

EXPERT OPINION

Open questions in the treatment of cancer pain: time for a strong evidence-based approach?

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Pain affects patients with cancer at any stage of their disease. Yet, it is not adequately treated in a significant percentage of cases. In 1986, the WHO proposed a three-step approach for the treatment of pain in cancer patients (from nonopioids to weak opioids to strong opioids, according to pain intensity) following the recommendations of an international group of experts. The application of the WHO strategy demonstrated that a clear and simple approach is of educational value and ensured worldwide dissemination. However, there is little evidence that the WHO approach is the best, and there are still several points to debate on the treatment of cancer pain.

Keywords: cancer pain, evidence-based approach, opioids, WHO guidelines

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Pain affects patients with cancer at any stage of their disease. Yet, it is not adequately treated in a significant percentage of cases, ranging from 56 to 82.3% [1,2]. In 1986, the WHO proposed a three-step approach for the treatment of pain in cancer patients (from nonopioids to weak opioids to strong opioids, according to pain intensity) following the recommendations of an international group of experts [3]. The document was translated into 22 different languages and has served to increase awareness around the world of the importance of treating pain. These guidelines have been updated in 1996 [4] and they still remain the referral point for pain management worldwide.

The cornerstone of the WHO document rests on five simple recommendations for the correct use of analgesics to make the prescribed treatments effective. These simple but still relevant advises are the following:

- 1) Oral administration of analgesics.
- 2) Analgesics should be given at regular intervals.
- 3) Analgesics should be prescribed according to pain intensity as evaluated by a scale of intensity of pain.
- 4) Dosing of pain medication should be adapted to the individual.
- 5) Analgesics should be prescribed with a constant concern for detail.

In addition, the WHO gives recommendation to treat neuropathic pain and encourages the use of adjuvants to enhance pain relief.

This approach applied over the years won several goals: it helped legitimize the use of opioids for treatment of cancer pain and encouraged numerous worldwide teaching campaigns on the use, benefits and side effects of opioids in the treatment of pain. Early studies on its effectiveness demonstrated that the method proposed by the WHO offered inexpensive treatment and adequate relief for 70 – 90% of cancer patients with pain [4], although this high percentage has been questioned several times. Indeed, studies validating the WHO analgesic ladder have been shown to

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have methodological limitations and different problems are unresolved due to a lack of controlled studies on this subject [5].

One point of debate is the role of long-term use of NSAIDs as part of the treatment of cancer pain at any stage of disease and of the WHO analgesic ladder, due to their severe toxicity on gastrointestinal tract, platelet and renal function, given the high percentage of patients on these drugs from the beginning of their cancer history who may have long life expectancy.

A second point of debate is the utility of step II of the WHO ladder. This step is recommended for patients suffering mild-to-moderate pain, and treatment with a combination of acetaminophen, aspirin or NSAID plus a weak immediate-release opioid such as codeine, dihydrocodeine, tramadol (depending of what is available in different countries) is suggested. A limitation in the use of weak opioids is represented by the 'ceiling effect,' for which more than a certain threshold of dose cannot increase the effectiveness of the drug but only influence the appearance of side effects. A further criticism on this point concerns the absence of a definitive proof of efficacy of weak opioids: the available studies do not demonstrate a clear difference in the effectiveness of the drugs between the first and the second step [6]. Moreover, in a meta-analysis of data reported from clinical randomized controlled trial (RCTs), no significant difference was found in the effectiveness between nonopioid analgesics alone and the combination of these with weak opioids [7].

Many authors have proposed the abolition of the second step of the WHO analgesic ladder, in favor of the early use of morphine at low doses. However, to address this relevant issue, an RCT is urgently needed, as also claimed by the European Society for Medical Oncology guidelines [6].

A further point to be evaluated in the future is when to declare the failure of opioids treatment to move on different approaches. Virtually, there is no limit to the dose of opioids prescribed until side effects appear or became untreatable. Given the vast availability of new invasive techniques for the treatment of pain, some authors have proposed a fourth analgesic step in the treatment of pain, mainly to treat chronic noncancer pain, but also applicable for cancer pain. These include consideration of neurosurgical procedures such as brain stimulators, and invasive techniques, such as nerve blocks and neurolysis (e.g., phenolization, alcoholization, thermocoagulation and radiofrequency) [5]. However, there is no consensus on when it is time for invasive treatment and if this should always follow an attempt with opioids. One major problem in this as well as in other settings may be the lack of definition of pain responsiveness and unresponsiveness to opioids. Some authors consider an opioid therapy as efficacious if a 30% decrease in pain intensity or a 2 point decrease on the 11-point scale is achieved [8]. However, the two criteria are different, since the first assumes a linear effect whereas the second assumes a nonlinear effect. Additional criteria are minimal analgesic benefit from one or two additional dose increases and no serious side effects. Yet, the

reduction pointed may not mean sufficient pain relief for the patient.

It is now established that patients may vary greatly in their response to different opioids both in terms of efficacy and tolerability although the biological basis of this attitude are multifactorial and for some aspects still unclear [9]. The availability of opioids other than morphine ensures more therapeutic options in difficult to manage situations such as when symptoms of opioid toxicity or when high tolerance to the previously used opioid occur. Indeed, a substantial minority of patients treated with oral morphine (10 – 30%) do not have a successful outcome because of excessive adverse effects, inadequate analgesia, or a combination of both adverse effects and inadequate analgesia [10]. In these cases, opioid rotation is recommended and has been shown to be useful in opening the therapeutic window and in establishing a more advantageous analgesia/toxicity relationship [11]. Still there is not a standard criteria for opioids switch, including equianalgesic dosage, and which opioid to switch to when morphine fails.

