Opioid-Related Side-Effects and Opioid-Induced Hyperalgesia

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ABSTRACT

Introduction: Opioids are widely used for the management of cancer and chronic non-cancer pain and the maintenance management of patients with a history of substance misuse. Increasingly the use of opioids is being scrutinised as patients are prescribed opioids for longer periods and the long-term effects of the opioids becomes clinically more relevant and evident. Our work has explored the prevalence of opioid-related side-effects in patients who are prescribed opioids and explored the clinically relevant phenomenon of opioid-induced hyperalgesia. .

Methods: Patients were recruited who were prescribed opioids for the management of cancer and non-cancer pain or substance misuse. Quantitative data was collected to explore the prevalence and severity of opioid related side-effects, the impact of opioids on cognitive function and the effect of opioids on peripheral nerve function through quantitative sensory testing. Testing the sensory processing of patients who are on opioids has revealed altered thermal thresholds and the presence of wind-up at non-painful sites indicating central sensitisation. Qualitative description was used to explore the patient experience of an episode of opioid toxicity.

Results: Patients have a significant burden of side-effects which have often not been recognised by clinicians. Using the Addenbrooke's Cognitive Examination much more cognitive impairment has been revealed than has previously been recognised. Altered thermal thresholds and wind-up at non-painful sites suggests altered pain processing as a result of opioids. Themes from the qualitative description highlighted the coping strategies patients' develop when managing with significant side-effects and toxicity, the covert self-management of their pain and the need to exert control. One of the most significant findings from the qualitative research was the finding of altered sensation and pain description associated with other features of opioid toxicity.

Conclusions: The impact of opioids on the cognitive function of patients has significant implications in terms of patients' involvement in decision-making and functioning in everyday life. The qualitative data reflects the burden of side effects and the descriptions of patients suggest that opioid-induced hyperalgesia exists as part of the spectrum of opioid toxicity. This finding may help physicians identify patients who are developing opioid-induced hyperalgesia and allow them to intervene earlier with a proactive approach.

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AUTHOR'S DECLARATION

The work presented in this thesis was performed entirely by the author except as acknowledged. This thesis has not been previously submitted for a degree or diploma at this or any other institution.

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ABBREVIATIONS

ACE-R	Addenbrooke's Cognitive Examination
BPI	Brief Pain Inventory
G	Grams
HADS	Hospital Anxiety and Depression Scale
IT	Intrathecal
IV	Intravenous
mcg	Microgrammes
MEDD	Morphine Equivalent Daily Dose
mg	Milligrammes
MMSE	Mini-Mental State Examination
PCA	Patient Controlled Analgesia
PO	Oral
QST	Quantitative Sensory Testing
S-LANSS	Self-completed Leeds Assessment of Neuropathic Symptoms and Signs
SOWS	Short Opioid Withdrawal Scale
VAS	Visual Analogue Scale

CHAPTER 1: INTRODUCTION

1.1 Introduction

Opioids are used throughout the world to manage pain and remain a key component of pain management. Increasingly we are recognising that there are side effects associated with the use of opioids on a long term basis about which we know very little. There are many clinically relevant questions relating to opioid usage which require exploration. These opioid related effects may impact on the health and well-being of patients but they may also affect pain processing.

1.2 Definition and Prevalence of Pain

The International Association for the Study of Pain define pain as

"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." (Loeser and Melzack, 1999, page 1607)

Pain is a major health problem worldwide. It is estimated that at any time 15 – 25% of the adults across the world are living with pain (Brennan, Carr and Cousins 2007). Some diagnoses are associated with pain for example up to 70% of the adults with cancer will experience pain (Brennan, Carr and Cousins 2007). In the UK and in other developed nations we have many resources to help manage pain. However across the world to ensure everyone has access to pain management there is a need to provide opioids at an affordable cost to all, to provide guidance to clinicians about the legal status of the opioids and how to safely prescribe them and to educate professionals so that opioids and other pain management therapies can be used effectively and safely. (Brennan, Carr and Cousins 2007)

In a review of symptoms by Miller Reilly and her colleagues in 2013 in people receiving active cancer treatment pain was one of the symptoms experienced most frequently (Miller Reilly et al, 2013). Cancer pain tends to be multiple in terms of the nature and sites of pain experienced by the patient. The pain may be due to the tumour invading adjacent structures for example nerves or destroying bony structures or due to the treatments given to manage the cancer. Patients with cancer may be restricted in their mobility and this can result in pain due to the complications of immobility, for example pressure sores.

All pain is recognised as a subjective experience. The individual response to a painful stimulus is affected by their previous experiences of pain and the emotional state at the time of the pain. In palliative medicine the importance of pain as having spiritual, social and psychological components as well as the physical component is well recognised. This concept of pain is fundamental to managing cancer pain.

When pain is not treated well there are physical and emotional sequelae including poor sleep, anxiety and depression, loss of time at work or reduced productivity at work (Brennan, Carr and Cousins 2007).

1.3 The Assessment of Pain

Pain can be described as sharp, burning, aching, dull or stabbing by patients. The descriptors used help the clinician form an understanding of the underlying cause of the pain. Clinicians may also use pain assessment tools such as numerical rating scales or visual analogue scales to help understand the severity of the pain and monitor the response to analgesia. Other scales give “multidimensional” information about the pain and describe both the severity and the extent to which it impacts on function or quality of life. In addition the clinician uses their knowledge of the disease process to recognise and predict patterns of pain and other symptoms. Ronald Serlin and colleagues that pain severity and interference are linked in a predictable way (Serlin, et al, 1995) however the extent to which pain is a subjective response would seem to dispute this.

Some authors have called for a classification of pain based on the underlying pathophysiology and suggest that this facilitates pain management as physicians could target different pathways. It is possible that this approach would facilitate research (Woolf et al, 1998) but it largely ignores the emotional element to pain.

In a survey of physicians Caraceni explored the link between cancer site and pain. He found that primaries of the head and neck, respiratory and upper gastrointestinal tracts had pains which were closely related to the primary. For patients with other cancers the pain was most likely to be in the low back or sacral area. (Caraceni, 2001)

1.4 Pathophysiology of Pain

Acute pain results from tissue injury and healing. It serves a physiological purpose in helping the body protect itself from further injury and enable healing. Several inflammatory mediators and neurotransmitters are released in response to the injury including substance P, prostaglandins and endorphins. Endorphins are opioid-like structures and they inhibit the pain signal peripherally. (von Gunten 2011; Loeser and Melzack,1999)

Nociceptors are transducers found in many of the tissues of the body including skin, bones and organs such as the bladder. Nociceptors respond to changes in their homeostatic environment for example heat, cold, pressure, chemical damage. When the nociceptors are activated the signal is transmitted via the A delta fibres which transmit pain signals quickly yielding an immediate response to the stimulus and via C fibres which generate a slower less localised response. Cancer will cause chronic nociceptive pain when local tumour presence causes ongoing stimulation of the receptors. (von Gunten 2011) The nociceptor can become sensitised and generate spontaneous firing of pain signals, and they respond at lower levels of stimulation. (Portenoy, 1992)

From the nociceptor the pain signal travels via the peripheral nerves and then to the brain via the contralateral spinothalamic tract. Third order neurones pass from the spinothalamic tract to the cerebral cortex where the pain is mapped. (von Gunten 2011)

When there is damage to one of the peripheral nerves or part of the central nervous system, neuropathic pain is generated. Neuropathic pain is a feature of pain for many cancer patients. It is recognised by its anatomical definition and associated features of altered sensation for example numbness.

Chronic pain can occur due to excitatory effects in the spinal cord which result in altered function of the spinal cord. Previous experience and learning about pain are very important and will temper the individual's response to any painful stimulus.

1.5 Management of Pain

There are many barriers to managing pain well. Some of these are physician related barriers for example a reluctance to prescribe opioids, lack of understanding about the drugs and the potential for side effects, failure to manage the side effects of opioids. There are also patient related barriers for example concern over starting morphine in case it heralds a poor prognosis, fear of side effects, concern over a perceived stigma of taking opioids. Some patients worry that discussing the pain will distract the physician from managing the cancer. Patients may believe pain is inevitable and needs to be tolerated and this is more likely if the patient is depressed (Jacobsen et al, 2009). In a literature review the importance of social and cultural influences over patients' responses to pain and their use of analgesia were highlighted (Jacobsen et al, 2009).

Pain is recognised as a multidimensional experience. As such a multimodal approach to the management of pain is required. Due to its availability, cost and the variety of preparations available morphine is the first line opioid for the management of pain. Not all pain will

respond to opioids and other drugs and pain management interventions are likely to be needed also. For example patients may be on adjuvant analgesia such as gabapentin or amitriptyline, they may be using a TENS machine and seeking psychological or spiritual support.

Understanding the pathophysiology of pain enables combinations of drugs and interventions to be chosen with a logical approach. Paracetamol and the non-steroidal anti-inflammatory agents reduce prostaglandin synthesis and will return the medium around the nociceptor to its usual state. Opioids act at central and peripheral receptors and reduce nociceptor signalling by altering potassium and calcium levels in the neurone.

Opioids are key to the management of cancer pain in particular however not all pain is opioid-responsive. Neuropathic pain is typically poorly responsive to opioid analgesia. Opioid responsive pain implies that the pain responds to opioid analgesia without unacceptable side effects. About 10 – 20% of patients will not experience good pain relief despite the introduction of opioids. (Hanks and Justins, 1992)

Patients who have cancer pain usually have more than one site of pain and more than one type of pain. In one study it was reported that 80% of patients with cancer have two or more pains and 34% have four or more pains. (Bennett, 2005) It is therefore unlikely that cancer patients will be relying on one form of analgesia alone.

Some physicians and patients have been concerned that the use of opioids shortens life. In a very large study based on the experience of 13 American hospices clinical data from 1,163 patients was reviewed. The last change in the opioid dose was a mean of 12.46 days (+/- 23.11) with a median of 5 days and a range of 0 to 231 days. They found that a higher dose was associated with a shorter time to death of the patent but the percentage dose change was not associated with shorter time to death. Overall the authors concluded the study should reassure clinicians that opioids can be prescribed at the end of life to alleviate pain and without concern that death will be hastened. (Portenoy et al, 2006)

1.6 Adverse Effects of Opioids

Morphine and the other strong opioids have many adverse effects and there is considerable overlap between the side effects of morphine and the side effects of the other strong opioids. Patients may respond better to one opioid than another. At the moment it is not possible to predict response unless a patient has impaired renal and / or liver function in which case the metabolism and excretion of certain opioids means they will accumulate and cause side effects and toxicity.

The side effects of opioids can be grouped into neuropsychiatric, gastrointestinal, respiratory, dermatological and pharmacological. (Lawlor and Bruera 1998). Delirium, sedation and impaired cognitive function are all in the neuropsychological group. Sedation is usually associated with either the initiation of opioid or a dose titration and most reports suggest this is a temporary side effect. The impact of opioids on cognitive function is discussed in detail in a later section. Overall there are mixed results from the studies done and a suggestion that residual pain may counter the effects of the opioids by the arousal it causes. The gastrointestinal side effects include nausea and vomiting and constipation. Nausea is due to stimulation of the area postrema (also known as the chemoreceptor trigger zone). Opioids cause gastroparesis and slow gastrointestinal transit which results in hard stool that is more difficult to pass. Constipation is a persistent side effect to which tolerance does not develop and ongoing management with laxatives is usually needed. Dermatological side effects include pruritus as a result of histamine release.

While there is considerable evidence for some of the adverse effects of the opioids, other effects are still being described and their implications fully recognised. Controversy still exists around the effects of opioids on the immune and endocrine systems and opioid-induced hyperalgesia. (Brennan, 2013)

Opioid endocrinopathy results from the effect of opioids on the hypothalamic – pituitary – gonadal axis and on the hypothalamic – pituitary – adrenal axis. Opioids bind to opioid receptors in the hypothalamus and reduce the secretion of gonadotrophic releasing

hormone. The opioids therefore exert an effect throughout the whole axis but they also act at other levels. The altered axis effects menstrual cycle, reduced sperm production and reduced testosterone in the testes. As soon as the patient is commenced on an opioid the endocrine system starts to be altered. Up to 90% of patients will have an altered endocrine system. Patients may describe reduced libido, infertility, fatigue, anxiety, hot flashes, night sweats. Osteoporosis may occur. (Brennan, 2013) There is also thought to be a link between hypogonadism and increased pain which may lead to opioid dose increases to help alleviate the pain. Low testosterone is the most frequently recognised hormone deficiency secondary to opioid prescription. (Ballantyne, 2006) Opioids also reduce the production of ACTH from the pituitary and impair the production of cortisol and DHEA by the adrenal gland. There have been case reports of patients presenting with Addisonian crisis secondary to opioids. (Brennan, 2013)

Activation of the hypothalamic-pituitary-adrenal axis causes the release of glucocorticoids and noradrenaline release is stimulated by the activation of the sympathetic nervous system. Both pathways are activated by opioids. Glucocorticoid and noradrenaline both act to suppress lymphocytes. Evidence of immune suppression by opioids is seen in the increased risk of infections after burns, risk of metastatic spread after cancer surgery and immune response to vaccine. (Hojsted and Sjogren, 2007) The immune system is also suppressed by pain (Ballantyne, 2006) and the influence of individual contributions is difficult to establish.

A proactive approach to the management of opioid side effects is required. Some patients will require the prescription of an anti-emetic, often just for a few days. If the side effects are not managed with the addition of these other drugs then the patient may need either a reduction in the dose of the opioid or to be changed to an alternative opioid. Although large studies reviewing the side effect profiles of the different opioids suggest no difference at a population level, there is no doubt that individuals respond differently to the different opioids.

