





The British Pain Society's

Cancer Pain Management

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

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Preface

This discussion document about the management of cancer pain is written from the pain specialists' perspective in order to provoke thought and interest through a multimodal approach to the management of cancer pain, and not just towards the end of life, but also pain at diagnosis, as a consequence of cancer therapies and in cancer survivors. The document 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 healthcare professionals who treat pain from cancer at any stage of the disease with the hope of raising awareness of the types of therapies that may be appropriate and increasing awareness of the role of the pain specialist in cancer pain management, which can lead to greater dialogue and liaison between oncology, specialist pain and palliative care professionals.

The document is accompanied by information for patients that can help them and their carers understand the available techniques and that will support treatment choices.

Methods

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

Executive summary

- It is recognised that the World Health Organisation (WHO) analgesic ladder, whilst providing relief of cancer pain towards the end of life for many sufferers worldwide, may have limitations in the context of long-term survival and increasing disease complexity. In order to address these weaknesses, it is suggested that a more comprehensive model of cancer pain management is needed that is mechanism-based and multimodal, using combination therapies including interventions where appropriate, which is tailored to the needs of an individual, with the aim of optimising pain relief while minimalising adverse effects.

- The neurophysiology of cancer pain is complex: it involves inflammatory, neuropathic, ischaemic and compression mechanisms at multiple sites. A knowledge of these mechanisms and the ability to decide whether 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, by treatment of cancer, by general debility or by concurrent disorders. Accurate and meaningful assessment and reassessment of pain is essential and optimises 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 non-pharmocological methods of pain control can optimise pain relief, but the limitations of these treatments must also be acknowledged.

- Opioids remain the mainstay of cancer pain management, but the long-term consequences of tolerance, dependency, hyperalgesia and the suppression of the hypothalamic/pituitary axis should be acknowledged and managed in both non-cancer and cancer pain, in addition to 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 their place in the management of complex cancer pain.

- Psychological distress increases with the intensity of cancer pain. Cancer pain is often under-reported and under-treated for a variety of complex reasons, partly due to a number of beliefs held by patients, families and healthcare professionals. There is evidence that cognitive behavioural techniques that address catastrophising and promote self-efficacy lead to improved pain management. Group format pain management programmes could contribute to the 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 both patient-focused and holistic. Therapists utilise strategies which aim to improve patient functioning and quality of life, but the challenge remains for them to practice in an evidence-based way and more research is urgently 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 coeliac plexus neurolysis and intrathecal drug delivery. Despite the limitations of running randomised controlled trials for interventional procedures in patients with limited life expectancy and severe pain, there is a body of evidence of data built up over many years that supports an important role for some procedures, such as cordotomy. Safety, aftercare and the 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 wellbeing. Safety issues are also a consideration in this area.

- Patients with cancer pain spend most of their time in the community until their last month of life. Older patients and those in care homes in particular may have under-treated 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 healthcare 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 their quality of life. Awareness of this problem may lead to preventative strategies, but treatment is currently symptom based and often inadequate.

- Management of acute pain, especially post-operative pain, in patients on high dose opioids is a challenge that requires in-depth knowledge of pharmacokinetics and the 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 post-operative pain control and certain surgical factors. Radiotherapy induced neuropathic pain has become less prevalent, but can cause long-standing 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 tumour 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 in the training programmes of doctors, but is also needed in established teams in terms of funding, time for joint working and the education of all healthcare professionals involved in the treatment of cancer pain.

- The principles of pain management and palliative care for adult practice are relevant to paediatrics, but the adult model cannot be applied directly to children.

Chapter 1 Introduction

Summary

It is recognised that the WHO analgesic ladder, whilst providing relief of cancer pain towards the end of life for many sufferers, may have limitations in the context of long-term survival and increasing disease complexity in many countries.

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

1.1 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 importance of recognising cancer related pain and to optimise management.
- To acknowledge the achievements and successes of modern multiprofessional pain treatments for cancer patients.
- To highlight areas of continuing poor achievement and gaps in services.
- To emphasise pain management for the cancer population with evidence based multimodal and mechanism-based treatments.
- To strengthen the relationship between Palliative Care, Oncology and Pain Medicine.

1.2 Approach to cancer pain management

The optimal control of chronic pain in cancer relies on an understanding of the underlying pathophysiology and molecular mechanisms involved, examples being:

- Direct tumour invasion of local tissues.
- Metastatic bone pain.
- Osteoporotic bone and degenerative joint pain in older people.
- Visceral obstruction.
- Nerve compression and plexus invasion.
- Ischaemia.
- Inflammatory pain.

- Chemotherapy induced neuropathy, paraneoplastic neuropathy and arthropathy.
- Post-surgical pain and radionecrosis.

Management thus starts with the diagnosis of the cause of pain by clinical assessment and imaging.

The ideal mode of palliation (symptom control) is the removal or minimisation of the cause (i.e. disease-directed therapies). For example, in malignant bone pain, surgery, chemotherapy, radiotherapy and/or bisphosphonates may be used. For an infection, antimicrobials or surgical drainage of an abscess may be required.

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

1.3 Need for better cancer pain management

Previous data has shown the need for better cancer pain management. UK Cancer Deaths numbered 153,397 in 2004 (UK National audit Office reports 2000, 2004). A conservative estimate has suggested that 10% fail to receive effective relief by WHO guidelines; however, this is an underestimation given recent surveys (EPIC 2007, Valeberg, 2008) which show that, in reality, upwards of 30% of patients receive poor pain control, especially in the last year of their lives.. Thirty percent represents 46,020 patients "failing per year". If we add in the figures for troublesome side-effects, then the present situation is even worse.

This is a higher percentage of uncontrolled pain than has previously been recognized. There is a variety of possible explanations, including complexity of conditions, better surveys, simple cases being treated within primary care - with more complex cases therefore being treated within specialised units - and compliance with treatments.

1.4 Role of pain service techniques

Several publications support the role of pain service techniques in cancer pain management (DH, 2002; SIGN, 2000; NICE, 2004).

Previous data has shown how pain services can contribute to better cancer pain management. In the Grampian survey (Linklater, 2002), regular weekly joint sessions with pain management contributed usefully in 11% of total cases, 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 (Kay, 2007).

1.5 Unmet needs

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

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

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

1.6 Working models

The WHO analgesic ladder, which has 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 realisation of the limitations of the stepped analgesia approach. There is a need for different working models that recognise the limitations of the WHO ladder (Hanks, 2001; Wiffen, 2007).

Pain management should not only be considered after all oncological treatments have been exhausted, but should begin much earlier at pre-diagnosis (NICE, 2004), when pain is often a patient's presenting symptom. During a patient's journey, there will be a need for pain management as a result of cancer treatments (Chapters 11,12) and the development of metastatic disease (chapter 4), in addition to the management of pain at the end of life. Increasingly, cancer patients are going into remission with an increasing length of survival, but they do suffer from persistent pain (chapter 6) (Ahmedzai, 2000). The importance of holistic care and support throughout this journey should be acknowledged (Ahmedzai, 2001).

In the treatment of bone pain, the second step on the WHO analgesic ladder is commonly unhelpful, with inadequate pain relief or the development of undesirable/intolerable side-effects (Eisenberg, 2005). There is currently no place for interventional treatment on the ladder and the earlier recommendations of a fourth step of interventional management are not applied widely enough.

The main principles of pain management, including the use of a biopsychosocial approach, should be applied, rather than simply following the WHO ladder.

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

There is value in minimally invasive investigations for 'difficult' pains, such as bone scans, MRI, CT and 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 also important.

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

It is time to move towards a new model of cancer pain management which is mechanism-based, multimodal, uses combination therapies, is interventional where justified and advocates personalised medicine with the aim of optimising pain relief while minimalising adverse effects.

Figure 1

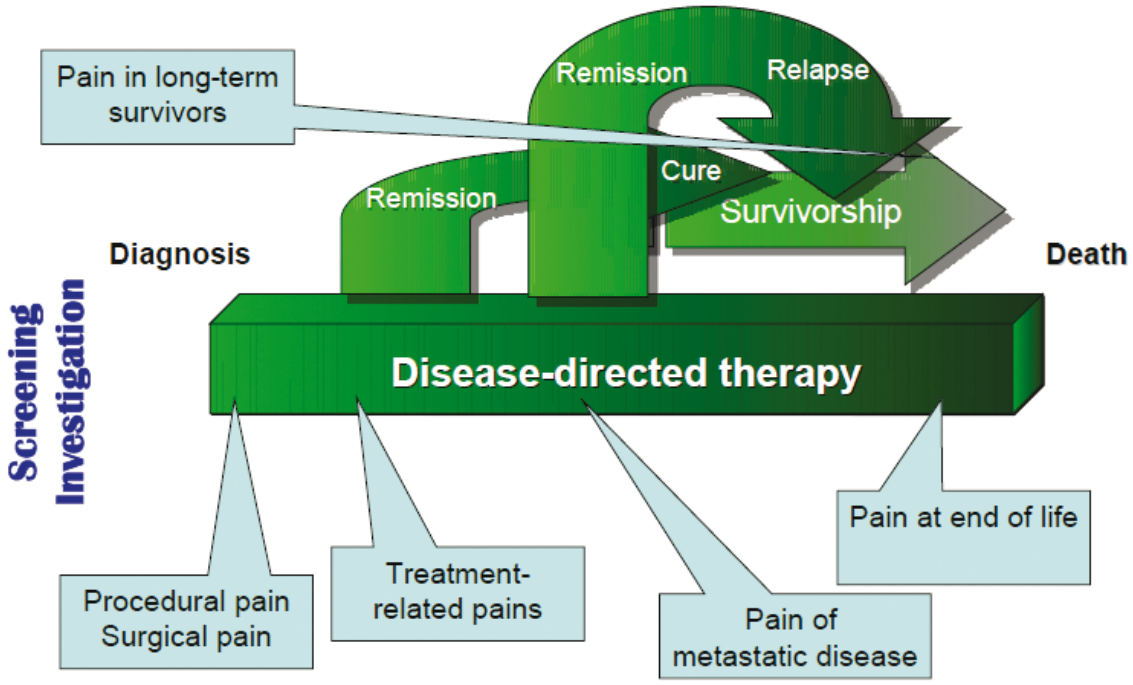
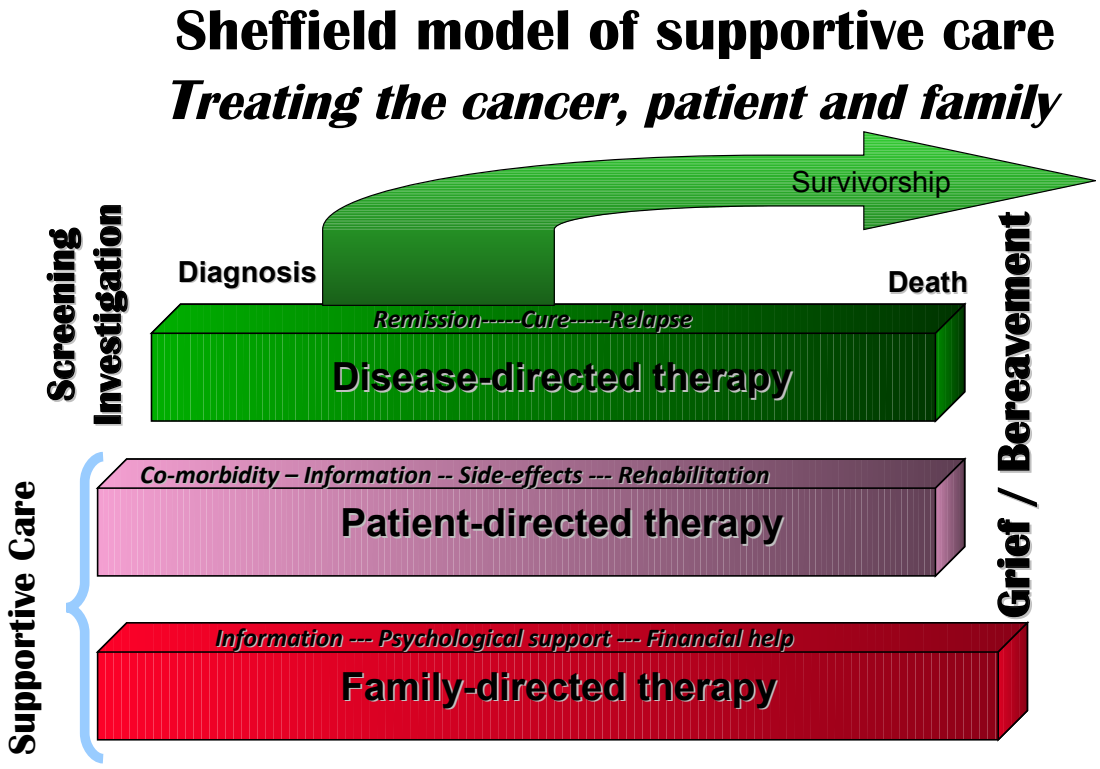


Figure 2



Adapted from: Ahmedzai, Walsh *Seminars in Oncol* 2000

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Chapter 2 Pathophysiology of cancer pain and opioid tolerance

Summary

The neurophysiology of cancer pain is complex: it involves inflammatory, neuropathic, ischaemic and compression mechanisms at multiple sites. A knowledge of these mechanisms and the ability to decide whether 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.

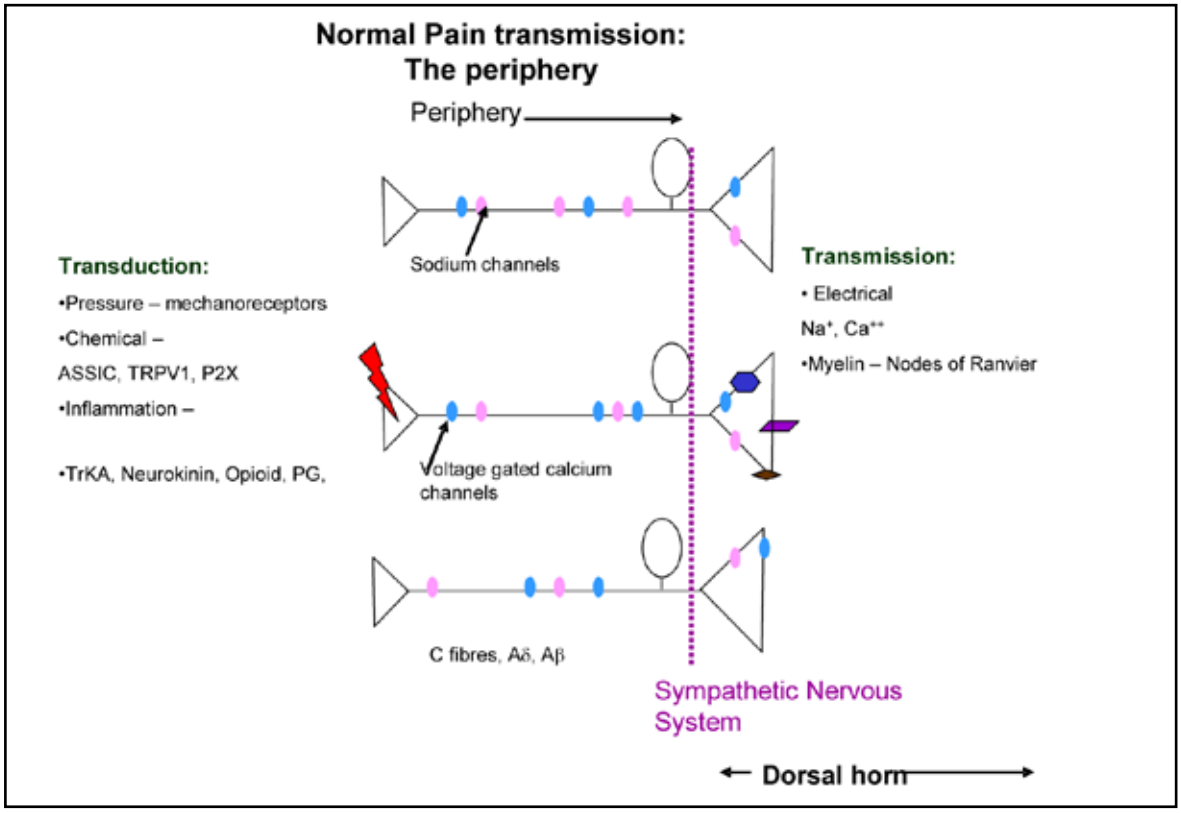
2.1 Introduction

- Cancer pain shares the same neuro-patho-physiological pathways as non-cancer pain.
- It is a mixed mechanism pain, rarely presenting as a pure neuropathic, visceral or somatic pain syndrome. Rather, it may involve inflammatory, neuropathic, ischaemic 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.

2.2 Normal Pain Transmission

2.2.1 Peripheral (Figure 1)

Figure 1



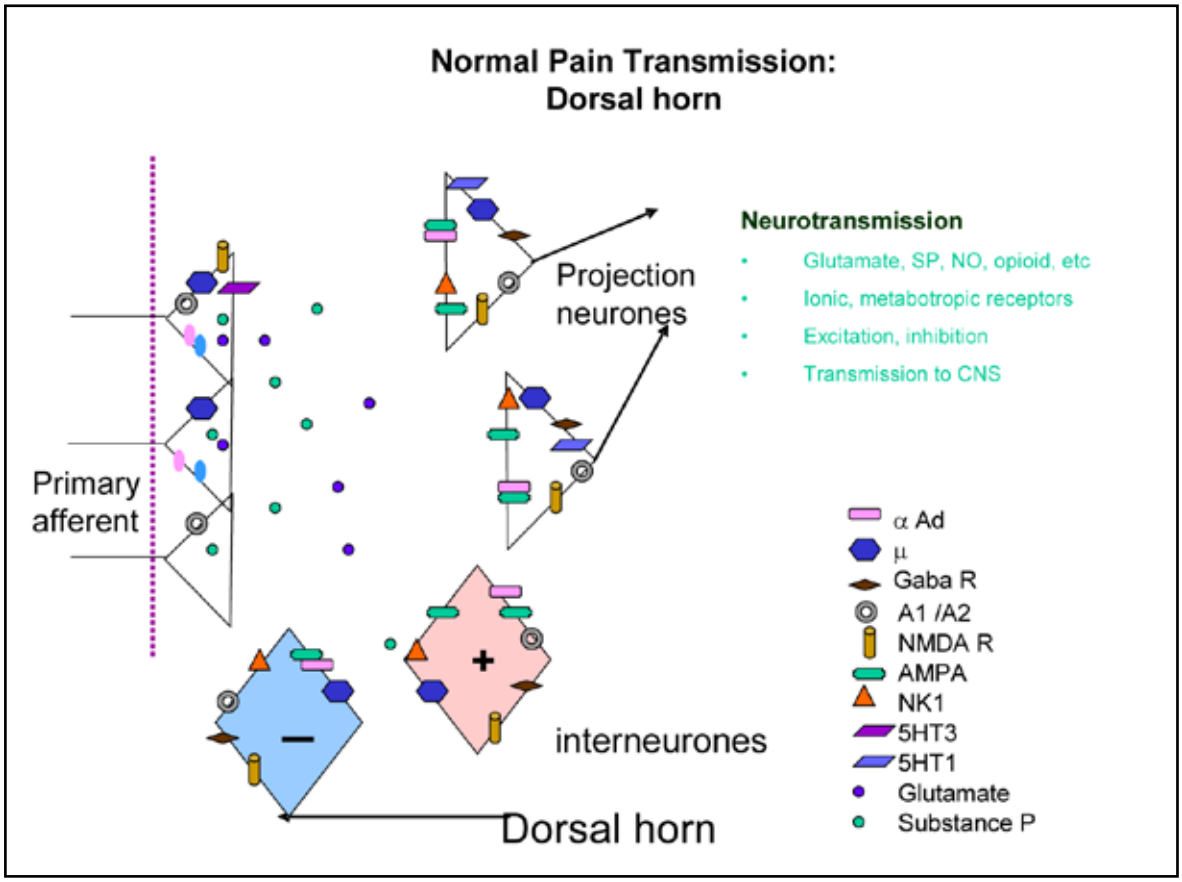
- There is a transduction of alterations in the milieu via specialised receptors (i.e. mechano – pressure, acid sensing ion channels – protons, vallinoid receptors – thermal, tyrosine kinase A (TrKA), nerve growth factor – inflammation, etc.).

