type 1. It concluded that the combination of exercise therapies or exercise and other psychological and medical interventions result in short-term improvement in signs and symptoms, and functional ability in children with CRPS type 1 [64]. **1+**

A Cochrane systematic review found very low quality but consistent evidence that exercise therapy for chronic Patella Femoral Pain Syndrome (PFPS) results in a clinically significant reduction in pain. This may also result in an improvement of functional ability, as well as enhancing long-term recovery. Hip plus knee exercises may be more effective in reducing pain in children with long term PFPS than knee exercise alone [65]. **1+ +** **1-**

A cost-utility study was performed in conjunction with a randomised clinical trial showing that exercise therapy in adolescents and young adults suffering from PFPS was cost effective when compared with a conservative strategy of background knowledge of the condition and its favourable prognosis [66].

In a small RCT of children with CRPS, Lee et al. (2002) reported that pain reduced and function significantly improved after physical therapy (low or high intensity), combined with CBT, when compared to pre- intervention levels ($p<0.01$). It was not possible to separate the benefits of exercise and its intensity from this study [67].

5.2 Manual Therapy

Manual therapy is an umbrella term that has increasingly been adopted to encompass various forms of hands-on treatment, including both manipulation and mobilisation. It is practised by a variety of healthcare professionals including physiotherapists, osteopaths and chiropractors. No evidence was identified for the use of manual therapy in children and young people with chronic pain.

5.3 Other Physiotherapy Modalities

A systematic review of CRPS in children and young people examined exercise, motor imagery and mirror feedback, relaxation, acupuncture, and electro-acupuncture, Transcutaneous Electrical Nerve Stimulation (TENS) and combined treatment programmes. Although there was some evidence of benefit with these treatments, overall the evidence was of low quality with many methodological weaknesses. Based on the quality of the available evidence, it is not possible therefore to recommend any of these specific interventions either alone, or in combination [68]. **2-**

Expert opinion suggests that due to the individual response and low risk of adverse side effects mirror therapy, relaxation and TENS may be of use in children and young people with chronic pain. **4**

5.4 Orthotic Interventions

A systematic review of children with long term PFPS appraised the addition of orthotics to exercise therapy. There was no additional effect of knee braces over exercise therapy alone on pain and functional outcomes. Conflicting evidence for the additional effect of tape and foot orthotics to exercise therapy on pain and function was found [69]. **1+**

Expert opinion suggest that the use of early immobilisation (i.e. plaster/moon boots) is not helpful in the treatment of CRPS. **4**

Recommendations

- Exercise should be considered as a key component of chronic pain management in children and young people.

- There should be consideration of early interventions to increase movement, physical activity and restore of function.

- Exercise should be used with the aim of producing functional improvement in children and young people with CRPS. Mirror therapy should be considered.

- Exercise therapy should be considered for children and young people with PFPS to enhance long term recovery and reduce pain.

- Relaxation and TENS are low risk interventions that should be considered for the treatment of children and young people with chronic pain.

6. Psychological Therapies

There is a range of psychological interventions available for children and young people with chronic pain. Most studies identified focussed on cognitive behavioural approaches, which include Behavioural Therapy [70] , Cognitive Behavioural Therapy (CBT) [71] , Acceptance and Commitment Therapy (ACT) [72] and Mindfulness-Based Interventions [73].

Typical treatments focus on the child/young person and family being actively involved in treatment, which often consists of psycho-education, behavioural strategies for engagement with normal daily activities, an increased awareness of the role of cognition in the exacerbation of suffering, self-regulation of emotion, techniques for reducing aversive arousal and skills training to parents and children/young people. This is delivered within a psychoeducational frame [74].
“The Matrix: A Guide to Delivering Evidence Based Psychological Therapies in Scotland” [75] gives further details on specific psychological interventions with strong evidence bases, together with intensity of intervention required. Most psychological interventions are high intensity and require commitment from the patient and family, and suitably trained and supervised psychological practitioners. The Matrix (Table 2, key overleaf in Table 3) suggests that psychological interventions generalise across various chronic pain conditions in the paediatric population.