Tolerance to opioids requires the opioid dose to be increased in order to achieve analgesia. In cancer patients it can be difficult to know whether the patient is tolerant to the opioid or has disease progression causing escalation of pain. In one study patients were found to have increased their opioid dose by 640% over a 15-month period with no change in their pain scores.

> "The premise that tolerance can always be overcome by dose escalation is now questioned" (Ballantyne, 2007 page 482).

Opioid-induced hyperalgesia is increasingly recognised and considered by clinicians who prescribe opioids. Opioid-induced hyperalgesia is a paradoxical increase in pain experienced by a patient when the dose of opioid is increased. Opioid-induced hyperalgesia can present as pain which is distributed beyond the original site of the pain or as whole body pain or sensitivity. The diagnosis relies on an awareness of opioid-induced hyperalgesia and may sometimes only be recognised by the clinician when the dose of opioid has been reduced in order to manage side-effects or features of toxicity and the patient's pain has improved. A review of the published literature pertaining to opioid-induced hyperalgesia is included in chapter seven.

Dependence may be a concern to patients. For some patients the stigma of being perceived as an addict outweighs the pain and they may decline opioids despite severe pain. Physical dependence manifests as the symptoms of withdrawal when the opioids are stopped suddenly for any reason. The symptoms can be avoided by slow reduction of opioids. Psychological addiction manifests as a craving for the drug. It was traditionally thought to be rare in patients who were prescribed opioids for pain under medical supervision (Lawlor and Bruera, 1998) but it is now recognised that the prevalence can be as high as 19%. (Ballantyne, 2006) Psychological addiction occurs as a result of the release of dopamine in the "reward area" of the brain after opioid has been taken. (Hojsted and Sjogren, 2007)

There is no agreed definition of prescription opioid misuse or the development of addiction to drugs originally commenced for pain. (Compton and Volkow, 2006; Manchikanti, et al,

2010; Hojsted and Sjogren, 2007) The increase in the consumption of prescription opioids means there is an inevitable risk of diversion of the drugs to illicit drug users which also makes it difficult to interpret the figures. Patients who are most at risk of addiction to prescription drugs are young men, those with a previous history of substance misuse and those with mental health issues. (Hojsted and Sjogren, 2007)

1.7 Opioid Consumption – cause for concern?

Opioids are widely and increasingly used to manage pain, both cancer and non-cancer in origin. They are prescribed with the best of intentions which is to improve pain. However the prescribing of opioids must be considered in context. There is little evidence about the longer-term effects of opioids. Many of the published studies on opioids only follow patients for a few short weeks and leave clinicians to extrapolate the longer -term effects. Evidence from the United States of America is of increasing addiction to prescription painkillers with associated increase in morbidity and mortality. Evidence is emerging about the effects of opioids on the endocrine and immune systems of patients. The time has come to reconsider our approach to opioids (Stannard, 2013).

Palliative medicine has developed as a specialty over the last fifty years. It has traditionally been involved in the management of symptoms associated with malignant disease. In more recent years there has been a shift towards an involvement with patients with non-malignant diseases amid recognition that they can have a similar burden of symptoms to patients with cancer.

Advances in oncology mean that many patients are now living with their disease and some will live with complications of treatment for example chemotherapy-induced peripheral neuropathy. Palliative medicine needs to keep pace with advances in oncology and change our approaches to the management of patients who are living with cancer and not dying of cancer.

We have much to learn from our colleagues in chronic pain teams about helping patients live with pain and other symptoms but we are not the only ones who must learn. All professionals who prescribe strong opioids need to stop and think. This is an opportunity to learn from the USA and from our increasing reliance on opioids as painkillers. We need to consider the evidence, ask questions and have discussions with our patients that help them make informed decisions.

When managing pain there is a need to balance the benefits of opioids and the adverse effects of the opioids. Over the years medical opinion has shifted massively. Initially there were attempts to regulate the prescription of strong opioids, borne of a fear of addiction. These regulations were particularly seen in the USA. Later in the 20th Century there were calls for the better management of chronic pain. Clinical leaders encouraged the use of opioids for chronic pain stating the use was safe despite little evidence to support the view. Now views are starting to change again. The evidence base for the use of opioids is being questioned in the face of increasing consumption of opioids, increasing deaths related to prescription drugs, increasing attendances at accident and emergency departments with drug related problems. In an invited review article Jane Ballantyne highlights the evidence on which opioids are prescribed for strong pain is based mainly on randomised controlled trials of relatively short duration (up to 32 weeks) and doses of morphine that are less than many patients are prescribed (approximately 180 mg /day). To establish the longer term effects of opioids it is necessary to look to case series. Dr Ballantyne also highlights that 56% of patients abandoned treatment with opioids because they were not gaining improvement in pain or because they were having unacceptable side effects (Ballantyne, 2007).

It is difficult to know how many people are addicted to prescription opioids or are at risk of addiction because there is a real lack of clarity and consensus about the diagnosis of addiction to prescription opioids. Cathy Stannard has raised some concerns from the UK (Stannard, 2007). While recognising that we do not have the same magnitude of problem in the UK she has highlighted the lessons that can be learned from the USA. She recommends the practice of "good medicine" (Stannard, 2007, page 347) – take a careful history, ensure relevant health problems are also taken into account when prescribing opioids,

Look for behaviours that may indicate the patient is at risk of opioid misuse and above all, review the patient to judge effect of the opioid on the pain. This recommendation echoes Jane Ballantyne's recommendations in 2006 that chronic opioid therapy is initiated following a detailed review of the pain, consideration of the risk factors for opioid misuse and ongoing review of the benefit for the patient's pain. (Ballantyne, 2006)

While opioid misuse is a clear issue on a worldwide basis, the purpose of this thesis is to evaluate the physical side effects of opioids, in relation to symptoms and indeed pain itself.

1.8 Research in Palliative Care

As a specialty palliative medicine is committed to providing the best care for patients and their families. It is increasingly necessary to provide the evidence base that the care provided is the best for patients, to be able to teach and engage with other specialties confident in the knowledge that we provide good care, to have informed conversations with patients about the various therapeutic options open to them and the risks and benefits that are associated with the different options.

There has been a reluctance to engage in research in palliative medicine however. Historically the reluctance to engage with research has come from a perception that palliative medicine is separate to other specialties – free from the medicalization of the rest of modern medicine. Janssens and Gordijn argue that as medicine became increasingly interventional and focussed on cure so palliative care separated and focussed more on the needs of the individual. As the specialty has come to realise the need to re-integrate with other medical specialties there has come the realisation that research is an essential component to arguing the value of palliative medicine. (Janssens and Gordijn, 2000) Kaasa and Dale argue that establishing the evidence base of palliative medicine is not at odds with the ethos of care provision. (Kaasa and Dale, 2005)

Hospice care developed from a wish to provide the best care for the dying patient and their family. Increasingly now there is a wish to take aspects of hospice care and transfer them to other care settings. Establishing an evidence base is an important step to transferring care. It can be difficult to persuade colleagues without the evidence.

The importance of research in palliative care was eloquently outlined in Research Active Hospices (Payne et al, 2013) which calls for collaboration between teams and an up-skilling of all staff in research skills for example critical appraisal skills.

Fine argues that research in patients who are nearing the end of life is "a classical deontological – utilitarian conflict" (Fine, 2003, s55) There is conflict between our wish to provide the best care for the individual patient, even though taking part in research may cause inconvenience at least and harm at worst, and a need to understand how we can ensure the best care for all our patients. Janssens provides a similar argument.

> "Caregivers in a palliative care setting are faced with a conflict between non-maleficence (not to harm current patients) and social justice (the societal duty to improve medical care for future patients). Both options are imperative and morally praiseworthy but at the same time they seem mutually exclusive." (Janssens and Gordijn, 2000, page 56)

It is often assumed that patients who have advanced disease and are frail do not wish to participate in research but this assumption should be challenged. Patients may wish to contribute to research and may find it helpful to contribute although they are unlikely to benefit from the results. (Addington-Hall (ed) 2007, page 6) Particular concern has been raised about recruiting palliative care patients into research studies due to the concern about their vulnerability. They are a frail group, who are coping with their disease and emotions; they may be cognitively impaired as a result of their disease or its treatment. Authors have suggested they are at risk of coercion by the professionals they depend on and that they may lack capacity to give informed consent. (Addington-Hall (ed) 2007, page 5) Others have argued that if they have capacity, they should be offered the chance to

participate in studies. It would be too paternalistic to not consider them for research. (Fine, 2003)

Fine argues that the ethical principles apply to all types of research and they should not alter simply because the patient is less well or nearing the end of life. (Fine, 2003). Is it then our own prejudices that colour the view of research at the end of life? Fine also argues that being too protective has stopped palliative medicine developing as a specialty and is against patient choice. There has been a tendency to rely heavily on expert opinion. (Kaasa and Dale, 2005) but "it is important to generate not just validated but also generalizable knowledge" (Aktas and Walsh, 2011, page 461)

A further ethical concern that has been raised is that research can take away the hope that comes from spending time with family, away from hospitals, and from achieving good symptom control and replace it with false hope generated by participation in a trial which may be intrusive and time consuming. (Janssens and Gordijn, 2000)

Research in palliative care is hindered by inadequate recruitment of patients and attrition which may occur as people become increasingly frail or require other interventions which mean they are not eligible for the original study or that the research is no longer a priority for them. It is important to define the symptom, intervention or outcome adequately otherwise there is little opportunity to strengthen research through the conduct of meta-analysis or systematic reviews. (Addington-Hall (ed) 2007, page 5) Palliative medicine research is also limited by confounding factors ie the number of different variables that can impact on the experience of a symptom by the patient, their family and other caregivers. For example the management of nausea depends on the underlying disease process, the multiple causes of nausea and the interventions used. It is much easier to study hypertension where there is a clear objective outcome measure. Randomised controlled trials can be difficult to design due to the confounding factors. (Aktas and Walsh, 2011)

The lack of consistent definition in the palliative care literature also affects the ability to conduct systematic reviews and meta-analysis. For example in one review article the lack of consistent definition of "dying" and "terminally ill" was highlighted. Lack of funding has been suggested as a barrier to the conduct of palliative care research. (Kaasa and Dale, 2005) but it is probably the lack of infrastructure and experienced research personnel within an organisation that is more important. (Whalen et al, 2007)

Both qualitative and quantitative research methods have a place in palliative research. Qualitative research is very positive as it gives the patients and their carers the opportunity to discuss their experience and the meaning of the experience for them. In quantitative research alternative methodologies can be useful and in fact offer more chance of succeeding at research than trying to follow RCT protocols rigidly. N = 1 studies have been suggested as a useful methodology for palliative care research. Care is still needed with case definition in order to allow comparison and aggregation of the studies. If the patient's disease progresses between cycles it can be difficult to judge outcome. (Nikles et al, 2011) It is sometimes possible to extrapolate from research done in other care settings (Kaasa and Dale, 2005) but this relies on a clear understanding of context of study and on the possible limitations of transferring the results of the study to a different disease or stage of disease. It is important to consider that not all research needs to be hospice based in order to establish the evidence base for palliative medicine researchers can look to other relevant settings. Dialysis units and accident and emergency units have been suggested as appropriate settings. (Whalen et al, 2007) Observational studies can be more practical to conduct than Randomised Controlled Trials. (Aktas and Walsh, 2011)

1.9 Outline of thesis

This thesis explores the burden of opioid related side effects and the nature of opioid induced hyperalgesia. The research was conducted in three parts initially with the first part of the study aiming to provide a point prevalence of side effects and the burden of these in the different patient groups. The second part of the study was qualitative research that aimed to give voice to patients with cancer pain who had experienced an episode of opioid

toxicity. The third part of the study was aiming to provide longitudinal information about opioid-induced hyperalgesia. As the study recruited patients and analysis was completed it became clear that there was a wealth of data across all the original aims of the study provided by the follow-up assessments and that the original division of the study into three parts was less relevant than anticipated. The study was providing information on four key aspects – opioid related side effects, effect of opioids on cognitive function, opioid-induced hyperalgesia and the patient experience of opioid toxicity. It became clear that the thesis would most logically follow these chapters.

The methods chapter provides an outline of each of the tools used with the details of the population in which they were validated, the strengths and limitations of the tool.

The same tools were used at each assessment that collected quantitative data and were:

- Opioid history and Short Opioid Withdrawal Scale
- Likert scales for the assessment of side effects of opioids
- Constipation Score
- Brief Pain Inventory
- Hospital Anxiety and Depression Scale
- Self-completed Leeds Assessment of Neuropathic Pain Scale
- Addenbrooke's Cognitive Examination – Revised
- Bond and Lader analogue scales
- Quantitative sensory testing.

Qualitative description has been used for one part of the study. The use of qualitative research within the main study will be explored and the rationale for using qualitative description as the method in this study will be discussed along with the results and not in the methods chapter.

Four chapters will follow, each one exploring one of the themes highlighted above. Each chapter starts with a statement of the aims of the section and a review of the relevant published literature. The patients who were included in the data analysis of relevance to that section will be described and results of the analysis presented. Each chapter will include comparison of the results to the literature, a reflection on the limitations of the study with particular relevance to the chapter and a brief discussion of the future work required.

In the chapter exploring the prevalence and burden of opioid-related side effects the morphine equivalent daily dose will be used to facilitate analysis of the data and look for a possible relationship between dose of opioid and the side effects experienced by the patients in the study. The analysis of the data will also explore possible correlations between the different strong opioids and rate of titration of the opioid and the side effects experienced. The side effects will be compared between the different patient groups.

