Pain Medicine 2010; 11: 742–764
Wiley Periodicals, Inc.

PALLIATIVE CARE SECTION

Cancer Pain: Part 1: Pathophysiology; Oncological, Pharmacological, and Psychological Treatments: A Perspective from the British Pain Society Endorsed by the UK Association of Palliative Medicine and the Royal College of General Practitioners

Jon Raphael, MB, ChB, MSc, FRCA, MD, FFPMRCA,* Sam Ahmedzai, BSc, MB, ChB, FRCP,† Joan Hester, MB, BS, FRCA, MSc, FFPMRCA,‡ Catherine Urch, BM, MRCP, PhD,§ Janette Barrie, RN, MSc,¶ John Williams, MB, BS, FRCA, FFPMRCA, Paul Farquhar-Smith, MB, BChir, FRCA, PhD, FFPMRCA,** Marie Fallon, MB, ChB, MD, FRCP, MRCGP,†† Peter Hoskin, BSc, MRCS, LRCP, MB, BS, FRCR, MD, FRCP,‡‡ Karen Robb, BSc, PhD, MCSP,§§ Michael I. Bennett, MB, ChB, MD, FRCP, FFPMRCA,¶¶ Rebecca Haines, DClinPsych,*** Martin Johnson, MB, ChB, MRCGP,††† Arun Bhaskar, MBBS, FRCA, FFPMRCA,‡‡‡ Sam Chong, BSc, MBBS, MD,§§§ Rui Duarte, BSc,* and Elizabeth Sparkes, BSc¶¶¶**

*Faculty of Health, Birmingham City University, Birmingham, UK;

†Palliative Medicine, Sheffield University, Sheffield, UK;

‡Pain Management, Kings College Hospital, London, UK;

§Palliative Care, St. Marys Hospital, London, UK;

¶Long-Term Conditions, Strathclyde Hospital, Scotland;

**Anaesthetics, Royal Marsden Hospital, London, UK;

††Palliative Medicine, Edinburgh University, Scotland;

‡‡Oncology, University College, London, UK;

§§Physiotherapy, St. Bartholemews Hospital, London, UK;

¶¶Observatory on End of Life, Lancaster University, UK;

***Psychology, Sheffield Health and Social Care, Sheffield, UK;

†††General Practice, Royal College of General Practitioners, London, UK;

‡‡‡Anaesthesia, Christie Cancer Hospital, Manchester, UK;

§§§Neurology, Kings College Hospital, London, UK;

¶¶¶Psychology, Coventry University, UK

Reprint requests to: Jon Raphael, MSc, MD, Faculty of Health, Graduate School, Birmingham City University, Ravensbury House, Westbourne Road, Westbourne Campus, Edgbaston, Birmingham B15 3TN, UK. Tel: +44(0)1384 244809; Fax: +44(0)1384 244025; E-mail: jon.raphael@bcu.ac.uk.

Abstract

Objective. This discussion document about the management of cancer pain is written from the pain specialists' perspective in order to provoke thought and interest in a multimodal approach to the management of cancer pain, not just towards the end of life, but pain at diagnosis, as a consequence of cancer therapies, and in cancer survivors. It relates the science of pain to the clinical setting and explains the role of psychological, physical, interventional and complementary therapies in cancer pain.

Methods. This document has been produced by a consensus group of relevant health care professionals in the United Kingdom and patients' representatives making reference to the current body of evidence relating to cancer pain. In the first of two parts, pathophysiology, oncological, pharmacological, and psychological treatment are considered.

Conclusions. It is recognized that the World Health Organization (WHO) analgesic ladder, while providing relief of cancer pain towards the end of life for many sufferers worldwide, may have limitations in

the context of longer survival and increasing disease complexity. To complement this, it is suggested that a more comprehensive model of managing cancer pain is needed that is mechanism-based and multimodal, using combination therapies including interventions where appropriate, tailored to the needs of an individual, with the aim to optimize pain relief with minimization of adverse effects.

Key Words. Palliative Care; Pain; Neoplasms; Therapeutics

Preface

This discussion document about the management of cancer pain is written from the pain specialists' perspective in order to provoke thought and interest in a multimodal approach to the management of cancer pain, not just toward the end of life, but pain at diagnosis, as a consequence of cancer therapies, and in cancer survivors. It relates the science of pain to the clinical setting and explains the role of psychological, physical, interventional, and complementary therapies in cancer pain.

It is directed at physicians and other health care professionals who treat pain from cancer at any stage of the disease and it is hoped that it will raise awareness of the types of therapies that may be appropriate, heighten awareness of the role of the pain specialist in cancer pain management, and lead to dialogue and liaison between oncology, specialist pain, and palliative care professionals.

This document, which can be more fully accessed at www.britishpainsociety.org/book_cancer_pain.pdf, is accompanied by information for patients to help them and their carers understand the available techniques and to support treatment choices.

Methods

This document has been produced by a consensus group of relevant health care professionals and patients' representatives making reference to the current body of evidence relating to cancer pain.

Executive Summary

- It is recognized that the World Health Organization (WHO) analgesic ladder, while providing relief of cancer pain toward the end of life for many sufferers worldwide, may have limitations in the context of longer survival and increasing disease complexity. To complement this, it is suggested that a more comprehensive model of managing cancer pain is needed that is mechanism-based and multimodal, using combination therapies including interventions where appropriate, tailored to the needs of an individual, with the aim to optimize pain relief with minimization of adverse effects.
- The neurophysiology of cancer pain is complex; it involves inflammatory, neuropathic, ischemic, and compression mechanisms at multiple sites. Knowledge of these mechanisms and the ability to decide if a pain is nociceptive, neuropathic, visceral, or a combination of all three will lead to best practice in pain management.
- People with cancer can report the presence of several different anatomical sites of pain which may be caused by the cancer, treatment of cancer, general debility, or concurrent disorders. An accurate and meaningful assessment and reassessment of pain is essential and optimizes pain relief. History, examination, psychosocial assessment, and accurate record keeping should be routine, with pain and quality of life measurement tools used where appropriate.
- Radiotherapy, chemotherapy, hormones, bisphosphonates, and surgery are all used to treat and palliate cancers. Combining these treatments with pharmacological and nonpharmacological methods of pain control can optimize pain relief, but limitations of these treatments also have to be acknowledged.
- Opioids remain the mainstay of cancer pain management, but the long-term consequences of tolerance, dependency, hyperalgesia, and suppression of the hypothalamic/pituitary axis should be acknowledged and managed in both noncancer and cancer pain, as well as the well known side-effects such as constipation. Nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptic drugs, tricyclic antidepressants, N-methyl D aspartate (NMDA) antagonists, sodium channel blockers, topical agents, and the neuraxial route of drug administration all have a place in the management of complex cancer pain.
- Psychological distress increases with intensity of cancer pain. Cancer pain is often underreported and undertreated for a variety of complex reasons partly due to a number of beliefs held by patients, families, and health care professionals. There is evidence that cognitive behavioral techniques that address catastrophizing and promote self-efficacy lead to improved pain management. Group format pain management programs (PMPs) could contribute to care of cancer survivors with persistent pain.
- Physiotherapists and Occupational Therapists have an important role in the management of cancer pain and have specific skills which enable them to be patient-focused and holistic. Therapists utilize strategies which aim to improve patient functioning and quality of life but the challenge remains to practice in an evidence-based way and more research is needed in this field.
- Patient selection for an interventional procedure requires knowledge of the disease process, the prognosis, the expectations of patient and family, careful assessment, and discussion with the referring physicians. There is good evidence for the effectiveness of celiac plexus neurolysis and intrathecal drug delivery. Within the limitations of running randomized controlled trials for interventional procedures in patients with limited life expectancy and severe pain, there is a body of evidence of data over many years that supports an important role for some procedures (e.g., cordotomy). Safety, aftercare, and management of possible complications have to be considered in the decision-making process. Where applied appropriately and carefully at

the right time, these procedures can contribute enhanced pain relief, reduction of medication use, and markedly improved quality of life.
- There is a weak evidence base for the effectiveness of complementary therapies in terms of pain control, but they may improve well-being. Safety issues are also a consideration.
- Patients with cancer pain spend most of their time in the community until the last month of life. Older patients and those in care homes may particularly have undertreated pain. Primary care teams supported by palliative care teams are best placed to initiate and manage cancer pain therapy, but education of patients, carers, and health care professionals is essential to improve outcomes.
- Surgery, chemotherapy, and radiotherapy are cancer treatments that can cause persistent pain in cancer survivors, up to 50% of whom may experience persistent pain that adversely affects quality of life. An awareness of this problem may lead to preventative strategies, but, at the moment, treatment is symptom based and often inadequate.
- The management of acute pain, especially postoperative pain, in patients on high-dose opioids is a challenge that requires in-depth knowledge of pharmacokinetics and formulation of a careful management plan to avoid withdrawal symptoms and inadequate pain management.
- Chronic pain after cancer surgery may occur in up to 50% of patients. Risk factors for the development of chronic pain after breast cancer surgery include: young age, chemo and radiotherapy, poor postoperative pain control, and certain surgical factors. Radiotherapy-induced neuropathic pain has become less prevalent but can cause longstanding pain and disability.
- Patient education is an effective strategy to reduce pain intensity.
- Cancer pain is often very complex but the most intractable pain is often neuropathic in origin, arising from tumor invasion of the meninges, spinal cord and dura, nerve roots, plexuses, and peripheral nerves. Multimodal therapies are necessary.
- The management of cancer pain can and should be improved by better collaboration between the disciplines of oncology, pain medicine, and palliative medicine. This must start not only in the training programs of doctors, but also in established teams in terms of funding, time for joint working, and education of all health care professionals involved with the treatment of cancer pain.
- The principles of pain management and palliative care in adult practice are relevant to pediatrics, but the adult model cannot be applied directly to children.

Part 1 of 2: Pathophysiology of Cancer Pain, Oncological, Pharmacological, and Psychological Treatments

Introduction

Summary

It is recognized that the WHO analgesic ladder, while providing relief of cancer pain toward the end of life for many sufferers, may have limitations in the context of longer survival and increasing disease complexity in many countries.

It is suggested that a new model of managing cancer pain is needed that is mechanism-based and multimodal, using combination therapies including interventions where appropriate, tailored to the needs of an individual, with the aim to optimize pain relief with minimization of adverse effects.

Focus and Purpose

The focus of this discussion document is on the patient with cancer pain. The purpose of this document is to highlight the recognition of cancer-related pain and to optimize management; to acknowledge the achievements and successes of modern multiprofessional pain treatments in cancer patients; to highlight areas of continuing poor achievement and gaps in services; to emphasize pain management for the cancer population with evidence-based multimodal and mechanism-based treatments; and to strengthen the relationship between Palliative Care, Oncology, and Pain Medicine.

Approach to Cancer Pain Management

The optimal control of chronic pain in cancer relies on the understanding of the underlying pathophysiology and molecular mechanisms involved, examples being direct tumor invasion of local tissues, metastatic bone pain, osteoporotic bone and degenerative joint pain in older people, visceral obstruction, nerve compression, plexus invasion, ischemia, inflammatory pain, chemotherapy-induced neuropathy, paraneoplastic neuropathy and arthropathy, postsurgical pain and radionecrosis.

