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Commentary

Pain in the cancer patient: different pain characteristics CHANGE pharmacological treatment requirements

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Abstract

Twenty years ago, the main barriers to successful cancer pain management were poor assessment by physicians, and patients' reluctance to report pain and take opioids. Those barriers are almost exactly the same today. Cancer pain remains under-treated; in Europe, almost three-quarters of cancer patients experience pain, and almost a quarter of those with moderate to severe pain do not receive any analgesic medication. Yet it has been suggested that pain management could be improved simply by ensuring that every consultation includes the patient's rating of pain, that the physician pays attention to this rating, and a plan is agreed to increase analgesia when it is inadequate. After outlining current concepts of carcinogenesis in some detail, this paper describes different methods of classifying and diagnosing cancer pain and the extent of current under-treatment. Key points are made regarding cancer pain management. Firstly, the pain may be caused by multiple different mechanisms and therapy should reflect those underlying mechanisms – rather than being simply based on pain intensity as recommended by the WHO three-step ladder. Secondly, a multidisciplinary approach is required which combines both pharmacological and non-pharmacological treatment, such as psychotherapy, exercise therapy and electrostimulation. The choice of analgesic agent and its route of administration are considered, along with various interventional procedures and the requirements of palliative care. Special attention is paid to the treatment of breakthrough pain (particularly with fast-acting fentanyl formulations, which have pharmacokinetic profiles that closely match those of breakthrough pain episodes) and chemotherapy-induced neuropathic pain, which affects around one third of patients who receive chemotherapy. Finally, the point is made that medical education should place a greater emphasis on pain therapy, both at undergraduate and postgraduate level.

Introduction

In a recent pan-European survey of cancer patients, the most common reason for the initial consultation that led to the cancer diagnosis was pain (Figure 1)[1]. Studies have found that pain is experienced by 25–30% of patients with recently diagnosed cancers[2], by over 80% of patients with advanced metastatic disease[3], and that approximately 50% of hospitalized cancer patients experience untreated pain during the last 3 days of life[4]. Importantly, the impact of this pain on the quality of life can be devastating; cancer patients with pain report significantly lower levels of performance status and higher levels of total mood disturbance than those who are pain-free, as well as significantly more anger, fatigue, depression, confusion, and lethargy[5]. However – and despite the fact that World Health Organization (WHO) guidelines for the management of cancer pain were published more than two decades ago[6] – there is a substantial body of evidence which indicates that the treatment of cancer pain is often suboptimal[1,7–9].

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Consensus points

The impact of cancer pain on quality of life can be devastating.
The treatment of cancer pain is often suboptimal.

The CHANGE PAIN Advisory Board of leading pain specialists from Europe and the USA has met regularly since 2009 to discuss issues related to the physiology and treatment of pain. Its main objectives are to increase the understanding of pain among the wider medical community, and to improve pain management by disseminating its conclusions and providing guidance to other clinicians. On March 30th and 31st, 2012, the Board met in Düsseldorf to review various aspects of the development and current treatment of cancer pain, and then considered specific topics in more detail.

Development of cancer and cancer pain

The neurobiology of cancer pain is best understood by summarizing current concepts of carcinogenesis. The initial change is a number of mutations occurring in a cell over time. These may be caused by hereditary or biological factors, or by exposure to physical or chemical agents, and they have a cumulative effect. Certain types of gene – such as proto-oncogenes and tumor-suppressor genes – play a key role in the transformation of a normal cell into a cancer cell, which ignores signaling mechanisms that instruct it to stop dividing, become specialized, or undergo apoptosis[10]. Typically, this is followed by pre-malignant cellular proliferation which is usually reversible and may include: hyperplasia (abnormal increase in the number of cells), hypertrophy (abnormal increase in the size of cells), or dysplasia (alteration in the size, shape and organization of the cellular components of a tissue). These cells are generally well differentiated and function similarly to the tissue from which they arose. Progression to 'cancer in situ' and then invasive cancer is accompanied by a gradual change in appearance and loss of physiological functions, as the cells divide haphazardly and accumulate into a non-structured tumor. These later stages are almost always irreversible and are characterized by the capacity to invade healthy tissue, both locally and in distant organs, via blood and lymphatic vessels.

Some cancer pain arises from within the cancer microenvironment[11]. The key cellular components here are primary afferent nociceptors, immune cells and the cancer cells, which produce and secrete mediators that modulate nociception. These mediators include endothelin-1 (ET-1), protons, proteases, nerve growth factor (NGF), bradykinin and tumor necrosis factor alpha (TNFα), which have an effect on primary afferent nociceptors to produce pain[11].

Low pH is characteristic of the cancer microenvironment, reflecting the elevated metabolic rates and anaerobic conditions that occur with carcinogenesis. This acidosis induces the expression of acid-sensing ion channels (ASICs) and is a well established cause of pain[11]. ET-1 produces nociceptive behavior[12,13] and drives cancer pain[14] by binding to G-protein coupled receptors that differentially affect opioid release from tumors. For example, there is evidence that an allelic substitution of adenine by guanine in position 118 (A118G) of the μ-opioid receptor gene (OPRM1) has an effect on angiogenesis and tumor growth[15]. The nociceptive effect of protons is produced by direct activation of the transient receptor potential vanilloid-1 (TRPV-1) channel, a Ca^{2+}-permeable ionotropic receptor. Proteolytic activity plays a major role in carcinogenesis and cancer pain; protease activated receptors (PARs) are present on primary afferent nociceptors and are activated either directly by proteases or