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

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

2.2.2 Spinal cord dorsal horn (Figure 2)

Figure 2



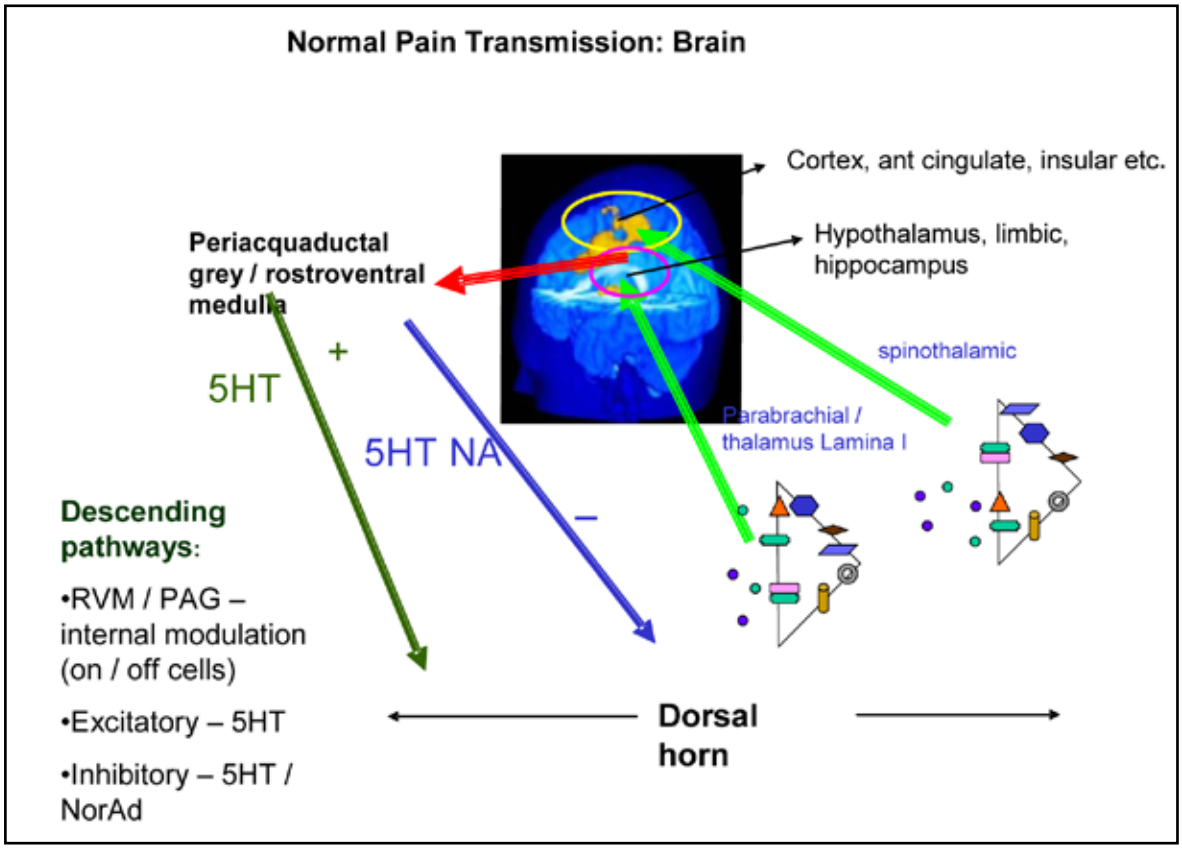
- This is 'divided' into laminae: Aβ fibres terminate in lamina III; Aδ in lamina I, IV/V; and C fibres in lamina II.

  Modulation of the primary afferent inputs occurs. Excitation is via stimulation of post-synaptic receptors such as: N-methyl D aspartate (NMDA); alpha amino hydroxy methyl isoxazole propionic acid (AMPA); 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, and to the initiation and maintenance of neuronal activation.

2.2.3 Central (ascending) (Figure 3)

Figure 3



- The ascending pathways are the spinothalamic and parabrachial neurones.
- The spinothalamic neurones connect the dorsal horn via the thalamus to the cortex. These give intensity and the 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.

2.2.4 Central (descending)

- These arise within the periaquaductal grey (PAG) and rostroventromedulla (RVM), and connect back to the dorsal horn.
- The descending noradrenergic pathways are inhibitory, whilst serotonin can be either inhibitory or excitatory (via 5HT3 receptors on primary afferents).

2.3 Neuropathic Pain

- This arises from damage to neurones, either peripheral or central (via compression, ischaemia / haemorrhage, chemical or transection).

- Peripheral damage results in the accumulation of abnormal sodium and calcium channels at the site of the injury.
- There is a gene expression alteration in the number and character of receptors.
- Damaged neurones discharge spontaneously, and there is cross-talk to normal fibres and the recruitment of silent nociceptors.
- An excessive or absent discharge from primary afferents within the dorsal horn results in an overall excitation and alteration in the expression of NMDA receptors and a functional loss of opioid and gabaminergic systems.
- There is resultant hyperexcitation with increased receptive fields, primary and secondary hyperalgesia and allodynia.
- Higher centres undergo re-mapping and alteration, resulting in an increased excitation of afferent and cingulate cortices.

2.4 Inflammatory Pain

- Peripheral and central mediators of inflammation, such as bradykinins, a nerve growth factor, cytokines, ATP and protons (from dying cells), establish a feed-forward loop that results in the sensitisation of primary afferents, the recruitment of silent nociceptors and peripheral hyperalgesia.
- The dorsal horn is hyper-excited, which results from an increase in the 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.

2.5 Visceral Pain

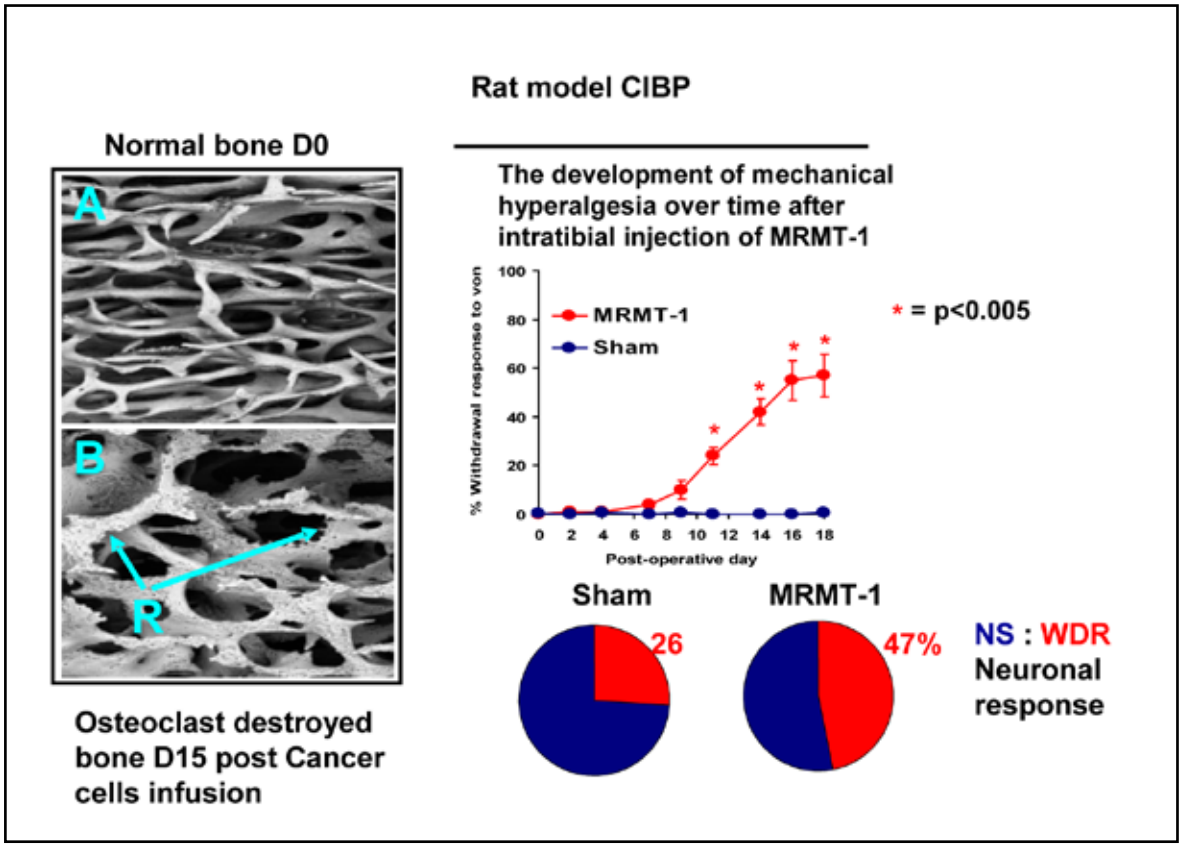
- This is fundamentally different from somatic pain. Symptoms include diffuse, poorly localised pain with different descriptors (i.e. spasm, heavy feeling).
- Visceral innervation is two-fold: autonomic (i.e. vagal) and spinal.
- Effective stimuli include: chemical, ischaemic, inflammatory, compression and distension–contraction.
- Key transmitters include: peripheral and central serotonin, calcitonin-gene-related peptide, vasoactive intestinal peptide and kinins.
- Dorsal horn modulation is transmitted centrally via the spino-thalamic cortex to the viscero-sensory cortex (mid-insular), where viscero-visceral cross-talk occurs.
- Dorsal columns relay predominately to the thalamus, giving rise to strong autonomic responses and afferent responses.
- There is cross-talk to the somatic sensory cortex and insular cortices.

2.6 Cancer Induced Pain

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

2.6.1 Cancer-Induced Bone Pain (CIBP) (Figure 4)

Figure 4



- Over the past decade, several murine models of contained bone tumour growth (cancer, sarcoma and myeloma cells) have been developed, and pain development parallels the clinical picture.

- Bone is highly innervated with C fibres, which are triggered by an inflammatory inflitrate (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 (neither pure neuropathic nor inflammatory), increased wide-dynamic range neurones in lamina I cells (50% compared with 25% in normals), hyper-excitation lamina I and V, increased glia activation and dynorphin expression.

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

2.6.2 Cancer Therapy Induced Pain

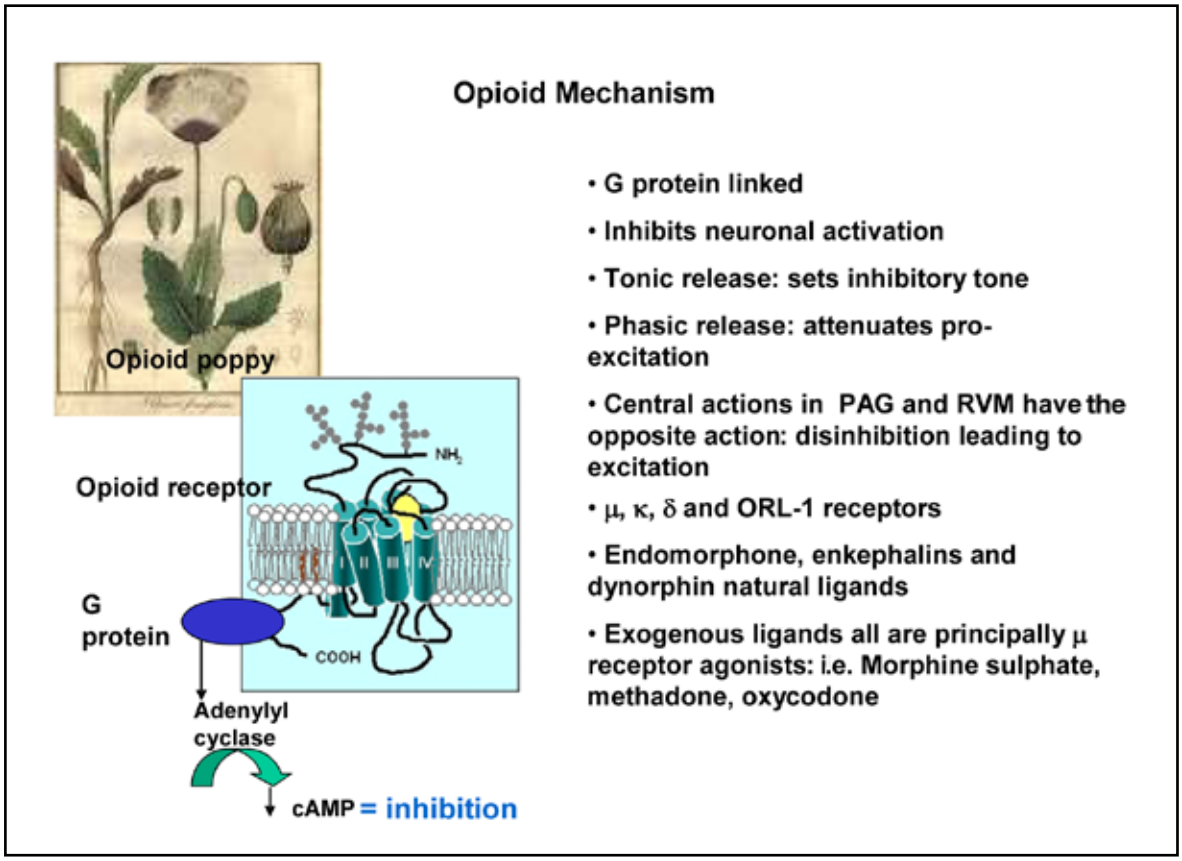
- Murine models of chemotherapy induced pain allow the investigation of cancer neuropathies with particular interest in taxols, platins, thalidomide, bortezomib, etc., or direct inoculation of the tumour cells around nerves.

- Cancer neuropathies have disadvantages in transient afferent alterations and a decline in motor function. Local inflammatory infiltrates 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 the activation of a neuro-immune reaction, which may account for the side-effects of taxols.

2.7 Opioid Therapy (Figure 5)

Figure 5



- This remains the mainstay analgesia for all cancer pain.

- The practice of opioid switching in order to improve analgesia while minimising side-effects is recommended after careful consideration and titration. While this is poorly explained at a receptor level (theories include genomic variations, altered internalisation or the activation of receptors to different opioids), clinical evidence in its favour is building.

2.7.1 Opioid hyperalgesia

- Increasing doses of opioids can be associated with hypersensitivity of the skin to touch and a lack of analgesic response. It is necessary to taper the dose in order to restore efficacy. This state is known as hyperalgesia (Compton, 2001; Doverty, 2001).

- The cellular mechanisms of opioid induced hyperalgesia have much in common with those of neuropathic pain and opioid tolerance (IASP, 2008).

2.7.2 Opioid tolerance

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

- Physiological receptor internalisation, uncoupling, decreased or increased activation and altered expression occur over varying periods from minutes to days, and are 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 the subject of heated debate. Many papers suggest that no significant analgesic tolerance occurs (patients continue on the same dose for months and years), while others suggest that incomplete cross-tolerance allows increased efficacy from different opioids.

Adjuvants are increasingly important for attaining good analgesic control.

2.7.3 Dependence

- Dependence (physical or psychological) can occur in many patients.

- Dependence is different from addiction, since patients remain compliant through opioid alterations, if the side-effects are controlled.

- Physical dependence results in withdrawal syndromes (upon dose reduction).

- Psychological dependence arises when a behavioural connection between analgesia and opioids is established.

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

2.7.4 Addiction

- Addiction is characterised by drug seeking behaviour (multiple sources, legal and illegal), compulsive use, abrupt withdrawal reactions, non-compliance with suggested opioid changes and craving.

- Addiction is a genetic, behavioural, physiological and environmental state that occurs in a 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 specialised and specialist referral (pain or palliative medicine teams) is recommended in any case of concern for a patient..

