

WHO

WHO Calls for Targeted Research on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses

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The WHO has undertaken an update of the 1998 WHO Cancer Pain Relief and Palliative Care in Children Guidelines, in extending the scope to persisting pain associated with other medical conditions. The new WHO Guidelines for Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses, using the GRADE approach for evidence synthesis and grading of recommendations, are expected to help reduce the enormous treatment gap for pain in children. The WHO aims to update these guidelines within the next five years. Given the paucity of studies in the paediatric population with persisting pain, a meaningful revision of these guidelines will need the international scientific community to invest in research on the topics that were identified as evidence gaps during the development process. For this reason, the WHO calls for a collaborative effort to cover the identified priority research areas and related systematic reviews of evidence.

Introduction

The World Health Organization (WHO) issued guidelines on Cancer Pain Relief and Palliative Care in Children in 1998 (1). Since then, the need for guidance on pain management in children with pain from non-cancer causes has grown, not least because of the large numbers of children with HIV/AIDS. In addition, the extremely low use of opioid analgesics in children and adults in many countries, acknowledged by several United Nations (UN) bodies and in a number of UN resolutions, has led to an analysis of the causes of this situation (2–6). The International Narcotic Control Board reported in 2003 that six developed countries accounted for 79% of global morphine consumption. Conversely, developing countries, which represent 80% of the world population, accounted for only about 6% of global morphine consumption (2). Improving knowledge of the rational use of opioid analgesics for the relief of pain has been identified as a prerequisite for adequate provision of pain management (7, 8). In 2008, a Delphi study identified the need

for internationally recognized pain treatment guidelines and identified the WHO as the most suitable body to undertake the development of such guidelines (9). Following this finding, the WHO initiated the development process, in accordance with the *WHO Handbook for Guideline Development* (10). In order to ensure that the guidelines were developed according to best practices and the best use of available evidence, the GRADE methodology was applied (11–14). The development of the *WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses* through this rigorous step-by-step process has led to the identification of several research gaps and the formulation of a research agenda for tackling the priority areas which deserve urgent attention by the international scientific community.

The purpose of this article is to underline the lack of high quality evidence for pharmacological treatment of persisting pain in children and to call for research on identified gaps. It is beyond the scope of the article to explain how recommendations were formulated based on the available evidence and also how considerations of the balance between risks and benefits, values, cost and feasibility of the interventions were weighed.

Epidemiology of pain in children

It is difficult to provide comprehensive and accurate epidemiological data on the extent of pain in children

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Table 1. Summary table of SRs and RCTs retrieved on pharmacological interventions in the pediatric population

Group of clinical questions	Numbers of SR and RCTs retrieved on the pediatric population	Comment
Two-step versus three-step treatment approach*, including comparative effectiveness of paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), codeine, tramadol	Two RCTs, One SR of RCTs	Two RCTs were performed in an acute pain setting (musculoskeletal trauma, tonsillitis and pharyngitis). The SR of RCTs identified three RCTs addressing pain from dental procedures and sore throat.
Balance between benefits and harms associated with the use of strong opioids	None	
Comparative effectiveness and harms among strong opioids and different routes of administration	Nine RCTs	Seven RCTs were performed in acute pain settings (bone trauma, injury, post-operative pain). One RCT on mucositis, one RCT on sickle cell disease.
Opioid rotation and switching	One SR of observational studies	The SR identified only one observational study in children with cancer pain.
Prolonged versus immediate-release morphine formulations	None	
Episodic or breakthrough pain	None	
Adjuvant medicines to relieve pain	None	

* The two-step treatment approach is based on the use of paracetamol or NSAIDs for mild pain and the use of strong opioids for moderate to severe pain. The three-step treatment approach (corresponding to the three-step WHO analgesic ladder introduced in 1987) is based on the use of paracetamol or NSAIDs for mild pain, codeine or another intermediate potency opioid for moderate pain and the use of strong opioids for severe pain.

worldwide. Pain is a symptom of several diseases and conditions, not only confined to the end-of-life. Several diseases such as cancer, HIV/AIDS, sickle cell and non-progressive conditions, including trauma, burns and amputations, cause persisting pain in children. Globally, there are an estimated 2.1 million children with HIV of which 280 000 die each year (15). Worldwide, some 160 000 new cases and 90 000 deaths from cancer occur in children annually (16). About 400 000 children are born with sickle-cell disease in Africa each year (17, 18). Persisting pain is often underestimated in pediatric practice, due to the inability of neonates, infants and children to express pain and the lack of attention the evaluation and management of pain receives in clinical practice.

Classification of pain and conditions covered

The definition of chronic pain used by the International Association of the Study of Pain has not been uniformly adopted by experts. Definitions of acute and chronic pain set an arbitrary time period for the distinction between the two. Moreover, pain classifications based on duration may not address distinctions based on physio-pathological causes of pain which are relevant for the treatment of pain, such as the differentiation between neuropathic and nociceptive pain. The expert panel convened for the development of these WHO guidelines opted for using the term 'persisting pain caused by medical illnesses' to encompass some of these limitations. Conditions considered included, but were not restricted to, persisting pain from cancer, major infection (e.g. HIV/AIDS), arthritis and other rheumatological diseases, sickle cell disease, trauma, burns and neuropathic pain following amputation.