Table 2: The Matrix (2015) - A Guide to Delivering Evidence Based Psychological Therapies in Scotland

Level of Pain Severity	Service Tier[2]	Intensity of Intervention[2]	Type of Intervention	Recommendation	
				Child	Adolescent
Moderate/Severe	3	High	Cognitive Behavioural Therapy	A [74, 76-78]	A [74, 76-78]
	3	High	Relaxation	A [74, 76-78]	A [74, 76-78]
	3	High	Biofeedback	A [74, 76-78]	A [74, 76-78]
Mild/Moderate	2/3	Low	Computer CBT (7+)	B [79]	B [79]
Moderate/Severe	3	High	Acceptance and Commitment Therapy	C [80]	C [80]
Mild/Moderate	2/3	Low	Internet-delivered Family CBT (11+)	C [81]	C [81]
Headache Pain					
Mild/Moderate	1/2	Medium	Computer CBT (7+)	B [79]	B [79]
	Tier 2-3	Medium	Internet-delivered Family CBT (11+)	C [81]	C [81]
Moderate/Severe	3	High	Biofeedback	A [74, 76-78, 82]	A [74, 76-78, 82]
	3	High	Relaxation	A [74, 76-78]	A [74, 76-78]
	3	High	Cognitive Behavioural Therapy	A [74, 76-78]	A [74, 76-78]
	Tier 3	High	Acceptance and Commitment Therapy	C [80]	C [80]

[2] Tier 1 = Universal services consisting of all primary care agencies including general medical practice, school nursing, health visiting
Tier 2 = Combination of specialist CAMHS services and community-based services including primary mental health workers
Tier 3 = Specialist multi-disciplinary outpatient CAMHS teams
Tier 4 = Highly specialist CAMHS inpatient unit and community treatment services

[2] Low Intensity Intervention = standardised interventions aimed at transient or mild mental health problems with limited effect on functioning.
High Intensity Intervention = formal psychological therapy delivered by a relatively specialist psychological therapist, aimed at common mental health problems with more significant effect on functioning

Table 3: The Matrix- Key for Level of Evidence

Matrix: Level of Evidence	**Recommendation**	
At least one meta-analysis/systematic review with medium-large effect sizes; or more than one RCT of high quality and consistency, aimed at target population, showing medium-large effect sizes	A	Highly Recommended
One RCT with medium-large effect size; or meta-analysis/systematic review or multiple RCTs showing small-moderate effect sizes, and demonstrating overall consistency of results	B	Recommended
One RCT with small effect size and/or multiple non-RCT studies with small effect sizes. There may be inconsistency in findings across studies but a general trend towards a positive effect should be noted	C	Limited/ developing evidence to date, no indication against use

There is evidence from a high quality Cochrane review, in which 37 studies were identified across a range of chronic pain conditions (including headache, abdominal pain, and fibromyalgia). A reduction in pain and improvement in disability was found, with maintenance of effect at follow-up, although some limitations in the evidence were identified, particularly in relation to the interaction between mood, pain and disability identified [83]. **1+**

A systematic review and meta-analysis of psychological interventions for children and young people with chronic pain found effective reductions in pain intensity in a range of pain conditions, and improvement in functional ability. For chronic headache, there was some evidence for a dose response, with better outcomes from higher treatment doses [74]. **1+**

There is more limited evidence for the effectiveness of computer or internet based psychological interventions in children and young people [25]. Children and young people with long term **2++**

conditions/chronic pain experience isolation through reduced school attendance and inability to take part in group activities like their peers. Provision of computer based CBT intervention may well exacerbate this situation. Online or computerised delivery of CBT interventions should therefore only be used if face to face therapy is not available or best used together with face to face support.

One of the limitations of the literature on psychological interventions is the target of intervention. While reduction in pain intensity is assumed to be the desired outcome, psychological approaches are often directed at improving daily functioning despite pain and/or addressing mood issues (which may affect how pain is processed).

Recommendations

- Psychological interventions should be part of a multi-disciplinary approach to managing chronic pain in children and young people.
- Face-to-face psychological interventions should be delivered by suitably trained and supervised practitioners.

- Online or computerised delivery of CBT interventions should be considered if face-to-face therapy is not suitable or not available.

7. Surgical interventions or other invasive procedures

7.1 Surgery

There is no significant literature in the surgical management of chronic pain in children other than that which details the transition of acute post-operative pain into chronic post-operative pain and those studies that look at chronic pain as a consequence of specific procedures (e.g. long-term pain after hernia repair in childhood) or site-specific chronic pain (e.g. chronic abdominal pain/headache/knee pain/back pain et cetera).

In the main, the role of surgery relates to investigation of chronic pain (principally chronic abdominal pain) rather than looking at the pain reduction effects of any specific surgical procedure or intervention.