2.7.5 Withdrawal

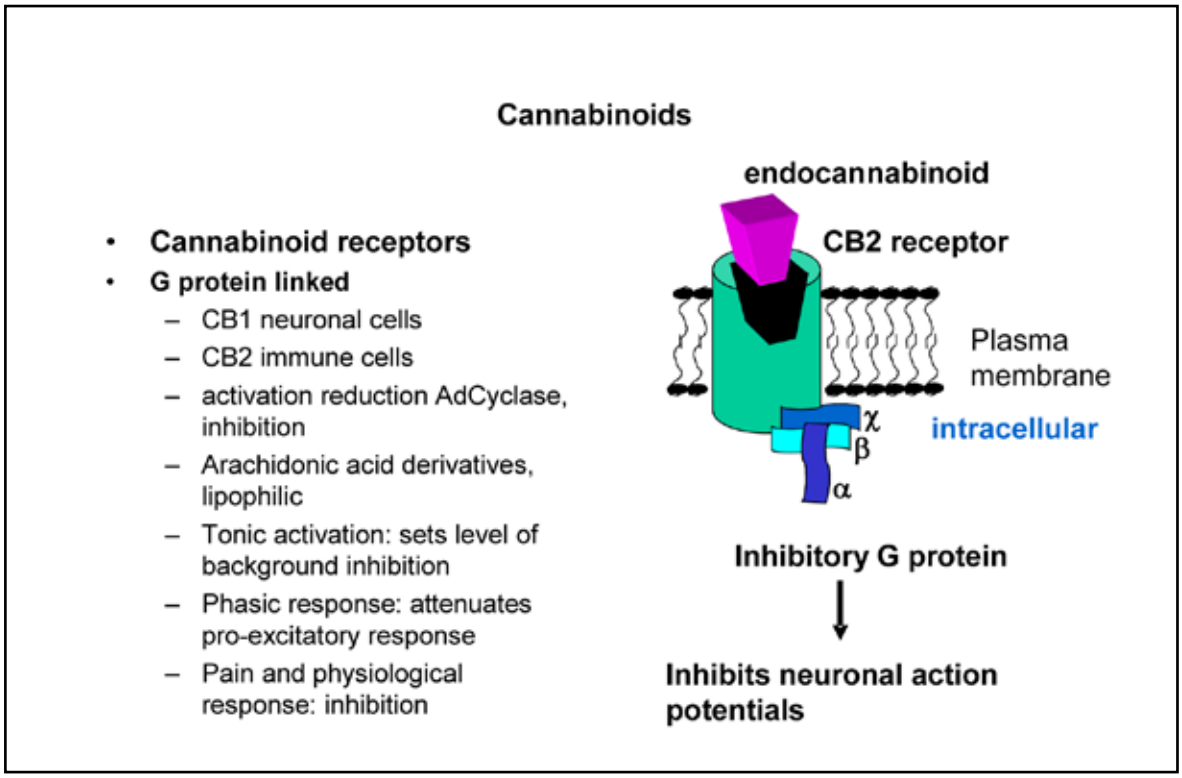
- Physical withdrawal, including abdominal cramps, diarrhoea and sweating, occurs in almost all patients to some extent upon reduction of opioid dose.

- 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.

2.8 Cannabinoids (Figure 6)

Figure 6



- Endocannabinoids are important in central inhibition.

- They act primarily on CB1 neuronal receptors.

- CB2 receptors are primarily immune cells, including glia.

- There is some evidence for other cannabinoid receptors.
- Cannabinoids are potentially an important clinical alternative to opioids for analgesia.
- There are problems with a lack of specificity and they are highly lipophilic, thus having non-receptor bound effects (via plasma membrane diffusion).

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Chapter 3 Cancer pain assessment

Summary

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

3.1 Introduction

- People with cancer can report the presence of several different anatomical sites of pain which may be caused by the cancer, by cancer treatment, by general debility or by concurrent disorders (Twycross, 1996).

- Inadequate assessment of pain and a lack of documentation are thought to be the greatest barriers to effective pain relief (Herr, 2004); therefore, enquiries into the presence of pain should be included in the assessment of all patients who are diagnosed with cancer.

3.2 Assessment

- All patients diagnosed with cancer who report pain should undergo a comprehensive assessment and reassessment of pain. Wherever possible, the patient should be involved in the assessment and reassessment of their pain (Cleeland, 1994).

- In an acute care setting, the initial pain assessment should be undertaken on admission. There should at least be a daily reassessment of pain; however, this may be more frequent depending on the severity of pain, the level of distress or any new reports of pain (de Rond, 1999).

- In the primary care setting, pain should be assessed on each visit to the patient. Timing of this assessment will depend on patient's individual circumstances (de Rond, 1999).

- In primary care, patients and their carers should be given and taught to use a pain diary in order to monitor pain levels, medication requirements, the effectiveness of analgesia and any side-effects of medication (Allard, 2001).

- Any evidence of the initial pain assessment, the reassessment and the effectiveness of analgesia must be documented within the patient's record (NMC, 2004).

3.2.1 Core Elements of Initial Assessment

These will include:

- a detailed history to determine the presence of persistent pain, breakthrough pain and their effect on function.

- a psychosocial assessment.

- a physical examination.

- a diagnostic evaluation for signs and symptoms associated with common cancer pain syndromes (Miaskowski, 2005).

3.2.2 Breakthrough pain

Breakthrough pain is defined as a transitory flare up of moderate to severe pain in patients with otherwise stable persistent pain (Bennett, 2005; Portenoy, 1990).

Factors to consider when assessing for breakthrough pain include:

- the presence of breakthrough pain.
- the frequency and number of episodes per day.
- the duration, with the time in minutes.
- the intensity and the time to peak in severity.
- the description of breakthrough pain.
- any precipitating factors.
- a current and previous analgesic history (Hwang, 2003).

3.2.3 Ongoing Assessment and Reassessment of Pain

People with cancer who report pain should be assessed using a formalised pain assessment tool which reflects the multidimensional nature of pain, an example being the Brief Pain Inventory (Cleeland, 2004b). 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 any pain management strategies employed (SIGN, 2000).

This should include:

- the location of pain.
- the characteristics/a description of the pain.
- the severity/intensity of the pain.
- the duration of the pain.
- any aggravating factors.
- any relieving factors.
- the effect of pain on function and activities of daily living.
- the impact on quality of life.
- the impact on psychological well-being.
- any social impact.

- any spiritual impact.
- pain expectations.
- medication – current and previous analgesics.
- opioid toxicity.
- complementary interventions.
- the 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.

3.3 Psychosocial factors

Fear, anxiety, depression and a lack of sleep have been reported as increasing pain and suffering in people with cancer (Anderson, 2003; Portenoy, 1994). A comprehensive pain assessment should include the personal and social influences that determine how pain is experienced and perceived (Miaskowski, 2005).

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. Factors associated with the patient's treatment which may contribute to their emotional distress and/or depression must be included in the assessment.

An assessment of the psychosocial factors influencing the experience of pain will include:

- the patient's 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.
- whether the pain influences the patient's mood.
- changes in mood.
- coping strategies adopted by the patient.
- the patient's sleep pattern.
- any economic impact.

3.4 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 (Mako, 2006). Spiritual care is not necessarily religious. However, religious care, at its best, should always be spiritual (NHS HDL, 2002). Spiritual care is given in a one-to-one relationship, is completely person-centred and makes no assumptions about personal conviction or life orientation (NHS HDL:76:2002).

3.5 Special Groups

Certain groups of individuals may be at a higher risk of under treatment for cancer pain. These groups include:

- older people.
- the cognitively impaired.
- people whose first language is not English.
- known or suspected substance abusers.
- patients at the end of their lives..

(NHS QIS, 2006; Miaskowski, 2005).

People who are being treated for cancer may also be at risk of developing pain syndromes as a direct result of cancer treatment strategies (Portenoy, 1999). Practitioners should use appropriate strategies to identify people at risk of under-treatment for cancer pain.

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

3.6 Barriers to Accurate Assessment

- The main barrier to optimal effective pain relief is the inadequate assessment of pain (Herr, 2004). Healthcare 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 (Loftus, 2007). Therefore, pain and its management should be discussed with the patient and their families. Patients with cancer pain should be encouraged to be active participants in the management of their own pain.

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Chapter 4 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 non-pharmacological methods of pain control can optimise pain relief, but the limitations of these treatments must also be acknowledged. Specifically, skeletal pain, abdomino-pelvic pain and headache are discussed.

4.1 Overview of Cancer Treatments for Pain

- Successful oncological management of any tumour, if it is only palliative, can result in a significant improvement in pain relief.
- Combining cancer treatments with pharmacological and non-pharmacological methods of pain control can result in optimum pain management.
- However, it should be acknowledged that oncological treatments themselves may induce persistent pain in some patients (see chapter 11).
- Cancer treatment includes loco-regional treatments, either surgery or radiotherapy, and systemic therapy with chemotherapy, hormone therapy and biological modifiers.

4.1.1 Surgery

Major surgery is rarely appropriate for a patient with advanced cancer and metastatic pain, and 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 the restoration of function can be achieved.
- A vertebral fracture may require stabilisation 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.

4.1.2 Radiotherapy

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

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

4.1.3 Chemotherapy

- Chemotherapy may also provide valuable pain relief for a patient with widespread metastatic disease; common indications of this are shown in Table 3.

- The principal limitation of chemotherapy is related to the limited tumour chemosensitivity encountered in advanced and recurrent cancer, e.g. breast, non-small cell lung cancer and colorectal cancer. However, some tumours that are associated with widespread severe metastatic bone pain (e.g. multiple myeloma and small cell lung cancer) remain more sensitive and chemotherapy can have a major palliative role.

4.1.4 Hormone therapy

Breast and prostrate cancer account for a large number of patients who present with metastatic disease and cancer pain and who 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 the median duration of response is between 18 months and two years.

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

4.1.5 Bisphosphonates

- Bisphosphonates are used increasingly in the management of cancer-induced bone pain (CIBP). They are drugs with poor oral bio-availability and are usually given as intravenous infusions, with 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 regular use of bisphosphonates reduced the number of skeletal-related events in numerous cancers (Ross, 2003).

- A Cochrane review in 2000 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 (Wong, 2002).

4.2 Specific pain problems in cancer patients

4.2.1 Skeletal pain

Skeletal pain in cancer patients is most commonly associated with bone metastese; 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 others may have scattered multi-focal pain often flitting from one area to another, which is the clinical scenario. Combining radiotherapy with pharmacological and non-pharmacological management is generally recognised as the most effective treatment in this setting.

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

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

- Where a 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 a pathological fracture of a long bone, since analgesia and radiotherapy alone are not sufficient to control the movement-related pain associated with this situation. One alternative may be percutaneous cervical cordotomy to treat unilateral incident pain resulting from a solitary long bone pathological fracture.

4.2.1.1 Localised external beam radiotherapy

- Localised external beam radiotherapy for metastatic bone pain is the usual modality for localised bone pain, and this has been the subject of a large number of randomised controlled trials and two Cochrane reviews (McQuay, 1997; Sze, 2003). These have confirmed its efficacy, with a complete response rate of 32 - 34% and NNT for complete response of 3.9 (95% 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 to 10Gy appear to be as effective as more prolonged, high dose schedules and response rates are generally not predicted by tumour histology.

- Toxicity is mild and is related to the site of treatment; treatment of areas which include significant amounts of bowel, such as the lumbosacral spine and pelvis for example, will result in nausea and increased bowel frequency in 20 to 30% of patients (Yarnold, 1999). These symptoms will respond to medication and are self-limiting over a period of 10 to 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 localised bone pain has been shown to evolve consistently over four to six weeks from treatment, with 50% of patients responding within two weeks of treatment and reaching a plateau two to four weeks later when, on actuarial analysis, around 80% of patients will have recorded a response.

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

4.2.1.2 Wide field external beam radiotherapy

- Wide field external beam radiotherapy is used to treat multiple sites of bone pain. This form of radiotherapy is 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 there needs to be a four to six week recovery period in the treated area for the remainder of the bone marrow is exposed to radiation.

- A simple two-fraction schedule delivering 8Gy over two days is used. Similar response rates to external beam radiotherapy have been reported, with a much more rapid pattern of response: 25% of patients responded within the first 24 hours in some studies (McQuay, 1997; Salazar, 2001). Inevitably, treating larger volumes results in greater toxicity when this technique is used, and around two-thirds of patients will report nausea and increased bowel frequency.

4.2.1.3 Radioisotope treatment

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

- Radioisotope treatment for metastatic bone pain has a similar efficacy to wide field external beam irradiation, but is associated with less toxicity and lower transfusion requirements (Bauman, 2005). Meta-analysis has not defined an individual NNT for radio-isotope therapy (McQuay, 1997; Sze, 2003).

- Although of similar efficacy to external wide field radiotherapy, this treatment has a better toxicity profile and the relative ease of delivery has meant that, in a wealthy healthcare system, radio-isotope therapy has become the treatment of choice in this setting. However, where this 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 3,000 to 5,000 MegaBequerels (MBq) following ablation of the thyroid gland.

4.2.1.4 Chemotherapy and hormone therapy

Sections 4.1.3 and 4.1.4 describe the palliative role of chemotherapy and hormone therapy. This section draws attention to their role in the management of bone metastases.

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

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

4.2.2 Thoracic pain

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

- The general approach that was outlined above, therefore, using dose-escalating analgesics through the WHO analgesic ladder, will be required for most patients, and this can be supplemented by other, more specific, therapies. Where chest wall infiltration has occurred, NSAIDs may be of value; and where there is neuropathic pain, anti-convulsants and anti-depressants will have an important role. Intercostal nerve blocks are also very effective in certain patients. More aggressive anaesthetic interventions, such as intraspinal analgesia or cordotomy, may be required, especially in mesothelioma.

4.2.3 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 resulting from lumbo-sacral plexus infiltration.

- Hepatic metastases typically cause pain as an enlargement of the liver results in the capsule being stretched at the point of the sensory innervation.. In general, unless there is gross hepatic dysfunction, the metabolism of the common drugs in the WHO ladder are not affected by the presence of liver metastasis. Steroids may be of value in reducing hepatic oedema and liver pain. Where a chemo-sensitive tumour is present, then reduction of the liver size using chemotherapy should be considered. However, whilst hormone therapy may reduce hepatomegaly from liver metastasis, the response is often slow, taking several months. Two randomised, controlled trials have addressed the role of hepatic irradiation in advanced malignancy and concluded that effective palliation of pain is achieved in 80% of cases and systemic symptoms can be achieved in 45% of selected cases (Borgelt, 1981).

- Splenomegaly may also be a cause of abdominal pain. Typically, this will be due to a haematological malignancy, such as chronic granulocytic leukaemia or lymphoma. These are chemosensitive tumours and chemotherapy will therefore 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 is often poorly controlled with analgesics, even with the titration of strong opioids. Randomised controlled trial evidence has confirmed the positive role of a neurolytic coeliac plexus block in this setting, with superior results in terms of pain relief over analgesics alone (Eisenberg, 1995).

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

4.2.4 Headache

- A headache resulting from malignant disease may arise from raised intracranial pressure due to brain metastasis or progressive incurable primary brain tumours. It may also be a result of hydrocephalus, typically from a tumour in the mid brain or posterior fossa that is obstructing the aquaduct. Diffuse meningeal disease may cause a communicating hydrocephalus, which is less commonly associated with a headache. It is important to remember that a headache may also be due to anxiety and depression and that other common, non-malignant causes of headache may be found in patients with advanced cancer, such as tension headache and migraine.

- Where there is raised intracranial pressure, then steroids are of value. A randomised controlled trial suggested that relatively low doses of dexamethasone are as effective as higher doses, with 4mg being equivalent to 8mg or 16mg and such doses are associated with fewer steroid induced side-effects (Vecht, 1994). The length of treatment should be as short as possible and any maintenance treatment should be at the lowest possible dose to minimise steroid-induced side-effects.

- Brain metastasis can be palliated successfully with brain irradiation (Hoskin, 2000). A solitary metastasis may be best treated with surgical decompression and post-operative radiotherapy; multiple metastases should be treated with whole brain radiotherapy. Chemotherapy is also of value in brain metastasis where there is a chemosensitive tumour and should always be considered for haematological malignancies, including non-Hodgkin's lymphoma, germ cell tumours, small cell lung cancer and breast cancer.

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

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

- Other associated causes of headaches should also be considered, including cervical spine metastasis, for which local radiotherapy will have an important role, and tumours of the head and neck region, particularly those involving the sinuses or orbit. Appropriate surgical resection or radiotherapy will be considered for these tumours along with pharmacological management of pain.

Table 1 Indications for surgery in management of cancer pain

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

Table 2 Indications for radiotherapy in management of cancer pain

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

Table 3 Indications for chemotherapy in the management of cancer pain

Pain	Cause	Primary tumour types
Bone pain	Bone metastases	Myeloma Breast cancer Lung cancer (small and non-small cell)
Headache	Brain metastases	Germ cell tumours Lymphoma and Leukaemias [Breast cancer] [Small cell lung cancer]
Abdominal pain	Ascites Subacute obstruction	Ovary Colorectal Stomach
	Pancreatic pain	Pancreas
Pelvic pain	Local tumour infiltration	Colorectal Ovary Cervix
Chest pain	Local tumour infiltration	Lung cancer (small and non-small cell) Metastases from chemosensitive sites e.g. breast, colorectal [Mesothelioma]
Note: [ ] indicates tumours with only modest (<50%) response rates when other modalities e.g. radiotherapy may be preferred.		

Table 4 Causes of bone pain in cancer patients

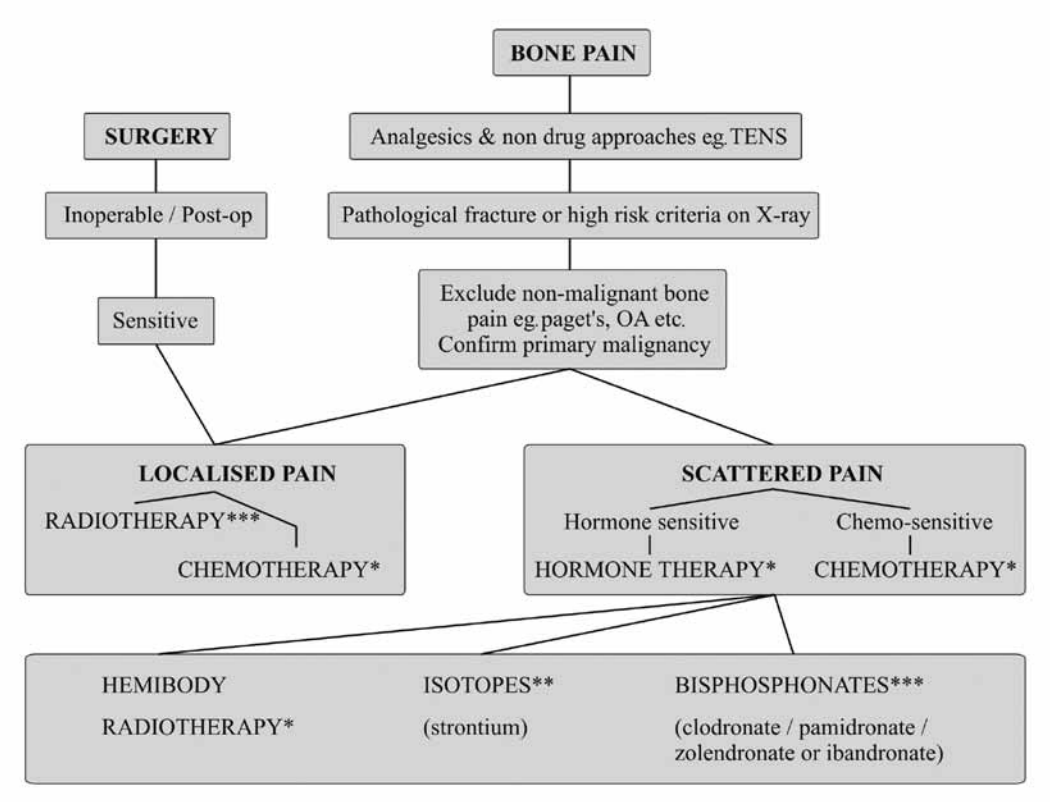
Metastases
Fracture
Degenerative bone disease e.g. osteoarthritis
Bone marrow pain
Non-metastatic hypertrophic osteoarthropathy e.g. HPOA (hypertrophic pulmonary osteoarthropathy)
Other bone disease e.g. Paget's

Table 5 Chemosensitivity of primary tumours commonly metastasising to bone

Primary site	Sensitivity *
Myeloma	High
Bronchus	High
Breast	High
Rectum	Mid
Oesophagus	Mid/low
Prostate	Low
Thyroid	Low
Kidney	Low

* High = >50% response rate
Mid = 25-50% response rate
Low = <25% response rate

Figure 1 Overview of the management of metastatic bone pain



For continuing pain, despite of all above, consider anaesthetic intervention.

