Difficult Cancer Pain

An examination of physical and psychological components

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Declaration

This thesis was composed by me. This was conducted whilst in post as a National Cancer Research Institute (SuPaC) Research Fellow at the University of Edinburgh. All chapters were written by me. Where others have been involved, this has been acknowledged.

Chapter 2 – The initial data collection was conducted by John Walley and Eleanor Clausen. Professor Murray (Professor of Medical Statistics) provided the additional statistical input necessary for the data analysis. All other aspects were undertaken by me.

Chapter 3 - The initial data collection was conducted by John Walley and Eleanor Clausen. Professor Murray (Professor of Medical Statistics) provided the additional statistical input necessary for the data analysis. All other aspects were undertaken by me.

Chapter 4 – The idea for a systematic review of cancer pain and depression was mine. The initial literature searching and review was conducted by me. Angela Scott (née Boyd) provided an independent review of papers which were potentially eligible and assisted with the interpretation of the included studies. This chapter was published: (Laird et al., 2008)

Chapter 5 – The idea for a longitudinal study between pain and depression was mine. I collected approximately 50% of the data for this study with the remainder provided by Angela Scott. I collated all the data, constructed a database and subsequently analysed all the data. Helen Christie MSc (Medical Statistician) provided statistical input necessary for the data analysis.

Chapters 6 and 7 – These chapters were based on clinical trials conducted by Professor KCH Fearon. The data and statistical analysis was performed by Professor Murray.

The work was conducted in the Beatson West of Scotland Cancer Centre, Glasgow and the Western General, Edinburgh. Other than the data in chapters 6 and 7, all other patients mentioned herein were under the care of one or other of these centres.

Abstract

Aims: The aims of this thesis are to characterise clinically, neuropathic cancer pain and CIBP, to examine the relationship between cancer pain and depression, to explore the relationship between pain and systemic inflammation and the possibility of pain, depression and fatigue existing, as a symptom cluster.

Methods: A combination of observational study, systematic review, longitudinal study and secondary data analysis methodology were utilised, as appropriate to the specific area being examined.

Results: In neuropathic cancer pain and cancer induced bone pain, worst pain is most closely associated with the impact of pain on function. In these pain syndromes, breakthrough pain is often of rapid onset, severe intensity and short duration. The systematic review demonstrated that there is insufficient evidence to support an interdependent relationship between pain and depression. The longitudinal study demonstrated that as pain improves, there is a trend towards an improvement in depression and there is an improvement in the Hospital Anxiety and Depression Scale (HADS) score. Pain, depression and fatigue cluster together in cancer patients although there is insufficient information to suggest systemic inflammation as an underlying cause. There is, however, a significant relationship between pain and systemic inflammation.

Conclusions: The difficult cancer pain syndromes of neuropathic cancer pain and cancer induced bone pain are best assessed using "worst pain" as a measure of the impact of pain on function. Pain and depression in cancer are likely to be related to one another although further research is needed to confirm this. Pain, depression and fatigue exist together as a symptom cluster in specific groups of cancer patients. Pain is related to systemic inflammation in cancer.

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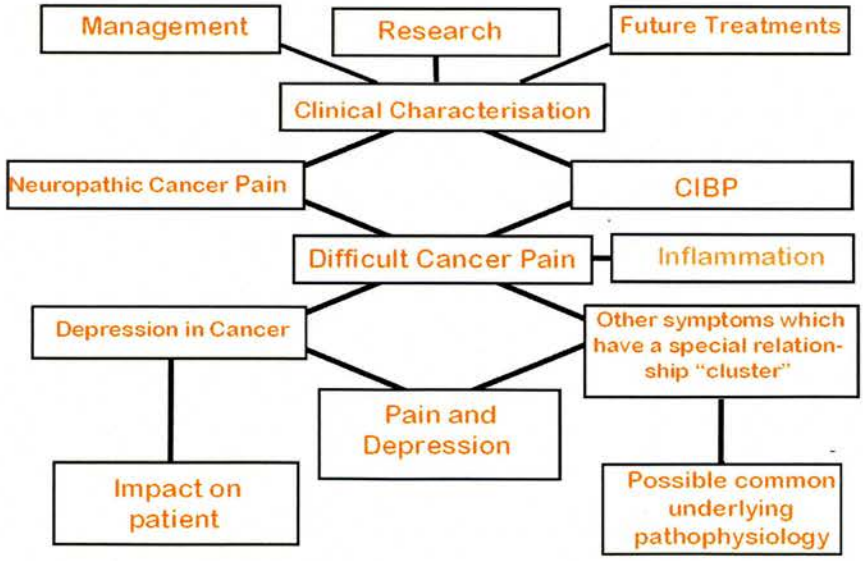
Chapter 1. Introduction

1.1. Overview

Although the individual cancer patient may have multiple symptoms, several are particularly common and associated with a significant symptom burden. Pain and depression are the most common physical and psychological symptoms in cancer patients (Caraceni and Portenoy, 1999, Lloyd-Williams et al., 2004). Of the various sub-types of cancer pain, neuropathic cancer pain and cancer induced bone pain (CIBP) are often difficult to manage and can prove distressing for patients (Caraceni and Portenoy, 1999). In addition to these physical symptoms, psychological symptoms, such as depression, are of equal importance. Depression in cancer patients is associated with significant distress and morbidity (Laird and Mitchell, 2005).

My thesis examines difficult cancer pain, exploring both neuropathic cancer pain and CIBP. The relationship between cancer pain and depression is examined along with a potential role of systemic inflammation. The possibility of a specific symptom cluster combination (pain, depression and fatigue) is explored - Figure 1.

Figure 1 - Thesis overview

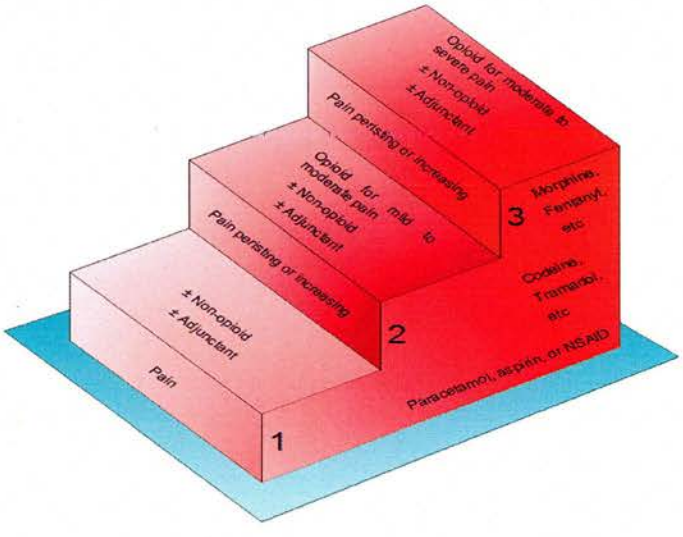


1.2. Difficult Cancer Pain

A single point prevalence survey, published in 1999 on behalf of the International Association for the Study of Pain (IASP), demonstrated that approximately 90% of patients with cancer, experience pain (Caraceni and Portenoy, 1999). Cancer pain is affected by many variables including the tumour site, the extent of local and metastatic disease, and cancer therapy (Daut et al., 1983).

Despite the high prevalence of pain amongst cancer patients, in a large proportion pain responds predictably to pharmacological treatment. Studies have shown that approximately 80% of patients with cancer pain, will respond to treatment using the World Health Organization Analgesic Ladder for Cancer Pain Relief - Figure 2 (Ventafridda et al., 1987). This high rate of response is usually achieved in specialist units or when practitioners are familiar and confident with prescribing strong opioid analgesia. Although this is encouraging, it does mean that there is a remaining 20% of patients with cancer pain, who will not achieve adequate analgesia with standard treatment. In non-specialist units, the proportion of patients whose pain is not controlled using the WHO ladder is expected to be even higher than 20%.

Figure 2 - WHO Analgesic Ladder for Cancer Pain Relief



Various factors determine why a proportion of cancer patients do not gain sufficient pain relief. Factors include the degree of response to opioid analgesics (which can be

limited by dose related side-effects), breakthrough pain (which can occur despite sufficient background analgesia) and psychological distress (Colvin et al., 2006). The underlying pathophysiology of the pain can also play a significant role in successful analgesia.

Neuropathic cancer pain and CIBP are particularly prevalent pain syndromes (Caraceni and Portenoy, 1999). It has been reported that the prevalence of neuropathic cancer pain and CIBP, are 34% and 35% respectively (Grond S, 1996).

Although neuropathic cancer pain and CIBP are common, they are often difficult to manage (Grond S, 1996). Traditionally a combination of therapies is used to manage these complex pain syndromes, however commonly used adjuvant analgesics are often ineffective; while dose related side-effects, constrain the use of opioids. It is reasonable, therefore, to conclude that neuropathic cancer pain and CIBP present a significant therapeutic challenge.

1.2.1. Neuropathic Cancer Pain

The IASP defines neuropathic pain as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (Merskey and Bogduk, 1994). Neuropathic pain exists as a diverse group of syndromes, ranging from complex regional pain syndromes to isolated peripheral nerve lesions.

Neuropathic pain occurs in 34% of cancer patients but it has been suggested that 50% of all difficult to manage cancer pain is neuropathic in origin (Caraceni and Portenoy, 1999, Grond et al., 1999). Furthermore, uncontrolled neuropathic pain is associated with anxiety, depression and reduced quality of life (Glover et al., 1995, Lloyd-Williams et al., 2004).

One of the reasons neuropathic cancer pain is difficult to manage is that, it can be poorly responsive to opioids. This is because higher doses of opioids are often required to provide analgesia, compared with other types of pain. The resulting increase in prevalence of unacceptable side-effects in turn limits dose escalation (Colvin et al., 2006, Mercadante D, 1999, Fallon and Hanks, 1993).

Adjuvant analgesics are an important part of our neuropathic pain armamentarium and include anticonvulsants and antidepressants. Recent evidence-based reviews have examined the use of adjuvant analgesics for neuropathic pain. Numbers needed to treat (NNT) are often used to convey a clinically meaningful outcome in pain studies, and although NNTs can be misleading, in this setting their appropriateness has been validated (Moore and McQuay, 1999). Anticonvulsants, such as gabapentin and pregabalin, are commonly used as adjuvant analgesics in neuropathic pain. To date, they have been shown to have a higher NNT than older anticonvulsants (Finnerup et al., 2005).

The use of antidepressants in neuropathic pain has also been examined (Saarto and Wiffen, 2007). In this study, tricyclic antidepressants (such as amitriptyline) were shown to provide at least moderate pain relief (NNT= 3.6). Data have also supported the use of newer antidepressants such as Venlafaxine (NNT= 3.1) (Saarto and Wiffen, 2007).

In summary, the widely-used adjuvant analgesics in neuropathic pain (amitriptyline and gabapentin) have a NNT of approximately 3 and 5 respectively (Finnerup et al., 2005). Newer adjuvant analgesics have even higher NNTs. This means that, at best, only one in every three patients will get any analgesic benefit from these drugs. Furthermore, adjuvant analgesics, either alone or in combination with opioids, may result in unacceptable side-effects which might hinder their use. Although treatments for neuropathic pain have been studied extensively, the clinical characteristics of neuropathic cancer pain have never been examined in a robust, systematic fashion. Clinical characterization is fundamental to gain a common baseline understanding of neuropathic pain, the future development of novel neuropathic pain treatments and to guide future research.

1.2.2. Cancer Induced Bone Pain

CIBP is the most common cause of cancer pain (Mercadante, 1997, Banning et al., 1991, Coleman, 1997). It is a major cause of morbidity in patients with cancer and commonly results in either hospice or hospital admission (Coleman, 1997, Neville-Webbe and Coleman, 2003). CIBP adversely affects performance status and

increases psychological symptoms such as anxiety and depression (Portenoy and Hagen, 1990, Bruera et al., 1995, Portenoy et al., 1999).

CIBP can be a consequence of metastatic disease or due to a primary tumour of the bone. Bone is the most common site of metastatic disease (Coleman, 1997). An accurate prevalence is not known as this is very much dependent on the primary tumour site and the likelihood that it metastasizes to bone. Data from post mortem studies have shown that bone metastases are present in 85% of patients who have died from lung, breast or prostate cancer (Nielsen et al., 1991).

Radiotherapy is currently regarded as the gold-standard treatment for CIBP. The mechanisms of analgesia from radiotherapy for CIBP are not fully understood, however it is becoming clear that tumour cell death is not the only mechanism (van As et al., 2007). The primary tumour site does not seem to affect responsiveness to radiotherapy and there is no difference in analgesic benefit from single or multiple fractions of radiation (Price et al., 1986, Hoskin et al., 1992).

Despite being a widely-used treatment, radiotherapy may not always confer an analgesic benefit. A systematic review examined the role of radiotherapy in the treatment of CIBP (McQuay et al., 2000). This showed that radiotherapy provided complete analgesic benefit in only one in four patients.

Bisphosphonates are also used in the treatment of CIBP. These act in a variety of ways including the inhibition of osteoclast activity (van Beek et al., 2003). Bisphosphonates also cause apoptosis of osteoclasts and inhibit the growth of tumour cells through various mechanisms. It has been shown that bisphosphonates may have some effect in the acute management of CIBP but are less effective than strong opioids or radiotherapy (Wong and Wiffen, 2002). In patients treated with bisphosphonates for pain relief, an NNT of 11 was reported at four weeks meaning that only one in eleven patients treated, will gain some analgesic benefit. There is thus insufficient evidence to recommend bisphosphonates alone as an adequate solution to the problem of CIBP.

Although treatments for CIBP have been studied extensively, current therapies are likely to be ineffective for a large proportion of patients. Despite the time invested in developing treatments for CIBP, it has never been characterized in the clinical setting. It is essential to understand completely the characteristics of CIBP in order to inform the development of new treatments and direct research.

1.2.3. Breakthrough Cancer Pain

Cancer pain, and in particular neuropathic cancer pain and CIBP, rarely exists as single entities but are often a combination of different types of pain. This pain can be separated into:

Background Pain

Breakthrough Pain - which can be divided into:

- spontaneous pain at rest
- incident pain (related to either movement or other action such as coughing or straining at stool)

Breakthrough pain has been defined as "a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain" (Portenoy et al., 2004). Varying terminology has been used to describe breakthrough pain. Incident pain is accepted as any pain precipitated by an event (Cleary, 2005). Episodic pain has been defined as "any pain that varies with time" (Swanwick et al., 2001). Advocates of the term "episodic pain" have argued that using this definition, includes patients who have no background pain but still suffer from episodes of breakthrough pain. In recent years however a consensus has been reached that breakthrough pain can only be present in combination with adequately controlled background pain.

The management of breakthrough pain presents a significant therapeutic challenge as some analgesics can be ineffective. Although there is some evidence for the use of short acting opioids for breakthrough pain (Zeppetella and Ribeiro, 2006), titration of opioids to doses required to deliver sufficient analgesia in spontaneous neuropathic

and bone pain usually results in unacceptable opioid side-effects, especially sedation. Thus, the use of opioids in the management of breakthrough pain is limited. This thesis explores breakthrough pain in neuropathic cancer pain and CIBP.

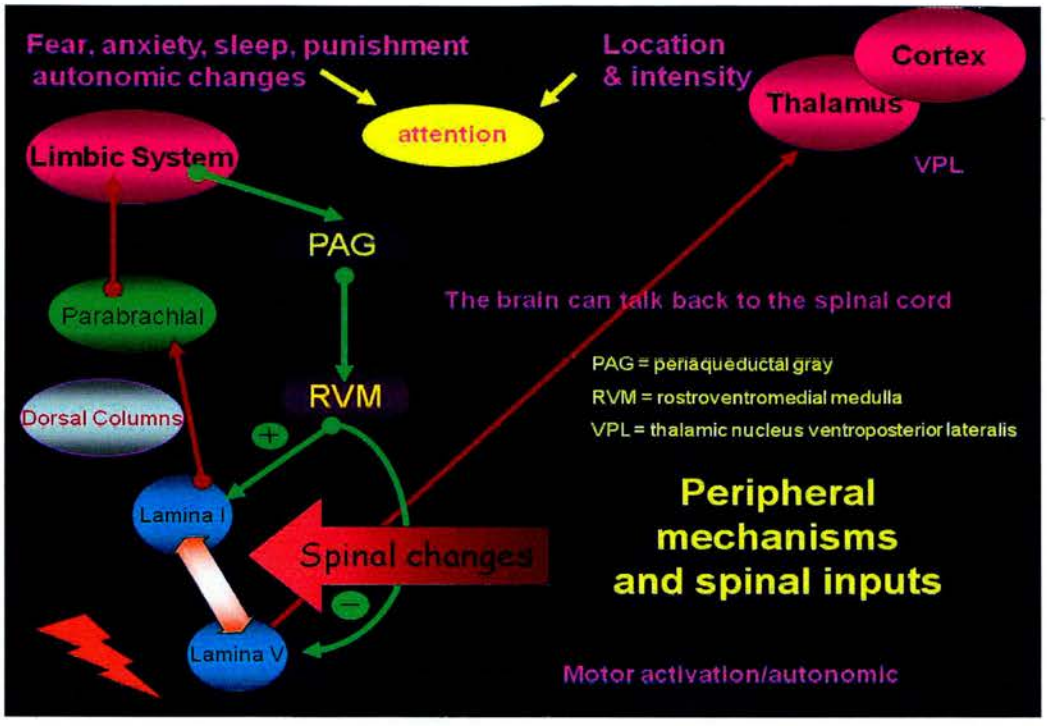
1.3. Psychological Components of Cancer Pain

Although pain is one of the most common symptoms in cancer, psychological symptoms should be assessed and viewed as a continuum with physical symptoms. In cancer patients, psychological wellbeing is equally as important as the treatment of physical symptoms. Physical and psychological problems can clearly coexist without being strongly related; however my thesis is that they are often related.

1.3.1. Cancer Pain and Depression

Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey and Bogduk, 1994). This definition illustrates clearly that pain is not a singular phenomenon but a complex process involving both physical and psychological components. It is now clear that the midbrain plays a major role in the processing and integration of factors such as anxiety, depression, sleep deprivation and fear into the pain pathways. In addition, this is also the area of a descending and ascending loop which can inhibit or accentuate the pain processing – Figure 3.

Figure 3 - Interaction between pain and psychological symptoms



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As pain and depression are common symptoms in cancer patients, the possibility of a relationship between these symptoms has been raised. These symptoms could be related in several ways.

1) Symptoms co-exist

Pain and depression are both common symptoms. It may be the case that as they are common they often exist together, but independently.

2) *Symptoms co-exist and are related*

One symptom may impact directly on the other. Patients who have pain may have increased levels of emotional distress which, if severe enough, this could result in depression. Similarly emotional distress and depression may amplify pain. As pain is a complex phenomenon that can result in physical and psychological symptoms; it would thus seem reasonable to accept that an

increase in depression per se, may magnify the emotional component of pain, increasing the severity of the overall pain experience.

3) *Symptoms co-exist and share common pathophysiology.*

It has been demonstrated that pain and depression both affect the same area of the cerebral cortex (Giesecke et al., 2005, Smith et al., 2002). Furthermore, several of the neurotransmitters involved in pain pathways have also been implicated in the pathophysiology of depression (Fava, 2003). Abnormalities of the neurotransmitter systems involving norepinephrine (NE) and serotonin (5-HT) have been shown to be abnormal in depression. These neurotransmitters are also involved in descending pain pathways and may modulate pain. As pain and depression share these common entities (anatomically and chemically), it is reasonable to consider that pain and depression may share a common pathophysiology.

As pain and depression are often present together clinically, it is possible that they may be linked at the molecular level. It would seem unlikely that a single pathway or interaction exists in isolation; it is more likely that the physical impact of one symptom on another, in addition to a common underlying pathophysiological pathway is implicated. This thesis examines the evidence, thus far, for a possible link between pain and depression.

In the non-malignant setting, pain and depression have been studied (Bair et al., 2004). The presence of pain was shown to be a strong predictor of depression and increased levels of pain were associated with a decreased response to depression treatment (Bair et al., 2004). Although this would suggest an association between pain and depression, this association has not been studied extensively in a cancer population.

A systematic review of cancer pain and depression would allow an appraisal of the current evidence of the relationship between these two symptoms. It has been shown in cancer, that an improvement in pain results in an improvement in quality of life (Thienthong et al., 2006). However, the specific relationship between pain and depression in cancer has not been studied. A longitudinal study, where pain is treated

while depression is observed, would allow a dynamic assessment of the relationship between these symptoms. The longitudinal study presented herein examines the relationship between pain and depression when one of these symptoms is altered whilst no intervention is given to the other. This allows a direct examination of the impact of one symptom on another.

