The misappropriation of the WHO analgesic ladder for painful chronic wounds: from repair to retirement?

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ABSTRACT

In a recently published EWMA document on the holistic management of wound-related pain, the only recommendation regarding systemic drug therapy was to follow the WHO analgesic ladder. Since that ladder was developed to specifically address cancer pain, its application in the field of painful chronic wounds represents another case of misappropriation, as there was no evidence to support such a decision. There is still no evidence.

Misappropriation carries risks. The first step of the ladder recommends nonsteroidal anti-inflammatory drugs, which act by inhibiting cyclooxygenase in the inflammatory focus. Therefore, the drug must reach the inflammatory focus. But most chronic wounds are ischemic in nature, and ischemia should at least partially prevent drugs from reaching the wound bed. Consequently, the risk-benefit would to be inadequate in ischemic wounds, but there is no evidence, since this topic has not been the subject of research either.

Wound-related pain has been largely forgotten and, as a direct consequence, there is an unacceptable paucity of studies. It is time for a change.

Keywords WHO analgesic ladder, painful chronic wounds, pain management, systemic drug therapy, nonsteroidal anti-inflammatory drugs, lack of evidence

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KEY MESSAGES

- Guideline recommendation to follow the WHO analgesic ladder for the treatment of painful chronic wounds is not based on scientific evidence.
- The first step of the WHO analgesic ladder should not be strictly followed to treat all kinds of painful chronic wounds.
- Health workers dealing with painful chronic wounds should start to research effective analgesic treatments.

Dear Editor-in-Chief,

I have read with interest the recent Supplement published by EWMA focused on the holistic management of pain.[1] I think documents and guidelines like this are truly needed to improve the management of pain through widening the scope beyond drug therapy.

As a pharmacologist, however, I am especially interested in drug therapy. In the above mentioned document, the reader will find a solitary sentence referring to the World Health Organization (WHO) analgesic ladder, which is not an uncommon finding in documents prepared by scientific societies focused on chronic wounds. For instance, the Wound Healing Society[2] and the Japanese Association of Dermatology[3] both recommended the WHO ladder (lacking any recommendation to use topical alternatives). In Spain, the document developed by the National Group for the research and advice on pressure ulcers and chronic wounds (*GNEAUPP, Grupo Nacional para el Estudio y Asesoramiento en Úlceras por Presión y Heridas Crónicas)*[4] included sections for both topical and systemic drug therapy, but the WHO analgesic ladder was also the only recommendation that appeared in the latter section.

In my opinion, the recommendation of using the WHO ladder to guide the analgesic treatment of painful chronic wounds should be revisited since the recommendation was a "misappropriation" not based on a sound scientific background; and the ladder first step needs to be 'repaired' at least. Either that, or the whole ladder needs to be retired from clinical practice to be preserved just as an educational tool.

In 1986, a panel of experts supported by WHO elaborated an easy-to-use guideline to treat specifically cancer pain which included the three-step analgesic ladder.[5] An updated version was launched in 1996.[6] Any other type of noncancer pain was out of the scope of those documents, including pain associated to chronic wounds. In a 1999, nurse Susan Senecal reviewed the state-of-the art to manage ulcer pain just to find a lack of evidence.[7] In such a situation, and based on common sense, she simply stated that the WHO had developed an analgesic ladder to guide the use of systemic analgesics for the treatment of cancer pain and that it may be used as a guideline to treat painful chronic wounds. Notwithstanding, Senecal's suggestion was later misinterpreted as if she had

applied the ladder to painful wounds.[8] From then on, the WHO analgesic ladder has been recommended in guidelines and documents developed by several wound societies or working groups.[1–4]