*** systematic review of meta-analysis
** one or more well-designed randomized controlled trials
* non-randomized controlled trials, cohort study, etc.

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Chapter 5 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 and the suppression of the hypothalamic/pituitary axis should be acknowledged and managed in both non-cancer 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 each have their place in the management of complex cancer pain.

5.1 WHO analgesic ladder

- The prevailing model since 1986 for the management of cancer pain, and latterly some forms of chronic non-malignant pain, has been the WHO 3-step analgesic ladder (WHO, 1990).
- This guideline was born from 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 in its construction (Meldrum, 2005).
- 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" in order to continue to provide "freedom from pain".
- The WHO ladder states that non-opioids (Paracetamol & NSAIDs) should be administered first, followed by weak opioids (Codeine) and then, if required, strong opioids (Morphine).
- It also recommends the use of adjuvant drugs to calm fears and anxieties (WHO, 1990).
- 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 45% to 100% of cases worldwide (Ferreira, 2006).
- The WHO approach relies heavily on the use of opioids, in particular morphine, and the role of "adjuvants" is not clearly defined, although this is usually interpreted as the addition of paracetamol and NSAIDs.

5.2 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 anti-emetics 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 (Ballantyne, 2007).

- The effectiveness of long-term use of opioids for persistent non-cancer pain has been disappointing. Studies show limited efficacy, and addication had developed in approximately 18% of cases (Ballantyne, 2007), with increasing evidence of the suppression of the hypothalamic/pituitary axis and immune suppression.

- It is well established that patients are going through long-term opioid therapy develop hypogonadotrophic hypogonadism and also opioid-induced androgen deficiency - OPIAD (Daniell, 2006).

- Long-term opioid therapy contributes towards bone demineralisation, thus predisposing the patient to osteoporosis (Vestergaard, 2006), and also significantly reduces serum HDL levels (Abs R, 2000).

- The analgesic effects of opioids are primarily achieved through the activation of G-protein coupled receptors on neurons, which open potassium channels to hyperpolarise their membranes. Opioids differ in terms of their affinity to bind to the receptor sites, their pharmocokinetics and their physicochemical properties. This means that certain opioids will have advantages over others due to differing side-effect profiles, routes of administration, development of tolerance and propensity for immunomodulation (Meert, 2005). Indeed, the current trend of 'opioid switching' may be partly driven by the need to move between incompletely cross-tolerant opioids in order to minimise their inherent toxicities (Holdcroft, 2003).

5.2.1 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 (Clark, 2004).

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

- Epidural and intrathecal routes for the administration of opioids (morphine, diamorphine and hydromorphone) with or without local anaesthetics increases effectiveness, while reducing side-effects, particularly drowsiness and constipation, and should be considered when pain cannot be controlled by simpler means (see section 8.8).

5.3 "Adjuvant " analgesics

- Opioids are not the only 'magic bullets' that can target pain signal transmission. The 'adjuvants' are now shown to work via other neuronal and synaptic receptors and ion channels, and may now be as important as opioids.

- Voltage-gated calcium channels can be blocked by gabapentin or pregabalin (Woolf, 1999).

- Sodium channels, which in turn activate calcium channels, can be blocked by local anaesthetics and older generation anti-epileptics such as carbamazepine (Dickinson, 2002). Lignocaine patches have been successfully used in the management of focal neuropathic pain, and are particularly effective in the symptomatic relief of allodynia and hyperpathia (Davies, 2004).

- Other drugs work by modulating noradrenergic and serotonergic transmission and re-uptake, such as tricyclic antidepressants, SNRIs (Sindrup, 2005) and also Tramadol (Hollingshead, 2006).

- NSAIDs and COX inhibitors may exert antinociceptic action by dampening down not only peripheral sensitisation of nerve endings, but also spinal synaptic transmission (McNichol, 2005).

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

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

5.3.1 Neuropathic pain in cancer patients

5.3.1.1 Incidence

- The reported incidence varies. In unselected cancer patients by history and examination alone, incidence rates are 0.5% neuropathic and 30% mixed (Grond,1999), while in a survey of clinicians in 24 countries, pure neuropathic pain numbered 8% and those with "neuropathic element" 40% (Caraceni,1999). Using Questionnaires, NPQ, LANSS, definite neuropathic 61/167 (37%), probable 37/167 (22%) (Mercadante, 2009).

5.3.1.2 Causes

- The main separation of cases is between peripheral neuropathic pain secondary to chemotherapy and other types of cancer-related neuropathic pain.

5.3.1.3 Treatment of neuropathic pain

- Peripheral neuropathic pain secondary to chemotherapy responds poorly to typical antineuropathic treatments such as amitriptyline (50mg), nortriptyline (100mg), lamotrigine (300mg) and gabapentin (2.7mg) (Kautio, 2008; Hammack, 2002; Rao, 2008; Rao, 2007) (see chapter 11).

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

- This was illustrated by a prospective study (Mishra, 2009), 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 a range of adjuvants (amitriptyline 30%, gabapentin 30%, gabapentin and steroids 20%, steroids alone 20%). Before treatment, 70% had VAS scores of 7 or greater, while after 6 months of treatment, 5% had VAS of 4-6, 42% had VAS of 1-3 and 53% had VAS of 0.

5.3.1.4 Outcomes

- The best evidence is for gabapentin, with 2 open-labelled studies (Ross, 2005; Keskinbora, 2007) as well as 1 short (10 day) placebo controlled study (Caraceni, 2004).

- The evidence for amitriptyline as an addition to opioids was not good from one placebo controlled study, but the assessment period was 10 days after starting treatment, which is generally thought to be too short for it to have an effect (Mercadante, 2002).

- Other adjuvant drugs with some evidence from open-labelled studies are Sodium Valproate as an add-on to opioids (Hardy, 2001) and Flecainide (von Gunten, 2007).

5.4 Non-analgesics drugs in pain management

- Some painful conditions that are 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 (Martinez-Zapata, 2003; Wong, 2002).

- Steroids alleviate pain due to CNS 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 to relieve intestinal colic; and Oxybutinin is used for painful bladder spasms.

- Calcium-channel blockers like Nifedipine are used for the management of oesophageal spasms and tenesmus (Nasrallah, 1985).

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

- Rather than simply adopting the WHO approach, which treats 'adjuvants' as optional, there is increasing evidence for the benefit of routinely combining opioids with these other pharmacological agents for synergistic effects, with the prospect of reduced toxicity (Gilron, 2005).

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

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

- The medical management of pain can use non-pharmacological options, such as hypnosis or distraction therapies, which act via the pre-frontal cortex to decrease the perception/sensation of pain. Acupuncture may work by causing the release of endogenous opioids.

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Chapter 6 Psychological aspects and approaches to pain management in cancer survivors

Summary

Psychological distress increases with the intensity of cancer pain. Cancer pain is often under-reported and under-treated for a variety of complex reasons, including a number of beliefs held by patients, families and healthcare professionals. There is evidence that cognitive behavioural techniques that address catastrophising and promote self-efficacy lead to improved pain management. Group format pain management programmes could contribute to the care of cancer survivors with persistent pain.

6.1 Psychological factors

- Persistent pain can have profound and widespread effects upon a 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, behavioural and environmental factors that interact to determine how pain is experienced, expressed and managed (Hanson, 1990). 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 their response to pain (including seeking healthcare) and treatment (Main, 2000).

- 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 (Turk, 1991; Main, 2000).

- The recognition of the importance of psychological, especially cognitive, factors in the experience of pain has lead to the development of cognitive-behavioural models of pain (Turk, 1983), and cognitive behavioural principles underlie effective interventions for adults with chronic pain (Morley, 1999).

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

- 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 between pain and distress and show that increasing pain intensity leads to greater psychological distress (Zara, 2002; Kelsen, 1995).

- Studies of pain coping strategies and their appraisal indicated that catastrophising (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 (Bishop, 2003; Wilkie, 1991), and suggested that cognitive-behavioural techniques that address catastrophising and promote self-efficacy would lead to improved pain management.

- Cancer-related pain is often under-reported and under-treated. 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 healthcare professionals, including:

    - fear of addiction to medication.

    - concerns about tolerance (i.e. the 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 (Ward, 1993).

- Within the cognitive model, a person's interpretation of the meaning of pain can influence their healthcare seeking behaviour 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.

6.2 Psychological approaches to pain management

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

6.2.1 Coping skills training

Coping skills training teaches patients cognitive and behavioural skills to manage pain, reduce distress, 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.

6.2.2 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 (Hanson, 1990). Engaging in meaningful and stimulating activities, for example talking to friends, listening to music and going out, can reduce awareness of pain.

6.2.3 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.

6.3 Pain Management Programmes

- Pain Management Programmes (PMPs) based on cognitive and behavioural principals are the treatment of choice for people whose persistent pain adversely affects their quality of life (The British Pain Society, 2007).

- A PMP aims to improve the physical, psychological, emotional and social dimensions of a person's quality of life, working towards achieving optimal functioning and self-reliance in managing persistent pain. Pain relief is not a primary goal, although improvements in pain have been reported (Morley, 1999; Van Tulder, 2000; Guzman, 2001).

- PMPs consist of education and guided practice. Education includes information on on the principles and rationales of treatment, pain physiology, the 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, a 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 healthcare professionals working in an interdisciplinary way (Turk, 1987).

Key staff include:

- A medically qualified person with a special interest in pain management (usually a pain clinic consultant).

- A chartered clinical psychologist or BABCP registered cognitive behavioural therapist.

- A physiotherapist (state registered).

Other health professionals, such as occupational therapists, nurses and pharmacists, have skills which are extremely useful for the delivery of PMPs.

- PMPs are delivered in a group format, since this contributes to the normalisation of the experience of pain and maximises opportunities for learning from other members of the group. This format is also cost effective.

- There is good evidence for the efficacy of cognitive-behavioural based PMPs (Morley, 1999; Van Tulder, 2000; Guzman, 2001) 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, as well as the impact upon quality of life, the treatment approach of PMPs could contribute to the care of cancer survivors with persistent pain (Robb, 2006). 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 in order to address issues related to willingness to report pain and to use analgesics.

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

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Chapter 7 Physical therapies for cancer pain

Summary

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 utilise strategies which aim to improve patient functioning and quality of life, but the challenge remains to practice in an evidence-based way. More research is needed in this field.

7.1 Introduction

- Physiotherapists (PT) and Occupational Therapists (OT) play an important role in the management of patients with cancer pain and encounter these patients at various stages in their 'cancer journey'. The rehabilitation of cancer patients is gaining increasing recognition and is now considered an essential component in the delivery of care (NICE, 2004).

- The main aims of therapy are to relieve pain (wherever possible) and to improve function and quality of life using treatments based on the best available evidence. Management should be patient-centred, collaborative and restorative and should involve family and carers to ensure a co-ordinated approach to treatment planning and goal-setting. The patient's engagement in the therapy partnership is vital.

- Early referral to therapies is important with palliative care patients, and also with others in order to prevent chronicity and help anticipate future problems. With in-patients, early referral should result in better discharge planning, which may stop bed blocking and help patients return to their preferred place of care.

- Much can be learned from therapists who work with musculoskeletal pain, and there is a plethora of literature examining the role of physiotherapy and occupational therapy for patients with benign pain. Therapists working with cancer patients may find some of these messages helpful, but must recognise that the majority of this work has focused on non-cancer populations..

7.2 Assessment

7.2.1 Impact of cancer-related pain

- Pain can reduce strength, vitality, activity tolerance and mobility (Cancerbackup, 2005; Gamlin, 2002). Cancer patients with pain report significantly lower levels of performance status than those without pain (Lin, 2003). Turk (1998) demonstrated that pain resulting from cancer was associated with higher levels of perceived disability and a lower degree of activity. Pain may affect a person's ability to care for themselves, to work or to participate in fulfilling activities. The experience of cancer pain may also result in disruption to the patient's family and to carers' quality of life (Ferrell, 1999).

- A common response to pain is the development of 'pain behaviours'. These include maladaptive behaviours such as guarding the painful area, pain watching (hyper-vigilance), developing an overly sedentary lifestyle and avoiding activities. This inactivity can result in deconditioning, increased muscular tension and increased attention to pain.

7.2.2 Responses to cancer-related pain

- It is essential to explore the meaning of pain to the patient and to those closest to them. An individual's cultural background, spiritual, religious and philosophical beliefs all impact upon a patient's perception and response to cancer pain.

- Thoughts and emotional responses can contribute to the intensity of the pain experience (Bates, 1993). Anxiety, depression, fear of the future, hopelessness, negative perceptions of personal and social competence, decreased social activity/social support and lack of control over pain may all be important (Breitbart et al., 2004).

7.2.3 Principles of assessment

Therapy assessments must include subjective and objective evaluations and must utilise all available information from medical notes, other members of the MDT and the patients and carers themselves. All relevant co-morbidities need to be considered. Assessment is rarely possible after one interaction; rather it involves an information-gathering exercise and is a continual process which guides both initial and ongoing treatment. Optimal timing of pharmaceutical management is often required to enable patients to participate fully in assessment.

7.2.4 Physiotherapy assessment

This will require detailed examination of physical factors (e.g. range of joint movement, muscle power, postural changes), with recognition and appropriate management of psychological co-morbidities (e.g. anxiety or depression). Assessment will focus on a patient's functional ability (e.g. their ability to transfer or mobilise). There are three components of assessment which must be considered in all patients:

- A description of the pain (including site, severity, irritability, nature).

- Responses to the pain.

- The impact of pain on the person's life

  (Strong et al., 2002).

Therapists must be aware of the dangers of placing too much attention on the correction of physical impairments at the expense of function (Simmonds, 1999). For many cancer patients (especially those with advanced disease), it will be more important to complete a task than to focus on the correction of individual impairments.

7.2.5 Occupational therapy assessment

OT assessment recognises that it is usual for cancer patients to identify and focus on those tasks and occupational roles which they are no longer able to manage or enjoy due to their pain. The OT will listen to the patient's narrative and begin to identify:

- aggravating, relieving factors.

- the beliefs held regarding pain.

- what the pain means to the patients, and to those around them

- how the patient is currently managing their activities in relation to their pain.

The OT will identify which activities the individual needs to do, wants to do and is expected to do by others.

7.2.6 Evaluating outcome

It is important to utilise reliable and valid outcome measures, as well as utilising a patient's subjective feedback. Outcome measures for use in clinical practice must be feasible (i.e. practical, inexpensive and easy to use), provide extra clinical information and be responsive to changes over time. A great variety of tools are now available, but there are no published guidelines for therapists to assist in the selection of measures.

7.2.7 Outcome measures

Both Visual Analogue Scales (VAS) and Numerical Ratings Scales (NRS) are commonly used in clinical practice. Previous research has suggested cut-off points for mild, moderate and severe pain on an NRS (Figure 7.1). This is useful to consider when assessing whether improvements in pain report are clinically significant.

Example: A drop in pain report from 9/10 to 7/10 may be less clinically significant than a drop from 7/10 to 5/10, although the incremental change is the same.

Fig. 7.1 Mild, moderate and severe pain as represented on NRS (Serlin 1995). 0-4 mild, 5-6 moderate, 7-10 severe.

The Brief Pain Inventory (BPI) (Cleeland, 1994) is a useful clinical tool for therapists because it reports both pain intensity and pain interference using an NRS.

It is important that the patient remains at the centre of the treatment process. A measure which can be used to detect the impact of therapy intervention on the patient's self-perception of occupational performance is the Canadian Occupational Performance Measure (Baptiste, 1993). This has also been show to empower and actively encourage patient participation in therapy interventions.

Other tools which can be used include pain drawings (often simple body charts) or descriptive questionnaires, such as the McGill Pain Questionnaire (Melzack, 1975).

7.3 Therapy Management

- The ultimate aim is for the patient to achieve full functional potential and become autonomous in managing the impact of pain on their daily life. There is currently a lack of evidence for the use of therapy interventions for patients with cancer-related pain, and research is required in this field.

- Interventions can be classified as physical, psychosocial and lifestyle adjustment. Psychosocial interventions are discussed fully in Chapter 6. The complimentary & alternative approaches that may be used by therapists are discussed in Chapter 11.

7.3.1 Physical approaches

- Some of these approaches are traditionally administered by physiotherapists (e.g. therapeutic exercise and TENS), but other HCPs may also have sufficient skills in this area (e.g. OT, clinical nurse specialists). Graded activity for a return to function is inextricably linked with therapeutic exercise, but may traditionally be considered the domain of the OT. When utilising these approaches, a certain amount of manual handling is required and therapists must pay special attention to patient comfort and position at all times.

7.3.2 Therapeutic exercise

The main goal of exercise is to address the problems associated with inactivity/immobility (specific or general) and fear of movement. The detrimental effects of immobilisation are well documented and include muscle wasting/weakness, joint stiffness, reduced motor control, mood changes, decreased self-efficacy, reduced coping capacity and cardiovascular deconditioning. Exercise programmes must be tailored to the individual needs of the patient and should start cautiously, build up gradually and be within the patient's tolerance levels. There are now many reviews of exercise in cancer patients, some of which include guidance on specific precautions (Douglas, 2005; Stevinson, 2004).

7.3.3 Graded and purposeful activity

Engagement in meaningful activities (which may include craft, recreation or work) has been shown to assist patients with cancer pain to improve their self-conception and attain task mastery (Kennett, 2000). Appropriately prescribed and graded activities can be used to increase activity tolerance, autonomy, social integration, self-esteem and competency, and can also decrease pain behaviours (Heck, 1997).

7.3.4 Postural re-education

Postural re-education is appropriate for patients who have altered posture or movement secondary to pain. It is important to attempt correction of such postural abnormalities early in rehabilitation in order to avoid further dysfunctional movement patterns. Examples include breast cancer patients who develop chronic post-surgical pain following breast cancer treatment (Macrae, 2001) and adopt protective postures resulting in muscle spasm and muscle imbalances (Cheville & Tchou, 2007). In head and neck cancer patients, there is growing evidence for the use of Progressive Resistive Exercise training to manage shoulder dysfunction and pain secondary to spinal accessory nerve damage. The importance of correcting posture and scapular stability prior to resistance exercise has been documented (McNeely, 2004).

