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Pharmacological Interventions for Chronic Pain in Pediatric Patients: A Review of Guidelines

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Abbreviations

CNCP	chronic non-cancer pain
NSAIDs	non-steroidal anti-inflammatory drugs
RCT	randomized controlled trial

Context and Policy Issues

Chronic pain is defined as recurrent or persistent pain that extends longer than the expected healing time (generally three months or more).[1,2] Chronic pain affects the individual, as well as the individual's family, society and the health care system.[3] Untreated chronic pain in childhood is associated with risk of subsequent pain as well as physical and psychological impairment in adulthood.[2] A higher proportion of chronic pain in adulthood was reported in those who had chronic pain in adolescence compared with those who were pain free in adolescence.[2] Pathophysiological classifications of chronic pain in the pediatric population include nociceptive pain (somatic or visceral), neuropathic pain (from damage to or dysfunction of the peripheral or central nervous system) and idiopathic pain (no known cause).[4,5] The most common chronic pain disorders in the pediatric population include primary headache, centrally mediated abdominal pain syndromes, and chronic/recurrent musculoskeletal and joint pain.[2]

Globally, pain is a common feature among children and adolescents, and in many it is chronic.[6,7] A systematic review[8] of studies on the prevalence rates of chronic pain in children and adolescents reported that there was wide variation in the prevalence rates depending on demographics and psychosocial factors; prevalence rates were 8% to 83% for headache, 4% to 53% for abdominal pain, 4% to 40% for musculoskeletal pain, 14% to 24% for back pain, and 5% to 88% for other pain. According to the 2007/2008 Canadian Community Health Survey of individuals in the age group 12 years to 44 years the prevalence of chronic pain was estimated as 9.1% in males and 11.9% in females; for the pediatric subgroup (12 years to 17 years) the prevalence was 2.4% in males and 5.9% in females.[3]

The development and persistence of chronic pain involve multiple, integral, neural pain networks (i.e., peripheral, spinal, and brain) that interact in a complex way to contribute to an individual's experience of pain.[8] In children these peripheral, spinal, and brain networks are not mature and change over time as the child matures, which adds further complexity to understanding, evaluating and treating pain in the pediatric population.[8]

Pharmacological agents have been used for treatment of chronic non-cancer pain in children and adolescents. These include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), anti-depressants, anticonvulsants, and opioids. NSAIDS include agents such as aceclofenac, acetylsalicylic acid, celecoxib, choline magnesium trisalicylates, diclofenac, etodolac, etoricoxib, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, parecoxib, phenylbutazone, piroxicam, sulindac, tenoxicam, and tiaprofenic acid.[4] Anti-depressants include agents such as amitriptyline, nortriptyline, imipramine, duloxetine, fluoxetine, and bupropion.[9] Anticonvulsants include agents such as gabapentin and pregabalin.[10] Opioids include agents such as buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, and tramadol.[7]

There appears to be limited evidence available with respect to pharmacological treatments for management of chronic pain in pediatric patients. One systematic review[6] reported that there was no evidence from RCTs to support or refute the use of paracetamol (acetaminophen) for treating chronic non-cancer pain (CNCP) in children and adolescents. A second systematic review[4] investigated the clinical efficacy of NSAIDs for treating CNCP in children and adolescents. The authors reported that there were few RCTs identified and they were of low or very low quality, and they had insufficient data for analysis; hence they were unable to comment on the efficacy or harm of NSAIDs for treating CNCP in children and adolescents. A third systematic review[9] investigated the clinical efficacy of anti-depressants for treating CNCP in children and adolescents. The authors reported that there were few RCTs identified and they were of small sample size and of very low quality, and they had insufficient data for analysis; hence they were unable to comment on the efficacy or harm of anti-depressants for treating CNCP in children. A fourth systematic review[7] reported that there was no evidence from RCTs to support or refute the use of opioids for treating CNCP in children and adolescents. There appears to be uncertainty regarding clinical effectiveness pharmacological interventions for treating CNCP in children and adolescents. Hence guidelines regarding the use of pharmacological interventions for treatment of chronic pain is pediatric and young people are important.

The aim of this report is to review the evidence-based guidelines regarding pharmacological interventions for pediatric and youth patients with chronic pain.

Research Question

What are the evidence-based guidelines regarding on- and off-label pharmacological interventions for pediatric and youth patients with chronic pain?