1.4. Pain and Systemic Inflammation

Pain is the commonest symptom in cancer patients whilst cancer, per se, is associated with systemic inflammation (Mantovani et al., 2008). Pain and inflammation have been associated for centuries. In the earliest definitions of inflammation, one of the key constituents was dolor (or pain). This observation that inflammation is associated with pain has been substantiated with clinical experience and more recently, a basic science evidence base.

Systemic inflammation, mediated by a pro-inflammatory cytokine drive, has been associated with pain in animal and human models (Watkins and Maier, 2000). As there is a high prevalence of pain and inflammation in cancer, the relationship between these is of interest. The study presented herein examines the relationship between pain and inflammation in a cohort of cancer patients.

1.5. Symptom Cluster: Pain, Depression and Fatigue

Cancer symptoms rarely exist in isolation, with some studies reporting a median of 11 symptoms (Walsh et al., 2000). Whilst multiple symptoms are often present, the relationship between these symptoms may affect both their underlying biological basis and optimal treatment.

In the last seven years the concept of symptom clustering in cancer patients has been discussed in the literature. A symptom cluster has been defined as " three or more concurrent symptoms that are related to each other" (Dodd et al., 2001a). Symptoms simply co-existing together is insufficient for them to be labelled as a cluster (Dodd et al., 2004). To be classified as a cluster, symptoms need to be related to one another and occur concurrently. Pain, depression and fatigue are highly prevalent in cancer patients and often exist together (Bower et al., 2000, Gaston-Johansson et al., 1999).

The possibility of these existing together as a symptom cluster has been raised, although there is currently insufficient evidence to support this (NIH, 2002). Evidence of pain, depression and fatigue existing together as a symptom cluster, would have a significant impact on the approach to the treatment of these symptoms.

It is clear that establishing the existence of this cluster of common cancer symptoms is fundamental. Common underlying pathways between symptoms would seem a possibility when symptoms often exist in unison. Systemic inflammation, which is known to exist in cancer, may be one possible underlying mechanism. The potential existence of a symptom cluster of pain, depression and fatigue is explored herein and a possible common underlying mechanism for this is examined.

1.6. Aims of this Thesis

This chapter emphasizes that difficult cancer pain, both alone and in combination with depression, is a common symptom in the cancer patient. It is clear that pain is complex but that cancer adds another layer to this complexity.

Common therapies for neuropathic cancer pain and CIBP are often sub-optimal. Clinical characterization of these pain syndromes is fundamental to developing appropriate treatments for these conditions. Although pain and depression are both common in cancer patients, little is known about the relationship between these symptoms. The potential role of systemic inflammation and its effect on pain is of interest in the cancer setting. The existence of pain, depression and fatigue existing together as a symptom cluster has also been questioned in the literature although this has not been identified formally in any robust studies.

The aims of this thesis are to characterise clinically, neuropathic cancer pain and CIBP, to examine the relationship between cancer pain and depression, to explore the relationship between pain and systemic inflammation and the possibility of pain, depression and fatigue existing, as a symptom cluster.

1.6.1. Summary of Aims

Aim 1: To characterize clinically, neuropathic cancer pain.

Aim 2: To characterize clinically, CIBP.

Aim 3: To undertake a systematic review of the literature examining the relationship between cancer pain and depression.

Aim 4: To assess the effect of pain on depression and the longitudinal relationship of these two entities.

Aim 5: To examine the relationship between pain and inflammation.

Aim 6: To examine the possibility of a symptom cluster of pain, depression and fatigue in cancer.

Chapter 2. A Characterization of the Temporal Components of Neuropathic Cancer Pain

2.1. Introduction

Neuropathic pain is one of the most common symptoms in patients with cancer, with a prevalence of 34% (Caraceni and Portenoy, 1999). Approximately 50% of all difficult to manage cancer pain is neuropathic in origin (Grond et al., 1999). Uncontrolled neuropathic pain is associated with anxiety and depression and can affect quality of life adversely (Glover et al., 1995, Lloyd-Williams et al., 2004).

As discussed in 1.2.1, neuropathic pain can be challenging to manage with standard treatments. Opioid analgesics can be used to treat non-malignant neuropathic pain and their efficacy has been demonstrated with a NNT of approximately 2.5 (Finnerup et al., 2005). In neuropathic cancer pain however the doses needed to provide analgesia often result in unacceptable side-effects (Colvin et al., 2006, Mercadante et al., 1999, Fallon and Hanks, 1993). Adjuvant analgesics are also key in our neuropathic pain armamentarium; although the choice of adjuvant analgesic is not based on potency superiority nor on underlying pathophysiology. In addition, at best they have a NNT of 3 (Finnerup et al., 2005).

Traditionally, a combination of opioid and adjuvant analgesics is used to manage neuropathic pain, however this may not provide adequate analgesia. To achieve effective pain control, a detailed understanding of the individual components of neuropathic pain and its clinical features is needed.

Neuropathic pain can be categorized by the underlying pathophysiology and while this may be useful in some settings, in day-to-day clinical practice, knowledge of the underlying pathophysiological process has little impact on the choice of treatment.

Neuropathic pain, in keeping with other pain syndromes, exists as a combination of background pain and breakthrough pain. Breakthrough pain can be either

spontaneous or incident-related (e.g. movement, coughing etc). Each of these components needs to be assessed. Although there has been a considerable amount of research into neuropathic cancer pain, the practical clinical features of the different components have never been characterized formally in a clinical setting.

This would be useful for several reasons:

1. To act as a template to aide more accurate clinical assessment
2. To provide greater understanding of why neuropathic cancer pain may be difficult to control
3. To improve assessment in research studies
4. To help with management decisions

The aim of this study was to characterize the clinical features of neuropathic cancer pain.

2.2. Patients and Methods

2.2.1. Overview

The study design used was a cross sectional prospective survey of patients with neuropathic pain related to the underlying malignancy. Ethical approval was obtained. Written informed consent was provided by all patients. Procedures of the Declaration of Helsinki and Good Clinical Practice were followed. The study was conducted in a regional oncology centre in the UK, where specialist oncology services are provided to a population of approximately 1.5 million.

2.2.2. Patients

Participants were inpatients or outpatients, attending the study centre. All were over 18 years of age and had a histologically proven cancer diagnosis. Eligible patients had a neuropathic pain syndrome which was defined as per recognised criteria and related to the underlying malignancy (Portenoy, 1989, Caraceni and Portenoy, 1999). To be eligible for inclusion, the neuropathic pain (referred to as the index site pain)

had to have been symptomatic in the previous 24 hours. Patients felt to be in the last week of their lives or who were unlikely to be able to complete the study due to their clinical condition, were excluded. Patients who did not have neuropathic cancer pain or in whom the origin of their pain was unclear were excluded.

2.2.3. Methods

A single interview was conducted with each patient. Demographics and information concerning each patient's underlying malignancy were gathered. Details of all analgesic drugs taken in the preceding 24 hours were recorded. For ease of comparison, opioid doses were converted to oral morphine equivalents (Morphine equivalent daily dose – MEDD) using a recognised and accepted conversion table (Fallon et al., 2009). Analgesics were classified as simple, weak opioids or strong opioids and corresponded with steps 1, 2 and 3 respectively, on the World Health Organization Ladder for Cancer Pain Relief - Figure 2 (Azevedo Sao Leao Ferreira et al., 2006).

Pain in the index pain site in the preceding 24 hours, was assessed using pain questionnaires. All patients completed the Brief Pain Inventory (BPI) and from this group, those who had breakthrough pain completed a breakthrough pain questionnaire (BTPQ) - Appendix 1.

Breakthrough pain was defined as pain that increased from a lower to a greater pain intensity by greater than two points (on a 0-10 Visual Analogue Scale (VAS)). This ensured that only those patients with definite breakthrough pain, were classified as such.

2.2.4. Pain Assessment

2.2.4.1. Brief Pain Inventory

The BPI is a multidimensional pain assessment tool that has been validated extensively in multinational studies of cancer pain epidemiology and clinical trials of analgesics (Cleeland and Ryan, 1994, Portenoy et al., 1999). It has two sections. One section assesses pain intensity and percentage relief from medication whilst the

other section assesses the effect of pain on various aspects of function (Daut et al., 1983).

Intensity - The pain intensity section assesses worst pain, average pain, least pain and pain right now. This is done on a 0 -10 scale with 0 indicating no pain and 10 indicating worst pain imaginable. The "relief from medication" question assesses percentage relief provided by current analgesia and this is rated on a 0-100 scale, 0 indicating no relief and 100 indicating complete relief.

Interference – The effect of pain on general activity, mood, walking, work, relationships, sleep and enjoyment of life are assessed. This is done on a 0-10 scale with 0 indicating pain does not interfere and 10 indicating pain completely interferes with the specific component. The total BPI interference score (sum of individual interference question scores) gives a useful indicator of the effect of pain on various aspects of physical, psychological and social function (Portenoy et al., 1992).

The BPI can be assessed using individual questions in isolation (e.g. worst pain), the sum of either the intensity or interference subscales, or the cumulative total of the intensity and interference subscales.

2.2.4.2. Breakthrough Pain Questionnaire

At the time of the study, a validated BTPQ had not been developed and the questionnaire used was based on previously published work (Portenoy et al., 1999). The BTPQ allowed patients' breakthrough pain to be described in greater detail and included assessment of severity of background and peak pain intensity. Further questions determined the frequency, speed of onset, duration and breakthrough pain predictability, all factors likely to be important clinically.

2.2.5. Data Analysis and Statistics

Demographics and pain characteristics were analysed. This analysis was subsequently summarised using proportions, means and standard deviations (SD) or medians and inter-quartile ranges (IQR).

Aspects of the BPI were analysed in further detail and BPI "average pain" and "worst pain" scores were then compared to the total BPI interference score. Regression analyses between these variables were then run. Subsequently, relationships between these pain scores and pain related interference with function scores were determined.

A subgroup analysis of the BPI was undertaken to compare those who had breakthrough pain with those who did not, using Mann-Whitney tests.

2.3. Results

The patient demographics are shown in Table 1. Thirty patients were recruited. Eighteen (60%) were male and the mean age was 61.5 years (SD 11.29, range 39-81). A wide variety of tumour sites were represented, however breast and lung cancer were the most common. Patients were either performance status 1, 2 or 3 (ECOG) with twenty-one patients (71%) performance status 2, which was the commonest group. Sixteen patients (53%) were inpatients and the remainder were outpatients.

Analgesia and tumoricidal therapy is shown in Table 2. Twenty-two patients (73%) were taking strong opioids. These included morphine, diamorphine, oxycontin, hydromorphone and fentanyl. The mean MEDD was 130.5mg (range 0 - 620mg). Twenty patients (67%) were taking gabapentin, amitriptyline or a combination of both of these. Three patients were using lidocaine patches.

Sixteen patients (53%) were not receiving any tumoricidal treatment while the remainder were receiving either chemotherapy, radiotherapy, hormonal treatment or a combination of these.

Table 1 - Patient demographics - Neuropathic cancer pain

Characteristic		n	%
Sex			
	Male	18	60
	Female	12	40
Type of cancer			
	Breast	7	23
	Lung	7	23
	Prostate	3	10
	Myeloma	2	7
	Renal	2	7
	Head&Neck	2	7
	GI cancer	2	7
	Carcinoid	1	3
	Cervical	1	3
	Sarcoma	1	3
	Unknown Primary	2	3
Extent of disease			
	Local disease	1	3
	Bone metastases	6	20
	Multiple metastases	10	33
	Unknown	13	43
Performance Status (ECOG - Eastern Cooperative Oncology Group)			
	1	2	7
	2	21	70
	3	7	23
Status			
	Inpatients	16	53
	Outpatients	14	47

Table 2 - Analgesia and tumoricidal therapy

		n	%
Current Analgesia			
	Simple*	5	17
	Weak Opioid (e.g. Codeine)	1	3
	Strong Opioid (e.g. Morphine	22	73
	Unknown	2	7
Neuropathic agent			
	Gabapentin	14	47
	Amitriptyline	6	20
	Gabapentin & amitriptyline	2	7
	Lidocaine patch	3	10
Non-steroidal Anti-Inflammatory Drugs			
	Yes	13	43
	No	17	57
Current cancer treatment			
	None	16	53
	Chemotherapy	3	10
	Radiotherapy	3	10
	Hormonal	8	26
*Simple – e.g. acetaminophen/paracetamol			

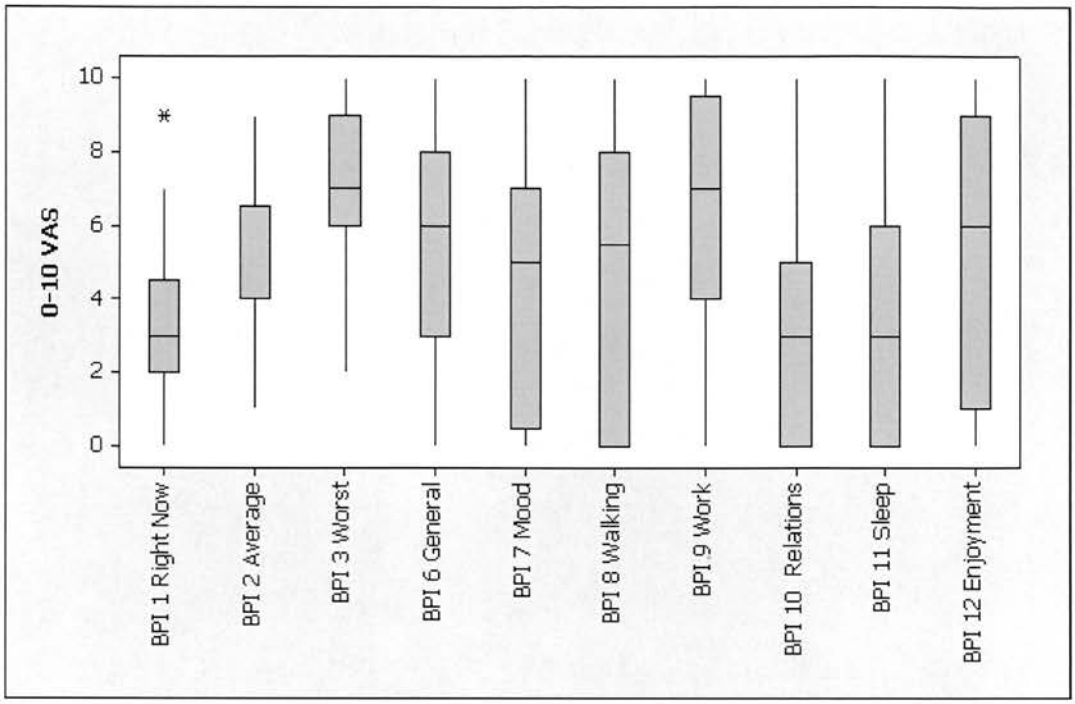
2.3.1. Pain Characteristics

Results of the BPI are shown in Figure 4. The median "average pain" was 4 and the median "worst pain" score was 7. The multiple regression analysis showed that the BPI worst pain score correlated more strongly with the BPI total interference score, than the BPI average pain score. The coefficient for worst pain was 5.54 (SE 2.14, p=0.016) and for average pain it was -2.40 (SE 2.29, p=0.30). Therefore worst pain relates more strongly to the effect of pain on function.

The BPI scores of those patients without breakthrough pain and those with breakthrough pain were compared. The median (IQR) BPI average pain for those without and those with breakthrough pain was 6 (4-7.5) and 4 (3-5) respectively. The difference in average pain between these groups was statistically significant ($p<0.05$). The median (IQR) BPI worst pain for those without and those with breakthrough pain, was 8 (6.5-9) and 7 (5.5-8) respectively. There was no statistically significant difference between the scores in these two groups ($p<0.05$ level).

Patients who had breakthrough pain had lower total BPI interference scores than those who did not have breakthrough pain (median [IQR]; 30 [14.5-45] vs 43 [23-49.5] respectively). However, this did not reach levels of statistical significance ($p<0.05$ level).

Figure 4 - Brief Pain Inventory – Neuropathic cancer pain



*Box and whisker plot representing the median value, with 50% of the data falling within the box [Interquartile range]. The whiskers extend to the 5th and 95th percentiles. *=outlier*

2.3.2. Breakthrough Pain

Results of the BTPQ are shown in Table 3. Nineteen patients (63%) met the study criteria for breakthrough pain. The median number of episodes of breakthrough pain (per 24 hours) was 3 and the median severity of the breakthrough pain episodes was 7 (based on a 0-10 VAS). Breakthrough pain was unpredictable in 11 patients (58%) which included those patients who had onset of pain in less than 10 seconds. Seventeen patients (90%) had a speed of onset of breakthrough pain (time from being first aware of pain, to pain reaching its peak) of less than 5 minutes. Ten patients (53%) had breakthrough pain of less than 30 minutes duration. Breakthrough pain was rapid onset (less than 5 minutes) and short duration (less than 15 minutes) in 8 patients (42%).

Table 3 - Breakthrough Pain Questionnaire - Neuropathic cancer pain

		Median	IQR
Number of BTP episodes in 24 hours			
		3	1 - 4.5
Severity of BTP episodes			
		7	5.5 - 8
Speed of onset of BTP		**n**	**%**
	unpredictable	3	16
	<10sec	8	42
	10s-5min	6	32
	6-30min	1	5
	31-60min	1	5
	Median (IQR)	<10secs (<10s – 10s-5mins)	
Duration of BTP			
	<1min	3	16
	1-15min	5	26
	16-30min	2	11
	31-60min	5	26
	60-120min	1	5
	>120min	3	16
	Median (IQR)	16-30 mins (1-15 -- 31-60 mins)	
Rapid Onset (<5 Mins) & Short Duration (<15mins)			
		8	42

2.4. Discussion

The study represents the first clinical characterization of the practical clinical aspects of neuropathic cancer pain. Previous work examining various aspects of neuropathic pain has been undertaken, however by focussing solely on the clinical characteristics, valuable information on neuropathic cancer pain, has evolved.

2.4.1. Worst Pain

The results suggest that worst pain is often higher than average pain, in neuropathic cancer pain. Worst pain was three points higher than average pain (on a 0-10 VAS) which is clinically significant (Farrar et al., 2000). Neuropathic pain has been associated with a higher pain intensity in larger studies and these results are in keeping with this (Portenoy et al., 1999). Worst pain also correlated more strongly with the interference score of the BPI than average pain. This suggests that worst pain is a more useful measure of the effect of pain on interference on function than average pain. Furthermore, worst pain is predictive of interference on function over and above average pain, but not vice versa.

2.4.2. Breakthrough Pain

The findings suggest that breakthrough pain is frequently present in neuropathic cancer pain with 63% of our study population having breakthrough pain. Median worst pain was higher than the average pain. Breakthrough pain was often of sudden onset (less than 5 minutes) and unpredictable. In approximately 40% of those patients with breakthrough pain, it was of rapid onset and short duration.

Breakthrough pain can have a considerable impact on, and has been shown to be related to, overall poor pain control (Mercadante et al., 1992, Mercadante et al., 2002a). Breakthrough pain is also associated with greater functional impairment (Portenoy et al., 1999), increased anxiety and depression (Portenoy et al., 1999) and may adversely affect healthcare costs (Fortner et al., 2002). The importance of breakthrough pain in other pain states (such as CIBP) has been highlighted. The findings suggest that breakthrough pain is also an important feature of neuropathic cancer pain.

2.4.3. Comparison - No breakthrough pain group versus breakthrough pain group

Patients without breakthrough pain had statistically significant higher average pain scores than those with breakthrough pain. Worst pain scores were also higher in the group with no breakthrough pain but this did not reach levels of statistical significance (at the $p>0.05$ level). Patients without breakthrough pain had higher BPI interference scores than those with breakthrough pain but this did not reach levels of statistical significance.

It could be postulated that one reason for this is that in neuropathic cancer pain, patients without breakthrough pain have higher background pain levels than those with breakthrough pain. This transfers into pain flares being smaller in magnitude. As those without breakthrough pain had higher levels of average pain, it is assumed that their background pain was generally less well controlled resulting in the higher BPI interference scores.

2.4.4. Relationships to previous studies

Studies examining cancer pain in general have been undertaken, however these have encompassed all types of cancer pain. It is thus difficult to compare these findings to other published work. Pain descriptors in neuropathic cancer pain have been examined previously although a detailed clinical characterization has never been performed (Mystakidou et al., 2007a). Breakthrough cancer pain in general has been described in the literature but breakthrough neuropathic cancer pain has not been described in isolation (Portenoy et al., 1999, Caraceni et al., 2004). By examining neuropathic cancer pain in detail, specific features of breakthrough pain in this group have been identified.