7.3.5 Massage and soft tissue mobilisation

Soft tissue mobilisation is widely practised in the management of pain and includes techniques such as scar mobilisation/massage, myofascial techniques and connective tissue massage. A wealth of information is available on such approaches (Hunter, 1994; Mannheim, 2001).

7.3.6 Transcutaneous Electrical Nerve Stimulation (TENS)

- TENS is a non-invasive form of electrical stimulation, which has been used for many years to treat a wide range of pain problems. Although experts suggest that TENS has an important role, there are currently no formal guidelines for the use of TENS in cancer patients. Only two RCTs evaluating TENS use in cancer-related pain have been identified (Robb, 2007; Gadsby, 1997) and the effectiveness of TENS remains inconclusive (Robb, 2008). However, some patients may find it beneficial.

- Conventional TENS is the most common mode of delivery and should be the first treatment option in most situations. It is generally recommended to start with TENS electrodes in the painful area or an adjacent dermatome. The intensity should be "strong but comfortable" and patients can safely increase treatment time up to several hours, as long as no side-effects occur and benefit continues.

7.3.7 Heat and cold therapy

The application of heat can be achieved through simple methods (e.g. a hot bath to aid relaxation or more localised applications such as heated packs). Cold can be delivered via ice-packs and home remedies can be devised (e.g. using frozen peas wrapped in a towel or a protective fabric to prevent frost burn). All standard contra-indications and precautions must be followed and the choice of treatment will depend on pain presentation and the therapeutic effects needed.

7.4 Lifestyle Adjustment

- Typically, it is the OT who addresses this aspect of management, although the PT can also be involved in some aspects (e.g. prescription of walking aids). An analysis of activity tolerance levels and education in skills can enable functional restoration without provoking painful episodes. Techniques such as pacing, planning, prioritising, energy management, activity analysis, work simplification, time management, compensatory techniques, ergonomic principles and the reorganisation of routines can be taught to provide the patient with the skills necessary to restructure their lifestyle, thus minimising painful episodes.

- Analysing, grading and adapting activities allow patients to continue managing themselves within their ability, tolerance level and pain parameters (College of Occupational Therapy, 2004; Strong, 2002). The restructuring of lifestyle and routine, environmental adaptation, task simplification, fatigue management, appropriate equipment and orthotic prescription and interventions regarding correct positioning and pressure relief during activity facilitate independence, conserve energy, minimise pain on exertion and enable valued activities to be continued.

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Chapter 8 Invasive procedures for cancer pain

Summary

Patient selection for an interventional procedure requires knowledge of the disease process, the prognosis, the expectations of patient and family, a careful assessment and discussion with the referring physicians. There is good evidence for the effectiveness of a coeliac plexus block and intrathecal drug delivery. Safety, aftercare and the 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 a markedly improved quality of life.

8.1 Introduction

- This chapter focuses on the interventional procedures that are considered to be the most effective. It deals with the pharmacological blockade of neural tissue by targeted injection or infusion; their destruction by chemical, physical or surgical methods; and the fixation of vertebral compression fractures.

- For a few procedures (coeliac plexus ablation, intrathecal infusions, see below), there is controlled trial evidence in cancer populations. For most procedures, there is less robust evidence of largely uncontrolled case series.

- A pragmatic approach is required when deciding whether to offer such therapies. The likely benefits and possible risks need to be considered and compared with those of continuing with pharmacological management. Typically, interventional management of cancer pain does not substitute for other modalities, but can improve pain relief and allow for a reduction in systemic medications and their side-effects.

- A careful assessment of the pain should be undertaken by an interdisciplinary team, usually including specialists in pain, palliative care and nursing, although the team might include others. Practical factors should be considered, such as the discharge home, as well as patient and family preferences. Complex situations will often require high-level discussion (Chapter 13).

- It has been traditional to consider exhausting oral or topical analgesia before considering invasive methods; however, this is not always in the patient's best interests. Where there are unacceptable side-effects from opioids, such as drowsiness, then invasive methods may be preferred; while a pump implanted early in advanced cancer can allow for the maximum benefit to be obtained.

- This chapter aims to provide information related to benefits and adverse effects for interventional procedures commonly used in cancer pain management.

8.2 Types of interventional procedures

- These most typically involve interruption to or modification of nerve conduction, with the aim of diminishing pain from a target area. The nerves involved include those of the peripheral, autonomic and central nervous systems.

- The procedures may be considered to be non-destructive or destructive. In non-destructive procedures, nerve blockade or modulation is achieved by the deposition of reversible pharmacological agents. These may be provided by bolus injection and most commonly involve local anaesthetic agents, often supplemented by depot steroids. Alternatively, catheter placement allows for the continuous delivery of agents. When placement is adjacent to peripheral or autonomic nerves, similar agents are used. For catheter placement in the spinal canal with the aim of modulating neuronal activity of the spinal cord, different agents are used. These are most commonly opioids, often supplemented by local anaesthetics and/or the alpha-2 adrenergic agonist, clonidine. More recently, the voltage gated calcium channel blocker, ziconotide, has been introduced (Staats, 2004).

- The destructive procedures involve the use of chemical agents (alcohol 50-100% and phenol 6-10%), physical methods of heat (radiofrequency) and cold (cryoablation) and surgery.

- Destructive procedures must only be provided by appropriately trained personnel, and are best offered within a multidisciplinary framework of care that recognises the psychosocial components of the pain experience. Failure to do so is likely to reduce the efficacy of such procedures.

- Patients should be thoroughly informed about any likely sensory deficits and possible complications.

- In most cases, destructive procedures should first be simulated with a local anaesthetic to allow the patient to experience the sensory changes that may occur (Cousins, 1998).

- The patient should be closely followed as an inpatient for several days after the destructive procedure, with close monitoring and planned opioid reduction in order to avoid drowsiness and respiratory depression when the respiratory stimulation of pain is removed.

8.3 Peripheral nerve blockade

- Peripheral nerve blocks have a limited role in cancer pain management. There is no controlled trial evidence, but case series describe pain relief for a short time with the local anaesthetic blockade of the regional nerve supply of a target area. They may therefore be useful for perioperative pain and other acute cancer pains, such as pathological rib fracture (intercostal nerve blockade). This may be achieved by the bolus injection of local anaesthetic. It is often supplemented with depot steroid with the aim of providing longer term relief, but there is no evidence to support this practice for peripheral nerves (McCarberg, 2007) . Alternatively, catheter infusions of local anaesthetic adjacent to the brachial plexus (Vranken, 2000) or other nerves may prolong the pain relief (Cooper, 1994; Amesbury, 1999).

- Neurolytic blockade of peripheral nerves produces short-term relief; for instance, intercostal neurolysis has a median duration of 3 weeks (Wong, 2007). Although this study found no incidences of neuritis, the survival time was short, and others have reported an incidence of neuritis of 30% (Doyle, 1982). Neurolytic agents should be limited to those with a short life expectancy.

8.4 Autonomic nerve blockade

It is known that the sympathetic nervous system carries pain afferents from the viscera and that blockading these can reduce pain.

8.4.1 Coeliac plexus ablation

- The coeliac plexus carries visceral afferents from several abdominal organs, including the pancreas, liver biliary tract, renal pelvis ureter, spleen and bowel up to the first part of the transverse colon.

- The injection of a neurolytic medication around the coeliac plexus has been most investigated for pancreatic cancer pain, but a role has been found for other upper gastrointestinal malignancies, such as gastric cancer, oesophageal cancer, colorectal cancer, liver metastasis, gallbladder cancer and cholangiocarcinoma (Eisenberg, 1995).

- Access to the plexus is most commonly posterior, with needle placement in front of or posterior to the crura of the diaphragm (Weber, 1996). However, other approaches are used such as anterior (Lieberman, 1988), endosopic (Abeldi, 2001) and transdiscal (Ina, 1996). Imaging most commonly involves fluoroscopy, but some of the alternatives used include computerised tomography (Haaga, 1984) and MRI (Hol, 2000). Whilst there is no apparent difference in outcome between these methods, they do allow for access in certain individuals where fibrous infiltration or tumour invasion may distort the anatomy affecting neurolytic spread (Akhan, 1997; DeCicco, 2001), or may be valuable when patients cannot lie on their front (Perello, 1999).

- In a single blind randomised controlled trial of 100 patients with pancreatic cancer, neurolytic plexus ablation was compared with pharmacological management combined with sham procedure. Pain relief was better in the interventional group for 6 weeks (Wong, 2004). A meta-analysis (Yan, 2007) of 5 randomised controlled trials of coeliac plexus ablation found significantly improved pain relief when compared with pharmacological management or local blockade of the plexus for 8 weeks, with reduced opioid consumption in the ablation group.

- Up to 30% of patients experience hypotension after a coeliac plexus block due to the loss of sympathetic tone and splanchnic vasodilatation (Fugere, 1993). This reaction usually manifests itself within the first 12 hours. Up to 60% of patients report diarrhoea resulting from a sympathetic blockade and unopposed parasympathetic efferent influence after coeliac plexus block, which usually resolves within 48 hours (Hastings,1991). Neurologic complications, including paraplegia, leg weakness, sensory deficits and paresthesias have been reported after coeliac plexus ablation, with a large study reporting four cases of paraplegia after 2730 coeliac plexus blocks (Davies, 1993). Paraplegia was attributed to either direct injury of the spinal cord during the procedure or spinal infarction secondary to spasm of the spinal artery.

- Theoretically, radiofrequency splanchnic denervation should avoid the risk of such paraplegia (Raj, 2002), but the outcome is less studied. It may be an option when the relative risks are discussed with the patient.

8.4.2 Superior hypogastric plexus block

- The superior hypogastric plexus carries afferent from the bladder, uterus, vagina, prostate, testes, urethra, descending colon and rectum. Superior hypogastric block may relieve pelvic pain and a block of these nerves has been described as reducing pain associated with pelvic malignancy (Plancarte, 1997). The posterior approach is commonest, but an anterior approach has been described (Kanazi, 1999).

8.4.3 Ganglion impar block

- This is the most inferior sympathetic ganglion, lying anterior to the sacrococcygeal junction. It has been shown in case series to provide pain relief for patients with advanced cancers of the pelvis and perineum, after abdominoperineal resection for rectal cancer (Plancarte,1997) and following radiation proctitis (Rabah, 2001).

8.5 Neuraxial blocks

- Neuraxial blocks may be epidural (outside the theca or dura mater) or intrathecal (into the cerebrospinal fluid).

- Epidural local anaesthetic and steroid can provide temporary pain relief where a vertebral metastasis is associated with nerve compression.

- Care should be exercised if an impending cord compression or an invasion of the epidural canal by a tumour is suspected, and imaging may be advisable in such circumstances.

- Despite the lack of evidence to support these interventions, several experienced practitioners have used and continue to use these techniques with reported benefit to patients. Epidurals with steroid and local anaesthetic can provide temporary pain relief.

8.5.1 Intrathecal and spinal nerve root neurolysis

- A saddle block with heavy intrathecal phenol can be used for perineal pain of somatic origin in advanced pelvic cancers, especially where bladder and bowel function are already compromised.

- Chemical neurolysis of spinal nerve roots is used less frequently than in the past, since safer interventions (e.g. neuraxial infusions) have been developed. Whilst there are case series describing the effective relief of pain, the duration is limited and the incidence of neurological deficits is high (Lynch, 1992).

8.6 Neuraxial infusions

- Some patients with advanced cancer may have pain which cannot be controlled with systemic medications, or the use of these medications may be limited by unacceptable side-effects at doses below those required to give adequate relief. For these patients, the administration of drugs by the spinal route, either epidurally or intrathecally, may be required and gives good control in the majority of cases (Baker, 2004).

- There are different types of procedures, ranging from percutaneous lines to fully implanted programmable pumps. The fully implanted systems carry less risk of infection and have lower maintenance, but the operation is more prolonged (Williams, 2000). The costs of the therapy currently suggest that implanted systems are more cost effective than the percutaneous after 3 months (Mueller-Schwefe, 1999).

- There is evidence from randomised controlled trials of improved pain relief and less drug-related side-effects compared with medical therapy for fully implanted systems. The reversal of drowsiness associated with systemic opioids is of great practical significance (Smith, 2002, 2005; Staats, 2004).

- These procedures carry a moderate level of minor adverse effects and a low level of serious adverse effects (Williams, 2000). They should be reserved for those patients whose pain cannot be controlled with systemic analgesia and undertaken in centres experienced with the techniques and with aftercare (British Pain Society, 2008).

- The most effective drugs are opioids, commonly morphine, and generally patients who respond to spinal morphine are those who only partially respond to systemic morphine and/or are limited by dose-related side-effects.. Patients who are unresponsive to large doses of systemic opiods are unlikely to respond to spinal opioids. Other drugs that appear to be effective spinally include local anaesthetics (typically bupivacaine) (Van Dongen, 1999), alpha-2 agonists (clonidine) (Eisenach, 1996) and ziconotide (Staats, 2004). In a randomised placebo controlled study of Zicomotide in ill patients, 50% on active therapy vs 17% on placebo achieved greater than 30% pain relief. However, 30% on ziconotide against 10% on placebo experienced "serious" side-effects, while 38% of those on ziconotide discontinued treatment and follow-up was generally thought to be too short. Fuller details of the use of intrathecal therapies can be found elsewhere (British Pain Society, 2008).

- Intraventricular opioids can be administered via an implanted pump and catheter for pain in the head and face. Cerebrospinal fluid diversion via a shunt or third ventriculostomy may be appropriate for palliation in some cases of obstructive hydrocephalus that are otherwise inoperable; craniotomy and subtotal removal of a malignant cerebral tumour is a routine neurosurgical palliative procedure.

8.7 Domiciliary Management of Spinal Catheters

Most patients want to die at home (Higginson, 1998), and while the safe management of spinal drug infusions does present challenges to this, these can be overcome to facilitate this aim (Gestin, 1997). In addition, with percutaneous drug delivery, intrathecal use allows lower dosage and therefore longer intervals between infusion refilling of ambulatory pumps, facilitating home care and reducing the risk of infection. Intrathecal catheters may be less prone to dislodgement and blockage due to fibrosis (Crul, 1991), and have been shown to be safer in the domiciliary setting (Nitescu, 1990).

8.7.1 Preparation

- Full involvement of the primary care team in the management of pain is vital. If, when considering the use of spinal drug delivery, management at home is identified as a priority, it is essential to establish that the patient and family are suitable and have appropriate goals and expectations. The community nursing and primary care teams should be happy to co-operate and be involved.

- Psychological assessment should be considered once pain has been relieved and sedation due to analgesics minimised, since some patients may be less distracted from the other psychological aspects of their illness. This can lead to difficulties with good symptom control. Full discussion and consent from the patient and family, taking factors such as these into consideration, is essential.

8.7.2 Procedure

- Percutaneous catheters, injection portals or fully implanted systems may be used, but a factor in patient selection is the shorter expectation of survival in this group compared with patients with non-malignant pain. Percutaneous catheters may be tunnelled or non-tunnelled; tunnelled catheters are less prone to displacement and infection (Baker, 2004).

- Implantation and other procedures are ideally undertaken in a sterile facility with resuscitation facilities in a hospital or hospice. Insertion as a domiciliary procedure has been reported (Mercadante, 1994), but this does raise issues with sterility and the ability to resuscitate in the event of side-effects.

- Very compact and reliable battery-powered infusion pumps are available that allow both continuous and patient-controlled bolus drug administration.

8.7.3 Aftercare

- It is imperative that those who will be involved in the patient's management at home are fully trained and confident in the necessary techniques and knowledge before discharge. The patient's management should also be stabilised as an inpatient or in a hospice prior to discharge home, with titration down of systemic analgesics to avoid opioid overdosage in particular (SIGN, 2000). The co-operation of the patient's general practitioner and out-of-hours service is important, and this is supported by the availability of detailed guidelines or protocols and back-up from members of the specialist pain or palliative care team is essential (British Pain Society, 2008). This should be recognised in job plans.

- With appropriate training and compliance with competencies, the refilling of infusion reservoirs can be performed by community nursing staff, as well as monitoring of the patient's condition, particularly pain relief, temperature and the state of implantation sites. Again, guidelines or protocols should support this.

8.10 Anterolateral cordotomy

- This can be undertaken as a percutaneous or open procedure, involving intervention on the side of the spinal cord opposite to that of the pain to ablate the spinothalamic tract fibres. Consequently, it reduces the sensation of touch and temperature in addition to pain.

- The awake percutaneous procedure ablates the spinothalamic tract using radiofrequency lesioning through a needle inserted between the first and second cervical vertebrae. Its value in mesothelioma is well documented (Jackson, 1999), and its use in other lateralised pains is recognised (Crul, 2005).

- Immediate pain relief is achieved in the majority, with 80% either stopping or reducing opioids; but pain recurs in a third of these after six to twelve months (Jackson, 1999). The main risk is of weakness of the leg contralateral to the side of the pain through damage to the corticospinal tract; mild effects are seen in up to 8-10% in the first few days, but prolonged effects are reported in only 1-2% (Crul, 2005). This risk increases, for topographical reasons, when the lower sacral dermatomes are targeted. Painful dysaethesias occur in about 5% of cases (Jackson, 1999).

- While percutaneous cordotomy can only be performed in the cervical area, the spinothalamic fibres can be divided by open operation in the thoracic cord. This avoids the risk to respiration and to the upper limb when the pain is below the waist (e.g. secondary to invasion of the lumbosacral plexus and is recommended for bilateral procedures to avoid fatal sleep apnoea). In a small series (Jones, 2003), no patients experienced motor weakness and all had complete or nearly complete and sustained relief of the target pain, allowing a substantial reduction in medication for all but one. This released them from being closely tied to the hospital/hospice, allowing greater freedom and independence, which was dramatic in some cases (e.g. holidays abroad). There were no new sphincter disturbances reported.

8.9 Midline myelotomy.

- Splitting the spinal cord in the midline posteriorly was intended to divide the spinothalamic fibres as they crossed, thereby controlling bilateral pain while simultaneously avoiding the risks of bilateral cordotomy. Introduced in 1926, it was not particularly successful until the serendipitous observation in 1970 that a single level myelotomy at C1 produced analgesia over a wide body area. It was subsequently found that a limited midline myelotomy at T10 was effective against pelvic visceral cancer pain (Gildenberg, 1991). The recent discovery of a specific pathway in the medial dorsal columns, which conduct visceral pain (Hirschberg, 1996), provides a possible substrate for this operation which appears to be very effective and safe (Nauta, 2000), but is rarely used.