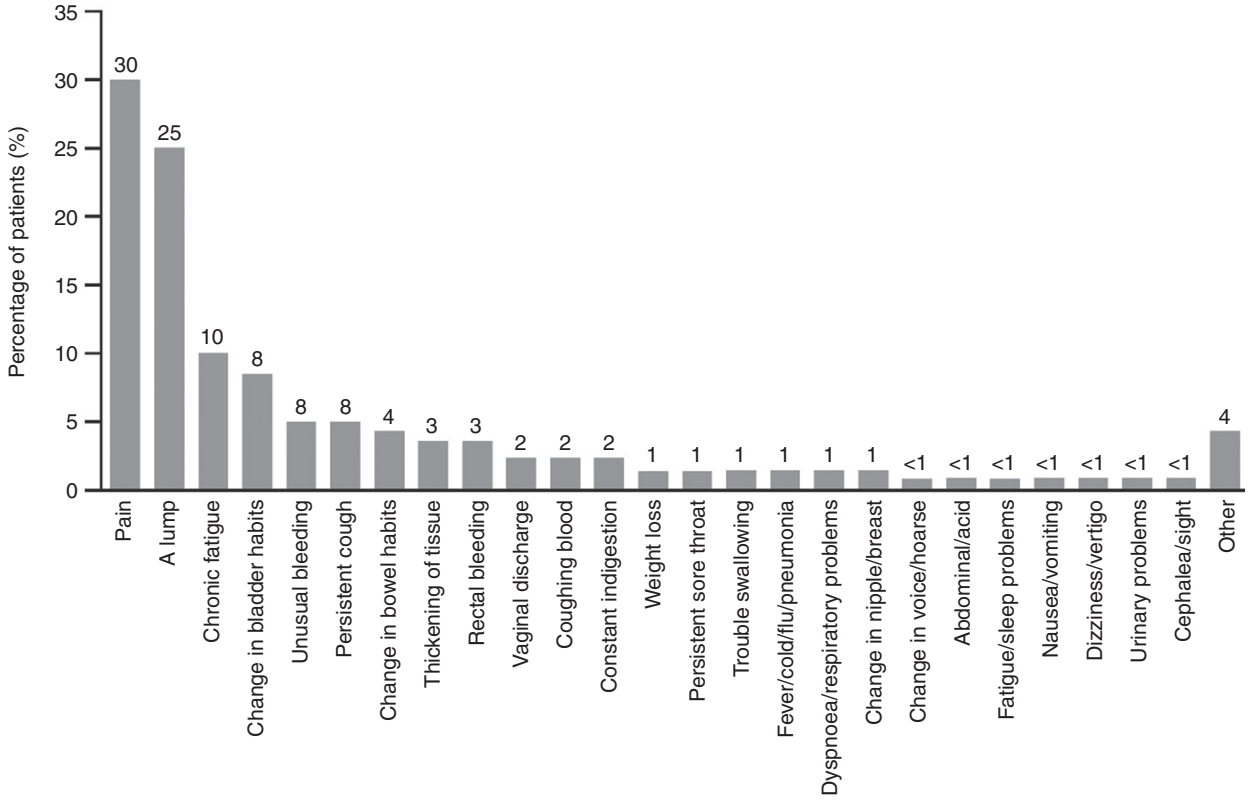

Figure 1. Reasons for consulting a healthcare professional that led to a diagnosis of cancer[1]. By permission of Oxford University Press.

by their peptide products. NGF is normally secreted to promote the local growth and survival of afferent sensory neurons, but its secretion into the microenvironment by cancer cells leads to a number of changes that produce pain, including modulation of inflammatory cell activity. Certain cancers secrete kallikrein, which increases the concentration of bradykinin in the microenvironment[16]. Bradykinin appears to have a direct nociceptive effect in cancer pain, since blockade of the bradykinin B_1 receptor reduces bone cancer pain[17], but it also induces increased expression and secretion of ET-1[18]. High levels of proinflammatory cytokines are produced in cancer and TNFα stimulates immune cells, which can produce nociceptive agents that interact with primary afferent nociceptors[19]. In addition, a direct local role for TNFα in the production of both mechanical and heat hyperalgesia has been demonstrated in animal models[20,21].

Inflammation is a key component of the tumor microenvironment and inflammation-mediated tumor progression is produced by transcription factors, cytokines, chemokines and infiltrating leukocytes[22]. By directly or indirectly downregulating DNA repair pathways and cell cycle checkpoints, these inflammatory mediators produce a genomically heterogenous population of expanding cells naturally selected for their ability to proliferate, invade and evade host defenses. A particularly insidious form of tumor growth is perineural invasion; i.e. the spread and proliferation of cancer within a nerve. This process is associated with NGF[23], linked to both pain and recurrence following surgical resection[24,25], and also indicates poor prognosis and reduced survival rates[25,26]. Early symptoms may include pain, burning sensations, paresthesias, numbness and formication[27], although the patient may be asymptomatic at first. Motor weakness is a late sign[27], while complete denervation may produce muscle atrophy. Perineural involvement is emerging as an important pathological feature of many malignancies, including those of the pancreas, colon and rectum, prostate, head and neck, biliary tract, and stomach[28].

Often, the first symptom for which patients consult a physician is pain from bone metastasis[29]. This is a multistep process which includes the following sequence of events: (I) tumor growth, detachment of cancer cells and invasion of the tissue stroma; (II) neoangiogenesis; (III) escape from the tissue by intravasation; (IV) survival in the circulation; (V) chemoattraction and arrest (docking and locking) in the bone marrow endothelial vessel wall; (VI) extravasation; and (VII) establishment of the metastatic microenvironment via the cross-talk between the cancer and bone cells[30–32]. Cyclooxygenase-2 (COX-2) is thought to play a major role in this process;

over-expression leads to increased tumor formation and pharmacological suppression of COX-2 inhibits metastasis.

Pain may arise not only from the presence of many different factors in the microenvironment, as previously described, but also from one or more of the following: nerve root infiltration, nerve compression, microfractures, stretching of the periosteum, increased intraosseous pressure and muscle spasm[33]. However, a significant portion of the pain seems to be related to osteoclastic bone resorption[34], and animal studies have demonstrated the involvement of both peripheral sensitization, as a result of physiological and morphological changes to primary afferent fibers[35], and central sensitization, by augmentation of excitatory synaptic transmission in the substantia gelatinosa which is mediated via A_δ and C fibers[36].

Classification of cancer pain

The clinical presentation of cancer pain can vary considerably, depending upon the histology of the cancer cells, the site of the primary neoplasm, and the location of any metastases. The pain may be classified in a number of different ways; for example, according to the type of pain, its relation to the cancer, the presence of pain syndromes (e.g. bone pain syndromes, visceral pain syndromes, post-chemotherapy pain syndromes), or the incidence and duration.