Breakthrough pain in general has been demonstrated to be associated with greater functional interference, however in subgroups with generally very poorly controlled background pain this could be different (Portenoy et al., 1999). These findings in neuropathic pain support the latter.

Studies of the temporal characteristics of breakthrough cancer pain (in all types of pain) have previously been conducted. Median durations of breakthrough pain range from 15 minutes,(Hwang et al., 2003) to 30 minutes (Hwang et al., 2003, Portenoy and Hagen, 1990, Gomez-Batiste et al., 2002). Breakthrough pain has also been reported as being unpredictable in 27% (Portenoy and Hagen, 1990) to 58% (Hwang et al., 2003) of patients. In these studies all types of cancer pain were included and this may explain these variable characteristics.

2.4.5. Implications for Practice

The findings presented highlight some issues regarding the treatment of neuropathic pain. The temporal characteristics of neuropathic breakthrough pain can make it challenging to manage. As breakthrough pain is often unpredictable, of rapid onset and short duration, standard immediate release (IR) opioids are likely to be effective only in some cases. Newer rapid onset, short duration opioids are now available and these may be of a benefit to some patients. Nevertheless, there may be a cohort of patients with neuropathic breakthrough pain for whom these will not be effective.

Opioids have been shown to be of use in neuropathic pain and their use is advocated as a first line therapy in neuropathic cancer pain (Dworkin et al., 2007). Tricyclic antidepressants (e.g. amitriptyline) and anticonvulsants (e.g. gabapentin) have also been recommended for neuropathic pain, although they have a NNT of approximately 3 and 5 respectively (Finnerup et al., 2005). Most of the patients in the study were taking strong opioids in addition to standard adjuvant analgesics for neuropathic pain, yet despite this analgesia was sub-optimal. Previous work has suggested that, at best, only 60% of patients will get some relief from their neuropathic pain. The findings presented would suggest that a considerable proportion of patients with neuropathic pain, will only achieve a degree of analgesia with standard therapies.

Basic science work has demonstrated that a range of pathophysiological processes exist in neuropathic pain (Urch and Dickenson, 2008). It is thus logical to target the various mechanisms which are present in neuropathic pain. The successful treatment

of neuropathic pain may require the use of several different therapies each targeting a different underlying process.

2.4.6. Limitations

The main criticism of this study is the small sample size, although some statistical inference can be drawn from the results. The study population were all under the care of oncologists and attending a regional oncology centre. Although this included inpatients, outpatients, and all tumour types, the sample may not be truly representative of a general cancer population with neuropathic pain. Patients in the study were not known to a specialist palliative care or pain service. Therefore patients who may have had more severe pain may have been missed. Patients who were near the end of life were also excluded and such a population may have a greater degree of pain.

The criteria for identifying breakthrough pain could be debated. Previous studies have excluded patients who did not have regular episodes of breakthrough pain or who were not on regular strong opioids (Portenoy and Hagen, 1990, Portenoy et al., 1999, Hwang et al., 2003). The rationale for this was to exclude patients who had transitory flares of pain that were likely to settle spontaneously. By excluding such patients in this study, a true picture of the diversity of breakthrough pain, would not be achieved.

Analgesics taken by patients in the study may, in theory, have altered the features of breakthrough pain. No patients in the study were taking rapid-onset, short acting opioid preparations (e.g. oral transmucosal fentanyl citrate) however some were taking standard IR opioids. At best IR opioids have an onset of effect at 30 minutes and a peak effect at 60 minutes (Bailey and Farley, 2006). As the study population had breakthrough pain which was usually of less than 30 minutes duration, it is unlikely that IR opioids would have affected this. It would have been interesting to note the opioid side-effect profile, particularly in those patients with poor background pain control. This aspect would be important in a future larger study. In addition future work in this area would need to address the other variables such as background opioid analgesia, breakthrough analgesia and the effects of this on

breakthrough pain. Accommodating such variable is challenging and highlights the tension between the internal and external validity in future study design.

2.5. Conclusion

Neuropathic cancer pain continues to be a clinical challenge. Worst pain is a useful indicator in the assessment of neuropathic pain and the impact of this on patient function. Breakthrough pain is often unpredictable and short duration and this has implications for practice. Despite the use of strong opioids and adjuvant analgesics, neuropathic cancer pain remains difficult to manage.

To treat neuropathic cancer pain adequately a greater understanding of the underlying pathological processes and also the clinical characteristics is required. This small characterization study highlights some key clinical features of neuropathic cancer pain; however larger characterization studies in the broader cancer population are needed.

Chapter 3. A Characterization of Cancer Induced Bone Pain

3.1. Introduction

Cancer-induced bone pain is the most common cause of cancer pain (Banning et al., 1991, Coleman, 1997, Mercadante, 1997). Common malignancies such as breast and prostate cancer frequently metastasize to bone. Increased morbidity, reduced performance status, increased anxiety and depression, and a reduced quality of life are associated with CIBP (Portenoy and Hagen, 1990, Portenoy et al., 1999, Bruera et al., 1995). Uncontrolled CIBP is a common cause of hospital or hospice admission, with up to 85% of patients with bone metastases having pain (Coleman, 1997, Mercadante, 1997, Neville-Webbe and Coleman, 2003).

CIBP is not a single entity but instead exists as background (tonic) pain, spontaneous pain at rest and movement-related (incident) pain (Portenoy et al., 1999). These components can be present either solely or in combination and the approach to the management of each element needs to be addressed differently.

As discussed in 1.2.2, current common treatments for CIBP can be suboptimal making this a considerable therapeutic challenge. Palliative radiotherapy remains the most effective anticancer treatment for CIBP, but it does not always provide total analgesia. Only 41% of patients achieve 50% pain relief within 4 weeks of treatment whilst only one quarter of patients will gain complete pain relief (McQuay et al., 2000, Chow et al., 2007). Bisphosphonates are proven to delay symptomatic skeletal events in certain tumour types, however their efficacy in the acute management of CIBP remains unproven (Ross et al., 2003).

Opioid analgesia is the main pharmacological treatment for CIBP, although this has several limitations. Titration of opioids to doses that control spontaneous pain at rest and movement-related bone pain, usually results in unacceptable opioid side-effects (Mercadante and Arcuri, 1998, Portenoy et al., 1999). In recent years the pharmaceutical industry has been developing short acting oral opioids to provide

rapid onset, short duration analgesia for use in breakthrough pain in CIBP and other pain types. Their efficacy in routine clinical practice is as yet unproven.

Although considerable time has been spent in developing new analgesics for CIBP, it has never been characterized in the clinical setting. Laboratory models of CIBP indicate that the mechanisms underlying CIBP have similarities and differences to other pain states such as inflammatory and neuropathic pain. Central sensitization is common to CIBP and neuropathic cancer pain and may explain the beneficial effects of gabapentin in both neuropathic pain and CIBP states (Donovan-Rodriguez et al., 2005). In studies comparing CIBP to inflammatory pain, vast variation in opioid doses required to achieve analgesia, have been reported, suggesting different mechanisms (Luger et al., 2002). These similarities and differences may have implications for clinical practice. A detailed clinical characterization of CIBP should underpin improved patient management. It may also allow symptoms and signs to be linked with underlying mechanisms and inform further research in this area.

The aim of this study was to characterize CIBP in a cross-section of patients with radiologically proven bone metastases and pain.

3.2. Patients and Methods

3.2.1. Overview

The study was part of the same study group as described in 2.2.1. and was a cross sectional prospective survey of patients with CIBP attending the study centre. All necessary ethical and regulatory procedures were as described in 2.2.1.

3.2.2. Patients

Patients were eligible if they had a radiologically proven site of bone metastasis and had corresponding pain (referred to as the index pain site) which had been symptomatic in the preceding 24 hours. If more than one type of pain was present, the index pain site had to be that chosen by the patient to be their most problematic pain. All patients were 18 years of age or over and were either inpatients or outpatients.

Patients who were unlikely to be able to complete the study protocol due to their clinical condition or who were in the last week of life, were excluded. In addition, patients who had pain produced by mechanisms other than CIBP or in whom the origin of their pain was unclear, were excluded.

3.2.3. Methods

Once consent had been obtained, a single interview was conducted with each patient. Demographics and information concerning the patient's underlying malignancy, was gathered. Types and doses of analgesic drugs (including non-steroidal anti-inflammatory drugs [NSAIDs]) taken in the preceding 24 hours were recorded. As per 2.2.3 opioid doses were converted to oral morphine equivalents (Morphine equivalent daily dose – MEDD) using a recognised conversion table, to allow comparison (Fallon et al., 2009). Analgesics were classified as either simple, weak opioids or strong opioids and correlated with steps 1, 2 and 3 respectively on the World Health Organisation Ladder for Cancer Pain Relief - Figure 2 (Azevedo Sao Leao Ferreira et al., 2006).

3.2.4. Pain Assessment

Pain in the index site in the preceding 24 hours, was assessed using several pain questionnaires to assess the different components of CIBP. All patients completed the Brief Pain Inventory (BPI) and a screening question to identify breakthrough pain. The sub-group of patients who had breakthrough pain also completed a Breakthrough Pain Questionnaire (BTPQ). Breakthrough pain was defined as pain that increased by 2 points or more (on a 0-10 Visual analogue scale [VAS]) from their background pain.

The BPI and BTPQ have been discussed previously in section 2.2.4.

3.2.5. Statistics and Analysis

Patient demographics and pain characteristics were summarized using proportions, and means and standard deviations (SDs) or medians and inter-quartile ranges

(IQRs). BPI "average pain" and "worst pain" scores were related to the BPI interference scale using multiple linear regression. A further analysis of the BPI interference scale was undertaken to compare those patients with, and those without, breakthrough pain, using Mann-Whitney tests.

3.3. Results

The basic demographics of all patients are shown in Table 4. Fifty-five patients were recruited of which 27 (49%) were male. The mean age was 63.5 years (SD 11.6, range 37-87). Breast and prostate cancer were the most common primary tumour groups. Twenty-eight (51%) patients were performance status 2 whilst 32 patients (58%) were outpatients, with the remainder receiving inpatient oncology centre care.

Patient's current analgesia and tumoricidal therapy is shown in Table 5. Seventeen patients (31%) were taking simple analgesia such as acetaminophen whilst 10 patients (18%) were using weak opioids. Twenty-one patients (38%) were taking a strong opioid which included morphine, diamorphine, oxycontin, hydromorphone, and fentanyl. The mean MEDD was 66.9mg (range 0-350mg).

While the majority of patients were receiving some form of tumoricidal therapy, 34% were not on any active treatment at the time of the study.

Table 4 - Patient demographics - Cancer induced bone pain

Characteristic		n	%
Sex			
	Male	27	49
	Female	28	51
Type of cancer			
	Breast	20	36
	Prostate	15	27
	Lung	6	11
	Myeloma	3	6
	Renal	2	4
	GI cancer	2	4
	Head&Neck	1	2
	Cervical	1	2
	Unknown Primary	5	9
Extent of disease			
	Single bone metastases	6	11
	Multiple bone metastases	25	46
	Multiple metastases	14	26
	Unknown	10	18
Performance Status (ECOG - Eastern Cooperative Oncology Group)			
	1	15	27
	2	28	51
	3	12	22
Status			
	Inpatients	23	42
	Outpatients	32	58

Table 5 - Analgesia and tumoricidal therapy

		n	%
Current Analgesia			
	None	3	6
	Simple*	17	31
	Weak Opioid (e.g. Codeine)	10	18
	Strong Opioid (e.g. Morphine)	21	38
	Unknown	4	7
Non-steroidal Anti-Inflammatory Drugs			
	Yes	22	40
	No	26	47
	Unknown	7	13
Current cancer treatment			
	None	18	34
	Chemotherapy	5	9
	Radiotherapy	8	14
	Hormonal	24	43
	Hormonal &radiotherapy	8	15
	Chemotherapy &bisphosphonates	2	4
Bisphosphonate therapy			
	Yes	12	22
	No	43	78
*Simple - for example acetaminophen/paracetamol			

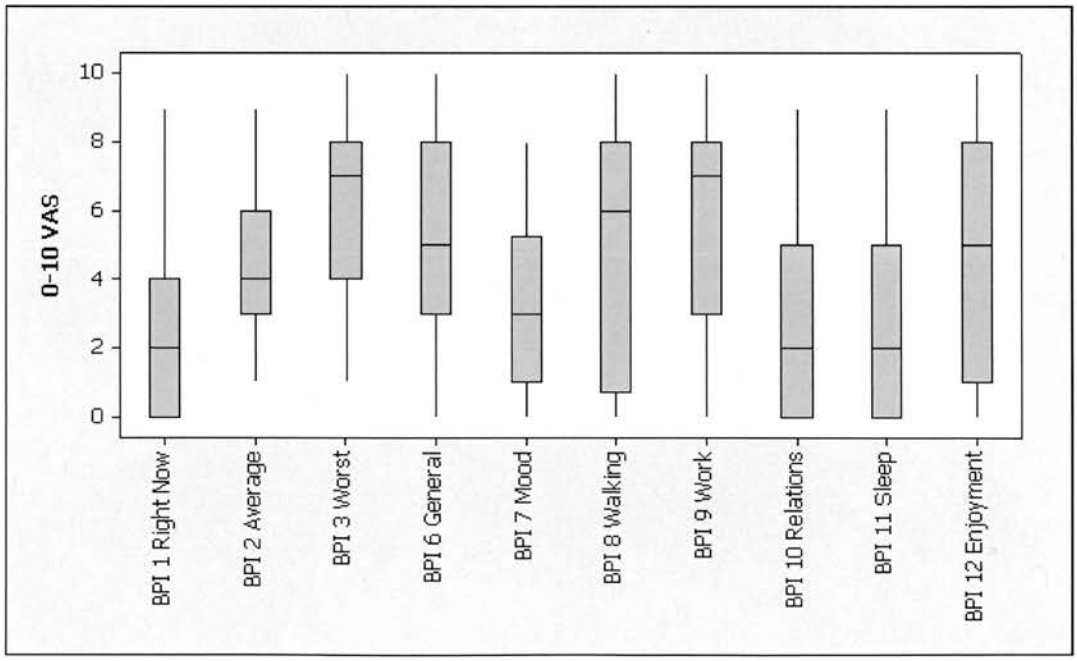
3.3.1. Pain Characteristics

The BPI results are shown in Figure 5. The median "pain right now" was 2 and the median "average" pain was 4. The median "worst pain" score was 7. In the multiple regression analysis, BPI worst pain was more strongly related to BPI interference score than average pain. The coefficient for worst pain was 3.17 (SE 0.93, p=0.001) and for average pain was 0.61 (SE 1.16, p=0.60).

The BPI scores were compared between those patients without, and those with, breakthrough pain. The median (IQR) BPI average pain for those without and those with breakthrough pain was 4 (3-5) and 5 (3-6) respectively. The median (IQR) BPI worst pain for those without and those with breakthrough pain, was 5 (4-7) and 7 (4-8) respectively. There was no statistically significant difference (at the $p<0.05$ level) between the scores in these two groups.

Patients who had breakthrough pain had higher BPI interference scores than those who did not have breakthrough pain (median (IQR); 35.0 (21.5-44.7) vs 18.5 (5.5-26.7) respectively). This was statistically significant at $p<0.01$ level.

Figure 5 - Brief Pain Inventory – Cancer induced bone pain



Box and whisker plot representing the median value, with 50% of the data falling within the box [Interquartile range]. The whiskers extend to the 5th and 95th percentiles.

3.3.2. Breakthrough Pain

The results of the BTPQ are shown in Table 6. Forty-one patients (75%) had breakthrough pain and completed the Breakthrough Pain Questionnaire.

The median (IQR) number of episodes of breakthrough pain over 24 hours was 4 (2-8). The median severity of the breakthrough pain episodes was 8 (based on a 0-10 VAS). The speed of onset (time from being first aware of pain, to pain reaching its peak) was less than 5 minutes in 33 patients (79%). Thirty–two patients (78%) had breakthrough pain of less than 30 minutes duration. Eighteen patients (44%) had pain which was unpredictable (including those patients who had onset of pain in less than 10 seconds).

Twenty patients (48%) had breakthrough pain which was of rapid onset (less than 5 minutes) and of short duration (less than 15 minutes).

Table 6 - Breakthrough Pain Questionnaire - Cancer induced bone pain

		Median	IQR
Number of BTP episodes in 24 hours			
		4	2-8
Severity of BTP episodes			
		8	4-9
Speed of onset of BTP		**n**	*%*
	unpredictable	5	12
	<10sec	13	32
	10s-5min	15	37
	6-30min	6	15
	31-60min	1	2
	unable to quantify	1	2
Duration of BTP			
	<1min	6	15
	1-15min	15	37
	16-30min	11	27
	31-60min	2	5
	60-120min	5	12
	>120min	2	5
Rapid Onset (<5 Mins) & Short Duration (<15mins)			
		20	49

3.4. Discussion

These data provide the first systematic characterization of CIBP which limits the ability to compare these findings to studies published previously. Previous work has examined breakthrough pain in cancer patients, however these studies included all types of cancer pain (Portenoy et al., 1999, Caraceni et al., 2004). By focussing on CIBP as a single entity, clinically valuable information about general pain characteristics and specific breakthrough pain characteristics in CIBP have been determined.

3.4.1. Worst Pain

"Worst pain" correlated more strongly to the interference score of the BPI (effect on general activity, mood, walking ability, work, relationships, sleep and enjoyment of life) than "average pain". Previous work in CIBP has shown that worst pain correlates with the interference scale of the BPI and our results support this (Harris et al., 2007, Shi et al., 2009). These findings, however, also demonstrate that worst pain is predictive of the interference score, over and above average pain, but not vice-versa. Therefore if the worst pain score is known, there is nothing to be gained by also knowing the average pain score. These findings have considerable clinical significance when considering how best to assess the impact of CIBP on the individual. Asking patients about their worst pain is more likely to give a meaningful picture of the impact of their pain and its effect on their life as a whole. "What is your worst pain?" is the crucial question in the assessment of a patient with CIBP.

The pain interference measures of the BPI have also been shown to correlate well with QoL tools (Yun et al., 2004). It is arguable whether worst pain is a useful surrogate measure of overall quality of life, however worst pain certainly correlates with general function in CIBP.

3.4.2. Breakthrough Pain

The findings demonstrate that breakthrough pain is highly prevalent in patients with CIBP. Seventy-five percent of the study population had breakthrough pain; pain that flared up from a stable background level to a more intense pain. This finding is

supported by the BPI data which demonstrated considerable differences between pain now, average pain and worst pain scores. The difference in these scores was at least 2 points (on a 0-10 VAS) which is clinically significant (Farrar et al., 2000).

Patients with breakthrough pain had higher BPI interference scores than those without breakthrough pain. This would suggest that breakthrough pain impacts more on day-to-day function than background pain. The psychological impact of breakthrough pain highlights its importance to patients' physical and psychological well-being and emphasizes the importance of asking the patient specifically about their worst pain.

Previous research has also shown that the presence of breakthrough pain predicts poor pain control,(Mercadante et al., 1992, Mercadante et al., 2002b) greater functional impairment (Portenoy et al., 1999), higher levels of anxiety and depression (Portenoy et al., 1999) and higher healthcare costs (Fortner et al., 2002).

This work has demonstrated that in CIBP, breakthrough pain is usually of short duration and often less than 15mins. The majority of patients found their breakthrough pain was rapid in onset and reached its peak intensity within 5 minutes. Breakthrough pain which was unpredictable was present in 18 patients (44%).

As detailed in 2.4.4, in previous studies of cancer breakthrough pain more variable characteristics have been reported, however these studies were in heterogeneous groups (Portenoy and Hagen, 1990, Gomez-Batiste et al., 2002, Hwang et al., 2003). Median durations of breakthrough pain have ranged from 15 minutes (Hwang et al., 2003) to 30 minutes (Gomez-Batiste et al., 2002, Portenoy and Hagen, 1990). Breakthrough pain has been reported as being unpredictable between 27% (Portenoy and Hagen, 1990) and 58% (Hwang et al., 2003) of patients. The work presented herein focuses exclusively on CIBP which enables a more meaningful analysis and easier translation into patient care.

