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UPCOMING ISSUES

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Time to Modify the WHO Analgesic Ladder?

The Analgesic Ladder

The World Health Organization (WHO) has promoted the three-step analgesic ladder as a framework for the rational use of analgesic medications in the treatment of cancer pain. Step I specifies the use of non-opioid analgesics for mild pain; step II recommends "weak" opioids, with or without non-opioids, for moderate pain; and step III comprises "strong" opioids, with or without non-opioids, for strong pain. If needed, adjuvant drugs can be used at each step.[1,2]

The three-step ladder specifies treatment according to the *intensity* of pain. By referring to drug classes, rather than specific drugs, the ladder maintains a level of flexibility that allows clinicians to work within the regulations and limitations employed in their respective countries. This flexibility is especially useful in countries where "weak" opioids are more readily available than "strong" ones.

Clearly, the WHO method has been of enormous benefit for the treatment of cancer pain worldwide.

Clearly, the WHO method has been of enormous benefit for the treatment of cancer pain worldwide. Several case series document that the application of this analgesic regimen will achieve pain relief in the majority of patients with cancer. Ventafridda and colleagues[3] from the WHO Collaborating Centre at the National Cancer Institute of Milan showed in a 2-year retrospective report of a 2-year experience with the use of the WHO analgesic ladder that the ladder was effective in 71% of cases, in which it reduced pain to one-third of its initial intensity. Zech et al.[4] reported "good" pain relief in 76% of 2,118 patients treated in accordance with the WHO guidelines over a 10-year period. Colleau and colleagues[5] assert that application of the WHO analgesic regimen can achieve pain relief in 90% of cancer patients.

Patients with cancer are likely to need strategies such as alternative routes of drug administration or invasive procedures.

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Challenges

Despite these reported success rates, challenges presented by the WHO method must be recognized as well. First, while 70–90% of patients with cancer pain treated according to the three-step ladder achieve effective analgesia, the remaining 10–30% do not. Thus, a significant portion of patients with cancer fail to obtain satisfactory pain relief and are likely to need other strategies such as alternative routes of drug administration, nerve blocks, or other invasive procedures. However, the WHO ladder does not address how best to integrate these procedures into the medical treatment of cancer pain. Second, the validation series cited above do not provide information on how quickly effective analgesia is achieved in those who respond to the different steps of the ladder. In all of pain treatment, an important goal is to attain pain relief as quickly as possible, regardless of etiology and setting. Lastly, some evidence suggests that the early application of invasive procedures may result in more effective analgesia with fewer adverse events, and perhaps with a higher survival rate, as compared to traditional analgesic treatment.[6-8] At least some of these challenges raise second thoughts regarding the WHO's concept of the analgesic ladder.

The WHO three-step ladder is likely to succeed in treating gradually progressive pain, but is it effective for treating pain that is severe to begin with?

Is It Really a Three-Step Ladder?

To climb a ladder, we employ the progressive, consistent, placement of one foot above the other, one rung at a time, with no shortcuts. The WHO three-step ladder is explicit in initiating treatment with step I medications, then ascending to step II only if effective analgesia is not achieved with non-opioid drugs. The same is true for the transition from step II to step III. This approach is likely to succeed in treating gradually progressive pain, but is it effective for treating pain that is severe to begin with? If a new patient comes in for initial evaluation of the recent onset of excruciating pain, should we climb the ladder step by step or initiate immediate treatment with "strong" opioids? The answer to this question is clear to those who treat cancer pain on a regular basis. For the less experienced clinician, however, the appropriate procedure may be more elusive, and the inevitable recourse to "strong" opioids may be delayed by the initial administration of step I and II medications in an attempt to follow the WHO recommendations. To avoid this potentially misleading interpretation of the ladder, the need *to select the strength of the opioid analgesic according to the current severity of pain* should be emphasized. This approach is closer to taking an "analgesic elevator" to the appropriate floor rather than climbing up a ladder.[6]

Is Step II Necessary?

While the use of non-opioids for step I and "strong" opioids for step III is widely accepted, the clinical usefulness of the "weak" opioids (or "step II" medications) in the management of cancer pain has been challenged. In a meta-analysis on the efficacy and safety of nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain, Eisenberg et al.[9] found no difference in efficacy between NSAIDs ("step I" medications) and "weak" opioids (step II medications) or the combination of NSAIDs with "weak" opioids. This meta-analysis was based, however, on only five single-dose trials and two multiple-dose trials that in aggregate enrolled 415 patients. Furthermore, single doses of "weak" opioid/NSAID combination drugs produced significantly more side effects than single doses of NSAIDs alone, although the side-effect profiles were comparable when multiple doses of the two drug classes were compared. The authors concluded: "These findings raise the question whether the WHO second analgesic step is an optimal treatment protocol or whether it should be modified so as to proceed directly from NSAIDs to strong opioids in the face of unrelieved pain."

The clinical usefulness of the "weak" opioids (or "step II" medications) in the management of cancer pain has been challenged.

A recent systematic review[10] of six trials compared the efficacy of an NSAID versus a "weak" opioid (three were single-dose trials and two were multiple-dose trials, and the duration of one trial was unclear). Again, the results failed to show the superiority of "weak" opioids over NSAIDs, although adverse events were either comparable or more frequent in the opioid-treated patients. An additional eight trials were conducted in 833 patients to compare an NSAID with the combination of an NSAID and an opioid. The results showed that the difference in the analgesic outcome measure for each trial was less than 25%. Based on these findings, the authors concluded: "There is insufficient evidence to either confirm or refute the WHO recommendation that an NSAID should be combined with a 'weak' opioid for the management of moderate cancer pain."