Pain type

In addition to the distinction between acute and chronic pain, pain syndromes can be divided into three classes according to their clinical features and etiology[37]. Nociceptive pain is caused by the activation of peripheral A_δ and C fibers (high-threshold nociceptor neurons) that respond only to noxious thermal, mechanical or chemical stimuli (e.g. pinprick, ligamentous stretch). Adaptive and biologically useful, it contributes to survival by protecting the organism from injury and promoting healing when injury has already occurred. It is usually short-lived and resolves once healing is complete[38]. Other conditions in which it is seen include arthritis, sports injuries and post-operative pain[39]. There are two subtypes of nociceptive pain: somatic and visceral. Somatic pain involves the skin, bones and soft tissues, and characteristically is easily localized, stabbing or boring in character, and movement-dependent. Visceral pain, which involves parenchymatous organs, hollow viscera and the peritoneum, is dull, difficult to localize and colicky in nature. Patients often describe it as a diffuse or 'pressure-type' sensation.

Inflammatory pain is essentially pain which occurs when active peripheral inflammation is detected by nociceptors, and leads to sensitization of the nociceptive system (e.g. joint pain such as facet pain).

The third class – neuropathic pain – is not adaptive, has no protective function, and represents a disease state of the nervous system. It may be defined as 'pain arising as direct consequence of a lesion or disease affecting the somatosensory nervous system'. Essentially, a maladaptive plasticity alters nociceptive signal processing, so that responses to noxious and innocuous stimuli are enhanced, and pain is felt in the absence of stimuli (e.g. radicular pain)[40]. The pain may be perceived as shooting, lancinating, 'electric shock-like' or burning, and may occur spontaneously. Positive signs, such as allodynia, hyperalgesia and hyperpathia may be accompanied by negative signs such as the loss of touch, vibration, pinprick, or thermal hypoalgesia. Neuropathic pain is typically present in cases of postherpetic neuralgia, peripheral diabetic neuropathy and multiple sclerosis.

Many patients with chronic pain experience a combination of different pain types – a condition sometimes referred to as mixed pain syndrome[41]. For the sake of simplicity, however, in clinical practice nociceptive and inflammatory pain are grouped under the term nociceptive pain, and a distinction is only made between nociceptive and neuropathic pain. Cancer pain may be nociceptive, neuropathic, or a combination of both types.

Relation to cancer

This classification system divides cancer pain into four categories. Firstly, cancer-related pain is directly linked to carcinogenesis and is most often caused by either compression – when a tumor physically presses on an organ or body part – or by the infiltration of hollow organs, soft tissue, bones, or nerves. Soft tissue infiltration causes localized pain as a result of tissue destruction and the infiltration of pain-sensitive structures such as fascia or tendons. Metastasis to the viscera is frequently seen in cases of lung and breast cancer, and this produces poorly localized, deep-seated pain in the chest, abdomen, or pelvis. Referred pain may also be present when a peripheral nerve is involved. Between 60% and 90% of cancer patients experience cancer-related pain[42].

Cancer-induced bone pain (CIBP) is an important example of cancer-related pain, which a review of 26 studies found to be undertreated in 43% of patients (range 8–82%)[43]. It often results in hospice or hospital admission and is associated with a reduced quality of life, increased psychological distress and decreased physical and social functioning[44]. Notably, the extent and location of bone metastases do not necessarily correlate with pain intensity[45]; patients with widespread metastases may have minimal pain, and patients with few metastases may experience severe pain.

The second category, cancer-associated pain, is only indirectly linked to the patient's cancer; for example, acute pain from herpes zoster or chronic post-herpetic neuralgia (PHN) due to tumor growth induced impairment of the patient's immune system, back pain as a result of being confined to bed for long periods of time, or coughing caused by lung cancer that triggers low back pain. This affects 5–20% of cancer patients[42].

Treatment for the disease – including diagnostic investigations, surgery, chemotherapy, or radiotherapy – leads to therapy-related pain in 10–25% of patients[42]. Surgery may produce pain as a direct result of tissue injury or indirectly following scar formation, and neuropathic pain may follow any surgical procedure. Chemotherapy may induce painful polyneuropathy and/or mucositis. Oral mucositis may produce ulceration so severe that the patient is unable to tolerate food or fluids, delaying treatment and limiting the effectiveness of cancer therapy. Radiotherapy can cause painful inflammation of any mucous membranes that are irradiated. Other examples of therapy-related pain include myelopathy after treatment of the spinal cord, and neuropathy, which may develop months or even years after irradiation of the brachial or lumbar plexus.

The final category is cancer-independent pain, in which pain is caused by conditions that were present before the cancer diagnosis or arise independently of carcinogenesis. Conditions such as rheumatoid arthritis and migraine are responsible for this category of pain in 3–10% of cancer patients[42].

Cancer pain syndromes

Approximately three-quarters of patients with chronic cancer pain have syndromes directly related to the neoplasm[46]. These may be subdivided into neuropathic syndromes (e.g. cranial neuralgias, peripheral neuropathies), visceral nociceptive syndromes (e.g. hepatic distension syndrome, peritoneal carcinomatosis), and somatic nociceptive syndromes (e.g. tumor-related bone pain, vertebral syndromes). Most of the remainder have syndromes caused by antineoplastic treatment. Again, these can be subdivided into those caused by chemotherapy (e.g. peripheral neuropathy, complex regional pain syndrome), radiotherapy (e.g. chronic radiation myelopathy, burning perineum syndrome), or surgery (e.g. post-mastectomy pain syndrome, post-thoracotomy pain syndrome and frozen shoulder, post-amputation pain). Identifying these syndromes can guide clinical assessment and treatment, clarify prognosis, allow preventive care, and provide reassurance to patients who interpret their pain as an indication of cancer progression[46].

The complex, multidimensional nature of cancer pain presents challenges for pain classification, but the Edmonton Classification System for Cancer Pain (ECS-CP) has been developed to detect the presence of complex pain syndromes and guide the management of patients with advanced cancer[47]. It uses five features – pain mechanism, incident pain, psychological distress, addictive behavior and cognitive function – and simultaneously integrates them within a cohesive framework to forecast the likely time to stable pain control, analgesic regimen and opioid dosage. Its predictive value has been confirmed in a study involving over 1000 patients from 11 palliative care centers in six different countries[47]. A pain syndrome was found to be present in 86% of subjects. Younger age, neuropathic pain, incident pain, psychological distress and pain intensity were independently associated with days to achieve stable pain control. Patients with neuropathic pain, incident pain, psychological distress or higher pain intensity required more adjuvants and higher final opioid doses, in contrast to those with addictive behavior who required only higher final opioid doses[47].

