WHO Guideline for the management of chronic pain in children

Scope and key question

I. Background

Pain in children is a public health concern of major significance in most parts of the world. For many children, this pain is chronic. Chronic pain is experienced by about a quarter to a third of children (1-3), with about 1 in 20 experiencing debilitating pain (4). As the leading cause of morbidity in children and adolescents in the world today, chronic pain is a major health concern.

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Chronic pain is pain that persists or recurs for longer than 3 months. The 11th revision of the International Classification of Diseases (ICD-11) categorizes chronic pain as follows:

- Chronic primary pain
- Chronic cancer-related pain
- Chronic postsurgical or post traumatic pain
- Chronic secondary musculoskeletal pain
- Chronic secondary visceral pain
- Chronic neuropathic pain
- Chronic secondary headache or orofacial pain

Chronic primary pain is characterized by significant emotional or functional disability and is diagnosed independent of identified biological or psychological contributors. Non-primary or “secondary” pain diagnoses is pain caused by a clear underlying aetiology such as a disease, injury, lesion or their treatment (5).

Initial theories behind the origin of pain included the “gate theory” that described nociceptors and touch receptors. When painful stimuli reaches a specific intensity, a gate opens and activate pathways leading to pain being experienced (6). This was later augmented with sensory-discriminative, affective-motivational and cognitive-evaluative components in a biomedical model of pain (7-11).

The biomedical model, however, explained pain as a dichotomy of physiological or psychological origin, where any pain response that did not correlate with the degree of tissue damage was considered psychological. Anatomical, physiological and biochemical pathology seen from physical examination and diagnostic tests, however, often do not adequately explain the persistence of chronic pain, even in chronic secondary pain related to a medical condition.

The biopsychosocial model of pain was introduced to try to explain the complexities of chronic pain (12). Illness results from a complex interaction between various biological, psychological and social factors. The “neuromatrix” model of pain (13, 14) further carried this forward by introducing the stress component into the pain equation.

Current models to explain chronic pain assumes a progression from homeostasis to dysregulated allostatic changes and spiralling distress cycle leading to chronic pain, mediated at least in part by changes in the central nervous system mechanisms (15-18). Recent epidemiological (19-24),
physiological (25-29) and neurobiological (16-18, 30-41) studies have strengthened this hypothesis of chronic pain. Interdisciplinary care of chronic pain in children and adolescents incorporates physical treatment with cognitive, behavioural, environmental and emotional interventions (42-50).

II. Review of latest evidence

A. Safety and efficacy of use of medicines for pain in children

A recent overview of reviews of pharmacologic management of chronic pain in children found 23 systematic reviews of randomized controlled trials investigating pharmacologic treatment of children and adolescents with chronic pain, further categorized into chronic cancer-related pain and chronic non-cancer pain (51). Sixteen of them did not find any studies of children with chronic cancer-related or non-cancer pain. The 7 remaining systematic reviews, combined, included 6 relevant trials, all were on chronic non-cancer pain in children. The characteristics of the 6 trials are shown in the table (see annex) (52-57). None of the trials had more than 200 subjects (range was 14 to 115 subjects). No trials were found on pharmacologic interventions for chronic cancer-related pain. The overview of reviews assessed that the quality of evidence was very low and gave little confidence in the effect estimates.

Pain in children differs to that in adults (58-60), due to immaturity in the anatomical expression of neurotransmitters and neuromodulators, developmental potential, plasticity of the central nervous system and psychosocial milieu (61-63). Exposure to chronic pain in early life have implications on the incidence, severity and duration of chronic pain, and for long term maladaptive neurologic changes (64-69). Yet, despite these differences, pharmacologic management of adult pain is often extrapolated downward to the paediatric population even when this management was not intended to be given to children. In part, this is due to the obvious lack of evidence for pharmacologic management of pain in children (70, 71).

The role of nonpharmacologic interventions for chronic pain, on the other hand, has had a longer history of research and success (72-81), with the neurobiological processes now being more clearly elucidated (16, 19, 20, 28, 35, 45, 46, 82, 83).

B. Dependence and misuse potential

Studies have shown an increasing prevalence of prescription opioid use and misuse among American adolescents and young adults (84, 85). Reported prescription opioid misuse is common among adolescents and young adults and often associated with additional substance abuse.