The finding in CIBP that breakthrough pain is often of sudden onset (less than 5 minutes) and short duration (less than 15 minutes), has several implications for clinical practice and further research. Previous work has suggested that breakthrough pain can be treated effectively using standard treatment regimens (Hwang et al.,

2003). The established strategy of using IR morphine to manage breakthrough pain is likely to be inadequate for this group of patients. IR oral morphine starts to provide benefit, at best, at 30 minutes and takes 45-60 minutes to reach peak plasma concentration. It has duration of action of 3-4 hours. As breakthrough pain in CIBP has a more rapid onset and is of considerably shorter duration, it is likely that patients will suffer significant opioid-related side-effects, as their pain resolves without gaining effective analgesia for their breakthrough pain. In addition, the dictum that patients take anticipatory analgesia prior to movement depends on a predictable relationship between pain and movement. This is clearly not the case for the significant number of patients with CIBP who have unpredictable breakthrough pain. Also, for this strategy to be effective, patients have to anticipate incident pain to allow time for their IR oral morphine to become effective.

In trying to mimic closely the time course of breakthrough pain, rapid onset, short duration opioid preparations have been developed. However, the novel fentanyl preparations still take 5-20 minutes to reach meaningful plasma levels, with duration of action ranging from 2-3 hours (Portenoy et al., 2006, Slatkin et al., 2007). Alfentanil is an another short acting opioid that has been used for breakthrough pain but there is limited evidence to support its use (Duncan, 2002). While this improved opioid armamentarium may be useful for some patients, for those with rapid onset, short duration breakthrough pain, this pain remains challenging.

Recent basic science work has increased the understanding of CIBP. In animal models of CIBP, it has been reported that the mechanisms of CIBP are different to those of inflammatory pain indicating that higher doses of opioids may be required to achieve analgesia (Luger et al., 2002). The mechanisms for this are unclear but alteration in mu opioid receptors and interaction with other receptors such as transient receptor potential (TRP) family of ion channels, are likely to contribute to this relative opioid resistance (Yamamoto et al., 2008, Niiyama et al., 2009). The underlying pathophysiology of CIBP may differ from other pain states, necessitating a fundamental change in the therapeutic approach to CIBP.

3.4.3. Limitations

The study has several limitations. Patients who were in their last days of life or too unwell to complete the study protocol were excluded from the study, but it seems likely that these patients would have had a greater incidence of pain flares, consistent with the finding that 86-89% of patients admitted to hospice services had breakthrough pain (Fine and Busch, 1998). The sample size was small, although various tumour types were included and the sample was likely to be representative of a general oncology population.

The criterion used to identify those with breakthrough pain is open to criticism. Patients had to have an increase of 2 or more points (on a 0-10 VAS) from their background pain to their breakthrough pain. It was felt that any smaller differences in pain scores may represent minor fluctuations in an otherwise stable pain and their inclusion may reduce the clarity of our description of breakthrough pain associated with CIBP.

In other studies, researchers have excluded patients who have not had regular episodes of breakthrough pain, over the week prior to assessment, or who were not on regular strong opioids (Hwang et al., 2003, Portenoy and Hagen, 1990, Portenoy et al., 1999). These studies aimed to exclude patients who had only transitory flares of pain, which were likely to settle spontaneously. As the included patients had pain at sites of known bone disease, it was felt unlikely that their pain would settle spontaneously. Excluding this group would miss of proportion of patients with breakthrough pain. Some of the patients may have had analgesic end-of-dose failure which may have resulted in unstable background analgesia and therefore a greater amount of breakthrough pain.

In this study, as patients may have been taking analgesics these may have affected the features of the breakthrough pain. In this patient group nobody was using rapid-onset, short acting preparations. A proportion, however, was taking standard IR opioids. In theory, if a patient had taken an IR opioid for their breakthrough pain this may have limited the duration of their pain. It has been reported that IR opioids have an onset of analgesic effect at 30 minutes with peak effect at 60 minutes (Bailey and

Farley, 2006). Most patients had breakthrough pain of less than 30 minutes duration so it is unlikely that IR opioids would have impacted on this.

3.5. Conclusion

The study provides the first systematic characterization of CIBP. It demonstrates that breakthrough pain is highly prevalent in CIBP and is associated with significant functional impairment. Breakthrough pain is often severe, rapid in onset and short in duration. In view of this, current management strategies for treating CIBP are likely to be inadequate for a sizeable number of patients. The increasing availability of rapid-onset, short acting opioids may redress this for some patients, but this too needs proper evaluation.

A single measure of pain is inadequate to describe the individual experience of CIBP. However, if a single measure were to be used, "What is your worst pain?" is the crucial question. Worst pain correlates more strongly with the effect of pain on function than average pain scores.

Further, larger studies are needed to determine the frequency and intensity of CIBP in the broader cancer population.

Chapter 4. A Systematic Review of Cancer Pain and Depression

4.1. Introduction

Pain and depression are both common in cancer patients and the relationship between these symptoms has been of increasing interest (Caraceni and Portenoy, 1999, Lloyd-Williams et al., 2004). The issue of a possible interdependent association between these two symptoms has been raised. Epidemiological studies have shown that depression and pain are often present together (Bair et al., 2004). There is also physiological evidence to support this theory. Imaging studies have shown that the areas in the cerebellar cortex which process pain are also implicated in depression (Giesecke et al., 2005, Smith et al., 2002).

Pain in cancer patients is affected by many variables including cancer stage, extent of disease and treatment (Andersen and Sjogren, 1998). A single point prevalence survey, published in 1999 on behalf of IASP demonstrated that approximately 90% of patients with cancer experienced pain (Caraceni and Portenoy, 1999). Despite the high prevalence of pain amongst cancer sufferers, 80% of cancer pain can normally be controlled if simple guidelines are followed (Ventafridda et al., 1987). It follows that approximately 20% of patients with cancer pain will not achieve adequate analgesia with standard treatments.

Depression is the most common psychiatric condition in cancer, occurring in approximately one quarter of patients with advanced cancer (Lloyd-Williams et al., 2004). It has been suggested that depression is four times more common in cancer patients than in the general population and is often under-diagnosed (Derogatis et al., 1983, Block, 2000).

Pain and depression have been examined in the non-malignant setting. A randomised controlled trial, (the ARTIST study) published in 2000 demonstrated that pain is a strong predictor of depression (Bair et al., 2004). Patients with severe pain were four times less likely to respond to depression treatment. As pain decreased, a

response to treatment for depression increased. This is one of the few studies that illustrate how the presence of pain affects response to depression treatment.

In chronic medical illness, the association of depression and anxiety with physical symptom burden, has been studied in a systematic review (Katon et al., 2007). It concluded that physical symptoms (such as pain) were associated with depression and anxiety. It has also been shown that an improvement in depressive symptoms is associated with an improvement in somatic symptoms (Borson et al., 1992, Lin et al., 2003b, Bair et al., 2003).

Less is known regarding the relationship between pain and depression in the oncological setting. Although the epidemiology and treatment of cancer pain and depression have been studied previously, the relationship between them has not been examined (Carr et al., 2002). A systematic review examining the relationship between these two symptoms has not been carried out previously.

Thus the aim of this systematic review was to assess the evidence for a relationship between cancer pain and depression.

4.2. Methods

Ethical approval was not required for this systematic review. The following databases were searched electronically: Medline (1950-2007), Embase (1988-2007), CINAHL (1982-2007) and the Cochrane Database of Systematic Reviews (Issue 2 2007). In addition, the following journals were searched manually: Palliative Medicine, Journal of Pain and Symptom Management, Progress in Palliative Care and the European Journal of Palliative Care.

The following search terms were used: "cancer" AND "pain" AND "depression", using MeSH terms; all subheadings were included. Results were limited to English language journals and studies involving humans. Due to the broad search terminology a large number of results was obtained. The titles of all the articles retrieved were subsequently reviewed and the abstracts of all the articles deemed relevant, in accordance with inclusion criteria, were retrieved in whole. Subsequently, all papers were reviewed independently by two authors. These were

analysed to assess quality, using a pre-determined schedule (Appendix 1) which was based on the Scottish Intercollegiate Guidelines Network (SIGN) appraisal guideline (SIGN, Edinburgh).

4.2.1. Inclusion Criteria

Studies were included if the sample examined cancer patients of any tumour type, at any stage of the disease. Papers that included cancer in addition to other medical conditions were eligible. In addition, studies had to define depression using a recognised tool. Some studies only examined distress or mood per se, however, if depression was studied as a component of this, then these studies were eligible. Eligible studies also had to assess pain. This was defined using an assessment tool which varied according to individual studies. Studies were required to explore the relationship between the two variables, pain and depression. Systematic reviews were deemed eligible.

4.2.2. Exclusion Criteria

Studies were excluded when they did not meet all inclusion criteria. Thus if studies did not include a cancer population, define depression and define pain, they were not eligible for this review. Studies which did not present original material were excluded, as were critical and narrative reviews (systematic reviews were eligible). Those articles examining pain and depression in non-malignant disease were also excluded as were papers which analysed distress or other psychiatric symptoms but did not define depression.

4.3. Results

The literature search retrieved 892 articles and the review process is shown in Figure 6. The titles of these were reviewed and, if deemed potentially appropriate, selected for further analysis. This resulted in 167 articles, which were reviewed in greater detail and, once again if potentially relevant, were selected for further analysis. Forty-one articles were subsequently reviewed independently by two of the authors. Consensus was agreed on 28 articles without discussion. Further debate among the authors led to agreement regarding all articles. Fourteen articles were deemed

appropriate for inclusion in this review as shown in Table 7. The date of the last literature search was 19th June 2007.

Figure 6 - Literature search

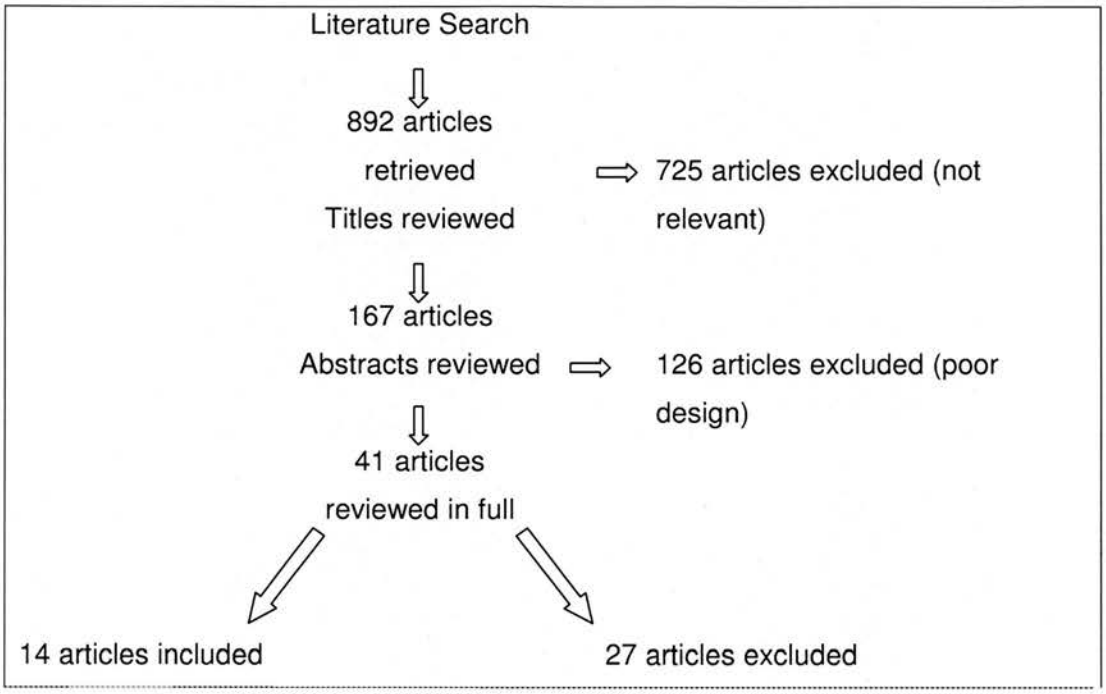


Table 7 - Studies included in the systematic review

Reference	Sample size	Depression Assessment	Pain Assessment
Cross sectional Studies			
Lin CC et al (Lin et al., 2003a)	484	POMS	BPI
Heim and Oei (Heim and Oei, 1993)	47	BDI	MPQ
Sze FK et al(Sze et al., 2000)	70	HADS	VAS
Ciaramella and Poli(Ciaramella and Poli, 2001)	100	SCID+ Endicott	VAS
Mystakidou et al(Mystakidou et al., 2006)	120	HADS	BPI
Chen et al(Chen et al., 2000)	203	HADS	VAS
Glover et al (Glover et al., 1995)	369	POMS	Numerical
Aukst-Margetic et al(Aukst-Margetic et al., 2005)	115	CES-D	VAS
Kelsen et al (Kelsen et al., 1995)	130	BDI	MPAC
Sist et al(Sist et al., 1998)	190	BDI	MPQ
Mystakidou et al (Mystakidou et al., 2007b)	82	BDI	BPI
Spiegel et al (Spiegel et al., 1994)	96	POMS/CES-D	VAS
Cohort Studies			
Zimmerman et al (Zimmerman et al., 1996)	60	BSI	MPQ
Williamson and Schulz (Williamson and Schulz, 1995)	268	CES-D	Numerical

Of the excluded articles, 18 were cross-sectional studies and were excluded on the grounds that pain and/or depression were not defined, or a relationship between these two entities was not examined. Excluded articles also included three reviews, two qualitative studies, one crossover trial, one intervention study, one consensus statement and one paper examining views of caregivers. All of these did not meet the inclusion criteria. A large number of excluded studies failed to define depression and instead looked at general areas such as "distress" and "suffering" of which clear boundaries and definition are lacking. No systematic reviews were found.

Of the included studies, the study design was categorized, based on recommendations described by Stephenson and Babiker (Stephenson and Babiker, 2000). All included studies were of a prospective design. Twelve studies were cross-sectional in design whilst two were cohort studies. Methodology varied among the studies. Some studies divided subjects into those with and those without pain. This allowed comparison between the groups. In other studies all patients had pain.

A selection of assessment tools for both depression and pain were utilised Table 7. Measurements of depression included the Hospital Anxiety and Depression Scale (HADS), Centre for Epidemiological Studies Depression Scale (CES-D), Profile of Mood States (POMS), Beck Depression Inventory (BDI), Structured Clinical Interview for Depression (SCID), Endicott Criteria and the Brief Symptom Inventory (BSI – where depression was measured as a component). Pain was assessed using a variety of assessment tools. These included the McGill Pain Questionnaire (MPQ), the Brief Pain Inventory (BPI), numerical rating scales, the Memorial Pain Assessment Card (MPAC) and Visual Analogue Scores (VAS). These pain assessment tools are not designed to assess prevalence and instead measure features of pain such as intensity and descriptors. However, by having a score greater than zero on any one of these tools, it is reasonable to conclude that these patients had pain.

Only four studies had the methodology to allow a combined prevalence of pain and depression to be calculated as shown in Table 8. In three of these studies, the entire

patient sample had pain and thus the prevalence of depression could be deduced. In the remaining study, the authors quoted the combined prevalence. In those patients with pain, the mean prevalence of depression was 36.5% (range 22.1 - 49). This prevalence must still be interpreted with caution as different assessment tools were used. A statistical association between pain and depression was demonstrated in some of the studies (Table 9).

Table 8 - Prevalence of depression in patients with cancer pain.

Reference	Depression Assessment tool	Depression Prevalence (%)
Sist et al(Sist et al., 1998)	BDI	22.1
Sze et al(Sze et al., 2000)	HADS	29.0
Ciaramella and Poli(Ciaramella and Poli, 2001)	SCID + Endicott	49.0
Spiegel et al(Spiegel et al., 1994)	SCID	46.0

Table 9 - Studies where a statistical association is demonstrated.

Reference	Pain & depression – statistical association
Heim and Oei(Heim and Oei, 1993)	F=3.892*** P=0.05
Sze FK et al(Sze et al., 2000)	0.1621**** P=0.18
Ciaramella and Poli(Ciaramella and Poli, 2001)	t=2.97** P<0.01
Chen et al (Chen et al., 2000)	t=7.00** p<0.001
Glover et al (Glover et al., 1995)	t=2.52 P<0.01
Aukst-Margetic et al (Aukst-Margetic et al., 2005)	U=1089* P=0.009
Kelsen et al (Kelsen et al., 1995)	0.3575***** P=0.001
Sist et al (Sist et al., 1998)	0.141****** P<0.05
Zimmerman et al (Zimmerman et al., 1996)	0.51***** P<0.01

*=Mann Whitney test **=t-test ***=univariate F tests

****=Spearman correlation coefficients

*****=Pearson correlations ******=ANOVA two analysis of variants

4.4. Discussion

None of the included studies were designed to examine a causal relationship between pain and depression, thus causality cannot be determined. Due to the methodology used in individual studies and variation in classification of depression and pain, meta-analysis of included studies was not possible. Thus common themes from the studies were examined.

4.4.1. Epidemiology of Cancer Pain and Depression

One of the main difficulties in ascertaining accurately the prevalence of depression in patients with cancer pain, lies in the variety of assessment tools used to define depression. As discussed, inferences regarding the combined prevalence of pain and depression could only be drawn from four studies (Table 8). The prevalence of depression seemed to vary according to the assessment tools used. Depression was least prevalent when using the BDI whilst studies using the SCID had a greater prevalence of depression.

The remaining studies did not allow calculation of the prevalence of co-existing depression and pain, however other conclusions were drawn by the authors. Depression was more common in those patients with increased pain severity and this group had a lower prevalence of major depression than those where pain was less severe (Spiegel et al., 1994). The authors suggested that pain caused depression and postulated that under-treatment of pain may cause increased suffering and depression.

Other factors such as sex and age are considerations. It has been shown that women are more likely to be depressed than men (Mystakidou et al., 2006). Older patients with cancer pain are more likely to be depressed than younger patients (Mystakidou et al., 2006). This association has, however, been refuted by other research work, including a recently-published systematic review examining age-related patterns (Williamson and Schulz, 1995, Gagliese et al., 2007).

4.4.2. Relationship between pain characteristics and depression.

Themes have emerged suggesting relationships between specific pain characteristics and depression. It has been shown that, as pain increased (as measured by all components of the MPAC), so did depressive symptoms (Kelsen et al., 1995). Many of the studies used detailed pain assessment tools allowing detailed analysis of specific components of pain and their relationship to depression.

4.4.2.1. Pain Intensity

Pain intensity correlated positively with depression (to levels of statistical significance $p<0.05$) (Kelsen et al., 1995, Sist et al., 1998, Ciaramella and Poli, 2001). Worst pain intensity also correlated positively with depression (to levels of statistical significance) (Glover et al., 1995). "Current pain intensity" correlated significantly with mood on POMS (Profile of Mood States), but this did not reach statistical significance on the CES-D (Spiegel et al., 1994). Patients who were depressed reported a higher intensity of pain than non-depressed patients (Sist et al., 1998). Increasing pain was associated with increased levels of depression (Spiegel et al., 1994). Sze et al examined whether pain intensity and disability differ in depressed patients (Sze et al., 2000). They showed no difference in the nature and severity of pain between depressed and non-depressed cancer patients. This did not reach statistical significance ($p =0.18$), perhaps due in part to the small sample size of 70 patients.

4.4.2.2. Pain Descriptors

When specific items on the MPQ were explored, patterns seemed to emerge. Patients who were depressed scored higher on the affective pain intensity scores and the affective pain descriptors, than their non-depressed counterparts (Sist et al., 1998). Words in the "punishment" and "tension" sections were more likely to be chosen by those patients with pain and depression. It was also shown that pain interference items such as "worst pain" and "enjoyment of life" (measured on the BPI) correlated significantly with depression (Mystakidou et al., 2007b).

4.4.2.3. Pain Perception

Patients' perception of their pain differed between those with depression and those without. Aukst-Margetic et al used a visual analogue score to assess pain and found a statistical difference (u=1089, p=0.009) in pain perception between depressed and non-depressed groups (Aukst-Margetic et al., 2005).

4.4.2.4. Pain Duration

It has been shown that the longer the duration of pain, the higher the risk of depression (Kelsen et al., 1995, Glover et al., 1995). It has also been suggested that as pain increased over time, so did depressed affect, but this was not statistically significant (Williamson and Schulz, 1995).

4.4.3. Is there an association between pain and depression?

Although it is reasonable to conclude that depression and pain are both highly prevalent in cancer patients, it does not necessary follow that these are related. Some of the studies included in this systematic review explore the relationship, by analysing the prevalence of depression in a cohort of patients with and without pain. One study examined patients with prostate cancer and showed that those who suffered from pain were more depressed than those who were pain-free (Heim and Oei, 1993). All patients with metastatic disease reported pain and there was a statistically significant difference in prevalence of depression between those with and those without pain. This finding was supported in other studies, showing that patients with pain had a higher prevalence of depression (Chen et al., 2000, Glover et al., 1995, Ciaramella and Poli, 2001, Aukst-Margetic et al., 2005). Such studies used specifically-designed tools to identify depression.

