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## Editorial

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# The World Health Organization three-step analgesic ladder comes of age

Eighteen years ago, the World Health Organization (WHO) published a document entitled *Cancer Pain Relief*, which set out the principles of cancer pain management based on the use of a ‘three-step analgesic ladder’.<sup>1</sup> The document was derived from consensus guidelines produced some four years earlier.<sup>2</sup> In 1996, the WHO published an updated version of *Cancer Pain Relief*, which again was based on the use of a ‘three-step analgesic ladder’, and also the principles ‘by mouth’, ‘by the clock’, ‘by the ladder’, ‘for the individual’ and ‘attention to detail’.<sup>3</sup> The updated version of the three-step ladder is shown in Figure 1.

Eighteen years is a long time in medicine. Admittedly, the WHO guidelines have been updated during this period, but the second edition is essentially the same as the first edition. Most commentators agree that the original guidelines were appropriate for their time, but some suggest that the current guidelines are less relevant in the new millennium. So, are the WHO guidelines still valid?

The WHO guidelines arose from evidence of poor management of cancer pain in both developing and developed countries. One of the reasons, if not the main reason, for this situation was the reluctance of individual health professionals, institutions and governments to use ‘strong’ opioids because of misplaced fears of addiction and tolerance amongst patients, and of illegal use amongst the wider community. Thus, one of the main aims of the WHO guidelines was to legitimize, and so increase, the prescribing of ‘strong’ opioids amongst patients with moderate to severe cancer pain. WHO data suggest that the publication of the guidelines has been associated with an increase in the usage of opioids in many parts of the world.<sup>3</sup>

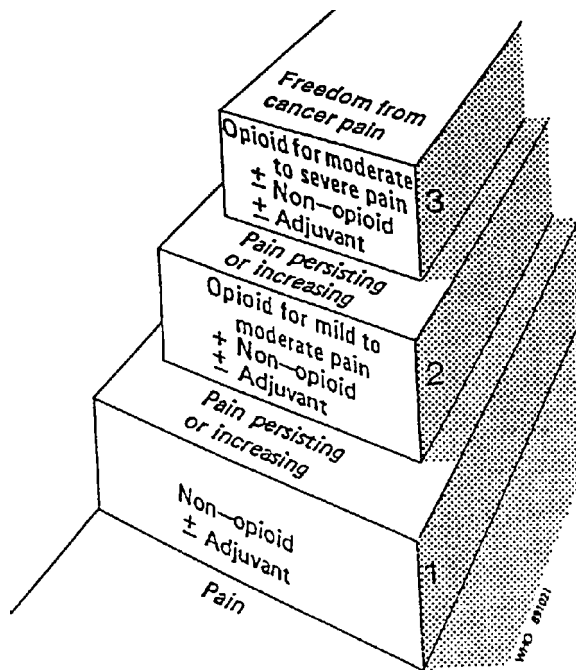
One of the major criticisms of the three-step ladder has been the lack of strong evidence of its effectiveness. In 1995, Jadad and Browman conducted a systematic review of the studies evaluating the WHO guidelines.<sup>4</sup> In the studies included in the review, 69–100% of patients achieved ‘adequate analgesia’. However, the authors comment that for methodological reasons ‘the evidence they (the studies) provide is insufficient to estimate confidently the effectiveness of the WHO analgesic

ladder’. Their criticisms were that the studies were small, had limited follow-up periods or high dropout rates, and lacked comparator groups. Because of this they conclude, ‘it would be difficult to know whether the WHO ladder has really improved the management of cancer pain’.

Jadad and Browman’s criticisms were subsequently addressed and dismissed by some of the developers of the WHO guidelines.<sup>5,6</sup> In essence, these authors argued that the guidelines were not suggesting a new treatment, but promoting better use of existing drugs, i.e. opioids for moderate to severe pain, and that the validation studies were setting out to prove that these drugs could be used effectively and safely for cancer-related pain, could be used at any stage of the disease, and could be continued for prolonged periods.

Another major criticism of the three-step ladder has been that it is nonspecific. Thus, physicians reviewing the same patient could prescribe different treatment regimens, despite using the same treatment template. A classic example of this phenomenon is the management of patients with neuropathic pain, where some physicians use ‘drugs for neuropathic pain’ (e.g. antidepressants and anticonvulsants)<sup>3</sup> at step one, whilst other physicians only use these drugs at step three. However, we would suggest that this lack of specificity is actually a positive feature, since it promotes the concept of individualised patient management.

More recently, a criticism of the three-step ladder has been that it overlooks the benefits of other methods of pain relief, such as disease-modifying therapies, non-pharmacological therapies, and interventional therapies.<sup>7</sup> However, the WHO guidelines do endorse the use of these other treatment modalities, although they do not appear on the illustration of the three-step ladder. *Cancer Pain Relief* contains much more information than just the three-step ladder, and so it is important that health care professionals refer to the WHO guidelines in their entirety, rather than basing practice on an isolated illustration of the three-step ladder. Ultimately, the use of these other treatment modalities, and also of opioids for moderate to severe pain, depends on their availability, which is likely to vary from country to country.



**Figure 1** The World Health Organization three-step analgesic ladder (1996).

Whilst the WHO guidelines have undoubtedly had a major (positive) impact on the management of cancer pain, the evidence base for the three-step ladder remains relatively weak. This lack of evidence needs to be addressed. It would not now be feasible to conduct a randomized controlled trial of the three-step ladder, but it would be possible to conduct randomized controlled trials of alternative models such as a two-step ladder (i.e. moving from step one to step three), and also of whether 'drugs for neuropathic pain' should be commenced at step one, two or three. The results of such studies would improve the evidence for the use of the three-step ladder, and might lead to the development of variations of the ladder based on the aetiology of the pain, or the availability of certain drugs.

In conclusion, we suggest that the WHO guidelines remain valid, and are likely to remain the cornerstone of cancer pain management for the foreseeable future. Certainly, there is no evidence that alternative regimens are better than the WHO guidelines. However, the WHO guidelines will need to continue to develop, and be tested, in order to maintain their validity.

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