Thus, management starts with the diagnosis of the cause of the pain by clinical assessment and imaging. The ideal mode of palliation (symptom control) is removal or minimization of the cause (i.e., disease-directed therapies). For example, in malignant bone pain, surgery, chemotherapy, radiotherapy, and/or bisphosphonates may be used. In infection, antimicrobials or surgical drainage of an abscess may be required.

Alongside disease-directed therapy, there are a host of pharmacological and nonpharmacological therapies, which should be used on an individual basis depending on the clinical situation. Cancer pain management remains an area where in selected difficult cases, destructive neurosurgical procedures can be appropriate because the limited life expectancy minimizes the risk of secondary deafferentation pain.

Need for Better Cancer Pain Management

Previous data show the need for better cancer pain management. UK Cancer Deaths were 153,397 in 2004 [1,2]. At a conservative estimate, it has been suggested that 10% fail to achieve relief by WHO guidelines; however, this

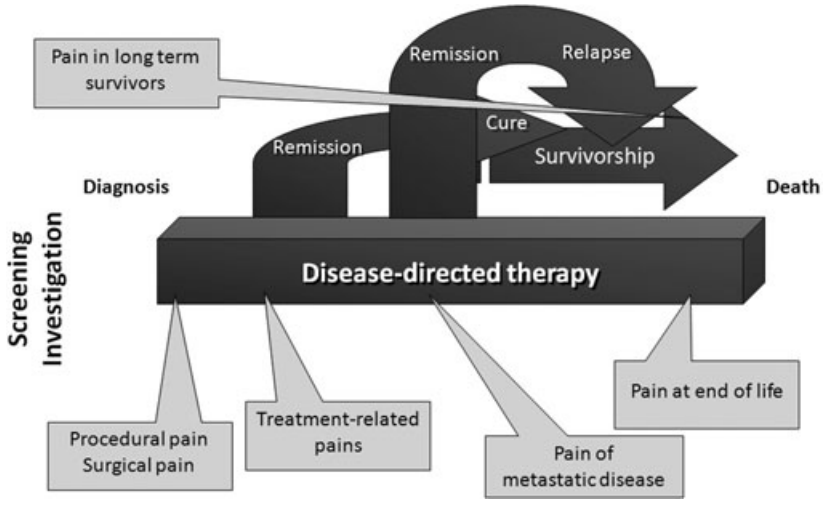

Figure 1 Model of cancer disease and pains.

is an underestimation with recent surveys [3,4] showing that in reality, 30% or more of patients have poor pain control, especially in the last year of life. Thirty percent represents 46,020 patients "failing per year" in the UK alone. If we add figures for troublesome side effects, then the present situation is worse.

This is a higher percentage of uncontrolled pain than previously recognized. A variety of possible explanations include complexity of conditions; better surveys; simple cases being treated within primary care, therefore more complex cases treated within specialist units; and compliance with treatments.

Role of Pain Service Techniques

Several publications support the role of pain service techniques in cancer pain management [5–7].

Previous data show how pain services can contribute to better cancer pain management. In the Grampian survey [8], regular weekly joint session with pain management contributed usefully in a further 11% of total cases seen with interventions such as nerve blocks performed in 8% of cases. Formal collaboration between palliative care and pain services have resulted in increased service activity [9].

Unmet Needs

Despite recommendations and demonstration of patients' needs, these needs are not being met. The trend over the past two decades to exclude pain specialists from mainstream cancer pain management means that they tend to be called in at a very late stage as "last resort." Patients may be missing out on benefits of combined multidisciplinary care from palliative care as well as pain medicine.

There is evidence of under-referral and referral structures are patchy. Pain clinics are not resourced to respond and the availability of interventions is limited.

There appears to be a lack of engagement with organizational structures such as cancer networks and lack of lead interventionist as recommended. There is a need to focus on a multidisciplinary approach to cancer pain management. Training must reflect this.

Working Models

The WHO analgesic ladder, with the clear principle of regular "by the clock" oral medication has helped cancer sufferers all round the world in a cost-effective manner. However, the increasing complexity of cancer and its treatment in the developed world has led to a dawning realization of the limitations of the stepped analgesia approach. There is a need for different working models with a recognition of the limitations of the WHO ladder [10,11].

Pain management should not be considered only after oncological treatments have been exhausted but should begin much earlier at pre-diagnosis [7] when pain is often a patient's presenting symptom. During a patient's journey, there are needs for pain management as a result of cancer treatments, and the development of metastatic disease in addition to the management of pain at the end of life. Increasingly, cancer patients are going into remission with increasing length of survival, but suffer with persistent pain [12]. The importance of holistic care and support throughout this journey should be acknowledged [13] (Figures 1 and 2).

In the treatment of bone pain, the second step of the WHO analgesic ladder is commonly unhelpful with inadequate pain relief or the development of undesirable/intolerable side effects [14]. There is currently no place for interventional treatment in the ladder and earlier recommendations of a fourth step of interventional management are not widely enough applied.

The main principles of pain management, using a biopsychosocial approach, rather than just WHO ladder should be applied.

Figure 2 Model of cancer pain therapies.

Mechanism-based strategies incorporating recent scientific discoveries of molecular and cellular changes in chronic and cancer pain are important. For example, treating bone metastases with bisphosphonates, neuropathic pain with NMDA antagonists, the use of palliative chemotherapy with biological treatments, radiation therapy and radioactive isotopes.

There is value in minimally invasive investigations for "difficult" pains (e.g., bone scans, magnetic resonance imaging, computed tomography, electrophysiological testing).

There is a need for clear information on what pain services can provide and how they may be accessed. Better links between palliative care and specialist pain services are important.

Care of the patient suffering cancer pain requires a holistic approach combining psychological support, social support, rehabilitation, and pain management to provide the best possible quality of life or quality of dying. The WHO 3-step analgesic ladder model has made an enormous contribution but has limitations. It has never been validated and morphine is arguably not the "gold standard" but rather the standard. Non-oral routes may be better and preferable at times.

It is time to move toward a new model of cancer pain management which is mechanism-based, multimodal, using combination therapies, interventional where justified, and personalized medicine with the aim to optimize pain relief with minimization of adverse effects.

Pathophysiology of Cancer Pain and Opioid Tolerance

Summary

The neurophysiology of cancer pain is complex; it involves inflammatory, neuropathic, ischemic, and compression mechanisms at multiple sites. Knowledge of these mechanisms and the ability to decide if a pain is nociceptive, neuropathic, visceral, or a combination of all three will lead to best practice in pain management. Prolonged opioid use may lead to the development of tolerance, hyperalgesia, dependency, or addiction.

Introduction

Cancer pain shares the same neuro-patho-physiological pathways as noncancer pain. It is a mixed mechanism pain, rarely presenting as a pure neuropathic, visceral, or somatic pain syndrome. Rather, it may involve inflammatory, neuropathic, ischemic, and compressive mechanisms at multiple sites.

Development over time is complex and varied, depending on cancer type, treatment regimes, and underlying concurrent morbidities. Opioids are the mainstay of treatment and are associated with tolerance. Tolerance, withdrawal, dependence, and addiction are separate states that are frequently confused and used interchangeably.

Normal Pain Transmission

Peripheral (Figure 3)

There is transduction of alterations in the milieu via specialized receptors (i.e., mechano—pressure, acid sensing ion channels—protons, vallinoid receptors—thermal, tyrosine kinase A (TrKA) nerve growth factor—inflammation, etc.).

Transmission occurs via primary afferents: Aβ low threshold, myelinated, transmit non-noxious stimuli; Aδ wide-dynamic range, thin myelinated, transmit noxious stimuli; C fibers wide-dynamic range, nonmyelinated, transmit noxious stimuli.

Transmission in the primary afferents occurs via depolarization, with sodium and calcium channels playing a crucial role, to synapse in the dorsal horn.

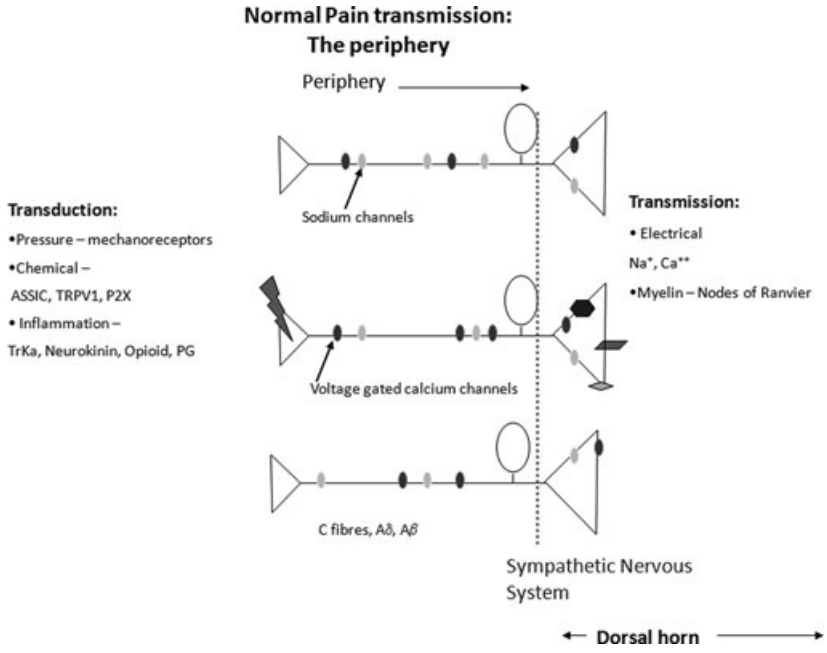

Figure 3 Normal pain transmission: the periphery.

Spinal Cord Dorsal Horn (Figure 4)

This is "divided" into laminae: Aβ fibers terminate in lamina III, Aδ in lamina I, IV/V, C fibers in lamina II.

Modulation of primary afferent inputs occurs. Excitation is via stimulation of postsynaptic receptors such as: NMDA, alpha amino hydroxy methyl isoxazole propionic acid, Substance P and descending serotonin release. Inhibition is via stimulation of gamma amino butyric acid (GABA) interneurones, enkephalin release (opioid receptors), and descending pathways (noradrenergic or serotoninergic).

Glial cells (microglia and astrocytes) are crucial to the regulation of synaptic glutamate, the initiation and maintenance of neuronal activation.

Central (Ascending) (Figure 5)

The ascending pathways are the spinothalamic and parabrachial neurones. The spinothalamic neurones

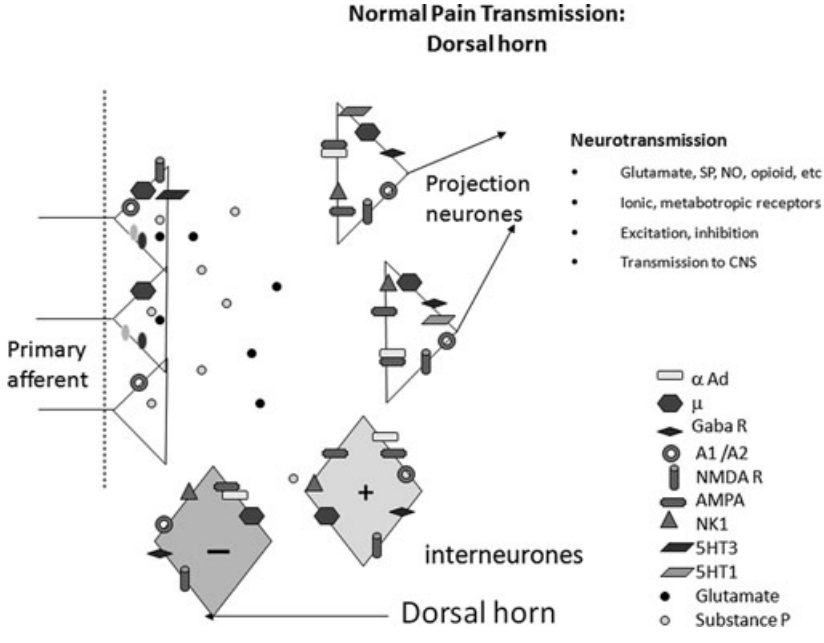

Figure 4 Normal pain transmission: dorsal horn.

