An examination of verbal descriptors of Cancer-Induced Bone Pain and Neuropathic Cancer Pain

By

Anne Todd BA (Hons), RGN

Submitted to the University of Glasgow for the Degree of Master of Science by Research in the College of Medical, Veterinary and Life Sciences

September 2016

Abstract

Aims: The aim of the thesis was to identify verbal descriptors of cancer induced bone pain (CIBP) and neuropathic cancer pain (NCP). An examination of the verbal descriptors associated with these two pain syndromes further considered the relationship between common verbal descriptors, cancer type, performance status and analgesia.

Methods: The project was conducted in two phases; Phase one was a systematic review of the literature to examine current evidence of verbal descriptors in CIBP and NCP. Phase two utilised secondary data analysis methodology. Data from 120 patients with confirmed CIBP and 61 patients with confirmed NCP were deemed eligible for entry into a de novo database for secondary analysis. Key descriptive data were considered such as gender, ECOG and pain scores to characterise the patient population. Verbal descriptors of CIBP and NCP were considered in detail across the secondary de novo database.

Results: Gender was not identified as a diagnostic characteristic of CIBP and NCP with similar distribution across prevalence of pain reporting and also pain severity. Patients with breast (n=52,43.3%), prostate (n=35,29.2%) and lung (n=14,11.7%) cancer were found to be at an increased risk of CIBP. Those with NCP more was found more commonly among patients with breast cancer (n=21,34.4%). Patients with CIBP were found to have an ECOG performance of 1 (n=49, 40.8%) or 2 (n=43, 35.8%) which was lower than those with NCP with an ECOG of 0 (n=32, 52.5%) or 2 (n=18, 29.5%). Comparisons were made across analgesia and treatment options for CIBP and NCP. Patients with CIBP received a greater variety of treatment options including bisphosphonates and radiotherapy while patients with NCP were more commonly treated with analgesia alone. Patients with CIBP and NCP were taking strong opioids, however those with NCP (n=45, 73.8%) were more likely to utilise strong opioids than those with CIBP (n=61, 50.8%). It was noted that those with NCP required a daily morphine equivalence of almost 50% higher than those with CIBP. Average consumption of opioids was 155.6mg, for patients with NCP, compared to 76mg in patients with CIBP. Common verbal descriptors of CIBP and NCP were identified. The most common verbal descriptors for CIBP were aching, gnawing and throbbing and the most common verbal descriptors of NCP were aching, tender and sharp. Of the most common 6 descriptors for CIBP and NCP only one descriptor was unique to each pain type, gnawing for CIBP and stabbing for NCP.

Conclusions: Patients with CIBP and NCP use similar verbal descriptors to characterise their pain with gnawing being unique to CIBP and stabbing being unique to NCP in the data considered within project. Further research is required to explore verbal descriptors which are both common and unique to CIBP and NCP. Further exploration of verbal descriptors would assist development of a comprehensive pain assessment tool which would enhance pain assessment for nurses, clinicians and patients.

List of Tables

List of Figures

Acknowledgements

This project would not be complete without the help and support of a number of people and to all I am most grateful.

I owe my most grateful thanks to Professor Marie Fallon and Dr Barry Laird for affording me the opportunity to undertake this MSc project and to Dr Barry Laird and Professor Lorraine Smith for their support, supervision and guidance throughout the first phase of the project.

My most grateful thanks are extended to Dr John Walley and Dr Angela Scott who very kindly allowed me access to their datasets required for this project.

I also wish to thank Gillian McHugh for statistical guidance and advice during my initial analysis of the various datasets.

I would like to make special thanks to Dr Anna O'Neill for her guidance and support during the final phase of this project. Without her encouragement, support and guidance I would not have recommenced my studies. I am most indebted to Dr O'Neill for her patience, understanding and time as I navigated writing up following an extended break in my studies.

Finally, I wish to thank my family for their support and to my parents for their helpful proof read. To my husband Chris for his continued support and to my daughter Rebecca for making me realise anything is possible.

Declaration

I declare that the thesis does not include work forming part of a thesis presented successfully for another degree. I declare that the thesis represents my own work except where acknowledged to others.

List of abbreviations

BPI	**Brief Pain Inventory**
CIBP	**Cancer Induced Bone Pain**
CTA	**Clinical Trial Authorisation**
ECOG	**Eastern Cooperative Oncology Group**
GCP	**Good Clinical Practice**
GP	**General Practitioner**
LREC	**Local Research Ethics Committee**
MEDD	**Morphine Equivalent Daily Dose**
MPQ	**McGill Pain Questionnaire**
NCP	**Neuropathic Cancer Pain**
NRS	**Numerical Rating Scale**
SDV	**Source Data Verification**

Table of Contents

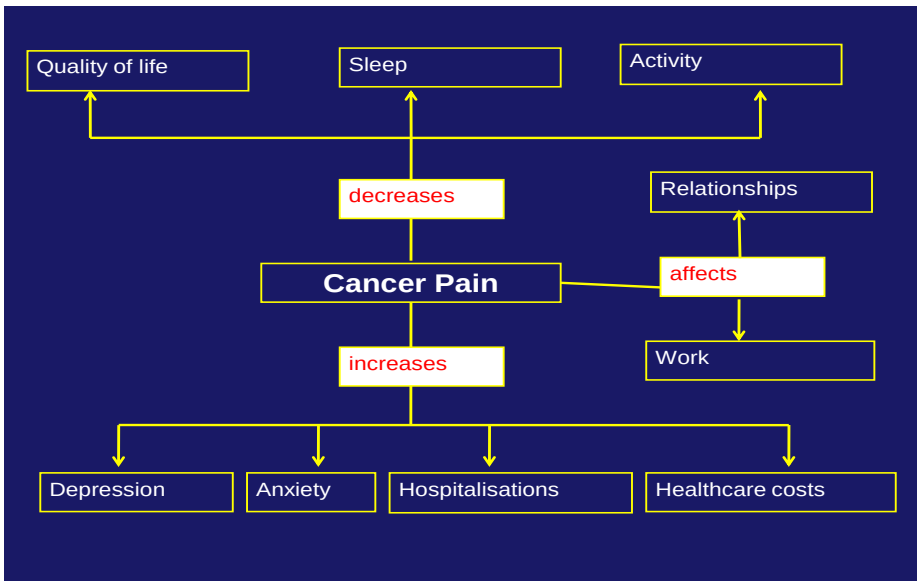
Chapter 1.

1.1 Introduction

As medicine advances and treatment options improve, patients with cancer are living longer. Consequently, the patient population changes and cancer becomes similar to a chronic disease. As such the role of the healthcare provider must modify to reflect these changes (Little 2000).

I have worked within oncology for almost twelve years. During this time, I have come to understand the enormous impact of poorly controlled cancer pain on the patient. It can adversely affect mood and exacerbate other symptoms, ultimately adversely affect quality of life. Family and caregivers often feel that death would be welcome when patients have difficult cancer pain (Coyle and Sculco, 2004). Figure 1 highlights the various aspects of daily living which can be adversely affected by poorly controlled cancer pain.

Figure 1 - Consequences of cancer pain



The prevalence of cancer pain varies due to poor standardisation of assessment (IASP 2008). It is estimated that 50% of patients with cancer will experience pain during the early stages of their disease which rises to 75% in those with advanced

disease. In cancer, pain can be as a result of treatment, the cancer itself or unrelated causes such as pre-existing conditions (IASP 2008).

The most common types of cancer pain are cancer induced bone pain and neuropathic cancer pain, hereafter described as CIBP and NCP (Caraceni and Portenoy, 1999, Nersesyan, 2007). It has historically been reported that the prevalence of CIBP and NCP, are 35% and 34% respectively (Grond S, 1996).

Although CIBP and NCP are common, they are often difficult to manage (Grond S, 1996). Whilst the majority of cancer pain can be effectively controlled in 80-90% of patients, CIBP and NCP are more difficult to manage effectively (WHO 1996). Standard analgesics can have limit of use as patients experience intolerable side-effects at the doses required to relieve pain (Campbell, 2011).

1.2 Personal experience

Previously I worked as a palliative care research nurse with patients participating in clinical trials. These trials were investigating novel treatments for CIBP and NCP. This position has afforded me the opportunity to assess the needs of this patient group and further allowed me to observe the adverse effects associated with pain treatments. I have, however, been surprised by the number of patients who experience considerable pain on a daily basis and accept this as part of living with cancer. I had not anticipated this level of acceptance amongst patients. From my experience many patients describe accepting pain as an inevitable compromise for living longer. One patient described pain as "I just accept nothing's taking it away and I just have to put up with it." Others feel pain is a constant reminder of the cancer, and some even feel pain may indicate the cancer is progressing. One patient became quite upset when describing her pain as she feels "On days when the pain is worse I'm sure it's (the cancer) spreading".

I realised the importance of pain for the patient and considered if cancer pain such as CIBP and NCP, could be better managed. Clearly, this can only occur if pain is recognised and routine pain assessment encompasses this. Whilst health professionals tend to want patients to quantify pain (for example rate pain on a numerical rating scale e.g. 0-10, where 0 is no pain and 10 is the worst pain imaginable), such measures are less likely meaningful to patients. As CIBP and NCP are both common and difficult to treat it is imperative that these are identified

promptly. Initial reading led me to the conclusion that there was a paucity of evidence regarding the assessment of CIBP and a moderate degree of evidence regarding the assessment of NCP. A number of studies have been conducted and a wealth of data on cancer pain has been collected, but data on verbal descriptors is less common. An accurate appreciation of verbal descriptors of CIBP and NCP would complement what is already known and perhaps enable nurses and other health care providers to enhance the clinical assessment of these difficult cancer pain types.

1.3 Objective

The overall objective of this study was to identify verbal descriptors of CIBP and NCP.

1.3.1 Secondary objectives

The study was designed to achieve this objective in two phases by examining the current evidence base on verbal descriptors of CIBP and NCP in phase one and through examination of a pre-existing dataset where information on verbal descriptors were available in phase two.

Secondary objectives were:

1. Identification of the verbal descriptors more commonly associated with CIBP. This was achieved by conducting a systematic review of the existing literature in phase one (Chapter 5) and by performing an analysis of a pre-existing dataset in phase two (Chapter 7).

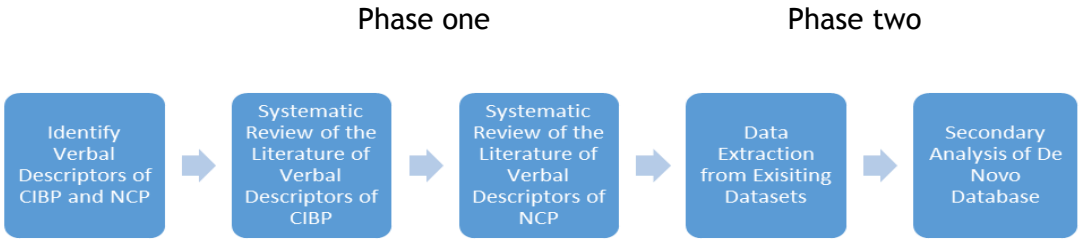
2. Identification of the verbal descriptors more commonly associated with NCP. This was achieved by conducting a systematic review of the existing literature in phase one (Chapter 6) and by performing an analysis of a pre-existing dataset in phase two (Chapter 8).

3. Examination of the relationship between pain intensity and gender, cancer type, performance status and analgesia in phase two through data analysis of a pre-existing dataset (Chapter 9).

4. Examination of any common or unique verbal descriptors of CIBP and NCP in phase two through data analysis of a pre-existing dataset (Chapter 9).

The study aims and design are summarised below in **Figure 2**;

Figure 2 - Study schema



1.3 An overview of CIBP and NCP

The aim of this study was to examine the verbal descriptors of cancer pain types, CIBP and NCP. This section provides a brief overview of cancer pain with a greater focus on CIBP and NCP.

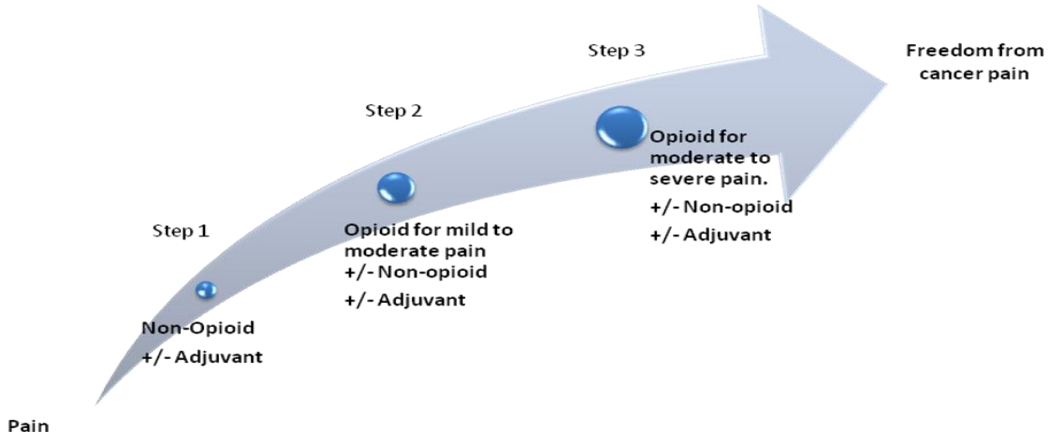
1.3.1 Introduction

In 2008 there were 309,500 new cases of cancer diagnosed within the UK ((CRUK), 2011) and 156,000 deaths from cancer accounting for 37% of all deaths in the UK (W.H.O, 2009, CRUK, 2008). Patients with cancer often have many symptoms and a study of 1000 patients with advanced cancer showed that a median of 11 (range 1-27) cancer-related symptoms were present (Walsh, 2000). These symptoms include nausea, fatigue, cachexia and pain amongst others; however, pain is the most common symptom. It is estimated that around 90% of cancer patients' experience pain during their illness (Caraceni, 1999). There are many causes of cancer pain and this can be related to the underlying disease or cancer treatment. Pain can be affected by psychological factors such as mood, anxiety or depression, it can adversely affect performance status and cause emotional and spiritual distress (Vainio, 1996, IASP, 2008). Although there are many types of cancer pain,

CIBP and NCP are the most common occurring in 35% and 34% respectively of patients with cancer-related pain (Caraceni and Portenoy, 1999, Grond S, 1996).

Treatment of cancer pain is supported by the World Health Organisation (WHO) analgesic ladder, see Figure 3 (Azevedo Sao Leao Ferreira et al., 2006). It was developed in the early 1980's and has been widely employed in the treatment of cancer pain. It is reported that, when used appropriately, 80-90% of cancer pain can be adequately controlled (WorldHealthOrganization, 1996).

Figure 3 - WHO analgesic ladder



Although cancer pain can be successfully managed using the WHO ladder, CIBP and NCP are more difficult to control (Grond et al., 1999). For CIBP and NCP, the effectiveness of analgesia is variable for each patient. Opioids are the mainstay of treatment however, their use can be limited due to adverse effects associated with higher dose levels. As such, clinicians often use opioids in combination with other medications to try and achieve better pain control. Anti-inflammatory drugs and adjuvant analgesics (e.g. antidepressants and anticonvulsants) are commonly used, however, based on numbers needed to treat adjuvant analgesics are effective in, at best, 1 in 3 patients (Finnerup et al., 2005). CIBP and NCP therefore represent common but difficult to control types of cancer pain. As these pain states have differences in the approach to management, it is fundamental that these are identified appropriately. This work examines verbal descriptors of CIBP and NCP however to enable a full appreciation of these pain states, key aspects of these will be discussed.

1.3.2 Study timescale

This project was commenced in 2009 while working as a research nurse in a palliative medicine research team across a cohort of pain studies. Due to unforeseen personal circumstances I required to take a break in my studies between 2011 and 2014. Consequently, between 2009 and 2011 the project was designed, data were analysed and much of the background reading was completed. When the project was resumed to write-up in early 2015 the final writing of this thesis was completed.

1.4 Cancer Induced Bone Pain

Cancer spreading to bone is known as a bone metastasis and multiple cancer deposits in the bone(s) are herein described as bone metastases. Bone metastases are most common in prostate or breast cancer; 85% and 75% respectively (Nathan et al., 2005). They are also common in lung and renal cancer (40% and 25% respectively)(Nathan et al., 2005). Bone metastases can have a considerable impact on patient morbidity and mortality. Bone metastases which develop at multiple sites can cause multiple areas of pain and may ultimately affect bone marrow function (IASP 2009). Bone metastases can increase risk of fracture, increase potential to develop hypercalcaemia and also predispose to spinal cord compression (Healey and Tyler 2010). Some of these complications are potentially life-threatening. Advances in treatment of patients with metastatic disease have enabled patients to live longer. Patients with Breast and Prostate cancer which has metastasised to the skeleton can expect survival to be considered in terms of years, while patients with Lung cancer with bone metastases will have survival measured in months (Coleman, 2006).

Metastatic bone disease can weaken the bone structure, such weakening can lead to pathological fractures and this is known to adversely affect the expected survival time (Hussain, 2001). For instance, patients with breast or prostate cancer, with a pathological fracture, can have a median survival of between 8 and 12 months (Nathan et al 2005). Similarly, patients with primary lung disease may have a limited prognosis of around 4 months (Nathan et al 2005). It is notable that those with multiple bone metastases have a lower survival expectation than those with a single bone metastasis. Bone metastases therefore represent a clinically significant problem (Nathan et al., 2005).

1.4.2 Pathophysiology of CIBP

Pain from bone metastases, CIBP, is the most common cause of pain in patients with cancer (Coleman, 2006). Bone metastases are reported to cause 30-35% of all cancer pain in patients with advanced cancer (Grond S, 1996). However, the presence of bone disease does not always mean the patient will have pain (Front et al 1979). A recent study by Koizumi et al of breast cancer patients with metastatic bone disease found 59.5% did not have pain (Koizumi et al., 2010). It is not yet established why bone metastases can be present, but yet the patient may not have pain.

Animal models of CIBP have greatly increased our understanding of bone pain (Urch, 2004). In these animal models, cancer cells are implanted into the long bones of rodents to observe the pain behaviour. As well as allowing CIBP to be observed, the effects of medication can also be examined (Urch, 2004).

Bone is a mineralized type of connective tissue but is not a static entity. It is made by osteoblast cells that construct the bone matrix but is constantly being broken down (resorped) by cells called osteoclasts (Urch, 2004). Therefore, within the bone there is a continuous process of construction and degradation. The balance of bone formation and resorption is delicate and subject to multiple influences. When cancer invades and grows within the bone, it affects osteoblast/osteoclast balance. Osteoclasts become activated resulting in the breakdown of bone, weakening its structure (Urch, 2004). Cancer cells also stimulate the release of cytokines and growth factors and this ultimately results in bone destruction (Goblirsch et al., 2005).

Stimulation of nerve fibres also contribute to CIBP. Sensory afferent nerve fibres are responsible for conducting impulses from the periphery of the body to the spinal cord; these are found in large numbers within the bone and also in the outer layer covering the bone. It is believed that increased protein production occurs when cancer is present which then elicits a pain response. This pain can differ from mechanical pain because the bone structure may not be damaged (Urch, 2004).

These animal models of CIBP have highlighted that CIBP is not simply mechanical pain from bone destruction; inflammatory and neuropathic processes are also

likely to be involved. Additionally, it has been shown that key central and peripheral nervous system mechanisms may too be involved. Different areas within the brain are stimulated in response to painful stimuli in CIBP (Colvin and Fallon, 2010). There are also changes in the spinal cord which occur in response to CIBP with alteration in lamina within the dorsal horn. A combination of multiple mechanisms contributing to the genesis of pain therefore highlighting the complex nature of CIBP.

Bone metastases occur in either the axial or appendicular skeleton (Coleman, 1997). The axial skeleton consists of 80 bones including skull, spinal column, ribs and sternum. Bone metastases are more common in the axial skeleton. The appendicular skeleton is composed of 126 bones; metastatic disease more commonly involves the humerus and femur (Healey, 2009). However, metastatic disease is less likely to affect the lower regions of the appendicular skeleton (Harrington, 1997).

The area of pain can be caused directly by localised metastatic disease but it may also result from radicular pain in the spine. It is important to differentiate between direct or radicular pain as radicular pain may indicate impending compression of the spinal canal (Healey, 2009). Similarly patients with diffuse pain, within the appendicular skeleton, which worsens with weight-bearing or activities of living may be at risk of impending pathological fracture (Healey, 2009).

Assessment of CIBP usually requires a patient history and clinical examination followed by confirmation of the presence of bone metastases radiologically, a number of diagnostic imaging tools are available to assist clinical assessment of pain.

1.4.3 Diagnostic Imaging Tools

There are a number of imaging techniques which can enable the clinician to assess damage to bone and any progression of disease. The common techniques are highlighted for the purposes of understanding what a patient experiences and what is required for accurate assessment.

Plain films, X-Ray - are a useful and cost-effective to assess any structural damage to the bone. They are limited as a diagnostic assessment as they can only detect a

lytic lesion (cancer) when there is a significant loss of bone density (30% cortical and 50% medullary).

Computed Tomography (CT) -CT scans can be advantageous over plain films as they provide greater detail review of bone structure and areas of damage. It also gives more information than a plain film as it can identify any soft tissue invasion or an occult fracture (a fracture which does not show on plain x-ray).

Bone scintingraphy (Bone scan) - Involves injecting a radioactive element held within a diphosphonate. Diphosphonates bind to the mineral matrix of the bone and the radioactive element helps highlight any area where cancer is stimulating new bone formation (Love, 2003). Bone scans detect metastatic bone disease in 72-84% of cases however cannot determine any structural damage. They have limited use in aggressive tumours which inhibit new bone formation and this is necessary to make the scan effective (Healey, 2009).

