Developing 'fully evidenced' paediatric pain guidelines

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In this issue, Andy Gray discusses the WHO Guidelines on the pharmacological treatment of persisting pain in children.[1 2] I had the honour to be the responsible officer in the WHO for developing these guidelines. It is the first time that WHO publishes guidelines on pain that go wider than cancer pain only. These new WHO Guidelines are not only intended to impact *how* patients are treated, but also to ensure *that* they are treated: WHO estimates that over 5.5 billion people live in countries where moderate and severe pain is not adequately addressed.[3 4] This is not only the case in developing countries, but a number of European countries clearly show insufficient use of opioid analgesics too. Therefore, there is a high need for new policies that improve patient access to pain treatment. These WHO Guidelines show healthcare workers and policy makers what is needed to provide adequate pain treatment; obviously, this includes availability of opioid analgesics. In order to make the guidelines more accessible, WHO published three brochures for quick reference simultaneously: one for policy makers, one for physicians and nurses, and one for pharmacists.

WHO planned two more guidelines on pain treatment: one on persisting pain in adults and the other on acute pain. Together, these guidelines should cover the pharmacological treatment of 'all' types of pain. The scoping document for the former is available[5] and the one for the latter is being drafted. Unfortunately, progress is insufficient, because potential donors want usually to fund only one aspect, such as 'pain in palliative care' and do not support the idea of a wider interest that treatment is facilitated for *all* patients with moderate and severe pain.

Several years ago, WHO developed a policy that its treatment guidelines should be evidence-based and transparent. Guidelines are reviewed by an overseeing body, the Guidelines Review Committee, before being released.[6] 'Evidence-based' and 'transparency' mean in practice that recommendations are, if possible, based on the highest quality of evidence available, and otherwise, they rely on expert opinion. The transparency requirement is to make clear to the reader on which evidence a recommendation is based. It allows the reader to make up his mind how compelling these recommendations are to him.

It may be clear that evidence is scarce for old medicines like opioid analgesics, of which the oldest substance morphine has been used now for almost two centuries. These substances were developed in a time in which nobody had ever heard of double-blind crossed-over randomised controlled clinical trials. Today, these medicines are out of patent, and hence, they have not much commercial interest; it is unlikely that the needed research will be conducted. In addition, it is apparent that evidence is even scarcer in paediatrics; such evidence that exists is often indirect and extrapolated from evidence on adults. If we look in Annex 2 of the WHO Guidelines, this can clearly be seen. For none of the 24 clinical questions is good or very-good evidence available; the evidence was considered to be 'low quality' for 11 questions and 'very low quality' for eight. There were even five clinical questions for which the experts found it impossible to make any recommendations.

It is for this reason that the WHO Guidelines include a research agenda, challenging investigators to conduct more research on this topic.[7] Such research will allow for a better evidence base for future editions. The International Children's Palliative Care Network (http://www.icpcn.org.uk) kindly offered to coordinate this research.

One example of lack of evidence is the paediatric dosage recommendations for opioids. Again, not much research is done on this topic, and most relevant books repeat one another. Those constituting the experts group that developed the WHO Guidelines considered that these usual dosage instructions are much too high, dangerous and often incomplete when it comes to dosage titration or cessation of treatment. Therefore, they took a more cautious approach.

The newly recommended dosages are much lower than usual and after a starting dose according to the tables in the WHO Guidelines, the dosage should be adjusted to the level that is effective (with no ceiling or maximum dose), but the maximum dosage increase is 50% per 24 h in outpatient settings. Experienced prescribers can increase up to 100% with close monitoring of the patient, increasing to the level that is effective. The preferred route is oral. If oral administration is not possible, subcutaneous administration or other parenteral routes can be considered, but intramuscular administration should be avoided as it is painful. On discontinuation, the dosage should be gradually reduced in order to avoid withdrawal syndrome.[8]

But in spite of the fact that the new WHO Guidelines could not be based on sufficient evidence, these guidelines are important for many reasons: they contain a statement that children's pain should always be addressed (new for WHO, and important, because paediatric pain is still too often ignored); they introduce a more logical two-step approach and make clear why the classic three-step ladder for pain relief, and in particular, codeine as its middle step, is obsolete; and they replace the old WHO guidelines 'Cancer Pain Relief in Children,'[9] which were groundbreaking at the time of their introduction, but completely expert opinion–based and recommending several medicines that are obsolete today.

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Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Scholten W. *Eur J Hosp Pharm* 2013;**20**: 262–263.

Linked

► http://dx.doi.org/10.1136/ejhpharm-2013-000367

Eur J Hosp Pharm 2013;**20**:262–263. doi:10.1136/ejhpharm-2013-000318

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