

Modern insights in the nature and treatment of cancer pain: focus on opioids

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History

Cancer pain management was identified as a priority in the overall programme of cancer control by WHO in 1982, considering that the majority of patients have solid tumours and at least 50% die of the disease, and this proportion is even higher in developing countries. While curative and disease-modifying therapies may not be available or accessible due to lack of resources, access to effective pain relief using simple pharmacological methods should be provided to all patients with cancer pain given the efficacy and low cost of oral morphine, which is the prototype opioid analgesic and the mainstay of an effective pharmacological strategy. The strategy summarised in the WHO analgesic ladder includes non-steroidal anti-inflammatory drugs, paracetamol, opioids and adjuvants, as well as other interventions in selected cases. The emphasis on pharmacological therapies and the relevance of opioid use were clearly highlighted in the WHO recommendations. The WHO campaign and the WHO analgesic ladder, published in 1986,¹⁻² had a major impact by disseminating knowledge and raising awareness worldwide when, in many countries, oral morphine was not available or accessible, there was professional and societal opposition to the use of opioids in pain clinics, and morphine and opioids in general were considered to be dangerous and inappropriate medications.

Unnecessary suffering depends on lack of drugs and lack of compliance with available guidelines

Over the past 30 years there has been a rich growth in interest, service provision

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and professional expertise in symptom management of patients with advanced incurable diseases, including cancer, thanks to the dissemination in Europe and the rest of the World of the palliative care movement. Palliative care, which is becoming an increasingly recognised field of medicine, has emphasised symptom control with a special focus on the use of opioids for managing cancer pain and facilitating fruitful dialogue with other specialties such as oncology and pain.

The lack of appropriate therapeutic approaches leading to unnecessary cancer pain in the past can no longer be considered acceptable. Clinical guidelines developed by scientific and professional associations, including recommendations on appropriate pain management strategies and opioid use, have been constantly updated and distributed worldwide. In addition, opioids have become more available and accessible in many countries worldwide and their use has increased, although not always at the same pace. There are still exceptions to this trend, with some countries, especially in less developed areas of the world, experiencing unacceptably limited and insufficient availability of opioids.³

The use of opioids for cancer pain has been the focus of a series of recommendations by the European Association of Palliative Care (EAPC), which can be seen as historically based on the original WHO analgesic ladder. The EAPC recommendations provide a general framework that can be used internationally as a benchmark for clinical practices and national healthcare policies.^{4,5} The most recent version of these recommendations meets the requirements of a rigorous methodology, updated evidence-based analysis of the literature and wide international consensus and participation.^{6,7}

A modern view of cancer pain can therefore be that we have the knowledge to effectively control cancer pain in most of the world and that lack of availability and access to opioids and lack of adequate

implementation of existing guidelines are still often the causes of unnecessary suffering for patients with cancer pain.

When is cancer pain not responding to opioids?

Even when opioids are used appropriately and available treatment guidelines are implemented, not all patients with cancer have the same clinical outcome in terms of pain control. Most patients will obtain satisfactory pain control but a proportion, which can reach 30% according to different studies, have pain which is more difficult to control. In some cases, pain remains unsatisfactorily controlled in spite of aggressive and well conducted opioid treatments.

This is a clinically relevant and socially significant problem awaiting more research and the allocation of more specific healthcare resources. In this commentary I only briefly address a number of topics that can be used to build an important agenda for better clinical standard approaches to the problem and for more focused research.

- ▶ Cancer pain assessment and classification is too vaguely defined and does not follow standard, homogenous and reproducible methods in research and in clinical practice. This prevents a consistent definition, across different experiences, of controlled or uncontrolled pain and of effective or ineffective treatments or treatment strategies. International collaborative efforts are trying to define common methodologies and clinical classification tools to be adopted in oncology and palliative care.⁸ The ability to explain the variability of opioid analgesia in patients with cancer is limited. We need a better way to describe pain, pain syndromes and clinically relevant associated factors to identify the 'difficult' pain cases.
- ▶ Several efforts have been made to use clinical descriptors and characteristics⁹ in a consistent and clinically useful

manner¹⁰ with limited results. The Edmonton Classification System for Cancer Pain is one example of a guide to emphasise and standardise some clinical features associated with more difficult to control pain conditions.¹¹ Matching a consistent and valid classification system with improved treatment guidelines is one challenge for the field of cancer pain in the near future.

- ▶ The recently updated EAPC opioid guidelines acknowledge that most of the available recommendations have a weak evidence base. In spite of a wide range of clinical practices, the clinical suggestions for more problematic indications such as neuropathic pain, incident and breakthrough pain and opioid rotation are limited by the lack of specific evidence.
- ▶ Clinical surveys and observational trials have shown that pain pathophysiology and mechanisms (neuropathic and incident), pain intensity, sleep interference and psychological distress have an impact on the complexity and outcomes of pharmacological pain management in patients with cancer.¹²
- ▶ The appropriate use of opioids can be limited in cases of severe pain with an incident component, and opioid dose titration can fail to produce sufficient pain relief and may cause significant side effects. Therapeutic modifications such as opioid rotation, adjuvant drugs, hypofractionated palliative radiation therapy or using the spinal route for administering a local anaesthetic can be alternative solutions if pain is due to a localised metastatic bone lesion affecting a weight-bearing body segment. In patients with neuropathic symptoms not responding to a high-dose morphine infusion, opioid tolerance, non-opioid sensitive pain mechanisms and opioid-induced hyperalgesia may be explanations for the poor response. Opioid rotation and the addition of specific adjuvant drugs for neuropathic pain are potential therapeutic options. These two clinical examples describe how incident pain and neuropathic pain may have a negative influence on the pain outcome of opioid-based therapies and highlight the complexity of the factors involved in a comprehensive pain evaluation. Such a comprehensive

approach for difficult cases may only be effective when implemented by a specialised palliative care team.

- ▶ Patient susceptibility to opioid side effects is variable and the efficacy of opioids is different for individual cases. This variability may be explained by genetic heterogeneity, affecting the pain-generating mechanisms in the nervous system and the ability of the nervous system to respond to opioid drug administration in clinically determined circumstances. The impact of genetic variability on opioid pharmacotherapy for cancer pain is a very complex area of research which requires dedicated efforts, accurate clinical evaluation, specialised settings of care and large patient populations, as shown by preliminary data from recent studies^{13,14}

Pain management, appropriate use of opioids and access to integrated palliative care

Pain diagnosis, assessment, classification and treatment is a fundamental part of the palliative care of patients with advanced cancer and a constitutive part of palliative care as a medical discipline. Offering optimal pain relief is therefore the responsibility of palliative care services. When service integration and clinical practice appropriateness are at their best, timely referral to palliative care services is way of reducing the burden of unnecessary suffering. Another almost totally neglected area of interest which needs better documentation of clinical practices and clinical outcomes is the symptomatic efficacy of antineoplastic interventions and the integration of oncological and palliative care approaches to improve pain outcomes and patient care.

The management of pain due to incurable cancer can only be part of a comprehensive programme addressing the physical, psychological, social and spiritual dimensions, originally described by Cicely Saunders when she invented, with the help of her patients, the term 'total pain'. It goes without saying that accurate professional attention to pain is part of accurately and compassionately listening to each patient's personal history. It is only the revolutionary idea of a discipline in medicine which combines in its professional armamentarium an interdisciplinary

approach of scientifically based symptom control together with the same interest in communication, psychological and spiritual support, which allows palliative care to try to understand each patient's individual pain and suffering and in the meantime 'to reach the most hidden places'.

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