Incidence and duration

Following a recent study, a new clinically based classification has been proposed which is based upon the temporal characteristics and nature of the pain experience[48]. Continuous pain alone, i.e. without any episodic increase in intensity, was experienced by 11% of the patient sample[48]. Intermittent or non-breakthrough pain (NBP) alone was reported by 29%[48]. This may be defined as episodic pain of any intensity without continuous pain and in the absence of prescribed 'around the clock' (ATC) analgesics. The three categories of NBP are incident, non-incident and mixed. Incident pain is predictable and related to a specific precipitant, which may be voluntary (e.g. eating) or involuntary (e.g. coughing), whereas non-incident pain has no apparent precipitating factor. Almost two-thirds (60%) of the patients had periods of intermittent pain superimposed upon continuous pain[48]. The episodic increase in severity, or breakthrough pain (BP), has been defined by Portenoy and Hagen as "a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy"[49]. This is sub-divided similarly to NBP, but some clinicians recognize a fourth category – end of dose failure – although there is a lack of evidence for this classification[50]. Patients experience intermittent pain that consistently occurs before a scheduled ATC dose, and it usually indicates that the ATC dose should be increased.

Consensus point

The various, often combined, mechanisms and different characteristics of continuous and breakthrough pain can make cancer pain management difficult.

Cancer pain – prevalence, intensity, and treatment

The European Pain in Cancer survey provided the first robust pan-European epidemiological data on cancer pain and its treatment in 2009[1]. A total of 5084 adult patients from 11 European countries and Israel, with a wide range of cancers and at all stages of the disease, took part in an initial telephone interview. From these, 573 patients who had experienced pain several times a week over the previous month, and with a pain intensity of ≥5 on a 0–10 Numeric Rating Scale (NRS), were randomly selected for a second in-depth interview[1].

The overall incidence of pain in the survey sample ($n = 4947$) was 73%, and ranged from 53% in patients with prostate cancer to 93% in patients with pancreatic cancer (Figure 2)[1]. A striking variation was seen in the proportion of patients reporting pain in different countries, from 43% in Sweden to 95% in Italy. However, this may be caused by the types of cancer being dissimilar from one country to another, and types with the highest prevalence of pain (pancreas, bone, brain, lymphoma, lung) being over-represented in some countries (Switzerland, Israel, Italy, UK, France, and Ireland)[1]. Almost a quarter (23%) of the respondents who reported an NRS score of ≥5 in this initial survey were receiving no analgesic medication, including 19% of those patients who experienced pain of this intensity daily or more frequently[1].

Most patients who were selected for the second interview reported that their pain was managed by either a medical oncologist (42%) or a general practitioner (19%), but the range of healthcare professionals who had this responsibility was quite diverse (Figure 3)[1]. For the majority (72%) of patients, their clinician asked about their pain at most (16%) or all (56%) consultations. However, more than a fifth (22%) were never, or only occasionally, asked about their pain, while more than half (55%) proactively described their pain at each consultation, to ensure that it was taken into consideration[1]. After prompting, 33% of patients recalled that their clinician had used a pain scale to measure their pain, but there were major differences between countries, with Italy (70%), France (52%), and Ireland (40%) using these instruments most frequently[1].

Although all these patients ($n = 573$) had moderate to severe pain, 11% were not receiving any analgesia and a further 8% were taking only over-the-counter (OTC) medication[1]. More than a quarter (28%) of

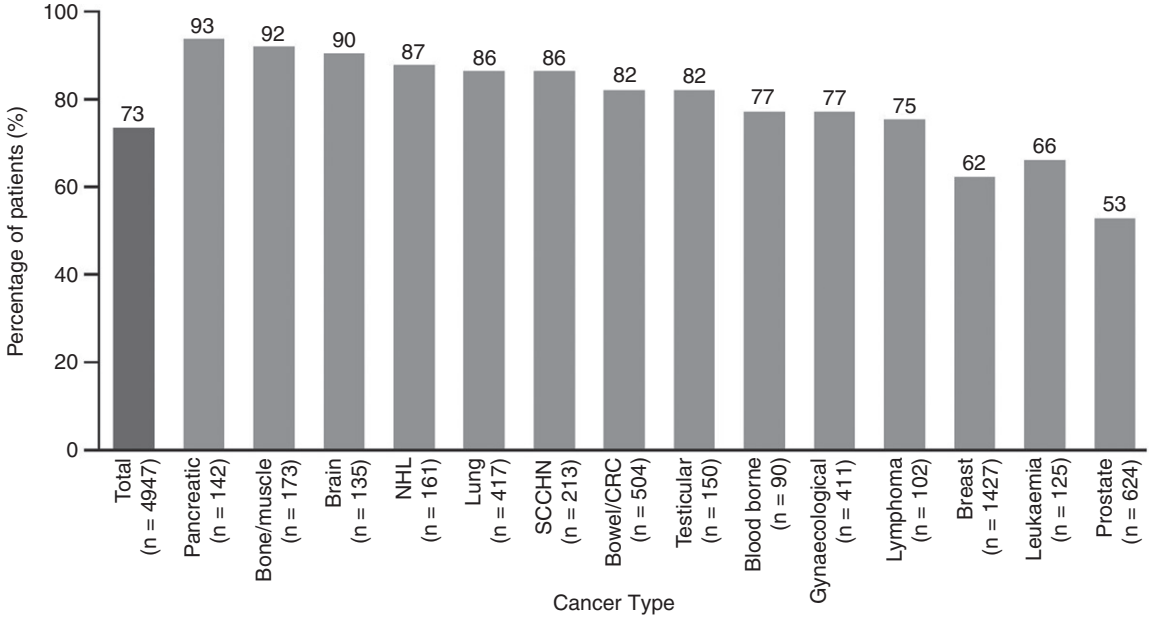

Figure 2. Incidence of pain by cancer type (CRC = colorectal cancer, NHL = non-Hodgkin's lymphoma, SCCHN = squamous cell cancer of the head and neck)[1]. By permission of Oxford University Press.