Further imaging techniques available are magnetic resonance imaging (MRI) and positron emission tomography (PET). However, these are most valuable when used in conjunction with the previously discussed imaging techniques. They are helpful when assessing soft tissue involvement but less helpful at assessing bone structure (Healey, 2009).

Diagnostic tools such as CT, PET and Bone scans, are helpful to examine evidence of bone metastases, however they do not assess the intensity of pain or the impact of pain on the patient. For this to be achieved, a detailed clinical assessment is required.

1.4.4 Presentation of Cancer Induced Bone Pain (CIBP)

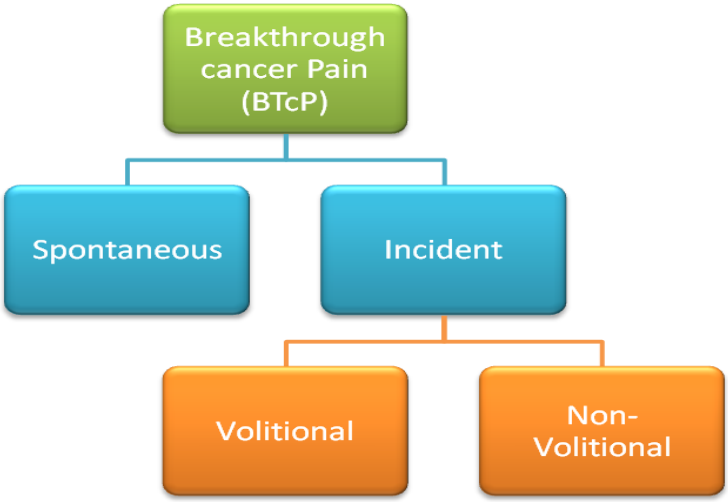
Cancer pain, and vis a vis CIBP and NCP, exists as a combination of background pain and breakthrough pain.

Background Pain - *"a constant or continuous pain of long duration"* (Ferrell et al., 1999). Background pain is characterised as continuous degree of pain which is often unrelenting. Areas of the skeleton more commonly associated with CIBP are the pelvis, femur, skull and vertebrae (Coleman, 2000).

Breakthrough cancer Pain (BTcP) - *"a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline*

pain.” (Portenoy et al., 2004). Patients with CIBP often have breakthrough pain (Laird et al., 2010a). It exhibits quick onset and short duration (less than 30 minutes). It can occur in response to movement particularly where pain is localised to weight bearing bones (volitional). It can also result from involuntary movements, such as coughing or breathing (non-volitional) as shown in Figure 4 (Colvin and Fallon, 2010).

Figure 4 - Breakthrough Cancer Pain (BTcP)



In CIBP, the pain experienced by patients is not related to the primary tumour type (Coleman, 1997). It is not related to volume of disease or the patient’s age or gender. The development of CIBP results in a hypersensitivity state originating from the spinal cord. When this occurs nerves, which are not normally involved in pain transmission, (nerves responsible for light touch, vibration etc) become involved. The patient then can experience pain from non-painful stimuli (Coleman, 2000). It has associated altered skin sensation which is expressed as;

- Altered sensation (paresthesia)
- Pain from light touch (dynamic allodynia)
- Pain from pressure (static allodynia)

- Pain from warm or cool stimuli (thermal hyperalgesia)

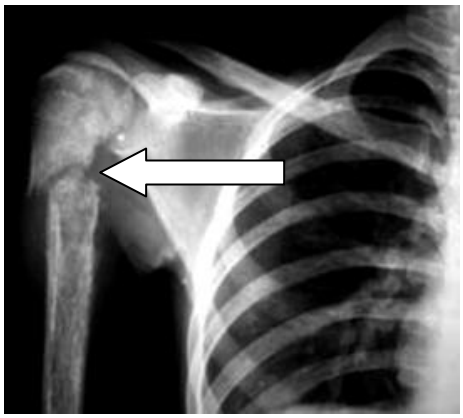
These clinical features highlight the complex mechanisms that exist in CIBP and may result in the wide range of symptoms experienced (Healey, 2009).

1.4.5 Treatment

The aim of intervention and treatment of patients with all types of metastatic disease is to enhance quality of life and where possible prolong survival (Walsh and Hauser, 2006). This often requires management of several symptoms. For example; pain, poor mobility, impaired function, disease burden and low mood (Walsh, 2000). As such treatment can be multi-modal and require a number of interventions.

CIBP can be mechanical in nature due to instability from bone destruction but it can also be caused by stimulation of afferent nerves. Surgery is typically utilised when the bone has sustained enough damage to risk a fracture or where a fracture has already occurred (Healey, 2009). Figure 5 - Pathological fracture below shows a pathological fracture in a plain film (X-Ray).

Figure 5 - Pathological fracture



(http://www.bhj.org.in/journal/2007_4902_april/images/379_fig3.jpg)

Surgery can relieve CIBP by stabilizing the bone and reducing mechanical pain or simply by reducing the burden of disease.

Pathological fractures are notoriously slow to heal and will usually require surgical intervention for long-term stabilization. Where possible, it is recommended to surgically fix the area prior to fracture, this reduces pain and the surgery is less complicated (Jawad and Scully 2010). For patients who experience pain, but

where the lesion does not pose risk of fracture or are perhaps are unable to receive surgical fixation, radiotherapy can provide symptomatic relief. Radiotherapy is the gold standard treatment for painful bone metastases. It is considered the most effective management for CIBP. However, studies have shown only 25% of those treated will have complete pain relief by four weeks following radiotherapy (McQuay et al., 2000). Other combinations of hormones, bisphosphonates, analgesia and chemotherapy can be employed to improve quality of life and prolong survival.

Opioid analgesia are useful in the treatment of CIBP however the dose varies between patients and therefore treatment must be individualised. In some patients, to experience a response, they require escalated doses (Laird et al., 2010b). Higher doses of opioids are linked with adverse side effects which therefore can limit their use. The WHO analgesic ladder advocate use of adjuvant analgesia such as non-steroidal anti-inflammatory (NSAIDs). Such adjuvants may be employed in treatment of CIBP although there is limited robust evidence to support NSAIDs use in treatment of CIBP (Laird et al., 2010b).

Bisphosphonates can also offer analgesic benefit by strengthen bones affected by metastatic disease. They a bind to the bone matrix and are anti-resorptive. Studies have shown that this process can help reduce risk of pathological fracture, cord compression and for some patients, can reduce the level of pain experienced (Mantyh, 2002).

1.5 CIBP Summary

Cancer induced bone pain affects many patients with metastatic cancer and is one of the major causes of cancer pain. Patients who experience CIBP have an increased morbidity and reduced quality of life. CIBP presents a challenge in both its assessment and treatment. The treatment options for CIBP are wide and it is important that they are initiated appropriately. Accurate diagnosis of CIBP is essential and the examination of verbal descriptors presented within this MSc will assist with future assessment.

1.6 Neuropathic Cancer Pain

Neuropathic cancer pain is described as a direct result of a lesion or disease which affects the somatosensory system" (Treede et al., 2008). Neuropathic cancer pain

often starts as an acute pain but can develop into chronic symptoms, some causing disability (Gray, 2008).

Approximately 40% of patients with cancer experience neuropathic pain and it can be a sign of disease progression (Caraceni, 1999, Bruera, 2003). Neuropathic cancer pain can be due to the direct effects of cancer (tumour compression) or as result of nerve damage caused by cancer treatment (such as surgery or chemotherapy) (Laird, 2008).

1.6.1 Pathophysiology of NCP

Neuropathic cancer pain is caused by damage to nerves which can lead to alterations in the peripheral and central nervous systems. Nerve damage can be caused by;

- Chemotherapy (abnormal protein processing)
- Direct tumour compression (ischaemia causing degeneration of axons)
- Surgical (abnormal afferent nerve signalling)
- Radiotherapy (Abnormal protein processing)

Cancer treatment often involves the use of chemotherapy. Chemotherapy use can be limited due to a wide spectrum of adverse effects such as, nausea/vomiting, anorexia, alopecia, pain and neutropenia.

Chemotherapies, both old and new treatments, are known to cause neuropathic cancer pain, most commonly peripheral neuropathy (Quasthoff, 2002). This is due to;

- Chemotherapy molecules damaging the structure of peripheral sensory neurone
- Chemotherapy induced inflammation of sensory fibres
- Decreases growth factor level production in the brain

These abnormalities cause increased central sensitivity by sending continuous erratic electrical signals. This increased sensitivity can manifest as pain when exposed to light touch such or in response to warm or cool stimuli. It can further

cause muscle weakness or autonomic responses such as diarrhoea or sweating (Quasthoff, 2002).

Anti-cancer treatments such as carboplatin, cisplatin, paclitaxel and thalidomide are just a few agents associated with development of neuropathic cancer pain (Quasthoff, 2002). The degree of neuropathic pain can be affected by the chemotherapy type, dose and number of chemotherapy cycles. Pain as a result of chemotherapy treatment can present as; Myalgia (Muscle pain), Arthralgia (Joint pain) or Sensory disturbances (Numbness, tingling, burning). Nerve damage can also be caused by direct tumour compression or surgical dissection which can lead to neuropathic pain, these will be explored to offer and understanding of the process of NCP.

Neuropathic cancer pain can also arise when the surgical dissection damages the peripheral nerves or plexus. Post-surgical pain, such as post-mastectomy pain affecting axilla/chest wall can occur immediately following surgery or develop over a period of weeks to months or years (Tasmuth et al., 1996).

1.6.2 Assessment of NCP

Like all cancer pain, the assessment of NCP requires a comprehensive approach including a pain history with medical and neurological examinations (Jensen et al., 2007).

A pain history should be inclusive of; locality, onset, duration, quality and intensity. Locality can be measured using a body chart or diagram and intensity can be measured by the patient on a numerical rating scale (For example select between 0 and 10, where 0 is no pain and 10 is the worst pain imaginable). Identification of the verbal descriptors of NCP would aid in assessing the nature of NCP which would facilitate comprehensive assessment. Comprehensive assessment of NCP should encompass measurable aspects such as pain duration, severity and impact on daily life (Jensen et al., 2007).

Advances in assessment can assist in diagnosis of NCP. Development of sensory testing enhances examination of any change in sensitivity to touch, pinprick and hot/cold stimuli. It enables the clinician to compare responses in the affected area to an area of the body unaffected by pain (Finnerup and Jensen, 2010). As

patients with NCP often experience pain from non-painful stimuli, sensory testing can allow the clinician to map the area affected and allow assessment of any intervention effect. Assessment of NCP can be enhanced through nerve conduction studies, and diagnostic imaging such as CT or MRI scans. However, nerve conduction studies are more useful for large nerve fibre function assessment rather than small nerve-fibre neuropathies. Similarly CT and MRI scans are only diagnostic if there is a clear area of damage or tumour invasion in the affected area (Finnerup and Jensen, 2010).

Patients often present with symptoms of sensory abnormality and pain which is characteristically similar to CIBP with a mix of background and breakthrough pain. Patients with NCP can often exhibit signs of sympathetic hyperactivity with excessive perspiration, changes in skin colour and temperature (Finnerup and Jensen, 2010). Patients may use terminology such as “burning”, “sharp” and “electric shocks” to describe their pain.

1.6.3 Treatment

Treatment of NCP is challenging because standard analgesics are often inadequate (Gilron et al., 2005). Combination of different analgesia, such as opioids, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants and topical local anaesthetics are often utlised. Although there are various treatments available, these can be sub-optimal in a proportion of patients (Colvin, 2008). Strong opioids are limited by side-effects at the high doses required for analgesia (Laird, 2008).

Adjuvant analgesics are drugs where the primary function is not analgesia but which can have an analgesic benefit. Common adjuvant analgesics used in NCP are;

- Antidepressants- Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSNRIs) have proven to have an analgesic effect at lower doses than required to provide antidepressant function. The use of antidepressants can however be limited in elderly patients or those with mental health issues (Portenoy and McDonald, 2006).

- Anticonvulsants- second generation anticonvulsants, such as gabapentin and pregabalin, have been shown effective in NCP. Gabapentin and

Pregabalin stop the hyperactivity of neurones which cause the pain. These can be taken in addition to other medications and may synergistic with opioid medication, allowing lower doses to be used. Efficacy varies between patients and again their use can be limited in elderly patients or those with impaired renal function (Portenoy and McDonald, 2006).

- Topical Lidocaine – Lidocaine is typically applied topically as a medicated plaster. The plasters suppress abnormal nerve behaviour without blocking electrical signals. Their use can be limited by mild skin irritation and it is contra-indicated for those taking class I anti-arrhythmic medications (Finnerup and Jensen, 2010).

Other pharmacological interventions such as cannabinoids, weak opioids and topical treatments can be utilised in conjunction with other treatments for NCP but all have limiting efficacy and restrictions of use (Finnerup and Jensen, 2010, Finnerup et al., 2005).

Due to the complex nature of NCP and the limiting aspects of some treatments, it is often beneficial to complement traditional treatment with non-pharmacological treatments to support the patient (Finnerup and Jensen, 2010). Patients with chronic pain, such as NCP, often have associated problems with lack of sleep, poor appetite, anxiety and depression. Cognitive behavioural therapy can help the patient develop coping mechanisms, relaxation techniques and distraction techniques. The use of cognitive therapy can be limited by availability and requires the patient to be a willing participant (Finnerup and Jensen, 2010). In extreme cases neurosurgery could be considered but is not always appropriate where survival and performance status are limited (Finnerup and Jensen, 2010).

1.7 Assessment tools for CIBP and NCP

A number of assessment tools are utilised in the assessment of CIBP and NCP. Two such tools are the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and the McGill Pain Questionnaire (MPQ).

The National Comprehensive Cancer Network (NCCN) advise in the Clinical Practice Guidelines for Adult Cancer Pain that a comprehensive approach to cancer pain assessment includes;

- Quantifying and characterising pain intensity and quality
- Using patient-centred self-rating pain intensity scales (using numerical and visual aids)
- Using patient descriptors of pain (burning, aching, shooting) (Lema et al., 2010)

It is important that any pain assessment tools use either some or all of these aspects.

1.7.1 Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)

The LANSS assessment tool has seven key elements (Bennett, 2001). There are five core symptom assessments and two sections for clinical examination. The assessment is usually performed by a clinician as part of a clinical assessment using an interview technique. The LANSS is designed to determine if the patients' pain is likely to be neuropathic in origin. It has been field tested as an assessment tool for neuropathic pain across many patient populations and varying nationalities and validated for use (Polit and Tatano Beck 2013). It has been further validated for use in distinguishing neuropathic pain from nociceptive pain (Bennett, 2001). The test is easy and quick to apply and has recently been developed further to allow self-report by patients. The test is scored out of 24, if the patient scores 12 or more it is likely that their pain has neuropathic mechanisms. In validity testing, the LANSS is considered accurate in discerning neuropathic pain from nociceptive pain in 4 out of 5 patients with chronic pain. While this is accurate, it is possible for those who score less than twelve to have an element of neuropathic pain. It should also be noted that the LANSS does not assess pain intensity or the impact of the pain on the patient's function or quality of life. As such it should be used in conjunction with other assessments and form part of a comprehensive assessment (Bennett, 2007).

1.7.2 The McGill Pain Questionnaire (MPQ)

The MPQ was the first tool developed which used verbal descriptors in pain assessment (Towery, 1996). Previous research studies have shown its reliability and validity across large samples of patients with chronic pain (Mercadante 1997b). The MPQ aims to elicit information from the patient on the locality,

intensity and behaviour of pain. The MPQ was seminal work, developed to allow patients to identify pain from a list of 78 words; which were believed to represent the multi-factorial nature of pain. These words included throbbing, shooting, hot-burning or sharp (Melzack, 1975). The questionnaire consists of three main classes of word descriptors; sensory, affective and evaluative. These are used by the patient to describe their pain experience (Mercadante, 1997b). The MPQ features a diagram of the human body to enable the patient to record the location of pain and a category to allow patients to score their pain from no pain to excruciating (Melzack, 1975). A short-form was later developed with a set of 15 word descriptors, 11 sensory and 4 affective, Appendix 4. Patients can score the pain as none, mild, moderate or severe. The responses are scored on an intensity scale from 0-3 where 0 is none and 3 is severe (Melzack, 1987). Both versions of the MPQ can be used to evaluate pain and can be used over a period of time to monitor the effects of any intervention (Mercadante, 1997b).

1.7.3 The Brief Pain Inventory (BPI)

The BPI is a widely used multidimensional pain assessment tool which is utilised in cancer pain assessment. It has been validated for use among many differing cultures and languages (Cleeland, 2006). The BPI has been psychometrically tested for reliability, validity and sensitivity across various pain origins and for different languages to ensure consistent and reproducible results (Kumar 2011). The BPI is a self-report pain assessment tool with two key components – Intensity and Functional;

Patients record intensity of their pain on a 0-10 numerical rating scale (NRS) where 0 is no pain and 10 is the worst pain imaginable. Patients are asked to score the severity of their pain at worst, least, on average and also at the time of completing the questionnaire. Additionally patients are asked to record pain location on a diagram of the human body (Cleeland, 2006).

The BPI records the effect of pain on several aspects of daily life. Specifically how pain impacts on general activity, mood, walking ability, normal work, relationships, sleep and enjoyment of life (Cleeland, 2006). A similar 0-10 NRS is adopted here (0 is pain does not interfere and 10 pain completely interferes with that function). The BPI also asks the patient to assess the effectiveness of current analgesia in relieving their pain.

The LANSS, MPQ and the BPI are all validated tools and the LANSS and MPQ have been used in the work presented later.

1.8 Summary

CIBP and NCP are clinically challenging to diagnose and require a comprehensive assessment to ensure that appropriate treatment is initiated. Treatment options for CIBP and NCP can differ but are most effective when implemented when pain is acute. Early detection is therefore fundamental in treatment, and requires accurate assessment tools to assist clinicians. The work presented herein describes verbal descriptors of these pain states which will assist in prompt identification.

Chapter 2: The pain experience

2.1 Introduction

Chapter one described CIBP and NCP and outlined the importance of comprehensive assessment. This chapter considers the pain experience for the patient and will explore the challenges of pain assessment. It will further comment on standardisation of reporting pain as an outcome measure for clinical research.

2.2 The Patient Perspective

A qualitative study by Gibbins et al explored the patient perspective for aims of pain management in advanced cancer (Gibbins, 2014). They conducted interviews with 12 patients who had advanced cancer with the aim of identifying how this patient population determine when/if their pain is controlled and additionally how they communicate this to those health care professionals in pain management (Gibbins, 2014). Interestingly, their research found patients had more practical focus for pain management. Two of the four themes which emerged centred on the ability to reduce pain to a level which would allow the patient to resume normal daily activities and a level of independence. Ultimately, the patients wished to maintain their identity and their role within relationships (Gibbins, 2014). The study, while small in numbers, is far less emotive than anticipated. It offers valuable insight from the patient perspective, where pain assessment is recommended to focus on the pain impact on function rather than an NRS of worst pain. Therefore, focus assessment on what effect pain has on activities of living and then set goals for pain management with that issue as the focus.

2.3 Assessment

Pain assessment has been discussed, analysed and reviewed extensively but new techniques for assessment continue to emerge. There have been many pain assessment tools validated for use in general, or for more complex pain syndromes such as the LANSS for neuropathic pain as discussed in Chapter 1. The paper by

Phillips et al (2008) discussed the importance of reviewing the evidence on chronic pain when driving healthcare policy. They acknowledged key challenges of chronic pain particularly on economic and healthcare costs. They more importantly noted the adverse impact on quality of life of the individual (Phillips, 2008). Although pain and pain assessment has been considered extensively in research and great improvements made to pain management, a number of people continue to experience pain as a permanent feature in daily life. It is often associated with anxiety, depression and loss of a sense of identity (Phillips, 2008). Within healthcare, policy and practice there is often focus on the caring dimension of nursing. It is encouraged that patients actively participate in their care. From clinical experience, anecdotally, many patients described a feeling of loss due to reduced physical function from chronic pain. It is from such experience the desire to improve pain assessment and management arose. It is important to determine if the validated tools such as MPQ and LANSS adequately define pain for the patient. Ultimately it would be exciting to lead policy in healthcare where pain is truly considered in a meaningful and accurate way for patients (McCaffery, 1983).

2.4 Patient Experience

Consideration of the patient experience is key to promote caring and dignity within health care. Work is emerging on emotional touchpoints which may facilitate the patient setting goals for healthcare professionals with pain management (Dewar, 2010). Patients can discuss their hopes, concerns, and desires about all aspects of care and could be readily applied in pain assessment and management (Dewar, 2010). Identifying key issues for patients may help set realistic targets. For example, performing daily tasks independently such as self-care or playing golf or eating out with family. MacArthur described a three year longitudinal qualitative study which utilised emotional touchpoints in trying to embed compassionate care into 33 clinical settings of their local NHS facility (MacArthur, 2014). While the study findings are yet to be published. The presentation described that emotional touchpoints enabled patients to give real-time feedback and to feel involved in their care. They found this encouraged staff to reflect on patient experiences and receive positive feedback for good practice. Additionally they described this improved staff confidence with relatives and care practices (MacArthur, 2014). Emotional touchpoints support the argument to use verbal descriptors in pain assessment. To ensure patient centred compassionate

care for patients with CIBP and NCP it is important to consider the emotional touchpoints in pain assessment.

The patient perspective is important in pain assessment and development of new assessment techniques. Accurate identification of meaningful verbal descriptors of CIBP and NCP would support emerging work in emotional touchpoints of pain and encourage dialogue between the patient and caregiver to achieve daily goals for pain control. The following section will explore the measurement of pain within clinical trials.