The introduction to the chapter which discusses opioids and cognitive function will provide an overview of our current understanding of the impact of opioids on cognitive function. Other factors of importance particularly in the cancer group will be briefly considered for example biochemical abnormalities and chemotherapy related impairment. This chapter will review the prevalence of opioid related cognitive impairment and will reconsider the most clinically relevant assessment tools. The results of the objective and subjective measures of cognitive function will be presented and any correlation sought.

The published literature regarding opioid-induced hyperalgesia in cancer patients is based on case reports currently. The case reports will be examined and common themes extracted. The introduction to this chapter will provide a brief summary of the literature relating to opioid-induced hyperalgesia and its assessment using quantitative sensory testing. The aim of this part of the study is to explore the prevalence of opioid induced hyperalgesia and possible associations including opioid, dose and rate of titration of opioid. The quantitative sensory thresholds will be compared over time and between patient groups. Morphine equivalent daily dose will again be used to facilitate comparison.

Patients who show features suggestive of opioid-induced hyperalgesia will be reviewed to look for possible contributory factors. The findings of this part of the study will be summarised and compared to the published literature.

The introduction to the qualitative research chapter will present a critical review of the published literature on patients' views of opioid toxicity. The process of developing codes and identifying themes will be described. The main themes found after analysis of the data will be presented and the implications for the care of future patients considered.

1.10 Summary

Pain is a subjective experience that is affected by the patient's previous experiences of pain and healthcare. Pain will have physical and psychological consequences if not managed well. The prevalence of pain throughout the world requires us to consider our approaches to the management of pain and ensure everyone has access to analgesia and support.

Strong opioids such as morphine are considered the mainstay of pain management especially in cancer pain. Traditionally opioids have been prescribed for patients with cancer with the expectation of fully controlling the pain and with the advice to professionals that there is no "ceiling dose". There has been increasing recognition in recent years about the lack of evidence about the effects of opioids over the long term but emerging understanding that opioids adversely impact on the endocrine and immune systems. This study aims to add to this literature with data about the burden of side effects, the impact of opioids on cognitive function and opioid induced hyperalgesia. Palliative medicine is shifting to keep pace with the developments made by our colleagues in oncology and we are involved in the management of patients who are living, not dying, with cancer. It is no longer acceptable to use opioids without serious regard for the future. Now is the time to review opioids and the way in which they are prescribed.

1.11 Aims of the Study

The aims of the study are detailed below.

- To assess the prevalence and severity of side effects of prescribed opioids
- To compare the symptom burden due to strong opioids in different patient groups
- To assess the impact of strong opioids on cognitive function
- To explore the patient experience of opioid toxicity
- To estimate the prevalence of opioid-induced hyperalgesia
- To describe the clinical features of opioid-induced hyperalgesia and thus enable clinicians to better recognise opioid-induced hyperalgesia
- To identify factors which may predict patients at risk of developing opioid-induced hyperalgesia

CHAPTER 2: METHODS

2.1 Introduction

This is an exploratory research study which represents a longitudinal review of patients who are prescribed strong opioids with the aims of assessing the burden of opioid-related side-effects and of characterising opioid-induced hyperalgesia. The study was planned and conducted in three parts. However as described in the introduction to the thesis the results which emerged from the different studies defined the chapters. The methods chapter describes each of the research tools used with an outline of the strengths and limitations of each tool. The same research tools were completed by all patients at all assessments. Information regarding demographic details and disease status were confirmed and updated at subsequent assessments.

2.2 Outline of Study

Multi-centre ethical approval was obtained and the study had the support of the Research and Development teams in each of the health boards from which patients were recruited. The approval numbers for the study were MREC: 09/S1103/11 and Research and Development project identification number: 2009/W/AN/03. Approval letters have been included as Appendix A.

Eligible patients were identified by the clinicians leading their clinical care. Patients were attending oncology clinics in the cancer centre, attending chronic pain or substance misuse clinics or under the care of the specialist palliative care team – either the one of the community clinical nurse specialists or the day hospice team. Once patients had been identified as eligible the possibility of participating in a research study was discussed and they were given a patient information leaflet which outlined the study. The patient was then contacted by a member of the research team in order to answer any questions they may have and to confirm their eligibility for the study. Patients who wished to participate

provided informed written consent prior to commencing the study. The patient information sheet and consent form for the study have been included as Appendix B and Appendix C respectively.

Patients were given a choice about where the study was completed. The majority of patients were seen in their own homes and usually chose to have a close family member with them. The exceptions to this were the patients with a history of substance misuse. They were seen in the substance misuse clinic. The assessments took between thirty and sixty minutes to complete at each visit. The majority of patients were seen once, some patients completed two or three assessments.

2.3 Patient Groups

Patients are prescribed opioids for several reasons as outlined in the introduction to the thesis. In order to provide comparisons between different patient groups it was necessary to recruit patients who were prescribed opioids with different indications. Patients were recruited who were prescribed opioids as part of the management of cancer pain, chronic non-cancer pain or to manage their substance misuse. In order to provide a comparison group for the quantitative sensory testing, a group of patients with chronic non-cancer pain but who were not prescribed opioids were also recruited. These patients were attending one of the chronic pain clinics in Lothian (n = 25). The majority of patients with cancer pain were recruited from Strathcarron Hospice. Additional patients with cancer pain were recruited from the Beatson West of Scotland Cancer Centre (n = 8) and the Western General Hospital, Edinburgh (n = 1). Patients with non-cancer pain and those with non-cancer pain who were not on opioids were mainly recruited from the chronic pain clinics in NHS Lothian. Additional patients in these groups were recruited from Strathcarron Hospice (n= 13). Patients with a history of substance misuse were recruited from NHS Lothian (n = 25).

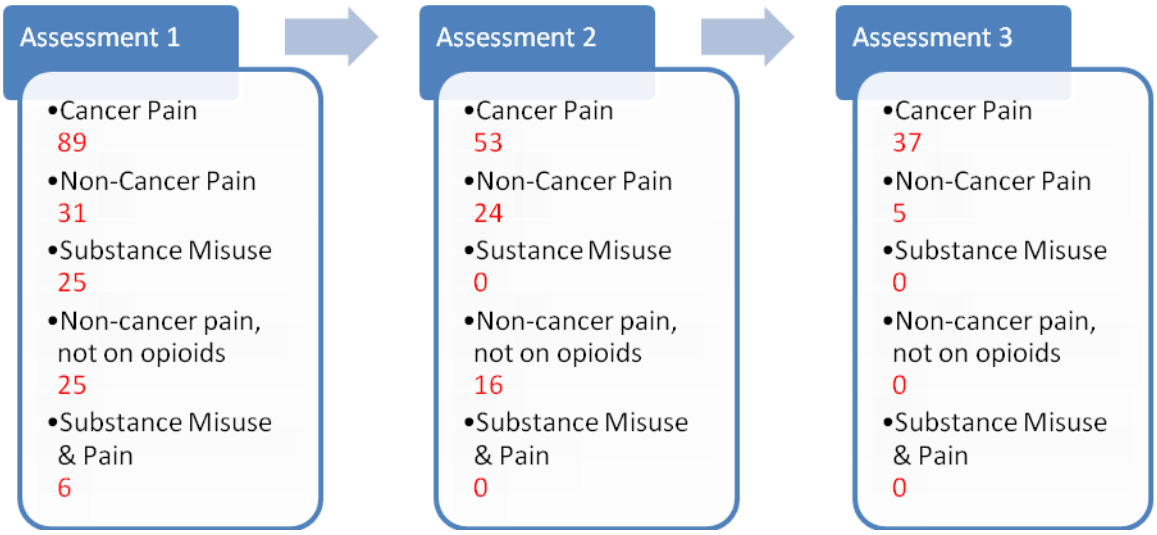
A group of healthy volunteers without chronic pain or opioids were also recruited in order to provide the population normal values for the quantitative sensory testing. The healthy population who did not have chronic pain and were not prescribed strong opioids were recruited from the staff and volunteers of Strathcarron Hospice (n = 102). They completed a questionnaire to confirm eligibility and collect basic demographic information. The quantitative sensory testing undertaken in this group provides a control group of quantitative sensory testing in healthy people. Approximately the same number of volunteers and patients was required to provide adequate comparison.

2.4 Inclusion and exclusion criteria

Patients were all aged over 18 years of age and able to communicate in written and verbal English. Some of the tools chosen for the study were only available in English. Patients must have an estimated prognosis of at least three months. Patients who were very frail or confused were excluded. It would not have been ethical to recruit patients who were confused as they would not have been able to give informed consent or to provide the information required during the assessments. Very frail patients were excluded as it was unlikely they would be able to complete two or three assessments with six to eight week intervals between assessments.

The initial three parts of the study are detailed in the diagram. The diagram shows the number of patients from each patient group who completed each assessment.

Figure 1: Number recruited in each patient group and the number of assessments completed by patients in each patient group



All patients had to have been prescribed and taking a strong opioid for at least a week prior to recruitment. Patients were required to be on at least 60mg of morphine each day or an equivalent dose of an alternative strong opioid in order to complete the full study i.e. assessments at three time points. The dose of 60mg was chosen as the majority of patients with cancer pain will be effectively managed at this dose of morphine or an equivalent dose of another opioid (From Oxford Textbook of Palliative Medicine, 4th Edition. Ed. Hanks, Cherny, Fallon et al). It therefore represents a clinically relevant dose rather than an extreme. Patients who were prescribed less than 60mg or an equivalent dose of an alternative strong opioid were eligible to complete the assessment on one occasion only. Some patients who were recruited to complete three assessments managed fewer than planned assessments due to increasing frailty which was usually due to progression of their cancer.

A third group of patients was recruited for the qualitative research component of this mixed methods study. All patients who were recruited for the qualitative research study were also participating in the quantitative research study. We purposively recruited patients

who had previously been opioid toxic. Eligibility for this part of the study was identified by the referring clinician or by the researcher when conducting the other assessments and it became clear the patient had been toxic previously. Patients recruited for this part of the study participated in semi-structured interviews.

2.5 Assessment Tools

Basic demographic data for all those who participated in the study was recorded. This included the patient's age, sex and ethnicity. The underlying diagnosis and treatments which had been completed or were ongoing were noted for example chemotherapy or hormone therapy. For those patients with cancer, the primary site and site of any metastases was noted. A detailed pain history was documented including the type of pain, duration of the pain and relevant investigations. Non-pharmacological interventions which had been tried and whether there had been any benefit in terms of improvement in pain were recorded. Past medical history and psychiatric history were also documented.

The patients recruited for the study all completed the research tools at each assessment during participation in the quantitative research study. An explanation of each of the research tools used and the reasons for choosing them is given below.

2.5.1 Opioid History

A comprehensive opioid history was obtained through questioning the patients about the opioid they were prescribed over the last six months. When the patient was unable to recall the opioid history with certainty, the details were clarified from notes and previous prescriptions. The patient was asked to state how long they had been on opioids and details about which opioids they had tried and the reasons behind any change of opioid.

The opioid, formulation i.e. instant release or modified release, route of administration and dose were all recorded. The number of doses of instant release opioid used in a 24-hour period were also recorded. The number doses of instant release opioid imply how well the patients' pain is controlled. The detail of the opioid history was necessary to enable the morphine equivalent daily doses to be calculated. It was also key to many of the planned statistical analyses as the analysis has explored possible relationships between strong opioid, dose and dose titration.

The reasons for taking the opioid were recorded and the patient was asked whether they had any concerns about becoming dependent on the opioid. The use of any non-prescribed drugs including opioids was documented. The features of opioid withdrawal were assessed using the Short Opioid Withdrawal Scale (SOWS).

The Short Opioid Withdrawal Scale comprises ten questions each with four possible responses. The responses indicate the presence of any of the symptoms in the last 24 hours and are graded from none (score zero) to severe (score three). A score is obtained out of a possible total of thirty. The Short Opioid Withdrawal Scale provides a subjective measure of the symptoms associated with withdrawal from any of the strong opioids. The symptoms included in the SOWS include feeling sick, stomach cramps, heart pounding and yawning.

The SOWS was developed from a 32-point questionnaire after analysis showed that some items were not needed. The questionnaire was reduced to 20 and then further to ten items. Questions were dropped when they were show to overlap with other questions or when patients found them unclear. The ten items which remained were all shown to have relevance and value when measuring withdrawal. The author of the SOWS suggests that presenting the mean of the scores is one way to present the results (Gossop, 1990).

There are both objective and subjective measures of opioid withdrawal. Originally clinicians completed objective tools but one research team were keen to consider the addicts perspective (Cohen, Klett, Ling, 1983). In 1983 they looked at 150 male veterans on methadone and asked them to complete a self-report questionnaire during detoxification. They were asked questions about the frequency with which symptoms occurred, the duration of the symptoms and the timing of the symptoms during the episode of withdrawal. Some symptoms were experienced by most patients. These were restlessness, lack of energy, craving for the drug, difficulty sleeping and aching bones and joints.

The Clinical Opiate Withdrawal Scale (COWS) was developed by clinicians in 1999. The COWS assesses 11 symptoms of withdrawal and assigns a variable score to each question. The maximum score possible is 42. A score of five to 12 indicates mild withdrawal and a score of 36 or greater indicates severe withdrawal symptoms. The symptoms assessed include sweating, gastrointestinal upset, bone or joint aches, runny nose and yawning so there is an expected overlap with the Short Opioid Withdrawal Scale. Resting pulse rate and pupil size are also required for the COWS though. Although grounded in clinical experience the questions were not refined through any validation studies until 2009. At this time the COWS was compared to the Clinical Institute Narcotics Assessment a tool which has been criticised due its reliance on pulse and BP measurement (see paragraph below) and which it has also been suggested is easy for patients to manipulate the questions and subsequent score obtained. The two studies were compared in a double-blind placebo-controlled study involving the administration of morphine to healthy volunteers and then the administration of either naloxone or placebo. The validation of the COWS has therefore not been undertaken in relevant patient groups (Tompkins et al, 2009).