Morphine is the cornerstone for the management of cancer pain, mainly due to the large experience existing among physicians and the wide availability in a variety of formulations. Nevertheless, there are no clear data about the superiority of one opioid over another [12]. Moreover, different opioids formulations and dosages, rather than new drugs, are available today. These formulations enhance compliance to therapy (controlled release opioids are given once or twice a day) [13] and may display a different profile in terms of tolerability compared to each other. However, to our knowledge, there are no published RCTs investigating on this specific topic. At the moment, the use of different opioids and of their different formulations is not standardized and there is not a definite consensus on whether one opioid or even one formulation has advantages over another in terms of tolerability and safety (including risk of abuse). In addition, some authors point out that there is a lack of comparisons between long-acting and short-acting opioids [14]. Moreover, the terminology of sustained release, extended release, modified release is not standardized and clearly some opioids such as methadone and buprenorphine are intrinsically 'long-acting' due to slow clearance.

Since opioids should be judged based on risk and benefits, a clear assessment of symptoms related to adverse effects is desirable. However, in many studies, adverse effects are not systematically assessed as responses. In a study by Jonsson *et al.*, the number of symptoms reported using systematic assessment was eightfold higher than those reported voluntarily [15]. Yet, most trials do not provide what symptoms related to adverse effects were assessed and when and how were symptoms assessed. In addition, the approach to side effects such as opioid-induced constipation may vary with respect to old approaches given the new drug formulation with the peripherally acting μ -opioid receptor antagonist naloxone.

A further issue to stress is the need of a clear and definite approach to breakthrough cancer pain (BTcP). Currently,

there is no universally accepted definition for BTcP, being the most accepted: 'a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain' [16]. Then, its diagnosis needs a well-controlled basal pain and its treatment mainly relies upon rapid onset fentanyl [17]. In this field, an anamnestic recall aimed at evaluating when the BTcP happens, which are its characteristics, how fast are onset and offset can address the right therapy. Yet, the most appropriate breakthrough dose interval using immediate release opioids and rapid acting fentanyl products has still to be defined.

On the other hand, there are still evidences of inappropriate treatment of pain exacerbations, even in a relatively advanced and progressive cancer stage, often treated with NSAIDs as first-line approach for BTcP [18].

Clinical trials available nowadays exploring opioid treatment in cancer pain have many flaws mainly due to how the trial was designed. Indeed, there is not a clear definition of 'cancer pain,' whereas the type of primary tumor and the actual stadiation may account for different etiology of pain, then responding to different treatment [19]. Moreover, placebo effect should be taken into account in the study design as it may hide differences between opioids as well as a classic non-inferiority design of confidence intervals around outcome measures may provide more reliability compared to P values [20,21]. Additionally, the result of a trial is applicable on the same population that was selected for the trial. Results are not generalizable. Finally, in the real-world opioid rotation, adjuvants addition and nonpharmacologic therapies may adjust pain treatment. However, these adjustments are not allowed by trials, then the results and observations are not always completely applicable in the real world [22]. All these issues should be taken into account when designing a study and also when recommendations are obtained from trial results.

The points raised here and other new acquisition on the pathogenesis and characteristics of cancer pain make the WHO strategy somehow inadequate. Experts now recommend a more rational approach to cancer pain, which may change the actual approach, indeed: as cancer pain has different etiologies, establishing the right diagnosis is the key to providing the right treatment. Then, for example, antiepileptics can represent the first and best approach to some kind of cancer pain, or acetaminophen or NSAIDs may have their

role in severe pain [23]. At the moment, the rule is to tailor the dosage, the type and the route of drugs administered according to each patient's needs: individualization of the treatment still remains the key of the best treatment.

Then our open questions about pain therapy are the following:

Is there still a role for NSAIDs in cancer pain? And if so, should it be for mild pain, independently of the patient's life expectancy?

Is there still need of the second step of the WHO ladder or can it be replaced by low-dose strong 'opioids'?

Which is the best opioid (active principle or formulation) to start with after morphine titration? Furthermore, validation of titration strategies is necessary.

Finally, the treatment of neuropathic cancer pain with nonopioids needs standardization as well.

RCTs specifically investigating on these and other issues are highly needed and an evidence-based approach is highly recommended to orientate in the maze of new nonvalidated treatment and therapeutic approaches proposed in this field in recent years. Most of the current guidelines for best treatment of cancer pain give mainly weak recommendations.

In conclusion, the actual approach needs a profound knowledge of drug characteristics and a good experience in evaluating the patients' response, also recognizing the possible alternative treatments. However, many cancer patients still suffer from unrelieved pain due to inappropriate pain management, insufficient knowledge and education, the physician's limited experience regarding the management of cancer pain, and the perception of the laws that govern opioid prescription and use. The WHO strategy demonstrated that a clear and simple approach is of educational value and ensures worldwide dissemination. Evidence-based certainty can help to achieve the standardization of what at present is the approach of experts.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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