2.5 The measurement of the pain experience in clinical trials

The International Association for the Study of Pain (IASP) describes pain as 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.' (IASP, 2011). The key word in this statement is experience. Experience by the very definition is subjective and when this is applied to pain it underlines that pain is subjective and therefore a personal experience.

2.5.1 Pain as a personal experience

Pain is a personal experience; it can be difficult to measure. As the pain experience varies from person to person, it follows that measuring pain may be different between individuals and therefore challenging to measure. For patients, the pain experience is heightened by the persistent chronic nature and presentation.

As highlighted in Chapter 1, CIBP and NCP can be difficult to assess. Assessment tools are required to meet the needs of as many users as feasible to ensure they are effective in identifying and discriminating between CIBP and NCP. It is widely accepted that pain assessment should be synonymous with good practice but a number of challenges have been identified (Gibbins, 2014); Lack of formal pain assessment; Difference between self-reported pain assessment and nurse pain assessment; Health care staff underrate patients pain.

It is considered that the patient is the most reliable source and to consider pain as what the patient describes it as. As early as 1997 recommendations were made to

consider pain assessment as routine patient review just as one would record blood pressure or temperature (Gibbins, 2014).

In pain assessment, nurses are often told pain is what the patient says it is (McCaffery, 1983). Many pain assessment tools are structured and aim to lead the patient to quantify and qualify their pain by predetermined parameters. These parameters are usually developed by textbook teaching and then validated by patients. There are a number of defined pain syndromes such as CIBP and NCP and more is required to be known about the patient experience of each. Such understanding would allow development of pain assessment tools designed with the patient at its core. The challenge is how to effectively and accurately measure patient pain.

2.5.2 Measuring pain

It is important to measure pain for a several reasons;

Patient- patient-centred care is a key goal of any healthcare interaction. Pain measurement allows insight into the pain experience of the individual. Pain may adversely affect quality of life therefore accurate pain measurement and assessment is key for the patient.

Treatment efficacy- Consistent measurement of pain at regular time intervals can indicate efficacy of a pain intervention by assessing responses to individual therapies.

Research- Pain measurement is important for research purposes, for example, assessment of new treatments or characterisation of pain.

While it is important to measure pain for the reasons outlined above, there are a number of challenges linked to assessing each patient experience. Pain assessment tools, in common use, have been validated across a spectrum of patients of various pain types, social circumstances and medical history. Patients with chronic and acute pain, who have a life-limiting illness, are at heightened risk of being affected by physical or emotional disposition and also symptom burden of the illness. It is possible that the issue of standardised tools in this patient group may not directly compare to those who have received curative treatment or those who do not have a life-limiting illness. It is therefore important to measure pain in a

comprehensive and consistent manner where possible and to utilise validated assessment tools.

2.6 Pain assessment tools

There are multiple pain assessment tools validated for clinicians to utilise in practice. Assessing pain systematically affords the nurse insight into the patient's pain experience and facilitate ongoing review of any intervention. Clinical environments which incorporate routine assessment techniques for symptom monitoring, particularly pain (Mock et al., 2000) are recommended. Due to the chronic nature of CIBP and NCP, they require any assessment to be comprehensive and to consider the multiple factors which can impact on chronic pain such as anxiety, depression, poor appetite and reduced quality of life (Benedetti, 2000).

Healthcare professionals often utilise visual analogue scales or numerical rating scales which are simple to use and allow for interpretation of responses. The numerical rating system, (rating pain on a scale where 0 is no pain and 10 is the worst pain imaginable), complements the World Health Organisation analgesic ladder as referenced in Figure 3. Confusion arises when the system is adapted or varying versions are used among staff. For example, some VAS or NRS systems are numerical from 0-5; others ask the user to rate pain as mild, moderate or severe. Inconsistent approaches make it difficult for patients to answer uniformly and also make it difficult to draw conclusions or to offer comparisons against pain interventions. A single point pain assessment tool may not allow for the 'whole' experience of pain. Similarly use of one assessment may prove too rigid and not allow for the unique individual. Currently there is no widely utilised technique for implementing symptom assessment in the clinical environment. Further work is required to achieve a comprehensive, user-friendly and validated symptom assessment tool.

2.7 Challenges of measuring pain

Symptom assessment can be challenging due to the subjective nature of the symptom experience (Sykes et al., 1997). Advanced cancer can cause a diverse spectrum of symptoms. These symptoms feature physical and psychological components which the patient tries to convey to the assessing clinician.

Patient description can prove difficult as pain can mean different things to different individuals. As pain, among other symptoms, is a subjective and personal it is also multi-dimensional (Sykes et al., 1997). Pain can impact on physical and emotional function while having implications for family, work, social, spiritual and finance. Research into pain is notoriously difficult due to the dynamic process of pain and the multidimensional nature of pain, for a patient pain is constantly changing. Successful results must allow for the individuality of the research participants involved and how they measure the value of the assessed intervention. The same could be true for assessing efficacy of pain assessment tools. As discussed in Chapter 1, CIBP and NCP are types of chronic pain which patients often receive sub-optimal analgesia or experience adverse effects of high doses required to impact pain. While pain assessment will often focus on severity and frequency, it is equally valuable to consider a variety of descriptors the patient associates with the experience. These descriptors offer insight into the impact of the pain on the quality of life of the patient. It may help indicate any anxiety, distress and impact on daily life. Therefore, assessment of pain should consider severity, frequency and the multi-dimensions of pain. For assessment to be valid, it must evidence reliability when repeated. Symptoms such as pain are a dynamic process and may change over time as such any assessment should assess for change. Similarly, pain research which express positive treatment outcomes often do not know the long term effects of the intervention. Others have applied rigorous outcome measures to allow dissemination of evidence and comparison across different groups.

2.7.1 Pain assessment challenges in nursing

Complex pain can be challenging to manage effectively; this is further impacted by increasing demand on nursing time and resources. Objective measurement tools such as a NRS are utilised to prompt patients to assess pain severity and for review of any effects of analgesia.

Barriers to pain assessment include (Luckett, 2013);

- Patient hesitant to report pain
- Lack of knowledge by healthcare provider
- Inadequate acknowledgment of pain by healthcare provider

- Misconceptions regarding strong analgesia such as opioids
- Healthcare professionals desire for objective pain assessment

A key, robust literature review by Luckett et al (2013) argue a belief among patients that objective pain assessment can lead to poor pain management through under treatment. They further describe that under treatment can be detrimental to the relationship between carer and patient. It is important to develop the relationship between the nurse, the patient and the family can afford the nurse a better understanding of the patient's pain (Luckett, 2013). They suggest the relationship between carer, patient and family may improve pain assessment and management. Luckett et al (2013) suggest potential in nurse prescribing to reduce delay in pain treatment.

2.8 Study design- standardising outcome measures for pain

Standardisation of outcome measures should be applicable over varying research projects and allow for different patient backgrounds and a variety of past medical histories. During development of pain research studies into pain assessment, a number of key recommendations can be utilised to assist the researcher in trial design. The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) developed a consensus framework for key considerations of trial design for pain as an outcome in research (Dworkin, 2010). Since 2002 a varied group from different specialties have held consensus meetings on pain. The group includes, among others, experience from nursing, oncology, pharmacology, surgery and psychology (Dworkin, 2010).

IMMPACT describe key outcome measures which should be considered when designing pain trials involving patients, including participant pain, physical and emotional needs. Standardisation of approach and comprehensive outcome measures may allow for direct comparison across multiple study populations (Dworkin, 2010). Comparative information is necessary to enable researchers to compare and contrast sample groups which feature different types or stages of disease and even those with differing demographics.

2.8.1 Participant disposition

Participant disposition is a motivating factor when consenting to take part research; in work previously completed, a key area of interest was patient attitudes toward research in advanced cancer (Todd, 2009). In palliative medicine research there are many 'gatekeepers' in the form of clinicians, health care staff and family. Often these 'gatekeepers' considered clinical trials with this patient population as burdensome and those with advanced cancer were 'too vulnerable' or 'too unwell'. What the review found was rather contrary to this opinion and many wished to be considered for clinical trials for altruistic reasons as they did not wish others to 'suffer' as they felt they were and others wished to participate as it renewed 'hope' for an improvement in symptom burden (Todd, 2009). These motivations may also make participant disposition of the patient group differ from another sample population. It may also affect translation of finding as makes the issue of standardising and comprehensive outcome measures ever more relevant (Todd, 2009).

Considering patients who have advanced cancer and chronic CIBP or NCP as a unique patient population is potentially inaccurate, perhaps pain is unique to each individual and it might be impossible to directly compare one to another. However, these patients offer an insight to debilitating pain which is likely to reduce quality of life, this is so important as they have a life-limiting illness where clinicians and nurses measure goals by quality, not quantity. Improvement of pain has the potential to greatly improve quality of life and as such requires accurate and prompt assessment and effective intervention.

2.9 Summary

Pain is challenging to assess due to the subjective nature of an individual assessment. There is not a single assessment tool that can effectively assess all patient groups and all different pain experiences. Some may be more discriminatory than others and some assist with assessment of pre/post intervention. While these challenges exist it is important, when designing research studies on pain, to ensure outcome measures can be expressed across varying populations. It is only possible to synthesise results if the questions and approaches become standardised. The following chapter will consider the

methodology utilised in performing the secondary analysis of patients with CIBP and NCP.

Chapter 3: Literature pertaining to the Methods

3.1 Phase one: Systematic Review Methodology

Systematic review is a robust examination of evidence on a given topic. A comprehensive systematic review aims to assess all available literature on that particular subject using a clearly defined search strategy (Lichtenstein, 2008). It combines many individual studies to answer important clinical questions. For example, one study of a particular drug or treatment may not be sufficient to support its efficacy but a number of studies which prove the same outcome may defend its use.

Research in healthcare has gathered momentum following advances in technology as users worldwide could access large volumes of information quickly and conveniently (Houde, 2009). This makes evidence based medicine more accessible but incorporating this into nursing practice requires an understanding of the research process and the value of the evidence. Some research is considered stronger than others which are illustrated below in Figure 6.

Figure 6 - Evidence hierarchy (Mazel and Pullman 2011)

Systematic reviews are located at the top of the evidence hierarchy as they are considered the cornerstone of evidence-based practice. They lead to the development of guidelines and policy to provide consensus of the best practice and care of patients (Loke, 2007). Within palliative medicine, rationale for

common practice is often based on evidence from expert opinion or case series and case reports. There is little evidence in this field which is derived from original research such as randomised controlled trials or cohort studies. Therefore, systematic reviews of the evidence are limited in this speciality due to the restrictive number of randomised controlled trials and cohort studies.

Systematic reviews are combined findings from a number of primary evidence sources (Smith, 2011). Primary evidence is sourced from original research which has involved research participants. Secondary evidence is usually systematic reviews, or meta-analyses which lead to clinical protocols/guidelines. Such secondary evidence (e.g. systematic reviews) enable multiple sources of research and evidence to be summarised. Systematic reviews help draw conclusions based on multiple studies and offer trends while also express conflicting results across different studies (Smith, 2011). Such a technique allows identification of what is already known on a subject when seeking to answer a research question.

Effective performance of a systematic review requires an understanding of the research process. At least one author requires experience of reviewing literature to allow for an appropriate search strategy, there also should be an experienced researcher who will be involved in the process of inclusion and exclusion of articles. A systematic review of the literature can achieve desired goals when applied in a systematic and robust manner. A tool can be utilised to assist the researcher with the process of performing a systematic review such as the SIGN guideline number 50 (SIGN, 2008).

The first step in a systematic review is to develop an important clinical question which is believed to have not yet been answered. Following this the primary author should seek to collaborate with at least one other researcher to ensure the review of the literature is comprehensive and robust. The authors should have a similar interest and develop the key question to assess what is currently known on the topic, they should ensure that there is no similar review recently published. The authors must develop a protocol or plan which will be used to perform the review, this must contain;

- Defined eligibility criteria for inclusion or exclusion of articles or research are identified and the rationale for these explained.

- Devise a clearly defined search strategy and offer support for why these were chosen, including the different literature databases and any journals to be hand searched.
- Identify keywords and phrases utilised in the search and the rationale for why these keywords should capture the most appropriate articles.
- Results should include reference to any independent review and discussion with peers. Any use of guidelines to assist this should also be documented.
- Conclusions should be justified according to the literature reviewed.

A variety of techniques and tools can be utilised to assist an author when considering what they wish to include in the search strategy (Holly, 2012). It is important to consider key aspects of research being included for example; what is the patient population (e.g. disease type, disease status, gender specific), What were the interventions- (e.g. effectiveness of treatment, assessment tools), what were the comparatives groups (e.g. comparing gender, age, social status) and what were the outcome measures (e.g. effect of patient, effect on care).

3.1.2 PRISMA diagram (Preferred Reporting Items for Systematic Reviews and Meta-analyses)

The value of a systematic review, as with any research, is providing transparency of the review process to allow peer appraisal and to evidence rigour of approach. A PRISMA diagram can assist with clarity of approach by displaying articles searched, considered and excluded at varying stages of a systematic review (Moher et al 2015).

3.1.3 Systematic review: Advantages and disadvantages

A systematic review encourages a transparent search strategy and rationale for inclusion and exclusion of keywords and articles. This allows duplication of the research process by another author and increase the validity and reliability the results (Chandler, 2013). A systematic review is only as good as the search strategy utilised by the author(s). However, if performed in a robust and systematic manner the author(s) can achieve sufficient results to answer the research question and gain an understanding of much what is known, or not known, on a key area of interest which will help direct future research.

3.1.4 Systematic review: Peer review

Systematic reviews are a scientific process and as such should evidence efforts to minimise bias and reduce risk of reporting error. Peer review can increase rigour when determining inclusion and exclusion criteria for data synthesis within a systematic review. Discussion with a peer on which fulltext records are to be included, or excluded, in data synthesis can help reduce decision influenced by prior experience or knowledge (McDonagh et al 2013).

3.2 Rationale for secondary analysis

Secondary analysis is the analysis of data or information collected by another researcher or for a different purpose than the secondary analysis proposed; it can be most easily defined as 'second hand' analysis rather than a primary data collection more common place in research.

Primary data collection is where information is obtained from research participants to answer a specific research question. This can involve a number of researchers over a period of time utilising a number of data collection techniques such as surveys, questionnaires, interviews or through observation (Pollack, 2001). Performing primary data collection can be time consuming and prove expensive. In times of austerity researchers are increasingly considering secondary data analysis to gain new knowledge from previously collated data (Aponte, 2010).

3.2.1 Prevalence of secondary analysis

Studies performed by Aponte (2010) and Smaldone and Connor (2003) identified 181 studies within nursing research which utilised secondary analysis between 1997 and 2008, of which 34 were performed on large data sets. This is a smaller number of studies than expected given the nine-year period considered. There are a number of reasons why secondary analysis is not a more common methodology in nursing research. It may be through lack of knowledge or understanding of how to perform secondary analysis. It may result from limited access to primary data sets or the data sets may be incomplete. Consideration should be given to the potential advantages and disadvantages to secondary analysis. Research has been performed in the health service for a number of years with the aims of improving quality, accessibility and delivery of care (Huston, 1996).

As previously described, secondary analysis uses existing data to explore new research questions or methods (Magge, 2006). This methodology enables data which were intended for one purpose to potentially be utilised for another (Pollack, 2001). Secondary analysis can be performed on a number of resources such as patient charts, surveys or databases.

3.2.2 Advantages and disadvantages of secondary analysis

A key advantage of secondary analysis is cost-effectiveness. As the primary data collection has already been achieved, the investigator is not required to perform questionnaires, interviews or similar (Windle, 2010). A misconception is that secondary analysis saves the researcher time. While there is no primary data collection, the researcher may expend a number of hours understanding the primary methodology and the variables involved. It can be further delayed where data are missing or incomplete. Original sources may feature design flaws or inaccurate data analysis. Such difficulties can be overcome where the researcher performing secondary analysis has access to the primary dataset or to the investigator who performed the original study (Windle, 2010). These difficulties could provide a rationale for the limited use of secondary analysis as a research method. While secondary analysis can prove challenging there are many advantages to performing secondary analysis. Data sets can comprise large sample sizes which increases the researcher's ability to answer research questions. The data being examined can be longitudinal which will further enable the researcher to identify trends and changes over a period of time (Nicoll, 1999). It is helpful for the researcher should have an understanding of the topic and the purpose for which the primary data were collected to ensure they maximise potential of secondary analysis. While it may save efforts of primary data collection, secondary analysis can prove time consuming where data is incomplete or requires extraction (Aponte, 2010). Understanding must be given to the primary data collection methods, how the data were coded and entered onto the database to limit errors in the secondary analysis.

3.2.3 Ethical issues of secondary analysis

As with all research, ethical consideration applies to using secondary data analysis. Typically, patients are advised during the informed consent process that their data may be looked at in the future for further analysis. Secondary data are likely to be free from any identifying information but researchers should always check with local ethics boards to ensure further ethical approval is not required (Windle, 2010, Fisher, 2002). Many support the argument that ethical approval is not always required for secondary data analysis (Huston and Naylor 1996) (Tripathy 2013). They argue that secondary data analysis is an observational study and there is no contact with the participant and no new data are collected. However, if the analysis requires access to confidential information, such as patient records, the investigator must seek the appropriate approval (Tripathy 2013).

3.3 Summary

The two methodologies utilised within this MSc are systematic review of literature and secondary analysis. Systematic review of the literature, provided its conducted in a robust manner, can provide much of what is already known on a particular topic. Secondary analysis is a useful technique for interrogation of data already gathered and can positively contribute to nursing knowledge and literature irrespective of the time since data collection.

Chapter 4: Methods

4.1 Introduction

Chapter 3 considered the methodology of systematic review and secondary data analysis. This chapter presents the research objectives of this MSc. It further describes the methods and datasets which were utilised to meet the objectives.

4.2 Research objective

Identify verbal descriptors of CIBP and NCP.

4.2.1 Secondary Objectives

1. Identification of the verbal descriptors more commonly associated with CIBP (Chapter 5 and Chapter 7).
2. Identification of the verbal descriptors more commonly associated with NCP (Chapter 6 and Chapter 8).
3. Examination of the relationship between pain intensity and gender, cancer type, performance status and analgesia (Chapter 9)
4. Examination of any common or unique verbal descriptors of CIBP and NCP (Chapter 9)

Study design	
Phase one	Phase two
Systematic review – Verbal descriptors of CIBP	Raw data extraction (multiple databases) and de novo database creation
Systematic review – Verbal descriptors of NCP	De novo database analysis

The research question was answered through a combination of systematic review and secondary analysis. The MSc was therefore conducted in two distinct phases:

Phase one was an examination of current literature on common verbal descriptors of CIBP and NCP, as detailed in Chapters 5 and 6. Following an understanding of current evidence, a de novo database was created and analysed.

4.3 Phase one: Systematic review of the literature

A systematic review was considered as the most effective method to understand evidence on verbal descriptors of CIBP and NCP, as discussed earlier in 3.1.3. To ensure a comprehensive review of the literature, as a novice researcher, peer review was sought throughout to ensure maximum potential to capture what is already known about verbal descriptors of CIBP and NCP. The peer review is discussed below and will be evidenced within systematic review chapters.

Discussion with one supervisor was undertaken at the beginning of this MSc. During these meetings, keywords were identified and databases were selected which were considered relevant for the information sought. This was to ensure keywords would capture appropriate articles and that rigorous search was conducted. An adaptation of SIGN 50, Appendix 3, was utilised to focus on key areas as recommended in 3.1, which also facilitated discussion on which articles should be included in review. Key areas of focus were; the patient population, the assessments conducted and any consideration of verbal descriptors. Following a number of searches and reading, further discussion was undertaken as follows;

1. Abstract review – discussion focused on the articles selected for abstract review to confirm potential relevance to the project and for agreement on those to be selected for full text review.

2. Full text review – articles selected for full text review were considered independently using a checklist adapted from the SIGN guidelines appraisal tool for systematic reviews. Discussion followed to achieve consensus on articles for inclusion.

This peer review allowed for quality check of articles selected and helped reduce bias through preconceived ideas.

4.3.1 Phase one: Systematic Review - search strategy

A comprehensive systematic review was undertaken where a number of electronic databases were searched including; Medline (1996-2010), Embase (1996-2010), British Nursing Index (1994-2010) and the Cochrane Database of Systematic Reviews (2010). Keywords and combination phrases were agreed with one supervisor in advance of search. In addition to an electronic search particular journals were hand searched including; Palliative Medicine, the European Journal of Palliative Care and the Journal of Pain and Symptom Management. All subheadings were included and results were limited to the English language and studies which involved humans.

4.4 Phase two – Secondary analysis

Phase two of the study was a secondary analysis of a raw data from three research studies involving cancer pain assessment, see Table 1.

Table 1: Secondary Analysis

Phase two	
Process	Output
Data selection from 3 raw datasets	1. Identify common descriptors of CIBP and NCP within literature
Data extraction	5. Identify if pain severity reported as higher among CIBP or NCP cohorts
De novo database design	
Analysis of De novo database	6. Identify if there is a higher opioid requirement among CIBP or NCP cohorts

4.4.1 Data selection process

A large volume of raw data were accessed from three anonymised datasets. These datasets were screened to identify suitable patient data for the purposes of identifying verbal descriptors of CIBP and NCP. It was expected that a number of patients would not contain sufficient relevant data relevant to meet the key aims of this study, for example recording of verbal descriptors. It was anticipated that 100 patients would be eligible for inclusion in the secondary analysis due to the participant numbers across the three studies. Primary eligibility for inclusion

within phase two, secondary analysis, was that the participants had to have participated in one of the following three studies:

Table 2: Studies utilised for De Novo database

Study	Title	Type	No. Participants
A	Characterization of physical properties of bone pain using the McGill Pain Questionnaire, the Brief Pain Inventory, Breakthrough Pain Questionnaire and Somato-sensory Testing	Cross-sectional survey	135
B	Development of a systematic approach to assess the sensory, cognitive, affective and functional components of cancer induced bone pain CIBP characterization	Observational	59
C	Ketamine in Pain Study; double-blind randomised controlled trial of Ketamine vs. placebo for patients with neuropathic pain in cancer patients	Randomised controlled trial	214

Study A. Characterization of physical properties of bone pain using the McGill Pain Questionnaire, the Brief Pain Inventory, Breakthrough Pain Questionnaire and Somato-sensory Testing.