Key Findings

One relevant evidence-based guideline on the management of chronic pain in children and young people was identified. The level of evidence going from the highest to the lowest was scored as 1++, 1+, 1-, 2++, 2+, 2-, 3, or 4 for the evidence presented in the guideline. Recommendations on various pharmacological treatments were presented but the strengths of recommendations were not provided and were based mainly on expert opinion (evidence level: 4).

Lidocaine (5%) patches should be considered in the management of children and young people with localized neuropathic pain, particularly when improving compliance with physiotherapy interventions (evidence level: 3).

Low dose amitriptyline should be considered for treating children and young people with functional gastrointestinal disorders (evidence level: 1-), chronic daily headache, chronic widespread pain or mixed nociceptive/neuropathic back pain (evidence level: 3).

Recommendations for use of acetaminophen, NSAIDs, gabapentin, pregabalin, bisphosphonate, baclofen, pizotifen, and famotidine for management of chronic pain varied depending on the types of chronic pain and were based on expert opinion.

Based on expert opinion, opioids are rarely recommended for chronic pain because of their adverse effect profile, and if used should be used as short a duration as possible.

The recommendations need to be considered in the light of the limitations (such as evidence available was of limited amount and limited quality, and recommendations were based on expert opinion; and it was unclear if generalizable to the Canadian context).

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pediatrics and chronic pain. Search filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and April 3, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients (aged 6 to 18 years) with chronic pain, including pain from chronic daily headaches, migraines, back pain, abdominal pain, idiopathic local pain, chronic widespread pain and fibromyalgia, and complex regional pain syndrome
Intervention	Both on- and off-label pharmacological interventions
Comparator	Not applicable
Outcomes	Recommendations regarding the use of pharmacological interventions to treat chronic pain; recommendations regarding the indications of the interventions; recommendations regarding interactions of pharmacological interventions
Study Designs	Evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Guidelines with unclear methodology or irrelevant populations were also excluded.

Critical Appraisal of Individual Studies

The included evidence-based guidelines were critically assessed by one reviewer, using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool.[11] Summary scores were not calculated for the included guidelines; rather, the strengths and limitations of the included guideline were described.

Summary of Evidence

Quantity of Research Available

A total of 107 citations were identified in the literature search. Following screening of titles and abstracts, 100 citations were excluded and seven potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full text review. Of these nine potentially relevant articles, eight publications were excluded for various reasons, and one publication met the inclusion criteria and was included in this report. This comprised one evidence-based guideline.[10] Appendix 1 presents the PRISMA[12] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Characteristics of the guideline[10] are summarized and additional details are provided in Appendix 2, Table 2.

Study Design

One relevant evidence-based guideline[10] was identified. The guideline development group was multidisciplinary and comprised of individuals representing relevant stakeholder groups, such as a consultant in pediatric anesthesia and pain management, pediatrician, pediatric surgeon, clinical psychologist, physiotherapist, pharmacist, nurse, and patient representative. A systematic literature search was conducted to identify evidence; study designs included in the literature search were not reported. The methodology of the Scottish Intercollegiate Guidelines Network (SIGN) was used for assessing the quality of evidence. The SIGN methodology has a recommendation grading system. However, it appears that recommendations that were relevant for this report could not be graded by the guideline development group. Recommendations were based on consensus; method for achieving consensus was not presented.

Country of Origin

The guideline[10] was from the UK and was produced by the Scottish government.

Patient Population

The guideline[10] was for use by health care professionals for the management of chronic pain in children and young people.

Interventions and Comparators

The guideline[10] presented several pain management strategies: pharmacological interventions, physical therapies, psychological therapies, dietary therapies, complementary and alternative therapies, and surgical interventions. Of these, pharmacological interventions (acetaminophen, NSAIDs, anti-depressants, anticonvulsants and opioids) were of relevance for this report and are discussed here.

Outcomes

The guideline[10] presented recommendations for management of chronic pain in children and young people. The impact of the pharmacological interventions on pain status and their safety were considered.

Summary of Critical Appraisal

The critical appraisal of the included guideline[10] is summarized and additional details are provided in Appendix 3, Table 3.

The scope and purpose were stated. The guideline development group comprised of individuals with relevant expertise, as well as a patient representative. The recommendations were clearly stated. A systematic literature search was undertaken to identify evidence, and the method for formulating the recommendations was according to the SIGN methodology. The guideline was externally reviewed. It appears that inclusion and exclusion criteria for evidence selection were not clearly described, hence it was unclear how the evidence was selected; also, the link between recommendation and supporting evidence was not always clear. For the recommendation on amitriptyline for functional gastrointestinal disorder, it was unclear why the level of evidence that was presented alongside the recommendation did not appear to match the evidence level presented for the related study on which it was based. Applicability of the guidelines was not described. Competing interests of the guideline development group members were not presented, hence it was unclear if there were any potential issues.