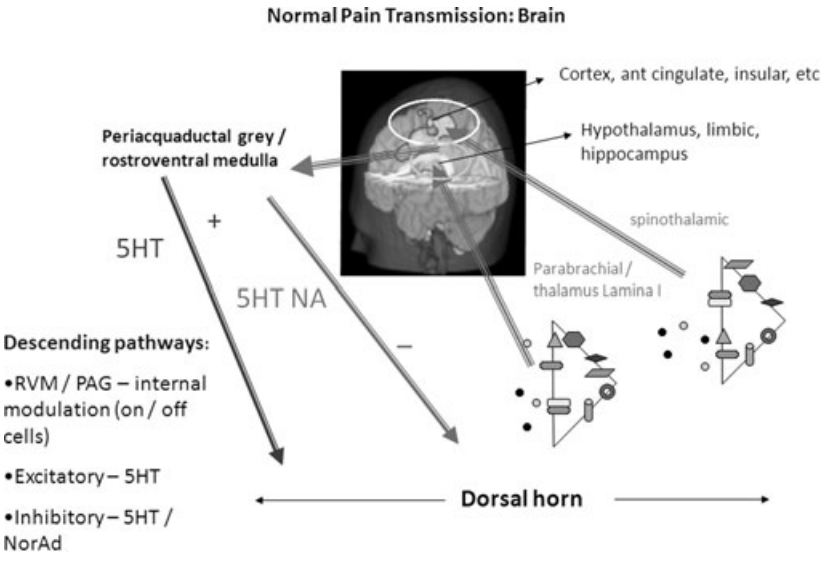

Figure 5 Normal pain transmission: brain.

connect the dorsal horn via the thalamus to the cortex. These give intensity and topographic location of stimuli. The parabrachial neurones connect lamina I to the hypothalamus and amygdala structures. These give rise to the affective component of pain.

Central (Descending)

These arise within the periaquaductal grey and rostroventromedulla, and connect back to the dorsal horn.

The descending noradrenergic pathways are inhibitory, while serotonin can be inhibitory or excitatory (via 5HT3 receptors on primary afferents).

Neuropathic Pain

This arises from damage to neurones either peripheral or central (via compression, ischamia/hemorrhage, chemical or transection).

Peripheral damage results in the accumulation of abnormal sodium and calcium channels at the site of injury.

There is gene expression alteration in number and character of receptors.

Damaged neurones discharge spontaneously and there is cross-talk to normal fibers and recruitment of silent nociceptors.

Excessive or absent discharge from primary afferents within the dorsal horn results in overall excitation and alteration in expression of NMDA receptors and functional loss of opioid and gabaminergic systems.

There is resultant hyperexcitation with increased receptive fields, primary and secondary hyperalgesia, and allodynia.

Higher centers undergo re-mapping and alteration, resulting in increased excitation of afferent and cingulate cortices.

Inflammatory Pain

Peripheral and central mediators of inflammation such as bradykinins, nerve growth factor, cytokines, ATP, and protons (from dying cells) establish a feed-forward loop resulting in sensitization of primary afferents, recruitment of silent nociceptors and peripheral hyperalgesia.

The dorsal horn is hyperexcited, resulting from an increase in primary afferent discharge and the activation of microglia.

Inhibition is peripheral via the activation of peripheral and central opioid receptors, COX pathways, and descending modulation.

Visceral Pain

This is fundamentally different from somatic pain. Symptoms include diffuse, poorly localized pain with different descriptors (i.e., spasm, heavy feeling).

Visceral innervation is dual-fold: autonomic (i.e., vagal) and spinal.

Effective stimuli include: chemical, ischemic, inflammatory, compression, and distension–contraction.

Key transmitters include: peripheral and central serotonin, calcitonin-gene-related peptide, vasoactive intestinal peptide, kinins.

Dorsal horn modulation is transmitted centrally via spinothalamic to viscero-sensory cortex (mid-insular) where viscero-visceral cross talk occurs.

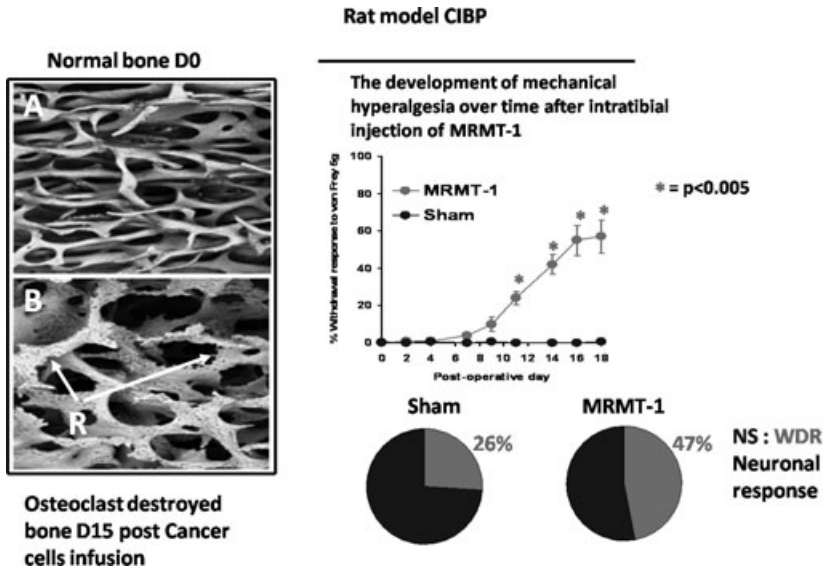

Figure 6 Rat model cancer-induced bone pain.

Dorsal columns relay predominately to thalamus, giving rise to strong autonomic responses and afferent responses.

There is cross talk to somatic sensory cortex, and insular cortices.

Cancer-Induced Pain

Animal models allow detailed investigation of neuro-mechanisms of pain although they can only give insight into part of the overall complexity. They nevertheless allow development and trial of novel therapies. Unfortunately, there are relatively few animal models of cancer-induced pain.

Cancer-Induced Bone Pain (CIBP) (Figure 6)

Over the past decade, several murine models of contained bone tumor growth (cancer, sarcoma, and myeloma cells) and pain development parallel the clinical picture.

Bone is highly innervated with C fibers, triggered by inflammatory infiltrate (secondary to cancer cells) and others (including acid, cytokine, growth factors, etc.) along with primary afferent destruction (following osteoclast activation).

The dorsal horn shows a unique pattern of excitation (not pure neuropathic or inflammatory), increased wide-dynamic range neurones in lamina I cells (50% compared with 25% in normals), hyperexcitation lamina I and V, increased glia activation and dynorphin expression.

There is attenuation of CIBP via opioids (although less efficacious than in inflammation), gabapentin, and peripheral inhibitors such as osteoprogeterin (inhibits osteoblast–osteoclast), TrKA receptor antagonist, endothelial receptor antagonist.

Cancer Therapy-Induced Pain

Murine models of chemotherapy-induced pain allow investigation of cancer neuropathies with particular interest in: taxols, platins, thalidomide, bortezomib, etc., or direct inoculation of tumor cells around nerves.

Cancer neuropathies have disadvantages of transient afferent alterations, and decline in motor function. Local inflammatory infiltrate and neuropathic damage illustrate the unique syndrome.

Chemotherapy-induced neuropathies have illustrated the diverse and unique nature of damage including taxol interruption of microtubular aggregation, accumulation in dorsal root ganglia, and activation of a neuro-immune reaction which may account for the side effects of taxols.

Opioid Therapy (Figure 7)

This remains the mainstay analgesia for all cancer pain. The practice of opioid switching in order to improve analgesia while minimizing side effects is recommended after careful consideration and titration. While this is poorly explained at a receptor level (theories include genomic variations, altered internalization, or activation of receptors to different opioids), clinical evidence in its favor is building.

Opioid Hyperalgesia

Increasing doses of opioids can be associated with hypersensitivity of the skin to touch and lack of analgesic response. Tapering of the dose is required to restore efficacy. This state is known as hyperalgesia [15,16].

The cellular mechanisms of opioid-induced hyperalgesia have much in common with those of neuropathic pain and opioid tolerance [17].

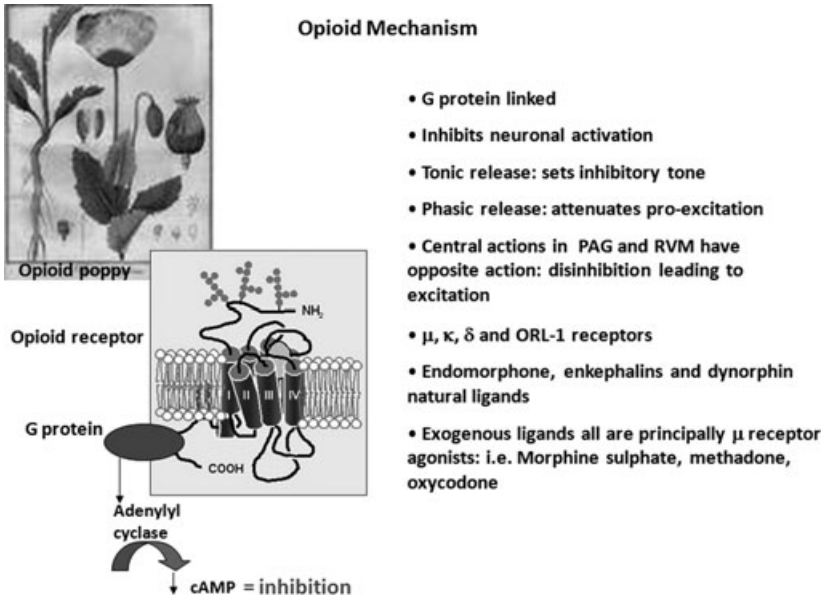

Figure 7 Opioid mechanism.

Opioid Tolerance

Clinical tolerance to opioids is complex. It is defined as the reduced effect for equivalent dose or the requirement of increased doses to attain the same effect.

Physiological receptor internalization, uncoupling, decreased or increased activation, and altered expression occur over minutes to days, which is not followed by clinical scenarios.

Tolerance may occur to nausea, vomiting, respiratory depression, and sedation. No tolerance is demonstrated to constipation or pupil constriction. Analgesic tolerance is easily demonstrated in rat or mouse models. Analgesic tolerance in humans is complex and subject to heated debate. Many articles suggesting that no significant analgesic tolerance occurs (patients continue the same dose for months and years), others suggest that incomplete cross tolerance allows increased efficacy from different opioids.