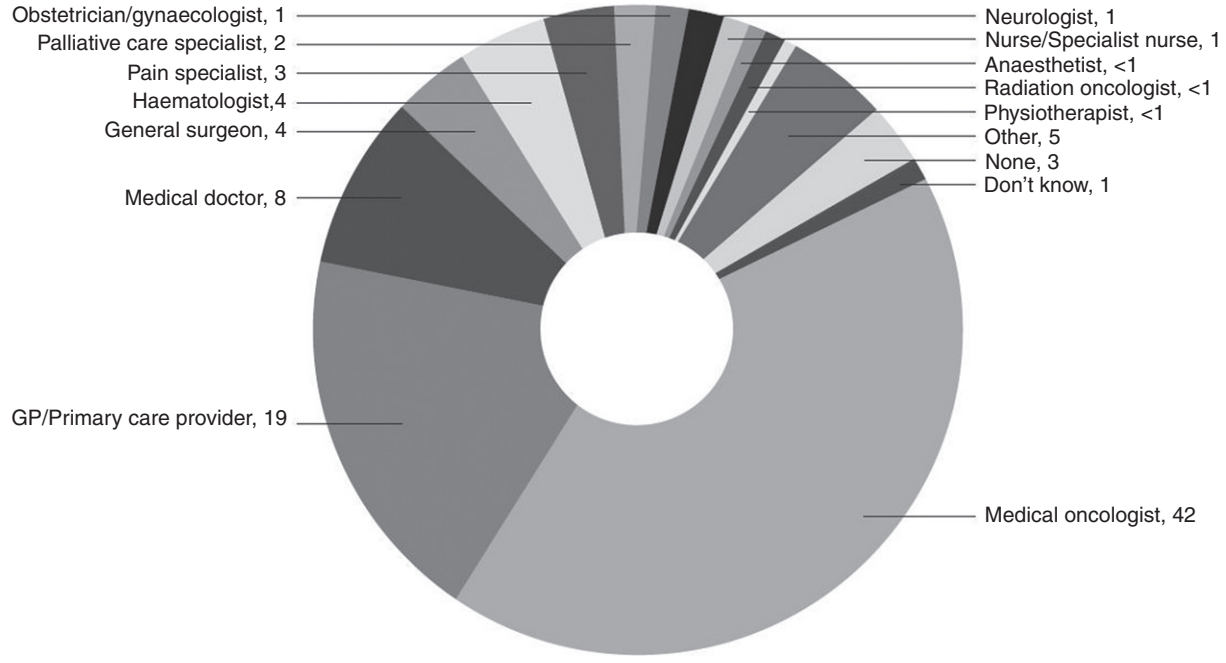

Figure 3. Healthcare provider responsible for pain management[1]. By permission of Oxford University Press.

those whose pain was rated at NRS ≥7 ($n = 241$) were not receiving strong opioids. Of the patient sample, 50% believed that their clinicians did not consider quality of life to be an important aspect of the overall care plan, and 12% believed their clinicians did not understand that pain was a problem. Substantial minorities believed that their clinicians would rather treat their cancer than their pain (38%) or did not know how to treat moderate to severe cancer pain (26%). Large majorities of those patients receiving prescription analgesics (84%; $n = 441$) and of those receiving strong opioids 87% ($n = 183$) rated their medication as 'quite effective' or 'very effective'[1]. However, breakthrough pain was common among those receiving prescription medication, affecting 63% of the patients. The authors concluded that "poor care of cancer pain is clearly unacceptably commonplace in Europe"[1].

These results were supported by a recent survey which found that the most significant barriers to successful cancer pain management were almost exactly the same as 20 years ago – poor assessment, patients' reluctance to report pain and to take opioids – and that efforts to improve treatment have had little effect on oncologists' attitudes and practice[51]. It has been suggested that improving the management of cancer-related pain could be as simple as ensuring that every consultation includes the patient's rating of pain, that the oncologist pays attention to the answer, and a plan is agreed to increase analgesia when it is inadequate[52].

Cancer pain management

General principles of treatment

The overall objective of treating cancer pain is to achieve pain relief and the highest possible quality of life for the patient. Therapy should address all elements of the patient's pain: cancer-related, cancer-associated, therapy-related, and cancer-independent. Successful management of these diverse types of pain requires a multidisciplinary approach combining both pharmacological and non-pharmacological treatment such as psychotherapy, exercise therapy, massage and electrostimulation[53,54]. General principles include the immediate relief of acute pain and, if possible, preventing the development of chronic pain.

As pain can be caused by multiple different mechanisms, it is important that pain therapy reflects these underlying mechanisms[55,56] and is not simply based on pain intensity, as recommended by the WHO three-step ladder. For example, bone metastases often produce a high local concentration of prostaglandins, so NSAIDs are generally effective against CIBP, because they act partly by blocking prostaglandin biosynthesis.

Also, beyond the physical distress it causes, pain may be accompanied by fear, anxiety, weakness, depression and insomnia. By explaining the causes of pain and the treatment options to the patient in straightforward terms, these symptoms can be alleviated, quality of sleep improved, and the patient's capacity for participating in daily life increased.

Consensus points

The key factor in successful cancer pain management is a thorough diagnostic assessment of the contributing pain mechanisms.

This should be supported by effective inter-disciplinary collaboration; better collaboration between pain specialists and oncologists should increase the use of multimodal pharmacotherapy and non-pharmacological treatment.

Choosing an appropriate pharmacological agent and its route of administration are vitally important. Oral administration is the most common and easiest route for most patients with cancer pain. However, the analgesic effect of the agent is largely dependent upon its rate of absorption from the gastrointestinal tract, so pain relief does not begin for 20–30 minutes. Furthermore, bioavailability may be compromised by, for example, emesis and/or first-pass hepatic metabolism. Transdermal patches are non-invasive and can produce steady-state concentrations in 12 hours, while the dose can be increased by simply adding further patches[57]. Side effects may be less when using this route and often limited to local irritation at the site of application[58,59], but absorption may be decreased in patients who are cachectic (e.g. by about 50% in the case of fentanyl)[60], and sweating may cause problems with adhesion (nocturnal hyperhidrosis is a common symptom in cancer patients). Intravenous or subcutaneous administration is usually combined with a patient-controlled analgesia (PCA) device to provide better control over the analgesia than does a continuous infusion[57]. The bioavailability of hydromorphone given subcutaneously has been shown to be approximately 80% in cancer patients, and steady-state plasma concentrations are reached within 24 hours[61].