Summary of Findings

One relevant evidence-based guideline[10] (on the management of chronic pain in children and young people) was identified and recommendations regarding pharmacological interventions are summarized below and details are presented in Appendix 4, Table 4.

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 experts. Recommendations were not graded. Most of the recommendations were based on expert opinion (i.e., evidence level: 4), unless the evidence level was indicated in the guideline publication along with the recommendation. Recommendations presented below relate to the management of chronic pain in children and young people.

Based on consensus opinion, this guideline recommends that pharmacological interventions should only be started after careful assessment, should be in the context of a multidisciplinary approach, and there should be ongoing planned reassessment of efficacy and side effects.

Additional recommendations for several classes of drugs were also provided:

Non-opioids

Simple analgesics and topical analgesics:

Acetaminophen and NSAIDs should be considered in the treatment of chronic non-malignant pain in children and young people; however, they should be limited to the shortest possible duration. Topical NSAIDs should be considered for localized, chronic regional pain syndrome and non-neuropathic pain in children and young people. Lidocaine (5%) patches should be considered in the management of children and young people with localized neuropathic pain, particularly when improving compliance with physiotherapy interventions (evidence level: 3).

Anticonvulsants and antidepressants:

Antiepileptic drugs may be considered as part of a multimodal strategy for managing neuropathic pain in children and young people. Low dose amitriptyline should be considered for the management of functional gastrointestinal disorders in children and young people (evidence level: -1), chronic daily headache, chronic widespread pain or mixed nociceptive/neuropathic back pain (evidence level: 3). Gabapentin should be considered as first line anticonvulsant, and pregabalin could be considered as second line, when gabapentin is either not tolerated or is ineffective.

Non-standard analgesics

Bisphosphonates should be considered for managing bone pain in children and young people with osteogenesis imperfecta. Intrathecal baclofen should be considered for managing pain associated with spasticity in children and young people with cerebral palsy. Pizotifen should be considered for abdominal migraine and famotidine for dyspepsia in children and young people.

Opioids

Opioids are rarely indicated for chronic pain due to their adverse effects. Opioids should be restricted to as short a time as possible with regular monitoring of efficacy and adverse effects. Treatment with codeine is not recommended in children under 12 years of age, and should be avoided in adolescents, particularly in those with respiratory problems or those who rapidly metabolize CYP2D6.

Limitations

As the evidence identified by the guideline authors was of limited amount and limited quality, the recommendations were mostly based on consensus opinion of the experts.

The pediatric population generally comprises infants (less than 1 year), children (1 to 9 years) and adolescents (10 to 18 years).[6,7] The selected guideline[10] presented recommendations for pharmacological treatments for management of chronic pain in children and young people; it was difficult to determine if the age group considered was specifically 6 years to 18 years or if the recommendations would apply to a particular age group and not to another age group within that range of 6 years to 18 years.

The guideline was prepared by the Scottish government, hence its generalizability to the Canadian context is unclear.

The recommendations need to be considered in the light of the limitations.

Conclusions and Implications for Decision or Policy Making

One relevant evidence-based guideline[10] on the management of chronic pain in children and young people was identified. There was limited evidence available with respect to pharmacological treatment of chronic pain in the pediatric patients and the evidence was not of high quality. The level of evidence going from the highest to the lowest was scored as 1++, 1+, 1-, 2++, 2+, 2-, 3, or 4 for the evidence presented in the guideline. Most of the recommendations were based on expert opinion (i.e., evidence level: 4), unless the evidence level was indicated along with the recommendation. The strengths of recommendations were not provided.

Lidocaine (5%) patches should be considered in the management of children and young people with localized neuropathic pain, particularly when improving compliance with physiotherapy interventions (evidence level: 3). Low dose amitriptyline should be considered for treating children and young people with functional gastrointestinal disorders (evidence level: 1-), chronic daily headache, chronic widespread pain or mixed nociceptive/neuropathic back pain (evidence level: 3). Recommendations for the use of acetaminophen, NSAIDs, gabapentin, pregabalin, bisphosphonate, baclofen, pizotifen, and famotidine for management of chronic pain were based on expert opinion. Based on expert opinion, opioids are rarely indicated for chronic pain because of their adverse effect profile, and if used, should be used for as short a duration as possible.