This was a cross-sectional survey (Jekel et al 2007) of patients who attended a large regional oncology unit (Edinburgh) between 2003 and 2004. A convenience sample (Polit and Tatano Beck 2013) of one hundred and thirty-five patients (n=135) with CIBP or NCP were assessed to provide individual detailed pain characterization. All patients consented, in study A, to provide demographic data, treatment history and current medication. Patients completed baseline assessments regarding their pain which included the MPQ and the BPI. Additional assessments were completed including a breakthrough cancer pain questionnaire and quantitative sensory testing (QST) to offer further characterization of pain. QST allows assessment of small nerve endings through a thermal threshold test and also assessment of large nerve endings through vibration assessment. Data

were anonymised and stored on an excel spreadsheet. Study A was a useful study for inclusion in the secondary analysis undertaken in phase two. It was deemed useful, despite the small scale, because consideration was given to characterising pain in patients with CIBP and NCP, it further captured verbal descriptors. It was however, a single site convenience sample of 135 participants, therefore a small scale study and limiting transferability (Polit and Tatano Beck 2013). It had a limited recruitment period of twelve months, which would account for the small sample size, however the rationale for this recruitment period was not given. Despite these limitations this was a very useful dataset for inclusion in the de novo database due to the patient cohort and assessments applied.

Study B. Development of a systematic approach to assess the sensory, cognitive, affective and functional components of cancer induced bone pain characterization.

Study B was an observational project to assess a number of characteristics of CIBP pre and post palliative radiotherapy. It followed a pre-post intervention design (Harris et al 2006) to validate assessment of CIBP and included patients with CIBP who were attending a regional oncology unit (Edinburgh) in 2008 for palliative radiotherapy to bone metastases. Fifty-nine patients (n=59) (34 Female, 25 Male) with a median age of 63 years (range 38 years to 88 years) completed both pre and post (6-8 weeks later) radiotherapy treatment assessments. The most common primary cancers were breast (52.5%) and prostate (25.4%) which would be expected in patients attending for palliative radiotherapy for CIBP, as described in chapter 2. The baseline assessments included demographic data, anti-cancer treatment history and current analgesia. Patients also completed BPI, SF-MPQ and quantitative sensory testing (QST). This was a small scale study as it was undertaken as part of a higher degree, this also accounts for the nature of the recruitment period. The data were included, despite this, because the patient population had clearly defined CIBP and therefore representative of the patient population sought for this secondary analysis. Additionally, verbal descriptors of CIBP were captured within a comprehensive baseline assessment. This comprehensive assessment increases understanding of the patient pain experience which is beneficial when performing a secondary analysis on raw data.

Study C. Ketamine in Pain Study; double-blind randomised controlled trial of Ketamine vs. placebo for patients with neuropathic pain in cancer patients.

Study C comprised patients who attended two regional cancer centres (Glasgow and Edinburgh). The Ketamine in Pain Study commenced recruitment in 2008 and remained open to recruitment where final accrual was anticipated at 214 patients (n=214). The study was a double-blind randomised controlled trial (Polit and Tatano Beck 2013) which examined the effects of Ketamine vs. Placebo on patients with neuropathic pain. Patients were recruited to the Ketamine in Pain study with a clinically confirmed neuropathic pain related to cancer or cancer treatment. All patients consented to provide demographic data, treatment history and current analgesia information. Patients also completed the sf-MPQ, EuroQol (Quality of Life Assessment), Distress Thermometer, Hospital Anxiety and Depression self-assessment (HADs), Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS). Of those patients who had already completed the Ketamine in Pain Study, raw data from 31 were included in this secondary data analysis. As this DB RCT remained open to recruitment at the time of this secondary analysis the results from the data used stand alone would not provide generalizable results. However, it was a multi-centre study using a number of validated pain assessment tools and the data from Study C increased the number of data in the NCP cohort to enable similar sample sizes for the CIBP and NCP datasets. Of note the data used in this secondary analysis were baseline data and therefore no intervention from investigational medicinal product

4.5 Phase two: Data selection

Anonymised, raw a data was utilised for the secondary analysis. Identification of relevant patient data key inclusion and exclusion criteria were developed to be applied across all studies. The criteria were developed following discussions with a statistician for robustness of data extraction;

4.5.1 Inclusion criteria

- Patient written informed consent to participate in study A, B or C
- Patients with incurable cancer
- Complete baseline assessments

- Worst pain score (VAS 0-10)
- Average pain score (VAS 0-10)
- Complete McGill Pain Questionnaire
- Analgesia history
- Key demographics
- Clearly defined CIBP or NCP

4.5.2 Exclusion criteria

- Patients receiving neo/adjuvant therapy
- Incomplete assessments
- Indistinct pain definition (mixed pain)

Anonymised, raw data were screened from studies A, B and C according to the above inclusion and exclusion criteria. A number of those who met all inclusion criteria were then excluded due to partial or incomplete data following discussion with the statistician.

The de novo database was developed from two datasets as illustrated in Figure 7 and Figure 8,

Figure 7 - CIBP dataset 1

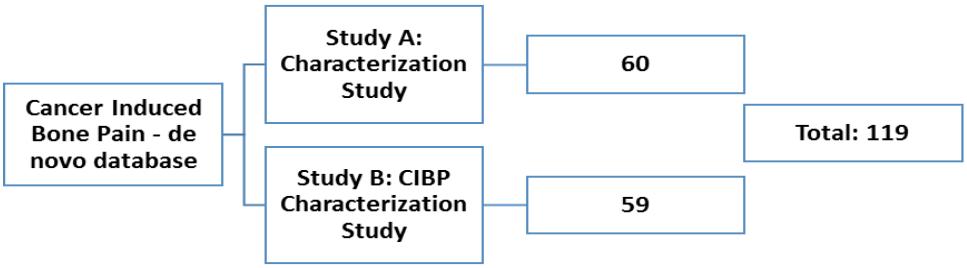
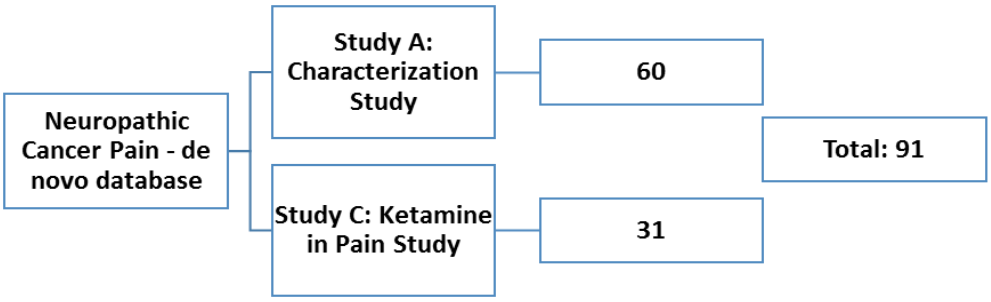


Figure 8 - NCP dataset 2



4.6 Phase two: Secondary analysis - data extraction

Data extraction, in this secondary analysis, involved raw data from three studies which made identification of common data important. As mentioned, guidance was sought from a statistician to ensure all data were appropriately considered. This was to minimise bias in patient selection. Discussion was undertaken to ensure agreement for any data deemed not to meet criteria for inclusion secondary analysis. From discussions with the statistician, a new database was designed to allow transcription of uniform data which were common to all. These parameters were;

1. Demographic data
2. Opioid medication
3. Pain intensity
4. McGill Pain Questionnaire

Phase Two Parameters

1. Demographic data: Key information was extracted on patients including age and gender. This was to allow characterization of the patient population.

2. Opioid medication: Patients received a number of different strong opioid analgesia with varying doses. Following discussion with study supervisors it was decided to enter the data and apply a conversion to a morphine equivalent daily dose (MEDD). The rationale for this was it would allow for direct comparison across the patients.

3. Pain intensity: While patients had completed a number of different pain assessment tools, all patients had data available on worst pain and average pain on a numerical rating scale (NRS) of 0-10 where 0 is described as no pain and 10 is considered the worst pain imaginable.

4. McGill Pain Questionnaire: The MPQ was performed across all studies in two different formats; the long form (lf) and the condensed short form (sf) version. While both tools are validated the information is captured differently. The database was therefore designed to capture common descriptors to both versions to allow direct comparison across the patient groups.

Once common data were extracted and entered onto the database it was then analysed according to the aims and outcome measures described below.

4.7 Phase Two: Secondary analysis - Outcome measures

The de novo database comprising data from studies A, B and C was analysed with the aim of answering the research question while also considering key secondary objectives;

1. Identify if pain severity reported as higher among CIBP or NCP cohorts
2. Identify if there is a higher opioid requirement among CIBP or NCP cohorts

4.8 Phase Two: Secondary analysis - Summary

A number of patients, who had previously participated in clinical studies which assessed CIBP or NCP, were considered for inclusion in the secondary analysis. Particularly patient data where pain scores and verbal descriptors were recorded. As the secondary data analysis utilised data from three different studies with varying researchers, a database was designed to collect relevant information pertaining to the aims of this research. The following chapters will present the

data collected for patients with CIBP and NCP respectively. Any findings will be presented and discussed in later chapters.

Chapter 5: Phase One – Systematic review of verbal descriptors of Cancer Induced Bone Pain

5.1 Introduction

As discussed in Chapter 1, Cancer Induced Bone Pain (CIBP), is the most common source of cancer-related pain. CIBP affects approximately 30,000 patients per year within the United Kingdom (Kane, 2015). Bone metastases are present in 60-84% of cancer patients, more typically with breast, lung and prostate cancer. Bony metastases can develop extensively throughout the skeleton however they are most common within the spine (Shaiova, 2006). CIBP is associated with increased morbidity and can often result in hospital or hospice admission. CIBP adversely affects mobility, mood, quality of life and pose an increased risk of pathological fractures (Kane, 2015).

In 50% of new diagnoses of bone metastases, pain is the presenting symptom. Typically, this pain increases over a period of weeks to months and is usually well localised. Patients may use particular words to describe their pain and these words can provide diagnostic identifiers of the underlying pain type (Mercadante, 1997a).

Traditional textbook teaching describes CIBP as a dull ache which can become exacerbated when pressure is placed on the area, for example during ambulation, sitting or standing (Kane, 2015). Currently the clinical descriptors for CIBP are based on dictum rather than a strong evidence base. As descriptors used by patients vary widely, the diagnosis of CIBP is usually only made in the presence of supporting radiological evidence.

Validated descriptors for CIBP would inform the clinician, assist with accurate assessment of pain and guide radiological investigations. Early detection of CIBP is likely to have a significant impact on the quality of lives of patients and enable treatment to commence at the earliest opportunity (Kane, 2015).

5.2 Systematic review CIBP: Aim

The aim of this systematic review was to explore the available literature on the characterisation of CIBP, namely the descriptors most commonly associated with this pain syndrome.

5.3 Systematic review CIBP: Search Strategy

A comprehensive literature search was undertaken. The following databases were examined electronically: British Nursing Index (1994-2010), the Cochrane Database of Systematic Reviews (2010), Embase (1996-2010) and Medline (1996-2010). The search terms used were “Cancer” AND “Bone” AND “Pain” AND “Descriptors” AND “Assessment” AND combinations of these”. Eligible studies had to examine verbal descriptors of cancer induced bone pain. Following independent abstract review by two researchers, relevant articles were appraised using a systematic review checklist, Appendix 3, adapted from the Scottish Intercollegiate Guidelines Network ((SIGN), 2008). Additionally, the following journals were hand searched: Palliative Medicine, Journal of Pain and Symptom Management, and the European Journal of Palliative Care. All subheadings were included. Results were limited to English-language journals and studies involving humans.

5.3.1 Inclusion Criteria

Articles were selected if they included patients with cancer who had clinically proven cancer induced bone pain of any tumour type. Studies were required to assess patient descriptors of pain using a recognized method such as interview or assessment tool. Articles were included until two researchers could reach agreement on full review.

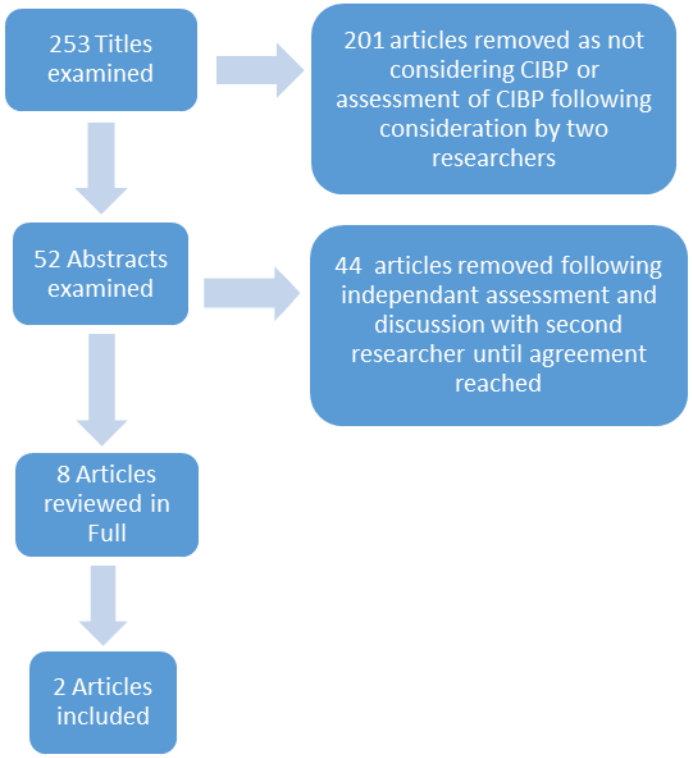
5.3.2 Exclusion Criteria

Articles were excluded if they did not meet all inclusion criteria or if they did not present original material.

As expected, the literature search produced a number of articles. The titles were reviewed and if deemed potentially relevant, were examined further. Due to the broad search terminology a number of irrelevant articles were retrieved. Subsequently 52 abstracts were reviewed, and where relevant for the purposes of this review, selected for further analysis. Some articles examined treatment of

pain rather than pain assessment and other involved patients with non-malignant disease. Where eligibility was unsure, following discussion, the article was reviewed in full. Eight articles were reviewed in full and two were deemed appropriate for inclusion in the review as agreed by two researchers. The final literature search was performed on the 27th October 2010 and the results are displayed in the Prisma diagram below;

Figure 9 - Prisma Diagram - Systematic review CIBP



5.4 Systematic review CIBP: Results

Fifty-two articles were identified of which two met all eligibility criteria and agreement for inclusion. The key findings from each study were identified and discussed and the key comparators are highlighted in Table 3;

Table 3: Systematic review - CIBP

Authors	Study type	No. of participants	Key findings
Laird et al 2010b	Cross-sectional survey	55	Verbal descriptors: Annoying, Gnawing, Aching, Nagging
Kerba et al 2010	Cross-sectional survey	98	17% expressed neuropathic features Neuropathic features expressed higher worst pain

5.4.1 Cross-sectional survey (Laird et al 2010b)

Laird et al (2010b) conducted an exploratory study examining the characterisation of CIBP (Laird et al., 2010b). It was a cross-sectional survey (Polit and Tatano Beck 2013) of 55 participants in one regional cancer centre. All patients had a clinical diagnosis of CIBP with supportive radiological evidence such as an X-ray or CT scan (Laird et al., 2010b). Patients were excluded if the pain mechanism was unclear, although it was not discussed if agreement was sought when mechanism unclear. The site of pain had to correspond to an area known to be affected by bone disease. Data were collected on patient demographics, past medical history and medication. A single interview was conducted. All patients completed a number of questionnaires, the Brief Pain Inventory (BPI), the McGill Pain Questionnaire (MPQ) and a tool specifically designed to identify breakthrough pain (Laird et al., 2010b).

Of the 55 patients included in the study 58% were inpatients and 42% outpatients. The majority had advanced cancer, 11% had a single bone metastasis, 46% had multiple bone metastases and 26% had multiple metastases. The vertebrae in the spine were the most common site of pain. Many of the patients (38%) were taking strong opioid analgesia for their pain with a daily dose morphine equivalent of 68mg. From the MPQ the most common descriptors (in 89% of patients) were selected from the “dullness” section (sore, hurting, aching, heavy). The descriptor most commonly selected was annoying in 42% (n=23). Others descriptors frequently selected were gnawing (38%), aching (38%) and nagging (38%). The patients had a median average pain score of 4 and a median worst pain score of 7

(0-10 NRS) (Laird et al., 2010b). This was a small convenience sample from one centre, this limits the transferability of results however it considered key aspects of CIBP, including verbal descriptors (Polit and Tatano Beck 2013). It was a valuable study as it conducted a comprehensive assessment of CIBP and offered characterisation of the pain therefore it merited inclusion in this systematic review.

5.4.2 Cross-sectional survey (Kerba et al 2010)

Kerba et al (2010) performed a prospective cross-sectional survey in a tertiary regional cancer centre (Polit and Tatano Beck 2013). Ninety-eight consecutive patients were consented to the study. All patients had been referred for palliative radiotherapy for metastatic bone pain (Kerba et al., 2010). Patients were given a physical examination, as per usual practice, and past medical history was obtained. Data were collected on analgesia and other pain treatments. Patient assessments included;

- BPI (Brief Pain Inventory)
- S-LANNS (Self-report Leeds Assessment of Neuropathic Symptoms and Signs)
- EORTC (European Organisation for Research and Treatment of Cancer)
- Quality of Life Questionnaire (version 3)

Assessments were performed at baseline and then 4-6 weeks later, a pre-test, post-test design (Polit and Tatano Beck 2013). Of the 98 patients recruited, the median age was 62 years. There was equal distribution across gender (male n=51, female n=47) (Kerba et al., 2010) which offers equal representation across gender. A number (n=11) of primary cancer sites were found, more commonly breast (34%), prostate (28%) and non-small cell lung cancer (11%), this would be typical of cancers which would feature CIBP. Many of the patients (n=75) were taking strong opioid medication equivalent to 45mg of morphine. The study found that 17% of patients with bone pain had neuropathic features in their pain (S-LANSS of ≥ 12, criteria indicative of neuropathic pain) (Kerba et al., 2010). Those patients with neuropathic elements reported a higher worst pain on a numerical rating scale (where 0 is no pain and 10 is the worst pain imaginable) of 8.3 (SD1.7)

compared to a worst pain of 7.0 (SD 2.0) (NRS) in those who did not. This is a valuable study as they identified an expression of neuropathic features through comprehensive assessment of CIBP. Similar to the study by Laird et al (2010b), the study by Kerba et al (2010) was a convenience sample within one centre which would limit transferability. The sample size was small but did include a comprehensive pain assessment on patients with varying types of advanced cancer, therefore generalisability is limited but it does add meaningful characterisation of this patient population. This study was further deemed suitable for inclusion as it noted a number of patients, with CIBP, to express neuropathic descriptions and features on assessment.

5.5 Discussion

Only two studies met all criteria for inclusion in this review, this suggests that verbal descriptors of CIBP remain an under-researched area. The study by Laird et al (2010b) was the first characterisation study of CIBP to be undertaken and provides useful insight into the impact of CIBP on the patient. Of the included participants who reported an average pain score (on an NRS of 0 to 10), the median value was 4/10. The study further showed exacerbations in CIBP with the median worst pain reported as 7/10. The work by Kerba et al (2010) was included for the purposes of this review as it met the criteria however it also complements the findings of study one. Laird et al (2010b) identified descriptors more commonly associated with neuropathic cancer pain in patients with proven CIBP. While Kerba et al (2010) also found evidence of descriptors, more typically associated with neuropathic pain, present in patients with CIBP. This suggests traditional teaching of NCP and CIBP may not be entirely accurate. Additionally, if neuropathic features in CIBP are more common than anticipated, perhaps treatment of CIBP requires adjuvant analgesia more commonly associated with the treatment of NCP. Both studies are limited by small study populations however raise important issues regarding the current understanding and assessment of CIBP. Both studies acknowledged further research is required.

5.6 Limitations

As results were limited to two studies, any interrelation or generalisability of results are restricted. There were few results which met inclusion criteria despite the broad search terms, suggesting this to be an under researched area. Of the

two included studies interpretation of results is limited due to the relatively small participant numbers. Similarly, the limited number of results suggest further research is required to characterise verbal descriptors of CIBP associated with this pain state.

5.7 Further reading

Due to a break in studies, the literature search for this chapter was most recently undertaken on the 27th October 2010, it was, therefore, deemed important to perform a further literature search for any information published on verbal descriptors of since undertaking this MSc. To ensure consistent methodology, the same search strategy and limitations were applied. The following databases were comprehensive searched and examined electronically: British Nursing Index (2010-2015), the Cochrane Database of Systematic Reviews (2015), Embase (2010-2015) and Medline (2010-2015). The same search terms were used, ("Cancer" AND "Bone" AND "Pain" AND "Descriptors" AND "Assessment" AND combinations of these). The final search was undertaken on the 30th July 2015. There were 253 titles examined, 23 abstracts considered and 8 articles read in full. Elements of the new literature identified through this updated search were incorporated into chapter 1 and 2, however, no further studies were found to meet the inclusion criteria for the data analysis. This reinforces the currency of this work despite the timeframe involved.

