Table 4: Summary of Recommendations in Included Guideline

Recommendations	Strength of Evidence and Recommendations
Scottish Government,[10] 2018, UK	
Evidence Summary High quality evidence with respect to pharmacological treatment of chronic pain in the pediatric patients was sparse and recommendations were based on consensus opinion of the expert group. Evidence related to pharmacological interventions such as acetaminophen, NSAIDs, anti-convulsants, anti-depressants, and opioids was reviewed and presented. The evidence reported by the authors are summarized below. Most of the recommendations were based on expert opinion (i.e. level: 4), unless the evidence level is indicated along with the recommendation. <u>Non-opioid analgesics</u> *Simple analgesics* The authors reported that evidence on use of analgesics in children with chronic non-cancer pain, is sparse. Aspirin is not recommended in children because of risk of Reyes syndrome (3 citations). Compared to acetaminophen (paracetamol), ibuprofen was more effective in short-term treatment of pain (immediately after surgery, but not in the following days) (1 citation; evidence level: 1-). A systematic review identified four studies (only one study being of high quality) on NSAIDs and showed short term pain reduction with naproxen in patellofemoral pain syndrome (1 citation, evidence level: 1+). *Topical analgesics* A small number of case series indicated that lidocaine patches were safe and effective in improving functionality in patients (3 citations; evidence level: 3). *Anti-convulsant* One RCT compared amitriptyline 10 mg at night) with gabapentin (300 mg, 3 times a day) for treating 34 pediatric patients with neuropathic pain. Both groups received physiotherapy. At 6 weeks, the proportions of patients achieving a decrease in pain score (MID in pain score of 1 or more), were 46% in the amitriptyline group and 60% in the gabapentin group, the between group difference was not statistically significant (P = 0.73) (1 citation; evidence level : 3). Case series studies showed some benefit with gabapentin used as a part of a multimodal approach to treat CRPS, neuropathic pain in Fabry disease, orchialgia, and distress behaviors in pediatric patients with severe neurological impairment (3 citations). A case series study with pediatric patients with CRPS showed that there was positive response with gabapentin (30 mg per kg per day) in five patients and with pregabalin (150 to 300 mg per day) in 2 patients (1 citation, evidence level: 3). Evidence from studies on epileptic pediatric patients indicate that the frequent side effects of gabapentinoids (including pregabalin) were sedation, nausea, and increased appetite (1 citation). Among the anti-convulsant drugs commonly used, gabapentin and pregabalin were reported to have the most favorable adverse effect profile (1 citation). One case series study on children with CRPS showed that the patients responded well to gabapentin or pregabalin (1 citation, evidence level: 3) *Anti-depressants* Two RCTs (described in a systematic review) showed that with amitriptyline 10 to 30 mg) the quality of life improved in pediatric patients with functional gastrointestinal disorders. It was also reported that there were no long-term studies on effectiveness of amitriptyline for treating pain in pediatric patients (1 citation, level of evidence: 1+). It was mentioned that based on clinical experience, low dose amitriptyline may have a favorable risk-benefit profile and may be considered for treating various chronic pain conditions in pediatric patients.	Level of evidence as indicated in the adjacent column. Strength of recommendations: not reported

Recommendations	Strength of Evidence and Recommendations

Non-standard analgesics
Three RCTs (small sample size) showed pain reduction with intrathecal baclofen in pediatric patients with cerebral palsy (1 citation, evidence level: 2+).
There is limited evidence on effectiveness of oral alendronate for treating bone pain in osteogenesis imperfecta, but not other bisphosphonates (citation not reported, level of evidence: -2).
One systematic review on treatments for recurrent abdominal pain in children suggested that pizotifen showed benefit in abdominal migraine and famotidine in dyspepsia (1 citation, evidence level: -2).
There is limited evidence on effectiveness of oral alendronate for treating bone pain in osteogenesis imperfecta, but not other bisphosphonates (citation not reported, level of evidence: 2-).
No good quality evidence was identified regarding the use of ketamine, cannabinoids, oral baclofen, diazepam or clonidine in managing chronic pain in children.

Opioids
Opioids are associated with potential harms such as misuse, overuse, endocrine dysfunction, and poorly understood effects on the immune system and there is concern regarding long term use (1 citation). There is considerable evidence available on opioid use for treating chronic pain in adult patients. However, there is limited evidence in case of opioid use in pediatric patients with chronic pain; in addition, there are issues such as lack of control group and small sample size (1 citation).

According to MHRA, codeine is not recommended in children under the age of 12 years.

Recommendations

Recommendation
"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." P. 26
"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." P. 26
"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." P. 26
"Topical NSAIDs should be considered for treatment of children and young people with localised, non CRPS and non-neuropathic pain." P. 26
"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." P. 26, (evidence level: 3).
"Antiepileptic drugs could be considered as part of a multimodal approach in the management of children and young people with neuropathic pain" P. 26

Recommendations	Strength of Evidence and Recommendations
“Gabapentin should be considered as first line anticonvulsant (specialist use only). It should be used in the lowest effective dose, with ongoing monitoring for efficacy and adverse effects.” P. 26	
“Pregabalin could be considered as a second line anticonvulsant drug if gabapentin is not tolerated or is ineffective (specialist use only).” P. 26	
“Low dose amitriptyline should be considered in the treatment of children and young people with functional gastrointestinal disorders.” P. 26, (evidence level: 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.” P. 27, (evidence level: 3)	
“If amitriptyline is effective but particularly sedative in an individual, nortriptyline should be considered as a less sedating alternative.” P. 27	
“Bisphosphonates should be considered in the management of children and young people with osteogenesis imperfecta who have bone pain.” P. 27	
“Intrathecal baclofen should be considered for reducing spasticity related pain in children and young people with cerebral palsy.” P. 27	
“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.” P. 27	
“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.” P. 27	
“Use of opioids should be for as short a time as possible with regular review and monitoring of efficacy and side effects.” P. 27	
“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.” P. 27	

CRPS = complex regional pain syndrome; MHRA = Medicines and healthcare products regulatory agency; NSAIDs = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial.