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ORIGINAL ARTICLE

Persisting pain in children: ensuring implementation of new guidelines

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ABSTRACT

The most obvious change introduced by the WHO Guidelines for the Pharmacological Treatment of Persisting Pain in Children with Medical Illness, issued in 2012, is the advocacy of a two-step rather than three-step pain 'ladder'. The guideline states that paracetamol and ibuprofen are the medicines of choice in the first step (for mild pain), and that the use of strong opioid analgesics is recommended for the relief of moderate to severe persisting pain in children with medical illnesses. The intermediate step, which dates from the 1986 and 1996 guidelines devised for adults, relied on the use of a weak opioid, notably codeine. This step is no longer advocated for children. However, there is much more than is new in the guidelines and they deserve careful consideration and deliberate action in order to ensure that children have access to the most appropriate pain relief. Hospital pharmacists are well-positioned to take a lead role in the implementation of the guidelines. They should also note the degree to which evidence to guide clinical practice is still lacking and contribute to efforts to address the priority research needs identified in the policy document.

Many pharmacists will have at least a passing familiarity with the concept of the 'WHO analgesic ladder', and will be able to, at the very least, describe the components of the three steps of that 'ladder'. However, how many would be able to accurately describe how to adapt that familiar approach to the management of the child with persisting pain? Would they assume that the same three 'steps' were appropriate for children? If not, on what evidence would they base their recommendations?

The initial WHO guidelines on cancer pain relief were issued in 1986, with a second edition issued in 1996.¹ These guidelines have entrenched the concept of a graded approach to the prescribing of analgesics in patients with chronic pain, starting with a non-opioid (such as paracetamol or a non-steroidal anti-inflammatory agent) for mild pain, then progressing to a weak opioid (notably codeine) for moderate pain, and finally a strong opioid (such as morphine) for severe pain. Although dated, and without a clear linkage to the evidence that underpinned those recommendations, the 'ladder' has been central to promoting appropriate access to pain relief in many settings, including access to opioid analgesics. Also key to these guidelines were the linked concepts of 'by the clock' and 'for the individual'. Balding, for instance, has praised the 'clarity, unambiguity and

flexibility' of the guidelines, and has credited them with 'resulting in improved pain control for countless patients with end stage cancer'.²

A 1998 guideline from WHO expanded the scope to cancer pain relief and palliative care in children.³ The 'close approximation of the children's strategy to those for adults and the reliance on expert opinion, rather than evidence base' has been noted.⁴ Nonetheless, there is evidence that these guidelines were closely followed in some practice settings.⁵

WHO GUIDELINES FOR THE PHARMACOLOGICAL TREATMENT OF PERSISTING PAIN IN CHILDREN 2012

The updated WHO guidelines for the pharmacological treatment of persisting pain in children with medical illness, issued in 2012, attempted to firmly entrench an evidence-based approach and to extend the scope of the guidelines beyond cancer-related pain. The process followed has been described previously.⁶ Briefly, a systematic search was performed, based on the clinical questions defined in the scoping document developed for the guidelines. Evidence was specifically sought from studies in the paediatric population from 0 to 10 years of age. Given the paucity of publications retrieved, the search was then expanded to include observational studies of the medicines under investigation. The extracted evidence, in the form of GRADE tables, was then reviewed by a panel of experts, in accordance with the *WHO Handbook for Guideline Development*.^{7 8} The extracted evidence was attached as Annex 4 to the guideline document.

That the available evidence base was severely limited was also acknowledged. Across the seven broad clinical questions, only one systematic review based on randomised clinical trials (RCTs), one systematic review based on observational studies, and 11 individual RCTs were retrieved. Even within this sparse evidence base, extrapolations needed to be made. Of the nine RCTs that were considered in assessing the comparative effectiveness and harms among strong opioids and different routes of administration, seven were performed in acute pain settings. As Drake and colleagues pointed out, while the guidelines are now based on evidence, this 'brings its own disquiet', as it has 'uncovered inadequacies' with the extent to which the available research evidence meets the needs of practice.⁴ The same authors have underscored the need to pay attention to the research agenda which is outlined in Annex 5 to the guidelines.



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The 2012 guidelines recognise that optimal pain management requires a comprehensive approach, using a combination of non-opioid, opioid analgesics, adjuvants and non-pharmacological strategies. While retaining some of the key concepts of previous guidance (dosing at regular intervals—‘by the clock’; using the appropriate route of administration—‘by the mouth’; and tailoring treatment to the individual child—‘by the individual’), it advocates for a two-step strategy, according to the child’s level of pain severity. The guideline states that paracetamol and ibuprofen are the medicines of choice in the first step (mild pain). Both of these medicines therefore need to be made available for treatment at this step. However, the use of strong opioid analgesics is recommended for the relief of moderate to severe persisting pain in children with medical illnesses. The intermediate step, which has largely relied on codeine, has thus been removed. The first-line strong opioid of choice is morphine, as there is insufficient evidence to recommend any alternative opioid in preference to morphine. In addition, while access to immediate-release oral morphine formulations is critical, it is also recommended that child-appropriate prolonged-release oral dosage forms be available, if affordable. When alternative opioid analgesics to morphine are selected, this process should be guided by considerations of safety, availability, cost and suitability, including patient-related factors. The oral route of administration is preferred and the intramuscular route of administration is to be avoided in children. The guideline states that, when the oral route is not available, the choice of alternative routes of administration should be based on clinical judgement, availability, feasibility and patient preference. Advice is also provided on the methods for opioid weaning.

Although morphine is identified as the first-line choice, the guideline advocates switching opioids and/or route of administration in the presence of inadequate analgesic effect with intolerable side effects. Accordingly, it recommends that alternative opioids and/or dosage forms as an alternative to oral morphine should be available. However, the routine rotation of opioids was not recommended. The need for alternatives has subsequently been recognised by a footnote inserted in the 4th WHO model list of essential medicines for children in April 2013.⁹ This reads that hydromorphone and oxycodone are to be considered as alternatives to morphine. The applications made in relation to this change and the expert reviews that were prepared can be accessed at the web site of the 19th Expert Committee on the Selection and Use of Essential Medicines (http://www.who.int/selection_medicines/committees/expert/19/applications/paediatric/en/index.html).

An area which clearly exposed the paucity of available evidence was that related to the use of adjuvant medicines in the management of persisting pain. While the use of corticosteroids as adjuvants and the use of bisphosphonates in the treatment of bone pain in children were not recommended, the guideline could not provide recommendations in relation to the following areas:

- ▶ for or against the use of tricyclic antidepressants and selective serotonin reuptake inhibitors as adjuvant medicines in the treatment of neuropathic pain in children;
- ▶ for any anticonvulsant as an adjuvant in the management of neuropathic pain in children;
- ▶ regarding the benefits and risks of ketamine as an adjuvant to opioids for neuropathic pain in children;
- ▶ regarding the benefits and risks of the systemic use of local anaesthetics for persisting neuropathic pain in children; or
- ▶ for the use of benzodiazepines and/or baclofen as an adjuvant in the management of pain in children with muscle spasm and spasticity.

This lack of guidance is particularly important, as the approach to pain management moves beyond a simple reliance on a choice of analgesics per ‘ladder rung’ to a multi-modal ‘platform’, including the optimal use of adjuvants.¹⁰ Providing the necessary evidence to guide paediatric practice will be an important research goal in the years to come.⁶

The guidelines also include pharmacological profiles of analgesics, which has been compiled based on a number of different references and reviewed by clinical paediatric experts. One of the striking elements in the compilation of such profiles is that the recommended dosing of naloxone that was present in the formulary consulted was only for opioid-naïve children. There was no mention of dosing for opioid-tolerant neonates, infants and children. This issue was therefore addressed in the guideline, with this important warning:

In children receiving regular opioid treatment for pain and children who are opioid-tolerant, naloxone needs to be used with caution, in order not to evoke extreme pain or withdrawal reactions. Doses needed to revert opioid overdose in such patients are lower than those normally indicated for opioid intoxication and overdose in opioid-naïve children.

The profile provides this recommended dosing strategy:

Dose in opioid-tolerant patients: *Intravenous*: neonate, infant or child—1 mcg/kg titrated over time, for example, every 3 min, until the child is breathing spontaneously and maintaining adequate oxygenation; a low dose infusion may be required thereafter to maintain adequate respiration and level of consciousness until the effect of overdose has resolved; close monitoring is needed.

IMPLEMENTING THE GUIDELINES—THE ROLE OF PHARMACISTS

The 2012 WHO guidelines also identified a number of health system imperatives, including the education of health professionals in the standardised management of persisting pain in children with medical illnesses and in the handling of the necessary medicines, including opioid analgesics.

Specifically, the guidelines identified potential barriers to access to necessary opioids that might need addressing. They recommended that health professionals be allowed to handle opioids within their scope of practice or professional role, based on their general professional license without any additional licensing requirements. It also recommended that countries might consider, subject to their situation, allowing professionals other than medical practitioners to diagnose, prescribe, administer and/or dispense opioids for reasons of flexibility, efficiency, increased coverage of services and/or improved quality of care. In such situations, it suggested that the conditions under which such permission was granted should be based on the demonstration of competence, sufficient training, and personal accountability for professional performance. In many countries, pharmacists play a prominent role in the determination of medicines regulatory practice and can engage with policymakers in ensuring that appropriate access measures are included. In this regard, WHO has also provided guidance on achieving balance between the control of opioids and access to necessary treatment.¹¹ In addition, an accompanying pamphlet highlighting the issues to be considered by policymakers and medicines regulatory authorities, hospital managers and health insurance managers was published together with the 2012 guidelines.¹²