7.2 Nerve blocks

Two systematic reviews have investigated the role of local anaesthetic sympathetic blockade (LASB) on Complex Regional Pain Syndrome (CRPS) in children and adults together. Neither looked specifically at children, with the majority of studies having a small sample size. There was not enough evidence to make any conclusions about the safety and efficacy of LASB in children and young people [84, 85]. **1-**

7.3 Other Interventions

Intravenous regional blockade with guanethidine, sympathetic block with botulinum toxin A, along with bupivacaine, intravenous lidocaine and IV phentolamine have all been used in the management of sympathetically maintained pain. There is no evidence of effectiveness in long-term pain relief in any of the groups studied. Quality of pain score differences between groups were not statistically compared [84, 85]. There is therefore no evidence base to support the recommendation of these other interventions.

No literature was available upon which to base a recommendation in the following interventions: sympathectomy, dorsal root rhizotomy, epidural, caudal or trigger point injection, Bier's block,

neuromodulation, plexus block.

Recommendations

- Local anaesthetic blockade or other interventions should be considered on an individual patient basis in specialist centres.

8. Dietary Therapies

Much of the work in this area has focussed on abdominal pain. Each systematic review noted that their conclusions are based upon a small number of studies [51, 86]. There is overlap between reviews on the use of fibre in functional gastro-intestinal disorders however the findings and conclusions are consistent.

The evidence suggests that dietary fibre does not influence pain in children with functional gastrointestinal disorders [86]. A good quality systematic review supported a positive effect for probiotics in treating irritable bowel syndrome [51] as a significant reduction in abdominal pain was found in the VSL#3 group (1.0 ± 0.2 versus 0.5 ± 0.2 in control participants). **1+** **1+**

Clinicians should consider the use of probiotics Lactobacillus rhamnosus GG (LGG) and VSL#3 in treatment of children and young people with functional gastro-intestinal disorders – especially if symptoms are severe. Probiotics are not available as a prescription medication so they must be obtained from health food stores or supermarkets etc., and are not subject to the same regulation as prescribed medications.

Recommendations

- The use of probiotics (LGG and VSL#3) should be considered in children and young people with functional gastro-intestinal disorders.

9. Complementary and alternative therapies

9.1 Acupuncture

One systematic review identified 23 RCTs and presented 8 meta-analyses focusing on acupuncture as an intervention. Nine of these trials enrolled children. All included trials were of low quality and small sample size and none looked at the effect of acupuncture specifically on pain in children [87].

The data presented on harm suggest a possible risk of 5:10,000 for severe or significant adverse events related to acupuncture in children such as sedation, needle pain and neuropathy/nervous system-related issues [87]. **1-**

9.2 Qigong and other exercise

A systematic review identified four (4) RCTs of Qigong (a form of gentle physical exercise and breathing control related to tai chi) in patients with fibromyalgia [88]. One trial involved children [89]. This trial assessed the effect of Qigong and aerobic exercise on symptoms including pain, in 30 children with fibromyalgia. There was no placebo group in this trial limiting the interpretation of the findings. **1-**

The results indicated that the C-HAQ (Childhood Health Assessment Questionnaire) Visual Analogue Scale scores measuring the severity of illness and pain improved significantly more in the aerobics group compared to the qigong group at the end of the exercise programme ($F[1,21] = 5.32$, $P = 0.03$ versus $F[1,21] = 9.75$, $P = 0.005$) [89]. Improvements from baseline in pain scores was seen in both the Qigong and aerobic exercise groups.

9.3 Music Therapy

One systematic review [90] included a single trial in children assessing the effect of music therapy in the treatment of childhood migraine [91]. The results of this trial which was of moderate quality suggested that active participation in music therapy (12 sessions over 28 weeks) reduced the frequency of migraine episodes by 62% compared to a 31% reduction in the placebo group, $p < 0.05$. Headache intensity was not reduced. **1+**

Recommendations

- Acupuncture may be considered for managing chronic pain in children and young people, for back pain and headache. If used, efficacy should be formally assessed.

- While evidence is very limited, music therapy may be considered for children and young people with chronic migraine.

10. Implementation

10.1 The aim of this guideline is to provide a resource based on the best available evidence, and expert consensus to inform the management of children and young people with chronic pain. Integrated joint boards need to consider existing resources and services, and to ensure that this guideline is used appropriately.

10.2 Research Recommendations

As there is a paucity of literature in this area there are too many specific research gaps identified throughout this document to present them all usefully. From the evidence discussed throughout this guideline it is clear that high quality evidence is needed in all areas of paediatric chronic pain. The list below is a summary of some of the key gaps.

