Letters

Update on Cancer Pain Guidelines

To the Editor:

It is now 26 years since Vittorio Ventafridda, MD, organized, with the help of the Floriani Foundation and on behalf of the World Health Organization (WHO), a meeting of experts from around the world (J. J. Bonica, K. M. Foley, A. Rane, M. Swerdlow, R. Twycross, V. Ventafridda, J. Birkham, P. B. Desai, M. Martelete, F. Takeda, and R. Tiffany) to develop the first international cancer pain guidelines.[1,2] These guidelines had an enormous impact on the attitudes and practices of professionals, and on patient care. Although this impact never was scientifically assessed, it was probably much more important than one can estimate from individual experiences and knowledge. Ten years later, concurrent with the second edition of the WHO guidelines, the European Association for Palliative Care (EAPC) published its first recommendations on the administration of morphine for cancer pain.[3] These guidelines were updated in 2001.

Considering the changes that have occurred in the worldwide recognition of the problem of cancer pain and the increasing availability of different opioids and opioid preparations in most countries during the last 20 years, there is considerable awareness of the need for updated international guidelines on the management of cancer pain, with particular attention to the role of opioids. For this reason, the European Palliative Care Research Collaborative (EPCRC), a research consortium funded by the sixth framework of the European Commission, in collaboration with the EAPC, has embarked on an update of the WHO and EAPC guidelines for the administration of opioids in cancer pain.

The EPCRC process of guideline development started with the review of guidelines presently available to users through the literature or Internet sites, and the involvement of several groups of experts and stakeholders who should, at different levels, influence the development of the guidelines themselves. Experts and stakeholders were identified according to established criteria, such as having participated in the development of previous guidelines; representing international, multiprofessional, and multidisciplinary areas of expertise; and having published about opioids and cancer pain. Needs and priorities of general practitioners and patients will be included later in the guideline development process. The project has been presented at several international and national conferences, and on the EAPC and EPCRC web sites, inviting professionals and volunteers working in palliative care to participate actively by answering a specific questionnaire (http://www.epcrc.org/doc_pain_guide.php).

As a first step, key points that should be included in the guidelines were formulated by the expert group using a standardized consensus procedure (Delphi procedure) (Table 1). The background for this work was a more strategic discussion on guideline development and implementation, which was initiated with a meeting of experts from different European countries (F. De Conno [Italy], S. Kaasa [Norway], P. Sjögren [Denmark], A. Caraceni [Italy], P. Stone [U.K.], M. Filbet [France], C. Wood [France], C. Centeno [Spain], M. Nabal [Spain], L. Radbruch [Germany], and F. Nauck [Germany]), in Budoni, Sardinia. Aspects of the recommendations concerning the use of morphine were discussed in light of the existing literature. In particular, the discussion focused on 1) the role of morphine as a first-line opioid for severe cancer pain; 2) the need for titration of the initial oral morphine dose; and 3) the role of opioids for the WHO "second step"

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Table 1

Provisional Key Points Summary Checklist in the Development of the EAPC Guidelines on the Administration of Opioid Analgesics in Cancer Pain