Adjuvants are increasingly important to attain good analgesic control.

Dependence

Dependence (physical or psychological) can occur in many patients. Dependence is different from addiction; patients remain compliant through opioids alterations, if side effects are controlled.

Physical dependence results in withdrawal syndromes (upon dose reduction). Psychological dependence arises when the behavioural connection between analgesia and opioids is established.

The fear of pain or incomplete analgesia can induce requests for increased opioids which can be mistaken for addiction. This subsides upon good analgesia even if this is via non-opioids. This is sometimes called pseudo-addiction.

Addiction

Addiction is characterized by drug-seeking behavior (multiple sources, legal, and illegal), compulsive use, abrupt withdrawal reactions, noncompliance with suggested opioids changes, and craving. Addiction is a genetic, behavioral, physiological, and environmental state that occurs in the minority of people exposed to opioids. It is more common when opioids are used outside the context of pain/analgesia.

Analgesia in opioid-addicted people is highly specialized and specialist referral (pain or palliative medicine teams) is recommended in any patient of concern.

Withdrawal

Physical withdrawal including abdominal cramps, diarrhea, and sweating occurs in almost all patients to some extent upon reduction of opioid dose.

Psychological withdrawal occurs in many patients who fear a resurgence of previous pain. This settles rapidly when pain does not reoccur.

Withdrawal is not a sign of addiction or dependence.

Cannabinoids (Figure 8)

Endocannabinoids are important in central inhibition. It acts primarily on CB1 neuronal receptors. CB2 receptors are primarily immune cells, including glia.

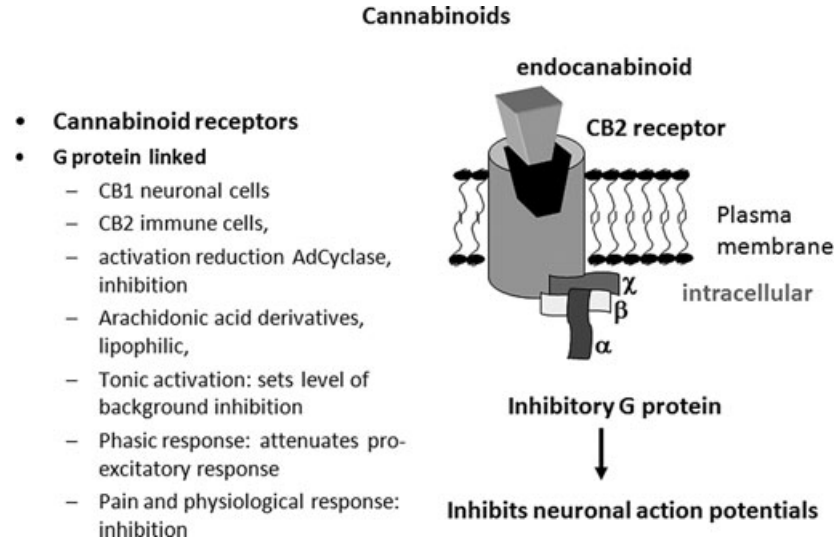

Figure 8 Cannabinoid receptor.

Some evidence for other cannabinoid receptors are as follows: 1) potentially an important clinical alternative to opioids for analgesia; 2) problems with lack of specificity; and 3) highly lipophilic, thus having nonreceptor-bound effects (via plasma membrane diffusion).

Cancer Pain Assessment

Summary

An accurate and meaningful assessment and reassessment of pain is essential and optimizes pain relief. History, examination, psychosocial assessment, and accurate record keeping should be routine, with pain and quality of life measurement tools used where appropriate.

Introduction

People with cancer can report the presence of several different anatomical sites of pain which may be caused by the cancer, treatment of cancer, general debility, or concurrent disorders [18].

The inadequate assessment of pain and lack of documentation are thought to be the greatest barriers to effective pain relief [19]; therefore, an inquiry into the presence of pain should be included in the assessment of all patients diagnosed with cancer.

Assessment

All patients diagnosed with cancer who report pain should undergo comprehensive assessment and reassessment of pain. Wherever possible, the patient should be involved in the assessment and reassessment of their pain [20].

In an acute care setting, the initial pain assessment should be undertaken on admission. As a minimum, the reassessment of pain should be undertaken daily; however, this may be more frequent depending on the severity of pain, level of distress, or on any new reports of pain [21].

In the primary care setting, pain should be assessed on each visit to the patient. The timing of this assessment will depend on patients' individual circumstances [21].

In primary care, patients and their carers should be given and taught to use a pain diary to monitor pain levels, medication requirements, effectiveness of analgesia, and side effects of medication [22].

The evidence of initial pain assessment, reassessment, and effectiveness of analgesia must be documented within the patients' record [23].

Core Elements of Initial Assessment

This will include a detailed history to determine the presence of persistent pain, breakthrough pain, and its effects on function; a psychosocial assessment; a physical examination; a diagnostic evaluation for signs and symptoms associated with common cancer pain syndromes [24].

Breakthrough Pain

Breakthrough pain is defined as a transitory flare up of moderate to severe pain in patients with otherwise stable persistent pain [25,26]. Factors to consider when assessing for breakthrough pain are the presence of breakthrough pain; frequency, number of episodes per day; duration, time in minutes; intensity, time to peak severity; description of breakthrough pain; precipitating factors; current and previous analgesic history [27].

Ongoing Assessment and Reassessment of Pain

People with cancer who report pain should be assessed using a formalized pain assessment tool which reflects the

multidimensional nature of pain, an example being the Brief Pain Inventory [28]. This will provide the opportunity to identify and record each individual site of pain experienced by the patient and its impact. The reassessment should include the effectiveness of pain management strategies employed [6].

This should include location of pain, characteristics/description of pain, severity/intensity of the pain, duration of the pain, aggravating factors, relieving factors, effect of pain on function and activities of daily living, impact on quality of life, impact on psychological well-being, social impact, spiritual impact, pain expectations, medication—current and previous analgesics, opioid toxicity, complementary interventions and outcome.

A comprehensive assessment of pain must be carried out following any new reports of pain. This should include a diagnostic evaluation and may result in a review of the pain management plan.

Any new complaint of pain could indicate a change in the underlying pathological process and may require urgent medical attention.

Psychosocial Factors

Fear, anxiety, depression, and lack of sleep have been reported to increase pain and suffering in people with cancer [29,30]. A comprehensive pain assessment should include the personal and social influences that determine how pain is experienced and perceived [24].

Patients displaying signs of distress should undergo a more detailed assessment of their emotional distress and/or depression. Patients should have the opportunity to express their emotions, thoughts, fears, and expectations regarding their pain. The factors associated with the patient's treatment which may contribute to their emotional distress and/or depression must be included in the assessment.

The assessment of the psychosocial factors influencing the experience of pain will include the patients understanding of their condition, what the pain means to the individual and their family, how the pain may impact upon relationships within the patient's family, if the pain influences the patient's mood, changes in mood, coping strategies adopted by the patient, sleep pattern and economic impact.

Spiritual Factors

Patients' spiritual beliefs can influence their health beliefs and sense of well-being. The concept of spiritual pain requires practitioners to go beyond the bounds of clinical treatments and be prepared to devote time to provide supportive and understanding care [31]. Spiritual care is not necessarily religious. Religious care, at its best, should always be spiritual [32]. Spiritual care is given in a one-to-one relationship, is completely person centered, and makes no assumptions about personal conviction or life orientation [32].

Special Groups

Certain groups of individuals may be at a higher risk of undertreatment of cancer pain. These groups include older people, the cognitively impaired, people where English is not their first language, known or suspected substance abusers, and patients at the end of life [24,33].

People being treated for cancer may also be at risk of developing pain syndromes as a direct result of cancer treatment strategies [34]. Practitioners should use appropriate strategies to identify people at risk of undertreatment of cancer pain.

Pain assessment tools to assess cancer pain in special groups should be made available.

Barriers to Accurate Assessment

The main barrier to optimal effective pain relief is inadequate assessment of pain [19]. Health care professionals working with cancer patients should be trained in pain assessment methods. Pain assessment should take place at regular intervals, following the start of any new treatments and at each new report of pain.

Patients with cancer may have a number of fears about their pain and might be reluctant to report pain. Pain control can be enhanced if management strategies include interventions on relieving anxiety and depression [35]. Therefore, pain and its management should be discussed with the patients and their families. Patients with cancer pain should be encouraged to be active participants in the management of their own pain.

Oncological Management of Cancer Pain

Summary

Radiotherapy, chemotherapy, hormones, bisphosphonates, and surgery are all used to treat and palliate cancers. Combining these treatments with pharmacological and nonpharmacological methods of pain control can optimize pain relief, but limitations of these treatments also have to be acknowledged. Skeletal pain, abdomino-pelvic pain, and headache are specifically discussed.

Overview of Cancer Treatments for Pain

The successful oncological management, even if only palliative, of any tumor can result in significant improvement in pain relief.

Combining cancer treatments with pharmacological and nonpharmacological methods of pain control can result in optimum pain management. However, it should be acknowledged that oncological treatments themselves

Table 1 Indications for surgery in the management of cancer pain

Pain	Cause	Surgery
Bone pain	Pathological fracture	Internal fixation
Headache	Obstructive hydrocephalus	Shunt
	Tumor bulk	Debulk
Dysphagia	Oesophageal tumour	Stent
Abdominal distension	Ascites	Drain and shunt
Soft tissue pain	Necrotic tumor	Toilet resection

may induce persistent pain in some patients. Cancer treatment includes loco-regional treatments, either surgery or radiotherapy, and systemic therapy with chemotherapy, hormone therapy, and biological modifiers.

Surgery

Major surgery is rarely appropriate in the patient with advanced cancer and metastatic pain but specific indications exist for surgical intervention (Table 1).

A pathological fracture of a long bone is a clear indication for internal surgical fixation following which rapid pain relief and restoration of function can be achieved.

Vertebral fracture may require stabilization to avoid spinal cord compression; for example, by open surgery or by vertebroplasty.

Progressive ascites can cause persistent abdominal pain and discomfort. Repeated paracenteses may not be possible or appropriate and a Le Veen shunt draining the ascitic fluid into the superior vena cava can be a valuable means of resolving this situation.

Radiotherapy

Radiotherapy is usually delivered as external beam treatment; common indications are shown in Table 2.

Table 2 Indications for radiotherapy in the management of cancer pain

Pain	Cause
Bone pain	Metastases
	Pathological fracture (nonsurgical, e.g., rib/pelvis)
Headache	Primary cerebral tumor
	Brain metastases
Abdominal pain	Hepatomegaly
Pelvic pain	Local tumor infiltration
Chest pain	Primary lung cancer
	Mesothelioma
Soft tissue pain	Local tumor infiltration

Radiation may also be delivered by systemic radioisotopes and this is particularly indicated in the management of scattered metastatic bone pain, for example, by using bone-seeking isotopes. Such treatments are predominantly used for primary tumors associated with osteoblastic metastases; for example, prostate and breast cancers.

Chemotherapy

Chemotherapy may also provide valuable pain relief in the patient with widespread metastatic disease; common indications are shown in Table 3.