Administering drugs into the intrathecal space is becoming increasingly popular for treating patients with intractable pain or intolerable side effects from systemic analgesic treatments[62]. The advantages of administration directly into the cerebrospinal fluid include a reduction of systemic side effects and the use of lower drug dosages[63]. For cancer pain, morphine is the agent most commonly administered via this route, but other opioid and non-opioid drugs are used in this way: for example, hydromorphone, fentanyl, clonidine, or ziconotide[62]. In reviewing studies of intrathecal drug delivery, predominantly with morphine, Smith *et al.* found strong evidence for short-term improvement in cancer pain, and reasonably strong evidence for the use of intrathecal analgesic therapy in long-term cancer pain management[64]. Similarly, intrathecal ziconotide has been shown to provide clinically and statistically significant analgesia in some patients with refractory cancer pain[63,65].

The first choice of analgesic is often a non-opioid; for example, paracetamol or a nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen or a cyclooxygenase II (COX II) inhibitor. Non-opioids are effective against pain caused by soft tissue and muscle infiltration, while NSAIDs are particularly useful for treating pain caused by bone metastases. This is because tumor cells often produce a high concentration of prostaglandins in the affected bone, and NSAIDs act partly by blocking prostaglandin biosynthesis[66]. However, some NSAIDs (but not COX II inhibitors) can also delay blood clotting, so may be best avoided in patients receiving anti-cancer drugs that can cause severe thrombocytopenia.

Biophosphonates introduced the concept of disease-modifying therapy for bone metastases, and increasing knowledge of the interaction between cancer cells and the bone matrix has led to the identification of new therapeutic targets[67,68]. These include compounds and processes involved in cancer-induced bone desorption (e.g. osteoprotegerin, RANK/RANKL interaction), in the metastasis of cancer cells to bone (e.g. Src, nerve growth factor), and also targets on nociceptors that innervate bone (e.g. TPRV1, Trk)[67,68].

Opioids are highly effective for treating moderate to severe cancer pain[69]: for example, in conditions such as visceral cancer pain, as well as soft tissue and bone pain, and pain caused by neural compression. Updated guidelines on the use of opioids for treating cancer pain have been issued by the European Association for Palliative Care (EAPC)[70]. Developed according to the Grading of Recommendations Assessment, Development and Evaluation system, the 16 evidence-based recommendations cover such topics as choice of opioid and the treatment of side effects[70]. For example, immediate-release formulations are much more flexible than long-acting preparations, but evidence suggests that immediate-release and extended-release oral formulations of morphine, oxycodone, and hydromorphone can be used for dose titration, supplemented by immediate-release oral opioids as required[70]. Also – possibly as a result of incomplete cross-tolerance – patients receiving opioids who do not achieve adequate analgesia and have severe or unmanageable side-effects may benefit from switching to an alternative opioid[70]. A common barrier to the use of opioids is fear of addiction in both physicians and patients, but this should not prevent their prescription in patients who need them.

In addition, there is an increasing use of adjuvant drugs; these are typically non-opioids that confer analgesic effects in certain medical conditions, but primarily treat conditions that do not involve pain. Examples such as tricyclic antidepressants and anticonvulsants are commonly and successfully used to manage pain in cancer patients[71].

A wide variety of non-intrathecal interventional procedures are available, which can be used alone or in combination. These include epidural drug infusions, sympathetic nervous system blockade, nerve blocks, vertebroplasty and kyphoplasty, as well as more invasive and even destructive neurosurgical procedures[72]. The specific intervention should be determined on an individual basis, taking into account the location and characteristics of the pain, as well as the patient's expectations and life expectancy. Regional analgesic techniques are usually considered first, because they do not compromise neurological integrity, while ablative or neurodestructive procedures – which have a narrow risk–benefit ratio – should be deferred as long as possible[72].

When patients have incurable, progressive and advanced disease with limited life expectancy, palliative care aims to alleviate the physical and emotional symptoms – as far as possible – during the final phase of life. The main focus is on pain therapy and symptom control. Radiotherapy is effective in treating pain not adequately controlled by analgesics, especially pain arising from skeletal metastases; 50%–80% of patients experience improvement in their pain, and 20%–50% of treated patients have complete pain relief[73–75]. As life expectancy is limited, radiotherapy schedules should provide maximum short- and long-term patient benefit consistent with minimum associated morbidity and disruption of patients' lives. To this end the relative efficacy of single and multiple treatment fractions have been investigated, but no firm conclusions have been drawn. Common dosage regimens include 30 Gy in 10 fractions, 20 Gy in 5 fractions, and a single fraction of 8 Gy. Palliative care also includes providing psychosocial support to both the patient and relatives, in order to maintain the patient's quality of life and allow him or her to die with dignity. This generally requires co-operation between physicians from various disciplines, nursing staff, and other professions involved in the treatment plan.

Breakthrough cancer pain

Breakthrough cancer pain (BTCP) occurs in patients who have persistent pain (i.e. present for $\geq$12 hours per day) which is stable and adequately controlled by ATC analgesic medication[76,77]. It comprises a transitory exacerbation that requires assessment and targeted treatment independent of the baseline pain[76,77], and is highly prevalent among patients with cancer pain. In one prospective survey, 64% of patients reported BTCP of severe or excruciating intensity[49]. In addition, BTCP predicts more severe pain, pain-related distress and functional impairment, and relatively poor quality of life[78].

BTCP may be divided into two categories: incident and spontaneous[77,79]. Incident BTCP is related to a specific identifiable cause which may be volitional (precipitated by a voluntary act such as walking), non-volitional (precipitated by an involuntary act such as coughing), or procedural (precipitated by a therapeutic intervention such as wound dressing). Spontaneous or idiopathic BTCP occurs unexpectedly and cannot be predicted. It should be noted that end of dose pain is not BTCP; it is caused by declining analgesic levels and indicates that the ATC analgesic medication should be re-assessed[77].