Specifically within hospitals and other health system settings, pharmacists can address a number of important elements that can aid implementation of the guidelines.¹³ In relation to the

Table 1 Recommended initial doses for morphine in opioid-naïve neonates and infants

Age group	Route of administration	Recommended starting dose
Neonates	Intravenous injection*	25–50 µg/kg every 6 h
	Subcutaneous injection	
Infants (1 month to 1 year)	Intravenous infusion	Initial intravenous dose* 25–50 µg/kg, then 5–10 µg/kg/h
	Oral (immediate release)	80–200 µg/kg every 4 h
	Intravenous injection*	1–6 months: 100 µg/kg every 6 h 6–12 months: 100 µg/kg every 4 h (max 2.5 mg/dose)
	Subcutaneous injection	
	Intravenous infusion*	1–6 months: initial intravenous dose: 50 µg/kg, then: 10–30 µg/kg/h 6–12 months: initial intravenous dose: 100–200 µg/kg, then: 20–30 µg/kg/h
	Subcutaneous infusion	1–3 months: 10 µg/kg/h 3–12 months: 20 µg/kg/h

*Administer intravenous morphine slowly over at least 5 min.

two-step ladder, pharmacists can educate other healthcare providers and patients on the important differences between the non-opioid analgesics in step 1 and the strong opioids in step 2. Paracetamol and ibuprofen have a fixed maximum dosage and can provide only limited analgesia. The strong opioids, like morphine, need to be initiated at a weight-appropriate starting dose, and then adjusted. The guidelines recommend that, as long as the pain is not sufficiently addressed, the dosage needs to be increased in steps of no more than 50% per 24 h. Opioids should be administered at regular intervals and not on an 'as-needed' basis. Importantly, the dosages recommended by WHO are lower than those recommended elsewhere. Table 1 shows the recommended doses for morphine in opioid-naïve neonates and infants. Recommendations for alternative opioids were also provided in the guideline.

In addition to ensuring that an appropriate range of opioids is available, pharmacists need to ensure that a sufficient range of dosage forms is accessible to allow for the use of the most appropriate route of administration. In many settings, while injectable dosage forms are more accessible, there is limited access to appropriate immediate-release oral liquids. Although a formula for extemporaneous compounding of an oral liquid dosage form was not included in the guideline document, an example provided by the Royal Dutch Pharmacists Association (KNMP) was included in the accompanying pamphlet for pharmacists. This would allow for the preparation of 1, 5 and 20 mg/mL solutions. Importantly, the formula provided is preserved with methylparahydroxybenzoate, added to the preparation as a concentrated solution (150 mg/mL in propylene glycol). Recommendations for taste correction are also provided.

The pamphlet also provides pharmacological profiles on a number of opioids that may be considered, in addition to morphine.

Pharmacists often have a strong influence over medicine selection or formulary management decision-making bodies at facility or regional levels. Pharmacists are also often in charge of procurement decisions at central and regional levels, and can play a role in ensuring that the needed medicines and formulations for adequate pain relief are included in procurement plans. In addition to considering the appropriate choice of opioids, consideration also needs to be given to the availability of other

medicines. The pamphlet reminds clinical pharmacists, for instance, of the need for active management of constipation in those receiving long-term opioids, and the need for stimulant laxatives and a stool softener. Weaning of opioids is also given high importance, in terms of general guidance and in the pharmacological profiles for morphine and other opioids. Access to antidotes such as naloxone also needs attention. Lastly, pharmacists can contribute to programmes aimed at addressing educational barriers to greater access to appropriate pain relief in children.

A pamphlet directed at medical practitioners and nurses was also published to accompany the 2012 guidelines.¹⁴

THE KEY ROLE OF PRIORITISED RESEARCH

No guideline process is ever complete. New evidence will inform revisions of the 2012 guidelines, but a deliberate and prioritised approach is needed. The guideline identified a prioritised list of such research questions. The first priority needs to be the assessment of the recommended two-step treatment strategy. Comparative trials of alternative strong opioids to morphine will also be needed. In particular the potential role of intermediate potency opioid analgesics such as tramadol in children needs investigation. Although strong recommendations were provided in relation to the step 1 agents, there is still a need for long-term safety data on ibuprofen and paracetamol.

The second tier of research priorities focused specifically on neuropathic pain and the potential role of various types of antidepressants, gabapentin and ketamine.

CONCLUSIONS

Just as no guideline process is never complete, no guideline is ever perfect. As Drake and colleagues pointed out, the 2012 WHO guidelines are a step forward, but also 'underscore the gaps in our knowledge'.⁴ That is no reason, though, to allow these guidelines to languish on a library shelf. In all practice settings, concerted effort is needed to ensure that outdated practices are reconsidered, and that the recommendations that have been made are taken into account in daily practice. Hospital pharmacists in particular are well positioned to contribute to this effort as they can influence local medicines policies, selection and procurement, and clinical practice.

Competing interests None.

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