Its principal limitation is related to the limited tumor chemosensitivity encountered in advanced and recurrent cancer (e.g., breast, nonsmall cell lung cancer, and colorectal cancer) (Table 5). However, some tumors that are associated with widespread severe metastatic bone pain (e.g., multiple myeloma and small cell lung cancer) remain more sensitive and chemotherapy has a major palliative role.

Hormone Therapy

Cancers of breast and prostate account for a large number of patients who present with metastatic disease and cancer pain and are hormone sensitive.

Anti-androgen therapy for prostate cancer results in dramatic pain relief for many patients with response rates of over 90% on initial exposure but median duration of response is between 18 months and 2 years.

Breast cancer may respond to second- and third-line hormone treatment using antiestrogen drugs like tamoxifen or toremifene, aromatase inhibitors such as anastrozole and letrozole, progestogens such as megestrol or medroxyprogesterone acetate and, occasionally, androgens. These hormone maneuvers may be used sequentially with useful responses for the patient with widespread disease and metastatic pain.

Bisphosphonates

Bisphosphonates are used increasingly for the management of CIBP. They are drugs with poor oral bioavailability and are usually given as intravenous infusions,

Table 3 Indications for chemotherapy in the management of cancer pain

Pain	Cause	Primary Tumor Types
Bone pain	Bone metastases	Myeloma Breast cancer Lung cancer (small and nonsmall cell)
Headache	Brain metastases	Germ cell tumors Lymphoma and leukemias [Breast cancer] [Small cell lung cancer]
Abdominal pain	Ascites Subacute obstruction	Ovary Colorectal Stomach
	Pancreatic pain	Pancreas
Pelvic pain	Local tumor infiltration	Colorectal ovary cervix
Chest pain	Local tumor infiltration	Lung cancer (small and nonsmall cell) Metastases from chemosensitive sites, e.g., breast, colorectal [Mesothelioma]

[ ] indicates tumors with only modest (<50%) response rates when other modalities, e.g., radiotherapy, may be preferred.

pamidronate and clodronate being the most commonly used although these may in due course be replaced by newer, more potent drugs such as zolendronate and ibandronate.

There is good evidence that in the adjuvant setting, bisphosphonates reduce morbidity from bone metastasis, for example by reducing skeletal events and preventing the need for radiotherapy. A recent review indicated that the regular use of bisphosphonates reduced the number of skeletal-related events in numerous cancers [36].

A Cochrane review in 2002 concluded that, despite methodological limitations, the evidence suggested that bisphosphonates provide modest pain relief for patients with bony metastases where analgesics and/or radiotherapy are inadequate [37] (Figure 9).

Specific Pain Problems in Cancer Patients

Skeletal Pain

Skeletal pain in cancer patients is most commonly associated with bone metastases; however, patients may have comorbidities (Table 4).

In some patients there will be a single, solitary site of severe pain (while other documented bone metastases are asymptomatic), whereas in others, scattered multifocal pain often of a flitting nature from one area to another is the clinical scenario. Combining radiotherapy with pharmacological and nonpharmacological management is generally recognized as the most effective treatment in this setting.

First-line pharmacological approaches include paracetamol and NSAIDs. Adjuvant analgesics include skeletal muscle relaxants (diazepam, baclofen), bisphosphonates, and occasionally, corticosteroids for intractable scattered pain.

Neuropathic pain may be a feature particularly related to vertebral metastasis requiring other specific treatment.

Table 4 Causes of bone pain in cancer patients

Metastases
Fracture
Degenerative bone disease, e.g., osteoarthritis
Bone marrow pain
Nonmetastatic hypertrophic osteoarthropathy, e.g., hypertrophic pulmonary osteoarthropathy
Other bone disease, e.g., Paget's

Table 5 Chemosensitivity of primary tumors commonly metastasizing to bone

Primary Site	Sensitivity*
Myeloma	High
Bronchus	High
Breast	High
Rectum	Mid
Esophagus	Mid/low
Prostate	Low
Thyroid	Low
Kidney	Low

* High ≥50% response rate; Mid = 25–50% response rate; Low ≤25% response rate.

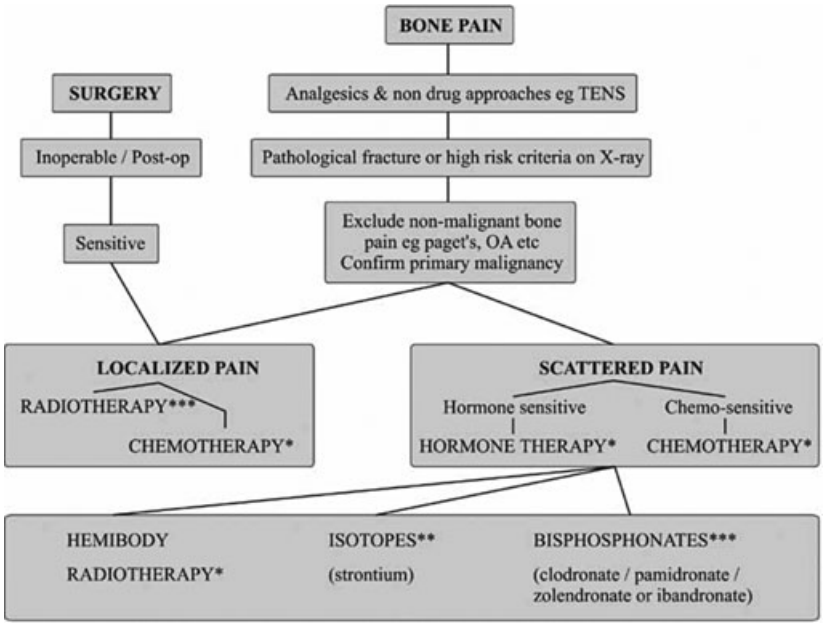

Figure 9 Overview of the management of metastatic bone pain. Continuing pain despite of all above, consider anesthetic intervention. * = nonrandomized controlled trials, cohort study, etc.; ** = one or more well-designed randomized controlled trials; *** = systematic review of meta-analysis.

Where pathological fracture of a long bone is encountered, internal surgical fixation remains the optimal management. Intraspinal analgesia or a nerve block is usually indicated if surgery is not possible for pathological fracture of a long bone, as analgesia and radiotherapy alone are not sufficient to control the movement-related pain associated with this situation. An alternative may be percutaneous cervical cordotomy to treat unilateral incident pain from a solitary long bone pathological fracture.

Localized External Beam Radiotherapy

Localized external beam radiotherapy for metastatic bone pain is the usual modality for localized bone pain and has been the subject of a large number of randomized controlled trials and two Cochrane reviews [38,39]. These confirm its efficacy with a complete response rate of 32–34% and number needed to treat (NNT) for complete response of 3.9 (95% confidence interval [CI] 3.5–4.4). Relief was achieved by 60% of patients with an NNT of 3.6 (95% CI 3.2–3.9). Single doses of 8–10 Gy appear to be as effective as more prolonged high- dose schedules and response rates are generally not predicted by tumor histology.

Toxicity is mild and related to the site of treatment; areas which include significant amounts of bowel, for example, the lumbosacral spine and pelvis, will result in nausea and increased bowel frequency in 20–30% of patients [40]. This will respond to added medication and is self-limiting over a period of 10–14 days. Peripheral sites in the upper and lower limbs are, in general, associated with no significant side effects.

The pattern of pain relief after external beam radiotherapy for localized bone pain has been shown consistently to evolve over 4–6 weeks from treatment, with 50% of patients achieving their response within 2 weeks of treatment and reaching a plateau 2–4 weeks later, when on actuarial analysis around 80% of patients will have recorded a response.

Pathological fracture may be treated with external beam radiotherapy where it is not surgically operable, for example ribs, vertebral bodies, and pelvic bones. Following doses similar to those given for local bone pain, healing is seen over a period of 6–12 weeks after treatment, preceded by early relief of bone pain.

Wide Field External Beam Radiotherapy

Wide field external beam radiotherapy is used for the treatment of multiple sites of bone pain, typically defined as upper hemibody radiotherapy, covering the ribs and cervico-dorsal spine, or lower hemibody radiotherapy, covering the lumbo-sacral spine, pelvis, and lower limbs. This technique can be used sequentially to cover the entire skeleton, but a 4–6-week interval is required to allow bone marrow recovery in the treated area before exposing the remainder of the bone marrow to radiation.

A simple two-fraction schedule delivering 8 Gy in 2 days is used. Similar response rates to external beam radiotherapy are reported, with a pattern of response that is much more rapid, 25% of patients responding within the first 24 hours in some studies [38,41]. Inevitably, treating larger volumes results in more toxicity when this technique is used and around two-thirds of patients will report nausea and increased bowel frequency.

Radioisotope Treatment

Radioisotope treatment involves the intravenous administration of a bone seeking radio-isotope that delivers localized radiotherapy to multiple sites of bone metastasis. This is achieved using isotopes which are attracted physiologically to sites of bone mineralization. Strontium (89Sr) is currently the most commonly used.

Radioisotope treatment for metastatic bone pain has similar efficacy to wide field external beam irradiation but is associated with less toxicity and lower transfusion requirements [42]. Meta-analysis has not defined an individual NNT for radio-isotope therapy [38,39].

Although of similar efficacy to external wide field radiotherapy, its better toxicity profile and relative ease of delivery have meant that in a wealthy health care system, radio-isotope therapy has become the treatment of choice in this setting. However, where it is not available, wide field external radiotherapy can achieve equivalent pain relief.

A further specific role of radio-isotope therapy relates to bone metastases from thyroid carcinoma. Around 80% of differentiated thyroid cancers will concentrate radio-iodine and this therefore provides a potential therapeutic isotope for these metastases at any site in the body. Radioiodine is given orally in this setting in doses of 3–5000 MBq following ablation of the thyroid gland.

Chemotherapy and Hormone Therapy

The sections on Chemotherapy and Hormone Therapy describe the palliative role of chemotherapy and hormone therapy. This section draws attention to their role in management of bone metastases.

Quite dramatic responses can be achieved within a few days of starting anti-androgen therapy in prostate cancer. Response in metastatic breast cancer is generally slower and additional measures for pain relief are usually required in the first few weeks of starting hormone therapy.

Hormone therapy, as with any other treatment which may induce acute new activity in bone, may be associated with a transient flare-up of pain which needs to be managed with appropriate manipulation of analgesia.

Thoracic Pain

The common causes of intra-thoracic pain in malignancy are non-small cell lung cancer and mesothelioma. The pain is often poorly localized in respect to the primary tumor site and, in mesothelioma, neuropathic pain due to local infiltration of the intercostal nerves may become a prominent feature.

The general approach outlined above, therefore, with the use of dose-escalating analgesics through the WHO analgesic ladder, will be required in most patients, supplementing this with other, more specific, therapies. Where chest wall infiltration has occurred, NSAIDs may be of value and where there is neuropathic pain, anticonvulsants and antidepressants will have an important role. Intercostal nerve blocks are also very effective in selected patients. More aggressive anesthetic interventions, such as intraspinal analgesia or cordotomy, may be required, especially in mesothelioma.

Abdomino-Pelvic Pain

Abdominal pain in malignancy is typically visceral due to hepatic metastasis or bowel obstruction. Pelvic pain may have a visceral component but is also likely to have a neuropathic element with pain from lumbo-sacral plexus infiltration.