5.8 Summary

In literature, CIBP is typically described as 'dull' or 'aching' but it has also been associated with descriptors such as 'annoying' and 'gnawing' which are typically used to describe neuropathic pain. The two studies included in the review identified some descriptors more commonly associated with NCP. From the limited number of studies which met the criteria for inclusion in the review, it is evident that verbal descriptors of CIBP have not been examined in a robust, systematic fashion. It is therefore recommended that future studies are required to identify verbal descriptors of CIBP. The studies included highlighted some descriptors more typically linked with neuropathic cancer pain and Chapter 6 explores verbal descriptors of NCP in greater detail.

Chapter 6: Phase One – Systematic review of verbal descriptors of Neuropathic Cancer Pain

6.1 Introduction

As discussed in Chapter 1, around 40% of patients with cancer will experience neuropathic cancer pain either as a direct result of cancer or damage caused by anti-cancer treatments (Caraceni and Portenoy, 1999, Laird, 2008). Neuropathic cancer pain (NCP) is described as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system." (Treede et al., 2008). Damage to nerves can lead to alterations in the peripheral, central and autonomic nervous systems. The alterations send abnormal electrical signals which results in increased sensitivity within the central nervous system. Patients can experience spontaneous pain with varying degree of duration and intensity (Finnerup and Jensen, 2010).

Neuropathic pain in cancer is particularly difficult to diagnose as patients typically exhibit inflammatory, neuropathic, ischemic, infiltrative and compressive components and often involves multiple sites (Lema et al., 2010). As the autonomic nervous system is also affected by NCP, it can cause dizziness, altered bowel habit or urinary retention (Paice, 2003).

NCP is particularly burdensome because onset and duration is unpredictable. It can be elicited through non-painful stimuli, which is described as allodynia (Finnerup and Jensen, 2010). For example, a patient can experience pain from simple acts such as putting on clothing or in response to warm or cool stimuli. A simple action of a warm shower or exposure to cold weather can evoke a pain response. These unique features of NCP can negatively impact on the daily life of the patient and considerably reduce quality of life (Finnerup and Jensen, 2010).

As discussed in Chapter 1, treatment of NCP is a clinical challenge. Common treatments and medications can have limited success and the high doses required to affect pain often have intolerable side effects (Farrar et al., 2001).

Traditional textbook teaching describes neuropathic pain as “burning” “stabbing” or “pins and needles”. However, it is important to identify if these results are also true for patients with neuropathic cancer pain. This chapter explores what is known on verbal descriptors of NCP through a systematic review literature.

6.2 Systematic review NCP: Aim

The aim of this systematic review was to examine available literature on verbal descriptors of neuropathic cancer pain.

6.3 Systematic review NCP: Search Strategy

A comprehensive literature was undertaken where a number of electronic databases were searched including; Medline (1996-2010), Embase (1996-2010), British Nursing Index (1994-2010) and the Cochrane Database of Systematic Reviews (2010). In addition to an electronic search particular journals were hand searched including; Palliative Medicine, the European Journal of Palliative Care and the Journal of Pain and Symptom Management. Searching terminology was “Neuropathic pain” AND “Cancer” AND “Descriptors” AND “Assessment” and a combination of these. All subheadings were included. Results were limited to the English language and studies which involved humans. Eligible studies were required to examine verbal descriptors of neuropathic cancer pain. Following consideration of sixty-seven article titles, 25 abstracts were reviewed independently by two researchers using a systematic review checklist, Appendix 3.

6.3.1 Inclusion criteria

Articles were required to include patients with a clinical diagnosis of neuropathic cancer pain irrespective of tumour type. Additionally, there must be assessment of patient descriptors of pain by a recognised methodology such as an interview or validated tool. Where eligibility was unsure, following discussion, the article was reviewed in full.

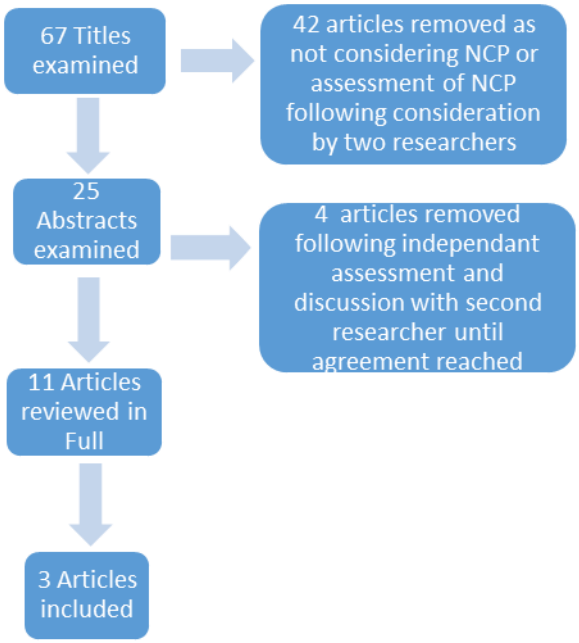
6.3.2 Exclusion criteria

Articles were excluded if they did not meet inclusion criteria and also if they did not present original material.

6.4 Systematic review NCP: Results

The literature search returned a number of articles, see Figure 10. Twenty-five of which were deemed eligible for further examination. Examination of titles and abstracts generated through literature search were performed independently by two researchers. Discussion between the researchers enabled a shortlist of 11 articles for review in full, where opinion differed the article was reviewed in full. Of the 11 articles reviewed, 3 were included for the purposes of this review. Others were excluded for a number of reasons; Some were review articles; others were not focused on the cancer patient population. The final literature search was performed on the 21st January 2011. The key findings were identified and discussed as follows;

Figure 10 - Prisma Diagram – Systematic review NCP



A summary of key features of the three articles selected for inclusion in this chapter have been displayed in Table 4;

Table 4: Review of verbal descriptors of NCP

Study type	**Secondary analysis** Wilkie et al 2001	**One-day prevalence** Holtan & Kongsgaard 2009	**Observational** Manfredi et al., 2003
No. of participants	123	453	187
Key cancer site(s)	Lung only	Gastrointestinal Haematological Lung	16 different primary cancers
Key verbal descriptors	Aching Exhausting Tiring Tender Throbbing	Aching Stinging Burning	Burning Electrical Cold Tingling Pins & Needles Numb

6.4.1 Secondary analysis (Wilkie et al 2001)

Wilkie et al (2001) performed a secondary analysis, as discussed in Chapter 4, of data collected from 123 patients between 1988 and 1996 across three western states in America. The patients included were those who had previously participated in studies of lung cancer pain. All patients had a diagnosis of lung cancer; the majority of patients, 90%, had non-small cell lung cancer (Wilkie et al., 2001). The stage of disease varied from stages I to IV however the majority of patients were stage IV (50%) or stage III (35%). Suggesting only 15% of patients did not have metastatic disease. All patients included had complete demographic data and McGill Pain Questionnaires (Wilkie et al., 2001). Patients also completed the Lung Cancer Etiology Tool (LCET) specifically designed for the purposes of their study. The LCET is a data list of 11 nociceptive and 14 neuropathic defining pain sites to clearly identify what type of pain was being assessed.

Key findings:

- Four hundred and fifty-seven (457) pain sites were reported by 123 patients
- Patients had a median of 4 pain sites
- Twelve patients (n=12, 10%) had all pain sites diagnosed as neuropathic pain.
- Sixty-two (n=62, 50%) were nociceptive and the remaining 40% had both neuropathic and nociceptive pain sites
- Most patients (n=66, 54%) reported continuous pain

Of sites classified as neuropathic pain, words more commonly selected from sensory section of the MPQ were aching n=60, 53%, tender n=30, 26%, throbbing n=27, 24%. Aching and tender are words commonly used to describe CIBP while throbbing would be expected where neuropathic pain is suspected. The most common descriptors from the affective section were exhausting n=40, 35% and tiring n=36, 32% (Wilkie et al., 2001) which are both emotive and may help identify impact on function see Table 5.

Table 5: Verbal descriptors for study by Wilkie et al 2001

Pain type	Key descriptors
Neuropathic	Aching (n=60, 53%) Tender (n=30, 26%) Throbbing (n=27, 24%)
Nociceptive	Stinging (n=32, 9%) Heavy (n=29, 9%) Lacerating (n=20, 6%)

Wilkie et al (2001) described a statistically significant difference (p=<0.5) between descriptors chosen for neuropathic pain and those chosen for nociceptive pain. For example, stinging, heavy and lacerating were typically indicative of nociceptive pain while aching, tender, throbbing and numb were more associated with neuropathic pain. However, they did not find a significant relationship between

pain intensity and descriptors chosen. Interestingly, the authors noted that patients with mixed neuropathic pain and nociceptive pain experienced a higher pain intensity than those with only one pain type (nociceptive OR neuropathic) (Wilkie et al., 2001). It could be that the mixed nature of pain magnified the pain sensations due to the increased expression of pain.

A noteable finding was they identified that verbal descriptors traditionally associated with neuropathic pain, such as burning, tingling and shooting, were not shown to be statistically significant as a descriptor of neuropathic pain. This could be due to pain being classified as nociceptive if there was no evidence to suggest it was neuropathic. This would further explain the larger numbers within nociceptive group (Wilkie et al., 2001). The small numbers of patients within the different pain groups limits statistical significance of results. This was a secondary analysis of data on lung cancer patients across 3 centres, this limits transferability across other cancer types, however it merited inclusion in the systematic review as it identified in a robust manner the verbal descriptors of patients with NCP.

6.4.2 One-day Prevalence (Holtan and Kongsgaard, 2009)

The second study selected for inclusion was a one-day prevalence study of hospitalised cancer patients at one hospital in Norway.

- 453 patients were included in the study
- Mean pain score of 3.99 (on a 0 to 10 numerical rating scale where 0 is no pain and 10 is the worst pain imaginable)
- Mean age of participants was 63.4 years
- Key primary tumours: gastrointestinal (n=70, 15%), haematological (n=60, 13%) or pulmonary (n=57, 12%)
- All completed a questionnaire which collected demographic data; verbal descriptors translated from the short form (12 pain descriptors) MPQ and an adaptation of the Brief Pain Inventory (BPI)
- 97% of participants successfully described their pain using the short form MPQ

- Most common descriptors selected were; aching (n=271, 59.8%), stinging (n=140, 30.9%) and burning (n=93, 20.5%)

- Patients with higher pain intensity score, piercing was found statistically significant (0.026, P<0.05)

Holtan and Kongsgaard (2009) noted that stabbing showed evidence of being chosen more commonly by those with higher intensity pain but it was not as statistically significant as piercing. A further trend was that patients who scored a higher intensity of pain tended to choose more descriptors than those with lower pain intensity (Holtan and Kongsgaard, 2009). Of the 453 patients included in the prevalence study, 201 were found to have altered skin sensitivity. This is often a characteristic of someone with neuropathic pain. As this was a questionnaire-based assessment, differentiation between pain mechanisms can be difficult to achieve, however the data collected showed significant results. Although the study did not find any clear evidence of a difference between verbal descriptors of neuropathic pain and verbal descriptors of nociceptive pain, they did find some clear similarities of descriptors chosen across a large patient population (Holtan and Kongsgaard, 2009). The authors of the study did not disclose information on disease status so conclusions could not be made regarding stage of disease and therefore it is difficult to characterise the patient cohort. The study was a one-day prevalence study and convenience sample from one hospital. It had a diverse patient population across primary tumour type which increases transferability of results. It was included in this review as it met criteria for inclusion and provided good evidence for verbal descriptors in patients with a neuropathic cancer pain.

6.4.3 Observational Study (Manfredi et al., 2003)

The third study was an observational study. It differed to the studies previously discussed as the focus was on describing neuropathic pain and identification of the cause of the pain (Manfredi et al., 2003). Clinical and demographic data were collected on 187 consecutive patients who attended a neuro-oncology department of a large cancer hospital (Manfredi et al., 2003). All patients had been referred to the service for assessment and treatment of pain. All patients were assessed by two neurologists who aimed to gather data on the history of the pain and who then performed a neurological examination (Manfredi et al., 2003). The assessors

utilised radiological films where available and performed electrophysiological assessment where possible.

- There were 187 patients included in the study
- Mean age was 48 with equal distribution across gender (male n= 90, 48.1% and female n=97, 51.9 %)
- There were 16 different sites of primary disease most common being sarcoma (n=22, 11.8%) and breast (n=21,11.2%)
- 157 participants had advanced (n=60, 32.0%) or metastatic (n=97, 51.8%) disease. The most common sites of pain were leg (n=47, 25.1%), back (n=34, 18.1%) or abdomen (n=29, 15.5)

Following assessment it was found that cancer was the direct cause of pain in the greatest number of participants (n=145, 77.5%) (Manfredi et al., 2003). Neuropathic pain was identified in 103 (55%) of participants. Neuropathic pain was considered if patients met two of four points on a checklist. One of the checklist gateways was where patients had to describe their pain using the following descriptors; burning, electrical, cold, tingling, pins and needles or numb.

A key finding was that of the 103 (55%) patients, with confirmed neuropathic cancer pain, 93 (49.7%) patients were found to have ongoing neural injury due to a progressing cancer. Almost half of patients would have further damage to the nerve as the cancer continued to progress and therefore have potential to experience poorly controlled pain. Manfredi et al (2003) argued that treatment in this group was likely to be ineffective while the injury is ongoing. Additionally, they described that if neural injury is not considered 'ongoing' that it is more effectively treated with adjuvant analgesia such as anticonvulsant or antidepressant medications. It was interesting to observe that a large proportion, 90%, of participants with neuropathic pain were considered unlikely to receive benefit from adjuvant analgesia if neural injury was ongoing. This could have significant implications for pain assessment and management (Manfredi et al., 2003). There were small numbers of patients included who expressed neuropathic pain without an ongoing neural injury, however Manfredi et al (2003) argue that identification of neural injury in patients with neuropathic pain will enable more effective treatment which is why it felt key for inclusion in this review. There was

inclusion of a number of different cancer types which increases translation of these results across cancer groups, there was also a comprehensive assessment performed which facilitates characterisation of patients with NCP. This study was included for the purposes of this review as it measured neuropathic pain using a predefined set of 6 verbal descriptors. Rationale for selection of these 6 descriptors was not given and it would have been meaningful to understand reasons for their selection.

6.5 Discussion

All three of the studies discussed varied in methodology and study outcome. There was strong representation of patients with advanced or metastatic disease across studies by Wilkie et al., 2001 and Manfredi et al., 2003. While Wiklie et al 2001 focused only on lung cancer, the others included patients with any type of primary cancer which affords some comparison across tumour types.

All studies included verbal descriptors, however, Manfredi et al., 2003 included a pre-defined set of six descriptors and did not reference frequency of results, most likely as this was not the focus of their research.

- Wilkie et al (2001) the most common descriptors were aching (n= 60, 53%), tender (n=30, 26%), throbbing (n=27, 24%) (Wilkie et al., 2001)

- Holtan and Kongsgaard (2009) identified aching (n=271, 59.8%), stinging (n=140, 30.9%) and burning (n=93, 20.5%) as most commonly selected

Interestingly, aching was the most common descriptor for neuropathic pain across the two studies, where data were available. It also had a strong expression and chosen by over 50% of patients in both studies. In contrast, Manfredi et al., 2003 did not include 'aching' as a descriptor for patients to select. Manfredi et al., 2003 did not offer a rationale for choosing the 6 descriptors they included in their classification of neuropathic pain was however it is anticipated that this is due to their strong feature as descriptors of neuropathic pain as evidenced in Chapter 1.

The descriptor burning was common to all when comparisons were made across all three studies, 6.4.1, 6.4.2 and 6.4.3. There was no clear consensus regarding definitive descriptors of neuropathic pain in cancer patients. Aching was most commonly selected across two studies. This descriptor is more typically associated

with CIBP and not traditionally used as a descriptor for neuropathic cancer pain. Due to the limited results for metastatic disease across multiple cancer types it would be useful to perform further research on patients who have completed assessment using verbal descriptors, for example the MPQ. It would be further helpful to further explore any relationship between higher pain intensity and verbal descriptors.

Manfredi et al., 2003 raised a key issue regarding neural injury. It would be helpful to assess verbal descriptors in those with and without ongoing neural injury. They identified that adjuvant analgesia for patients with ongoing neural injury may be ineffective and it would therefore be helpful to differentiate between those with ongoing injury and those without (Manfredi et al., 2003). Consensus across all three studies was that neuropathic pain in cancer patients is difficult to assess and a clearer definition of NCP is necessary to formalise assessment.

6.6 Limitations

Only three studies met inclusion criteria for inclusion in the review. There were 763 patients across the three studies but there are few comparisons that can be made due to different patient populations and assessment methodology. The small number of studies which met criteria suggests further research is required in this area.

6.7 Further reading

The final literature search for this chapter was conducted on the 21st January 2011 due to a break in studies. It was therefore important to perform an additional literature search to determine if any studies had been published since that time which would add further to this chapter on verbal descriptors of NCP. The same search criteria and terminology were used as had previously and a number of electronic database searches including; Medline (2010-2015), Embase (2010-2015), British Nursing Index (2010-2015) and the Cochrane Database of Systematic Reviews (2015). Keywords applied to the search were “Neuropathic pain” AND “Cancer” AND “Descriptors” AND “Assessment” and a combination of these. The new search identified 35 titles of which 11 abstracts were reviewed and 3 articles considered in full. The articles provided useful information about assessment tools

and NCP however did not add further insight to verbal descriptors of NCP and therefore were not included within the review chapter. The information gained through this additional search has been added to discussion within Chapter 2.

6.8 Summary

Following a comprehensive search only three studies met inclusion criteria. Aching was the most common verbal descriptor chosen by patients in two studies. Burning was frequently chosen by patients in study two and this was a descriptor which patients had to select in study three for inclusion. Further research is required in patients with metastatic disease across multiple tumour sites to assess any descriptors which are clearly evident of neuropathic pain. This would enhance clinical assessment and facilitate initiation of appropriate treatment.

Chapter 7: Phase 2, Secondary analysis - Results CIBP

7.1 Introduction

This chapter considers the de novo database which utilised a dataset obtained from studies A and B to identify common descriptors of CIBP. As previously noted, data was collected on patients with clearly identifiable bone pain. The results for these patients are presented as follows;

- Demographic data
- Current treatment
- Pain intensity McGill
- Pain Results

Data are initially presented in summary and are subsequently analysed in greater detail in reference to key aspects of the data and aims of the study. In summary the key aim of this study was to identify common verbal descriptors of CIBP and NCP. The objectives were:

- Identify common verbal descriptors
- Any relationship between pain intensity and verbal descriptors
- Any relationship between verbal descriptors of CIBP and NCP

In this chapter the study aims and objectives will be discussed in relation to CIBP data.

7.1.1 Impact of living with CIBP

This study has explored the nature and impact of CIBP on patients with advanced cancer. Increased morbidity and significantly reduced quality of life are highly associated with CIBP (Coleman, 1997, Nathan, 2005, Grond S, 1996).

7.2 Patient population

Patient data were available on 146 patients with CIBP. Data from 16 patients were excluded because the pain was not clearly identifiable as CIBP. A further 10 were excluded due to incomplete or missing data. The patients ages ranged from 37 to 88 with equal distribution across gender, (Male n=59, 49.2% and Female n=61, 50.8%). There were 11 different types of primary cancer within the patient group. As expected the most common types of primary cancer were breast (n=52, 43.3%), prostate (n=35, 29.2%) and lung (n=14, 11.7%).

All patients had metastatic disease with 111 (92.5%) patients having multiple bone metastases. Forty-nine patients (40.8%) had multiple metastases, involving other organs which highlights that the patient population had advanced cancer and would be representative of this patient group. The majority of patients were outpatients n=91 (75.8%) with a performance status of between zero and three n=119 (99.2%). Therefore, the patients included were actively living with cancer in the community. A large proportion, (n=68, 56.6%) of patients were receiving palliative radiotherapy, this would be anticipated as radiotherapy is the 'gold standard' treatment for CIBP. Key demographic data are expressed in Table 6 and Table 7;

Table 6: Patient demographics – gender and disease

Characteristic	Number (n)	Percentage (%)
Gender		
Female	61	50.8
Male	59	49.2
Cancer type		
Breast	52	43.3
Prostate	35	29.2
Lung	14	11.7
Bladder	4	3.3
Myeloma	4	3.3
Large bowel	3	2.5
Unknown	3	2.5
Renal	2	1.7
Bone	1	0.8
Cervical	1	0.8
Oesophageal	1	0.8
Metastatic disease		
Multiple bone metastases	111	92.5
Multiple site of metastases	49	40.8
Single bone metastasis	9	7.5

Table 7: Patient demographics - ECOG and status

Characteristic	Number (n)	Percentage (%)
ECOG performance status		
0	12	10.0
1	49	40.8
2	43	35.8
3	15	12.5
4	1	0.8
Status		
Inpatient	91	75.8
Outpatient	29	24.2

7.2.1 Current treatment

It was noted that a number of patients (n=61, 50.8%) were receiving strong opioid analgesia which would be expected for patients with CIBP. Patients on average were receiving a morphine equivalence daily dose of 76mg. Bisphosphonates are often used to treat patients with bone metastases, however only 27 (22.5%) of patients included were receiving bisphosphonates. The most common treatments were radiotherapy, as mentioned and hormonal treatment (n=69, 57.7%). Few patients receiving active treatment in the form of chemotherapy (n=20, 16.7%) which again indicates that patients were likely to be receiving palliative treatments only. The various treatments are displayed in Table 8 below;

Table 8: Current anti-cancer treatment

Treatment	Selected by (n)	Percentage (%)
Analgesia		
Simple	33	27.5
Weak opioid (e.g. codeine)	41	34.2
Strong opioid (e.g. Morphine)	61	50.8
NSAID		
Yes	52	43.3
No	48	56.7
Current cancer treatment		
None	13	10.8
Hormonal	69	57.5
Chemotherapy	20	16.7
Radiotherapy	68	56.7
Bisphosphonates		
Yes	27	22.5
No	93	77.5

7.3 McGill Pain Questionnaire (MPQ)

The MPQ is utilised to elicit information about the pain experience from patients as discussed earlier in 1.7.2. The key descriptors selected from the MPQ will be discussed to assess any common descriptors for CIBP. The key data is highlighted in Table 9. The most common descriptors selected were aching (n=60, 50%), gnawing (n=51, 42.5%) and throbbing (n=44, 36.7%). As highlighted in Chapter 1, these are descriptors which are traditionally associated with CIBP. Other descriptors which were commonly selected were sharp (n=39, 32.5%), tender (n=37, 30.8%) and shooting (n=36, 30%). These descriptors are not typically connected with CIBP and are familiar in textbook teaching when describing neuropathic cancer pain.