8.10 Other neurosurgical procedures

In the past, many surgical targets in the brain have been tried with varying degrees of success and morbidity, but none is now used more than sporadically. They include sites in the medulla, pons, midbrain, thalamus and hypothalamus, as well as the somatosensory and cingulate cortices. The pituitary gland provided one of the most useful targets; transnasal alcohol-induced hypophysectomy was very effective against hormone-dependant and diffuse cancer pain, particularly when this resulted from bone metastases from breast and prostate. Diabetes insipidus occurred in half the patients and visual disturbances were common; pharmacological hormonal manipulation has made this redundant. Dorsal root entry zone (DREZ) lesions are rarely used for cancer pain. An extensive laminectomy is required, the morbidity is relatively high, only paroxysmal pain responds well and cordotomy or rhizotomy are likely to be preferable.

8.11 Vertebroplasty

Painful pathological fractures of vertebra that do not respond to the conservative therapies of medications, TENS or steroid epidurals can be considered for fixation by cemented vertebroplasty. Open studies in myeloma and metaststic cancers report pain relief that is often complete in around 80% of patients (Gangi, 1999; Fourney, 2003; Dudeney, 2002). Cement leak is the commonest risk at around 5%, and complications from this are rare but serious (Hentschel, 2005).

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Chapter 9 Complementary therapies for cancer pain

Summary

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.

9.1 Introduction

- Complementary and alternative medicine (CAM) refers to a diverse array of treatment modalities and diagnostic techniques. It has been defined as, 'diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, satisfying a demand not met by orthodoxy, or diversifying the conceptual framework of medicine' (Ernst, 2007).

- A large proportion of cancer pain patients use CAM (Goldstein, 2005). The reasons for this include dissatisfaction with conventional medicine, desperation, compatibility between the philosophy of CAM and the patients' own beliefs and the wish for more control over one's own health (Ernst, 2008).

- CAM therapies have the potential to increase wellbeing and thus influence pain. They are often employed in addition to conventional treatments in palliative and supportive cancer care.

9.2 Acupuncture

This is the insertion of needles into the skin and underlying tissues for therapeutic or preventive purposes at specific sites, known as acupuncture points.

- A systematic review identified two randomized clinical trials (RCTs) and found no compelling evidence that acupuncture controls cancer pain (Lee, 2005), which was confirmed by other reviewers. Subsequent RCTs did not produce convincing evidence of effectiveness. However, it is effective in alleviating chemotherapy-related nausea and vomiting and may hence contribute to pain control (Ernst, 2006).

9.3 Aromatherapy

This is the controlled use of plant essences, applied either to the skin through massage, added to baths or inhaled with steaming water.

- A Cochrane systematic review concluded that aromatherapy and/or massage have beneficial short-term effects on well-being in cancer patients (Fellowes, 2004). However, it has not been convincingly demonstrated whether it is associated with clinically relevant analgesic effects.

9.4 Herbal medicine

The medical use of preparations, which contain exclusively plant material.

- There is no convincing evidence for any herbal medicine to suggest effectiveness for treating cancer pain (Ernst, 2007).

9.5 Homeopathy

This is where the diluted preparations of substances are taken whose effects when administered to healthy subjects correspond to the symptoms and clinical signs of the disorder in patients.

- A systematic review of 6 RCTs found no convincing evidence that homeopathic remedies have analgesic effects in cancer patients (Milazzo, 2006).

9.6 Hypnotherapy

This is the induction of a trance-like state to facilitate relaxation and enhance suggestibility for treating conditions and introduce behavioural changes.

- Studies have suggested the usefulness of hypnotherapy in palliative cancer care. A systematic review found encouraging evidence that hypnotherapy can alleviate cancer pain (Rajasekaran, 2005). Due to the often poor methodology of the primary data, this evidence was deemed inconclusive. Similar conclusions were reached in two systematic reviews for procedural pain in paediatric cancer patients (Wild, 2004; Richardson, 2006).

9.7 Massage

This is the manipulation of the bodies soft tissue using various manual techniques and the application of pressure and traction.

- Massage seems to increase well-being through the reduction of stress and anxiety levels, and thus may contribute to pain control. The evidence for analgesic effects in cancer patients is encouraging but not convincing (Corbin, 2005).

9.8 Music therapy

The use of receptive (passive) and/or active music therapy, most commonly based on psychoanalytical, humanistic, cognitive behavioural or developmental theory.

- There is no convincing evidence from RCT data to suggest effectiveness for pain control in cancer patients (Ernst, 2007).

9.9 Reflexology

The use of manual pressure applied to specific areas, or zones, of the feet (and sometimes the hands or ears) that are believed to correspond to other body areas or organs.

- A few small RCTs generated no convincing evidence that reflexology improves quality of life or pain of cancer patients (Stephenson, 2000).

9.10 Relaxation

This involves techniques for eliciting a relaxation response of the autonomic nervous system, resulting in the normalizing of blood supply to the muscles and a decrease in oxygen consumption, heart rate, respiration and skeletal muscle activity. Most commonly, progressive muscle relaxation is used.

- Relaxation techniques have the potential to increase well-being and thus may contribute to controlling pain. Whether these techniques have direct analgesic effects remains, however, unknown.

9.11 Supplements

Oral medical use of preparations of herbal or non-herbal origin.

- A systematic review of nine RCTs that tested cannabinoids concluded that they are not superior to codeine in controlling cancer pain. As cannabinoids cause central nervous depression, their introduction into routine care was deemed undesirable (Campbell, 2001).

9.12 Safety issues

Complementary therapies are often used because they are erroneously considered safe and harmless, which can be dangerously misleading. Some treatments like homeopathy, massage, music therapy, reflexology and relaxation are associated with only mild and rare direct risks if administered appropriately by a trained practitioner. Others have been associated with potentially serious risks: herbal medicines and supplements with herb-drug interactions, toxicity and contamination, acupuncture with pneumothorax and hypnosis with negative physiological and psychological effects. General safety issues include misdiagnosis or delayed access to effective treatments. Self-medication is another problem due to the potential interactions with conventional cancer treatments. In addition, patients often do not disclose their use of complementary medicines to their healthcare provider, who needs to seek the relevant information.

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Chapter 10 Cancer pain management in the community

Summary

Patients with cancer pain spend most of their time in the community until the last month of their lives.. Overall, cancer pain prevalence in the community in Europe is 72%. Older patients and those in care homes in particular may have under-treated pain. Primary care teams supported by palliative care teams are best placed to initiate and manage cancer pain therapy, but the education of patients, carers and healthcare professionals is essential to improve outcomes.

10.1 Introduction

Managing patients with cancer pain in secondary or tertiary care settings has several advantages compared to management in community settings (defined as the patient's home, care homes or hospices). These advantages include more comprehensive assessment and observation, better access to investigations and more direct influence on prescribing and administration of therapy.

Increasingly, however, the patient's wishes and UK government policy advocates improved palliative care, and therefore cancer pain management, for patients in the community. Hospice patients consistently rate pain management as a top research priority within palliative care, above other symptoms and aspects of care (Perkins, 2008). An understanding of cancer pain management in the community is therefore important for planning services and interventions (See also chapter 8, section 8.7 for some practical guidance on domiciliary spinal infusions).

10.2 Epidemiology of cancer pain in the community

10.2.1 Prevalence

Systematic reviews (Hearn, 2003; van den Beuken-van Everdingen, 2007) have demonstrated that cancer pain is common and its prevalence is related to the stage of illness:

- 48% of patients with early disease.
- 59% undergoing cancer treatment.
- 64-74% with advanced disease.

These findings are in keeping with those in the recent European Pain in Cancer (EPIC) survey of 11 European countries, which indicated an overall pain prevalence of 72% of patients with cancer in the community. The rate was slightly higher in the UK at 77% (Breivik, 2008).

10.2.2 Pain severity

Most research on cancer pain severity has been conducted in secondary care settings (Klepstad, 2002; Yates, 2009). Using a 0-10 numerical rating scale, hospitalised cancer patients typically report:

- mean scores for worst pain of 4.8.
- mean score for average pain of 3.7.

- worse pain intensity greater than 5 in two-thirds of patients.

There has been less research in community based patients with cancer pain. The EPIC survey invited patients with cancer pain in the community to participate who were specifically not recruited through palliative care or pain services (Breivik, 2009). For the 617 patients from the UK:

- the mean pain intensity was 6.4 (identical to the European average).
- over 90% rated their pain greater than 5 out of 10.
- a quarter were not receiving any analgesia.

This survey suggests that community based patients have greater, not less, pain intensity than those in secondary care and highlights the need for effective strategies in primary care.

10.2.3 Effects of age on pain and treatment

Concerns exist that older people with cancer experience less effective pain management than younger people (Clearly, 1997; Mercadante, 2007; Delgado-Guay, 2008). Recent research suggests that when older people with cancer are compared to a younger group:

- there is no significant difference in pain intensity (Viganō, 1998; Yates, 2002; Mercadante, 2006, 2008; Bennett, 2009a).
- older people with cognitive impairment report greater intensity of cancer pain than those without (Allen, 2002).
- older people are less likely to receive adequate analgesia than younger people (Cleeland, 1994; Bernebei, 1998); but importantly, these studies only compared the category of the analgesic prescribed for a given pain intensity, and not on the basis of whether the analgesic therapy was effective in reducing pain.

Further research into the differences in analgesic prescription between older and younger people has shown that:

- older people generally require lower doses of analgesia, especially opioids, than younger people, even when controlling for pain intensity (Vigano, 1998; Hall, 2003; Mercadante, 2006, 2008). This may be due to a physiological phenomenon, for example, impaired analgesic metabolism and excretion.
- older people may sometimes need higher doses of analgesia: 58 older people aged over 75 years attending a German pain clinic received higher doses of opioids than those aged under 65 years (Loick, 2000).
- older people do not experience more adverse effects, dose escalation or the need for opioid switching than younger people (Mercadante, 2006; Loick, 2000).
- older people may have poorer attitudes and knowledge about pain and analgesia than younger people and, therefore, are reluctant to have stronger analgesia (Yeager, 1997; Closs, 2008).

In summary, age does not appear to impact upon pain intensity, but older age does appear to be associated with lower doses or potency of analgesic therapy in secondary care settings. These settings include hospital or hospice inpatient units and out-patient clinics. There is a paucity of research on community based patients with cancer pain.

10.2.4 Time spent by patients in the community

Patients with cancer pain spend most of their time in the community. Randomised controlled trials from Italy and Norway that have examined the impact of home-based palliative care teams (Higginson, 2003; Jørdhoy, 2000) have shown that, in the last 6 months of life:

- patients referred to such teams spend between 65% and 81% of their time at home compared with between 65% and 70% of time in a control group.
- less time was spent at home and more time in hospital in the last month of life.

Primary care teams supported by home-based palliative care teams are therefore usually best placed to initiate and manage cancer pain therapy for the majority of patients.

10.3 Barriers to pain management

10.3.1 Patient based barriers

Attitudes or behaviours that prevent successful pain management are referred to as barriers and can be assessed using the Barriers Questionnaire (BQ) (Ward, 1993; Gunnarsdottir, 2002). Research suggests that the most important of these barriers are:

- fear of consequences of analgesic use (addiction and tolerance).
- fatalism about pain.
- inadequate communication with healthcare professionals.
- some religious and cultural beliefs may also impede effective pain control (Bosch, 2002; Peacock, 2008).

However, a UK study (Closs, 2009) which interviewed older and younger patients with cancer pain at home highlighted that:

- knowing when to take and titrate analgesia was the most important barrier for all ages.
- older people found taking and titrating analgesia significantly more of a barrier than younger people.
- fear of adverse effects was an important barrier for both groups.
- fatalism and communication issues were of less importance.

10.3.2 Role of carers

Carers and family members are important sources of support for patients with cancer pain. However, carers can have a powerful influence on the management of pain in an individual patient. Carers' barriers are often similar in nature to patient barriers, but also include hesitancy to administer analgesia. The ethnicity of carers may also influence BQ scores.

High scores by carers on the Barriers Questionnaire have been shown to:

- more strongly predict inadequate cancer pain management than patient scores (based on patient pain scores and level of analgesia).
- be associated with reports from carers that a patient's pain is uncontrolled (Lin, 2000; Letizia, 2004).

10.3.3 Healthcare professionals

The knowledge and attitudes of healthcare professionals towards cancer pain management vary. When these have been compared directly (Furstenberg, 1998; Xue, 2007):

- nurses have been shown to have better pain assessment skills than doctors or pharmacists.
- doctors had better knowledge of clinical therapy.
- pharmacists had most knowledge about opioid pharmacology.
- all three professional groups scored poorly in some areas.

These comparisons demonstrate the need for clinical teams rather than individuals to be involved in managing cancer pain.

10.3.4 Place of care

Primary care or community settings include care homes (nursing or residential), and patients with cancer pain in this context can sometimes be at a disadvantage. There is a high prevalence of daily pain in nursing home residents with cancer, and this is often untreated, particularly in older patients (Bernabei, 1998). Nursing homes can vary in their level of staffing and the equipment (e.g. syringe drivers) necessary for effective cancer pain management, particularly at the very end of life.

10.3.5 Access to opioids

Opioids are central to effective cancer pain management, but access to opioids in the community may be an additional barrier faced by patients. In the United States, pharmacies in predominantly ethnic minority areas are significantly less likely to carry sufficient opioids than in other areas (Morrison, 2000; Green, 2005). There is no comparative data specific to the UK.

10.4 Patient-based educational interventions

10.4.1 Types of interventions

Interventions designed to improve knowledge of and attitudes towards cancer pain and analgesia have been studied extensively. These have been a combination of:

- a brief coaching session (20–40 minutes) in which patient or carer barriers are indentified and addressed, with advice on using analgesia.
- written material.
- and occasionally audiovisual material that patients and carers can review at home.

Some studies have examined more intensive interventions that consist of repeated coaching and support by a nurse or researcher. Comparators in these randomised trials have included either usual care or a placebo, such as a booklet on nutrition.

10.4.2 Evidence of effectiveness

A recent meta-analysis of 21 clinical trials (Bennett, 2009b) has shown that educational interventions for community patients with cancer pain significantly improve knowledge of and attitudes towards pain and analgesia, and reduce pain intensity. Compared with control, educational interventions:

- resulted in a mean reduction of around 1 point on a 0-10 numerical rating scale for both worst and average pain intensity.
- produced a similar effect to that seen when adding paracetamol or gabapentin to patients already treated with opioids (Caraceni, 2004; Stockler, 2004).

Patient and carer education is therefore an important, though probably under-used, component of successful cancer pain management.

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Chapter 11 Pain related to cancer treatments

Summary

Chemotherapy, surgery 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 their quality of life. Awareness of this problem may lead to preventative strategies, but, at the moment, treatment is symptom-based and often inadequate.

11.1 Introduction

- Chemotherapy, surgery and radiotherapy are cancer treatments that can cause persistent pain in cancer survivor patients and adversely affect quality of life and function.
- Up to 50% of cancer survivors may experience chronic pain secondary to treatment, yet this is under-recognised and under-reported (Burton, 2007). Pain in cancer survivors has an additional burden in that it is often perceived to be indicative of disease recurrence.

11.2 Painful chemotherapy-induced peripheral neuropathy (CIPN)

Neurotoxicity is a dose-limiting side-effect of many chemotherapies and biological therapies (also known as biological response modifiers, which modulate the natural response to tumour cells) used in the treatment of cancer. Peripheral neuropathy is the most prevalent form of neurotoxicity.

11.2.1 Risk factors for the development of CIPN

- Longer duration of therapy.
- High cumulative dose.
- Type of chemotherapeutic agent (e.g vincristine, cisplatin, paclitaxel).
- Pre-existing neuropathy (including CIPN).

11.2.2 Common features of CIPN (Hausheer, 2006)

- Symmetrical symptoms.
- Length dependency: 'stocking-glove' distribution, distal limb long nerves affected.
- Signs and symptoms of neurosensory dysfunction.
- Onset related to the administration of neurotoxic therapy: Rapid, delayed or even after therapy has finished.
- Relative sparing of motor function.

In addition to interference with microtubular mediated axonal transport and anatomical damage, alterations in nerve function mediated by pro-inflammatory cytokines, immune cells and mitochondria have been postulated as important in CIPN (Flatters, 2006; Cata, 2006). Pain is not synonymous with neuropathy, but is associated with higher grades of peripheral neuropathy.

11.3 Assessment

- Several assessment tools have been used and validated (Quasthoff, 2002). Many are clinician rather than patient-based, and do not all include assessment of pain, function and quality of life. A specific CIPN pain scale could reduce under-reporting and therefore under-treating of CIPN pain.

- Quantitative sensory testing (QST) does not always reflect symptoms or correlate with chemotherapy dose, nor does it identify neuropathy earlier than clinical history and examination (Hausheer, 2006). However, QST is an objective assessment that is useful for the surveillance of recovery.

11.3.1 Neuropathies associated with specific chemotherapies and biological therapies

Chemotherapy	Type of neuropathy (incidence)	Onset time (coasting)	Duration/recovery	Other differences
Cisplatin (carboplatin)	Chronic	c. 1 month (+)	Some resolution in 80% over months/years	Carboplatin less CIPN
Oxaliplatin (Cersosimo, 2005)	Acute (90%) and chronic	Acute: hours Chronic: c. 1 month (+)	Acute: Chronic: as cisplatin	Acute pain in up to 90%, cold induced
Vincristine (Quasthoff, 2002) (vinblastine)	Chronic (30% severe)	Peak 2-3 weeks (+)	Some recovery 1-3 months, longer recovery into years	Paraesthesias common, vinblastine less CIPN
Paclitaxel (docetaxel) (Hausheer, 2006)	Chronic	Within days (+)	@6/12 19% complete recovery, 25% no recovery (Verstappen, 2003)	More CIPN with more frequent dosing; docetaxel less CIPN
Bortezomib (Velcade®) (Richardson, 2006)	Chronic (35%)		At 2y 71% some recovery	High incidence of neuropathy before starting bortezomib
Thalidomide	Chronic	Any time (+)	Recovery less likely (Richardson, 2006)	No cumulative dose response, daily dose

11.4 Prevention and treatment

- The modification and refinement of chemotherapy dosage schedules (especially in a palliative setting) can reduce CIPN. Specific preventative treatments such as amifostine, glutathione, N acetyl carnitine, N acetyl cysteine and glutamine/glutamate have been studied in humans and animal models with variable success. Vitamin E can reduce cisplatin and paclitaxel-induced neuropathy (Argyriou, 2005, 2006). More research is needed to ascertain effective agents without appreciable side-effects or affecting anticancer efficacy.

- Supportive education and non-pharmacological treatments are important. Simple strategies to reduce the impact of numb and painful hands and feet are important, such as reducing water temperature and using aids to help holding cups and utensils. Psychological support, physiotherapy and occupational therapies are part of a multidisciplinary approach.