Using data from the US National Longitudinal Study of Adolescent to Adult Health (with almost 15,000 participants), Groenewald and colleagues (86) showed adults with a history of adolescent chronic pain were more likely to misuse opioids than those without history of chronic pain, even after controlling for other known risk factors. Among those who experienced adolescent chronic pain, race (White), exposure to trauma, and other substance use were associated with subsequent opioid misuse. Conversely, nonmedical prescription opioid use was prospectively associated with subsequent heroin use in adolescence (87).

More lifetime prescriptions of opioids among young adults lowers their perceived risk of occasional misuse (88). In turn, higher frequency of opioid misuse is associated with opioid use disorder and withdrawal symptoms (89). Among American adolescents, any use, prescription drug misuse, medical misuse, nonmedical misuse and presence of substance use disorder symptoms were more likely among children with poor school adjustment or those not in school (90).
Recently, neuroscience research has provided some mechanistic understanding of the effects of opioids and addiction-related processes, and may in the future suggest avenues for management of chronic pain, both pharmacologic and nonpharmacologic (91-94).

C. Public health benefits and risks of different strategies for ensuring appropriate access

The UN Office of Drugs and Crime World Drug Report 2019 (95) highlight the “global paradox of too much and not enough” in describing the difficulty of ensuring the availability of controlled substances for medical and scientific purposes while preventing their diversion and misuse. International drug control conventions aim to remove barriers that limit the availability of accessibility of controlled drugs for medical use, based on legal and regulatory frameworks and clinical guideline on rational prescription practices.

Many low-income countries face difficulties in balancing necessary access for medical purposes while curbing abuse with limited resources and health care systems that are already struggling to provide universal health coverage. The management of pain requires a broad and multidisciplinary approach that addresses its physical and psychosocial dimensions. Human rights norms require that pain management be incorporated as part of the basic health package under their universal health coverage schemes (96). Chronic pain in children should be a high priority for public health research and policy.

III. Analytical framework or logic model

A possible analytic framework for the effect of the intervention to modulate pain is presented in the following figure:

IV. Key question

Based on the analytical framework (above), the questions were drafted in population, intervention, control, outcomes (PICO) format, and summarized in the table below.
Among children with chronic pain associated with a medical illness or condition, would giving nonpharmacologic, pharmacologic or a combination of management interventions compared to placebo produce significant pain reduction and other critical outcomes?

### Population
- Children and adolescents (0-19 years) in chronic pain (pain that persists or recurs for longer than 3 months)
  
  This population will include children with any medical illness or condition where pain is a symptom or where pain is related to an illness or the treatment of an illness, i.e., chronic secondary pain.

  This population will exclude children with chronic primary pain.

### Subgroups
- By severity: Mild or moderate pain vs. severe pain
- By age: Less than 10 years of age vs. 10 years of age or older

### Interventions
- Nonpharmacologic and pharmacologic interventions
  - Cognitive and behaviour interventions such as pain neuroscience education, activity pacing, relaxation, distraction, mindfulness, sleep hygiene
  - Psychological interventions such as cognitive-behavioural therapy, acceptance and commitment therapy
  - Physical treatments such as physiotherapy, occupational therapy, interventional procedures (e.g. nerve blocks)
  - Pharmacologic: acetaminophen (paracetamol), non-steroidal anti-inflammatory drugs, opioids, antidepressants, anti-epileptic drugs

### Comparator
- Active or placebo comparators

Comparison may include comparisons between different combinations of management options, pharmacologic vs. non-pharmacologic management, or within drug class comparisons and between drug comparisons.