Table 9: CIBP MPQ descriptor

McGill descriptor (CIBP)	Selected by (n)	Percentage (%)
Aching	**60**	**50**
Gnawing	51	42.5
Throbbing	44	36.7
Sharp	39	32.5
Tender	37	30.8
Shooting	36	30.0

7.4 Summary

Patients with CIBP were found more commonly to be outpatients with a moderate performance status. Patients with breast, prostate and lung cancer were more affected by CIBP than other tumour types. It was noted that a number of patients with CIBP received strong opioid medication with an average daily dose of 76mg of morphine. Patients with CIBP had a variety of recent or ongoing treatments including hormonal therapy, bisphosphonates and chemotherapy. One of the most common treatments was radiotherapy which is a treatment often utilised to treat painful bone metastasise which cause CIBP. The most common verbal descriptors associated with CIBP were aching (n=60, 50%), gnawing (n=51, 42.5%) and throbbing (n=44, 36.7%). This chapter has characterised the patient cohort with

CIBP and highlighted key verbal descriptors associated with CIBP. The following chapter aims to present the same information for patients with NCP and explore verbal descriptors of NCP.

Chapter 8: Phase 2, Secondary analysis - Results NCP

8.1 Introduction

This chapter considers data obtained from studies A and C as, highlighted in Chapter 4, to identify common descriptors of NCP. In studies A and C, data were collected from patients with clearly identifiable neuropathic pain. The results for these patients are presented as follows;

- Demographic data
- Current treatment
- Pain intensity McGill
- Pain Results

The data are presented in summary but are subsequently analysed in greater detail with reference to key aspects of the data and study aims. On statistical advice it was not useful to perform Confidence Intervals (CIs) on the data as the raw data numbers were too small for meaningful statistical analysis. As previously stated the key aim of this study was to identify common verbal descriptors of CIBP and NCP. The objectives were:

- Identify common verbal descriptors
- Any relationship between pain intensity and descriptors used
- Any relationship between verbal descriptors of CIBP and NCP

In this chapter the study aims and objectives will be discussed in relation to NCP data.

The impact of living with cancer, as discussed in Chapter 1, NCP occurs in approximately 40% of patients with cancer and can often indicate disease progression (Bruera, 2003). The damage to nerves by cancer or cancer treatment can affect patient quality of life and is potentially debilitating. The pain can be expressed as a mixture of background pain with spontaneous or triggered exacerbations.

8.2 Patient population

Patient data were available on 91 patients with NCP. A number (n=30) were excluded due to incomplete or missing data, some key data are highlighted in Table 10 and Table 11.

Table 10: Patient demographics – Gender and disease

Characteristic	Selected by (n)	Percentage (%)
Gender		
Female	36	59.0
Male	25	41.0
Type of cancer		
Breast	21	34.4
Lung	9	14.8
Other	17	27.9
Myeloma	4	6.6
Prostate	3	4.9
Renal	2	3.3
Number of metastatic sites		
0	17	27.4
1	24	38.7
2	11	17.7
3	8	12.9
4	1	1.6
Common metastatic sites		
Multiple bone metastases	25	41.0
Lung	15	24.6
Liver	12	19.7
Lymph nodes	7	11.5

The age of patients ranged from 38 years to 83 years, the majority of which were female, Female n=36 (59.0%) and Male n=25 (41.0%). There were 22 different types of primary cancer within the patient group. There was wide distribution across primary tumour type, the most common types of primary cancer were breast (n=21, 34.4%) and lung (n=9, 14.8%). A large percentage of patients had one site of metastatic disease, n=24, 38.7%, however over 25% of patients had no metastatic disease (n=17, 27.4%). It should be noted that while these patients did not have metastatic cancer, they would have had loco-regionally advanced disease for which there was no cure.

Table 11: Patient demographics - ECOG and status

Performance status (ECOG)		
0	32	52.5
1	2	3.3
2	18	29.5
3	8	13.1
4	1	1.6
Status		
Outpatient	40	65.6
Inpatient	18	29.5
Analgesia		
Simple	12	19.7
Weak opioid	3	4.9
Strong Opioid	45	73.8

The majority of patients were outpatients, n=40, 65.6% with a performance status either zero (n=32, 52.5%) or two (n=18, 29.5%) and over 70% (n=45, 73.8%) of patients were receiving a strong opioid with a morphine equivalence on average on 155.6mg.

8.3 McGill Pain Questionnaire (MPQ)

As discussed, the MPQ can elicit information about the pain experience from patients as discussed earlier in 1.7.2. The most common descriptors selected from the MPQ are highlighted to assess any common descriptors for NCP. The key data is highlighted in Table 12. The most common descriptors selected were; tender (n=34, 55.7%), aching (n=31, 50.8%), and sharp (n=28, 45.9%). Other descriptors which were commonly selected were throbbing (n=27, 44.3%) shooting (n=24, 39.3%), stabbing (n=24, 39.3%) and hot (n=23, 37.7%).

Table 12: NCP McGill descriptors

McGill descriptor (NCP)	Selected by (n)	Percentage (%)
Tender	34	55.7
Aching	31	50.8
Sharp	28	45.9
Throbbing	27	44.3
Shooting	24	39.3
Stabbing	24	39.3

The two most commonly selected verbal descriptors by those with NCP, tender and aching, were chosen by over 50% of the patient group indicating these are important descriptors of NCP. These two descriptors are more commonly associated in the literature with CIBP as described in Chapter 5.

8.4 Summary

Patients with NCP were found more commonly to be outpatients with a good performance status which suggests they continue to maintain a level of independence. Patients with breast cancer were more affected by NCP than other tumour types however there was wider distribution across tumour type than those in the CIBP patient cohort. It was noted that a number of patients with NCP received strong opioid medication with an average daily dose of 155.6 mg of morphine. The most common verbal descriptors associated with NCP were tender (n=34, 55.7%), aching (n=31, 50.8%) and sharp (n=28, 45.9%). This chapter has characterised the patient cohort with NCP and highlighted key verbal descriptors associated with NCP. The following chapter will compare and further discuss the patient cohorts with CIBP and NCP.

Chapter 9: Phase 2 – Secondary objectives

9.1 Introduction

Results presented in Chapters 7 and 8 considered the characterisation of patients with CIBP and NCP through secondary analysis. This understanding is pivotal in acknowledging the impact of pain for patients. Meaningful assessment can be developed through a greater understanding of the impact of pain. It is important to understand the unique characteristics of pain but also to acknowledge any similarities in pain description. Such understanding will help identify where current pain assessments are limited and facilitate identification of how assessment tools could be further developed. The primary objective was to compare verbal descriptors of CIBP and NCP. However, this chapter will consider relationships in the following areas:

- Gender and worst pain score
- Pain scores across cancer type
- Patients performance status
- Comparative analgesia and treatment

9.2 Gender and worst pain score

The data were considered to determine if any relationship existed between gender and worst pain score. Gender was the terminology utilised in literature around this topic and as such is adopted in this thesis (Deandrea, 2014). This was to identify if patients could be characterised by gender; for example, would one group experience pain at heightened severity compared to the opposite gender? A variation in pain experience by gender could be a key consideration in pain assessment and would allow for development of gender specific assessment. The worst pain more commonly selected across CIBP and NCP groups is displayed in Table 13 and it demonstrates no difference in pain scores between genders.

Table 13 Gender and worst pain score

Gender	Worst pain score (CIBP)	Worst pain score (NCP)
Male	8/10 (n=12, 20.3%)	8/10 (n=8, 32%)
Female	8/10 (n=10, 16.7%)	10/10 (n=7, 19.4%)

There was consensus in worst pain scores of those in the CIBP cohort where worst pain score of 8/10, (on a 0-10 NRS), was selected by both male and female participants. Interestingly, no greater pain expression was identified between gender groups. The male cohort of patients with NCP scored worst pain most commonly as 8/10 (n=8, 32%) while the women chose 10/10 for worst pain more commonly (n=7, 19.4%). It should be noted that due to the small numbers there is not a strong relationship between worst pain score and gender. Due to the small numbers considered, further exploration in a larger group is required to clearly identify any difference in pain reporting measures between genders.

While considering the impact of gender on pain reporting, it was found that irrespective of pain origin, there was similar distribution between male and female participants. Table 14 highlights that both genders were represented in similar numbers across the pain groups.

Table 14: CIBP vs. NCP key demographics

Gender	CIBP (n=120)		NCP (n= 61)	
	n	%	n	%
Female	61	50.8	36	59
Male	59	49.2	25	41

The data demonstrates no difference between gender and prevalence of either CIBP or NCP nor a gender bias for reporting CIBP or NCP. This means there is not a strong case to recommend a gender specific assessment tool. Gender is not a

strong characteristic in pain. However, an opportunity to explore a larger sample size would be useful.

9.3 Pain scores across cancer types

While considering key characteristics in pain assessment in parallel with verbal descriptors, the data were assessed for any relationship between type of primary cancer and the incidence of CIBP or NCP. The results displayed in Table 15 were used to identify if a cancer type increased risk of CIBP or NCP.

Table 15: Cancer type

Type of Cancer	CIBP		NCP	
	n	%	n	%
Breast	52	**43.3**	21	**34.4**
Prostate	35	29.2	3	4.9
Lung	14	11.7	9	14.8
Large Bowel	3	2.5	5	8.2
Myeloma	4	3.3	4	6.6
Renal	2	1.7	2	3.3
Other	10	8.3	17	**27.9**

It was evident that breast cancer was most common across both CIBP and NCP groups, over 43% or CIBP patients and over 34% of NCP patients were breast cancer patients. As described in Chapter one, cancers which commonly metastasize to bone are breast, lung and prostate and therefore it is reasonable that over 80% of those with CIBP expressed these as the primary cancer type. Patients with NCP are more difficult to predict as it is not strongly associated with a specific cancer type. This is shown in Table 15 as there was greater distribution across cancer type. As previously described in Chapter 1, NCP can be caused by any tumour and by a variety of treatments; therefore, it could be possible for patients with many different tumours to experience NCP.

It is important to note that data presented within Table 16 relates to disease progression, it refers to how advanced the cancer was at the time of data collection. Patients included for the purposes of the secondary analysis could have

had varying degrees of disease progression but it is important to identify that all patients included had to have progressive disease by definition, for which there was no possible cure.

Table 16: Disease progression

Type of distant disease	**CIBP**		**NCP**	
	n	%	n	%
Multiple bone	**111**	**92.5**	25	41
Multiple mets	49	40.8	**42**	**67.7**
Singe bone	9	7.5	2	3.3

Patients with CIBP, in this dataset have, by definition, metastatic bone disease; CIBP would not exist without skeletal disease. Patients could have a single bone metastasis or multiple cancer deposits throughout the skeleton. Those with bone metastases could also have other sites of distant disease and this information is included as it helps describe the patient population and highlight the burden of disease.

It is clear that those with CIBP had progressive disease. Almost 93% had multiple sites of bone metastases with 40% of patients having had multiple sites of distant disease. Those with NCP also had advanced disease with almost 68% having had multiple sites of distant disease. The data did not highlight any trend between type of primary cancer and whether a patient had CIBP or NCP but it was evident that patients with CIBP and NCP had progressive cancer.

While the majority of patients with NCP had progressive disease, almost 30% of patients did not have distant sites of cancer. This is noteworthy as those with loco regionally advanced cancer could also experience significant pain as compared to those with progressive, distant disease. It is evident for both CIBP and NCP, patients with a primary breast cancer are at greater risk of developing CIBP and/or NCP due the risk of metastatic bone disease and locality of a primary breast tumour to large nerve pathways in the axilla as highlighted in 1.6.

Patients with CIBP have metastatic bone disease which can serve as a predictor of pain. It is more difficult to predict those at risk of NCP which in turn increases difficulty in assessment of NCP. This is an indication that further research is required to test for any risk factors in development of NCP across a larger patient population.

9.4 Patient performance status

Further characterisation was achieved through assessment of performance status as defined by ECOG and discussed earlier in Chapter 7. This section will compare how functionally fit the patients were at the time of assessment. It was examined if those with CIBP or NCP are considered less well or experience a greater loss of functionality compared to those in the other cohort. The key findings are shown in Table 17.

Table 17: Patient function

Performance status (ECOG)**		**CIBP (n=120)**		**NCP (n=61)**	
		n	%	n	%
Decreasing function ↓	0	12	10	**32**	**52.5**
	1	**49**	**40.8**	2	3.3
	2	**43**	**35.8**	18	29.5
	3	15	12.5	8	13.1
	4	1	0.8	1	1.6
Inpatient/outpatient Status					
Outpatient		**91**	**75.8**	**40**	**65.6**
Inpatient		29	24.2	18	29.5
** Eastern Cooperative Oncology Group (ECOG)					

Table 17 shows that patients with CIBP exhibited poorer function than those in the NCP group. Using the Eastern Cooperative Oncology Group (ECOG) performance status (PS) scale, over 75% of patients with CIBP were either performance status one (n=49, 40.8%) or two (n=43, 35.8%). This indicates that these patients, at best, could perform all self-care and, at worst, be unable to complete any light

work either at home or at the office. It's worth noting that while the majority of CIBP patients were expressed within the mid-section of the ECOG, as many as 76% (n=91,75.8%) were outpatients at time of data collection.

The group with NCP were more functionally fit than the CIBP counterparts. Over 50% (n=32, 52.5) of patients with NCP had a performance status of zero. Patients with an ECOG PS of zero are described as fully active and capable of performing all pre-disease activities without restriction. There were a considerable number, n=18 (29.5%) of those with NCP who were assessed as ECOG PS of 2. Therefore, patients were either able to continue with normal daily living activities or quite restricted in daily life. Within the NCP cohort, n=18, 29.5% were inpatients and n=40, 65.6% remained as outpatients at time of inclusion Patients with CIBP expressed a poorer performance status than those with CIBP.

The majority of patients with pain, irrespective of mechanism, were supported in the community. It is not known how much support these patients received from the community teams, through symptom management or home adaption to facilitate and promote independence. This is particularly relevant for those with CIBP as these patients tended to have a lower ECOG performance status but 75% remained as outpatients and this would have implications for community support.

These findings support further objective research to explore the experience of patients with pain and varying performance status as inpatients and outpatients. A qualitative study could explore any emerging themes on what is important to patients with pain such as CIBP and NCP. Particularly to identify what is required to support patients with CIBP and NCP effectively within the community. To understand the needs of this patient group a prospective study or audit would be useful to assess services utilised, for example community MacMillan nurses, occupational therapy, hospice.

9.5 Comparative analgesia and treatment of CIBP vs. NCP

It has been identified that patients with CIBP and NCP often require multiple analgesia and Chapter 8 explores the requirements of patients. Theme four compares the use of opioid and adjuvant analgesia across the pain groups to assess any difference in doses required or type of analgesia utilised. This information will

assist in understanding if CIBP or NCP appears more challenging to manage. Table 18 displays strong opioids analgesia utilised by patients.

Table 18: Strong opioids

	CIBP (n= 120)		NCP (n= 61)	
	n	%	n	%
Strong opioid (e.g. Morphine)	**61**	**50.8**	**45**	**73.8**

In the NCP cohort, almost 74% of all patients were taking a strong opioid compared to almost 51% of those with CIBP. The high frequency of those on strong analgesia reflects high levels of pain experienced by the patients included in analysis.

There is a higher than expected degree of difference between those prescribed strong opioids with CIBP and those with NCP. It was highlighted in Chapter 1 that both CIBP and NCP were complex types of pain and therefore it was considered that both patients groups might have similar opioid requirements (Shaiova, 2006) but within this patient cohort there is a marked difference.

As evidenced below in Table 19, patients with CIBP had similar distribution between simple analgesia and weak opioids while those in the NCP group appeared to either have simple analgesia or strong opioids. This might suggest there were very few who found adequate pain relief on simple analgesia.

Table 19: Simple and Weak analgesia

	CIBP (n= 120)		NCP (n= 61)	
	n	%	n	%
Simple	33	**27.5**	12	19.7
Weak opioid (e.g. codeine)	41	**34.2**	3	4.9

Table 20 displays anti-cancer treatment the patients were receiving at the time they were assessed. This information enhances understanding of the patient

cohort as it allows comparison of the variety of treatments given to the different pain groups to identify any similarities or differences.

Table 20: Comparative anti-cancer treatment

Anti-cancer treatment	CIBP		NCP	
	n	%	n	%
Hormone (e.g. breast, prostate)	69	57	11	18
Radiotherapy (e.g bone metastases)	68	56.7	4	6.6
Bisphosphonates (e.g. bone metastases)	27	22.5	0	0
Chemotherapy (control disease progression)	20	16.7	10	16.4
No treatment	13	10.8	**33**	**54.1**
NB All treatments given with palliative intent & some patients on combination treatments				

Unsurprisingly, the patients with CIBP were receiving hormone treatment. This is because the most common cancer types were breast and prostate cancers, both often employ hormonal therapies to manage disease. As identified in Chapter 1, patients are offered palliative radiotherapy for painful bone metastases; therefore, it is entirely not unexpected that almost 57% of those with CIBP had received palliative radiotherapy, as they had bone metastases.

Patients within the NCP group received very little anti-cancer treatment and over 50% of NCP patients were not receiving any anti-cancer treatment. This could be explained by the greater diversity in primary tumour type as highlighted Table 14. Patients would be unlikely to receive bisphosphonates if they did not have bone metastases however it was observed that 44.3% had some metastatic bone disease. It may have been inappropriate to offer chemotherapy or radiotherapy to manage the disease with the types of cancer or expected results.

Patients with CIBP commonly reported radiotherapy and bisphosphonates as anti-cancer treatments. Radiotherapy and bisphosphonates could be employed to specifically treat CIBP which could explain the disparity in current treatments between CIBP and NCP. The anti-cancer treatment could be utilised to treat the CIBP and therefore, while they can be used to treat NCP, you would expect to see

less prevalence in the NCP cohort as these treatments are not commonly employed.

Further research is therefore recommended to explore further treatment options for patients with NCP. While the data within the secondary analysis are limited it merits further exploration of the topic. With less treatment options available for patients with NCP compared to those with CIBP, it would be beneficial to explore the role of poly-pharmacy and early detection of pain to achieve meaningful analgesia for patients.

9.6 Summary

This chapter has shown that NCP is harder to predict, more difficult to treat effectively and has fewer treatment options available. It has further shown that while patients with CIBP and NCP express similarities in pain severity, patients with NCP often require more strong opioids while those with CIBP express poorer performance status. This chapter has identified more research is required to fully explore these four themes across a larger group of patients with CIBP, NCP and mixed pain. Only then can definitive assessment be developed.

A key aspect of assessment of CIBP and NCP has been considered as the verbal descriptors of CIBP and NCP. The following chapter will demonstrate the most common verbal descriptors of CIBP and NCP and discuss the implications of these on pain assessment.

Chapter 10: Key comparisons and Common Verbal descriptors

10.1 Introduction

The previous chapter explored four characteristics of patients with CIBP and NCP. These have afforded an insight to severity, impact and treatment of their pain. Although the primary objective of this project was to identify verbal descriptors of CIBP and NCP, it was also hoped to gain a better understanding about the two types of pain and the other features of patients who experience CIBP and NCP. This chapter summarises the key comparisons between the two groups with a focus on the common verbal descriptors selected by patients. Table 21 presents the characteristics considered as important for comparison.

Table 21: Analgesia and ECOG performance status

	NSAID	Adjuvant analgesia	ECOG
CIBP	n=52,43.3%	n=17,13.9%	2
NCP	n=22,36.1%	**n=43,70.5%**	2

From personal clinical experience and from literature in Chapter 1, it was expected that patients with CIBP and NCP would experience high levels of pain and perhaps be on multiple analgesia. To achieve effective pain management for patients it is important to have an appreciation of the mechanism of pain but moreover the impact of pain on the patient.

From Table 21, it is apparent that patients were five times more likely to be on adjuvant analgesia if they had NCP compared to those with CIBP (70.5% compared to 13.9%). This difference is remarkable considering the similar challenges in managing both types of pain. While it is known that adjuvant analgesia such as

antidepressants and anticonvulsants are often utilised to treat NCP, it would have been anticipated for the CIBP cohort to have expressed a higher use of adjuvant analgesia than 13.9%. This was certainly expected to be higher than 13.9% because often this patient group experience inadequate analgesia with opioids alone (Nabal, 2012). Table 22 offers further comparative information and each will be discussed below.

Table 22: Opioids, pain and verbal descriptors

	MEDD (Opioids)	Worst pain (VAS ≥ 5/10)	Average pain (VAS ≥ 5/10)	Most common descriptors
CIBP	76mg	N=93,79.5%	N=48,43.2%	Aching, Gnawing, Throbbing
NCP	155.6mg	**N=55,90.2%**	N=39,63.9%	Aching, Tender, Sharp

10.2 Morphine Equivalence Daily Dose

Another area which offered interesting comparison was the opioid morphine equivalence daily dose (MEDD). Patients with NCP were found to have a morphine equivalence daily dose of twice that of the patients in the CIBP cohort. This was higher than expected as opioids are known to be utilised in CIBP.