1. What are the effects of early detection and management of chronic/persistent pain on outcomes?
2. What interventions are effective?
3. What is the best type and intensity of exercise for improving pain and function in children and young people with chronic pain?
4. What is the configuration, intensity and duration of interdisciplinary management and the efficacy of remote versus direct delivery of some or all components?
5. How common is the chronic use of (strong) opioids in children and has prescribing changed in line with patterns seen for adults with chronic pain?
6. How effective are opioids for chronic pain in children?
7. What are the long term effects of opioid use in children and adolescents?
8. What is the efficacy and safety of topical therapies in children?
9. What is the effectiveness of nutritional supplementation in other pain conditions; e.g. headache, musculoskeletal pain?
10. What is the role and effectiveness of ‘nutraceutical’ dosing of dietary compounds, e.g. Vitamins C, D and E, Magnesium, Co-enzyme Q10, in diverse pain conditions?

11. What is the economic impact for patients and families acquiring these compounds?
12. What are the potential underlying mechanisms of action in acupuncture for children and young people with pain? Does it reduce pain and improve function in children?

11. Further information and useful links

http://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/03/Strategy-Chronic-Pain-Quality-Prescribing-for-Chronic-Pain-2018.pdf
www.painconcern.org.uk
http://www.sign.ac.uk/pdf/SIGN136.pdf [11]
Other national/ international guidelines: WHO Guidance (2012):
http://www.who.int/medicines/areas/quality_safety/guide_perspainchild/en/
Japanese Clinical Guidelines for Chronic Pain in Children and Adolescents(2009):
https://pdfs.semanticscholar.org/443d/a37193613e5df3bf0a21f29f4715695bcb84.pdf

12. Online Resources for Children and Young People

13. Development of the guideline

13.1 Development group

This guideline was developed by the Short Life Working Group for Paediatric Pain (*see Appendix 1*) chaired by Professor Lesley Colvin and co-chaired by Dr Mary Rose, at the request of the CMO.

13.2 Methodology

The key questions for this guideline were developed using the PICO principle (population, intervention, control and outcome). Predefined search strategies were utilised by SIGN researchers. The quality of the research was assessed and graded by experts in the respective fields, adhering to accredited SIGN methodology [11, 13]. However the majority of recommendations were based on group consensus opinion rather than high-grade evidence.

13.3 Consultation and peer review

The consultation for this guideline was officially launched at the Scottish Pain Research Community 7th Annual Scientific Meeting on the 24th March 2017. The guideline was also sent out to various organisations for comment, and was freely available for comment through www.sign.ac.uk.

Appendix 1: Development of the Guideline

The Guideline Development Group

Professor Lesley Colvin (Chair)	Consultant/Honorary Professor in Anaesthesia and Pain Medicine	University of Edinburgh NHS Lothian
Dr Mary Rose (Co-Chair)	Consultant in Paediatric Anaesthesia and Pain Medicine	NHS Lothian
Ms Pauline Beirne	Educational Projects Manager (Child Health)	NHS Education for Scotland
Ms Katherine Berlouis	Research Assistant in Chronic Pain	University of Dundee
Dr Ross Fairgrieve	Consultant in Paediatric Anaesthesia and Pain Management	NHS Greater Glasgow and Clyde
Dr Peter Fowlie	Consultant Paediatrician	NHS Tayside
Dr Stephen Gilbert	Consultant in Anaesthesia and Pain Medicine	Townsville Hospital, Queensland, Australia
Dr John Goddard	Consultant in Paediatric Pain Medicine	Sheffield Children's Hospital

Ms Heather Harrison	Education Development Pharmacist Senior Prescribing Advisor	NHS Education for Scotland (Pharmacy) NHS Greater Glasgow and Clyde
Ms Dawn Houston	Highly Specialist Physiotherapist	Kids Physio Scotland Ltd
Dr James Lemon	Consultant Clinical Psychologist	NHS Dumfries and Galloway
Dr Stewart MacLeod	Consultant Paediatric Neurologist	NHS Greater Glasgow and Clyde
Dr Kevin McCarthy	Consultant in Paediatric Anaesthesia and Pain Medicine	Our Lady's Children's Hospital, Trinity College, Dublin
Ms Erin McGuigan	Patient Representative	
Ms Pierette Melville	Highly Specialist Paediatric Physiotherapist	NHS Fife
Dr Tony Moores	Consultant in Paediatric Anaesthesia and Pain Management	NHS Greater Glasgow and Clyde
Ms Cara Richardson	Research Assistant in Chronic Pain	University of Dundee
Ms Mandy Sim	Clinical Nurse Specialist, Pain Management	NHS Lothian
Ms Ailsa Stein	Programme Manager	Scottish Intercollegiate Guidelines Network