Objective measures include measurement of pupil dilatation, heart rate and blood pressure. In a study by Turkington and Drummond however these objective measures were shown to be unreliable measures. Comparisons were also made between objective and subjective measures and it was noted that there is poor correlation between the two (Turkington and

Drummond, 1989).

Overall the Short Opioid Withdrawal Scale offers the more meaningful and reliable subjective measure of the symptoms of opioid withdrawal when compared to the other available tools. It has also been more robustly validated than the other available tools. None of the tools to measure opioid withdrawal have been validated in patient groups other than those with a history of substance misuse and therefore any tool chosen is limited in its application to patients who are prescribed opioids for the management of cancer and non-cancer pain.

2.5.2 Summary: Opioid History and Short Opioid Withdrawal Scale

A detailed history of the opioids which had been prescribed and taken over the six months prior to assessment was documented. A subjective measure of the symptoms of opioid withdrawal was used given the poor correlation between subjective and objective measures and the importance for this study of establishing the burden of side effects on patients. The Short Opioid Withdrawal Scale has been included as Appendix D.

2.5.3 Morphine Equivalent Daily Dose

Strong opioids are prescribed for cancer and non-cancer pain. Different opioids are available and individual patients can find particular opioids are more effective for their pain or that there are fewer side effects. Patients may be prescribed opioids by different routes also for example oral, transdermal, buccal or subcutaneous. In order to be able to compare the opioids used by patients for the purposes of research the opioids are converted to a morphine equivalent daily dose in milligrams (MEDD). "The equianalgesic dose is defined as that dose at which two opioids (at steady state) provide approximately the same

pain relief." (Shaheen et al, 2009)

Some opioids have established conversions which are used clinically and have relevance to healthcare professionals. Other opioids do not have established conversions and it was necessary to use a conversion which we found clinically meaningful. The fast acting short acting preparations of fentanyl are in this category. If the opioid conversions are not accurate the analysis will be open to bias.

There are many different opioid conversion tables available. The conversions used in this study are those which most closely represent clinical practice in the areas from which patients were recruited. The wide variation in opioid conversion tables has been highlighted in the literature. (Shaheen et al, 2009) The main concerns highlighted by Shaheen and colleagues are clinical and the potential for significant harm to patients from inaccurate dose calculations. (Shaheen et al, 2009)

O'Bryant and her colleagues highlight that many studies are not transparent about the opioid conversions used and simply present the MEDD and the results based on it. The data is then likely to be interpreted according to the reader's usual clinical practice. Results may be wrongly interpreted due to false assumptions. (O'Bryant et al, 2008)

It is most complex to convert from one opioid to methadone or from methadone to a different opioid. Methadone is a strong opioid which is also an N-Methyl – D –Aspartate antagonist. This dual action lends methadone clinical utility beyond other strong opioids however renders it difficult to convert between opioids and methadone. There are many different suggested protocols to manage patients who require methadone to be commenced.

There is sparse guidance on how to convert methadone to morphine (or any other strong opioid). A pragmatic approach was taken based on the best available evidence. (Wong and Walker, 2012; Pollock et al, 2011; Lawlor et al, 1997; Walker et al 2008)

2.5.4 Summary: Use of MEDD

Various strong opioids are prescribed for patients and the opioids may also be taken by different routes. The morphine equivalent daily dose represents a conversion to a single opioid and route and has been used to facilitate statistical analysis. The opioid conversion chart used in the study has been included as Appendix E.

2.5.5 Likert Scales

Likert scales were used to assess the presence of symptoms. There are validated tools that would explore patient's symptoms for example the EORTC QLQ-C30 (Aaronson et al, 1993) however these can be extensive and are not specifically designed to look for the side effects of opioids. A pragmatic approach was therefore taken of using Likert scales written particularly for this study which therefore had not been tested or validated but were specific to meet the aims of the study.

Patients were asked to think about the seven days prior to the assessment and to think about the frequency of each of five symptoms. Each of the symptoms was a recognised side effect of opioids. The symptoms included were nausea, vomiting, dry mouth, myoclonus and hallucinations. There were five possible responses to each statement about the presence and frequency of the symptom moving through very often, quite often, occasionally, very rarely and none.

Likert scales are frequently used in studies and are therefore a familiar tool for many in the general population. The familiarity brings an intrinsic value. However they are not without problems. It has been suggested that Likert scales are less responsive to change than visual analogue scales and that Likert scales may be harder for those with a lower educational achievement to complete. There is no consistent advice on how many possible responses should be available for each question but it appears that too few or too many responses result in poor completion of the questions. (Hassan and Arnetz, 2005)

In a study designed to compare Likert scales with visual analogue scales Hassan and Arnetz recruited participants through the use of a website for those seeking advice on stress management and self-motivation. Recruitment bias is immediately clear given the population involved however they went on to exclude students, unemployed and pensioners in order to make the group as homogeneous as possible. They found Likert scales and visual analogue scales to be similar but the results of this study must be questioned given the clear bias. (Hassan and Arnetz, 2005)

The optimum number of responses in a Likert scale is five or seven. Maximum information is extracted from the results if a scale with at least 20 responses is used. Scales with only two or three possible responses are not useful. (Preston and Colman, 2000)

The analysis of Likert scales is contentious and the subject of several articles. In 2004 Jamieson (Jamieson, 2004) argued that the responses given by study participants are ranked with unequal intervals between them. If this is not recognised, some of the value of the responses can be lost. The comparative validity of alternative scales to measure the intensity of symptoms was discussed in the section describing the Brief Pain Inventory. Through the study we have used a variety of measures.

The EORTC-QLQ-C30 would have offered a more robust measure of symptoms than the Likert scales. It was validated in 305 patients with lung cancer and found to be a reliable measure of quality of life (Aaaronson et al, 1993). Importantly it is not used in patients with non-cancer or substance misuse however. Although the tool includes questions about nausea, vomiting, constipation and some questions relevant to cognitive function, anxiety and depression, it does not provide any measure of the other side effects of opioids or the depth of assessment gained from using tools to assess the other research questions specifically eg the Hospital Anxiety and Depression Scale.

2.5.6 Summary: Likert Scales

Likert scales were written for this study to assess the frequency with which patients experienced opioid-related side-effects. This was a pragmatic approach given the number of research tools being used at each study assessment. The Likert scales had five responses and were analysed using a Spearman rank correlation which requires no assumption about the equality of the intervals between responses. The Likert scales have been included as Appendix F.

2.5.7 Assessing Presence of Constipation

The constipation score provides information about the frequency of bowel movements, the ease with which the patient can move their bowels and the consistency of their stool. Each response is scored from zero to two. A score of four or more represents normal bowel function and a score of three or less indicates constipation. (Fallon and Hanks, 1999)

The tool was developed during a study of constipation in patients who were prescribed morphine. All the patients in the study had advanced cancer and had been referred to the specialist palliative care team in a cancer centre. The purpose of the study was not to

validate the constipation score and it has not been subject to a validation study since. It is therefore not possibility to comment on construct validity, sensitivity, specificity or predictive values of the tool. (Fallon and Hanks, 1999) It is also a tool that was developed for use in a palliative care patient group yet we have used it as an outcome measure in all patient groups recruited for the study.

In a review article Clark and Currow reviewed the available outcome measures for constipation in palliative care patients. The lack of a definition of constipation in palliative care is discussed. There is also lack of guidance about how best to measure constipation – even whether this should be with objective or subjective measures. (Clark and Currow, 2013) The lack of a validated tool is also clear in the Cochrane review on opioid-induced constipation (Candy et al, 2011). The authors of the review (Clark and Currow, 2013) suggest the Rome Criteria which were developed and are used by gastroenterologists could be used when looking at constipation in palliative care. In reviewing the various outcome measures used to assess constipation in palliative care the authors found six themes used to define constipation in the literature. These were "time between bowel actions, time between bowel actions with concurrent opioid use, opioid use, use of laxatives, self-report or health professional's opinion (Clark and Currow, 2013)." The lack of consistency of definition of constipation in patients who were prescribed opioids for the management of non-cancer pain was also highlighted in a review by Panchal and colleagues in 2007 (Panchal, Muller-Schwefe, Wurzelmann, 2007). The tool used in this study overlaps with some of the less comprehensive tools used in the literature.

The Rome criteria provide clear diagnostic criteria with both subjective and objective measures of constipation. The constipation score we have chosen successfully addresses some of the Rome criteria. The Rome Criteria for the diagnosis of functional constipation require the presence of sufficient symptoms to meet the criteria for at least three months with the onset of symptoms at least six months prior to diagnosis. Although the criteria are robust and well defined they are specifically designed to provide consistency around the diagnosis of functional constipation and are less well suited to opioid-induced constipation due to the time stipulations.

2.5.8 Summary: Use of Constipation score

The constipation score provides a total score based on three questions. A score of three or less indicates constipation. An un-validated tool was chosen as it offers a patient- centred approach to the assessment and a priority of this study is to assess the burden of opioid-related side effects on patients. The constipation score has been included as Appendix G.

2.5.9 Measuring anxiety and depression

Various tools exist for the purposes of screening of anxiety and depression. These include the Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory, Edinburgh Depression Scale and Distress Thermometer.

The Beck Depression Inventory (BDI) was developed in 1961. It can be used as a screening tool in both psychiatric and non-psychiatric populations. It was designed to be completed by an interviewer but is widely used as a self-completed tool. (Beck, Steer and Garbin, 1988) The BDI consists of 21 questions each with four possible responses. A spectrum of cut-off values for the diagnosis of varying severity of depression are provided. Questions include those around fatigue, appetite and concern about health that could be difficult for patients with physical illness. However the BDI has shown to be a valid and reliable screening tool when compared to the HADS in patients with cancer (Mystakidou et al, 2006) and to have good construct validity and internal consistency in patients with chronic pain (Harris and D'Eon, 2007).

Ultra-short methods of screening (for example the distress thermometer) for anxiety and depression were also considered given the number of assessments and questionnaires patients were asked to complete at each research visit. However in a large review of 38 analyses exploring the accuracy of these methods in cancer patients the ultra-short screening methods were found to lack sufficient accuracy to be used as screening tools (Mitchell, 2007).

Given the inclusion of somatic symptoms of depression in the BDI and the apparent lack of reliability of short methods the use of the HADS for the purposes of identifying anxiety and depression in this study were explore further.

The hospital anxiety and depression scale (HADS) is widely used in palliative medicine both as a screening tool and as an outcome measure in research in several patient groups. The popularity of the HADS has been in part as a result of its non-reliance on the somatic symptoms of anxiety and depression as these can significantly overlap with the physical symptoms of illness.

The HADS tool has been designed to be completed by the patient and the wording of each question was considered and revised in order to ensure patients could understand the question. The use of English colloquialisms has been criticised as these do not translate well into other languages and the value of the HADS could be lost.

Patients are asked to complete fourteen questions. Each question has four possible responses. Each response is a descriptive term with an attributed score of zero to three. A score of three indicates the presence of one of the symptoms suggestive of anxiety or depression and that the symptom is severe. Two total scores are then obtained – one for anxiety and one for depression. The HADS was designed to provide separate score for anxiety and depression and not to provide a total score which would represent distress as a more global concern. Much has been written about the use of the individual scores and the validity of this approach. This will be discussed further.

The questions ask about the patient's experience of the last week. The score provided is therefore very contemporary. The authors of the HADS suggested that the HADS can be used at time intervals in order to review the patient's progress.

Annunziata and colleagues recruited 512 consecutive hospitalised cancer patients to address the question of whether the HADS scores are best used as separate scores for anxiety and depression or as a combined score. They also wanted to identify the appropriate cut-off scores. 544 patients were recruited but 32 were excluded because the HADS forms were not properly completed. No further detail about the incomplete forms was provided. It is therefore not clear whether 5.8% of the patients recruited for the study found the forms too difficult – which would have implications for the use of the HADS – or whether there were patient related factors which precluded completion of the form, for example fatigue, difficulty reading the questions due to eyesight or comprehension difficulties. In this study of cancer patients in hospital the use of two scores ie anxiety and depression rather than one global score was found to be the "best fit." Of note the HADS was valid in an Italian population and its usefulness had survived the translation process. The study recruited a relatively large sample of patients but generalizability may be limited by the fact they were all in hospital (Annunziata, Muzzatti, Altoe, 2011)

Mari Lloyd Williams and her colleagues looked at the HADS in a population of patients who all had metastatic malignant disease (Lloyd-Williams and Friedman, 2001). They recognised the difficulties of diagnosing depression in frail patients. They specifically recruited patients with a limited prognosis (estimated to have less than six months to live). The study compared the accuracy of the HADS in diagnosing anxiety and depression with present states examination interviews which require specialist training to conduct but are regarded as a gold standard diagnostic tool and therefore chosen for the validation of other screening tools. Lloyd Williams argued that in patients with advanced malignancy higher cut-off scores should be used and that the highest sensitivity and specificity came from using the HADS as a one factor tool ie with a total score calculated. They recommended a cut-off total score of 19.