Sustained release opioids are utilised for background pain and immediate release opioid preparations are used in CIBP to manage incident pain and breakthrough pain as illustrated in Chapter 1. Opioid doses are escalated in parallel with pain severity until satisfactory management or unacceptable adverse effects, it would therefore have been anticipated that the CIBP cohort would have had a higher MEDD than those in the NCP group. The use of opioids to treat NCP has been documented as having limited effect. Opioids are usually used in combination with other analgesia which was discussed in Chapter 1. Moreover, for patients with NCP there are a number of adjuvant analgesia which are known to offer benefit and that have been used to treat NCP such as antidepressants, NSAIDs and

anticonvulsants as highlighted in Chapter 1. It could be postulated that patients with CIBP have access to a wider range of treatments compared to those with NCP which has potential to influence the opioid doses required.

The higher incidence of adjuvant use and the higher MEDD in the NCP would suggest those with NCP have worse pain than those in the CIBP group. It was further observed that patients with NCP more commonly scored a worst pain score of ≥ 5/10 across than in the CIBP cohort. Patients with NCP were also found to be more likely to have an average pain score of ≥ 5/10 than those with CIBP.

A difference in average pain could be explained by characterisation of CIBP and pain existing as a lower level background pain with episodes of worsening breakthrough pain. As described in Chapter 1, those with NCP may have experienced prolonged periods of heightened pain therefore expressing a higher average pain than those with CIBP.

10.3 Common verbal descriptors

While CIBP and NCP were expected to be more similar in severity and treatment the verbal descriptors were anticipated to be quite different. We know from the literature in Chapters 1, 5 and 6 that there are verbal descriptors associated with CIBP such as aching and dull and for NCP sharp and shooting.

From the data extracted for the secondary analysis, a prominent descriptor for CIBP and NCP was aching. Aching is traditionally associated with CIBP and not typically considered as an identifier of NCP. Throbbing was commonly selected in the CIBP cohort although this is traditionally thought to be an identifier of NCP. Tender is known to be linked to those with a painful bone metastasis however this was found as popular within the NCP group.

Within medicine, research is always being conducted. Research helps to drive change in healthcare through improved assessments, technology, tests, and treatments, while hopefully improving the patient experience.

Pain has been assessed by numerical scales, colourful visual analogue scales and verbal descriptors; however, we still have more to learn as a proportion of patients fail to achieve meaningful analgesia. The degree of meaningful analgesia will vary between each individual and it would be helpful for the patient and care

giver to have a pain assessment tool which facilitates diagnosis of pain and supports prompt initiation of appropriate treatment. Consideration of the emotional touchpoints along with validated pain assessment tools may offer a more comprehensive pain assessment.

10.4 Verbal descriptor similarities

Previous sections have considered the difference and similarities of characteristics such as pain intensity and analgesia. The following section focuses on any similarities between the verbal descriptors selected by participants. As health care providers we ask patients to rate their pain, describe their pain, and measure their pain. The aim of this MSc was to gain understanding of the verbal descriptors of CIBP and NCP to identify any difference between these two difficult and debilitating pain experiences. The desire is to characterise these two pain conditions and identify gaps in knowledge. Only through understanding of the patient experience can we determine if current pain assessments accurate capture and diagnose pain mechanisms. Once pain mechanism is accurately determined appropriate treatment can be commenced.

It is shown below in Table 23, the six verbal descriptors most commonly selected by patients with CIBP and NCP, this is further expressed in Figure 11.

Table 23: Common Verbal Descriptors

McGill descriptor (NCP)	CIBP	NCP
Aching	n=60 (50.0%)	n= 31 (50.8%)
Gnawing	n=51 (42.5%)	
Sharp	n=39 (32.5%)	n= 28 (45.9%)
Shooting	n=36 (30.0%)	n=24 (39.3%)
Stabbing		n= 24 (39.3%)
Tender	n=37 (30.8%)	n=34 (55.7%)
Throbbing	n=44 (36.7%)	n= 27 (44.3%)

For patients with CIBP, the most common is aching and for NCP, Tender was most commonly selected. The only unique descriptor to CIBP was gnawing and within the NCP cohort, stabbing was the only descriptor across the top six most common which was unique to NCP. The six most common descriptors feature several similarities across CIBP and NCP which are presented further in Figure 11.

Figure 11 - Crossover descriptors

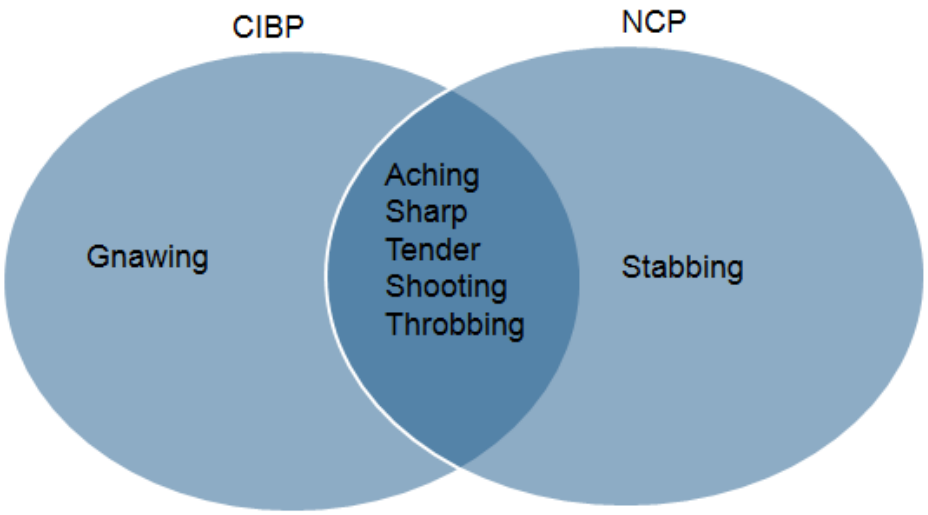


Figure 11 shows quite clearly that of most common descriptors for CIBP and NCP, five out of the six selected are the same for CIBP and NCP. This indicates that patients may describe a similar pain experience irrespective of mechanism of pain and these descriptors are not discriminating. Therefore, differentiating between CIBP and NCP using verbal descriptors would be inaccurate using current pain assessment tools which utilise such verbal descriptors to differentiate between CIBP and NCP. Descriptors currently used to define CIBP and NCP may be inaccurate and result in inadequate analgesia. It is therefore required that accurate assessment moves beyond the common toward the unique.

10.5 Summary

This chapter has shown a crossover of verbal descriptors between CIBP and NCP. Of the most commonly selected descriptors from the dataset, gnawing and stabbing were identified as more definitive of CIBP or NCP.

Due to the similarities in verbal descriptors across both pain groups, more research is required to develop an assessment tool which can discriminate between CIBP and NCP. An assessment tool is required to facilitate communication of their experience of pain.

A large prospective study to explore the themes identified within this chapter is recommended to investigate which verbal descriptors differentiate between CIBP and NCP. Using the verbal descriptors identified in this chapter, a prospective study could map of priorities for pain assessment. It would further allow exploration of verbal descriptors noted to be important within this chapter such as tender, aching and sharp. The following chapter will consider conclusions from this secondary analysis and explore recommendations for future research and practice.

Chapter 11: Conclusions and Recommendations

11.1 Conclusions

The secondary analysis utilised within this MSc has permitted exploration of verbal descriptors of CIBP and NCP in pre-existing datasets. While secondary analysis has proven challenging, it has afforded some insight into the patient pain experience. This chapter will offer conclusions on the study objectives drawn from the data analysed and will make recommendations for future practice and research.

11.2 Overall objective

Identify the verbal descriptors of CIBP and NCP.

Conclusion - Patients with CIBP selected aching as the most common verbal descriptor while tender was most commonly selected for NCP.

11.3 Secondary objectives

1. Identify verbal descriptors more commonly associated with CIBP by conducting a systematic review of the existing literature.

   Conclusion – CIBP is traditionally associated with dull or aching but also noted to be described within literature as annoying or gnawing.

2. Identify verbal descriptors more commonly associated with NCP by conducting a systematic review of the existing literature.

   Conclusion – NCP is described as aching and burning within literature.

3. To perform an examination of the relationship between pain intensity and gender, cancer type, performance status and analgesia.

   Conclusion - The data demonstrates no difference between gender and prevalence or reporting of either CIBP or NCP. Metastatic bone disease can serve as a predictor of CIBP but is more difficult to predict those at risk of NCP. Patients with CIBP had a lower ECOG performance status than those with NCP. Patients with NCP were found to have twice the daily opioid

requirements of those with CIBP, they were further noted have greater opioid requirements.

4. To examine any common or unique verbal descriptors of CIBP and NCP.

   Conclusion – Gnawing was found more common in patients with CIBP, while stabbing was found more common in NCP. A crossover of verbal descriptors was identified therefore many common verbal descriptors of pain could not be used to distinguish between CIBP and NCP.

11.4 Recommendations

Education

- Education of nurses and patients about communication of pain is recommended.
- Facilitating patients to communicate their pain effectively to achieve their goals to maintain quality of life.

Research

- Further research is required to assess the role of verbal descriptors in pain assessment. Particularly any role for use of verbal descriptors to diagnose pain origin.

Practice

- Person-centred pain assessment is recommended.
- Tools to support clinical assessment are useful for patients and healthcare providers to communicate and encourage discussion about pain.

11.5 Summary

In summary, verbal descriptors of CIBP and NCP have been shown to express similarities when using pain assessments tools which employ verbal descriptors. Further research is merited to explore both the common descriptors and also those unique to CIBP or NCP. Through this MSc it has been identified that a comprehensive assessment tool with task-orientated goal setting at its core would

be of benefit to both patients and nurses. This would facilitate accurate pain assessment and pain management where person-centred quality of life is the ultimate goal. The final chapter will offer reflection on the experience of undertaking a secondary analysis and consider any skills learned which would be taken forward to the next project.

Chapter 12: Reflection – Lessons learned

12.1 Introduction

The focus of this project was derived from experience in palliative care clinical trials. Exposure to this patient group enabled access to the datasets used for this MSc. Similar questionnaires employed different formats among different patient cohorts where pain was the common denominator. Discussions with a colleague surrounding the importance placed on verbal descriptors in pain assessment led to the development of this thesis. Throughout the process, from data extraction through to analysis and discussion, I have gained many new research skills and gained a greater understanding of the cancer journey and pain assessment. This chapter will discuss this journey and those new skills. It will further identify what could have been performed differently and what I would take forward to my next project.

12.2 Systematic review

The process of conducting systematic review of the literature was challenging but I gained new skills in critical appraisal. I gained confidence to argue with an experienced researcher on articles I felt merited inclusion in review. Using an adaptation of SIGN 50 checklist enabled me to focus on the key components of each article and apply the same methodical, critical approach. I further learned to have conviction in my review of research articles, to assess methodology and make comment on rigour. Through describing my methodology, I also learned of other techniques such as PICO which can support systematic review of the literature and this knowledge I will take onto future projects.

12.3 Database management

Creation of a de novo database through data extraction across three studies was challenging. Learning to assess appropriate data for inclusion was aided by an experienced statistician who reviewed the data entered into the de novo database. The statistician further assisted by reviewing the database design and screening appropriate exploratory outcome measures. Through the process I developed a high threshold for data inclusion in the de novo database as the data had to be

sufficiently complete to allow comparison. I identified challenges in comparing data across studies and the expectations of data to answer outcomes. I found it important to set clearly defined aims and goals while also managing sample size expectation. I firmly believe these key areas of will help with designing future research and also for advising others considering a secondary data analysis.

While I have always known the importance of complete data I have gained a greater understanding of the implications of missing data on potential for secondary analysis and have applied this knowledge in my work as a research nurse.

12.4 Resubmission

Following VIVA examination, and consideration of the comments, I was afforded an opportunity to revisit my thesis and revise the work undertaken. Revision of this project has taught me to ensure I make detailed notes to enable the work to be reproduced and to understand how I made assessments or study decisions. I learned that I must be explicit in my explanation of my research process and to signpost for the reader how I achieved study outcomes.

12.5 Verbal descriptors

I previously considered CIBP and NCP as distinct and separate pain experiences. Through this MSc I have learned more about verbal descriptors and the crossover between CIBP and NCP. I have a greater understanding of the impact undertreated pain on the patient and the importance of comprehensive pain assessment. This has affected my discussions with patients when assessing pain where I now rely on patient description before prompting with my preconceived descriptors. I have further disseminated my experience with colleagues and opened discussions and reflection around pain and pain assessment.

12.6 Limitations of the study

Extracting data from existing datasets offered challenges due to incomplete data and difficulty in direct comparison across three datasets. The secondary nature of this study meant the results could only be interpreted against the anonymised patient sample available and therefore any generalisations are limited. Careful selection of data sets is imperative to maximise comparability to ultimately

improve patient care. Using reflection throughout the process of developing a de novo database allowed any learning from the CIBP data extraction to be transferred into extraction of NCP data. As a part-time student, feasibility was key to the success of the research however; having reflected on the processes a key contribution to the patient care has been identified.

Appendix 1: Descriptors of CIBP and NCP

Database Coding Version 3

Reason for attendance

T	Treatment of bone disease or its complication
O	Other

Primary cancer site

Code	Site
1	Breast
2	Lung
3	Prostate
4	Renal
5	Large Bowel
6	Anal
7	Pancreatic
8	Stomach
9	Head and Neck
10	Brain
11	Thyroid
12	Myeloma
13	Lymphoma
14	Ovarian
15	Mesothelioma
16	Cervical
17	Oesophageal
18	Bone
19	Bladder
20	Uterine

21	Unknown
22	Plasmacytoma
23	Sarcoma
24	Carcinoid
25	Chronic Myeloid Leukaemia
26	Squamous cell carcinoma
27	Adenoid cystic carcinoma
28	Rectum
29	Waldenstrom's macroglobulinaemia

Disease Status

N	No active disease
LD	Local disease
LR	Loco-regionally advanced
M	Metastatic disease

Metastatic sites

B	Bone unspecified
BS	Bone Single
BM	Bone Multiple
LI	Liver
LU	Lung
BR	Brain
AD	Adrenal
PE	Peritoneal
OV	Ovarian
PL	Pleural
LN	Lymph Node
RE	Renal
SK	Skin
LM	Leptomeningeal
MD	Mediastinum

VA	Vaginal
SC	Subcutaneous
CU	Cutaneous
AB	Abdomen

Current anti-cancer treatment

N	None
H	Hormonal
C	Chemotherapy
RT	Radiotherapy
RI	Radioisotopes
S	Surgery
BI	Biphosphonates
MA	Monoclonal Antibody

Previous treatment to Pain site

RT	Radiotherapy
C	Chemotherapy
S	Surgical
RA	Regional anaesthesia
H	Hormonal
RI	Radioisotope
BI	Biphosphonates

Opioids

1	Nil
2	MST
3	Oxycontin
4	Hydromorphone SR
5	Severedol
6	Oramorph

7	Oxynorm
8	Hydromorphone IR
9	Diamorphine
10	Fentanyl
11	Zomorph
12	Alfentanyl
13	Methadone
14	Unspecified strong opioid

Non-Opioids

1	Ibuprofen
2	Voltarol
3	Naproxen
4	Paracetamol
5	Co-Codamol 8/500
6	Co-Codamol 30/500
7	Codydramol
8	Dihyrdrocodeine
9	Rofecoxib
10	None
11	Celebrex
12	Homeopathic remedies
13	Amitriptlline
14	Lignocaine patch
15	Gabapentin
16	Coproxamol
17	Aspirin
18	Flurbiprofen
19	Imipramine
20	Arthrotec
21	Dexamethasone
22	Fluoxetine
23	Venlafaxine

24	Unspecified NSAID
25	Unspecified anticonvulsant
26	Unspecified antidepressant
27	Unspecified other
28	Unspecified weak opioid
29	Unspecified simple analgesia
30	Ketamine
31	Tramadol
32	Buscopan
33	Duloxetine
34	Pregabalin

Time since treatment (tx) to pain site

1	>6 weeks
2	<6 weeks
3	Current systemic treatment likely to reduce pain

Pain Site

Site of Pain	Code
Lumbar Spine	1
Thigh	2
Scapula	3
Shoulder	4
Cervical spine	5
Thoracic Spine	6

Sacrum	7
Groin	8
Leg	9
Hip	10
Arm	11
Lower Chest Wall	12
Upper Chest Wall	13
Rib	14
Sacro-Ileac Joint	15
Other	16
Buttocks	17
Foot	18
Pelvis	19
Groin	20
Femur	21
Tibia/Fibula	22
Skull	23
Sternum	24
Radius/Ulna	25
Hands	26

McGill Pain Descriptors

Subsections	Word	Code
Temporal	Flickering	1
	Quivering	2
	Pulsing	3
	Throbbing	4
	Beating	5
	Pounding	6
Spatial	Jumping	7
	Flashing	8
	Shooting	9
Punctate pressure	Pricking	10
	Boring	11
	Drilling	12
	Stabbing	13
	Lancinating	14
Incisive pressure	Sharp	15
	Cutting	16
	Lacerating	17
Constrictive pressure	Pinching	18
	Pressing	19
	Gnawing	20

	Cramping	21
	Crushing	22
Traction pressure	Tugging	23
	Pulling	24
	Wrenching	25
Thermal	Hot	26
	Burning	27
	Scalding	28
	Searing	29
Brightness	Tingling	30
	Itchy	31
	Smarting	32
	Stinging	33
Dullness	Dull	34
	Sore	35
	Hurting	36
	Aching	37
	Heavy	38
Misc (sensory)	Tender	39
	Taut	40
	Rasping	41
	Splitting	42

Tension	Tiring	43
	Exhausting	44
Autonomic	Sickening	45
	Suffocating	46
Fear	Fearful	47
	Frightful	48
	Terrifying	49
Punishment	Punishing	50
	Gruelling	51
	Cruel	52
	Vicious	53
	Killing	54
Misc (Affective)	Wretched	55
	Blinding	56

Appendix 2 - ECOG Performance status

- 0 – Asymptomatic (Fully active, able to carry on all predisease activities without restriction)
- 1 – Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
- 2 – Symptomatic, <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours)
- 3 – Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
- 4 – Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
- 5 – Death

Appendix 3 - Systematic Review Checklist

Study identification (*Include author, title, year of publication, journal title, pages*)			
Guideline topic:			
Checklist completed by:			
Section 1: Internal validity			
1.0	What is the study type	Case-control RCT Intervention	Intervention Review Other:
1.1	Does the paper include CIBP or NCP or both	CIBP NCP	Both Neither
1.2	The study addresses patient descriptors of CIBP or NCP	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	A description of the methodology used is included	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	Were any assessment tools used eg BPI or McGill		
1.5	What was the sample size?	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

1.6	Study quality is assessed and taken into account.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	Does this answer key question: verbal descriptors of CIBP and NCP?	Yes No	Unsure
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias? Code ++, +, or –		
2.2	If coded as +, or – what is the likely direction in which bias might affect the study results?		
2.3	Should this be included in literature review?	Yes Unsure	No
2.4	Comments		

Appendix 4 - SF- McGill Pain Questionnaire

SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME:_____ DATE:_____

	NONE	MILD	MODERATE	SEVERE
1. THROBBING	0) ____	1) ____	2) ____	3) ____
2. SHOOTING	0) ____	1) ____	2) ____	3) ____
3. STABBING	0) ____	1) ____	2) ____	3) ____
4. SHARP	0) ____	1) ____	2) ____	3) ____
5. CRAMPING	0) ____	1) ____	2) ____	3) ____
6. GNAWING	0) ____	1) ____	2) ____	3) ____
7. HOT-BURNING	0) ____	1) ____	2) ____	3) ____
8. ACHING	0) ____	1) ____	2) ____	3) ____
9. HEAVY	0) ____	1) ____	2) ____	3) ____
10. TENDER	0) ____	1) ____	2) ____	3) ____
11. SPLITTING	0) ____	1) ____	2) ____	3) ____
12. TIRING-EXHAUSTING	0) ____	1) ____	2) ____	3) ____
13. SICKENING	0) ____	1) ____	2) ____	3) ____
14. FEARFUL	0) ____	1) ____	2) ____	3) ____
15. PUNISHING-CRUEL	0) ____	1) ____	2) ____	3) ____

0 NO PAIN — 10 WORST POSSIBLE PAIN

P P I

0	NO PAIN	____
1	MILD	____
2	DISCOMFORTING	____
3	DISTRESSING	____
4	HORRIBLE	____
5	EXCRUCIATING	____

References:

(CRUK), C. R. U. (2011) CancerStats Incidence 2008-UK.

(SIGN), S. I. G. N. (2008) SIGN 50 A guideline developer's handbook.

APONTE, J. (2010) Key elements of large survey data sets. *Nursing Economics,* 28**,** 27-36.

AZEVEDO SAO LEAO FERREIRA, K., KIMURA, M. & JACOBSEN TEIXEIRA, M. (2006) The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? *Support Care Cancer,* 14**,** 1086-93.

BENEDETTI, C., BROCK, C., CLEELAND, C., COYLE, N., DUBÉ, J.E., FERRELL, B., HASSENBUSCH, S., JANJAN, N.A., LEMA, M.J., LEVY, M.H., LOSCALZO, M.J., LYNCH, M., MUIR, C., OAKES, L., O'NEILL, A., PAYNE, R., SYRJALA, K.L., URBA, S., WEINSTEIN, S.M. (2000) NCCN Practice Guidelines for Cancer Pain. *Oncology,* 14**,** 135-150.

BENNETT, M. (2001) The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain,* 92**,** 147-57.