- There is little data on effective pharmacological treatments of CIPN. Current management is predominantly based on evidence from other neuropathic pain. Although gabapentin was effective in an animal model of CIPN (Xiao, 2007), it had no effect in humans in a controlled, randomised crossover trial (Wong, 2005). Until there is more data, current neuropathic pain treatment guidelines may be used (Attal, 2006; Finnerup, 2005; Dworkin, 2007). However, the mechanisms of CIPN may be different to other neuropathic pain and more research is needed.

11.5 Post-cancer surgical pain

Pain syndromes after cancer surgery have been found following breast, thoracic head and neck surgery.

11.5.1 Post-breast cancer surgery pain (PBCSP)

- Chronic pain following surgery for breast cancer has been reported, with an incidence of over 50%. Similar to other pain in cancer survivors, it is under-reported, under-recognised and under-treated. Classification is varied and potentially confusing, yet PBCSP is likely to be predominantly neuropathic in origin, secondary to surgical damage. Pain can occur in the scar, arm, chest wall or the breast and is commonly associated with sensory disturbance. Pain often interferes with function and quality of life.

11.5.1.1 Risk factors

Various risk factors predicting the development of PBCSP have been suggested, although the data is conflicting, including: young age (although this may be linked with more aggressive disease and treatment), previous chemotherapy and radiotherapy, poorly controlled post-operative pain, pre-existing anxiety and depression and surgical factors.

11.5.1.2 Surgical factors

- Damage and dysfunction of the intercostobrachial nerve has been proposed as the main mechanism for PBSCP. Some studies showed lower incidence of pain after preservation of the nerve. Thirty percent still develop pain after preservation, while 30% do not develop PBCSP after the nerve is cut. Pain is less common after sentinel node biopsy when compared to axillary dissection (Barranger, 2005).

- Surgical factors are influenced by their impact on post-operative pain. Certain studies found that breast conserving surgery led to less chronic pain than more radical surgery, but others have suggested the opposite (Tasmuth, 1995; Fassoulaki, 2001).

- Reconstructive surgery may be an additional risk factor; however, few studies have examined the more contemporaneous free flap techniques such as the deep inferior epigastric perforator flaps (DIEPs). Post-operative pain following DIEP flap is less than after latissimus dorsi flap, and therefore putatively associated with less chronic pain.

11.5.1.3 Treatment and prevention

- The reduction of risk factors for the development of PBSCP, such as attention to good post-operative pain control, the careful choice of surgical procedure and meticulous technique, could reduce PBSCP.

- A few small trials of treatments for PBSCP have demonstrated modest and variable benefits from capsaicin and EMLA cream, gabapentin, amitriptyline and venlafaxine. Nevertheless, treatment includes best practice for general neuropathic pain management in a multidisciplinary approach.

11.5.2 Post-thoracotomy pain

- Persistent pain following thoracotomy for malignant and non-malignant indications may occur in more than 50% of patients (Maguire, 2006) and, as for other types of chronic post-operative pain, may be related to perioperative nerve damage (Perkins, 2000). Similarly, post-operative pain is a risk factor for chronic pain. Video-assisted thoracoscopic lung surgery (VATS) is associated with a lower incidence of persistent pain.

11.5.3 Post-head and neck surgery pain

- Surgery, in addition to chemotherapy and radiotherapy, is associated with chronic long-term pain for patients with head and neck cancer. Pain can occur in the oral cavity, face, neck or shoulder. The incidence of chronic pain after surgery is similar to other post-cancer surgery pain, about 40% at 1 year and 15% at 5 years (Burton, 2007). Of the 33% of patients who had pain 1 year after neck dissection, most had features of neuropathic pain (van Wilgen, 2004). Treatment depends on careful assessment, providing information to patients and a combination of physical and pharmacological approaches.

11.6 Radiotherapy-induced pain

Radiotherapy is used as a primary adjunctive treatment for many types of cancer. Certain tissues such as skin, mucous membranes and nerves are more susceptible to damage.

11.6.1 Radiation-induced brachial plexus neuropathy (BPN)

Radiation-induced BPN was associated with breast conservation strategies and the deep delivery of radiotherapy in the 1960s and 70s. Modification of radiotherapy treatments have reduced the incidence of BPN (Galecki, 2006; Olsen, 1993). BPN usually occurs at least 6 months after therapy, although higher doses may have a reduced latency. The major differential diagnosis is tumour-related plexopathy. In addition to clinical factors, MRI may aid diagnosis.

11.6.1.2 Features suggestive of radiation-induced neuropathy:

- Progressive forelimb weakness (upper or lower arm, depending on which roots are involved).
- Pain less common.
- Initial involvement of upper plexus divisions.
- Slow progression and long duration.
- Incidence increases with time.

11.6.1.3 Treatment

There are no standard treatments for radiation-induced BPN, but opioids may be beneficial (Fathers, 2002). Other non-pharmacological treatments such as chemical sympathectomy have been used, but evidence for these is limited. Current therapies are also based upon existing treatments for other neuropathic pain.

11.6.2 Pelvic pain after radiotherapy

Radiotherapy for pelvis malignancy can also lead to radiation-induced chronic pain syndromes. Pain results from multiple mechanisms, including effects on the gut, nerves and pelvic and hip fractures. Dysuria may occur in 20% of patients 1 year after pelvic radiation (Burton, 2007). In one study, nearly 50% of patients reported pain in back and lower extremities, and this pain was poorly controlled with analgesics and had a negative influence on quality of life (Bye, 2000). Treatment is symptom-based although, as for BPN, preventative strategies are being explored.

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Chapter 12 Management of acute pain in cancer patients

Summary

The management of acute pain, especially post-operative pain, in patients on high-dose opioids is a challenge that requires in-depth knowledge of pharmacokinetics and the formulation of a careful management plan in order to avoid withdrawal symptoms and inadequate pain management.

12.1 Introduction

Patients with cancer who present for surgery on high-dose opioids are a heterogeneous group with a number of complex perioperative analgesic management problems. The main issues include: physical dependence and the precipitation of withdrawal symptoms if insufficient post-operative opioid is prescribed; and tolerance to the effect of post-operative opioids. Additionally, there may be difficulties in calculating dosage conversions between different types of opioid and different routes of administration.

12.2 Tolerance

- Tolerance is a phenomenon in which exposure to a drug results in the diminution of an effect or the need for a higher dose in order to maintain an effect. This may develop 1-2 weeks or more after the initiation of opioid therapy. A larger dosage of opioid will be required to achieve the desired effect. Short-acting opioids should be titrated to effect in a controlled, monitored environment.

- Tolerance also develops to some of the side-effects of opioids, making patients less likely to suffer from respiratory depression, itching and nausea than opioid naïve patients (See chapter 2).

12.3 Acute pain management

The management of pain in this population of patients is of increasing importance as the cancer survivor population grows and as a greater number of patients are using convenient, sustained-release opioid preparations and transdermal delivery systems.

- In general, the issues of physical dependence withdrawal and tolerance only relate to patients who have been on WHO Step 3 strong opioids such as Morphine or Oxycodone for more than 1-2 weeks preoperatively. These issues are not likely to be a problem in patients taking WHO Step 2 analgesics such as Codeine or Tramadol unless the patient is taking larger than normal doses.

- It is common to underestimate and under-treat pain in opioid dependent patients because most post-operative analgesic regimes are based on the opioid-naïve patient. Opioid dependent patients should be identified preoperatively and a perioperative analgesic plan should be devised after discussions with the patient's opioid prescriber and with the pain team. The aim is to achieve effective analgesia without the precipitation of withdrawal phenomena.

12.3.1 Opioid management

Management involves the regular provision of the pre-existing opioid, supplemented with an additional short-acting opioid, local anaesthetic, non steroidal anti-inflammatory drug and paracetamol. Patient controlled analgesia with a short lock-out and a higher bolus dose may be useful. Neuraxial and regional analgesia is recommended where appropriate.

- Patients will present for surgery having been on many different types of opioid for varying periods of time (e.g. Morphine, Oxycodone, Methadone, Hydromorphone, Pethidine, etc.), which may have modified release (e.g. MST, Fentanyl patch) or immediate release preparations (e.g. immediate release morphine). The route of delivery may be oral, subcutaneous via a syringe pump or transdermal. Dosages range from MST 10mg twice a day to very large doses such as MST 1g per day or more.

- Standard post-operative opioid regimes are generally developed for the opioid naïve patient. Patients on high-dose opioids may have developed a physiological dependence and, if managed using standard post-operative analgesia regimes, may not receive adequate analgesia and develop a 'withdrawal syndrome'. This results in adrenergic hyperactivity and common symptoms such as fatigue, generalised malaise, abdominal cramps, perspiration, fever, piloerection, dehydration and restless sleep.

- Patients will require a baseline opioid dosage postoperatively – referred to as the baseline opioid requirement – calculated using their pre-operative opioid dosage. This can either be given using the same opioid or using an alternative opioid in an equi-analgesic dosage. A continuous parenteral infusion may be needed if the patient is unable to take oral drugs. Provision will need to be made for 'as required' dosing for breakthrough pain. Patient controlled analgesia machines have been successfully used in opioid dependent patients, with the advantage that dosages and lock-out intervals can be adjusted according to need.

- In the pre-op and per-operative period, regular opioids (usually oral) may be discontinued for several hours, which amounts to the opioid "debt". This should be replaced with systemic opioids during the operation.

12.3.2 Parenteral opioid delivery

Transdermal drug delivery systems have the disadvantage of being relatively inflexible in their dosage delivery, with clinically relevant dosages still being absorbed for up to 12 hours. One strategy is to leave the patch in place and to titrate to analgesic effect using immediate release opioids. Similarly, it may be appropriate to leave implanted analgesic pumps throughout the perioperative period and use additional short-acting opioids and non-opioids to control breakthrough pain.

12.4 Non-opioid analgesia

Non-opioid analgesic drugs and local anaesthetic procedures will have the effect of reducing opioid requirements – 'opioid sparing effect' (e.g. non steroidal anti-inflammatory drugs (NSAIDs), Paracetamol and Clonidine). Local anaesthetic blocks such as epidurals, brachial plexus block, paravertebral or ilioinguinal blocks will also have an 'opioid sparing' effect.

12.5 Effects of surgery

Surgery itself will have a variable effect on opioid requirements and parenteral routes will have to be considered if the oral route is not available. It is difficult to predict the precise post-operative analgesic requirements because the effect of surgery may be to increase (if the surgery results in pain due to local tissue trauma) or decrease opioid requirements. Increases of 20% or more above the baseline opioid requirement have been reported, depending on the surgical procedure. However, surgery may alleviate pain due to the removal of direct tumour pressure effects on local structures (e.g. the removal of a retroperitoneal sarcoma tumour pressing on the lumbosacral plexus). In this group of patients, opioid requirements may reduce but they will still need baseline opioid administration.

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Chapter 13 Complex problems in cancer pain

Summary

Cancer pain is often very complex, but the most intractable pain is often neuropathic in origin, arising from tumour invasion of the meninges, spinal cord and dura, nerve roots, plexuses and peripheral nerves. Accurate diagnosis of the causes of pain is necessary with the use of multimodal therapies. Case studies illustrate some of these points.

13.1 Introduction

Cancer pain can be complex and difficult to treat. Up to 50% of patients may have pain at diagnosis, and greater than 75% may experience pain with advanced cancer.

- Pain may occur in more than one site in over half of cases and may have different aetiologies. Such complexity can be challenging and require a truly multidisciplinary approach. As for non-malignant pain, the management of cancer pain can be challenging for the very young or old, for patients with medical problems such as heart disease, respiratory disease, renal or liver compromise and for those with mental health issues. Often these factors may present in combination and generate demanding clinical problems.

- Certain pain problems related to the nature of the pain or patient factors may make the conventional WHO ladder approach to pharmacological therapy difficult to utilise and, in some cases, this approach may not be totally effective. Other pharmacological or more invasive treatments may be required.

To exemplify these complex issues, we will discuss case studies concerning:

- The problems of breakthrough pain.
- Cancer pain control in patients addicted to opioids.
- The treatment of pain of mucositis.
- Cancer pain in patients with dementia.
- Alternatives to the conventional WHO ladder approach.
- Interventional procedures.
- Ketamine.

13.2 Breakthrough pain

- Breakthrough pain has been referred to as a brief exacerbation of pain on a well-controlled baseline. The terminology of 'breakthrough pain' is undergoing subtle revisions, but is made up of many different types of pain. Breakthrough pain can be of any aetiology. Certain authors feel that 'breakthrough pain' does not include exacerbations of pain in the titration phase, nor should an end of dose exacerbation of pain be called 'breakthrough' (William, 2008).

Breakthrough pain can be divided into

- Spontaneous: no obvious cause.
- Incident pain: clear cause evident.
- Non volitional: pain caused by an involuntary act.
- Volitional: pain caused by a voluntary act.
- Procedural: pain caused by a therapeutic procedure.

As for any cancer pain, treatment relies on detailed assessment and formulation of a multidisciplinary therapy plan. Rapid acting opioids have been successfully used to treat breakthrough pain, but it remains a difficult therapeutic problem. Newer preparations of rapid release opioids are being developed.

Case study (breakthrough pain)

A 77-year old man with metastatic cancer of the prostate was admitted to hospital for pain control. He had been treated for severe back pain and was receiving 30 mg Oxycontin b.d. with 10mg Oxynorm when required. He had significant renal impairment (creatinine 340 mol/l) and a history of a previous myocardial infarction. His main complaint was a significant worsening of pain on walking, which would keep him in agony for an hour after walking and meant that he was reluctant to get his usual morning paper. He tried taking the Oxynorm before going out, which helped with the pain but made him sleepy for the rest of the morning. He was titrated up with oral transmucosal fentanyl to be used just before walking, and found that 400 µg was sufficient to enable him to walk without causing increased drowsiness.

Case study (breakthrough pain)

A 68-year old female with metastatic breast cancer, including bony disease in thoracic and lumbar spine, was admitted to hospital from home for pain control. Whilst in hospital, she received palliative radiotherapy and a review of analgesics by the palliative care team. She was taking regular opioids and gabapentin. Physiotherapy assessment was requested because the patient was keen to return home, but needed to mobilise short distances indoors. The patient's pain was well controlled at rest, but she experienced significant breakthrough pain (volitional incident pain) whilst transferring out of bed and on mobilising.

Her physiotherapy intervention included:

- TENS machine: the patient was taught where to place pads in the thoracic and lumbar area and she was advised to use this on the conventional mode. She started treatment 30 minutes prior to getting out of bed and continued whilst mobilising.
- Relaxation: the patient was taught simple diaphragmatic breathing exercises to help her prepare for mobilising.
- Mobility work: timed with the use of the Fentanyl lozenge and mobility with a Zimmer frame to assist weight-bearing. Pacing techniques were used to gradually increase the distances covered.
- Using the above techniques ensured that the patient was able to get out of bed independently and mobilise short distances (<10metres) using her walking aid.

13.3 Pain in opioid addiction and substance misuse

- In the UK, the prevalence of drug misuse is around 9 per 1,000 of the population aged 15-64 years, and around 3 per 1,000 injected drugs in the case of most opioids. Opioid abuse and dependence are associated with a wide range of problems, including overdose, HIV infection, Hepatitis B or C, thrombosis, anaemia, poor nutrition, dental disease, infections and abscesses, criminal behaviour, relationship breakdown, unemployment, imprisonment, social exclusion and prostitution.

13.3.1 Pain from cancer in people who are addicted to opioids may be under-treated for the following reasons:

- Lack of understanding of opioid addiction and methadone maintenance.
- Lack of training on prescribing analgesia in this group of patients.
- Attitude of healthcare professionals about illicit drug users; fear of diversion.
- Failure to recognise the potential for tolerance to other opioids in Methadone-maintained patients.
- Acute pain may be under-treated leading to misunderstandings, patient anxiety, depression, dissatisfaction and complaints.

13.3.2 Principles of giving analgesia in opioid-addicted patients:

- Prevent withdrawal symptoms/complications.
- Assess opioid load (in an intravenous (i.v.) drug user this is difficult; withdrawal symptoms can be prevented using low doses of opioids).
- Diagnose the cause of the pain: nociceptive, inflammatory, neuropathic, visceral, mixed.
- Use balanced analgesia wherever possible: NSAIDs, paracetamol, local anaesthetics, tricyclic antidepressants, anticonvulsants.
- Use oral/ transdermal/ subcutaneous routes, rather than intravenous ones. Consider epidural or intrathecal drug delivery systems, remembering the infection risk.
- Use long-acting opioids and minimise analgesia for breakthrough, as this may be rapidly escalated. Set a limit and review frequently. Use tablets (Sevredol, Oxynorm) for breakthrough pain, not Oramorph.
- Make a "contract" with the patient before starting therapy, explaining the limitations and setting a clearly defined upper limit of opioids before the next review. Write clear instructions for the whole team.
- Use a sole prescriber (usually GP). Prescriptions may have to be issued daily, every 2 -3 days or weekly.
- Use psychological therapies and treat anxiety and depression.

13.3.3 Maintenance Therapy

Methadone substitution is the primary maintenance treatment in the UK, usually 60-120 mg daily. There may be tolerance to other opioids, and a rapid escalation of doses can be dangerous, especially when combined with alcohol or other sedative drugs.

Naltrexone (opioid antagonist) is used in detoxification programmes to help maintain abstinence. It is long acting (>48hrs) and will lead to opioid resistance and then opioid sensitivity when it has been eliminated systemically.

Buprenorphine (partial agonist) is also used to prevent withdrawal symptoms in opioid dependent patients. Its action on the μ receptors reduces the effects of any additional opioids. Average maintenance doses range between 12 and 24 mg daily. Patients with severe cancer pain may have to be changed from buprenorphine to methadone.

Case Study (opioid addiction)

A man of 52 years was admitted to a hospice from prison. He had been an i.v. drug user and had hepatitis B and C and carcinoma of the lung. He was complaining of severe upper chest pain and neuropathic pain radiating down the right arm. There were no focal neurological abnormalities. He had had radiotherapy and chemotherapy. No further treatment of his cancer was planned. He was due to return home after this admission for symptom control. He denied taking drugs while in prison, and was not on methadone, but morphine sulfate slow release (MST) 300mg b.d. and Oramorph, which had escalated from 200mg to 600mg daily over a 48-hour period. Despite this, the pain had not been relieved.

Adjunct therapy: gabapentin 600mg tds, amitriptyline 50mg, diazepam 10mg tds.

An agreement was made that oramorph was ineffective for his pain and would be stopped completely. MST was halved to 150 mg b.d. and methadone 10 mg b.d. started. Over two weeks, his MST was reduced gradually and stopped and methadone increased to 60mg b.d.