Alex Mitchell and colleagues also looked at how well the HADS performs in those with cancer or under the palliative care team. A meta-analysis was conducted. He concluded the HADS performed better earlier in the disease trajectory but there were few studies which could be included in this part of the meta-analysis and a small sample size therefore

caution is applied to the finding. Overall they recommended the HADS for use as a screening too (Mitchell, Meader, Symonds, 2010). This conclusion was also discussed by Luckett in 2010 in a systematic review of the use of HADS in English-speaking patients. This review only looked at papers published in the last ten years. They assumed that anything described more than ten years ago had been superseded by a better tool. This is a fundamental flaw and source of significant inclusion bias. The results must therefore be interpreted with caution. The review suggests that there is some evidence to support the use of HADS rather than other screening tools, the HADS appears to perform better earlier in the cancer journey and that a total score is useful. Overall they recommended using the HADS anxiety, depression and total scores to describe the patient's distress (Luckett et al, 2010).

Johnston et al reviewed the use of the HADS in different patient populations. They concentrated on the internal consistency of the HADS ie how well it performs in different patient groups. They concluded the HADS has good internal consistency with 13 of the 14 questions leaning to the psychological, rather than somatic, symptoms of anxiety and depression. The question "I feel as if I am slowed down" was a poor predictor of distress in all patient groups (Johnston, Pollard, Hennessey, 2000). A meta-analysis published by Brennan et al found that the HADS performs as well as other screening tools in primary care populations (Brennan et al, 2010).

In a group of patients with lung cancer the most helpful HADS cut-off for diagnosing depression was 8. If the cut-off was increased to 11, the number of false positives increased from one to three. This increase was thought to be more reassuring for clinicians than the possibility of failing to recognise some patients with depression. This study was very small with only 53 patients and was conducted in Italy (Castelli, 2009). The Italian version of the HADS has appeared valid in a larger group though (Annunziata, Muzzatti, Altoe, 2011).

Ultra- short screening tools have been suggested as valid by some practitioners. These tools rely on five or fewer questions to make the diagnosis. A review of the ultra-short methods of detecting anxiety and / or depression in cancer patients found that although they were popular with clinicians they can only be relied upon to "rule-out" that patients have anxiety and depression and could not be relied upon to "rule-in" the diagnoses (Mitchell, 2007). This study did not use an ultra-short screening tool due to the lack of reliability.

2.5.10 Summary: Use of HADS

The Hospital and Anxiety Scale was therefore chosen for the study due to its internal consistency and known validity in different patient groups. Cut-off values for anxiety and depression have been used in accordance with the recommendations of the authors of the HADS in the absence of clear guidance to the contrary. In addition for those patients with cancer a total cut off score of 19 was also used. The HADS questionnaire has been included as Appendix H.

2.5.11 Measuring pain severity and interference

There have been two significant reviews of the use of tools to measure pain. The IMMPACT recommendations reviewed the use of outcome measures for chronic pain studies. They considered the use of visual analogue scales, numerical rating scales and verbal rating scales, and several tools which explore pain and its impact on function. This consensus meeting and subsequent paper recommended the use of the Brief Pain Inventory. (Dworkin et al, 2005) In a paper on behalf of the European Association of

Palliative Care (Caraceni et al, 2002) both the McGill Pain Questionnaire and the Brief pain Inventory were found to be valid multidimensional research tools.

The validity of single dimension pain scores was considered in a study by Ferreira-Valente and colleagues in 2011. They compared the visual analogue scale (VAS), numerical rating scale (NRS), Faces Pain Scale – Revised (FPS-R) and the verbal rating scale (VRS). All four provide a measure of pain intensity. The study recruited healthy volunteers and subjected them to acute cold pressor pain. It therefore fails to include the important emotional aspects of chronic pain and the authors recognised this important limitation. Overall there was little difference between the four scales. (Ferreira-Valente, Pais-Ribeiro, Jensen, 2011) Although the use of a visual analogue scale would only have addressed one dimension of pain and a tool which addressed the multiple dimensions was preferred it is helpful to note the validity of the visual analogue scale in general given that they have been used to address other research questions. In addition the visual analogue scale has not been shown to be responsive to change especially when the pain is decreasing (Carlsson, 1983).

The Brief Pain Inventory (BPI) is a self-completed pain assessment tool which measures both intensity of the pain and the interference of pain on everyday activities. It was developed by Professor Charles Cleeland in response to a call for better documentation of cancer pain, better management and better understanding of the epidemiology of cancer pain. In the 1970s when the BPI was developed, patients reported that the existing tools were too long and complex. Some of the questions were felt to lack relevance to the cancer pain group. The BPI was the result of refinement of earlier drafts. It has largely been validated in patients with cancer pain which is unusual. Most tools are initially validated in patients with non-cancer pain and then transferred to the cancer pain setting. The first version of the BPI was called the Wisconsin Brief pain Inventory. It was tested in 667 patients with cancer and 32 patients with rheumatoid arthritis. Following some refinement the questions were looked at in 1200 patients. The test – re-test characteristics were looked at. (BPI 1) The validation studies were robust in terms of the numbers of patients included. The internal consistency has been confirmed in subsequent studies. (Cleeland, 2009)

Two forms of the BPI exist. The long form is used in clinical trials but its length means it is burdensome. The short form is used in clinics and most research studies. For the most part, where the BPI is used it can be assumed to be the short form. (Cleeland, 2009)

The scores provided by the Brief Pain Inventory (Cleeland, 2009) were recommended for use in all trials looking at aspects of the management of chronic pain by the IMMPACT panel. The BPI provides best, worst, average and current pain scores – each question about the severity of their pain is given a score from zero to ten by the patient. The worst and average scores can be used as standalone scores or the mean of the four scores can be presented. There are seven questions which measure the interference with daily activities for example walking, enjoyment of life and sleeping. Each of the seven interference questions is also given a score by the patient from zero to ten. The mean of the seven scores is presented as the measure of interference. The mean of the interference scores is valid provided four or more of the seven questions has been answered. (Cleeland, 2009) The European association of Palliative Care recommend the use of pain tools which are multidimensional and completed by patients not observers given that pain is a very subjective experience. (Caraceni et al, 2002)

The interference questions can be divided into two groups – known as WAW and REM. Much has been written about the use of the BPI as a three factor research tool.

WAW includes the questions on walking, general Activity and ability to do normal Work. It is the activity sub dimension of the BPI. REM includes the questions on relations, enjoyment and mood. It is the affective sub dimension of the BPI. (BPI 1) The question on the interference of pain on sleep does not seem to fit clearly with either of the sub dimensions. Published studies keep sleep separate when looking at the validity of the three factor approach. (Atkinson et al, 2011; Cleeland, 2009; Wu et al, 2010; Zalon, 2006)

In a study by Wu both the two and three factor model was shown to be valid. Wu and

colleagues used confirmatory factor analysis in 258 patients with cancer pain due to bone metastases. Removing sleep from the analysis improved the internal consistency (Wu et al, 2010) and was consistent with other studies in the removal of sleep. The authors of the study suggested that sleep may not be subject to the same interference by pain as the other factors if physical splinting is used at night to support the painful body part, patients may spend longer in bed to make up for disrupted sleep and opioids may affect the patient's sleep. All these factors were thought to mask the real effect of pain on sleep. (Wu et al, 2010)

Some authors favour one approach or other – ie either a two or three factor approach. A study in acute pain supported the two factor use of the BPI. However this study was in patients with acute pain so is limited in relevance to my study. (Lapane et al, 2014) A study in men with castration-resistant prostate cancer favoured the three factor use however it should be noted that this study recruited relatively small numbers (n=184) of men with a single diagnosis (Atkinson et al, 2012). The strength of the study in recruiting such a homogenous group limits its transferability to other studies.

Of more relevance was the study conducted by Atkinson and colleagues who looked at 364 patients with either HIV/AIDS related pain or cancer pain. Using confirmatory analysis they found that either the two or three factor approach was valid. They highlighted that the three factor model could be particularly useful in different clinical situations. For example, in patients with a limited prognosis the affective component of the BPI would be most relevant for patients for whom the priority was spending quality time with their families. The authors of this study also highlighted that the question about the interference of pain on the ability to carry out normal work is a difficult question for patients with a diagnosis such as cancer which affects this ability for many reasons including but not limited to pain. (Atkinson et al, 2011)

Tan et al evaluated the use of the BPI over time and found it detects improvement in pain.

The BPI was used when patients attended for out-patient review with a mean of 27.73 days between assessments. (Tan et al, 2004) Keller also found the BPI is sensitive to change when used over time (Keller et al, 2004). Dworkin suggested that a change of one point on the pain interference scale is the minimal clinically important change. (Dworkin et al, 2005)

2.5.12 Summary: Measuring Pain Severity and Interference

The Brief Pain Inventory measures both pain intensity and the extent to which it interferes with the patient's daily activities. It can be used as either a two factor or three factor tool. When used as a three factor tool it provides a mean severity score, an affective sub dimension (mean of three interference scores) and an activity sub dimension score (mean of three further interference scores). The BPI has been validated in cancer patients and is available for use in different countries and languages. The Brief Pain Inventory has been included as Appendix I.

2.5.13 Quantitative Sensory Testing

Quantitative sensory testing (QST) provides a functional assessment of the peripheral nervous system. There is some variation in protocols used which is discussed below, but QST is the only method of clinicians assessing peripheral nerve function in an objective manner.

> "QST measures the detection threshold of accurately calibrated sensory stimuli." (Shy et al, 2003)

QST provides an objective stimulus which generates a subjective response. In this study patients were asked to compare sensations between index and control areas and record the sensation at the index site as “no change, increased, significantly increased, decreased, significantly decreased or not detected.” They were also asked to provide a pain score for each of the sensations tested using a numerical scale from zero (no pain) to ten (severe pain). The sensations tested were light touch with a brush, cool and warm sensation, detection and pain threshold using Von Frey filaments, pinprick sensation and the presence of wind-up.

Table 1: Different thresholds are tested and provide information about different sensory pathways

The information in the table has been drawn from two papers – Zaslanski and Yarnitsky, 1998; Yarnitsky, 1997

Sensory modality	Fibres conveying signals
Cold sensation	Small myelinated fibres (Aδ)
Warm sensation	Unmyelinated warm specific C-fibres
Cold pain	Cold fibres and Small myelinated and unmyelinated nociceptors
Heat pain	Small myelinated and unmyelinated nociceptors
Vibration	Large myelinated fibres

In clinical neurological examination the examiner looks for discrepancies between the affected and unaffected sides where possible. The patient becomes their own control. The same approach is taken in QST. Clinical examination is not standardised though. QST aims to standardise the process and to quantify the response. (Gruener and Dyck, 1994) We used an index area and wherever possible a contra-lateral area to provide the control data. At times it was not feasible to test the index site for example a patient who had intra-oral pain. Patients who were in the study and prescribed opioids to manage their substance misuse did not usually have pain. In both these clinical situations the forearm was used as the index site.

A standardised approach to the test is vital. The way the stimulus is delivered is as

important as the stimulus if the results are to be reliable over time. Several authors have highlighted the importance of this. We conducted each QST assessment in the same order of sensory modalities and used the same wording to explain the testing to the patient. Wherever possible subsequent testing in the same patient was also conducted by the researcher. One advantage of QST is that the stimuli used are relevant to life and to the patients' experience of situations which may trigger their pain, for example, cold. (Gruener and Dyck, 1994)

We used the method of levels which requires the participant to remain concentrated for the duration of the test but does not require them to make a rapid decision so it is easier for fatigued patients who may be fatigued due to their pain or disease or both. Normal values for QST are determined by the stimulus used – and can vary between different manufacturers – age, sex and ethnicity of the patient. Although values are available in the published literature which give normal values most authors recommend using normal values from the population patients are drawn from. (Gruener and Dyck, 1994; Shy et al, 2003; Yarnitsky, 1997) When this is not possible then researchers can look to the literature but accept the limitations of the approach.

Other QST protocols have been developed and validated however the protocol we used takes much less time to complete. This is an important consideration in a patient group who are likely to be fatigued due to cancer or other chronic disease. The German team who provided much of the normal data used a protocol which took three hours to complete and required the participants to either have closed eyes or remain fixed and looking at a single spot on the wall. It would seem unlikely that participants' concentration remained constant throughout the whole test. It seems more likely that in the later stages of the test the responses were tempered by tiredness or inability to concentrate further. One hundred and eighty healthy volunteers were recruited for the main study which provided the normative data. They were recruited from ten different sites in Germany. Although the study aimed to provide consistency across the testing, two different thermal kits were used and given the number of different sites there must have been at least as many testers. Both factors introduce inconsistency and therefore bias to the study. (Rolke et al, 2006) The protocol

used by the team is more comprehensive than the one we used. Although it provides more information the length of time to complete the protocol would be difficult in our patient group. They found that there is significant difference between sensory thresholds at different sites of the body. Body site was more important than age, sex or ethnicity of the patient. They recommended that testing is done at both index and control site to provide best comparison data. (Rolke et al, 2005; Rolke et al, 2006)

In a further validation study which recruited patients who were thought to have small fibre pathology due to their use of descriptors including "tingling, prickling and burning" QST improved the sensitivity of diagnosing the underlying pathology. The team found that thermal thresholds were the least useful modality in "detecting small fiber dysfunction" and noted variation when patients were re-tested. The authors of this study argued against using thermal thresholds alone as a diagnostic tool and suggested they were most useful in following –up patients with a known diagnosis. This study was very small with only 15 patients and it is therefore possible that the findings were due to chance and not a real difference. (Tobin, Giuliani, Lacomis 1999)

QST can be used to provide a diagnosis and treatment approach to pain by characterising the somatosensory changes observed and therefore understanding the underlying aetiology. (Rolke et al, 2006) The authors of one review article called for all chronic pain subtypes to be phenotyped using QST in order to provide clarity around diagnosis.