BENNETT, M. I., ATTAL, N., BACKONJA, M.M., BARON, R., BOUHASSIRA, D., FREYNHAGEN, R., SCHOLZ, J., TÖLLE, T.R., WITTCHEN, H.U., JENSEN, T.S. (2007) Using screening tools to identify neuropathic pain (Topical review). *Pain,* 127.

BRUERA, E., PORTENOY, R. (2003) *Cancer Pain Assessment and Management*, Cambridge University Press.

CAMPBELL, V. (2011) The challenges of cancer pain assessment and management. *Ulster Medical Journal,* 80**,** 104-106.

CARACENI, A. & PORTENOY, R. K. (1999) An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain,* 82**,** 263-74.

CARACENI, R. K., PORTENOY, R.K., A WORKING ROUP OF THE IASP TASK FORCE ON CANCER PAIN (1999) An International survey of cancer pain characteristics and syndromes. *Pain,* 82**,** 263-274.

CHANDLER, J., HOPEWELL, S. (2013) Cochrane methods - twenty years experience in developing systematic review methods. *Systematic Reviews,* 2**,** 1-6.

CHEING, G. L. & LUK, M. L. (2005) Transcutaneous electrical nerve stimulation for neuropathic pain. *J Hand Surg Br,* 30**,** 50-5.

CITROME, L., KETTER, T.A. (2013) When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *International Journal of Clinical Practice,* 67**,** 407-411.

CLEELAND, C. S. (2006) The measurement of pain from metastatic bone disease:capturing the patient's experience. *Clinical Cancer Research,* 12**,** 6236s-6242s.

COLEMAN, R. E. (1997) Skeletal complications of malignancy. *Cancer,* 80**,** 1588-94.

COLEMAN, R. E. (2000) Management of Bone Metastases. *The Oncologist,* 5**,** 463-470.

COLEMAN, R. E. (2006) Clinical Features of Metastatic Bone Disease and Risk of Skeletal Morbidity. *Clinical Cancer Research,* 12**,** 6243s-6249s.

COLVIN, L. & FALLON, M. (2010) Cancer-induced bone pain. IN HANKS, G., CHERNY, N., CHRISTAKIS, N., FALLON, M., KAASA, S. & PORTENOY, R. K. (Eds.) *Oxford Textbook of Pallaitive Medicine*. Fourth ed. New York, Oxford University Press.

COLVIN, L., FALLON, M. (2008) Challenges in cancer pain management- bone pain. *European Journal of Cancer,* 44**,** 1083-1090.

COYLE, N. & SCULCO, L. (2004) Expressed desire for hastened death in seven patients living with advanced cancer: a phenomenologic inquiry. *Oncol Nurs Forum,* 31**,** 699-709.

CRUK, C. R. U. (2008) Latest UK Cancer Incidence and Mortality Summary- numbers.

DEANDREA, S., CORLI, O., CONSONNI, D., VILLANI, W., GRECO, M.T., APOLONE, G. (2014) Prevalence of Breakthrough Cancer Pain: A Systematic Review and a Pooled Analysis of Published Literature. *Journal of Pain and Symptom Management,* 47**,** 57-76.

DEWAR, B., MACKAY, R., SMITH, S., PULLIN, S., TOCHER, R. (2010) Use of emotional touchpoints as a method of tapping into the experience of receiving compassionate care in a hospital setting. *Journal of Research in Nursing,* 15**,** 29-41.

DWORKIN, R. H., TURK, D.C., PEIRCE-SANDNER, S., BARON, R., BELLAMY, N., BURKE, L.B., CHAPPELL, A., CHARTIER, K., CLEELAND, C.S., COSTELLO, A., COWAN, P., DIMITROVA, R., ELLENBERG, S., FARRAR, J.T., FRENCH, J.A., GILRON, I., HERTZ, S., JADAD, A.R., JAY, G.W., KALLIOMAKI, J., KATZ, N.P., KERNS, R.D., MANNING, D.C., MCDERMOTT, M.P., MCGRATH, P., NARAYANA, A., PORTER, L., QUESSY, S., RAPPAPORT, B.A., RAUSCHKOLB, C., REEVE, B., RHODES, T., SAMPAIO, C., SIMPSON, D.M., STAUFFER, J.W., STUCKI, G., TOBIAS, J., WHITE, R.E., WITTER, J. (2010) Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain,* 149**,** 177-193.

ELLIOTT, E. (2014) Psychological impact of cancer pain on patients and their quality of life. *British Journal of Nursing,* 23**,** 805-8.

FARRAR, J. T., YOUNG, J. P., LAMOREAUX, L., WERTH, J. L. & POOLE, R. M. (2001) Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain,* 94**,** 149-158.

FERRELL, B. R., JUAREZ, G. & BOURNEMAN, T. (1999) Use of routine and breakthrough analgesia in home care. *Oncology Nursing Forum,* 26**,** 1655-1661.

FINNERUP, N. B. & JENSEN, T. S. (2010) Neuropathic pain. IN HANKS, G., CHERNY, N. I., CHRISTAKIS, N. A., FALLON, M., KAASA, S. & PORTENOY, R. K. (Eds.) *Oxford Textbook of Palliative Medicine*. Fourth ed. New York, Oxford University Press.

FINNERUP, N. B., OTTO, M., MCQUAY, H. J., JENSEN, T. S. & SINDRUP, S. H. (2005) Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain,* 118**,** 289-305.

FISHER, C. B. H., K., BOYCE,C., DUSTER,T., FRANK, D.A., GRISSO,T., LEVINE, R.J., MACKLIN, R., BEALE SPENCER, M.,TAKANISHI, R., TRIMBLE, J.E., ZAYAS, L.H. (2002) Research Ethics for Mental Health Science Involving Ethnic Minority Children and Youths. *American Psychologist,* 57 1024-1040.

GIBBINS, J., BHATIA, R., FORBES, K., REID, C.M. (2014) What do patients with advanced incurable cancer want from the management of their pain - a qualitative study. *Palliative Medicine,* 28**,** 71-78.

GILRON, I., BAILEY, J. M., TU, D., HOLDEN, R. R., WEAVER, D. F. & HOULDEN, R. L. (2005) Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med,* 352**,** 1324-34.

GOBLIRSCH, M. J., ZWOLAK, P. & CLOHISY, D. R. (2005) Survival in patients operated on for pathological fracture: implications for end-of-life orthopedic care. *Journal of Clinical Oncology,* 96**,** 682-688.

GRAY, P. (2008) Acute neuropathic pain: diagnosis and treatment. *Current Opinion in Anaesthesiology.,* 21**,** 590-595.

GROND, S., RADBRUCH, L., MEUSER, T., SABATOWSKI, R., LOICK, G. & LEHMANN, K. A. (1999) Assessment and treatment of neuropathic cancer pain following WHO guidelines. *Pain,* 79**,** 15-20.

GROND S, Z. D., DIEFENBACH C, RADBURCH L, LEHMAN KA (1996) Assessment of cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. *Pain,* 64**,** 107-114.

HAGGER-JOHNSON, G. (2014) *Introduction to Research Methods and Data Analysis in the Health Sciences,* Oxon, Routledge.

HARRINGTON, K. D. (1997) Orthopedic surgical management of skeletal complications of malignancy. *Cancer,* 15**,** 1614-1627.

HARRIS, A.D., MCGREGOR, J.C., PERENCEVICH, E.N., FURUNO, J.P., ZHU, J., PETERSON, D.E., FINKELSTEIN, J. (2006) The Use and Interpretation of Quasi-Experimental Studies in Medical Informatics. Journal of the American Medical Informatics Association. Vol 13(1) pp 16-23

HEALEY, J. H., TYLER, W.K. (2009) The role of orthopaedic surgery in the palliative care of patients with cancer. IN HANKS, G., CHERNEY, N.I., CHRISTAKIS, N.A., FALLON, M., KAASA, S., PORTENOY, R.K. (Ed.) *Oxford Textbook of Palliative Medicine*. 4th ed. Oxford, Oxford University Press.

HOLLY, C., WARNER SALMOND, S., SAIMBERT, M.K. (2012) *Comprehensive Systematic Review for Advanced Nursing Practice,* New York, Springer Publishing Company LLC.

HOLTAN, A. & KONGSGAARD, U. E. (2009) The Use of Pain Descriptors in Cancer Patients. *Journal of Pain and Symptom Management,* 38**,** 208-215.

HOUDE, S. C. (2009) The Systematic Review of the Literature- A Tool for Evidence-Based Policy. *Journal of Gerontological Nursing,* 35**,** 9-12.

HUSSAIN, A., PRASAD, K.S. (2001) Surgical Treatment of Pathological Fractures of Long Bones. *International Journal of Current Medical Science & Practice,* 8**,** 256-261.

HUSTON, P., NAYLOR, D. (1996) Health services research: reporting on studies using secondary data sources. *Canadian Medical Association,* 155**,** 1697-1702.

IASP (2011) IASP Taxonomy.

IASP, I. A. F. T. S. O. P. (2008) Total Cancer Pain. *Global Year Against Cancer Pain*.

JANJAN, N. (2001) Bone metastases: Approaches to management. *Seminars in Oncology,* 28**,** 28-43.

Jekel, J.F., Katz, D.L., Wild, D., Elmore, J.G. (2007) Epidemiology, Biostatistics, and Preventative Medicine. 3rd Edition. Saunders Elsevier.

JENSEN, M. P., CHODROFF, M. J. & DWORKIN, R. H. (2007) The impact of neuropathic pain on health-related quality of life: review and implications. *Neurology,* 68**,** 1178-82.

KANE, C. M., HOSKIN, P., BENNETT, M.I. (2015) Cancer Induced Bone Pain. *British Medical Journal,* 350:h315.

KERBA, M., WU, J. S. Y., DUAN, Q., HAGAN, N. A. & BENNETT, M. I. (2010) Neuropathic Pain Features in Patients With Bone Metastases Referred for Palliative Radiotherapy. *Journal of Clinical Oncology,* In Print.

KOIZUMI, M., YOSHIMOTO, M., KASUMI, F., IWASE, T. & OGATA, E. (2010) Post-operative breast cancer patients diagnosed with skeletal metastasis without bone pain had fewer skeletal-related events and deaths than those with bone pain. *BMC Cancer,* 10**,** 1-9.

KUMAR, S.P. (2011) Utilization of brief pain inventory as an assessment tool for pain in patients with cancer: a focused review. Indian Journal of Palliative Care. Vol 17(2) pp 108-115

LAIRD, B., COLVIN, L., FALLON, M. (2008) Management of Cancer Pain: Basic Principles and Neuropathic Pain. *European Journal of Cancer,* 44**,** 1078-1082.

LAIRD, B. J., WALLEY, J., MURRAY, G. D., CLAUSEN, E., COLVIN, L. A. & FALLON, M. T. (2010a) Characterization of cancer-induced bone pain: an exploratory study. *Support Care Cancer*.

LEMA, M. J., FOLEY, K. M. & HAUSHEER, F. H. (2010) Types and Epidemiology of Cancer-Related Neuropathic Pain: The Intersection of Cancer Pain and Neuropathic Pain. *The Oncologist,* 15**,** 3-8.

LICHTENSTEIN, A. H., YETLEY, E.A., LAU, J. (2008) Application of Systematic Review Methodology to the Field of Nutrition. *The Journal of Nutrition.,* 138**,** 2297-2306.

LOKE, Y. K., PRICE, D., HERXHEIMER, A. (2007) Systematic reviews of adverse effects: framework for a structured approach. *BMC Medical Research Methodology,* 7**,** 1-9.

LOVE, C., DIN, A.S., TOMAS, M.B., KALAPPARAMBATH, T.P., PALESTRO, C.J. (2003) Radionuclide Bone Imaging: An Illustrative Review *RadioGraphics,* 23.

LUCKETT, T., DAVIDSON, P.M., GREEN, A., BOYLE, F., STUBBS, J., LOVELL, M. (2013) Assessment and Management of Adult Cancer Pain: A Systematic Review and Synthesis of Recent Qualitative Studies Aimed at Developing Insights for Managing Barriers and Optimizing Facilitators Within a Comprehensive Framework of Patient Care. *Journal of Pain and Symptom Management,* 46**,** 229-253.

MACARTHUR, J. (2014) Embedding compassionate care in local NHS practice. *Royal College of Nursing Conference*. London, University of Glasgow.

MAGGE, T., LEE, S.M., GIULIANO, K.K., MUNRO, B. (2006) Generating new knowledge from existing data: The use of large data sets for nursing research. *Nursing Research,* 55**,** S50-S56.

MANFREDI, P. L., GONZALES, G. R., SADY, R., CHANDLER, S. & PAYNE, R. (2003) Neuropathic Pain in Patients with Cancer. *Journal of Palliative Care,* 19**,** 115-118.

MANTYH, P. W., CLOHISY, D.R., KOLTZENBURG, M., HUNT, S.P. (2002) Molecular mechanisms of cancer pain. *Nature Reviews Cancer,* 2**,** 201-209.

MATHIAS, B., PARRY-JONES, B., HUWS, J.C. (2014) Individual experiences of an acceptance-based pain management programme: An interpretative phenomenological analysis. *Psychology & Health,* 29**,** 279-296.

MCCAFFERY, M. (1983) *Nursing the patient in pain,* London, Harper and Row.

MCDONAGH, M., PETERSON, K., RAINA, P., CHANG, S., SHEKELLE, P. (2013) Avoiding Bias in Selecting Studies. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

MCQUAY, H. J., COLLINS, S. L., CARROLL, D. & MOORE, R. A. (2000) Radiotherapy for the palliation of painful bone metastases. *Cochrane Database Syst Rev*, CD001793.

MCQUAY, H. J., COLLINS, S.L., CARROLL, D., MOORE, R.A. (2000) Radiotherapy for the palliation of painful bone metastases. *Cochrane Database Systematic Review*, 2.

MELZACK, R. (1975) The McGill Pain Questionnaire: major properties and scoring methods. *Pain.*, 1, 277-299.

MELZACK, R. (1987) The short-form McGill pain questionnaire. *Pain*, 30, 191-197.

MERCADANTE, S. (1997a) Malignant bone pain: pathophysiology and treatment. *Pain*, 69, 1-18.

MERCADANTE, S. (1997b) Malignant bone pain: pathophysiology and treatment. *Pain*, 69, 1-18.

MOCK, V., ATKINSON, A., BARSEVICK, A., CELLA, D., CIMPRICH, B., CLEELAND, C., DONNELLY, J., EISENBERGER, M. A., ESCALANTE, C., HINDS, P., JACOBSEN, P. B., KALDOR, P., KNIGHT, S. J., PETERMAN, A., PIPER, B. F., RUGO, H., SABBATINI, P. & STAHL, C. (2000) NCCN Practice Guidelines for Cancer-Related Fatigue. *Oncology (Williston Park)*, 14, 151-61.

MOHER, D., SHAMSEER, L., CLARKE, M., GHERSI, D., LIBERATI, A., PETTICREW, M., SHEKELLE, P., STEWART, L.A., PRISMA-P GROUP. (2015) Preferred Reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. *https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/2046-4053-4-1*

NABAL, M., LIBRADA, S., RE DONDO, M.J., PIGNI, A., BRUNELLI, C., CARACENI, A. (2012) The role of paracetamol and nonsteroidal anti-inflammatory drugs in addition to WHO Step III opioids in the control of pain in advanced cancer. A systematic review of the literature. *Palliative Medicine*, 26, 305-312.

NATHAN, S. S., HEALEY, J. H., MELLANO, D., HOANG, B., LEWIS, I., MORRIS, C. D., ATHANASIAN, E. A. & BOLAND, P. J. (2005) Survival in Patients Operated on for Pathologic Fracture: Implication for End-of-Life Orthopedic Care. *Journal of Clinical Oncology*, 23, 6072-6082.

NATHAN, S. S., HEALEY, J.H., MELLANO, D., HOANG, B., LEWIS, I., MORRIS, C.D., ATHANASIAN, E.A., BOLAND, P.J. (2005) Survival in Patients Operated on for Pathologic Fracture: Implication for End-of-life Orthopedic Care. *Journal of Clinical Oncology.*, 23, 6072-6082.

NERSESYAN, H., SLAVIN, K. V. (2007) Current approach to cancer pain management: Availability and implications of different treatment options. . *Therapeutics and Clinical Risk Management,* 3**,** 381-400.

NICOLL, L. H., BEYEA, S.C. (1999) Using secondary data analysis for nursing research. *Association of peri-Operative Registered Nurses Journal,* 69**,** 428-433.

PAICE, J. A. (2003) Mechanisms and Management of Neuropathic Pain in Cancer. *Supportive Oncology,* 1**,** 107-120.

PEREZ, D. J., POWLES, T. J., MILAN, J., GAZET, J. C., FORD, H. T., MCCREADY, V. R., MACDONALD, J. S. & COOMBES, R. C. (1983) Detection of breast carcinoma metastases in bone: relative merits of X-rays and skeletal scintigraphy. *Lancet,* 2**,** 613-6.

PHILLIPS, C., MAIN, C., BUCK, R., AYFWARD, M., WYNNE-JONES, G., FARR, A. (2008) Prioritising Pain in Policy making: The needfor a whole systems perspective. *Health Policy,* 88**,** 166-175.

POLIT, D.F., BECK TATANO, C. (2013) Essentials of Nursing Research: Appraising Evidence for Nursing Practice. 8th Edition. Lippincott Williams & Wilkins.

POLLACK, C. D. (2001) Measuring Health Care Outcomes with Secondary Data. *Outcomes Management for Nursing Practice,* 5**,** 99-101.

PORTENOY, R. K., FORBES, K., LUSSIER, D. & HANKS, G. (2004) Difficult pain problems: an integrated approach. IN DOYLE, D., HANKS, G., CHERNY, N. & CALMAN, K. (Eds.) *Oxford Textbook of Palliative Medicine*. 3rd ed. Oxford, Oxford University Press.

PORTENOY, R. K. & MCDONALD, A. A. (2006) How to use antidepressants and anticonvulsants as adjuvant analgsics in the treatment of neuropathic cancer pain. *The Journal of Supportive Oncology.,* 4**,** 43-52.

QUASTHOFF, S., HARTUNG, H.P. (2002) Chemotherapy-induced peripheral neuropathy *Journal of Neurology* 249**,** 9-17.

SHAIOVA, L. (2006) Difficult pain syndromes: bone pain, visceral pain, and neuropathic pain. *Cancer J,* 12**,** 330-40.

SIGN (2008) Scottish Intercollegiate Guidleines Network; A Guideline Developers Handbook. 50**,** 2008.

SMITH, V., DEVANE, D., BEGLEY, C.M, CLARKE, M. (2011) Methodology in conducting a systemtatic review of systematic reviews of healthcare interventions. *BMC Medical Research Methodology,* 11**,** 1-6.

SYKES, J., JOHNSON, R. & HANKS, G. W. (1997) ABC of palliative care. Difficult pain problems. *BMJ,* 315**,** 867-9.

TASMUTH, T., VON SMITTEN, K. & KALSO, E. (1996) Pain and other symptoms during the first year after radical and conservative surgery for breast cancer. *British Journal of Cancer,* 74**,** 2024-2031.

TODD, A. M. H., B J.A. LAIRD, B.J.A., BOYLE, D., BOYD, A.C., COLVIN, L.A., FALLON, M.T. (2009) A Systematic Review Examining the Literature on Attitudes of Patients with Advanced Cancer Toward Research. *Journal of Pain and Symptom Management,* 37**,** 1078-1085.

TOWERY, S. M. A., FERNANDEZ, E. (1996) Reclassification and Rescaling of McGill Pain Questionnaire Verbal Descriptors of Pain Sensation: A Replication. *Clinical Journal of Pain,* 12**,** 270-276.

TREEDE, R. D., JENSEN, T. S., CAMPBELL, J. N., CRUCCU, G., DOSTROVSKY, J. O., GRIFFIN, J. W., HANSSON, P., HUGHES, R., NURMIKKO, T. & SERRA, J. (2008) The epidemiology of chronic pain of predominantly neuropathic pain and a grading system for clinical use: consensus statement on clinical and research diagnostic criteria. *Neurology,* 70**,** 1630-1635.

URCH, C. (2004) The pathophysiology of cancer-induced bone pain: current understanding. *Palliat Med,* 18**,** 267-74.

VAINIO, A., AUVINEN, A. (1996) Symptom Prevalence Group: Prevalence of symptoms among patinets with advanced cqancer: an international collaborative study. *Journal of Pain and Symptom Management.,* 12**,** 3-10.

W.H.O, W. H. O. (2009) Cancer. Fact Sheet No 297 ed.

WALSH, D., DONNELLY, S., RYBICKI, L. (2000) The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. *Supportive Care in Cancer,* 8**,** 175-179.

WALSH, D. & HAUSER, K. (2006) Symptoms in cancer: the myth of the pain, depression, and fatigue cluster. *Journal of Palliative Care,* 22**,** 211.

WILKIE, D. J., HUANG, H., REILLY, N. & CAIN, K. C. (2001) Nociceptive and Neuropathic Pain in Patients With Lung Cancer: A Comparison of Pain Quality Descriptors. *Journal of Pain and Symptom Management,* 22**,** 889-910.

WINDLE, P. E. (2010) Secondary data analysis: Is it useful and Valid? *Journal of PeriAnesthesia Nursing.,* 25**,** 322-324.

WORLD HEALTH ORGANIZATION (1996) *Cancer pain relief,* Geneva, WHO.

WU, J. S. Y., WONG, R., JOHNSTON, M., BEZJAK, A., WHELAN, T. (2003) Meta-Analysis of Dose-Fractionation Radiotherapy Trials for the Palliationof Painful Bone Metastases. *International Journal of Radiation Oncology, Biology & Physics,* 55**,** 594-605.