1. Identify the opioid of first choice for moderate to severe cancer pain (opioid of choice).
2. Identify the optimal route of administration of opioid of choice.
3. Clarify the optimal method of opioid dose titration at the beginning of therapy.
4. Suggest when a regular dose of opioid should be increased.
5. Identify the roles of short-acting and long-acting opioid of choice (while taking into account the availability of such formulation) to suggest different titration schedules.
6. Clarify that available formulations of long-acting first choice (and other) opioids do not differ in terms of efficacy.
7. Identify the preferred alternative route/s of administration for patients who are unable to take oral opioids.
8. Establish the average relative potency ratio/s of oral opioid of choice to the parenteral route of choice.
9. Identify the optimal way to administer continuous parenteral opioid of choice.
10. Establish the average relative potency ratio of oral to intravenous opioid of choice.
11. Identify the role of other alternative routes of opioid of choice administration.
12. How should breakthrough pain be managed?
13. Identify the role of opioids in the treatment of breakthrough pain.
14. Address the needs of patients who do not achieve adequate analgesia without excessive adverse effects with the use of opioid of choice by considering the spinal administration of analgesic, alternative opioids, and nondrug methods of pain control.
15. Identify the role of hydromorphone.
16. Identify the role of oxycodone.
17. Identify the role of methadone.
18. Identify the role of transdermal fentanyl.
19. Identify the role of buprenorphine (sublingual and transdermal).
20. Identify the role of spinal administration of opioid analgesics.
21. Identify the role of adjuvants in combination with analgesics.
    - 21a. Antidepressants
    - 21b. Anticonvulsants
    - 21c. Gabapentin and pregabalin
22. Identify the role of opioids for mild to moderate cancer pain as suggested by Step II of the WHO analgesic ladder.
23. Identify the role of nonsteroidal anti-inflammatory drugs.
24. Identify the equivalent potency ratio of oral morphine to transdermal fentanyl.
25. Suggest an evidence-based equipotency table for opioid conversion and its use in equianalgesic dose calculation.
26. Identify how and when to start management to prevent and treat opioid side effects.
27. Identify the treatment of constipation related to opioids.
28. Identify the role of using more than one opioid in combination.
29. Identify which opioids to use in renal failure.
30. Identify which opioids to use in liver failure.

therapy. The debate underlined that there is no evidence to dismiss the worldwide role of oral morphine as the first-line therapy for severe cancer pain.[4] No evidence is available that any other opioid is superior to morphine, either in terms of efficacy or tolerability. The expert opinion confirmed that its pharmacological characteristics, clinical experience, and economic considerations should reinforce a fundamental role for morphine in the pharmacological management of cancer pain.

More controversy was found regarding the need for titration for initial dose finding of oral morphine therapy. Even if the literature about this topic[5,6] is not too abundant, it seemed reasonable to conclude that a number of patients require dose adjustments that are sufficient to justify a recommendation of titration for initial dose finding and for supplemental dosages required for treatment of breakthrough pain.

In recent years, extensive discussion and some papers[7–9] have challenged the need for the second step of the WHO ladder. However, the experts were skeptical that this step should be omitted from the ladder, as it offers low-barrier treatment for opioid-naïve patients with slight to moderate pain intensity.

The discussion focused not only on the content of the guidelines, but also on the importance of the guideline development process to reflect on the target groups. For example, guidelines targeted at decision makers should emphasize adequate availability of opioids (fast and slow release). Aiming at professionals (specialists) who frequently see patients with cancer pain as a target group, the comparative advantages of different opioids, as well as safety and

pharmacokinetic details are important. For basic clinical guidelines that provide information on a palliative care approach to nonspecialist practitioners and clinicians, a simple algorithm would be preferable to detailed pharmacological analysis.

These considerations, and a plan on guideline implementation, are most important and have to be taken into account from the start of the guideline process. The recent update of the cancer pain guidelines of the drug commission of the German Medical Board (Arzneimittelkommission der Ärztekammer) can be used as an example for implementation procedures. These guidelines are available as a long version for physicians, with detailed information and complete set of references; as a desktop short version (approximately six pages as hard copy); and as a version for patients and caregivers. The approach provides concurrent information in a format adapted to the recipient (specialist, general practitioner, patient). Similar implementation strategies might be useful for the EPCRC–EAPC guidelines, producing documents of different extent, available through different media systems, and with different programs of dissemination.

The EPCRC program will not produce the guidelines until the end of 2010. However, we want to facilitate discourse with broad participation and consensus among all the relevant groups to formulate an authoritative international guide for the control of cancer pain worldwide. For this reason, we encourage all readers to join the debate on the EPCRC Web site.

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Successful Pain Relief of Cutaneous Leiomyomata Due to Reed Syndrome with the Combination Treatment of Pregabalin and Duloxetine

To the Editor:

Cutaneous leiomyoma is a rare benign tumor that is derived from the arrector pili muscle. Females with multiple cutaneous leiomyomas may also have uterine leiomyomas. This autosomal dominant genetic disorder is called Reed