To support guideline development, good quality evidence on the effectiveness of various pharmacological agents for treatment of chronic pain in children and young people is needed. Therefore, further studies are needed to investigate the clinical effectiveness of the various pharmacological agents in treating chronic pain in various age groups in the pediatric population. Also, long-term studies targeting younger children with pain, may be useful to determine the protective effect of early intervention if any, in preventing or reducing transition to chronic pain later in life.

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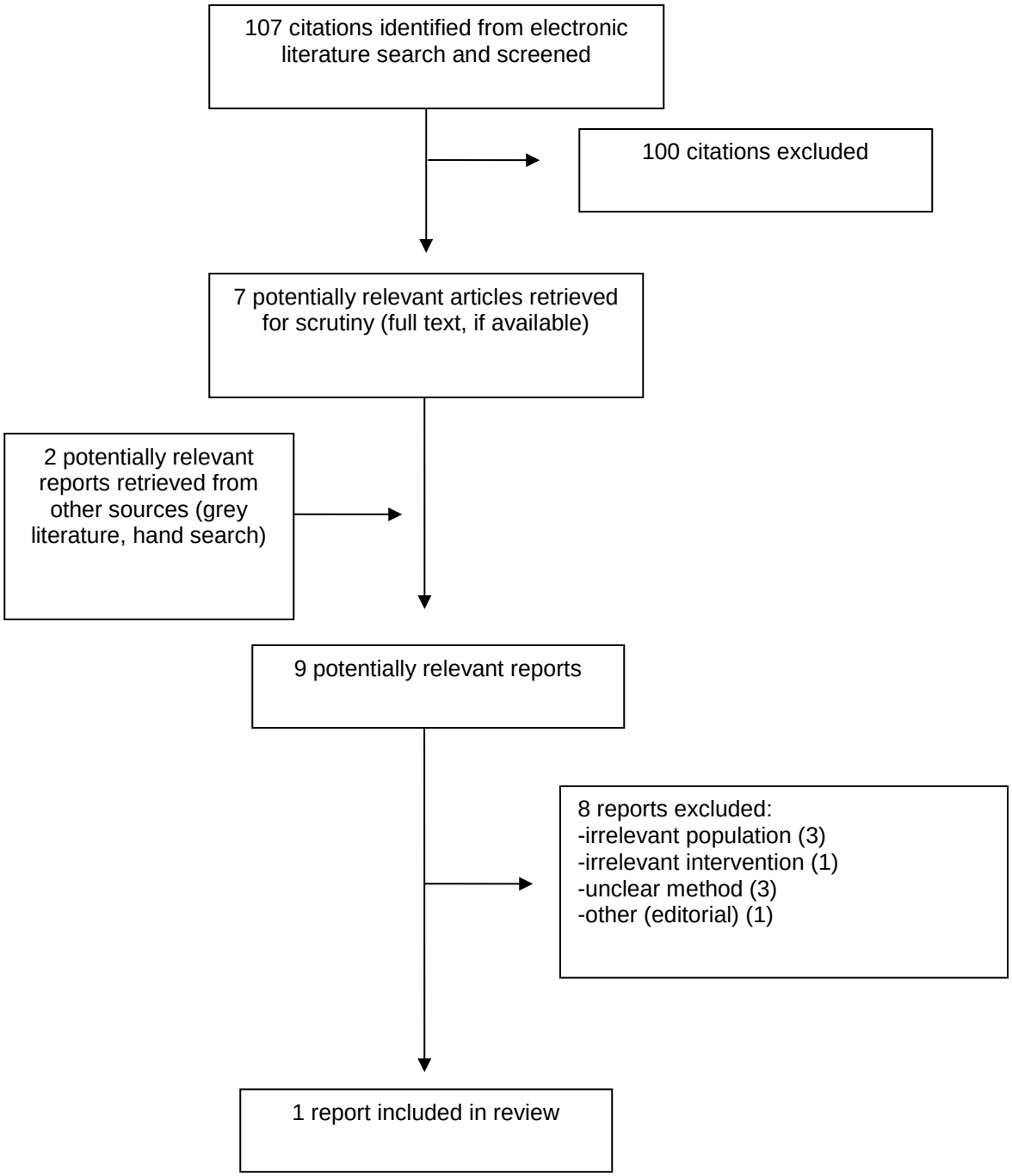
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publication