Hepatic metastases typically cause pain as enlargement of the liver results in stretching of the capsule where the sensory innervation is found. In general, unless there is gross hepatic dysfunction, the metabolism of the common drugs in the WHO ladder is not affected by the presence of liver metastasis. Steroids may be of value in reducing hepatic edema and liver pain. Where a chemo-sensitive tumor is present, then a reduction of the liver size with chemotherapy should be considered. However, while hormone therapy may reduce hepatomegaly from liver metastasis, the response is often slow, taking several months to achieve. Two randomized controlled trials have addressed the role of hepatic irradiation in advanced malignancy and conclude that effective palliation of pain is achieved in 80% and systemic symptoms can be achieved in 45% of selected cases [43].

Splenomegaly may also be a cause of abdominal pain. Typically, this will be due to a hematological malignancy, such as chronic granulocytic leukemia or lymphoma. These are chemosensitive tumors and therefore chemotherapy will be the main line of attack. High-dose steroids will also be of value and on occasions in chemo-resistant disease, either surgical splenectomy or splenic irradiation will have a role in pain relief.

Pancreatic pain is a characteristic severe visceral pain radiating into the back and often poorly controlled with analgesics, even with titration of strong opioids. Randomized controlled trial evidence confirms the positive role of neurolytic celiac plexus block in this setting with superior results in terms of pain relief over analgesics alone [44].

Pelvic pain, if not due to bone metastases, will most commonly be due to presacral recurrence of rectal carcinoma or pelvic recurrence of cervical cancer. Lumbo-sacral plexus infiltration is common, resulting in severe pain with a major neuropathic component.

Headache

Headache due to malignant disease may arise from raised intracranial pressure due to brain metastasis or progressive incurable primary brain tumors. It may also be a result

of hydrocephalus, typically from a tumor in the mid-brain or posterior fossa obstructing the aquaduct. Diffuse meningeal disease may cause a communicating hydrocephalus which is less commonly associated with headache. It is important to remember that headache may also be due to anxiety and depression and that other common, nonmalignant causes of headache may be found in patients with advanced cancer, for example, tension headache and migraine.

Where there is raised intracranial pressure, then steroids are of value. A randomized controlled trial suggested that relatively low doses of dexamethasone are as effective as higher doses, with 4 mg being equivalent to 8 mg or 16 mg and associated with fewer steroid induced side effects [45]. The length of treatment should be as short as possible and any maintenance treatment should be at the lowest possible dose to minimize steroid-induced side effects.

Brain metastasis can be palliated successfully with brain irradiation [46]. A solitary metastasis may be best treated with surgical decompression and postoperative radiotherapy; multiple metastases with whole brain radiotherapy. Chemotherapy is also of value in brain metastasis where there is a chemosensitive tumor and should always be considered for hematological malignancies including non-Hodgkin's lymphoma, germ cell tumors, small cell lung cancer, and breast cancer.

Primary brain tumors are best managed by surgical debulking followed by postoperative radiotherapy. Dexamethasone and, in acute situations, mannitol, may be required to control intracranial pressure which is the usual cause of headache. High-dose (60 Gy) chemoradiation for primary gliomas is now a standard treatment for patients with good performance status.

Obstructive hydrocephalus is best treated by surgical decompression followed by appropriate local treatment to the tumor, which will often include radiotherapy. An internal shunt may be effective when decompression is not possible.

Other associated causes of headache should also be considered including cervical spine metastasis for which local radiotherapy will have an important role, and tumors of the head and neck region, particularly those involving the sinuses or orbit. An appropriate surgical resection or radiotherapy will be considered for these tumors alongside pharmacological management of pain.

Modern Pharmacological Management of Cancer Pain

Summary

Opioids remain the mainstay of cancer pain management but the long-term potential complications of tolerance, dependency, hyperalgesia, suppression of the hypothalamic/pituitary axis should be acknowledged and managed in both noncancer and cancer pain, as well as the well-known side effects such as constipation. NSAIDs, antiepileptic drugs, tricyclic antidepressants, NMDA antagonists, sodium channel blockers, topical agents, and the neuraxial route of drug administration all have a place in the management of complex cancer pain.

WHO Analgesic Ladder

The prevailing model since 1986 for the management of cancer pain and latterly some forms of chronic nonmalignant pain has been the WHO 3-step analgesic ladder [47]. This guideline was born of a need for a simple, public health tool, especially for developing countries with little access to opioids. It was not, in the modern sense, evidence-based [48].

According to the WHO ladder, if pain occurs, there should be prompt administration of analgesic drugs via the oral route until the patient is free of pain. It also advises that drugs should be given "by the clock," that is, every 3–6 hours, rather than "on demand" to continue to provide "freedom from pain."

The WHO ladder states that non-opioids (paracetamol and NSAIDs) should be administered first, followed by weak opioids (codeine) and then, if required, strong opioids (morphine). It also recommended the use of adjuvant drugs to calm fears and anxiety [47]. This three-step approach of administering the right drug in the right dose at the right time is inexpensive and has shown to be effective in between 45% and 100% of cases worldwide [49].

The WHO approach relies heavily on the use of opioids, in particular morphine, and the role of "adjuvants" is not clearly defined, though usually interpreted as the addition of paracetamol and NSAIDs.

Opioids

Opioids remain the mainstay of cancer pain management. When used as the sole analgesic, high doses are often required which may be associated with troublesome side effects, particularly sedation, constipation, and even respiratory depression.

Side effects can be managed with the appropriate use of antiemetics and laxatives in the majority of cases. Cognitive disturbances, tolerance, and opioid-induced hyperalgesia may occur when high doses of opioids are used for a prolonged period [50].

The long-term use of opioids for persistent noncancer pain has been disappointing. Studies show limited efficacy, the development of addiction in approximately 18% [50], increasing evidence of suppression of the hypothalamic/pituitary axis and immune suppression. It is well established that patients who are on long-term opioid therapy develop hypogonadotrophic hypogonadism and also opioid-induced androgen deficiency [51].

Long-term opioid therapy contributes toward bone demineralization, thus predisposing to osteoporosis [52] and also significantly reduces serum high-density lipoprotein (HDL) levels [53].

The analgesic effects of opioids are primarily by the activation of G-protein coupled receptors on neurons, which open potassium channels to hyperpolarize their membranes. Opioids differ in terms of their affinity to bind to the receptor sites, pharmacokinetics, and their physicochemical properties. This means certain opioids will have advantages over others due to differing side effect profile, routes of administration, development of tolerance, and propensity for immunomodulation [54]. Indeed, the current trend of "opioid switching" may be, in part, driven by the need to move between incompletely cross-tolerant opioids to minimize their inherent toxicities [55].

Routes of Administration

Modern technologies for administration including transdermal, oral transmucosal, and spinal delivery bring advantages in terms of increased bio-availability, reduced side effects, and/or convenience for many patients [56].

Buccal, sublingual, and intra-nasal routes can be used to deliver rapid-acting opioids on demand in addition to the "around the clock" long-acting opioids providing background analgesia.

Epidural and intrathecal routes of administration of opioids (morphine, diamorphine, and hydromorphone) with or without local anesthetics increase the effectiveness while reducing side effects, particularly drowsiness and constipation, and should be considered when pain cannot be controlled by simpler means.

"Adjuvant" Analgesics

Opioids are not the only "magic bullets" to target pain signal transmission. The "adjuvants" are now shown to work via other neuronal and synaptic receptors and ion channels, which may be as important as the opioid ones.

Voltage-gated calcium channels can be blocked by gabapentin or pregabalin [57].

Sodium channels, which in turn activate calcium channels, can be blocked by local anesthetics and older generation antiepileptics such as carbamazepine [58]. Lignocaine patches have been used successfully in the management of focal neuropathic pain, particularly effective in the symptomatic relief of allodynia and hyperpathia [59].

Other drugs work by modulating noradrenergic and serotonergic transmission and reuptake, e.g., tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors [60], and also tramadol [61].

NSAIDs and COX inhibitors may exert antinociceptic action by dampening down not only peripheral sensitization of nerve endings but also spinal synaptic transmission [62].

GABAA receptors and possibly CB1 receptors reduce neuronal excitability, which can be exploited therapeutically by benzodiazepines, alcohol, or cannabinoids.

In most forms of chronic pain, postsynaptic NMDA receptors are opened and these cause calcium influx, nitric oxide induction, neuronal excitability, and gene expression leading to neuronal plasticity, central sensitization, allodynia, and hyperalgesia. Specific NMDA channel blockers such as ketamine and dextro-isomers of many opioids, notably methadone, can attenuate these destructive changes.

Neuropathic Pain in Cancer Patients

Incidence

The reported incidence varies. In unselected cancer patients by history and examination alone, 0.5% neuropathic, 30% mixed [63] and by survey of clinicians in 24 countries pure neuropathic pain 8%, those with "neuropathic element" 40% [64]. Using Questionnaires, NPQ, LANSS. Definite Neuropathic 61/167 (37%), Probable 37/167 (22%) [65].

Causes

Main separation into peripheral neuropathic pain secondary to chemotherapy and other types of cancer-related neuropathic pain.

Treatment of Neuropathic Pain

Peripheral neuropathic pain secondary to chemotherapy responds poorly to typical antineuropathic treatments such as amitriptyline (50 mg), nortriptyline (100 mg), lamotrigine (300 mg), and gabapentin (2.7 mg) [66–69].

For other types of cancer-related neuropathic pain, there is much better success with combination therapy of morphine, gabapentin, amitriptyline, and steroids.

This is illustrated by a prospective study [70] in which over 800 patients with cancers of tongue, mouth, and lung with symptom-based neuropathic pain diagnoses were treated with opioids (morphine 52%) and range of adjuvants (amitriptyline 30%, gabapentin 30%, gabapentin and steroids 20%, steroids alone 20%). Before treatment, 70% has visual analog scale (VAS) scores of 7 or greater and at 6 months after treatment, 5% had VAS of 4–6, 42% had VAS of 1–3, and 53% had VAS of 0.

Outcomes

The best evidence is for gabapentin with two open-labeled [71,72] as well as one short (10 days) placebo-controlled study [73].

Evidence for amitriptyline as add-on to opioid was not good from one placebo controlled study but the assessment period was 10 days after starting treatment, generally thought to be too short for it to have an effect [74].

Other adjuvant drugs with some evidence from open-labeled studies are sodium valproate add-on to opioids [75], flecainide [76].

Non-Analgesic Drugs in Pain Management

Some painful conditions seen in cancer patients can be successfully managed by the use of non-analgesic drugs. Bisphosphonates and calcitonin are used in treating bone pain and hypercalcemia in metastatic bone disease and multiple myeloma [37,77].

Steroids alleviate pain due to central nervous system involvement, plexus or peripheral nerve compression, and visceral organ infiltration.

Muscle relaxants like baclofen, diazepam, or tizanidine can be used to relieve painful muscle spasms.

Anticholinergics are used to relieve smooth muscle spasms; hyoscine is used for relieving intestinal colic and oxybutinin for painful bladder spasms.

Calcium-channel blockers like nifedipine are used for the management of esophageal spasms and tenesmus [78].