When tools that are less sensitive at measuring depression are used, it is not surprising that fewer inferences can be drawn. Where depression was assessed as part of the BSI, it was shown that whilst patients with pain had more psychological symptoms, this did not reach statistical significance when depression was analysed (Zimmerman et al., 1996). Another study of approximately 500 patients revealed

that patients with pain had higher levels of overall mood disturbance, but did not have statistically-higher levels of depression (Lin et al., 2003a).

Due to the variety of assessment tools and criteria used to define pain and depression in the included studies, direct comparison and amalgamation of data is not possible. Yet it has been demonstrated that there are statistically significant associations between specific pain characteristics and depression. Furthermore, some studies have shown a general association between pain and depression (Table 9). However, the evidence available is not sufficient to support a causal relationship between pain and depression.

4.5. Conclusion

Psychological symptoms (depression, anxiety, somatisation) are more prevalent in cancer patients with pain than those without (Zimmerman et al., 1996). This systematic review has demonstrated that both pain and depression are highly prevalent in cancer patients. It is also reasonable to conclude that specific features of pain (such as intensity or effect on enjoyment of life) are related to depression. The question remains as to whether these two entities are interdependent. It would seem reasonable to conclude that pain, depression and anxiety are closely linked, given what we know about their common central pathways and neuropharmacology (Remy et al., 2003). The evidence presented does suggest an association, but is insufficient to assign a causal relationship.

Until a firm evidence-base can be established, the question of a bidirectional relationship between cancer pain and depression remains unresolved, with management based on individual assessment. Both pain and depression have significant clinical impact. It is important, therefore, in further studies to establish whether or not there is a causal relationship. This would have implications for the way individual patient management is approached. To provide further weight to the hypothesis that pain and depression may be connected, different study methodology is needed. Such studies require to be of a longitudinal design. Uniformly-agreed assessment tools will also allow comparisons to be made between studies. Through

these, the theoretical interdependent relationship between cancer pain and depression could be studied. This would be an important step in the research agenda.

Chapter 5. A Longitudinal Study of Cancer Pain and Depression

5.1. Introduction

Pain and depression are common symptoms in cancer patients. It has been reported that 90% of cancer patients experience pain (Caraceni and Portenoy, 1999). Depression occurs in approximately 25% of patients with cancer and is the most common psychiatric condition in cancer patients (Derogatis et al., 1983, Lloyd-Williams et al., 2004). As pain and depression are both common in cancer patients, the possibility of an interdependent relationship between these two symptoms has been suggested. It has also been suggested that these symptoms may form a symptom cluster in combination with fatigue (NIH, 2003). Although pain and depression are often present together in cancer patients there is little evidence to support that these symptoms are related (NIH, 2003, Glover et al., 1995).

In addition to depression, the term "distress" has become increasingly commonplace when discussing psychological morbidity in cancer patients. Depression and distress are often used interchangeably thus it is difficult to define what distress is and its prevalence. The National Comprehensive Cancer Network (NCCN) defines distress as:

> "a multi-determined unpleasant emotional experience of a psychological (cognitive, behavioural, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and spiritual crisis" (NCCN, 2002).

As this definition may include a vast number of cancer patients the term "emotional distress" has also been used. It is helpful as patients may have symptom patterns that do not fit neatly into a diagnosis of anxiety or depression, however still have a

psychological symptom burden (Costantini et al., 1999). Emotional distress is an important part of the spectrum of psychological symptoms that can affect cancer patients.

A discussed in chapter 4, a systematic review has examined the evidence for a link between pain and depression (Laird et al., 2008). In patients with pain the mean prevalence of depression was 36.5%, although this was dependent on the assessment tool used. Pain intensity has also been shown to correlate with depression (Kelsen et al., 1995, Ciaramella and Poli, 2001, Sist et al., 1998). It has also been shown that the longer duration of pain, the higher the risk of depression (Glover et al., 1995, Kelsen et al., 1995).

It is reasonable to conclude that pain and depression are highly prevalent in cancer and that some pain features may be associated with depression. Despite this, previous work was not designed to assess a causal link and whilst this work does suggest an association, there is insufficient evidence to support an interdependent relationship (Laird et al., 2008).

As both pain and depression can have a significant clinical impact, it is important to develop a greater understanding of the relationship between these symptoms. This would impact on the management of these symptoms in a clinical setting and the way individual patient management is addressed.

Examining the relationship between pain and depression poses several methodological challenges. In the cancer setting, symptomatology can often vary on a day-to-day basis. The use of treatments targeting pain and depression can render the assessment of these symptoms in a controlled setting, challenging. It has been suggested that any research conducted to assess a possible link between these symptoms should be of a longitudinal design (Laird et al., 2008). By treating one of these symptoms in isolation, the effect on the other could be assessed.

In the cancer setting, there have been no previous studies which have examined the relationship between pain and depression, using a longitudinal methodology. The aim of this longitudinal study, therefore, was to assess depression and distress, when pain is treated.

5.2. Methods

5.2.1. Overview

The study took the form of a secondary analysis of two clinical studies datasets. The datasets were combined to allow an analysis to be undertaken. These two studies examined the effect of radiotherapy on CIBP. In both studies, patients received palliative radiotherapy for CIBP. Assessments of pain and depression were performed at study baseline and endpoint. One of the studies used an investigational medicinal product (IMP) or placebo, in addition to radiotherapy. The IMP was pregabalin and its role as an adjuvant analgesic for CIBP was being investigated. The second study was a clinical characterization study with no additional intervention.

As this was an analysis of existing data, no additional ethical approval was required. The original studies had appropriate ethical approval and were conducted in accordance with the International Committee for Harmonisation, Good Clinical Practice and the Helsinki Declaration.

5.2.2. Inclusion Criteria

Patients, with metastatic cancer and radiologically confirmed bone metastases, attending one of two regional oncology centres in the United Kingdom, were included. All patients had CIBP with a worst pain score (at the site of CIBP) of ≥ 4 (on a 0-10 VAS). All patients were, at baseline, about to receive palliative radiotherapy for CIBP. Patients had a life expectancy of greater than two months. Patients were allowed to take standard analgesia (including strong opioids) for the duration of the studies and doses were increased or decreased as required for symptom control. Patients were also allowed to take adjuvant analgesics or antidepressant medication.

5.2.3. Exclusion Criteria

Patients felt to be in the last two months of their lives or who were unlikely to be able to complete the study protocol due to their clinical condition, were excluded. In

addition, patients who had did not have CIBP and were not due to receive palliative radiotherapy were excluded.

5.2.4. Procedures

Written informed consent was obtained. Demographics and information concerning the patient's underlying malignancy was gathered from their medical records.

Two structured interviews were conducted with each patient; at study baseline (prior to radiotherapy) and study endpoint (four to eight weeks later).

During these interviews, pain and depression were assessed using validated assessment tools. Types and doses of analgesic drugs taken in the preceding 24 hours were recorded. For ease of comparison, opioid doses were converted to oral morphine equivalents (Morphine equivalent daily dose – MEDD) using a recognised and accepted conversion table (Fallon et al., 2009). Anti-depressant medication and any dose change in the previous four weeks (which could ,in theory, have affected mood) was documented. Some patients were taking tricyclic antidepressants (e.g. amitriptyline) for neuropathic pain. This was only classified as an anti-depressant if the dose per day was greater than 75mg.

5.2.5. Assessment Tools

All patients completed the Brief Pain Inventory (BPI) and the Hospital Anxiety and Depression Scale (HADS).

5.2.5.1. Brief Pain Inventory

The BPI has been discussed in 2.2.4.1. An improvement in the total BPI score of >30% was defined as being a clinically significant improvement in pain. Patients whose total BPI score fell by 30% or more were classified as responders. Those whose pain did not fall by 30% were classified as non-responders.

5.2.5.2. Hospital Anxiety and Depression Scale

The HADS (Appendix 1) was developed as an assessment tool for depression and anxiety in hospital outpatients (Zigmond and Snaith, 1983). It has been used in

cancer patients and has been validated in this population (Le Fevre et al., 1999). The HADS consists of two subscales – an anxiety subscale and a depression subscale, which total 14 questions. Each question can score between 0 – 3 on a scale (the higher the score the greater the symptom) and a maximum score of 42 is possible.

The subscales can be analysed either independently or a combined score can be calculated. The combined score is the most widely used clinically and it has been shown that combining the anxiety and depression scores is predictive of depression, as opposed to using the depression score alone (Le Fevre et al., 1999, Walker et al., 2007). A combined score of $\geq$ 15 has been suggested as a cut-off for major depressive disorder (MDD) and therefore was used for the study (Walker et al., 2007). This cut-off score was based on a comparison study with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (Walker et al., 2007, APA, 1994).

A combined HADS score of $\geq$ 10 been suggested as a valid measure of emotional distress and this cut-off was used in our study (Razavi et al., 1992, Costantini et al., 1999, Walker et al., 2007). For the sake of brevity, patients whose HADS score was $\geq$ 15 are referred to as "depressed" and those whose HADS score was < 15 are referred to as "not-depressed". Patients whose HADS score was $\geq$ 10 are referred to as "distressed" and those whose HADS score was < 10 are referred to as "not-distressed".

5.2.6. Statistics and Analysis

Patient demographics were summarised using proportions, and means and standard deviations (SDs). Analysis was undertaken of all patients. These were divided into groups whose pain had improved during the course of the study (responders) and those who had no improvement (non-responders). The baseline and endpoint data for the BPI and the HADS were summarised using medians and inter-quartile ranges (IQRs).

Due to the small sample size, a Fishers exact test was performed on these data. An initial analysis was done assessing the relative proportions of depressed and non-depressed patients in each group (responders and non-responders). Further analysis

taking into account patients' baseline characteristics was performed. An analysis of covariance was done to assess the change in HADS score between responders and non-responders.

5.3. Results

The patient demographics are shown in Table 10. Sixty-nine patients were recruited. Forty (58%) patients were male and the mean age was 67.1 years (SD 10.4, range 38-88). Breast and prostate were the most common tumour sites. All patients received radiotherapy for CIBP following the initial interview.

Sixty two (90%) patients were receiving strong opioids at study baseline. The mean MEDD at baseline was 76 mg (range 0-800mg). Fifty nine (86%) patients were receiving strong opioids at study endpoint. The mean MEDD at endpoint was 90mg (range 0-600mg). Patients were taking various adjuvant analgesics including NSAIDs, amitriptyline, gabapentin and lidocaine patches. Where amitriptyline was used as an adjuvant analgesic for neuropathic pain, the dose was 75mg per day or less, and unlikely to exert any antidepressant effect. No other antidepressants were used as adjuvant analgesics. Two patients were taking antidepressants at study baseline (Fluoxetine and Losepramine). The doses of these had not altered in the previous four weeks. At study endpoint the same two patients were on antidepressants, however in one patient this had changed from Losepramine to Mirtazapine.

Table 10 - Baseline demographics

Characteristic		n	%
Sex			
	Male	40	58
	Female	29	42
Type of cancer			
	Prostate	26	38
	Breast	24	35
	Lung	14	20
	Melanoma	1	1
	Renal	1	1
	Colorectal	1	1
	Larnyx	1	1
	Bladder	1	1

5.3.1. Hospital Anxiety and Depression Scale

The baseline and endpoint HADS scores of responders and non-responders are shown in Table 11. Both groups were similar at baseline. No statistically significant difference was observed between "responder" status and the categorised depression baseline score (at the $p>0.05$ level).In the non-responder group the HADS score increased by 3 points whereas in the responder group, this fell by 4 points.

Table 11 - Baseline and endpoint HADS score

		Baseline			Endpoint		
		Anxiety Subscale	Depression Subscale	Total	Anxiety Subscale	Depression Subscale	Total
Non-Responders	Median (IQR)	5(3-10)	6(4-8)	11(8-16)	6(3-9)	8(4-11)	14(8-17)
Responders	Median (IQR)	4(3-7)	5.5(3-6)	10(8-14)	3 (1-4)	3 (2-6)	6 (4-11)

5.3.2. Brief Pain Inventory

The total BPI score and the interference component of the BPI score were assessed at baseline and endpoint. The results are displayed in Table 12. At baseline, the BPI total and interference scores in both groups, were similarly matched. There was an increase in the median total score and interference score in the non-responders. In those whose pain did respond, there was a decrease in the median total score and interference score.

Table 12 - Baseline and endpoint BPI

		Baseline		Endpoint	
		Total	Interference	Total	Interference
Non-Responders	Median (IQR)	52(38-61)	30(23-40)	55(39-65)	33(23-43)
Responders	Median (IQR)	49(34-62)	30(19-40)	11 (2-20)	4 (0-13)

5.3.3. Relationship between pain and depression

The relationship between pain and depression was assessed. Those patients whose HADS score was $\geq$ 15, were defined as being depressed. When considering the depression as a qualitative variable, the cross-tabulation is observed as shown in Table 13.

Table 13 - Pain and depression - not adjusted for baseline depression status

	Not Depressed (at endpoint)	**Depressed (at endpoint)**
Non-Responders	11 (58%)	8 (42%)
Responders	43 (86%)	7 (14%)

Of the responders 86% of patients are not depressed at endpoint, compared with 58% in the non-responder subset. There is a statistically significant difference ($p = 0.0203$) in the depression status between the non-responders and the responders. However, these results do not adjust for the baseline depressive status of the patient.

When taking into account patients' baseline HADS status, the cross-tabulation is observed as shown in Table 14.

Table 14 - Pain and depression - adjusted for baseline depression status

	NOT Depressed at BASELINE (n=51)		**Depressed at BASELINE (n=18)**	
	Not Depressed (at endpoint)	Depressed (at endpoint)	Not Depressed (at endpoint)	Depressed (at endpoint)
Non-Responders	9 (69%)	4 (31%)	2 (33%)	4 (67%)
Responders	35 (92%)	3 (8%)	8 (67%)	4 (33%)

Of those patients who are not depressed at baseline, most of them remain not depressed. Of the 38 patients whose pain improved (responders), 35(92%) remain depression-free. Of the 13 patients whose pain did not improve, 9 (69%) remained depression-free. The Fishers exact test p-value for this was 0.06, suggesting there was no association between responder status and depressive status at the 5% level.

Of those patients who were depressed at baseline; in the 12 patients whose pain improved, 8 (67%) had a change in their depression in status from depressed to non-depressed. Of the 6 patients whose pain did not improve, only 2 (33%) had a change in their depression status from depressed to non-depressed. The Fishers Exact Test p-value was 0.32 suggesting that there was no association between these groups at the 5% level.

5.3.4. Emotional Distress

The relationship between pain and emotional distress was assessed. Those patients who had a HADS score $\geq$ 10 were defined as being emotionally distressed. When considering the depression as a qualitative variable the cross-tabulation is observed as shown in Table 15.

Table 15 - Pain and distress - not adjusted for baseline distress status

	NOT Distressed (at endpoint)	**Distressed (at endpoint)**
Non-Responders	6 (32%)	13 (68%)
Responders	36 (72%)	14 (28%)

Of the "responders" 72% of patients were not distressed at endpoint, compared with 31% in the "non-responder" subset. A Fishers exact test of association concludes a statistically significant association with a p-value of 0.0048. In other words there was a statistically significant association between the pain-responder status and emotional distress.

When taking into account patients' baseline HADS scores as an indicator of distress, the following cross tabulation is observed as shown in Table 16.

Table 16 - Pain and distress - adjusted for baseline distress status

	NOT Distressed at BASELINE (n=31)		**Distressed at BASELINE (n=38)**	
	Not Distressed (at endpoint)	Distressed (at endpoint)	Not Distressed (at endpoint)	Distressed (at endpoint)
Non-Responders	4 (57%)	3 (43%)	2 (17%)	10 (83%)
Responders	23 (96%)	1 (4%)	13 (50%)	13 (50%)

Of those patients who were not distressed at baseline, most of them remained not distressed. Of the 24 patients whose pain improved (responders), 23(96%) remained distress-free. Of the 7 patients whose pain did not improve, 4 (58%) remained distress-free. The Fishers exact test p-value for this was 0.02 suggesting these was a statistically significant association between pain-responder status and emotional distress at the 5% level.

Of those patients who were distressed at baseline; in the 26 patients whose pain improved, 13 (50%) changed from distressed to non-distressed. Of the 12 patients whose pain did not improve, only 2 (17%) had a change in their distress status from distressed to non-distressed. The Fishers exact test p-value was 0.07 suggesting the observed association between the two groups was not statistically significant at the 5% level.

5.3.5. Effect on HADS score

The effect of pain on the HADS score is shown in Table 17.

Table 17 - Effect of pain on HADS score

	Mean change (S.D.)*	minimum, maximum
Non-Responders (n=19)	0.73 (5.36)	-10, 8
Responders (n=50)	-2.52 (5.47)	-16, 18

**Standard Deviation*

Responders are on average, dropping 2 points on the HADS score between baseline and endpoint. The non-responders are on average increasing 1 point on the HADS between baseline and endpoint. An analysis of covariance shows a statistically significant difference between the two response categories. An F-test with a p-value of 0.006 with an estimate difference in LS (Least Squared) means = 4.6. This is statistically significant in favour of those whose pain improved, (responders) reducing the HADS score. In conclusion an improvement in pain will, on average, reduce the HADS score.

5.4. Discussion

The study examines the natural evolution of depression, distress and pain in cancer patients. Treating pain reduces the HADS score whereas if pain does not improve, the HADS score increases. There is a trend towards an improvement in depression score in those in whom pain is reduced, however this was not statistically significant. When pain improves so does distress. These findings suggest an association between depression, emotional distress and pain. When pain is treated, depression and distress appear to improve which suggests a possible unidirectional relationship between pain and depression/distress. This would support the theory that depression and distress may be influenced by pain, but is not sufficient to support the reverse, i.e. that pain is influenced by depression and distress.

As similar studies in a cancer population are lacking, a comparison with other work is difficult. In the non-cancer setting, pain and depression have been examined and in this setting depression seems to influence pain (Bair et al., 2004). Some work has been done (as discussed in Chapter 4) but none of these studies employed the necessary longitudinal design required to assess the relationship between pain and depression.

This study would suggest that treating pain may modify depression and distress. This may be due to the impact of one symptom on another clinically, through a common underlying pathophysiological process or a combination of these as discussed in 1.3.1. In cases where pain and depression co-exist, it could be argued that treating pain may improve depression, negating the need for anti-depressant therapy in some cases. Emotional distress may also improve if pain is managed sufficiently well.

5.4.1. Limitations

One of the main problems when assessing depression is in the definition. The HADS is a *screening* tool for depression and not a diagnostic tool. In this study, major depressive disorder was defined as being a combined HADS score of ≥ 15. This cut-off point has been shown to be a reasonable, sensitive and specific guide when screening for major depressive disorder (Walker et al., 2007). However, this cut-off point may have missed some cases of MDD.

The HADS has been used as a surrogate marker of distress in many studies (Razavi et al., 1992, Costantini et al., 1999, Walker et al., 2007). The specific HADS cut-off point used to assess for emotional distress is open to debate. A score of ≥ 10 but <15 was used in this study, however scores of ≥ 15 have been used and been suggestive of clinically significant emotional distress (Ibbotson et al., 1994). It could be argued that patients defined as having emotional distress in this study would not been classified as having clinically significant emotional distress when higher cut-offs are used. A degree of pragmatism is needed, as such definitions are open to cultural interpretation and can also vary in severity based on underlying psychological coping mechanisms.

The study population was highly selective, consisting of oncology outpatients with a limited group of primary tumour sites. All patients received radiotherapy at baseline as part of a larger study and all patients were in a clinical trial setting. This gold standard treatment for CIBP allowed prediction of at least a 50% reduction in pain, in 50% of patients.

Patients in a clinical trial are under close medical and nursing supervision and this may have had some impact on depression and distress. Furthermore, the majority of patients were taking strong opioids, suggesting that this group may have a higher pain burden or may have been in regular contact with primary or palliative care. In turn, this may have been therapeutic in improving depression. It is difficult to minimize the effect of such confounding variables within a research context. It is important to emphasize, however, that despite the homogeneous nature of the study population, a proportion of patients failed to achieve an improvement in pain control, depression and distress.