Dr Ewan Wallace	Consultant in Paediatric Anaesthesia and Pain Medicine	NHS Greater Glasgow and Clyde
Ms Carolyn Wesson	Consultant Clinical Psychologist	NHS Lothian
Dr Graham Wilson	Consultant in Paediatric Anaesthesia and Pain Medicine	NHS Grampian
Professor George Youngson	Emeritus Professor, Paediatric Surgery	University of Aberdeen
Ms Diane Dempster (Secretariat)	Business and Policy Support Officer	Scottish Government

Collaborators

Dr Paul A. Cameron	National Chronic Pain Coordinator/Acting National Lead Clinician/Lead Advanced Practice Physiotherapist	NHS Fife
Professor Blair H. Smith	Professor and Clinical Director, Division of Population Health Sciences	University of Dundee
	Consultant in Pain Medicine	NHS Tayside
	National Lead Clinician for Chronic Pain	Scottish Government

Organisations Invited to Comment

Arthritis Research UK Primary Care Centre, Keele University, UK

Faculty of Pain Medicine

Action for Sick Children Scotland

Association of Paediatric Anaesthetists of Great Britain and Ireland

Paediatric Psychology Network (British Psychological Society)

Royal College of Paediatrics and Child Health

Reviewers

Dr Line Caes	Lecturer in Psychology	University of Stirling
Dr Amanda C de C Williams	Reader in Clinical Health Psychology	University College London
Professor Tim Eden	Emeritus Professor of Paediatric and Adolescent Oncology	University of Manchester
Dr Emma Fisher	Research Fellow	Seattle Children's Research Institute

Abbreviations

ACT	Acceptance and Commitment Therapy
AEDs	Anti-epileptic Drugs
BNFC	British National Formulary for Children
CBT	Cognitive Behavioural Therapy
CP	Chronic Pain
C-HAQ	Childhood Health Assessment Questionnaire
CRPS	Complex Regional Pain Syndrome
ECG	Electrocardiogram
GMC	General Medical Council
IASP	International Association for the Study of Pain
LASB	Local Anaesthetic Sympathetic Blockade
NSAIDs	Non-steroidal anti-inflammatory drugs
MHRA	Medicines and Healthcare Products Regulatory Agency
PFPS	Patellofemoral Pain Syndrome
PPST	Paediatric Pain Screening Tool
RCT	Randomised Controlled Trial
SIGN	Scottish Intercollegiate Guidelines Network
SPC	Summary of Product Characteristics
TENS	Transcutaneous Electrical Nerve Stimulation
UNCRC	United Nations Convention on the Right of the Child

Appendix 2: Key questions

1. In patients with chronic non-malignant pain being managed is there any evidence that timing of referral or treatment impacts on outcomes?

2. In patients with chronic non-malignant pain is there any evidence that the nature of interaction with healthcare professionals, education system and parents affects patient outcomes?

3. In patients with chronic non-malignant pain are opioids effective compared with placebo or other interventions in pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions, dependency (physiological or psychological).

4. In patients with chronic non-malignant pain what are the most effective simple analgesics compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions, dependency (physiological or psychological).

5. In patients with chronic non-malignant pain what is the effectiveness of anticonvulsants compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse drug reactions, dependency (physiological or psychological).

6. In patients with chronic non-malignant pain what is the effectiveness of topical analgesics compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions, dependency (physiological or psychological)?

7. In patients with chronic non-malignant pain what is the effectiveness of antidepressants compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions, dependency (physiological or psychological).

8. In patients with chronic non-malignant pain what is the effectiveness of non-standard analgesics compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions, dependency (physiological or psychological).

9. In patients with chronic non-malignant pain what is the effectiveness of physical therapies compared with no physical therapy or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events.

10. In patients with chronic non-malignant pain what is the effectiveness of complementary and alternative therapies compared with no treatment or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events.

11. In patients with chronic non-malignant pain what is the effectiveness of expert/clinician guided self-help management advice/ programmes/psychological treatments compared with no treatment or other interventions on pain scores, functional ability, mood, QoL and adverse events.

12. In patients with chronic non-malignant pain is there any evidence for the effectiveness of dietary interventions compared with usual care on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events.