Depending on the pathophysiology, it may therefore make good pharmacological sense to combine analgesics.

Rather than the WHO approach which treats "adjuvants" as optional, there is increasing evidence of the benefit of routinely combining opioids with these other pharmacological agents for synergistic effects, with the prospect of reduced toxicity [79].

There is even emerging evidence that combining different opioids (with differing receptor binding/modulating properties) may lead to similar advantages.

The concept of multidrug regimens working simultaneously on different cellular targets is not new, as the modern management of cancer, rheumatoid arthritis, or heart failure show.

The medical management of pain can use nonpharmacological options, e.g., hypnosis or distraction therapies which act via the prefrontal cortex to decrease perception/sensation of pain. Acupuncture may work by causing the release of endogenous opioids.

Psychological Aspects and Approaches to Pain Management in Cancer Survivors

Summary

Psychological distress increases with the intensity of cancer pain. Cancer pain is often underreported and undertreated for a variety of complex reasons partly due to a number of beliefs held by patients, families, and health care professionals. There is evidence that cognitive behavioral techniques that address catastrophizing and promote self-efficacy lead to improved pain management. Group format PMPs could contribute to care of cancer survivors with persistent pain.

Psychological Factors

Persistent pain can have profound and widespread effects upon patient's quality of life. Mobility, physical functioning, sleep, and concentration are typically affected by pain. Unrelieved pain can engender anxiety, a sense of helplessness and hopelessness and is a major risk factor for depression.

Psychological factors are central to the experience of pain and for treatment delivered within a biopsychosocial model which incorporates sensory, cognitive, emotional, behavioral, and environmental factors which interact to determine how pain is experienced, expressed, and managed [80]. It is important to stress that psychological factors do not "cause" pain directly but contribute to a person's perception of pain and its effects, and response to pain (including health care seeking) and treatment [81].

A range of psychological factors have been identified that modulate the perception of pain including expectancy, perceived controllability, fear and anxiety, appraisal processes, perceived self-efficacy, and contingencies of reinforcement [81,82].

The recognition of the importance of psychological, especially cognitive, factors in the experience of pain has led to the development of cognitive–behavioral models of pain [83] and cognitive-behavioral principles underlie effective interventions for adults with chronic pain [84].

How people think about their pain, and the assumptions and expectations they hold, will affect their experience of pain and determine emotional and behavioral responses. For example, believing that rest and avoidance of physical activities is a helpful response to pain may lead to withdrawal from rewarding and enjoyable activities which in turn may result in loss of confidence and self-esteem, and depression. People who believe that an increase in pain indicates progression of disease, are more likely to become distressed and more focused on pain. Cognitive

behavioral approaches help to identify, evaluate, and change unhelpful thoughts, beliefs, and patterns of behavior.

Research on psychological factors related to cancer pain has focused on two main areas: psychological distress and strategies for coping with pain. Studies examining the relationship between cancer pain and psychological distress (predominately anxiety and depression) indicate a strong correlation, and that increasing pain intensity leads to greater psychological distress [85,86].

Studies of pain-coping strategies and appraisal indicated that catastrophizing (dwelling on the worst possible outcome of a situation and overestimating the probability that it will occur) is associated with increased pain, pain interference and anxiety [87,88], and suggest that cognitive–behavioral techniques that address catastrophizing and promote self-efficacy would lead to improved pain management.

Cancer-related pain is often underreported and undertreated. The reasons for this are complex and still poorly understood but they appear to be partly due to a number of beliefs held by patients, families, and health care professionals, including fear of addiction to medication, concerns about tolerance (i.e., risk of uncontrolled pain later in illness), concerns about side effects, the belief that pain is inevitable in cancer, concern that pain means disease progression, fear of injections, concern that talking about pain may distract the doctor from treating the cancer, the belief that "good" patients do not complain about pain [89].

Within the cognitive model, a person's interpretation of the meaning of pain can influence health care seeking behavior and treatment adherence, for example, if a person believes that effective analgesia may mask their pain, making it difficult to gauge whether their disease is progressing, they may be less willing to report pain and adhere to analgesic regimens.

Psychological Approaches to Pain Management

Personal beliefs and appraisals, emotional reactions, coping behaviors, and social contextual factors are the primary targets of psychological interventions.

Coping Skills Training

Coping skills training teaches patients cognitive and behavioral skills for managing pain, reducing distress, and to enhance their perceptions of control over pain and promote an active self-management approach. Coping skills can be broadly grouped into attention–diversion techniques and cognitive coping strategies.

Attention-Diversion Strategies

Attention-diversion involves redirecting attention to competing external or internal stimuli and strategies may include relaxation training, diaphragmatic breathing, guided imagery, self-hypnosis, mindfulness meditation, and distracting thoughts and activities [80]. Engaging in meaningful and stimulating activities, for example, talking to friends, listening to music, and going out, can reduce awareness of pain.

Cognitive Coping Strategies

Using methods drawn from cognitive therapy, patients are taught how to identify and change unhelpful or negative thoughts (cognitive restructuring) that contribute to psychological distress and facilitate more adaptive coping thoughts that reduce distress and enhance other coping efforts.

PMPs

PMPs based on cognitive and behavioral principals are the treatment of choice for people when persistent pain adversely affects their quality of life [90].

A PMP aims to improve the physical, psychological, emotional, and social dimensions of quality of life, working toward achieving optimal functioning and self-reliance in managing persistent pain. Pain relief is not a primary goal, although improvements in pain have been reported [84,91,92].

PMPs consist of education and guided practice. Education includes information on treatment principles and rationales, pain physiology, psychological aspects of pain, exercise and improving function, and self-management of pain problems. The emphasis, however, is upon guided practice in the use of physical, psychological, and practical methods to improve quality of life (e.g., exercise to improve fitness and mobility, gradual return to goal-defined activities, cognitive therapeutic methods to identify and challenge appraisals, beliefs and processing biases, relaxation and distraction techniques, and communication skills).

PMPs are delivered by a multidisciplinary team of health care professionals working in an interdisciplinary way [93]. Key staff include medically qualified person with a special interest in pain management (usually a pain clinic consultant), chartered clinical psychologist or BABCP-registered cognitive behavioral therapist, physiotherapist (state registered), and other health professionals (e.g., occupational therapists, nurses, and pharmacists have skills which are extremely useful for the delivery of PMPs).

PMPs are delivered in a group format as this contributes to the normalization of the experience of pain and maximizes opportunities for learning from other members of the group. This format is also cost effective.

There is good evidence for the efficacy of cognitive–behavioral based PMPs [84,91,92] in reducing distress and disability and improving coping, outlook, and activity levels.

Given the increase in cancer survival rates and the incidence of chronic pain related to cancer treatments and the impact upon quality of life, the treatment approach of PMPs could contribute to the care of cancer survivors with persistent pain [94]. PMPs for this patient group would need to incorporate an educational component that addresses misconceptions about pain, concerns related to addiction and side effects, and encourages open communication about pain between patients and health professionals to address issues related to willingness to report pain and to use analgesics.

PMPs would not, however, be appropriate for this patient group when pain is associated with active or progressive disease.

References

1 National Audit Office Report. The NHS Cancer Plan: A Plan for Investment, A Plan for Reform. London: Department of Health; 2000.

2 National Audit Office Report. Tackling cancer: Improving the patient journey. Session 2004–5. HC 288. February 24, 2005.

3 Breivik H, Cherny N, Collett B, et al. Cancer-related pain: A pan-European survey of prevalence, treatment and patient attitudes. Ann Oncol 2009;20(8):1420–33.

4 Valeberg BT, Rustoen T, Bjordal K, et al. Self-reported prevalence, etiology, and characteristics of pain in oncology outpatients. Eur J Pain 2008;12(5):582–90.

5 DH. Specialised Services National Definition Set: 31 Specialised pain management services (adult). 2002.

6 Scottish Intercollegiate Guidelines Network (SIGN 44). Control of Pain in Patients with Cancer. Edinburgh: NHS Quality Improvement Scotland; 2000.

7 Gysels M, Higgenson IL. Improving supportive and palliative care for adults with cancer. NICE guidance on cancer services. Available at: nice.org.uk

8 Linklater GT, Leng MEF, Tiernan EJJ, Lee MA, Chambers WA. Pain management services in palliative care: A national survey. Palliat Med 2002;16:435–9.

9 Kay S, Husbands E, Antrobus JH, Munday D. Provision for advanced pain management techniques in adult palliative care: A national survey of anaesthetic pain specialists. Palliat Med 2007;21(4):279–84.

10 Hanks GW, de Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: The EAPC recommendations Expert Working Group of the Research Network of the European Association for Palliative Care. Br J Cancer 2001;84:587–93.

11 Wiffen PJ, McQuay HJ. Oral morphine for cancer pain. Cochrane Database Syst Rev 2007;(3):CD003868.

12 Ahmedzai SH. Window of opportunity for pain control in the terminally ill. Lancet 2001;357(9265):1304–5.

13 Ahmedzai SH, Walsh TD. Palliative medicine and modern cancer care. Semin Oncol 2000;27:1–6.

14 Eisenberg E, Marinangeli F, Birkahahn J, Paladini A, Varrassi G. Time to modify the WHO analgesic ladder? Pain Clin Updates 2005;13(5):1–4.

15 Compton P, Chanuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts. Effect of long-acting maintenance agent. Drug Alcohol Depen 2001;63:139–46.

16 Doverty M, White JM, Somogyi AA, et al. Hyperalgesic responses in methadone maintenance patients. Pain 2001;90:91–6.

17 International Association for the Study of Pain (IASP). Opioid-induced hyperalgesia. Pain Clin Updates 2008;XVI(2):1–4.

18 Twycross R, Harcourt J, Bergl S. A survey of pain in patients with advanced cancer. J Pain Symptom Manag 1996;12(5):273–82.

19 Herr K, Titler MG, Schilling ML, et al. Evidence based assessment of acute pain in older adults: Current nursing practices and perceived barriers. Clin J Pain 2004;20(5):331–40.

20 Cleeland CS, Ryan KM. Pain assessment: Global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23(2):129–38.

21 de Rond M, de Wit R, van Dam F, et al. Daily pain assessment: Value for nurses and patients. J Adv Nurs 1999;29:436–44.

22 Allard P, Maunsell E, Labbe J, Dorval M. Educational interventions to improve cancer pain control: A systematic review. J Palliat Med 2001;4(2):191–203.

23 The NMC Code of Professional Conduct: Standards for Conduct, Performance and Ethics. London: Nursing and Midwifery Council; 2004. Available at: www.nmc-uk.org

24 Miaskowski C, Cleary J, Burney R, et al. Guideline for the Management of Cancer Pain in Adults and Children, American Pain Society Clinical Practice Guidelines Series (3). Glenview, IL, USA: American Pain Society; 2005.

25 Bennett DS, Burton AW, Fishman S, et al. Consensus panel recommendations for the assessment and management of breakthrough pain. Pharmacol Ther 2005;30(5):296–301.

26 Portenoy RK, Hagen NA. Breakthrough pain: Definition, prevalence and characteristics. Pain 1990;41(3): 273–81.

27 Hwang SS, Chang VT, Kasimis B. Cancer breakthrough pain characteristics and responses to treatment at a VA medical centre. Pain 2003; 101(1–2):55–64.

28 Cleeland C, Gonin R, Hatfield A, et al. Pain and its treatment in outpatients with metastatic cancer. New Engl J Med 1994;330(9):592–6.

29 Anderson KO, Getto CJ, Mendoza TR, et al. Fatigue and sleep disturbance in patients with cancer patients with clinical depression, and community-dwelling adults. J Pain Symptom Manage 2003;25(4): 307–18.

30 Portenoy RK, Thaler HT, Kornblith AB, et al. Symptom prevalence, characteristics and distress in a cancer population. Qual Life Res 1994;3(3):183–9.

31 Mako C, Glaek K, Poppito SR. Spiritual pain among patients with advanced cancer in palliative care. J Palliat Med 2006;9(5):1106–13.

32 NHS HDL.76. Spiritual Care in Scotland, Guidelines on Chaplaincy and Spiritual Care in the NHS in Scotland. Edinburgh: Scottish Executive Health Department; 2002.

33 NHS Quality Improvement Scotland. Management of Chronic Pain in Adults, Best Practice Statement. Edinburgh: Author; 2006.

34 Portenoy RK, Lesage P. Management of cancer pain. Lancet 1999;353(9165):1695–700.

35 Loftus LA, McIntosh J, Peace E, Tolsen D. Implementation of SIGN 44 guidelines for managing cancer pain in a community setting. Int J Palliat Nurs 2007;13(7):315–24.

36 Ross JR, Saunders Y, Edmonds PM, et al. Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. Br Med J 2003;327: 469–72.

37 Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database Syst Rev 2002;CD002068.

38 McQuay H, Carroll D, Moore RA. Radiotherapy for painful bone metastases: A systematic review. Clin Oncol 1997;9:150–4.

39 Sze WM, Shelley MD, Held I, Wilt TJ, Mason MD. Palliation of metastatic bone pain: Single fraction versus multifraction radiotherapy a systematic review of randomised trials. Clin Oncol 2003;15(6): 345–52.

40 Yarnold JR; for the Bone Pain Trial Working Party. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: Randomised comparison with a multifraction schedule over 12 months of patient follow-up. Radiother Oncol 1999;52:111–21.

41 Salazar OM, Sandhu T, DaMotta NW, et al. Fractionated half-body irradiation (HBI) for the rapid palliation of widespread, symptomatic metastatic bone disease: A randomised phase III trial of the International Atomic Energy Agency (IAEA). Int J Radiat Oncol Biol Phys 2001;50:765–75.

42 Bauman G, Charette M, Reid R, Sathya J. Radiopharmaceuticals for the palliation of painful bone metastases a systematic review. Radiother Oncol 2005;75:258–70.

43 Borgelt B, Gelber R, Brady LW, Griffin T, Hendrickson FR. The palliation of hepatic metastases: Results of the Radiation Therapy Oncology Group pilot study. Int J Radiat Oncol 1981;7:587–91.

44 Eisenberg E, Carr DB, Chalmers CT. Neurolytic coeliac plexus block for treatment of cancer pain a meta-analysis. Anesth Analg 1995;80:290–5.

45 Vecht CJ, Hovestadt A, Verbiest HBC, van Vliet TJ, van Putten WLJ. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumours: A randomised study of 4.8 and 16 mg per day. Neurology 1994;44:675–80.

46 Hoskin PJ, Brada M. On behalf of the participants of the Second Workshop on Palliative Radiotherapy and Symptom Control, London. Clin Oncol 2000;13: 91–4.

47 World Health Organization. Cancer pain relief and palliative care. WHO Tech Rep Ser 804. Geneva: WHO; 1990.

48 Meldrum M. The ladder and the clock: Cancer pain and public policy at the end of the twentieth century. J Pain Symptom Manage 2005;9(1):41–54.

49 Ferreira SL, Kimura M, Teixeira MJ. The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? Support Care Cancer 2006;14:1086–93.

50 Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. Pain 2007;129(3):235–55.

51 Daniell HW. DHEAS deficiency during consumption of sustained action prescribed opioids: Evidence for opioid-induced inhibition. J Pain 2006;12:901–7.

52 Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with the use of morphine and opiates. J Intern Med 2006;260(1):76–87.

53 Abs R, Verhelst J, Maeyaert J, et al. Endocrine consequences of long-term intrathecal administration of opioids. J Clin Endocrinol Metab 2000;85(6):2215–22.

54 Meert TF, Vermeirsch HA. A preclinical comparison between different opioids: Antinociceptive versus adverse effects. Pharmacol Biochem Behav 2005; 80:309–26.

55 Holdcroft A, Power I. Recent developments: Management of pain. Br Med J 2003;326:635–9.

56 Clark AJ, Ahmedzai SH, Allan LG, Camacho F. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. Curr Med Res Opin 2004;20(9):1419–28.

57 Woolf CJ, Mannion RJ. Pain: Neuropathic pain: Aetiology, symptoms, mechanisms and management. Lancet 1999;353:1959–64.

58 Dickinson AH, Matthews EA, Suzuki R. Neurobiology of neuropathic pain: Mode of action of anticonvulsants. Eur J Pain 2002;6(suppl A):51–60.

59 Davies PS, Galer S. Review of Lidocaine Patch 5% Studies in the treatment of postherpetic neuralgia. Drugs 2004;64(9):937–47.

60 Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol 2005;96:399–409.

61 Hollingshead J, Duhmke RM, Cornblath D. Tramadol for neuropathic pain. Cochrane Database Syst Rev 2006;(3):CD003726.

62 McNicol ED, Strassels S, Goudas L, Lau J, Carr DB. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. Cochrane Database Syst Rev 2005;(1):CD005180. DOI: 10.1002/14651858. CD005180.

63 Grond S, Radbruch L, Meuser T, et al. Assessment and treatment of neuropathic cancer pain following WHO guidelines. Pain 1999;79(1):15–20.

64 Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. Pain 1999;82(3):263–74.

65 Mercadante S, Gebbia V, David F, et al. Tools for identifying cancer pain of predominantly neuropathic origin and opioid responsiveness in cancer patients. J Pain 2009;10(6):594–600.

66 Kautio AL, Haanpää M, Saarto T, Kalso E. Amitriptyline in the treatment of chemotherapy-induced neuropathic symptoms. J Pain Symptom Manage 2008;35(1):31–9.

67 Hammack JE, Michalak JC, Loprinzi CL, et al. Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. Pain 2002;98(1–2):195–203.

68 Rao RD, Michalak JC, Sloan JA, et al.; North Central Cancer Treatment Group. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: A phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer 2007;110(9):2110–18.

69 Rao RD, Flynn PJ, Sloan JA, et al. Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: A phase 3 randomized, double-blind, placebo-controlled trial, N01C3. Cancer 2008;112(12):2802–8.

70 Mishra S, Bhatnagar S, Gupta D, et al. Management of neuropathic cancer pain following WHO analgesic ladder: A prospective study. Am J Hosp Palliat Care 2009;25(6):447–51.

71 Ross JR, Goller K, Hardy J, et al. Gabapentin is effective in the treatment of cancer-related neuropathic pain: A prospective, open-label study. J Palliat Med 2005;8(6):1118–26.

72 Keskinbora K, Pekel AF, Aydinli I. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: A randomized open trial. J Pain Symptom Manage 2007;34(2): 183–9.

73 Caraceni A, Zecca E, Bonezzi C, et al. Gabapentin for neuropathic cancer pain: A randomized controlled trial from the Gabapentin Cancer Pain Study Group. J Clin Oncol 2004;22(14):2909–17.

74 Mercadante S, Arcuri E, Tirelli W, Villari P, Casuccio A. Amitriptyline in neuropathic cancer pain in patients on morphine therapy: A randomized placebo-controlled, double-blind crossover study. Tumori 2002;88(3): 239–42.

75 Hardy JR, Rees EA, Gwilliam B, et al. A Phase II study to establish the efficacy and toxicity of sodium valproate in patients with cancer-related neuropathic pain. J Pain Symptom Manage 2001;21(3):204–9.

76 von Gunten CF, Eappen S, Cleary JF, et al. Flecainide for the treatment of chronic neuropathic pain: A Phase II trial. Palliative Med 2007;21(8):667–72.

77 Martinez-Zapata MJ, Roqué i Figuls M, Alonso-Coello P, Català E. Calcitonin for metastatic bone pain. Cochrane Database Syst Rev 2006;(2):CD003223. DOI: 10.1002/14651858.CD003223.pub2.

78 Nasrallah SM, Tommaso CL, Singleton RT, Backhaus EA. Primary oesophageal motor disorders: Clinical response to nifedipine. South Med J 1985;78(3): 312–15.

79 Gilron I, Bailey JM, Tu D, Holden RR. Morphine, gabapentin, or their combination for neuropathic pain. New Engl J Med 2005;352:1324–34.

80 Hanson R, Gerber K. Coping with Chronic Pain—A Guide to Patient Self Management. New York: Guildford Press; 1990.

81 Main C, Spanswick C. Pain Management: An Interdisciplinary Approach. New York: Churchill Livingstone; 2000.

82 Turk D, Fernandez E. Pain: A cognitive-behavioural perspective. In: Watson M, ed. Cancer Patient Care: Psychosocial Treatment Methods. Leicester: Cambridge University Press; 1991.

83 Turk D, Meichenbaum D, Genest M. Pain and Behavioural Medicine: A Cognitive-Behavioural Perspective. New York: Guildford Press; 1983.

84 Morley S, Eccleston C, Williams A. Systematic review and meta analysis of randomised controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain 1999;80:1–13.

85 Zara C, Baine N. Cancer pain and psychosocial factors: A critical review of the literature. J Pain Symptom Manage 2002;24:526–42.

86 Kelsen D, Portenoy R, Thaler H, Niedzwiccki D, Passik S. Pain and depression in patients with newly diagnosed pancreas cancer. J Clin Oncol 1995;13:48–55.

87 Bishop S, Warr D. Coping, catastrophising and chronic pain in breast cancer. J Behav Med 2003;26:265–81.

88 Wilkie D, Keefe F. Coping strategies of patients with lung-cancer related pain. Clin J Pain 1991;7:792–9.

89 Ward S, Goldberg N, Miller-McCauley V, Mueller C, Nolan A. Patient related barriers to management of cancer pain. Pain 1993;52:319–24.

90 The British Pain Society. Recommended Guidelines for Pain Management Programmes for Adults. London: The British Pain Society; 2007.

91 Van Tulder M, Ostelo R, Vlaeyen S, et al. Behavioural treatment of chronic low back pain: A systematic review within the framework of the Cochrane Back Review Group. Spine 2000;25:2688–99.

92 Guzman J, Esmail R, Karjalainen K, Irvin E, Bombardier C. Multidisciplinary rehabilitation for chronic low back pain: Systematic review. Br Med J 2001;322: 511–16.

93 Turk DC, Stieg RL. Chronic pain: The necessity of interdisciplinary communication. Clin J Pain 1987;3: 163–7.

94 Robb KA, Williams JE, Duvivier V, Newham DJ. A pain management programme for chronic cancer-related pain: A preliminary study. J Pain 2006;7(2):82–90.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Cancer Pain Management: A perspective from the British Pain Society, supported by the Association for Palliative Medicine and the Royal College of General Practitioners

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.