Combining two datasets, such as was done here, has some limitations. In particular a proportion of patients were in a trial of an IMP (pregabalin) and may have been taking this (half of patients would have been on placebo). Pregabalin may have had mood altering effects and this may have impacted on HADS scores. This highlights the difficulties in combining two datasets, as although the populations were similar in many ways, there were some particular differences which may have affected findings.

One of the main reasons that limited conclusions can be drawn from these results is the small sample size. Fifty-one (74%) patients were not depressed at baseline meaning the proportion of depressed patients in the study was very small. As mentioned previously, the population was homogeneous, however approximately 25% of patients were depressed. This is in keeping with other studies in the cancer population (Derogatis et al., 1983, Lloyd-Williams et al., 2004).

5.5. Conclusion

The study is the first to examine the natural evolution of depression and emotional distress in patients where only pain is treated. These findings suggest that depression

and distress may influenced by pain. Treating pain decreases the HADS score, whereas if pain does not improve, the HADS score increases.

Further work is needed to assess the relationship between pain, depression and distress. Such research should take place in the broader cancer population and with a larger sample size. A more robust method of diagnosing depression, such as a SCID, should also be used to improve the sensitivity and specificity of diagnosing depression. The impact of depression and distress on pain also requires to be assessed. If future work supports associations between these, it may have considerable implications on the management of these common and challenging symptoms.

Chapter 6. Cancer Pain and its Relationship to Systemic Inflammation

6.1. Introduction

Systemic inflammation is part of the complex pain jigsaw. As cancer progresses, patients tend to experience more pain and whilst in a simplistic way, this may be due to an increase in the symptom burden, it may also be due to other mechanisms such as systemic inflammation.

It has been widely accepted, that there is a relationship between cancer and systemic inflammation. Systemic inflammation has been shown to predispose to certain tumour types,(McKay et al., 2008) has been implicated in oncogenic mutations and is present in experimental animal models of tumour development (Mantovani et al., 2008). Systemic inflammation can also be a result of cancer. Targeting systemic inflammation through various therapies has been shown to reduce cancer risk and cancer spread (Mantovani et al., 2008).

6.1.1. Pain and inflammation

Pain has also been shown to be related to inflammation. This is not a new concept as the four key components of inflammation were first described as calor (heat), dolor (pain), rubor (redness) and tumour (swelling). In recent years the relationship between pain and systemic inflammation has been widely accepted both as a mechanism and as a possible therapeutic target, for treating pain (Zhang and An, 2007).

6.1.2. C-reactive Protein

Systemic inflammation can be assessed using C-reactive protein (CRP). This biomarker has been used to demonstrate systemic inflammation in both hormone dependent and hormone independent cancer (Falconer et al., 1995, O'Gorman et al., 1998, Crumley et al., 2006). CRP is an acute-phase plasma protein, manufactured in the liver (Gaw et al., 1995, Pepys and Hirschfield, 2003). CRP concentrations rise

dramatically during inflammation and remain elevated, whilst the underlying inflammatory process remains active. As the half-life of CRP is 19 hours, levels only remain elevated if there is ongoing stimulus for production, usually underlying inflammation or malignancy (Vigushin et al., 1993).

6.1.3. Interleukin-6

CRP is produced under the control of interleukin 6 (IL-6). IL-6 acts as a pro-inflammatory cytokine and has multiple roles although is a critical mediator of inflammation and the pro-inflammatory cytokine response (Hodge et al., 2005). It has been demonstrated in cancer patients that IL-6 is independently associated with CRP and that CRP, is a useful surrogate measure of IL-6 (McKeown et al., 2004, Ramsey et al., 2006). It is, therefore, reasonable to conclude that as CRP production is dependent on IL-6, CRP concentrations are directly related to IL-6. Thus CRP serves as a biomarker for systemic inflammation in general, but also acts as a measure of IL-6.

6.1.4. Aim

The aim of this study was to assess the relationship between pain and systemic inflammation (using CRP as a measure of IL-6) in a cohort of cancer patients.

6.2. Methods

6.2.1. Overview

Secondary analysis was undertaken of two existing clinical trial datasets. The two clinical trials were as follows:

Trial 1 – Double-blind, placebo-controlled, randomised study of eicosapentaenoic acid (EPA) diester in patients with cancer cachexia (Fearon et al., 2006). This study examined the effect of EPA in weight-losing patients with advanced gastro-intestinal or lung malignancy.

Trial 2 – Effect of a protein and energy dense n-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia; a randomised double blind trial

(Fearon et al., 2003). This study examined the nutritional supplements in patients with unresectable pancreatic cancer.

The baseline data from both trials were examined. As this was an analysis of existing clinical trial data, no additional ethical approval was required. The original studies had appropriate ethical approval and were conducted in accordance with the International Committee for Harmonisation, Good Clinical Practice and the Helsinki Declaration.

6.2.2. Patients

Included patients had gastrointestinal (GI) or lung cancer (trial 1) or unresectable pancreatic cancer (trial 2). Diagnosis was made on the basis of histological, cytological, radiological or operative evidence. Included patients had lost 5% or more of their pre-illness stable weight. Patients were excluded if they were undergoing tumoricidal therapies, or had undergone chemotherapy, radiotherapy, surgery in the four weeks prior to study entry. All patients had a Karnofsky performance status of 60 or more and had an estimated life expectancy of greater than two months.

6.2.3. Symptom Assessment

Symptoms were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C-30 (Aaronson et al., 1993). This is a cancer-specific tool designed to assess symptoms. It includes pain and fatigue symptoms, and emotional and physical functioning. The pain component of the EORTC was analysed.

Plasma C-reactive protein was measured at study baseline.

6.2.4. Statistics

Baseline data, common to both studies were combined to create a dataset. This enabled any possible associations to be investigated. CRP was analysed to allow the relationship between this and pain to be assessed. Histograms of variables were inspected and as CRP was judged to be skewed, a transformation was required to

achieve approximate normality. CRP, in units of mg/dl, was replaced by $\log_{10}$ (CRP+0.1) for analysis.

A regression analysis between pain and CRP was run. Pearson correlation coefficients were calculated between all pairs of variables.

6.3. Results

6.3.1. Patient Demographics

The characteristics of the patients are presented in Table 18. In total 718 patients entered the trials, of which 465(64.8%) were men. Lung cancer was the primary cancer in 231 (32.2%) patients. Two hundred patients (27.9%) had pancreatic cancer whilst 198 (27.6%) had upper GI cancer. The remainder had lower or unclassified GI cancer

Both trial populations were well matched, therefore allowing comparison. Patients had lost on average 17% of their pre-illness body weight and had a BMI of approximately 22kg/m^2. This suggested that patients had moderately severe under-nutrition. Lean body mass was approximately 44% of total body weight.

Karnofsky performance status, physical functioning and global health (as defined by EORTC) were similar in both trials.

Table 18 - Baseline Demographics

Characteristic		Trial 1	Trial 2	Total (n=718)	%
Sex					
	Male	355	110	465	64.8
	Female	163	90	253	35.2
Type of cancer					
	Upper GI	198		198	27.6
	Pancreatic		200	200	27.9
	Lower GI	83		83	11.6
	Lung cancer	231		231	32.2
	Unclassified GI Cancer	6		6	8.4
Percentage weight loss from usual weight					
	Median	17.3			
	Mean		17.5		
	Range	2.6-55.6			
Body Mass Index					
	Median	21.1			
	Mean		21.9		
	Range	11.3-38.6			
Lean Body Mass					
	Median	44.9			
	Mean		43.4		
	Range	24.7-74.9			
Karnofsky performance status					
	Median	76.7			
	Mean		74.4		
	Range	70-100			
EORTC physical functioning (out of 100)					
	Median	60			
	Mean		65.9		
	Range	0-100			
EORTC global health					
	Median	48.7			
	Mean		51		
	Range	0-100			

6.3.2. Relationship between pain and CRP

The relationship between pain and CRP is shown in Table 19. CRP was only available for analysis in 275 patients in trial 1 and 174 patients in trial 2. There was no statistical difference in the specific characteristics (e.g. type of cancer, age group, sex or study centre) between the groups in which CRP was available and those in which CRP was not.

Table 19 - Relationship between pain and CRP

		Trial 1 N=275	**Trial 2 N=174**
		CRP	CRP
Pain	Pearson Correlation	0.126*	0.163*
	Significance (2-tailed)	0.036	0.032
	Number of patients	275	174

*Correlation significant at the 0.05 level (2-tailed)

Pain positively correlated with CRP in both trials. The Pearson correlation coefficient was 0.126 and 0.163 for trials 1 and 2 respectively. This correlation was statistically significant at the $p < 0.05$ level. Patients in trial 2 had a higher correlation between pain and CRP than in trial 1.

6.4. Discussion

The results demonstrate that pain is related to CRP. As CRP is a surrogate measure of IL-6, it is reasonable to conclude that pain is related to IL-6, which is a measure of the pro-inflammatory cytokine response.

The results presented provide some further evidence of the relationship between pain and systemic inflammation, in cancer patients. The degree of correlation between pain and CRP, although positive, was low. There was a proportion of patients in whom CRP was not taken. The reasons for this are not clear but it could be due this

group being less well, or other reasons which are not readily apparent. As a result any conclusions that can be drawn are limited. In trial 2, pain was more correlated with CRP than in trial 1. This may be because patients in trial 2 had pancreatic cancer which has been associated with chronic systemic inflammation, resulting in higher CRP levels (McKay et al., 2008).

The results could be interpreted to mean that pain is related to some degree to the underlying pro-inflammatory cytokine activity, particularly IL-6. These results are in keeping with the established body of evidence that pain is related to systemic inflammation, and in particular IL-6.

IL-6 has been shown to be elevated in a number of pain states in animal models. The administration of IL-6 resulted in allodynia (pain produced from a normally non-painful stimulus) and thermal hyperalgesia (exaggerated pain response from heat) in rodent models (DeLeo et al., 1996). Such changes are akin to those seen in neuropathic pain in humans. In other animal models, where IL-6 is absent (IL-6 knockout mice), physiological pain mechanisms are affected resulting in a diminished pain response (Ramer et al., 1998). In other types of pain, such as in animal models of inflammatory pain, IL-6 concentrations are increased (Xie et al., 2006).

Also of interest is the relationship between pro-inflammatory cytokines (such as IL-6) and modification of pain processing within the spinal cord. It has been established, and widely accepted, that the perception of pain is, in part, affected by altered mechanisms in the spinal cord which occur in chronic pain states. One such mechanism is glial activation. Glia are the supporting cells within the spinal cord and are important in pain perception. When chronic pain states exist, glia become activated resulting in the release of chemicals which can amplify pain (Watkins et al., 2003). Of these chemicals IL-6 and other pro-inflammatory cytokines produced seem critical components in the amplification of pain observed following glial activation (Wieseler-Frank et al., 2004).

Although IL-6 has been mentioned extensively, it is only one of the many pro-inflammatory cytokines that exist. It is unlikely that these pro-inflammatory

cytokines act in isolation and any painful effects that they have are likely to be produced by a multiple pro-inflammatory cytokine-induced response.

There is considerable evidence to support that other pro-inflammatory cytokines (Interleukin 1B, Tumor necrosis factor-alpha – TNF-α) are also involved (Zhang and An, 2007).

6.4.1. Implications for practice

The pro-inflammatory cytokine response and the disruption of the normal balance between pro- and anti-inflammatory cytokines associated with pain, may provide possible therapeutic opportunities.

IL-6 itself may be a specific therapeutic target. In animal models, pro-inflammatory cytokines have been shown to diminish analgesia previously provided by opioids in both acute and chronic pain states (Hutchinson et al., 2008). As mentioned, IL-6 knockout mice have been shown to have a delayed development of pain, in controlled studies (Ramer et al., 1998). Such an intervention is unlikely to be appropriate in humans, although this basic science work clearly illustrates the important part IL-6 plays in the development of pain. Recently, the role of IL-6 in cancer pain has been substantiated. In cancer patients in whom polymorphisms in IL-6 exist, pain severity has been shown to be increased (Reyes-Gibby et al., 2008). This further supports the role of IL-6 in pain mediation and, in turn, underlines the potential impact that interfering with this cytokine may have, on the treatment of pain. The use of human IL-6 receptor monoclonal antibody in inflammatory bowel disease has been studied and was shown to reduce inflammation (Ito et al., 2004). The role of IL-6 receptor antibody in cancer pain modulation remains unsubstantiated thus far, although pilot work has shown inhibitors of TNF-α, are effective in neuropathic pain of non-malignant origin (Genevay et al., 2004).

In addition to targeting the IL-6 pro-inflammatory response, targeting anti-inflammatory cytokines may be appropriate. In patients with chronic pain, decreased levels of anti-inflammatory cytokines have been demonstrated (Uceyler et al., 2006). Increasing the relative concentrations of anti-inflammatory cytokines (e.g. interleukin 4 and interleukin 10) may serve to reduce pro-inflammatory cytokine

driven inflammation that exists in pain states. It is clear however that there is a third variable which exists which may affect the results presented. Cancer per se is associated with inflammation and as disease progresses both pain and inflammation may increase. In this study the effects of cancer-related inflammation cannot be disentangled from these findings.

6.5. Conclusion

These findings support the theory that pain is related to systemic inflammation, in keeping with published work. The majority of previous work was in non-malignant disease, therefore the relationship between pain and systemic inflammation observed in cancer is of interest. Inflammation, and in particular pro-inflammatory cytokine activity, may provide an effective target for the treatment of cancer pain.

Chapter 7. Symptom Cluster: Pain, Depression and Fatigue

7.1. Introduction

Symptoms are the physical and psychological manifestations of the underlying cancer and may be modulated by tumoricidal therapy. Cancer symptoms, however, rarely exist in isolation and in patients with advanced cancer, a median of 11 symptoms (range 1-27) are present commonly (Walsh et al., 2000).

7.1.1. Symptom Clusters

As many symptoms often co-exist in cancer patients, it has been postulated that common symptoms may be related. As discussed (Chapter 1), symptoms may be related in several ways. Symptoms can simply co-exist (e.g. pain and breathlessness), symptoms can co-exist and be related (e.g. painful hepatomegaly and nausea) or symptoms can co-exist and share a common pathophysiology.

Symptoms that co-exist and are related to each other have been referred to as "symptom clusters". In recent years symptom clusters have been increasingly discussed in the literature. The concept of symptom clusters has provoked debate for three reasons; how are they defined, what types are there and what is the best way to model symptom clusters statistically?

7.1.1.1. Defining symptom clusters

In general terms, symptom clusters are symptoms which tend to occur together. It has been argued that symptoms simply co-existing is insufficient for them to be labelled as a cluster (Dodd et al., 2004). In a symptom cluster, symptoms need to be related to each other and occur concurrently.

There is also debate on the number of symptoms required to form a symptom cluster. Some have suggested that two or more concurrent symptoms that are related to one another is sufficient to be labelled as a symptom cluster (Kim et al., 2005). Others

have argued that " three or more concurrent symptoms that are related to each other" is the most appropriate definition (Dodd et al., 2001b). This latter definition had been used extensively and is the most widely accepted.

7.1.1.2. Types of symptom clusters

Due to the large number of potential cancer-related symptoms, the number of different symptom clusters is vast. Several symptom clusters have been described, which vary in the number of symptoms in the cluster (ranging from two – five symptoms) and in their focus (e.g. GI or psychological). There is also a great deal of overlap between such clusters (Chow et al., 2008, Wang et al., 2008, Chen and Lin, 2007). Currently no consensus on specific symptom cluster types has been agreed.

7.1.1.3. Statistical methods of modelling symptom clusters

One of the challenges in modelling symptom clusters is that a different statistical approach is needed. Although there are various approaches that can be used, a standardized "best" practice method has not yet been established (Barsevick et al., 2006). Both factor analysis and cluster analysis have been used to assess symptom clusters, and these methods do so in different ways. Factor analysis examines individual variables (or factors), the relations between these variables and identifies a commonality that links these symptoms (Kim et al., 2005). One of the limitations of factor analysis is that it serves only to identify the structure of a group of symptoms. Cluster analysis employs methodology where groups of individuals with the same set of symptoms, are identified. Both of these approaches have advantages and disadvantages when applied to symptom cluster analysis. One other approach is to assess the number of patients with each combination of symptoms and to compare this to the numbers that would be expected to have these symptoms if there were no tendency for the symptoms to cluster. This has the advantage of highlighting the cluster in a more meaningful way, depicting the inherent strength of the cluster, by showing the co-existing prevalence of symptoms and by comparing this to symptoms in isolation.

7.1.2. A symptom cluster of pain, depression and fatigue

Studies have shown that pain, depression and fatigue are highly prevalent and often co-exist in cancer patients (Glover et al., 1995, Smets et al., 1998, Gaston-Johansson et al., 1999, Bower et al., 2000). The symptoms of pain, depression and fatigue and their possible co-existence as an important symptom cluster was addressed by The National Cancer Institute in its State-of-the-Science conference (NIH, 2002). It concluded that there is insufficient evidence to support the concept of a symptom cluster of pain, depression and fatigue but that more research is required. It has also been argued that research into symptom clusters should be driven theoretically.

7.1.3. Systemic inflammation as a basis for a symptom cluster of pain, depression and fatigue

Symptoms may co-exist and also share a common pathophysiology and this may be the case with pain, depression and fatigue. Systemic inflammation may be a possible underlying mechanism of this symptom cluster. In animal models, the administration of inflammatory agents and pro-inflammatory cytokines results in "cytokine-induced sickness behaviour" (Konsman et al., 2002, Dantzer, 2004). This cytokine-induced sickness behaviour produces pain and behavioural changes which are comparable with pain, depression and fatigue in humans (Yirmiya, 1996, Watkins and Maier, 2000). In humans the response to infection, results in increased production of pro-inflammatory cytokines (IL-1, IL-6 and TNF-alpha). These pro-inflammatory cytokines correlate with clinical symptoms which mirror animal models of sickness behaviour (Vollmer-Conna et al., 2004). Thus in animal models and human studies, cytokine-induced sickness behaviour resulting in pain, depression and fatigue, has been shown to exist. These symptoms are similar to those in cancer patients but this has not yet been examined in the malignant setting.

As discussed in 6.1.2, C-reactive protein (CRP) can be used as a biomarker of systemic inflammation in cancer (Falconer et al., 1995, O'Gorman et al., 1998, Crumley et al., 2006). Elevated CRP has been demonstrated in patients with both early and later stages of disease. The primary stimulus is thought to be a pro-inflammatory host-tumour interaction which may depend partly on constitutive

tumour cell pro-inflammatory cytokine release, but may also relate to a pre-existing pro-inflammatory tendency in the host (e.g. due to comorbidity or genetic). Systemic inflammation has been related to anorexia, fatigue, hypermetabolism, weight loss and shortened survival in a range of types of cancer. The inflammatory response (as measured by CRP) may therefore be a common physiological pathway for symptom clusters and signs in cancer patients.

7.1.4. Aim

Although it is has been suggested that pain, depression and fatigue may exist together as a symptom cluster, this has never been demonstrated in a robust, systematic fashion. The present study examines this potential cluster and its link with systemic inflammation, in two different cohorts of patients, with advanced cancer.

7.2. Methods

7.2.1. Overview

Secondary analysis was undertaken of the two existing clinical trial datasets as described in 6.2.1.

7.2.2. Patients

Patients included had been diagnosed with GI or lung cancer (trial 1) or unresectable pancreatic cancer (trial 2) as described in 6.2.2.

7.2.3. Symptom Assessment

As discussed in 6.2.3, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C-30 was used to assess symptoms (Aaronson et al., 1993). Pain, depression and fatigue were assessed using the EORTC subscales. Emotional functioning (as per the EORTC) is used as a surrogate measure of depression/distress. The EORTC questionnaire was completed by all patients at baseline.

To allow pain, distress (depression) and fatigue to be defined, thresholds were chosen for the each of the various EORTC subscales as shown in Table 20.

Table 20 - EORTC thresholds

Symptom	EORTC Sub-scale	Threshold for a positive diagnosis
Pain	Pain Symptoms	≥50
Distress(Depression)	Emotional function	≤70
Fatigue	Fatigue Symptoms	≥60

7.2.3.1. CRP measurement

C-reactive protein was measured at baseline.

7.2.4. Statistics

The dataset as described in 6.2.4 was utilised. An analysis of symptom clusters was undertaken. To allow data analysis, cut-off points for each of the EORTC symptom subscales, were determined. This was done to get approximately 50% of the patients over both studies, to have each symptom, to enable a comparison between the observed prevalence of symptoms if clustering was present and an expected prevalence of symptoms, if clustering did not exist. This had the advantage that if there was no tendency for the symptoms to cluster, then approximately one-eighth of the patients would have each of the 8 possible combinations of the 3 symptoms.