Patients who were started on "strong" opioids had significantly better pain relief than those who were treated according to the WHO guidelines.

In a recent randomized, controlled trial, the efficacy and tolerability of "strong" opioids (step III drugs) as first-line treatment was compared with the recommended WHO regimen (steps I and II) in 100 terminal cancer patients who suffered from mild to moderate pain.[11] Outcome measures included pain intensity, the need for change in therapy, quality of life, Karnofsky

Performance Status, the patient's general condition, and adverse events. The two groups did not differ in age, gender, diagnosis by organ system involved, initial mean pain intensity (about 4 on a 0–10-point scale), or mean duration of prior treatment (about 11 weeks). Patients who were started on "strong" opioids not only had significantly better pain relief than those who were treated according to the WHO guidelines, but they also required significantly fewer changes in therapy, had greater reductions in pain when therapeutic changes were initiated, and reported greater satisfaction with treatment. No differences were observed in quality of life or performance status between the two groups. These data, according to the authors, "suggest the utility of strong opioids for first-line treatment of pain in patients with terminal cancer."

The routine use of step II medications may be associated with significant disadvantages.

Thus, it seems that the routine use of step II medications may be associated with significant disadvantages. The evidence provided here suggests that the transition from step I to step II drugs does not necessarily improve analgesia. This apparently ineffective transition may delay achieving optimal pain control, especially in patients with rapidly progressive pain or in those who need quick titration of analgesic therapy. Further, the fear of administering "strong" opioids may instead lead physicians to increase the doses of step I and step II medications to levels associated with a higher risk of adverse events, compared to the adverse events expected with the use of equianalgesic doses of "strong" opioids.[11]

The practical implication of adherence to the three-step analgesic ladder is that pharmacological treatment is "pushed" as hard as possible before alternative options are considered.

Invasive Procedures for the Relief of Cancer Pain

The use of invasive procedures is commonly recommended whenever less invasive therapies, mainly pharmacological ones, are ineffective due to either insufficient analgesia or intolerable side effects.[12] The practical implication of adherence to the three-step analgesic ladder is that pharmacological treatment is "pushed" as hard as possible before alternative options are considered. This approach has been called into question by several controlled trials comparing medical management to the use of neurolytic celiac plexus blockade (NCPB) in the treatment of pain due to abdominal and pelvic cancer.[6] For example, in a recent double-blind, randomized controlled trial of 100 patients with unresectable pancreatic cancer, Wong et al.[8] showed a greater decrease in pain intensity with NCPB, as compared with systemic analgesic therapy plus a sham injection, over a follow-up period of at least 1 year or until death. No differences between groups were noted in quality of life or survival. In another trial, de Oliveira et al.[13] showed that neurolytic celiac, superior hypogastric, or lumbar sympathetic ganglion blocks resulted in significant reductions in both pain ($P < 0.004$) and opioid consumption ($P < 0.02$), as well as improved quality of life ($P < 0.006$), compared with pharmacological therapy. Similar results have been reported by others,[14,15] demonstrating the benefit of invasive procedures. A recent randomized, controlled trial compared implantable intrathecal drug delivery systems (IDDSs) with comprehensive medical management in 202 patients with refractory cancer pain (with an intensity of 5 or more on a 0–10-point visual analogue scale).[7] Significantly greater pain relief and less drug toxicity were reported by the IDDS-treated group. Intriguingly, the IDDS patients had higher 6-month survival rates than the comprehensive medical management group (53.9% vs. 37.2%, respectively; $P = 0.06$). Taken together, these controlled trials indicate that invasive procedures should be considered as an adjuvant to common analgesic regimens at any stage and should not be regarded as "a last resort" to be withheld until all else fails.

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An Alternative Algorithm

Clearly, the WHO three-step analgesic ladder should not be discontinued, but it may require refinement in light of clinical experience that has accumulated in the 20 years since the ladder was proposed. We wish to suggest an alternative cancer pain treatment algorithm. First and most importantly, just as was true for the original WHO recommendation, this algorithm requires the worldwide availability of various forms of "strong" opioids (including oral formulations) and trained clinicians to prescribe them. Second, this algorithm is also based on the same three levels of pain intensity—mild, moderate, and severe.

The new algorithm proposes the following three stages of treatment for cancer pain. (1) For mild pain, non-opioid analgesic treatment should be initiated. If pain is not adequately controlled, then low doses of "strong" opioids should be added and titrated according to the individual patient's needs. (2) For moderate pain, low doses of "strong" opioids should be initiated and titrated, with or without non-opioids. (3) The treatment of severe pain obviously requires the immediate use of "strong" opioids, with or without non-opioids. Invasive procedures such as neurolytic blocks, if available, should be considered as an alternative or adjunct to pharmacotherapy at any stage of disease in patients with moderate or severe cancer pain. Adjuvant drugs should be used for all stages when indicated. As a rule,

"weak" opioids should be dropped in the treatment of cancer, other than in countries where "strong" opioids are not readily available or physicians are not well trained in using them. In such cases, clinicians must bear in mind that the efficacy of "weak" opioids is limited. Finally, although a number of controlled trials provide data to support the efficacy and safety of this suggested algorithm, further validation should be provided by prospective studies in broad populations of patients with cancer pain.

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