His pain was controlled and he left the hospice with only paracetamol for breakthrough pain and strict instructions not to increase methadone without medical advice.

(NB. Alcohol should not be used while switching to methadone from other opioids because cases of sudden death have been reported.)

13.4 Mucositis

Mucositis is the painful inflammation and ulceration of the mucousmembranes, which usually occurs in the mouth but can affect other areas of the mucosa in the gastro-intestinal tract (Trotti, 2003; Clarkson, 2007). It can be caused by radiation therapy or chemotherapy and is very common after radiotherapy for cancer of the head and neck and after certain types of chemotherapy, such as 5-fluorouracil. High-dose chemotherapy and hematopoietic stem cell transplantation have an especially high incidence of oral mucositis (Sonis, 2004; Clarkson, 2007).

- Non-pharmacological treatment strategies include meticulous oral hygiene, gel-based barrier protection, the reduction of known painful precipitants (e.g. alcohol), local anaesthetic mouth washes and other oral lubricants. Opioids provide the mainstay of pharmacological treatment, but newer anti-inflammatory therapies are being developed. However, severe oral mucositis often causes difficulties in swallowing, precluding the use of oral medication.

Case study (mucositis)

A 36-year old man with acute lymphocytic leukaemia developed grade 3 mucositis (unable to eat solids) 7 days after an autologous stem cell transplantation. Although he had little pain most of the time, severe pain prevented him eating, and drinking was very uncomfortable. He had been put on regular four-hourly Oromorph, which helped with the pain, but he was reluctant to take it because this hurt so much and he was unhappy at being drowsy. Barrier gel helped slightly, but he was still unable to tolerate much oral intake. A morphine patient controlled analgesic (PCA) device was used with a 2 mg bolus, 5 min lockout time, without a background infusion. By using the PCA, he managed to accept a soft diet and experience very little drowsiness. He continued the PCA for 5 days until the mucositis was healing.

13.5 Pain in Dementia sufferers

Adults with dementia will probably express their pain in ways that are quite different from their cognitively intact counterparts, which can result in inadequate pain assessment and consequently poor pain management.

The processing of sensory-discriminative aspects of pain in the brain are thought to occur in the lateral pain system, whereas motivational-affective aspects are processed by the medial system. The recognition of these two systems is important when dealing with patients with dementia. Pain thresholds (which are the sensory-discriminative aspects) do not differ between patients with Alzheimer's disease and those older adults without dementia, although pain tolerance (motivational-affective aspect) does. Older adults with Alzheimer's disease perceive the presence of pain, but the intensity and affective aspects are different to those experienced by their cognitively intact counterparts. This might explain the atypical behavioural responses observed in this group.

Observation of the behaviour for pain assessment in patients who do not have the ability to communicate their pain can be helpful, but typical pain behaviours may be absent or difficult to interpret. The involvement of healthcare professionals, informal care providers and the family in the identification of pain is essential.

The American Geriatric Society (2002) lists 6 categories of pain behaviours and indicators for older people with dementia:

- Facial expressions.
- Verbalisations and vocalisations.
- Body movements.
- Changes in interpersonal interactions.
- Changes in activity patterns or routines.
- Mental status changes.

A number of behavioural pain assessment tools exist for detecting the presence of pain in patients with dementia. Care providers are advised to select a tool that is appropriate to the patient and that can be used for initial and ongoing assessments. However, the assessment of behavioural pain indicators should consider only one strategy to identify pain in patients with dementia, and should be used in conjunction with other pain assessment strategies and the evaluation of pain relieving interventions.

Case study (dementia)

A 63-year old woman with disseminated breast carcinoma and a previous history of Alzheimer's disease was admitted after becoming unwell at home. She had previously been on 20 mg Zomorph (sustained release morphine) twice a day for pain associated with lumbar spinal metastasis. Severe constipation and a urinary tract infection were diagnosed and after two days of treatment, her family said that she was returning back to normal. Opioids were switched to 10 mg Oxycontin (sustained release oxycodone) twice a day. However, on the 3rd day she became withdrawn first towards staff and then towards her family, and became reluctant to get out of bed, often shouting out when this was attempted. She refused any type of examination. After careful assessment, it was recognised that she was in pain and she agreed to take 10mg Oxynorm (immediate release oxycodone) liquid. Half an hour later, she started interacting with her family and staff. She then allowed examination and tenderness was elicited in her right groin. A pelvic X-ray revealed a pathological fracture of her right pubic ramus.

13.6 Use of interventional techniques

- Invasive techniques provide analgesic possibilities when conventional treatments fail. This might be because of the unacceptable side-effects of opioids, or if the pain is less opioid sensitive. Spinal and epidural infusions can be highly effective in relieving refractory severe pain, albeit requiring anaesthetic input and specialist equipment.

- Nerve blocks add to the treatment options available for pain that is challenging to manage, although achieving long-term benefits can be problematic. Nerve ablation provides a method of sustained relief, but increases the risk of side-effects. Direct tumour ablation or cement fixation of metastatic bony disease is being used more frequently for bone pain, with good results (Gangi, 1994, 2003).

- Interventional techniques are by definition more invasive, often requiring nursing and medical input, and are associated with potential side-effects and problems. However, the possibility of analgesia often outweighs the risks in patients with uncontrolled pain. Although the evidence base for many of these interventions is limited and some is extrapolated from other studies of cancer pains or nonmalignant pain, interventional techniques are used extensively, safely and effectively (see chapter 8). They form an integral part of the multidisciplinary approach to cancer bone pain management, and their early consideration may often be warranted.

Case study (interventional management)

A 57-year old man with a history of metastatic colonic carcinoma was admitted to an acute hospital with a pathological fractured neck of femur. His pain was difficult to control with opioids and NSAIDs, especially the pain on movement. The acute pain team inserted an epidural catheter. Unfortunately the block was unilateral, blocking the uninjured side and decreasing mobility without any meaningful analgesia for the fractured limb. The fracture was considered inoperable and the patient was transferred to a specialist cancer hospital for consideration of further treatment. Analgesia continued to be problematic. High doses of morphine managed to reduce rest pain, but were associated with increased somnolence and continuing constipation. The patient was unwilling to have another epidural catheter due to a fear of a repeated unilateral block. After discussion, the patient was offered a lumbar plexus catheter, which was inserted easily when the patient was awake using only local anaesthetic. A bupivacaine (0.1%) and fentanyl (2mcg/ml) infusion at 10ml/hr into the lumbar plexus achieved good pain relief at rest and on movement. The increased analgesia on movement and the retained motor strength on the uninjured side allowed the patient to mobilise.

13.7 Atypical pharmacological treatments: ketamine

- The N-methyl-D-aspartate (NMDA) receptor has been implicated in mechanisms of neuropathic and inflammatory chronic pain. It is one of the key components of central sensitisation that contributes to increased pain and abnormal pain perception. It is also thought to be involved in many cancer pains. When the conventional WHO ladder approach fails, NMDA receptor antagonists could provide a novel and powerful site of analgesia.

- There is evidence for the efficacy of NMDA receptor antagonists in many chronic pains (including cancer pain), yet the situation is not so clear from a clinical perspective. There are few NMDA receptor antagonists available. Dextromethorphan has been used for acute pain. Methadone also has some NMDA antagonist activity and may help in some cases of opioid refractory pain. However, ketamine is the most used NMD receptor antagonist for cancer pain.

- Ketamine is an anaesthetic, but in smaller doses appears to have analgesic properties. There are many case reports and case series demonstrating significant efficacy in refractory cancer pain, either alone or concomitantly with opioids. However, there is little higher quality evidence (such as RCTs) at present. The lack of data is reflected in the variability of suggested protocols in both dose and route of administration. Side-effects are potentially problematic, including tachycardia and cognitive disturbances such as hallucinations. Nevertheless, ketamine may provide some empirical benefit in refractory cancer pain.

Case study (ketamine)

A 41-year old man with recent diagnosis of myeloma was undergoing investigation prior to chemotherapy. He was noted to have a creatinine of 250 mmol/l. While an in-patient, he experienced sudden extreme and severe pain in the centre of his centre chest after minimal trauma. An X-ray confirmed a fracture of his sternum. Parenteral (i.v.) opioids were only partially effective and were associated with dizziness, sickness and sleepiness. NSAIDs were not considered in view of his renal impairment. Use of i.v. ketamine bolus (0.15 mg/kg) followed by a continuous infusion (1mg/kg/hr) rapidly brought the pain under control to allow an MRI scan. After 36 hours of infusion, he was assessed for and received a thoracic epidural. The ketamine was stopped and 0.15 % bupivacaine with 4 mcg/ml fentanyl was infused at 10 ml/hr to give good analgesia. The epidural remained in situ for 5 weeks until sternum was healing well, although a persistent pyrexia and subsequent MRI scan showed the complication of an epidural abscess. This resolved on conservative management.

Case study (ketamine)

A 37-year old woman with previous cancer of cervix and a recurrence three years ago (treated with chemotherapy and radiotherapy) was admitted for the relief of severe back pain. This had made her unable to get out of bed. She also had a previous history of degenerative back disease and long-term steroids. She had been given 20 mg 4 hourly of Oromorph by her GP, which made her sick. Investigation diagnosed vertebral collapse of her 4th lumbar vertebra. Pain was controlled with i.v. ketamine in the acute phase. Subsequently, she had a tunnelled intrathecal catheter inserted with an implanted pump that infused intrathecal diamorphine. She was pain free and managed to mobilise well. She was referred for vertebroplasty and in the interim managed to go home with the pump in situ.

13.8 Pain in children and adolescents with cancer

Pain in children and adolescents with cancer is a significant, debilitating, acute and chronic symptom during or after treatment that affects the quality of life of young patients and their families. In recent years, advances in pain management have been made; however, pain remains often under-treated and there is a need for improvement.

The principles of pain management and palliative care in adult practice are relevant to paediatrics; nevertheless, the adult model cannot be applied directly to children for the following reasons (McCulloch, 2008):

(a) The types of malignancy and disease trajectory in children are different from those in adults;

(b) Special considerations are required when selecting analgesics, doses and modalities during childhood. Factors that influence prescribing are quite distinctive from adults and include metabolism, renal clearance, changing size and surface area and the ability to manage medication, among others;

(c) A child's family and social context is different to that of an adult: relationships with parents and siblings, school and friends and the extended family network are of paramount importance when treating young patients;

(d) A child's developmental stage and continuous psychological, spiritual and cognitive development need to be taken into account when treating their pain (e.g. a child's conceptualization of what causes and eases pain, their understanding of time and their ability to implement behavioural and cognitive strategies for coping with pain);

(e) The legal and moral positions regarding the decision-making ability of both those with parental responsibility and the child/ young person themselves is very different to those of an adult.

Effective pain management in children and young people with cancer requires that paediatric healthcare providers take into account the multitude of physiological and psychological changes that occur from infancy through adolescence, including changes in relationships with parents (Wolfe, 2000). The multidisciplinary approach to providing pain management for children and adolescents includes integrating pharmacological and psychosocial care in the context of each patient's physical, cognitive, emotional and spiritual level of development (Liossi, 2002).

Every child/ young person with pain management and palliative care needs should have access to universal paediatric services, core palliative care services (hospice, community palliative care nurses) and specialist palliative care support when required (Department of Health, 2005).

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Chapter 14 Cancer pain: recommendations for service design and training

Summary

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 in the training programmes of doctors, but also in established teams in terms of funding and time for joint working, and in the education of all healthcare professionals involved in the treatment of cancer pain.

14.1 Surveys of working with Pain Management and Palliative Care

- Despite the recognised need for improved pain management in palliative care, there is currently inconsistent partnership between the specialities of pain medicine and palliative medicine.

- A national survey of pain management services in palliative care was conducted in 2002 by Linklater, who sent a postal questionnaire to all consultant members of the Association for Palliative Medicine, asking whether they had contact with a pain management specialist. Most respondents had access to "as-required" anaesthetic pain consultations, with 72% feeling that the frequency of consultation was adequate, but 20% desiring more frequent input. 15% had access to regular weekly sessions; trainee anaesthetists featured in only 7% of sessions. Half the respondents used pain management advice less than four times a year. All respondents felt that the anaesthetist's input involved advice on performing practical procedures, but only 25% felt that a joint consultation about analgesic therapy would be useful. The authors advocated the establishment of a regular weekly session with a pain specialist, and their experience showed that this rapidly increased the number of referrals to 11% of in-patients, with procedures performed on 8% and advice given on 3% of cases.

- A survey of anaesthetists in UK clinics was conducted in 2007 by Kay using a postal questionnaire and they found that referrals rates from palliative medicine to pain clinics were low; only 31% of respondents received more than 12 referrals per year. Only 25% of anaesthetists' job plans had time allocated for palliative medicine referrals, and joint consultations were rare.

- A 2007 survey of hospices and palliative care units in England (Petrovic, personal correspondence) has shown that, while 92% of palliative care units have access to specialist pain management advice, only 16% have regular sessions; the situation has not changed over the past 5 years, despite the increasing complexity of illness. Only 41% of pain services provided a comprehensive range of pain treatments, including non-invasive therapies such as TENS and minimally invasive therapies such as acupuncture and trigger point injections, and in about 50% of palliative care units, neuraxial infusions are not available. There are distinct barriers to sending patients home with invasive therapies related to multiple factors, but particularly to a lack of training and the experience of the home care team and drug supply issues.

14.2 Barriers to links between specialist pain management and palliative medicine

These can be summarised as follows:

- Short survival of patients following referral to palliative care services.

- Funding of the service.
- Time on the part of the pain specialist for proper assessment and discussion.
- Facilities for performing interventions may not be easily accessible.
- Complexity/lack of real understanding.
- Staff training in the management of pumps and catheters.
- Pharmacy issues; procurement of solutions/ availability of preservative free opioids/ lack of sterile facilities for making up infusions.
- Cost of implanted devices.
- Who is going to manage neuraxial infusions at home?
- Lack of availability of pain specialists out of hours.
- The palliative care doctor may be unaware of potential benefits/ unsure how to access expertise.
- The pain doctor may not be adequately trained in the management of cancer pain/ selection of an appropriate technique.

There are examples in the literature of improved treatment outcomes from a multidisciplinary cancer pain clinic. A Danish study in 1991 showed an improvement in pain scores in over 50% of patients using medical pain treatment supplemented by analgesic tailoring, epidural opioid therapy, non-neurolytic blockades and combinations of these (Banning, 1991).

14.3 What can specialist pain management offer in palliative care?

- Assessment of complex cases.
- Detailed knowledge of the neurophysiology of pain.
- Specialist knowledge of treating different types of pain (e.g. neuropathic pain, complex regional pain syndrome).
- Interventional techniques.
- TENS, acupuncture.
- Psychological aspects of pain management.
- Provision of sedation.
- Management of non malignant pain.
- Recognition and advice about dependency and addiction.
- Withdrawal from opioids.

14.4 What can palliative medicine offer to specialist pain management?

- Detailed knowledge of using opioids.
- Management of opioid toxicity.
- Understanding of cancer pain and all cancer treatments.
- Excellent communication skills.
- Team working.
- Family therapy.
- Holistic medicine.
- Home care.
- End of life care.

14.5 Improving collaboration

Palliative medicine has been a recognised speciality since 1987, when speciality training programmes were established by the Royal College of Physicians. Funding of the speciality was further enhanced as a result of the Calman-Hine report in 1995, when palliative care was integrated with cancer services. Pain medicine is not yet a recognised speciality, although a Faculty of Pain Medicine of the Royal College of Anaesthetists was established in April 2007 to set and uphold standards in the training of doctors practising pain medicine in the future. Cancer pain management will be an essential part of this training. Interventional pain control is also a vital part of the training of palliative medicine doctors, thus providing hope for enhanced collaboration in the future. The training requirements detailed in 14.6 will enhance the knowledge of doctors in the future about pain management and palliative care. It is hoped that similar provision will be made in the training programme of medical oncologists.

It is important that nurses, physiotherapists, pharmacists and other healthcare professionals will also introduce the principles of multimodal pain management into their curricula.

14.5.1 Other ways in which collaboration can be improved

- Regular funded sessions for the pain specialist to work in palliative care, whether in hospital, the community or a hospice.
- Regular discussion about individual cases.
- Timetabled attendance of all types of healthcare professionals on joint ward rounds and at multidisciplinary meetings.
- Joint educational seminars, local and national.
- Joint national and international meetings (e.g. British Pain Society Annual Scientific Meeting, World Congress on Pain).
- Joint research projects and publications.

- Provision for out-of-hours management of neuraxial infusions should be decided by local protocols and agreement.

There is no doubt that the management of cancer pain could and should be improved by the breaking down of professional barriers between disciplines, not only of doctors, but also of nurses and other professional bodies. The hospice movement in the UK can lead to professional isolation, so more effort needs to be made to establish coherent, funded, collaborative pain services. The training of pain doctors must include a significant time devoted to the management of cancer pain.

14.6 Education and training

The Specialist Advisory Committee for Palliative Medicine at the Royal College of Physicians is responsible for the curriculum for trainees in palliative medicine and includes such topics as physiology, the management of chronic pain, nerve blocks, the management of spinal catheters, opioid dependency and the psychology of pain.

The Faculty of Pain Medicine of the Royal College of Anaesthetists was established in April 2007 to set and uphold standards in the training of doctors practising pain medicine. The curriculum for advanced pain trainees is not yet finalised, but there is a clear intention to improve training in the management of cancer pain and trainees must acquire experience of interventional techniques and know when to apply them.

There are MSc courses available in pain management and palliative care. A joint course on interventional pain control in cancer pain management is held annually between King's College Hospital and St Christopher's Hospice.

National scientific meetings are held by the British Pain Society (www.britishpainsociety.org) and the Association for Palliative Medicine (www.palliative-medicine.org), and international meetings are held by the International Association for the Study of Pain (www.iasp-pain.org) and the European Association for Palliative Care (www.eapcnet.org).

14.7 Research agenda

There is a need for further study in the following areas:

- Better understanding of the basic mechanisms of cancer pain (visceral, neuropathic and bone pain).
- Researching ways of implementing existing knowledge into routine practice (e.g. pain assessment, feeding assessment data to clinicians, the use of prescribing protocols).
- Review and standardise the methodology for evaluating non-pharmacological interventions in cancer pain.
- Understanding mechanisms through which patient based education on cancer pain and analgesia works (e.g. does it improve medication adherence, reduce anxiety by allying fears, increase coping, etc.?).
- Clinical trials of add-on therapies (e.g. are combination opioids better than mono-opioid therapy?).
- Building capacity to undertake clinical studies in cancer pain management (e.g. investing in academic departments to support pain management and palliative medicine, identifying CLRNs and cancer research networks that can undertake these trials, increase opportunity for PhD studies in cancer pain management).

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