As was the case in 6.2.4, CRP was skewed so a transformation to logarithms was done. Kruskal-Wallis test was performed between the median CRPs (mg/dl) of all possible symptom combinations.

For the sake of brevity, in the results and discussion sections that follow, the term "depression" is used when describing the EORTC emotional functioning analysis.

Clearly depression is only truly diagnosed via a gold standard psychiatric interview.

7.3. Results

7.3.1. Patient Characteristics

The characteristics of the patients are as presented in Chapter 6 - Table 18.

7.3.2. Symptom Clusters

The results of the symptom cluster analysis are presented in Table 21 and Table 22. Although 718 patients entered the studies, EORTC symptom data were only available on 654 patients (473 trial 1, 181 trial 2) for the symptom cluster analysis. The numbers of patients assessed for the symptom cluster analysis is smaller than the total number of patients because the analysis was based on patients who had pain, depression and fatigue all recorded. Missing data resulted in the overall numbers being lower.

The various observed and expected symptom prevalences are presented. These were sub-divided into the total sample and CRP sample (the group of patients in which CRP was available). There was no statistical difference in the specific characteristics (e.g. type of cancer, age group, sex or study centre) between the total sample and the sample of patients where CRP was available.

Data on all three symptoms (pain, depression and fatigue) and CRP, were available in 264 patients in trial 1 and 172 patients in trial 2.

7.3.2.1. Trial 1

The results are shown in Table 21.

Total Sample

One hundred and thirty (27.5%) patients had no symptoms of pain, depression and fatigue. This was considerably higher than the expected number of participants who were thought to have no symptoms (71.2 [15.1%]). There was clear evidence of pain, depression and fatigue clustering with 101(21.4%) patients having this combination of symptoms. This is more than double the number of participants (21.4% compared with 9.9%), that would be expected to have this combination of symptoms. In all

other possible symptom combinations, the observed prevalence was less than the expected prevalence of symptoms.

Sample of patients with CRP available

In the group of patients who had CRP taken, findings were in similar proportion to the total sample. With the exception of those with no symptoms and those with all three symptoms, the observed prevalence of symptoms was less than the expected prevalence. Pain, depression and fatigue were present together in a greater proportion of patients than would be expected if clustering were not present (18.2% compared with 7.2%).

The median CRP for all possible symptom combinations was analysed. There was no statistically significant difference between the median CRPs, between each of the various possible symptom combinations.

7.3.2.2. Trial 2

The results are shown in Table 22.

Total Sample

Fifty-eight (32.0%) patients had no symptoms of pain, depression and fatigue. This was approximately 50% higher than the expected number of participants who were thought to have no symptoms (39.0 [21.6%]). There was evidence of pain, depression and fatigue clustering with 28 (15.5%) of patients having this combination of symptoms. This was approximately 2.5 times the number of participants (15.5% compared with 6.3%) that would have been expected to have this combination of symptoms. In all other possible symptom combinations, the observed prevalence was less than the expected prevalence of symptoms.

Sample of patients with CRP available

There were similar findings in this group of patients, to the total sample. With the exception of those with no symptoms and those with all three symptoms, the

observed prevalence was less than the expected prevalence. Pain, depression and fatigue were present together in a greater proportion of patients than would be expected if clustering were not present (16.3% compared with 6.2%).

The median CRP for all possible symptom combinations was analysed. The median CRPs for trial 2 were higher than those in trial 1. There was no statistically significant difference between the median CRPs across each of the various possible symptom combinations.

Table 21 - Symptom Clusters - Trial 1

			Total Sample (n=473)		Sample with CRP available (n=264)		Summary statistics for CRP (mg/dl)	
Distress*	**Fatigue****	**Pain*****	**Observed**	**Expected@**	**Observed**	**Expected@**	**Median@@**	**Inter-quartile Range**
No	No	No	130 (27.5%)	71.2 (15.1%)	86 (32.6%)	50.6 (19.2%)	1.8	3.5
No	No	Yes	25 (5.3%)	48.7 (10.3%)	14 (5.3%)	30.4 (11.5%)	4.2	5.4
No	Yes	No	40 (8.5%)	58.7 (12.4%)	19 (7.2%)	31.9 (12.1%)	2.8	5.0
No	Yes	Yes	24 (5.1%)	40.2 (8.5%)	13 (4.9%)	19.1 (7.2%)	4.4	3.5
Yes	No	No	62 (13.1%)	82.6 (17.5%)	38 (14.4%)	50.6 (19.2%)	2.4	4.9
Yes	No	Yes	42 (8.9%)	56.5 (11.9%)	24 (9.1%)	30.4 (11.5%)	1.5	3.9
Yes	Yes	No	49 (10.4%)	68.3 (14.4%)	22 (8.3%)	31.9 (12.1%)	1.6	4.7
Yes	Yes	Yes	101 (21.4%)	46.6 (9.9%)	48 (18.2%)	19.1 (7.2%)	3.4	7.3

* EORTC Emotional Function ≤ 70 ** EORTC Fatigue Symptoms ≥ 60 *** EORTC Pain Symptoms ≥ 50

@ Under the assumption that the symptoms are independent – i.e. no 'clustering'

@@ No statistically significant difference between these medians by Kruskal-Wallis test (p=0.17)

Table 22 - Symptom Clusters - Trial 2

			Total Sample (n=181)		Sample with CRP available (n=172)		Summary statistics for CRP (mg/dl)	
Distress*	**Fatigue****	**Pain*****	**Observed**	**Expected@**	**Observed**	**Expected@**	**Median@@**	**Inter-quartile Range**
No	No	No	58 (32.0%)	39.0 (21.6%)	57 (33.1%)	37.5 (21.8%)	7.9	14.7
No	No	Yes	23 (12.7%)	29.6 (16.3%)	23 (13.4%)	29.0 (16.9%)	9.9	27.0
No	Yes	No	11 (6.1%)	22.4 (12.4%)	10 (5.8%)	21.7 (12.6%)	19.4	78.9
No	Yes	Yes	16 (8.8%)	17.0 (9.4%)	15 (8.7%)	16.8 (9.8%)	11.1	14.9
Yes	No	No	23 (12.7%)	26.4 (14.6%)	20 (11.6%)	23.9 (13.9%)	8.3	19.9
Yes	No	Yes	11 (6.1%)	20.0 (11.0%)	9 (5.2%)	18.5 (10.8%)	13.0	16.4
Yes	Yes	No	11 (6.1%)	15.1 (8.4%)	10 (5.8%)	13.8 (8.0%)	29.5	99.5
Yes	Yes	Yes	28 (15.5%)	11.5 (6.3%)	28 (16.3%)	10.7 (6.2%)	16.1	41.3

* EORTC Emotional Function ≤ 70 ** EORTC Fatigue Symptoms ≥ 60 *** EORTC Pain Symptoms ≥ 50

@ Under the assumption that the symptoms are independent – i.e. no 'clustering'

@@ No statistically significant difference between these medians by Kruskal-Wallis test (p=0.18)

7.3.2.3. CRP and relation to symptoms

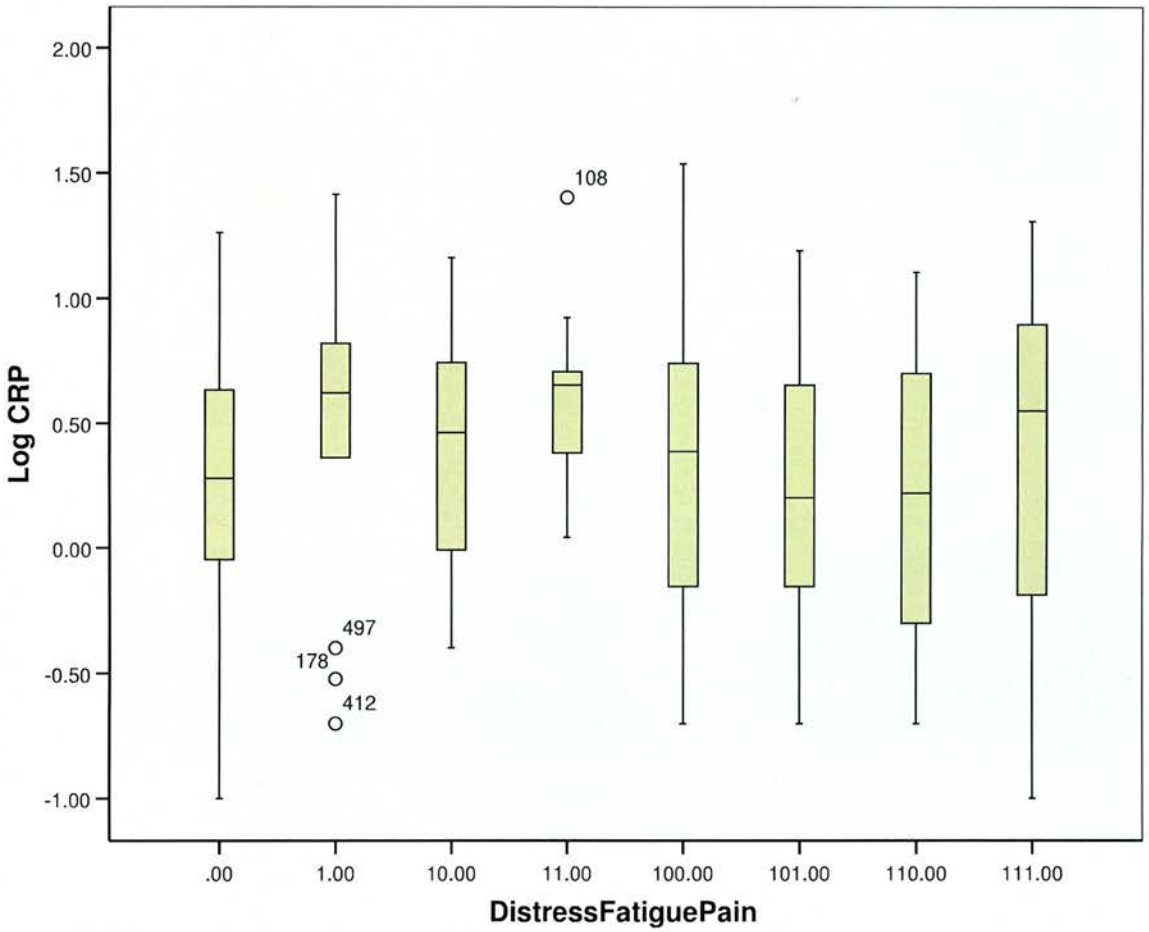
CRP was measured in 436 patients (264 trial1, 172 trial 2) and an analysis of CRP and its relation to pain, depression and fatigue, was done.

Figure 7 and Figure 8 show the boxplots for CRP for trials 1 and 2 respectively. This does not support an association between CRP and the type and number of symptoms.

Table 23 shows the sample data and median CRPs from both trials. Patients in trial 1 had more symptoms in all groups, than those in trial 2. The cluster of pain, depression and fatigue was also more common in trial 1. In contrast median CRPs were higher in trial 2 than in trial 1.

Figure 7 - Boxplot of CRP versus symptom clusters - Trial 1

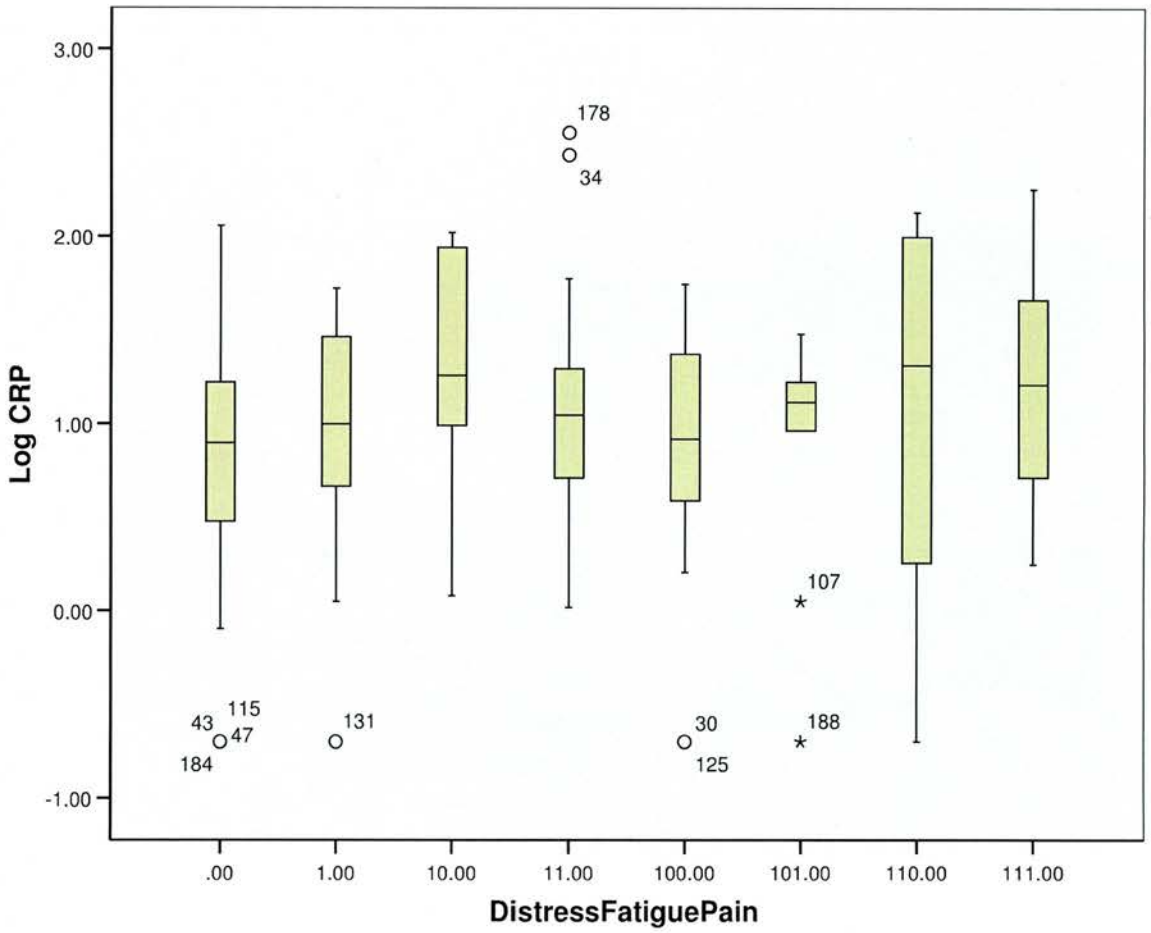
(Boxplot for Log_{10} CRP for the 8 subgroups with the same order as Table 21)



NB With the log_{10} scale -1 corresponds to 0.1 mg/dl; 0 corresponds to 1 mg/dl; 1 corresponds to 10 mg/dl; 2 corresponds to 100mg/dl

Figure 8 - Boxplot of CRP versus symptom clusters - Trial 2

(Boxplot for Log_{10} CRP for the 8 subgroups with the same order as Table 22)



NB With the log_{10} scale -1 corresponds to 0.1 mg/dl; 0 corresponds to 1 mg/dl; 1 corresponds to 10 mg/dl; 2 corresponds to 100mg/dl

Table 23 - Combined data - Trial 1 and 2

			Trial 1			Trial 2		
			Total Sample (n=473)		CRP (n=264)	Total Sample (n=181)		CRP (n=172)
Distress*	**Fatigue****	**Pain*****	Observed	Expected	Median	Observed	Expected@	Median
No	No	No	130 (27.5%)	71.2 (15.1%)	1.8	58 (32.0%)	37.5 (21.8%)	7.9
No	No	Yes	25 (5.3%)	48.7 (10.3%)	4.2	23 (12.7%)	29.0 (16.9%)	9.9
No	Yes	No	40 (8.5%)	58.7 (12.4%)	2.8	11 (6.1%)	21.7 (12.6%)	19.4
No	Yes	Yes	24 (5.1%)	40.2 (8.5%)	4.4	16 (8.8%)	16.8 (9.8%)	11.1
Yes	No	No	62 (13.1%)	82.6 (17.5%)	2.4	23 (12.7%)	23.9 (13.9%)	8.3
Yes	No	Yes	42 (8.9%)	56.5 (11.9%)	1.5	11 (6.1%)	18.5 (10.8%)	13.0
Yes	Yes	No	49 (10.4%)	68.3 (14.4%)	1.6	11 (6.1%)	13.8 (8.0%)	29.5
Yes	Yes	Yes	101 (21.4%)	46.6 (9.9%)	3.4	28 (15.5%)	10.7 (6.2%)	16.1

* EORTC Emotional Function ≤ 70 ** EORTC Fatigue Symptoms ≥ 60 *** EORTC Pain Symptoms ≥ 50

@ Under the assumption that the symptoms are independent – i.e. no 'clustering'

@@ No statistically significant difference between these medians by Kruskal-Wallis test (p=0.17)

7.4. Discussion

The study supports the symptom cluster of pain, depression and fatigue in cancer patients. There are more patients with all three symptoms than would be expected. The findings also show that each symptom can occur in isolation and every possible pair of symptoms can occur without the third being present. When single, or pairs, of symptoms do occur this is often less than would be expected which further supports the existence of pain, depression and fatigue as a specific symptom cluster. Although this cluster is suggested, it cannot be deduced that screening for one of these symptoms will identify the other symptoms in the cluster.

The role of systemic inflammation as a possible basis for the symptom cluster of pain, depression and fatigue has not been demonstrated in this analysis. The boxplot and summary statistics do not support an association between CRP and the type and number of symptoms.

Overall, the results demonstrate a clear tendency for a symptom cluster of pain, depression and fatigue, in a large cohort of cancer patients. There were, however, considerable differences between the two trial groups. This may be in part to the different patient populations. Patients in trial 1 had either GI or lung cancer whilst all those in trial 2 had pancreatic cancer. Patients in trial 1 had a higher prevalence of symptoms overall which may have been due to a greater burden of metastatic disease. Metastatic disease is likely to result in a higher symptom burden. Pancreatic cancer is associated with cachexia which, in turn, is associated with systemic inflammation (McKay et al., 2008). This may have resulted in the higher median CRP, seen in this group.

7.4.1. Comparison of findings with other work

The need for evidence to support the cluster of pain, depression and fatigue has been identified as a research necessity (NIH, 2002). Previous work examining symptom clusters has been undertaken, however comparison is difficult, due to differing symptom assessment tools and methodological analysis.

A prevalence study of 1000 patients reported that pain, depression and fatigue, co-occur in 1 in 4 cancer patients (Hauser et al., 2006). This is slightly higher than that reported here but a different definition of symptoms, and different patient groups and statistical analysis, were used making a direct comparison challenging. A study of lung cancer patients has supported the symptom cluster (pain, depression and fatigue) although this was in combination with other symptoms (Wang et al., 2008). In a study of 321 patients with various primary cancers, pain and fatigue have been reported as clustering together (in combination with disturbed sleep, anorexia and drowsiness) (Chen and Lin, 2007). This study did not support depression clustering with pain and fatigue; however this was in a heterogeneous group. To date there has been no robust evidence to support pain, depression and fatigue as a symptom cluster in cancer patients.

7.4.2. A biological basis of symptom clusters

Systemic inflammation has been suggested as a possible underlying mechanism for a symptom cluster of pain, depression and fatigue. This was the rationale for the analysis of CRP (as a surrogate measure of systemic inflammation) undertaken in this study and its relation to pain, depression and fatigue. Although the results do not support systemic inflammation as a possible underlying mechanism, this may be due to the fact that CRP was used. CRP is a sensitive marker of inflammation but is not specific and may been affected by other variables (Tsilidis et al., 2008).

Systemic inflammation, as one possible mechanism for the symptom cluster of pain, depression and fatigue, would seem plausible. Basic science work and studies in non-malignant disease in humans, would support cytokine-induced sickness behaviour as a possible biological basis for the symptom cluster of pain, depression and fatigue. Currently, however, there is insufficient evidence to support cytokine-induced sickness behaviour as a mechanism for a symptom cluster of pain, depression and fatigue in cancer patients.

7.4.3. Limitations

Studying symptom clusters in cancer patients is challenging. Consideration should be given to the many dimensions that affect symptom clusters and the effects these can

have on the examination of clusters (Barsevick et al., 2006). The type of cancer, staging and current therapy can affect magnitude of the symptoms studied (Barsevick et al., 2006).

It has been argued that when examining symptoms clusters, a longitudinal study design is best (Armstrong, 2003). This allows the evolution of symptoms, and their relationships to each other to be examined. The study presented here examines symptom clusters at a single point in time which may not have allowed the dynamic relationship between these symptoms to be fully appreciated.