The pathophysiology of BTCP can be nociceptive, neuropathic, or a combination of the two – often it is the same as that of the underlying persistent pain. Differentiating the causative mechanisms involved may be difficult, but peripheral and/or central sensitization may play a major role, initiated by mechanical stimuli, changing chemical environments, and release of tumor growth factors[80]. Although highly variable in character, BTCP is typically rapid in onset, moderate to severe in intensity, and relatively short in duration[81]. In 163 oncology patients receiving palliative care who experienced BTCP, 31% of episodes lasted <15 minutes, 64% lasted <30 minutes, and 87% lasted <60 minutes[82]. The mean intensity was 7.3 on a 10 cm Visual Analogue Scale (VAS), compared with 2.9 for persistent pain[82]. Other studies have found the mean incidence to be four episodes per day, with a mean duration of 30 minutes each (range 1–240 minutes)[49], and the median time from onset to peak intensity to be 3 minutes (range 1 second to 30 minutes)[81]. Although BTCP follows a circadian pattern[83], there is considerable variability in duration and intensity from one patient to another, and from one episode to another in an individual patient.

BTCP is under-diagnosed and under-treated. In one study of patients with advanced cancer who participated in a palliative home care program, only 32% were receiving medication for BTCP on admission to the program, and 67% of the survivors 1 month later[84]. There are various reasons for this. Firstly, BTCP is a complex phenomenon which is dependent upon the stage of the disease, the individual patient, and therapeutic factors[84]. Secondly, the phenomenon is often not fully understood by healthcare professionals so that patient assessment is poor, and thirdly, there is often a reluctance to prescribe opioids because of cultural or regulatory factors, or concerns about side effects.

Moreover, even when BTCP is treated, the most appropriate analgesic is not always prescribed. For example, one study reported that the median time to peak intensity of pain was 10 minutes (range <1 minute to 240 minutes) and the median duration of untreated episodes was 60 minutes (range <1 minute to 360 minutes), although the variability between patients was considerable[85]. Many patients, however, are treated with oral opioids, for which the onset of analgesia takes at least 20–30 minutes and the peak effect is not experienced for 60–90 minutes[86]. Ideally, treatments for BTCP should

have a rapid onset, short duration (1–2 hours), and sufficient analgesic potency to relieve severe pain. Intravenous or subcutaneous patient-controlled analgesia (PCA) pumps come close to matching these criteria for hospitalized patients, but may not be practical for outpatients[76].

Transmucosal rapid-onset opioids (fast-acting fentanyl formulations) – such as oral fentanyl citrate (OTFC) sublingual tablets[87], the effervescent fentanyl buccal tablet (FBT)[88,89] and the intranasal fentanyl spray (INFS)[90,91] – utilize novel formulations to produce an onset of analgesia often ≤15 minutes, making them suitable for BTCP episodes with a rapid or unpredictable onset. Maximum plasma concentrations are reached after median times of 91 minutes (OTFC)[89], 30–60 minutes (transmucosal fentanyl tablets)[92], 47 minutes (FBT)[89] and 12–15 minutes (INFS)[91]. Fentanyl is highly potent because of its lipophilicity and has no ceiling effect, i.e. analgesia is proportional to the dose. When used to treat BTCP, OTFC gives lower pain intensity scores and higher pain relief scores than placebo and morphine at all time points[93]. Similarly, randomized clinical trials have shown FBT and INFS to be efficacious and well tolerated, with a rapid onset of analgesia (within 10 minutes) and sustained effect[88,90,91]. A systematic review of the use of opioids for managing breakthrough pain in patients with cancer found that transmucosal and parenteral opioids were equally effective after 30 minutes[94], but one study which compared OTFC with oral morphine found the latter to be an inferior comparator[95].

These properties have been taken into consideration by recent guidelines, such as those produced by the European Association for Palliative Care[70]. These state "In some cases the buccal or intranasal fentanyl preparations are preferable to immediate-release oral opioids because of more-rapid onset of action and shorter duration of effect. Additionally, the data permit a weak recommendation that immediate-release formulations of opioids with short half-lives should be used to treat pre-emptively predictable episodes of breakthrough pain in the 20–30 min preceding the provoking manoeuvre." The different fentanyl formulations vary in pharmacokinetic properties and ease of use, but all of them have a rapid onset and a relatively short duration of analgesia. It should be noted that fast-acting fentanyl formulations are only indicated for the treatment of BTCP, and not as supplemental opioid therapy to address circadian variations in pain intensity.

Consensus point

Fast-acting transmucosal fentanyl formulations are considered a more appropriate choice for treating breakthrough cancer pain with a rapid or unpredictable onset.

Chemotherapy-induced neuropathic pain

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting adverse effect of many chemotherapeutic agents that affects 30–40% of patients receiving chemotherapy[96]. The incidence and severity depend upon the type of cytotoxic drug(s), duration of administration, cumulative dose, pharmacogenetics and presence of any pre-existing peripheral neuropathy. Classes of agent which can cause CIPN include platinum compounds, taxanes, vinca alkaloids, thalidomide and bortezomib. The intensity of pain is generally mild, with other symptoms being more prominent, but it may be debilitating and reduce the quality of life of the patient. Recent research indicates that satellite glial cells in dorsal root ganglia are activated by cytotoxic agents, which leads to increased gap junction-mediated coupling between these cells and lowering of the pain threshold[97].

The precise mechanism by which platinum compounds induce CIPN remains unclear[96]. Neuropathy due to cisplatin is usually reversible, typically appears 3–6 months after treatment starts and continues after discontinuation of treatment. Symptoms are predominantly sensory and include paresthesias, loss of vibration sense, and decreased tendon reflexes[96]. Between 85% and 95% of patients receiving oxaliplatin develop sensory neuropathy, which presents as two different types of neurotoxicity[98]. Shortly after infusion, most recipients develop an acute, mainly cold-triggered neuropathy with distal paresthesias, dysesthesias, and mild muscle contractions of the hands, feet and perioral region[96]. This is followed by a chronic sensory neuropathy with diminished or absent proprioception, vibration, touch, two-point discrimination, sharp/dull discrimination, temperature, and touch/pain, typically in a stocking-glove distribution[96,99]. In approximately one-third of patients, symptoms disappear completely in 6–8 months.

In some patients receiving the taxane paclitaxel, a cumulative, dose-dependent, painful neuropathy with burning pain and hyperalgesia develops 24 to 72 hours after administration[100]. Docetaxel produces CIPN much less frequently than paclitaxel (1–9% vs. 30%)[96], with mild symptoms that usually disappear spontaneously after discontinuation. Vinca alkaloids, of which vincristine is the most toxic, induce alterations in the cellular microtubuli structure and disrupt the axonal flow[96], causing a painful sensory neuropathy and, in some patients, autonomic dysfunction. The changes produced are usually reversible on discontinuation, but recovery may be slow. Other chemotherapeutic agents which may cause CIPN include thalidomide and bortezomib.