Nerve conduction studies also provide information on the peripheral nervous system and altered signalling within the system. However to undertake nerve conduction studies requires specialist training and it is not a portable investigation. QST is easier for the non –specialist to perform. (Zaslanski and Yarnitsky, 1998) Pain scores alone are commonly used as outcome measures in clinical trials but using QST adds more value and depth if the relevant sensory thresholds are studied. For example the authors of one paper (Stubhaug 2002) suggest using heat and pain thresholds to assess the effect of non-steroidal anti-

inflammatory agents.

2.5.14 Summary: Quantitative Sensory Testing

Quantitative Sensory Testing provides a subjective response to an objective sensory threshold. QST thus provides information on the functioning of the peripheral nervous system. A consistent approach to the delivery of sensory testing and questions asked of the patients is very important to ensure the results are valid. We used index and contralateral control areas where possible. If it was not possible to test the painful area directly the forearm was used. In order to provide normal data from our own population we also recruited 103 healthy volunteers who also underwent QST of the forearm. The chart used to record the quantitative sensory testing protocol is included as Appendix J.

2.5.15 Measuring Cognitive Function

Cognitive function is an important outcome measure in the study. It was important to provide both subjective and objective measures of cognitive function. Cognitive function can be impaired by delirium, dementia and age-related "cognitive impairment not dementia". (Woodford and George, 2007) Many of the measures of cognitive function require specialist training or assess specific aspects of function, for example the finger tapping test, trail making test. A priority when choosing a tool for this study was the ability to provide a global assessment of cognitive function and to be clinically relevant in order to facilitate application of results to the clinical setting.

2.5.16 Objective measure of cognitive function

The use of a clinically relevant tool that had been validated in different patient groups was a priority for the research study given that one of the main objectives was to assess the impact of opioids on cognitive function. A review and meta-analysis by Baldacchino explored the neuropsychological consequences of chronic opioid use (Baldacchino et al, 2012) and found that the cognitive domains most likely to be affected were those of working memory, verbal fluency and cognitive impulsivity. The use of a tool which measured these domains was therefore key. Ismail and colleagues reviewed the available screening tools and their validity in screening for dementia. This review provided useful information and comparison of the available tools for assessing cognitive function. (Ismail, Rajji, Shulman, 2010) Based on these papers the Addenbrooke's Cognitive Examination, the Mini-mental State Examination and the Montreal Cognitive Assessment were explored further. Many authors have used more specific tests of psychological function which lack a comprehensive overview of cognitive function (for example Kendall et al, 2010). These findings are discussed further in the chapter on the impact of opioids on cognitive function.

The Montreal Cognitive Assessment assesses short-term memory, visuospatial abilities, executive function, attention and concentration, language and orientation to time and place. It has been validated in a memory clinic and an elderly out-patient population. It is available in several languages including Arabic and Korean. Of note in one study in a British memory clinic the specificity of the Montreal Cognitive Assessment to detect dementia was just 50% (Smith, Gildeh and Holmes, 2007), although the specificity has been higher in other studies. Overall the Montreal Cognitive Assessment has been recommended for use in conjunction with the Mini-mental State Examination and that it can be a useful additional screening tool for patients with a Mini-mental State Examination score greater than 25 out of 30 (Ismail, Rajji, Shulman, 2009; Smith, Gildeh and Holmes, 2007). This approach would not have been as useful for the study as it would have added burden in terms of number of tools and the need to score one tool and then decide whether to carry out a second cognitive assessment in some patients. Overall this approach did not consistent with the objectives of the study and the Addenbrooke's Cognitive Examination – Revised (ACE-R) was chosen.

The Addenbrooke's Cognitive Examination – Revised (ACE-R) was chosen to measure cognitive function objectively. It provides a comprehensive assessment of cognitive function. In addition it is user-friendly and does not require specialist training. It takes ten to fifteen minutes to complete the ACE-R. The ACE-R is based on the mini-mental state examination which has been a very popular means of assessing cognitive function. The mini-mental state examination remains widely used in many clinical settings despite widespread acceptance that it is limited in the information that it provides. In their article outlining the use of the ACE-R Bak and Mioshi explain that the mini-mental state examination only verbally assesses memory and attention. "It is insensitive to frontal-executive dysfunction and visuospatial deficits." (Bak and Mioshi, 2007, page 246) The mini-mental state examination therefore provides limited information on cognitive function and is unable to differentiate between different pathologies. (Bak and Mioshi, 2007; Kipps and Hodge, 2005; Larner, 2007; Woodford and George, 2007) The ACE-R provides a score out of 30 based on the items from the mini-mental state examination and a score out of 100. The original Addenbrooke's cognitive examination was developed in 2000 and was more heavily weighted towards memory and less weighted towards visuospatial abilities. The revised version was published in 2006. The majority of the published literature which provides the evidence for using the ACE or ACE-R is actually based on the ACE. However the ACE-R is the tool which is now more widely used. (Crawford et al, 2011; Mathuranath et al, 2000)

The ACE-R has been designed for use by the non-specialist. It provides information on five domains of cognitive function and normative values based on age and education of the subject. The quality of the information provided enables the user to distinguish between causes of dementia. There are three versions of the ACE-R and subsequent assessments should be carried out using different versions. (Bak and Mioshi, 2007)

The domains of cognitive function which are assessed are – attention and orientation, verbal fluency, language, visuospatial and memory. Using a cut-off score of 82 / 100 has a sensitivity of 84% and a specificity of 100%. (Bak and Mioshi, 2007) Cut-off scores of 75

and 88 / 100 have also been used.

The possibility that a patient with severe dementia could have a normal mini-mental state examination was noted during early clinical studies using the ACE-R (Bak and Mioshi, 2007) and has since been highlighted by other authors (Jones et al, 2010). During an early study using the original version of the Addenbrooke's Cognitive examination a cut-off score of 24 /30 on the mini-mental state examination missed dementia in up to 50% of cases as compared with a cut-off value of 83 on the ACE. The need to assess the patient further if a normal mini-mental state examination score is obtained despite clinical concern about cognitive function has been discussed. This is particularly important if the patient has a "high educational background" (Jones et al, 2010). A meta-analysis and results from the national dementia research register have shown the ACE-R to be a superior diagnostic tool to the mini-mental state examination. (Larner and Mitchell, 2014; Law et al, 2013)

In a review of 100 patients attending a memory clinic the ACE-R was found to be acceptable to the patients and to have "excellent diagnostic accuracy". (Larner, 2007) The author of this paper also used a lower cut-off value than the one suggested by the authors of the ACE-R. A cut-off of 75 / 100 showed a sensitivity and specificity of >0.9. The lower cut-off value was used to improve the specificity associated with cut-off values of 82 or 88 / 100. In a further study Larner also explored the use of the ACE-R over time and found it to be useful in assessing cognitive function over time. This was a very small sample though with only 23 patients completing more than one ACE-R. (Larner, 2006) In patients with established Alzheimer's disease however the mini-mental state examination has been shown to be as useful as the ACE-R in monitoring change in cognitive function. (Law et al, 2013) In patients with established Parkinson's disease the ACE-R has been shown to be useful at monitoring changes in cognitive function. (Ritman et al, 2013) The value of the ACE-R over time in a palliative care population has not been demonstrated.

Another study found that the ACE-R correlated well with quality of life of the patient when assessed by the carer and the patient. (McColgan et al, 2012)

Although only a small number of patients were recruited a study by Ahmed and colleagues showed the ACE-R to have a high discriminatory ability when used in elderly patients with normal and mildly impaired cognitive function. The ability of the ACE-R to detect mild cognitive impairment is relevant to this study. (Ahmed, de Jager, Wilcock 2011)

A systematic review of the ACE and ACE-R in the diagnosis of dementia (Crawford et al, 2011) highlights that education was found to affect the score obtained when using the ACE. This finding was noted in only one paper and other studies had failed to report on the educational attainments of the patients. This is one area of importance when interpreting the ACE and ACE-R which needs clarifying. Two of the nine studies included in this review described the internal consistency and convergent validity of the tools. No studies have yet looked at inter or intra-rater reliability. (Crawford et al, 2011)

There have been no studies published which report on the use of the ACE-R in a palliative care population.

2.5.17 Summary: Use of Addenbrooke's Cognitive Examination – Revised

The ACE-R provides a comprehensive assessment of cognitive function for the non-specialist clinician. It has been shown to be of excellent diagnostic accuracy in patients with dementia and it is able to provide information on particular aspects of cognitive function which enables the clinician to distinguish between types of dementia. The ACE-R has not been used in a palliative care population previously. There are some limitations to its use. The lack of evidence for inter-rater and intra-rater reliability is of obvious importance to this study given the number of staff assessing patients. The ACE-R is available on-line for anyone who wishes to use the tool. A cut-off score of 85 was used for this study. The Addenbrooke's Cognitive Examination has been included as Appendix K.

2.5.18 Subjective measure of cognitive function

A subjective measure of cognitive function was also felt to be very important in this study. Palliative medicine is a patient-centred speciality with an emphasis placed on the patient experience and opinion. The Bond and Lader scales were chosen in part due to previous experience of their use in patients who were prescribed strong opioids.

Bond and Lader published their experience and development of the analogue scales in 1974. (Bond and Lader, 1974) The authors describe the benefits of analogue scales. They are straightforward for patients to complete and allow for very fine discrimination by the patient. They enable small changes in mood and feelings to be detected when other tests would be likely to overlook the change. In their initial work sixteen 100 mm scales were given to 500 participants for completion. All subjects were healthy volunteers with an age range of 16 – 64 years (mean 27 years) (Bond and Lader, 1974).

The sixteen scales are anchored at each end by positive and negative descriptors of an emotion for example alert and drowsy, attentive and dreamy. The patients are asked to make a mark anywhere along the 100 mm line indicating the strength with which they respond to the emotion. Some of the scales are anchored with the positive emotion at the left hand side and some at the right hand side. The scales require inversion before analysis to ensure all are read from the left hand side. The scales can be divided into four groups.

- Mental sedation or intellectual impairment
- Physical sedation or bodily impairment
- Tranquillization or calming effects
- Other types of feelings or attitudes (from Bond and Lader, 1974)

The scales are completed by the patient on the basis of how they feel at the time of completion. They are sensitive to changes when used to assess response to medication for example. Several studies have used them to assess medication including butobarbitone sodium and flurazepam in healthy volunteers (Bond and Lader, 1974), temazepam in healthy volunteers (Begg, Drummond, Tiplady, 2001), mirtazapine and paroxetine in healthy subjects (Ruwe et al, 2001) and tetrahydrocannabinoid in healthy volunteers (Kleinloog et al, 2014). All the studies showed the Bond and Lader scales to be useful in assessing subjective responses of mood and feelings to medication.

The cognitive failures questionnaire provides a description of self-reported failures in perception, memory and motor function. Patients answer 25 questions that are rated from four (very often) to zero (never). The questions pertain to the six months prior to completion of the questionnaire and are designed to be ecologically relevant ie close to real life. (Broadbent et al, 1982) Wagle and Berrios suggested that the cognitive failures questionnaire may correlate highly with stress (Wagle and Berrios, 1999). This could make interpretation in a group of patients with life limiting illness more challenging. Although recognising the positive aspect of the tool's ecological validity Wagle and Berrios also questioned its ability to measure change (Wagle and Berrios, 1999).

A further option for the measurement of the subjective view of cognitive function would have been to use verbal rating scales or visual analogue scales anchored by terms relevant to this study. Klepstad and colleagues took this approach (Klepstad et al, 2002). They also relied on the cognitive function domain of the EORTC QLQ-30. As with the Likert scales used to assess opioid related side effects this approach would have offered relevance to the study objectives but lacked validity.

The EORTC QLQ-30 (Aaronson et al, 1993) was one of the tools used by the studies included in a review of objective and subjective cognitive impairment following chemotherapy for cancer (Hutchinson et al, 2012). Semi-structured interviews and the cognitive failures questionnaire were also commonly used in the included studies. Although the EORTC QLQ-30 is a well-validated and relevant tool the cognitive function

scale relies on the responses to two questions only. Overall therefore the Bond and Lader analogue scales offer a validated relevant assessment that has been shown to be responsive to change after the administration of medications.

2.5.19 Summary: Use of Bond and Lader analogue scales

The Bond and Lader analogue scales provide a contemporary view of the patient's mood and emotions. They are easy for patients to complete and have been used in other studies looking at the effect of medications on functioning. The Bond and Lader Scales have been included as Appendix L.

2.5.20 Assessing the nature of the pain

Clinicians are able to distinguish between types of pain based on the history and examination of the patient. Patient descriptors, distribution of the pain and associated features such as altered sensation or colour all guide the clinician and the management of the pain. For the purposes of research however a tool to provide quantitative evidence of the quality of the pain was required. The tools which have been developed are compared to clinician diagnosis of the presence of neuropathic pain. Clinician diagnosis is regarded as the gold standard for the diagnosis of neuropathic pain (Hardy et al, 2013).

PainDETECT, Self-completed Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS), Neuropathic Pain Questionnaire, Douleur Neuropathique en 4 questions (DN4) and ID – pain are all measures of neuropathic pain. In a review of the available screening tools Bennett et al outlined the tools and their sensitivity and specificity (Bennett et al, 2007). The tools share a reliance on the sensory changes which suggest neuropathic pain for example a description of electric shocks or shooting, pins and needles or tingling, and numbness. All the tools were validated in heterogeneous chronic non-cancer pain settings

and were compared with clinician diagnosis in the validation studies. All the tools result in a total score with defined cut-off values which indicate neuropathic pain. Only the LANSS (ie original version) has been looked at over time and in one study (Khedr et al, 2005) was shown to be responsive to the effects of treatment. There is little to discriminate between the tools in terms of sensitivity or specificity (Bennett et al, 2007). However the S-LANSS has recently been studied in a group of patients with cancer and this adds strength to our choice of tool (Hardy et al, 2013).