The study population comprised lung, GI and pancreatic cancer patients, all with a degree of weight loss. As a result, the generalisability of the findings may be limited. However, it is possible to regard this as one of the strengths of the study as several different cancers are included. Furthermore, as these cancers often produce a high symptom burden, it could be argued that these groups were an ideal cohort in which to study symptom clusters.

7.5. Conclusion

The study results support the presence of pain, depression and fatigue as a symptom cluster. There is insufficient evidence to suggest that systemic inflammation (as measured by CRP) is an underlying mechanism. Although the results support pain, depression and fatigue as a cluster, there is insufficient evidence to support that screening for one or two of these symptoms will identify everyone who has this cluster.

The cluster of pain, depression and fatigue demonstrated here may have implications for practice. The direct treatment of one symptom (e.g. analgesia for pain) may indirectly reduce another symptom in the cluster which may in turn mean that diagnosing these symptoms in isolation may be of less importance than previously thought. It would seem likely that diagnosis and treatment of individual symptoms will remain the primary focus, although the impact that individual treatment may have on other symptoms, should be appreciated fully.

Basic science work suggests that systemic inflammation (mediated through cytokine-induced sickness behaviour) can result in pain, depression and fatigue. Although it cannot be supported here, the presence of the cluster and the small degree of heterogenecity of the patients within this study raises the likelihood that the underlying mechanism may not differ among cancer types.

Future work should examine the symptom cluster of pain, depression and fatigue in the broader cancer population. Systemic inflammation as a possible underlying mechanism of this cluster requires further examination. If a common underlying modality is identified, therapeutic targets could be developed to address the underlying pathological mechanisms, targeting each treatment at the cellular level. This would have considerable implications for clinical practice.

Chapter 8. Conclusion

The difficult cancer pain states (neuropathic cancer pain and cancer induced bone pain) have been examined and physical and psychological components have been explored.

Neuropathic cancer pain and CIBP have never been characterized clinically, in a robust systematic fashion. In doing this, detailed characteristics have been gathered about these common but challenging cancer pain states. The findings in neuropathic cancer pain and CIBP have implications for the assessment and management of these pain states.

In neuropathic cancer pain and CIBP, worst pain is predictive of the interference score of the BPI. The interference component of the BPI gives a meaningful measure of the impact pain is having on patients' lives and is likely to be more important to patients than a 0-10 pain score. Worst pain is predictive over and above average pain suggesting that if a single measure is to be used in assessing these pain states, worst pain is the key assessment.

Breakthrough pain in neuropathic cancer pain and CIBP has been examined in detail. In these pain states, the detailed examination of breakthrough pain has revealed some important characteristics. Frequently, breakthrough pain is unpredictable, rapid in onset, severe in intensity and short in duration. Between 40-50% of patients in both groups had breakthrough pain which was of rapid onset (less than 5 minutes) and short duration (less than 15 minutes).

Although studies of breakthrough pain in cancer have been carried out previously, this was in heterogeneous groups of cancer pain, resulting in a great degree of variation in breakthrough pain characteristics (Portenoy et al., 1999, Gomez-Batiste et al., 2002). As these studies presented here examine specifically the pain states of neuropathic cancer pain and CIBP, an accurate characterization has been realized. The temporal characteristics of neuropathic cancer pain and CIBP would suggest that IR opioids (e.g. oral morphine) are unlikely to be effective in a considerable proportion of patients. Newer, rapid-onset fentanyl preparations may address this to

some extent; however there will continue to be patients for whom our current armamentarium of analgesics will be ineffective.

There is a clear need for a greater understanding of the underlying processes which exist in these pain states. Basic science and translational work has already suggested that there may be key differences in these pain states at the cellular level and this may influence how these pain states are managed (Luger et al., 2002, Urch and Dickenson, 2008). Such work could result in a radical change of practice where such pain states are successfully controlled through a proactive, as opposed to the current, reactive approach. Fundamental to this development is the issue of specific adjuvant analgesics.

The relationship between cancer pain and depression may also be explained at the cellular level in the future. The work presented here does not support categorically, a relationship between pain and depression. This may be due to the lack of appropriately designed studies (as highlighted in Chapter 4), although it is clear that some pain features (such as intensity and duration of pain) are related to depression.

The longitudinal study of pain and depression in Chapter 5 presents some key findings. Treating pain decreases the HADS score, whereas if pain does not improve, the HADS score increases. As the HADS is a screening tool and not diagnostic of depression, limited inferences can be drawn. Distress and pain may be associated but this has not been clearly demonstrated. Furthermore, as distress is hard to quantify, it is challenging to draw any meaningful conclusions. Future work examining a possible relationship between pain and depression will require a broad sample of the cancer population and formal assessment of depression.

If an interdependent relationship between pain and depression exists it may influence the treatment of these symptoms. A multimodal approach may be warranted with the specific targeting of common neurotransmitters and pathways.

Chapter 6 has demonstrated the relationship between cancer pain and systemic inflammation. Pain is related to systemic inflammation and this supports both basic science work and work in non-malignant disease. This relationship is of particular interest and may provide another avenue for the treatment of cancer pain. As

previous chapters have illustrated current therapies can be ineffective and it is important that new treatments are based on a strong scientific foundation. Although current anti-inflammatory therapies (e.g. IL-6 monoclonal receptor antibody) are not widely used, there is clearly strong supporting evidence that new treatments targeting inflammation, may be of benefit.

Chapter 7 has shown that pain, depression and fatigue exist together as a specific symptom cluster. This supports the possible relationship between pain and depression and demonstrates further that symptoms rarely exist in isolation. Systemic inflammation as a possible underlying basis for this was not supported; however this may be due to the biomarker (CRP) that was used here. Currently, there is insufficient evidence to support the premise that only one symptom in a cluster should be treated and other symptoms will improve without intervention. It is reasonable to assume, however, that if one symptom in a cluster does improve, there may be an improvement in other symptoms.

This thesis has presented some key challenges for the future assessment and management of these symptoms. Breakthrough pain requires to be assessed specifically to enable a true measure of the impact of neuropathic cancer pain and CIBP. The temporal characteristics of these pain states mean that current and novel therapies are often sub-optimal. Future work needs to be based on a solid basic science foundation and therapies should meet the specific nuances of these cancer pain states.

Assessing symptom relationships at a clinical level is testing. Nevertheless, this should not discourage further, appropriately powered and designed work to assess these relationships in the hope of translating into an improvement in the physical and psychological components of cancer pain.

Future work should continue to examine the fundamental components of cancer pain and in particular, broader studies examining CIBP and neuropathic cancer pain are a necessity. Examination of these key areas will be aided by basic science. The emerging fields of translational research in symptom management and detailed examinations of cancer pain syndromes and psychological symptoms are to be

embraced. These developments are fundamental to building on the foundations of palliative care already laid; that optimum physical and psychological symptom control are fundamental components, of all good patient care.

Appendix 1

Brief Pain Inventory

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

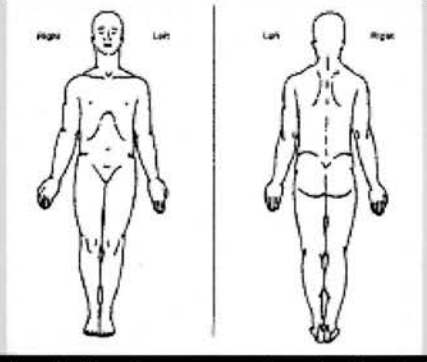
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Breakthrough Pain Questionnaire

1. Thinking about your usual or background pain, on average, how severe has this been in the last 24 hours? (please circle how severe the pain has been).

0 1 2 3 4 5 6 7 8 9 10

2. In the last 24 hours, how many times has your pain flared up or become severe? (please circle the number of times that you have had flare-ups of pain)

Not sure

1 2 3 4 5 6 7 8 9 10
>10

3. If more than 10, how many times: Not sure

4. In the last 24 hours on average, how severe does the pain become when it flares up? (please circle how severe the pain has been).

0 1 2 3 4 5 6 7 8 9 10

5. Over the last 24 hours, on average, how long does the flare up of pain last for? (please circle the number of minutes)

(less than 1min) (1-15mins) (16-30mins) (31-60mins)

(60-120mins) (more than 120 mins)

6. Over the last 24 hours, on average, from the time you first feel this pain start to flare-up or worsen, how long does it take to get as bad as it gets?

(please tick the appropriate box)

Unpredictable ☐ **6 minutes to 30 minutes** ☐

Less than 10 seconds ☐ **31 minutes to 60 minutes** ☐

10 seconds to 5 minutes ☐

7. Are you able to tell or predict when your pain is going to flare-up or become severe? (please circle the phrase that most closely represents what you think)

never sometimes often almost always always

8. How often do you take extra pain killers or a "rescue" dose for your flare ups of pain? (please circle the response that you feel most accurately describes what normally happens)

every time most of the time some of the time hardly ever never

Paper assessment pro forma

Study identification: (eg author, year, journal)		
Completed by		
INTERNAL VALIDITY		
		(please circle)
1.0	What is the study type	Case-control RCT Intervention Review Cohort Other.....
2.0	Is depression clearly defined?	YES NO UNSURE
2.1	If yes, what method was used to record this? (eg HADS, Beck Depression etc)	
3.0	Is pain clearly defined?	YES NO UNSURE
3.1	If yes, what method is used to record this? (eg VAS, numerical rating etc)	
4.0	What was the sample size?	
4.1	Does study sample include cancer patients	YES NO UNSURE
5.0	Does the paper explore the relationship between pain and depression?	YES NO UNSURE
5.1	Was study population divided into this either with or without pain or those with or without depression?	YES NO UNSURE
5.2	If YES what factor separated the groups?	Pain Depression
6.0	Does this study help to answer your key question: is cancer pain and depression related?	
7.0	Should this paper be included in the systematic review?	YES NO UNSURE
8.0	Comments	

Hospital Anxiety and Depression Scale

Doctors are aware that emotions play an important part in most illnesses. If your doctors know about theses feelings he will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

Tick only one box in each section

I feel tense or 'wound up':		**I feel as if I am slowed down:**	
Most of the time		Nearly all of the time	
A lot of the time		Very often	
Time to time, occasionally		Sometimes	
Not at all		Not at all	
I still enjoy the things I used to enjoy:		**I get a sort of frightened feeling like 'butterflies in the stomach':**	
Definitely as much		Not at all	
Not quite so much		Occasionally	
Only a little		Quite often	
Not at all		Very often	
I get a sort of frightened feeling like something awful is about to happen:		**I have lost interest in my appearance:**	
Very definitely and quite badly		Definitely	
Yes, but not too badly		I don't take as much care as I should	
A little, but it doesn't worry me		I may not take quite as much care	
Not at all		I take just as much care as ever	

I can laugh and see the funny side of things:		**I feel restless as if I have to be on the move:**	
As much as I always could		Very much indeed	
Not quite so much now		Quite a lot	
Definitely not so much now		Not very much	
Not al all		Not at all	
Worrying thoughts go through my mind:		**I look forward with enjoyment to things:**	
A great deal of the time		A much as I ever did	
A lot of the time		Rather less than I used to	
From time to time but not too often		Definitely less than I used to	
Only occasionally		Hardly at all	
I feel cheerful:		**I get sudden feelings of panic:**	
Not at all		Very often indeed	
Not often		Quite often	
Sometimes		Not very often	
Most of the time		Not at all	
I can sit at ease and feel relaxed:		**I can enjoy a good book or radio or TV programme:**	
Definitely		Often	
Usually		Sometimes	
Not often		Not often	
Not at all		Very seldom	

Appendix 2 – Publications

Laird BJA, Boyd A, Colvin L, Fallon M. Are cancer pain and depression interdependent? A systematic review. Psycho-oncology 2008 DOI: 10.1002/pon.1431

Laird BJA, Colvin L, Fallon M. Management of Cancer Pain: Basic Principles and Neuropathic Cancer Pain. European Journal of Cancer. European Journal of Cancer. 2008;44(8):1078-82

Appendix 3 – Published Abstracts and Invited Lectures

Laird BJA, Scott AC, Todd AMH, Colvin LA, Fallon MT. Are pain and depression interdependent in cancer: a longitudinal study. Proceedings from the EAPC Congress. European Journal of Palliative Care 2009. (Invited Lecture)

Aims: Pain and depression are highly prevalent symptoms in cancer patients. Epidemiological studies have shown that pain and depression often co-exist and thus the relationship between these symptoms is of interest. Studies have shown a statistically significant association between pain and depression and it has been suggested that these symptoms may be inter-dependent. Although associations exist, there are no published studies that examine the relationship between these symptoms. The aim of this study is to examine the relationship between cancer pain and depression.

Methods: 60 patients with advanced cancer and cancer induced bone pain were assessed as part of this study. All patients had assessments of mood (Hospital Anxiety and Depression Scale) and pain (Brief Pain Inventory) at study baseline. Patients then received a therapeutic intervention (radiotherapy + optimisation of analgesia). Further assessments of mood and pain were undertaken four weeks from study baseline. No patients had commenced antidepressant medication (in the four weeks prior to study entry) or had started antidepressants during the study period.

Results: Full statistical analysis of study results is awaited. Preliminary results show an improvement in pain following the therapeutic intervention. The median total BPI score pre- and post- intervention was 49 (range 32-88) and 13 (range 0-52) respectively. The median total HADS score pre- and post- intervention was 13 (range 2-22) and 9 (range 1-18) respectively. In patients who had a 30% or more reduction in their BPI score (total score) there was a statistically significant reduction in HADS score ($p<0.05$).

Conclusions: This is the first study that examines the natural evolution of anxiety and depression in patients with pain who have pain treated actively, whilst no anti- depressive intervention is administered. Results support the theory that the active treatment of cancer pain results in an improvement in anxiety and depression.

Laird BJA, Walley J, Murray G, Colvin LA, Fallon MT. What is the key question in the assessment of Cancer Induced Bone Pain: results from a characterisation study. British Pain Society Annual Scientific Meeting, London, April 2009. (Published Abstract)

Aim: Cancer induced bone pain (CIBP) is a common cause of pain in patients with cancer. CIBP is associated with increased morbidity, reduced performance status, increased anxiety and depression, and a reduced quality of life. CIBP is also a considerable therapeutic challenge. Palliative radiotherapy remains the most effective anticancer treatment for CIBP however it is not always effective and only one quarter of patients will get complete pain relief. Opioid analgesia is the main pharmaceutical treatment for CIBP however titration of opioids to doses that control spontaneous bone pain and movement-related bone pain, usually results in unacceptable opioid side-effects. Recently rapid-onset, short-duration opioids have been suggested for breakthrough pain in CIBP and other pain types. Despite the clinical time invested in trying to help patients with CIBP and the development of new analgesic strategies, CIBP has never been characterised in the clinical setting. Detailed characterisation is fundamental to meaningful clinical and translational research, and to develop more effective analgesic strategies. The aim of this study was to characterise CIBP.

Patients and methods: A cross-sectional survey of patients with CIBP in a regional oncology centre. Patients had a radiologically proven site of bone metastases and pain in keeping with this site. A single interview was conducted with each patient during which the Brief Pain Inventory (BPI) and a screening question to identify breakthrough pain were completed. Patients who had breakthrough pain also completed a Breakthrough Pain Questionnaire (BTPQ). Statistical analysis was performed. BPI "average pain" and "worst pain" scores were then compared to the total BPI interference scale. Regression analyses between these variables were then run. The relationships between these pain scores and pain related interference with function, were then determined. A subgroup analysis of the BPI was undertaken to compare those patients with, and those without, breakthrough pain.

Results: 55 patients were recruited, 28 (49.1%) were male and the mean age was 63.7 years. Median average pain was 4, median worst pain was 7. BPI worst pain correlated more strongly with BPI total interference than average pain score. Patients who had breakthrough

pain had significantly higher total BPI interference scores than those who had no breakthrough pain (median (IQR); 18.5 (5.5-26.7) vs 35.0 (21.5-44.7) $p<0.01$). The median severity of the breakthrough pain was 8 (based on a 0-10 VAS). The speed of onset of pain was less than 5 minutes in 33 patients (78.6%). 20 patients (48.1%) had breakthrough pain which was rapid onset (less than 5 minutes) and of short duration (less than 15 minutes). 18 patients (43.9%) had pain which was unpredictable

Conclusion: These data provide the first systematic characterisation of cancer induced bone pain. Single measures of pain are unlikely to describe CIBP, but if a single measure is to be used, BPI "worst pain" most accurately reflects the characteristics of breakthrough pain and associated functional impairment. Breakthrough pain is highly prevalent in patients with CIBP. This is often unpredictable, rapid onset and short duration. Patients with breakthrough pain have higher BPI interference scores than those with no breakthrough pain highlighting the importance of breakthrough pain to patients' physical and psychological well-being.

Our findings suggest that current management strategies for treating CIBP are likely to be inadequate for a sizeable number of patients. An improved opioid armamentarium will be useful for some patients however those patients with rapid onset, short-duration breakthrough pain, will remain challenging. Some basic science work also questions if CIBP is opioid responsive suggesting a different underlying pathophysiology from background CIBP. Further research is required to develop effective delivery systems for rapid onset, short acting opioids that reflect the characteristics of the breakthrough pain that commonly affect patients with CIBP.

Laird BJA, Murray GM, Colvin LA, Fallon MT, Fearon KCH. Symptom clusters in advanced cancer: role of systemic inflammation. Proceedings from the EAPC Congress. European Journal of Palliative Care 2009. (Published Abstract)

Aims: Cancer symptoms rarely exist in isolation and in recent years the concept of symptom clusters has been increasingly discussed in the literature. Systemic inflammation has been suggested as a possible underlying mechanism of cancer symptom clusters. This study examines whether pain, depression and fatigue exist as a symptom cluster. The relationship of C-reactive protein (CRP- as a measure of pro-inflammatory cytokine activity) to pain, depression and fatigue is examined and a possible biological explanation of these cancer symptoms is explored.

Design and methods: Analysis was undertaken of two large cancer trials (n=718). Symptoms were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C-30. Measurement of plasma CRP was performed. Multivariate analysis was undertaken and Pearson correlation coefficients were calculated between all pairs of variables. A series of regression analyses were run relating pain, depression, fatigue and CRP.

Results: Pain, fatigue and emotional functioning (mood) were strongly related (correlation significant at the 0.01 level – 2 tailed). CRP was related to pain and fatigue (to levels of statistical significance, $p<0.05$). CRP was positively correlated with emotional function but this did not reach levels of statistical significance.

Conclusions: In this dataset, there are strong associations between pain, fatigue and mood. This apparent symptom cluster has a statistical relationship with plasma CRP. While we cannot conclude a definite causal relationship between systemic inflammation (CRP) and this cluster of symptoms, these results give a strong indication that further elaboration of this concept could be of great clinical interest as well as moving the research agenda forward.

Laird BJA, Boyd A, Colvin L, Fallon MT. Cancer Pain and Depression; A systematic review. Palliative Medicine 2008;22(4):481 (Published Abstract)

Introduction: A single point prevalence survey demonstrated that approximately 90% of patients with cancer experience pain. Depression occurs in approximately one quarter of advanced cancer patients. The relationship between depression and pain is of great importance in routine clinical practice.

Aim: The aim of this systematic review is to examine the relationship between cancer pain and depression.

Methods: An extensive literature search was undertaken. The following databases were searched electronically: Medline (1950-2007), Embase (1988-2007), Cinahl (1982-2007) and the Cochrane Database of Systematic Reviews (Issue 2 2007). Relevant journals were also searched by hand.

Results: As a consequence of a broad search strategy, 892 articles were identified. A consensus was reached that 41 papers were suitable for detailed review using a pre-determined proforma. Subsequently 14 articles were deemed appropriate for inclusion. The mean prevalence of depression and pain was 31.5% (range 20.2 – 46.0) and 63.3% (range 37-100%) respectively. In 10 out of 14 studies a statistically significant association was demonstrated between pain and depression: Pain intensity positively correlated with depression (to levels of statistical significance $p<0.05$). Pain interference items such as "worst pain" and "enjoyment of life"(measured on the BPI) correlated significantly with depression. When using the McGill Pain Questionnaire, depressed patients used more affective descriptors. It was also shown that the longer the duration of pain, the higher the risk of depression. Conversely as pain decreased so did depression, to levels of statistical significance.

Conclusions: Both pain and depression are highly prevalent in cancer patients however there have been no appropriately designed studies to examine a causal relationship. A suitably designed longitudinal study to examine causality would be a highly, clinically relevant step in the research agenda.

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