### Outcomes
- Reduction in pain intensity (30% reduction; 50% reduction; etc.); continuous pain intensity
- Global judgement of satisfaction with treatment
- Health-related quality of life; functional disability; role functioning
- Depression
- Sleep
- Cost
- Disorders due to use of psychoactive substances
- Other adverse events (such as misuse of prescription medicines and non-medical use of related psychoactive substances)
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References

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### Annex:

**Table: Characteristics of individual randomized controlled trials**

<table>
<thead>
<tr>
<th>First year</th>
<th>author, year</th>
<th>Drug class (drug name)</th>
<th>Pain condition</th>
<th>Sample size; age</th>
<th>Outcomes reported</th>
<th>Adverse events (AE) reported</th>
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</thead>
<tbody>
<tr>
<td>Arnold, 2016 (52)</td>
<td>Antiepileptic (pregabalin)</td>
<td>Fibromyalgia</td>
<td>$n = 107$; 12-17 years old</td>
<td>No significant difference in mean pain score compared to placebo</td>
<td>38 (70.4%) children in the pregabalin arm experience 1 or more AE</td>
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<td>Better patient global impression of change compared to placebo (53% vs. 30%)</td>
<td>Common AEs: dizziness, nausea, headache, increased weight, fatigue, somnolence, oropharyngeal pain, pain in extremity, pyrexia, back pain, upper respiratory tract infection, vomiting</td>
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<td>1 child from pregabalin arm had serious AEs (cholelithiasis, major depression)</td>
<td>3 children from pregabalin arm had severe AE (migraine, cholelithiasis, major depression, pain, ligament sprain)</td>
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<td>Bahar, 2008 (53)</td>
<td>Antidepressant (amitriptyline)</td>
<td>Recurrent abdominal pain (irritable bowel syndrome)</td>
<td>$n = 33$; 12-18 years old</td>
<td>No difference in reduction in abdominal pain intensity or frequency compared to placebo</td>
<td>Weight gain was seen in both amitriptyline and placebo groups</td>
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<td></td>
<td>No difference in overall quality of life scores compared to placebo</td>
<td>No other adverse events were reported</td>
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<td>No difference in interference with schoolwork, sports or friends compared to placebo</td>
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<td>Brown, 2016 (54)</td>
<td>Antidepressant (amitriptyline) vs. antiepileptic (gabapentin) [no placebo arm]</td>
<td>Complex regional pain syndrome</td>
<td>$n = 34$; 7-18 years old</td>
<td>Decrease in pain intensity on a coloured analogue scale (above minimally important difference of 1/10) from both drugs (no difference between groups): Amitriptyline decrease of $1.16 \pm 2.26$</td>
<td>Three children discontinued the trial due to adverse events: one child on amitriptyline developed secondary pain; one child on gabapentin developed secondary pain; and one child on gabapentin had an unexpected</td>
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<tr>
<td>Study</td>
<td>Intervention</td>
<td>Condition</td>
<td>Sample Size</td>
<td>Outcomes</td>
<td>Side Effects</td>
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<td>Roohafza, 2014 (55)</td>
<td>Antidepressant (citalopram)</td>
<td>Recurrent abdominal pain</td>
<td>115; 6-18 years old</td>
<td>No difference in reduction in pain intensity, depression, anxiety, somatization score compared to placebo</td>
<td>Children from the citalopram group experienced more drowsiness and dry mouth. Other side effects included insomnia, nausea, fatigue, headache, dizziness, allergic reaction and loss of appetite. No serious AE reported</td>
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<td>Saps, 2009 (56)</td>
<td>Antidepressant (amitriptyline)</td>
<td>Recurrent abdominal pain (irritable bowel syndrome, functional abdominal pain or functional dyspepsia)</td>
<td>90; 8-17 years old</td>
<td>No difference in overall sense of improvement from treatment compared to placebo</td>
<td>No difference in pain relief compared to placebo 3 children from the amitriptyline arm withdrew from the study from AE (fatigue, rash, headaches)</td>
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<td>Symon, 1995 (57)</td>
<td>Serotonin antagonist (pizotifen)</td>
<td>Recurrent abdominal pain (functional abdominal pain)</td>
<td>14; 5-13 years old</td>
<td>8 fewer days of abdominal pain noted compared to placebo (unclear total duration of observation) Significantly lower index of pain severity and lower index of misery (tools were not validated) compared to placebo</td>
<td>2 children had adverse events (drowsiness, increased appetite) Children given pizotifen gained more weight compared to placebo (1.25 kg vs. 0.38 kg)</td>
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Gabapentin: decrease of 1.56 ± 2.27 Better sleep score for both drugs (no difference between groups)