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) tool was developed in 2000 to facilitate early accurate diagnosis of pain with neuropathic features and thus ensure appropriate management. (Bennett, 2001) The S-LANSS was developed from the LANSS. It is designed to be completed by the patient ie Self-completed. (Bennett et al, 2005)

The S-LANSS comprises seven questions about their pain and patients are required to choose one of two possible answers which they feel best describes their pain and the symptoms and signs they experience. The answers are weighted and therefore contribute different values to the total score. A pain is regarded as neuropathic if the total score is above 12. The total score is 24.

The LANSS was developed in patients with chronic pain who were attending a pain management clinic in England. Patients with pain which was clearly either nociceptive or neuropathic were recruited. Patients with more complex pain were excluded. The study recruited eight patients with cancer out of a total of 60 patients. The exclusion of patients with mixed pain has clear implications for the use of the S-LANSS in patients with cancer pain as the majority of them have mixed pain and pure neuropathic pain is uncommon. The LANSS was shown to have good internal consistency. Some of the descriptors had better discriminant ability when the patient used them without prompt than when the LANSS required them to consider their pain. This applies to “burning” and “shooting” which are

often used by patients with neuropathic pain. Of note the LANSS has never been tested in a mixed pain population. (Bennett, 2001)

The S-LANSS was developed from the LANSS with the aim of making the tool more useful to researchers by removing the need for examination by a clinician. Instead the S-LANSS requires the patient to rub the affected area themselves and then answer questions. The S-LANSS was tested in a clinic and by postal survey. (Bennett et al, 2005) Patients were recruited from a pain management clinic in the UK and a primary care population in Scotland. The S-LANSS was found to have construct validity with each item contributing positively to the total score. It was shown to be acceptable to patients in both settings.

In a further study using the S-LANSS Bennett and colleagues explored the use of the S-LANSS in determining the extent to which pain is neuropathic. They found that an increasing S-LANSS score correlated with a clinicians rating of the likelihood that a pain was unlikely or very likely to be neuropathic. (Bennett et al, 2006) This is relevant to our study and patient population although again only a minority of those recruited had malignant disease (17 out of 200 recruited).

In 2013 Janet Hardy and colleagues undertook an analysis of a group of patients with cancer pain which was difficult to manage and who had been recruited for a study exploring the use of ketamine. Patients with mixed pain as reported by a clinician were excluded from the analysis so there is still a lack of evidence regarding the use of the S-LANSS in this group. However when the S-LANSS was used for patients with either neuropathic or nociceptive pain it was found to have “excellent diagnostic properties” (Hardy et al, 2013).

2.5.21 Summary: Use of the Self-completed Leeds Assessment of Neuropathic Symptoms and Signs

The S-LANSS provides a useful measure of the nature of the patient's pain with a score of 12 or greater indicting a neuropathic component to the pain. There is also some evidence that a higher S-LANSS score indicates that the pain is predominantly neuropathic and this may be helpful in this study where patients in the cancer pain group are likely to have pain of mixed character. The S-LANSS is included as Appendix M.

2.6 Summary of Chapter

This chapter has provided an outline of the research tools used to collect the quantitative data and to address the aims of the study pertaining to the assessment of opioid-related side-effects, impact of opioids on cognitive function and exploration of opioid-induced hyperalgesia. The qualitative research methodology used to explore the patient experience of having been opioid toxic is described in the relevant chapter of the thesis.

CHAPTER 3: CHARACTERISTICS OF THE PATIENTS RECRUITED FOR THE STUDY

3.1 Characteristics of the Patients Recruited

This chapter provides a description of the patients recruited for the study. Patients were recruited who were prescribed opioids for the management of either cancer or non-cancer pain or to manage substance misuse. Patients were also recruited who had non-cancer pain but were not prescribed opioids.

One hundred and two healthy volunteers were recruited as a control group for the quantitative sensory testing.

A total of 178 patients were recruited. Figure 2 shows the number recruited in each patient group and the number of assessments completed by patients in each patient group. Only the cancer pain patients were asked to complete three assessments. In part this was a pragmatic approach as many of the patients in the other groups were working or had other commitments which meant time was more limited for them. The cancer patients were in a more structured follow-up system which facilitated research assessments also. The patients with chronic non-cancer pain were attending specialist clinics less frequently and managing other personal commitments. In addition, more changes in medication were expected in the cancer pain group. The cancer pain patients welcomed the opportunity to continue with further assessments.

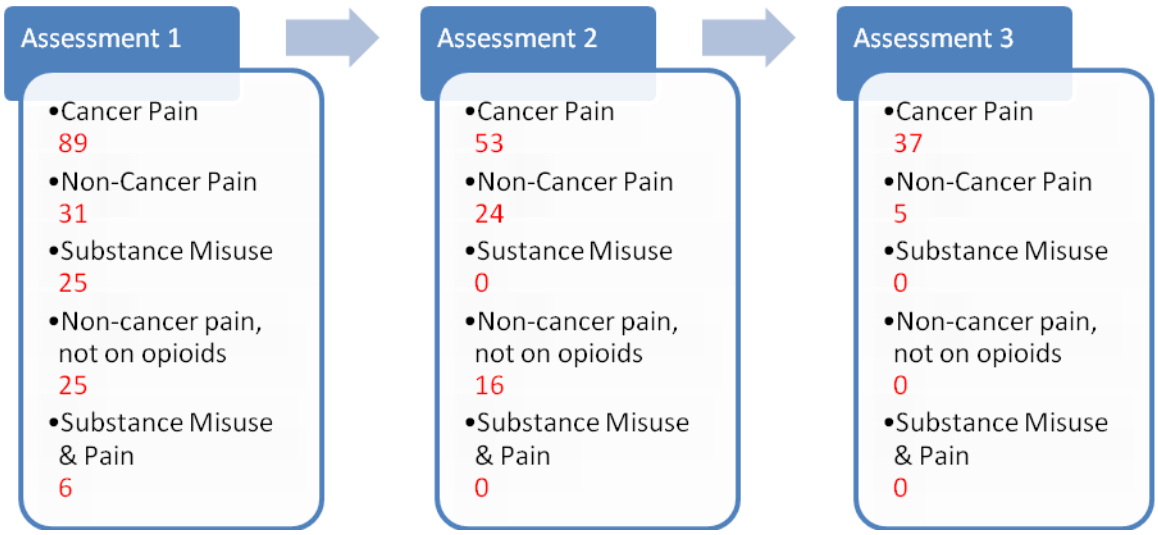
Less than ten patients declined to take part in the study after reading the patient information leaflet. A screening log was found to be impractical and inaccurate given the number of clinicians who could potentially refer patients to the study.

The first patient was recruited on 20th August 2010. The majority of patients were recruited by 16th January 2012. One patient (chronic non-cancer pain, not on opioids) was recruited on 23rd May 2014 just prior to full statistical analysis in order to complete the planned recruitment of 25 patients in the particular patient group.

Inevitably there was attrition in the cancer pain group. This is expected given the nature of the diagnoses. The attrition indicates that patients were becoming less well and less able to complete the assessments. It is important to note that their commitment to the study persisted. The recruitment of frailer patients could limit the extrapolation of results to a more general population who are under the care of a specialist palliative care team but at an earlier stage in their illness. However the study draws some conclusions based on the impact of opioids in all the different patient groups ie the effect is by drug not diagnosis. These results are more generalisable to other patients who are prescribed opioids.

Assessments were carried out every six weeks. In situations where this was not possible due to other patient commitments the assessment was carried out as close as possible to the planned date. In an ideal situation all patients would have had at least three research assessments however this proved easier for the cancer patients as they are followed up more frequently and in a more structured way compared to some of the chronic non-cancer pain patients who were attending specialist clinics more sporadically and in some cases also trying to return to work or care for families.

Figure 2: Number recruited in each patient group and the number of assessments completed by patients in each patient group



3.2 Demographics

Table 2: Characteristics of the patients recruited where n = 178

Age (years)		
Range	18 to 88	
Mean	55.5	
SD	13.9	
Gender		
Female	n = 84	47.2%
Male	n = 94	52.8%
Primary Cancer Site (n = 89)		
Breast	14	15.7
Myeloma	13	14.6
Lung	12	13.5
Prostate	9	10.1
Colorectal	6	6.7
Ovarian	6	6.7
Bladder	5	5.6
Pancreatic	4	4.5
Other	20	22.5

The table above shows the demographic details of the patients recruited for the study. Approximately equal number of males and females were recruited. The age of those recruited ranged from 18 years to 88 years with a mean of 55.5 years and a median of 57.0 years. Cancer diagnoses relating to only one patient have been grouped together in the "other" group. This group includes cervical, laryngeal and melanoma amongst others.

At assessment one 68 (76.4%) of the patients with a cancer diagnosis had metastatic disease; 12 (13.5%) had loco-regionally advanced disease and others had local malignant disease.

In addition to the patients who were recruited with cancer pain, four patients had a previous history of cancer but were known to be disease free at the time of recruitment to the study and their pain was due to non-cancer causes. The patients had a past diagnosis of bladder, breast, colorectal and oral cancers. For the purposes of the analysis these patients were included in the group with chronic non-cancer pain.

3.3 Pain History

The pain history for 151 patients is presented below. Twenty-five patients with a history of substance misuse were excluded from this analysis as they did not have a history of longstanding or significant pain. Two patients had data missing from the pain history and were also excluded from this analysis.

Table 3: Duration of pain in weeks for patients with cancer and non-cancer pain where n = 151

	Duration (weeks)				
	N	**Min**	**Mean**	**Median**	**Max**
Non-cancer	62	24	381	268	1700
Cancer	89	1	68	36	999
All	151	1	197	75	1700

The minimum duration of cancer pain is one week. Patients reported more than one pain so it may be that patients describing pain of short duration also had a pain which had present for a longer time. Patients with non-cancer pain had a much longer duration of pain in general. Three patients described pain lasting longer than 1000 weeks. These patients were managed without opioids at the time of the study.

Table 4: Pain types based on descriptors used by patient for 229 pain reports at first assessment where n = 151

	All		Non-cancer		Cancer	
	N	**Percent**	**N**	**Percent**	**N**	**Percent**
Bone	52	22.7	8	7.4	44	36.4
Central	1	0.4	1	0.9	-	-
Fibromyalgia	1	0.4	1	0.9	-	-
Inflammatory	9	3.9	2	1.9	7	5.8
Mixed	48	21.0	22	20.4	26	21.5
Musculoskeletal	17	7.4	12	11.1	5	4.1
Neuropathic	70	30.6	43	39.8	27	22.3
Post-surgical	5	2.2	5	4.6	-	-
Visceral	18	7.9	7	6.5	11	9.1
Other	8	3.5	7	6.5	1	0.8
All	229	100.0	108	100.0	121	100.0

Overall the most common pain types were bone, neuropathic and mixed pain types. 70 (30.6%) patients had neuropathic pain based on the descriptors they used. In the cancer pain group the number of patients with neuropathic pain was lower (n = 27, 22.3%) and the number of patients with bone pain was much higher than the patient group overall (n = 44, 36.4% in the cancer pain group). Interestingly, the number of patients reporting a mixed pain picture was almost the same in the two patient groups ie 20.4% in the non-cancer pain group compared to 21.5% in the cancer pain group.

Table 5 shows the frequency of pain occurring at each of the anatomical sites coded in the database. Many patients recorded pain at a site other than the originally identified sites but the provision of free text enables the sites to be identified as hips (n = 8), abdomen (n = 7), legs (n = 6), headache (n = 3) and ankles (n = 3). Other sites of pain included “joints”, “ear” and “whole body”.

Thirty-six patients reported pain at a site that was not an anatomical site coded for in the database. Twenty-two of these patients had cancer pain.

Table 5: The frequencies of reporting 28 pain sites in database list in descending order

Site	No. of patients reporting pain at site
Back	51
Other	36
Anterior abdominal wall	16
Anterior chest wall	15
Neck	13
Anterior knee	11
Posterior chest wall	10
Arm	8
Whole leg	8
Anterior thigh	7
Inguinal region	7
Shoulder	7
Face	6
Anterior lower leg	5
Scalp	4
Posterior abdominal wall	3
Plantar aspect of foot	2
Posterior thigh	2
Unknown	2
Axilla	1
Dorsum of foot	1
Fingers	1
Hands	1
Oral/mouth	1
Perineum	1
Posterior knee	1
Posterior lower leg	1
Upper limb stump	1

Table 6: Patient responses to questions 2 to 5 of the Brief Pain Inventory reflecting pain severity at assessment one where n = 146

	N	Mean	Median	Min	Max
Cancer Pain					
Worst pain in last 24 h	88	5.3	6	0	10
Least pain in last 24 h	89	2.5	2	0	8
Average pain	88	4.2	4	0	9
Current pain	89	3.0	2	0	9
Non-cancer Pain, On Opioids					
Worst pain in last 24 h	33	7.6	8	0	10
Least pain in last 24 h	33	4.4	4	0	10
Average pain	33	6.2	6	0	10
Current pain	33	5.5	6	0	10
Non-cancer, non-opioid					
Worst pain in last 24 h	24	5.9	6	0	10
Least pain in last 24 h	24	2.7	2	0	10
Average pain	24	4.9	5	0	10
Current pain	24	4.5	5	0	10
ALL three groups					
Worst pain in last 24 h	145	5.9	7	0	10
Least pain in last 24 h	146	3.0	3	0	10
Average pain	145	4.8	5	0	10
Current pain	146	3.8	4	0	10

The table above shows the responses to the questions from the Brief pain Inventory which describe the severity of the pain. In all patient groups there were patients who were pain-free with the analgesia they had been prescribed and patients who still had very severe pain despite analgesia. The patients with cancer pain have lower mean and median pain scores for each of the four questions than patients in the other two groups.