13. In patients with chronic non-malignant pain what is the effectiveness of surgery, nerve blocks compared with no intervention on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events.

Appendix 3: Search Strategies

Guideline topic: Paediatric Chronic Pain		
General comments The systematic literature search involved searching for evidence for 13 questions. Systematic reviews were identified for all questions by using a generic stem search strategy combined with a filter for systematic reviews. **Primary literature studies were identified for 6 questions (1, 5, 6, 7, 8, 13) by combining the generic stem search with a search strategy for each individual question.**		
Search coverage		
Systematic reviews ***Databases covered:*** *Medline, Embase, CINAHL, PsycINFO, Cochrane*		***Dates covered: to 14 Jul 2015***
Total hits: 483	*Sifted result: 59*	*Papers requested: 55*
Primary literature ***Databases covered:*** *Medline, Embase, CINAHL, PsycINFO, Cochrane*		***Dates covered: (with variations depending on topic; see Scope of Searches below)***
Total hits: see table below	*Sifted result: see table below*	*Papers requested:*

Search strategies

The following are listings of the main Medline strategies used for this guideline. All conventions and symbols are from the Ovid implementation of Medline. Strategies used in other databases were substantially the same, though different terminology may have been used to take account of different thesauri used in non-Medline databases.
Search filters were added to identify studies of a particular type (systematic review, RCT etc.) Listings of the search filters used by SIGN can be found on the SIGN website.

Generic Stem:

Medline Generic stem

1. exp Chronic Pain/
2. exp Pain/
3. exp Chronic Disease/
4. 2 and 3
5. (chronic adj5 pain).tw.
6. (persist* adj3 pain).tw.
7. (long* adj3 pain).tw.
8. (paediatric* adj5 pain).tw.
9. (pediatric* adj5 pain).tw.
10. exp Complex Regional Pain Syndromes/
11. CRPS.tw.
12. (pain adj3 syndrome*).tw.
13. (complex adj3 pain).tw.
14. (recurrent adj3 pain).tw.
15. Fibromyalgia/
16. fibromyalgia*.tw.
17. or/4-16
18. 1 or 17
19. limit 18 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")
20. Adolescent/
21. exp Child/
22. exp Infant/
23. adolescen*.tw.

24. teenager*.tw.
25. (teen or teens).tw.
26. child*.tw.
27. infant*.tw.
28. (baby or babies).tw.
29. toddler*.tw.
30. (pre-schooler* or preschooler or schoolchild*).tw.
31. (girl* or boy*).tw.
32. or/20-31
33. 18 and 32
34. 19 or 33

Scope of searches for Primary literature searches (NOF = no filter search ie no study type filters applied)

KQ	Type of studies	Date range	Initial recall	Sifted result
1	NOF	To 18/01/16	1021	19
5	NOF	To 04/12/15	602	28
6	NOF	To 04/12/15	797	23
7	NOF	To 10/12/15	762	37
8	NOF	To 16/12/15	445	24
13	NOF	2006-18/01/2016	1881	62

Medline Search strategies used for specific key questions:

KQ 1

1. "Referral and Consultation"/
2. (early adj5 refer*).tw.
3. (late adj refer*).tw.
4. (timing adj5 refer*).tw.
5. (time adj5 refer*).tw.
6. (early adj5 treatment*).tw.
7. (late adj5 treatment*).tw.
8. (timing adj5 treatment*).tw.
9. (time adj5 treatment*).tw.
10. (early adj5 intervention*).tw.

11. (late adj5 intervention*).tw.
12. (timing adj5 intervention*).tw.
13. (time adj5 intervention*).tw.
14. Early Diagnosis/
15. (earl* adj5 diagnos*).tw.
16. (earl* adj5 detection).tw.
17. Critical Pathways/
18. (clinical adj5 (pathway* or journ*)).tw.
19. (care adj5 (pathway* or journ*)).tw.
20. or/1-19

KQ 5

1. exp Anticonvulsants/
2. (anticonvulsant* or anti-convulsant*).tw.
3. (antiepileptic* or anti-epileptic*).tw.
4. gabapentin*.tw.
5. pregabalin*.tw.
6. exp Valproic Acid/
7. sodium valproate*.tw.
8. exp Carbamazepine/
9. carbamazepine*.tw.
10. oxcarbazepine*.tw.
11. oxcarbamazepine*.tw.
12. topiramate*.tw.
13. lamotrigine*.tw.
14. lacosamide*.tw.
15. levotiracetam*.tw.
16. or/1-15