Misappropriation means using one instrument (the WHO analgesic ladder) to treat conditions it was not designed for, such as postoperative pain[9] or painful chronic wounds.[7] Misappropriation carries the risk of bad consequences. As an example, some authors have specifically advised against following the WHO ladder for the treatment of postoperative pain, since pain intensity evolves from high to low over the course of postoperative days, while the ladder recommends using less potent analgesics first before climbing up to more powerful ones over time.[9] According to those authors, it makes no sense, and as an anesthesiologist I totally agree with them. In line with this and for the same reason, I disagree with the recommendation of following the ladder to perform painful debridements on wounds, that is, starting with the less potent analgesics.[8]

But misappropriating the WHO ladder for the systemic treatment of painful chronic wounds may be harmful for another reason related to pharmacokinetics and nonsteroidal anti-inflammatory drugs (NSAIDs). The ladder's first step is based on the use of paracetamol and NSAIDs. The mechanism of action of NSAIDs as anti-inflammatory drugs involves the inhibition of the enzyme cyclooxygenase: in the inducible form *at the inflammatory focus* to elicit the beneficial effect, and the constitutive form responsible for causing adverse effects in kidneys, stomach, etc. As any other drug, NSAIDs must reach their pharmacological target, the cyclooxygenase, for the drug effect to be elicited.[10] Reaching the drug target should not be a problem when dealing with cancer-related inflammatory pain, as cancers usually secrete vascular growth factors to assure a proper blood supply.[11] But many chronic wounds are of vascular etiology, and ischemia plays a key etiological role.[12] The delivery of NSAIDs – or any other drug –to their pharmacological target at the inflammatory focus in the wound bed should be limited under ischemic conditions and, consequently, the beneficial effect of NSAIDs is potentially reduced. In this situation, the risk-benefit balance seems clearly unfavorable for treating ischemic painful wounds with systemic NSAIDs.

As stated, the WHO ladder was first developed in 1986 by a panel of experts in cancer pain management to cover a worrisome lack of recommendations to specifically treat oncologic pain.[5] The document was further revised in 1996, always keeping cancer pain management as the main topic covered. The initial recommendations for the administration of analgesics were expanded, as medicines should be given 'by mouth' 'by the clock', 'by the ladder', 'for the individual' and with 'attention to detail'.[6] Then, it was subjected to a third revision which was published as recently as in 2018.[13] This time, interestingly, the five prior recommendations were reduced to four ('by mouth', 'by the clock', 'for the individual' and with 'attention to detail') as 'by the ladder' was removed. The authors explained their decision based on the individualised nature of pain, saying: "A cancer pain management ladder is useful as a teaching tool and as a general guide to pain management based on pain severity. However, it cannot replace individualised therapeutic planning based on careful assessment of each individual patient's pain".[13] Thus, the ladder was removed because the authors were concerned by a widespread one-size-fits-all approach. Sir William Osler expressed the same idea in a few words: "The good physician treats the disease; the great physician treats the patient who has the disease". In my opinion, the same applies to treating *all* painful wounds in the same way, whatever key issues present, such as the underlying disease or patient comorbidities.

Regardless any eventual personal agreement or disagreement with the decision of removing the ladder, the curious fact is that the EWMA and other organisations dealing with chronic wounds currently recommend guiding analgesic therapy following an instrument that its own developers withdrew from clinical use five years ago. It sounds strange, to say the least, and it is even more strange after considering that such instrument was never intended to cover the pain associated to chronic wounds. Maybe it is time for us to retire the WHO analgesic ladder.

It is clear to me that pain management in the field of chronic wounds has not been adequately studied for decades. It is time for a change. Health workers lacking resources for conducting clinical trials (a vast majority of us) could report our experiences treating either isolated patients or series of cases and describe the real world effectiveness of usual systemic analgesics, as well as depict the profile of unwanted effects. At the same time, those health workers with adequate resources should conduct clinical trials comparing analgesic alternatives (the lack of comparative studies was denounced by the European Academy of Dermatology and Venereology eight years ago,[14] but comparisons are still lacking).

CONFLICT OF INTEREST

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