Retrieval of Evidence for Clinical Interventions

Anticipating that not many studies would be available on pain in children, the retrieval of evidence was not limited to systematic reviews (SRs) of randomized controlled trials (RCTs), but also included SRs of observational studies. A systematic search was performed, based on the clinical questions defined in the scoping document developed for the guidelines (19). The clinical questions are presented, grouped by broad topics, in Table 1. Given the differences in developmental pharmacology expected in the pediatric population, the effectiveness and/or safety of an intervention in neonates, infants and children could not simply be extrapolated from evidence developed in adults (20, 21). Evidence retrieval targeted studies in the pediatric population from 0–10 years of age. The extracted evidence was reviewed by an expanded panel of experts in July–August 2009. Given the paucity of publications retrieved, the search was subsequently expanded in February 2010 to include observational studies of the medicines under investigation for pain relief in children.

Table 1 provides a crude reporting of the number of SRs and RCTs in pediatric populations that were retrieved for each group of pharmacological interventions. No RCTs were retrieved which dealt with the rotation of opioids to prevent dose escalation and opioid adverse effects, with breakthrough pain, or with the use of adjuvant medicines for pain relief. The expanded search revealed only two systematic reviews which addressed a pharmacological intervention under investigation. Of the 11 RCTs in Table 1, ten were performed in the acute pain setting. The majority of the studies collated data for broad age ranges and many included adolescents up to 18 years

of age. Sample sizes were small, typically including about 20–30 participants per cohort. The studies evaluated effectiveness of pain relief, but very rarely provided qualitative and quantitative data on adverse effects.

Morphine has been used for the relief of pain since the 19th century, long before the advent of evaluation of intervention effectiveness through clinical studies. The lack of controlled studies to estimate the balance between the harms and benefits of using morphine and other strong opioids for relief of moderate to severe pain in the pediatric population is partly due to their long-established use. However, the same cannot be said for more recent synthetic and semi-synthetic opioids, marketed for pain relief in the 1970s, for which controlled studies in the pediatric population with persisting pain are also lacking.

Identified Gaps for a Research Agenda

The expert panel formulated a limited set of recommendations to provide clinical guidance for the relief of persisting pain in children. However, it also underscored the lack of a reliable evidence base for all clinical questions covered in the guidelines and advocated for orienting future research to fill this gap and better inform the future updating of these recommendations.

Clinical studies needed on paracetamol, NSAIDs and opioid analgesics

- Long term safety data for the prolonged use of paracetamol and NSAIDs in chronic pain settings, using observational studies and/or patient registries in defined pediatric populations
- Comparative (head-to-head) trials of strong opioids in terms of effectiveness, adverse effects and feasibility of use in persisting pain
- Research on the efficacy and safety of intermediate potency opioid analgesics, such as tramadol, in children below 12 years of age.
- Randomized controlled trials of the efficacy and safety of alternatives to the oral route of administration, including RCTs comparing the subcutaneous to the intravenous route.
- Assessment of a two-step treatment strategy, based on the use of paracetamol or NSAIDs for mild pain and the use of strong opioids for moderate to severe pain.
- Research on dose conversion between opioids in different age groups.
- Randomized controlled trials of short-acting opioids for breakthrough pain.
- Prospective clinical trials to investigate opioid rotation policies (and their efficacy in preventing adverse effects, opioid tolerance and dose escalation).

Clinical studies needed on adjuvant medicines for neuropathic pain

The following medicines and classes of medicines should be investigated for their efficacy as adjuvant medicines in treating neuropathic pain:

- Antidepressants, including tricyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs).
- Gabapentin
- Ketamine (as an intervention for refractory pain).

Comparative studies among adjuvant medicines of the same therapeutic category are necessary to inform and support the formulation of recommendations for the various target pediatric populations (for example, comparing gabapentin to carbamazepine).

The outcomes measured in clinical studies comparing different pharmacological interventions should include both positive (efficacy, quality of life) and negative outcomes (incidence, prevalence and severity of adverse effects). Furthermore, pain assessment should be performed with psychometrically validated tools for the age, developmental level, language and culture of the pediatric population included in such studies. Evaluation should not only be limited to pain intensity, but include other dimensions of pain (e.g. location of pain, characteristics, onset, duration).

Pharmacokinetics

The safety and the dosing of non-opioid and opioid analgesics in different age groups should be investigated. There is a need for research on the pharmacokinetics of analgesics in neonates, infants and children, similar to the efforts undertaken to define appropriate dosing of anti-tuberculosis medicines in the paediatric population (22). Research on dose conversion among strong opioid analgesics and their formulations in the paediatric population is also required to ensure safe switching. Naloxone dosing in opioid-tolerant children should also be studied, given the lack of information reported in the literature and in available formularies.

Pain assessment tools

Research is needed on psychometric validation of observational behavior measurement tools for chronic pain clinical settings for neonates, infants, preverbal children and children with developmental problems. Research is also needed on multidimensional tools to be used in persisting pain in clinical practice. Tools should be easy to explain and use and be validated for different socio-cultural contexts.

Conclusions

There is an urgent need for research on clinical interventions for the relief of persisting pain associated

with medical conditions in children. It is possible to design and perform studies in children to assess and compare the benefits and harms of pharmacological interventions in this field. There is no reason not to undertake such research as pain presents as a symptom across many medical conditions. We hope that the WHO call for research will foster the design, performance and publication of new evidence, enabling the revision of the guidelines within a reasonable time period. Given the paucity of clinical research in this field, there is urgent need for a collaborative effort involving the clinical community and research institutes. In order to provide sufficient power and to assure the external validity of such studies, multi-center studies may present a way forward. In addition, the preparation of appropriate systematic reviews on the key pharmacological pain interventions in the pediatric population will also serve to improve clinical practice and the quality of subsequent guidelines.

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