KQ 6

1. exp Analgesics/
2. exp Administration, Topical/
3. 1 and 2
4. exp Lidocaine/
5. exp Capsaicin/
6. exp Clonidine/
7. exp Transdermal Patch/
8. exp Ointments/

9. or/4-8
10. (topical* or transdermal or cream* or patch* or ointment*).tw.
11. 3 or 9 or 10

KQ 7

1. exp Antidepressive Agents/
2. exp Serotonin Uptake Inhibitors/
3. exp Lithium/
4. lithium*.tw.
5. duloxetine*.tw.
6. mirtazapine*.tw.
7. venlafaxine*.tw.
8. fluoxetine*.tw.
9. citalopram*.tw.
10. amitriptyline*.tw.
11. nortriptyline*.tw.
12. clomipramine*.tw.
13. imipramine*.tw.
14. (antidepressant* or antidepressive*).tw.
15. (selective adj3 inhibitor*).tw.
16. (SSRI* or SNRI*).tw.
17. or/1-16

KQ 8

1. Ketamine/
2. exp Cannabinoids/
3. Baclofen/
4. Clonidine/
5. Diazepam/
6. ketamine*.tw.
7. cannabinoid*.tw.
8. nabilone*.tw.
9. THC.tw.
10. tetrahydrocannabinol*.tw.
11. baclofen*.tw.
12. clonidine.tw.
13. diazepam.tw.
14. Marijuana Smoking/

15. marijuana*.tw.
16. or/1-15

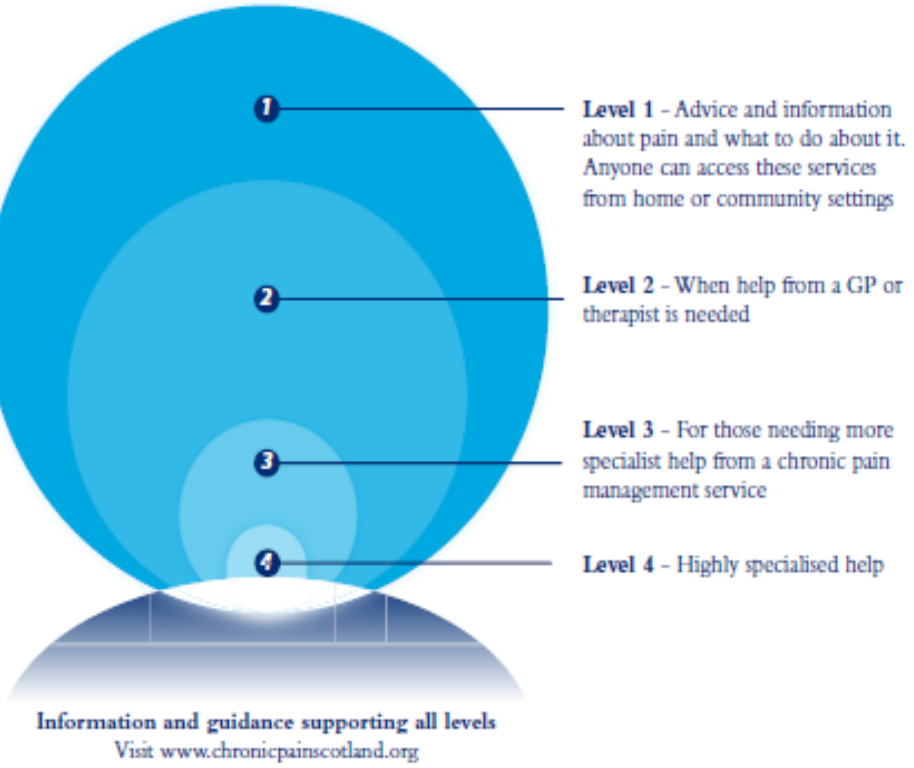
KQ 13

1. General Surgery/
2. Surgical Procedures, Operative/
3. surgery.tw.
4. exp Sympathectomy/
5. sympathectom*.tw.
6. Rhizotomy/
7. rhizotom*.tw.
8. exp Nerve Block/
9. nerve block*.tw.
10. biers block.tw.
11. ganglion block.tw.
12. plexus block.tw.
13. exp Botulinum Toxins/
14. botox.tw.
15. exp Electric Stimulation Therapy/
16. neuromodulation.tw.
17. exp Analgesia, Epidural/
18. exp Anesthesia, Epidural/
19. exp Injections, Epidural/
20. epidural.tw.
21. caudal.tw.
22. or/1-21
23. trigger point*.tw.
24. exp Injections/
25. injection*.tw.
26. 23 and (24 or 25)
27. 22 or 26

Appendix 4: The Scottish Service Model

Figure 2: Scottish Service Model for Chronic Pain

Most people get back to normal after pain that might come on after an injury or operation or for no apparent reason. Sometimes the pain carries on for longer than 12 weeks despite medication or treatment – this is called chronic or persistent pain.