Table 2: Characteristics of Included Guideline

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Scottish Government,[10] 2018, UK						
Intended users: Health professionals involved in the management of chronic pain in children and young people Target population: children and young people chronic pain (acute and cancer pain was not considered) Aim: To provide guidance on managing chronic pain (improving quality of life and minimizing risks of long-term adverse effects)	Pharmacological treatments (relevant for this report), This guideline had a broad objective and included as well other management strategies (not relevant for this report): physical therapies; psychological therapies; dietary therapies; complementary and alternative therapies; and surgical interventions.	Pain, functional ability, quality of life, and adverse effects.	The methodology used was the SIGN methodology.[13,14] A systematic literature search was conducted to identify evidence. The inclusion and exclusion criteria for selecting the evidence were not presented. A summary of the evidence identified was presented.	The assessment of quality of evidence was conducted using the SIGN methodology. [13,14] Levels of evidence[a] are listed in the footnote below.	Recommendations were based on consensus. The procedure for achieving consensus was not presented Guideline development group was multidisciplinary (such as consultants in pediatric anesthesia and pain management, pediatrician, pediatric surgeon, clinical psychologist, physiotherapist, pharmacist, nurse, and patient representative). The SIGN methodology has a recommendation grading system. However, it appears that the recommendations that were relevant for this report, could not be graded	The document was externally reviewed. The document was sent to six organizations in the UK for comment. Also, it was reviewed by four academics (3 from the UK, and one from the US).

[a]Levels of evidence:
1++ indicates evidence was based on high quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias;
1+ indicates evidence was based on well conducted meta-analysis, systematic reviews of RCTs, or RCTs with a low risk of bias;
1- indicates evidence was based on meta-analysis, systematic reviews of RCTs, or RCTs with a high risk of bias;
2++ indicates evidence was based on high quality systematic reviews of case control or cohort studies; or 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+ indicates evidence was based on 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- indicates evidence was based on case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal;
3 indicates evidence was based on non-analytic studies, e.g. case reports, case series;
4 indicates evidence was based on expert opinion.

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Strength of recommendation: A indicates highly recommended ("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"[10] P. 33) B indicates 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"[10] P. 33) C indicates limited/developing evidence to date, no indication against use ("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."[10] P. 33)						

RCTs = randomized controlled trials; SIGN = Scottish intercollegiate guidelines network.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline
	Scottish Government,[10] 2018, UK
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	yes
2. The health question(s) covered by the guideline is (are) specifically described.	yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	yes
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	yes
6. The target users of the guideline are clearly defined.	yes
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	yes
8. The criteria for selecting the evidence are clearly described.	not clearly described
9. The strengths and limitations of the body of evidence are clearly described.	not always clear
10. The methods for formulating the recommendations are clearly described.	yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	not always clear
12. There is an explicit link between the recommendations and the supporting evidence.	not always clear
13. The guideline has been externally reviewed by experts prior to its publication.	yes
14. A procedure for updating the guideline is provided.	not stated
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	yes
16. The different options for management of the condition or health issue are clearly presented.	yes
17. Key recommendations are easily identifiable.	yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	not stated

Item	Guideline
	Scottish Government,[10] 2018, UK
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	not stated
20. The potential resource implications of applying the recommendations have been considered.	not stated
21. The guideline presents monitoring and/or auditing criteria.	not stated
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	not stated
23. Competing interests of guideline development group members have been recorded and addressed.	not stated

Appendix 4: Main Study Findings and Authors' Conclusions

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.

Appendix 5: Additional References of Potential Interest

Guidelines with unclear methodology

Chronic pain. Care for adults, adolescents and children. (draft). *Quality standards*. Toronto (ON): Health Quality Ontario; 2019: https://www.hqontario.ca/portals/0/documents/evidence/quality-standards/qs-chronic-pain-clinical-guide-1810-en.pdf. Accessed 2020 May 04.

Politei JM, Bouhassira D, Germain DP, et al. Pain in Fabry disease: practical recommendations for diagnosis and treatment. *CNS Neurosci Ther.* 2016;22(7):568-576. PubMed:PM 27297686

Politei JM, Gordillo-Gonzalez G, Guelbert NB, et al. Recommendations for evaluation and management of pain in patients with mucopolysaccharidosis in Latin America. *J Pain Symptom Manage.* 2018;56(1):146-152. PubMed: PM 29649527