Any candidate chemoprotective agent must fulfill certain criteria: it must prevent or mitigate the CIPN associated with chemotherapy without interfering with

the antitumor activity of cytotoxic agents, and be devoid of significant toxicity itself[101]. In a prospective, randomized, double-blind, placebo-controlled crossover trial, the serotonin–norepinephrine reuptake inhibitor duloxetine significantly reduced the average pain score (mean decrease 1.06 vs. 0.34 for placebo; $p = 0.03$) in patients with painful CIPN following paclitaxel, other taxane, or oxaliplatin treatment[102]. A similar study evaluated venlafaxine for the prevention and relief of acute neurotoxicity caused by oxaliplatin, and found this agent significantly reduced symptoms compared with placebo (full relief achieved by 31.3% vs. 5.3%; $p = 0.03$), whilst having an acceptable toxicity profile[103]. Topical treatment with a baclofen/amitriptyline/ketamine gel has demonstrated a trend for improving CIPN symptoms – without evident systemic toxicity – in a double-blind, randomized, placebo-controlled clinical trial[104], but further research is needed with higher doses. Promising results have also been obtained in a pilot study of patient-specific cutaneous electrostimulation in patients with CIPN following treatment with taxanes, platinum drugs or bortezomib[105]. The mean NRS pain score fell by 59% over the course of 10 days' treatment ($p < 0.0001$), and a reduction of >20% was achieved by 94% of the patients ($p < 0.0001$)[105].

Tricyclic antidepressants are often used to treat CIPN and have been reported to relieve the paresthesia associated with peripheral neuropathies. However, in a phase III study to evaluate the alleviation of symptoms of cisplatin-induced CIPN, nortriptyline increased patients' hours of sleep but its effect on paresthesia was modest at best, and there was no significant improvement in quality of life or daily activities[106]. Similar results have been obtained for amitriptyline[107].

At the present time, preventative treatment should be limited to patients at high risk of developing CIPN (e.g. with diabetes, hypothyroidism, or a diagnosed neuropathy) but this may change as more data are acquired on potential agents such as TRPA1 (ankyrin) antagonists, topical menthol, and antioxidants such as acetyl-L-carnitine[108–110].

Pain-related problems after cancer

Increasing numbers of patients are clear of cancer following treatment, but often experience chronic pain syndromes on the completion of treatment. Others are not cured, but remain in a chronic, stable disease state for many years. There is a lack of scientific evidence and clinical guidelines for the management of these patients, and optimal pain relief is hindered by barriers such as fear of side effects, lack of professional knowledge of pain management, lack of timely access to pain medication and fear of addiction.

Various studies have estimated the prevalence of opioid addiction in cancer patients to be between 0% and 7.7%[111]. The literature suggests that there is no single predictor or tool capable of identifying patients likely to misuse opioid medication, but certain patient characteristics such as younger age, anxiety, fatigue and depression are associated with greater risk[112]. Known risk factors should be identified and monitored in order to detect misuse; for example, by completing a Screener for Opioid Assessment for Patients with Pain–Short Form (SOAPP–SF), establishing an opioid agreement and obtaining a psychological evaluation[112]. However, it is difficult to differentiate between inadequate analgesia (pseudoaddiction), addiction, and use of opioids as an emotional coping strategy[113]. Misuse increases the complexity of pain management, and unchecked addiction can lead to impaired quality of life, decreased pain control, and caregiver stress[114]. The risk of abuse may be greater for fast-acting fentanyls than other formulations, owing to their rapid onset of effect. Many hospice and palliative care physicians report having had very little training in this field, and survey results suggest that additional postgraduate training focusing on opioid misuse might prove beneficial[113].

Pain management programs which take cognitive and behavioral principles into account are the treatment of choice, delivered by a multidisciplinary team working in an interdisciplinary way[115]. This team should include a pain specialist as well as a clinical psychologist, pain should be taken into consideration from the beginning of treatment, and team members should be closely acquainted with each others' roles and responsibilities.

Conclusions

Pain is the most common reason for consulting a healthcare professional that leads to a cancer diagnosis and its effect on patients' quality of life can be devastating, but the treatment of cancer pain is often suboptimal. Almost three-quarters of cancer patients experience pain, but almost a quarter of those with moderate to severe pain do not receive any analgesic medication and more than a fifth are never, or only occasionally, asked about their pain.

General principles for treating cancer pain include the immediate relief of acute pain and preventing the development of chronic pain. A multidisciplinary approach and the choice of an appropriate pharmacological agent are vital. Two particular challenges are BTCP and CIPN. Treatments for BTCP should have a rapid onset, short duration, and sufficient analgesic potency to relieve severe pain – fast-acting fentanyl formulations meet these criteria and are suitable for BTCP episodes with a rapid or unpredictable onset. CIPN is a dose-limiting

adverse effect of many chemotherapeutic agents. Several potential neuroprotective agents have been investigated, and duloxetine or venlafaxine significantly reduce CIPN symptoms, but preventative treatment should currently be limited to patients at high risk of developing the condition.

Addressing the unmet needs of cancer pain patients will depend largely upon improving medical education, both at undergraduate and postgraduate level. There should be greater emphasis upon pain management at undergraduate level[116], a change of focus from symptom control to mechanism-based, multi-modal therapy, and more encouragement for healthcare professionals to participate in Continuing Medical Education related to pain and analgesia, such as the PAIN EDUCATION Program which is an integral part of the CHANGE PAIN initiative.

Transparency

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G.M.-S., K.A., D.A., E.A., S.C., F.C., F.H., W.J., E.K., M.K.-K., H.-G.K., A.C.M., C.M.F., B.M., A.N., C.P.H., J.P., M.S., and P.S. have disclosed that they are members of the CHANGE PAIN International Advisory Board; as such, they have received honoraria for attending the meetings upon which this paper is based. In addition, H.-G.K. and G.M.-S. have disclosed that they are chairmen of the International Advisory Board on CHANGE PAIN for Grünenthal GmbH, and receive honoraria in this context. None of the authors received honoraria for the writing of this paper.

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