Appendix 5: Further Cochrane Reviews

The Cochrane collaboration has produced a number of relevant systematic reviews on the pharmacological management of chronic pain in children and young people, since the completion of the literature search for this guideline. As these are highly relevant to the guideline, they have been summarised here. While the methodology of the reviews themselves is of high quality, the published primary research in this area remains limited. The conclusions of these reviews do not change the recommendations of the guideline.

Cooper et al (2017a) investigated the use of antiepileptic drugs for chronic non-cancer pain in children and adolescents. This systematic review identified two small studies but due to a lack of data further analysis could not be completed. As a meta-analysis was not conducted the authors were unable to comment on the efficacy or harm from the use of antiepileptic drugs in the treatment of chronic non-cancer pain in children and adolescents. The authors could not comment on the secondary outcomes of the study: Carer Global Impression of Change; requirement for rescue analgesia; sleep duration and quality; acceptability of treatment; physical functioning; and quality of life. It is recognised that some antiepileptics, including gabapentin and pregabalin, can be effective in adults with certain chronic pain conditions. Therefore, the authors found no evidence to support or contest the use of antiepileptics in the treatment of chronic non-cancer pain in children and adolescents.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents was explored by Eccleston et al (2017). The authors identified seven studies but the data available were insufficient to undertake a meta-analysis. Due to the inability to conduct further analyses the authors could not comment on the efficacy or harm of the use of NSAIDs in the treatment of chronic non-cancer pain in children and adolescents. There were also no definitive conclusions made on the secondary outcomes: Carer Global Impression of Change; requirement for rescue analgesia; sleep duration and quality; acceptability of treatment; physical functioning; and quality of life. It is

known that from randomised controlled studies (RCTs) in adults with chronic pain some NSAIDs are effective in some conditions.
Cooper et al (2017b) conducted a systematic review investigating the use of paracetamol (acetaminophen) in the treatment of chronic non-cancer pain in children and young people and found no studies that were eligible for inclusion in the review. The quality of evidence was rated as very low. Thence the authors found no evidence from randomised controlled trials to support or refute the use of paracetamol (acetaminophen) to treat chronic non-cancer pain in children and adolescents. The authors were also unable to comment on the efficacy or harm of paracetamol in children and young people. It is known, from randomised controlled trials in adults, that paracetamol can be effective (in certain doses) in certain pain conditions (not always chronic).
Opioids for chronic non-cancer pain in children and adolescents was examined in the systematic review by Cooper et al (2017c). No studies were eligible for inclusion in this review and the evidence was rated as very low quality. As there was no evidence from randomised controlled trails the authors were unable to support or disprove the use of opioids in the treatment of chronic non-cancer pain in children and young people. Evidence from adult randomised controlled trials have found that some opioids, such as morphine and codeine, can be effective in some chronic pain conditions. Therefore, no conclusions could be made in relation to the efficacy or harm of opioids in the treatment of chronic non-cancer pain in children and adolescents.

Cooper et al (2017d) conducted a systematic review examining the efficacy of anti-depressants for chronic non-cancer pain in children and adolescents. Four studies were found with information retrieved from 272 participants (6-18 years of age) who had chronic neuropathic pain, complex regional pain syndrome type 1, irritable bowel syndrome, functional abdominal pain or functional dyspepsia. All studies were small. One study explored amitriptyline versus gabapentin (34 participants), two studies investigated amitriptyline versus placebo (123 participants), and one study examined citalopram versus placebo (115 participants). The authors were unable to complete any quantitative analysis due to a lack of data. As a meta-analysis was not conducted the authors were unable to provide conclusions on the efficacy or harm from

the use of antidepressants in children and adolescents with chronic pain. The authors also could not comment on the secondary outcomes of the study: Carer Global Impression of Change; requirement for rescue analgesia; sleep duration and quality; acceptability of treatment; physical functioning; and quality of life. There is evidence from randomised controlled trials in adults which has found that antidepressants, such as amitriptyline, can provide some pain relief in some chronic non-cancer pain conditions.

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