The table below shows the same information at assessment two. The patients with cancer pain have lower mean and median pain scores for each of the severity questions. A t-test was used to explore possible significance of the change in mean score between assessments one and two for each of the four measures in each group. Of the 12 t-tests only two were significant current pain in cancer patients had a p value of 0.026 and average pain in non-cancer pain group with a p value of 0.004.

Table 7: Patient responses to questions 2 to 5 of the Brief Pain Inventory reflecting pain severity at assessment two where n = 90

	N	Mean	Median	Min	Max
Cancer					
Worst pain in last 24 h	50	4.7	5	0	10
Least pain in last 24 h	50	2.3	2	0	8
Average pain	50	4.1	4	0	9
Current pain	50	2.0	1	0	8
Non-cancer					
Worst pain in last 24 h	24	6.9	7	3	9
Least pain in last 24 h	24	3.8	4	0	9
Average pain	24	5.4	6	2	8
Current pain	24	4.5	5	0	9
Non-cancer, non-opioid					
Worst pain in last 24 h	16	6.3	7	0	10
Least pain in last 24 h	16	3.5	3	0	10
Average pain	16	5.3	6	0	10
Current pain	16	4.4	5	0	10
ALL three groups					
Worst pain in last 24 h	90	5.6	7	0	10
Least pain in last 24 h	90	2.9	3	0	10
Average pain	90	4.7	5	0	10
Current pain	90	3.1	2	0	10

Table 8: Average of responses to seven questions about pain interference in Brief Pain Inventory at assessments 1 and 2 where n = 146 at assessment 1 (Ass 1) and n= 90 at assessment 2 (Ass 2)

	N missing	N	Mean	SD	Median	Min	Max
Cancer							
Interference score(Ass1)	24	65	6.0	2.0	6.3	1.0	9.4
Interference score(Ass2)	14	36	5.4	1.9	5.4	1.0	10
Non-cancer							
Interference score(Ass1)	3	30	7.4	2.0	7.4	2.6	10.0
Interference score(Ass2)	1	23	7.0	2.1	7.6	1.1	9.4
Non-cancer, non-opioid							
Interference score(Ass1)	3	21	5.1	2.3	4.8	2.0	10.0
Interference score(Ass2)	2	14	6.6	1.8	6.9	3.5	9.4
All three groups							
Interference score(Ass1)	30	116	6.2	2.1	6.4	1.0	10.0
Interference score(Ass2)	17	73	6.1	2.1	6.0	1.0	10.0

The mean of the interference scores is valid provided four or more of the seven questions has been answered. (Cleeland, 2009) The average score is therefore recorded as missing if fewer than three out of seven items have been scored. In the cancer pain group many of the patients did not manage to complete the Brief Pain Inventory. The patients found it difficult to recall a time at which they had not been in pain and also found it difficult to separate the effect of pain on activity from the effects of other symptoms they were experiencing. The patients with cancer pain who managed to complete the questions reported a lower level of interference due to pain than patients with non-cancer pain who were prescribed opioids. At assessment one the patients with non-cancer pain who were not prescribed opioids reported the lowest mean interference score. At assessment two the patients with cancer pain reported the lowest mean interference score.

There were no significant changes in mean pain interference scores between assessments one and two.

Table 9: Total morphine equivalent daily dose (MEDD) in the 24 hours prior to assessment and at each assessment by patient group where n = 147 at first assessment and patients with non-cancer pain who were not prescribed opioids and those with pain and substance misuse history were excluded

MEDD							
		N	**Mean**	**Median**	**SD**	**Min**	**Max**
Assessment No							
1	Cancer	89	191.7	130	209.2	20	1120
	Non-cancer	33	343.9	200	483.2	25	2440
	Substance misuse	25	412.2	300	367.0	36	1350
	All	147	263.4	160	328.8	20	2440
2	Cancer	51	215.7	140	210.2	40	1120
	Non-cancer	23	358.0	160	529.9	60	2400
	Substance misuse	1	80.0	80	.	80	80
	All	75	257.5	140	343.7	40	2400
3	Cancer	34	219.9	140	217.6	20	1120
	Non-cancer	5	268.0	220	196.3	60	520
	Substance misuse	1	92.0	92	.	92	92
	All	40	222.8	140	211.5	20	1120

The table above shows that patients with cancer pain are on lower total opioid doses than patients with non-cancer pain. The mean MEDD for patients with cancer pain was 191.7 mg and the mean MEDD for patients with non-cancer pain was 343.9 mg. Patients with a history of substance misuse are on the highest doses of opioid with a mean MEDD of 412.2 mg. For all patient groups the range of MEDDs was large and overall the MEDD range was from 20 mg to 2440 mg. From assessment one to three the mean MEDD

increased for the patients with cancer pain. For patients with non-cancer pain the mean MEDD decreased from assessment one to two. A further decrease was seen for the few patients in this group who had a third assessment also. Only one patient in the substance misuse group had more than one assessment. Patients who were on a dose of 20mg to 60mg MEDD were only eligible for a single assessment. Patients on 60mg MEDD were eligible for the follow-up assessments.

Table 10: Distribution of the total Morphine Equivalent Daily Dose (MEDD) for the four main opioids prescribed at assessment one where n = 167 and over the six months prior to recruitment to the study

Total MEDD dose (regular + breakthrough)							
		N	**Mean**	**Median**	**SD**	**Min**	**Max**
Opioids in last 24 hours	Fentanyl	23	266.5	129	409.4	20	1800
	Methadone	27	508.5	300	412.4	56	1500
	Morphine	65	121.9	90	101.0	10	480
	Oxycodone	52	227.9	150	256.3	16	1120
Opioids in last 7 days	Fentanyl	25	243.3	111	399.0	10	1800
	Methadone	26	539.6	375	422.5	56	1500
	Morphine	67	119.9	90	99.6	10	400
	Oxycodone	49	244.7	160	260.3	10	1120
Opioids in last 4 weeks	Fentanyl	19	338.5	150	502.7	20	1800
	Methadone	25	558.9	375	590.1	135	2813
	Morphine	71	114.7	80	98.4	10	400
	Oxycodone	45	232.8	160	250.2	16	1120
Opioids in last 2 months	Fentanyl	17	370.5	180	523.4	36	1800
	Methadone	23	511.3	263	432.6	135	1500
	Morphine	57	125.4	90	136.2	10	860
	Oxycodone	39	237.7	150	263.8	20	1120
Opioids in last 4 months	Fentanyl	18	347.9	155	515.6	36	1800
	Methadone	22	548.2	375	425.2	135	1500
	Morphine	51	144.3	100	133.7	10	600
	Oxycodone	29	224.3	150	221.9	40	1120
Opioids in last 6 months	Fentanyl	18	427.3	203	655.7	36	2400
	Methadone	22	501.1	413	363.4	90	1500
	Morphine	46	124.8	85	120.8	10	600
	Oxycodone	26	259.8	190	247.8	24	1120

In this study the four most frequently prescribed opioids were fentanyl, methadone, morphine and oxycodone. One hundred and sixty-seven reports were reviewed. The total MEDD dose reflects the regular opioid and the breakthrough opioid used in 24 hours. There will be patients for whom the opioids used regularly and as breakthrough will not be the same and this accounts for the number of reports being higher than the number of patients who were on opioids. Patients who are prescribed methadone are on a much higher MEDD than patients who are prescribed the other opioids. Patients who were prescribed oxycodone were on a higher MEDD than patients who were prescribed morphine. The range of MEDD for morphine is lower than for the other opioids with a maximum at any time point of 600 mg compared to a maximum MEDD of oxycodone of 1200 mg and a maximum MEDD of fentanyl of 2400.

Not all patients had been on opioids for six months. One hundred and twelve opioid reports were reviewed for the time pint six months prior to recruitment to the study. Over the six months prior top recruitment there had been an increase in the use of morphine and oxycodone. The mean MEDDs of the opioids prescribed did not vary much over the six months.

The same information was recorded at assessment two and is shown in the table below. At assessment two a shorter opioid history was recorded. The MEDD of methadone is much lower than at assessment one but is based on data from only two patients. The MEDD of morphine is higher at all the time points recorded at assessment two.

Table 11: Distribution of the total Morphine Equivalent Daily Dose (MEDD) for the four main opioids prescribed at assessment two where n = 85 and over the four weeks prior to recruitment to the study

		Total MEDD dose (regular + breakthrough)					
		N	**Mean**	**Median**	**SD**	**Min**	**Max**
Opioids in last 24 hours	Fentanyl	17	279.3	150	442.2	10	1800
	Methadone	2	65.6	66	13.3	56	75
	Morphine	33	150.9	110	127.2	10	600
	Oxycodone	33	242.7	160	239.2	20	1120
Opioids in last 7 days	Fentanyl	15	312.3	180	462.1	10	1800
	Methadone	2	65.6	66	13.3	56	75
	Morphine	32	160.3	130	134.1	50	600
	Oxycodone	35	235.0	160	233.2	6	1120
Opioids in last 4 weeks	Fentanyl	15	306.0	180	463.7	10	1800
	Methadone	2	65.6	66	13.3	56	75
	Morphine	36	155.1	100	140.4	10	600
	Oxycodone	31	261.6	160	232.7	40	1120

3.4 Summary of Patient Characteristics

This chapter describes the patients recruited for the study and provides information on the site and nature of the pain they were experiencing. The severity of the pain and the extent to which it interfered with their lives were described using the Brief Pain Inventory. The opioid drugs and doses prescribed have been outlined.

Neuropathic pain was the most common type of pain reported by patients who were involved in the study. Bone and mixed pain were also common. Back pain, pain of the

anterior abdominal wall or chest wall and neck pain were the most frequently reported sites of pain.

Cancer pain appeared better controlled amongst patients recruited and the patients reported lower scores on the Brief Pain Inventory. Not all the patients with cancer pain were able to complete the interference scores on the Brief pain Inventory. This could mean the patients did not feel the scores were relevant to them. At the time of assessment many patients commented that they had become used to living with pain every day. For many patients there were other reasons for example nausea, fatigue or altered body image which were also interfering with the activities and social relationships scored by the Brief pain Inventory. This is an interesting finding given that the Brief Pain Inventory was developed in cancer patients initially. It may be that this patient group was frailer in general than the patients included in the original studies. The patients with cancer pain who were able to complete the scores reported a lower level of interference by pain than patients in the other groups.

Patients with cancer pain were on lower morphine equivalent daily doses of morphine than patients with non-cancer pain. Patients with a history of substance misuse were prescribed the highest MEDDs. Methadone was the opioid with the highest MEDD. These two results are not unexpected based on clinical experience but may also reflect the liberal conversion used from morphine to methadone.

It is interesting to note the lower MEDD when morphine was prescribed compared to oxycodone. This may be due to patients having more complex pain and that the opioid was switched in an attempt to better control the pain. It is also interesting to note that the non-cancer patients on opioids were on higher opioid doses than the cancer patients. In addition the cancer patients had overall better pain control.

The substance misuse group appeared to be on the highest opioid doses; however they were on methadone, which has the added complication of conversion to oral morphine equivalent dose.

CHAPTER 4: OPIOID-RELATED SIDE EFFECTS

Outline of chapter:

- Explains the pathophysiology of opioid-related side effects and the management of the side effects.
- Describes the role of morphine and its metabolites in causing the opioid-related side-effects and introduces the role of genetics.
- Describes the burden of opioid-related side-effects in patients recruited for this study and compares the burden of side-effects between different patient groups.

4.1 Hypothesis

Patients who are prescribed strong opioids will experience side effects due to the opioids and the prevalence of side effects will vary according to the opioid and dose which has been prescribed

4.2 Aims

- To assess the opioid-related side effects of patients who are prescribed opioids for different indications
- To compare the prevalence of side effects between the different groups
- To explore possible factors which may contribute to the presence of side effects including choice of opioid, opioid dose and the effect of titration of the opioid

4.3 Introduction

Several authors have discussed the lack of convincing evidence about the side effects of opioids prescribed for pain including the prevalence of the side effects and the most effective approach to their management. Many of the trials of opioids do not have side effects as an end-point and in addition the trials may not be long enough to determine whether side effects persist and how this impacts on the patients. (McNicol, 2008) In an editorial in 2010 Colette Reid and Geoff Hanks reflected on the Opioid Conference held in Bristol in 2010 at which experts from Specialist Palliative Care across Europe presented several systematic reviews. The evidence regarding the use of opioids and the side effects they can cause was found to be lacking and the authors of the editorial concluded the "reviews must surely represent a "call to arms" for the palliative medicine research community." (Reid and Hanks, 2010)

It is well documented that not all pain will respond to opioids. Schrivers suggested up to 20% of cancer patients fall into this group. (Schrivers, 2007) For some patients it is the side effects caused by the opioids that limit the effectiveness. Up to 22% of patients who are prescribed opioid to manage chronic non-cancer pain will discontinue therapy due to intolerable side effects (McNicol, 2008). The side effects of the opioids and the subsequent limits on analgesia may cause poor quality of life. (Harris, 2008) In order to manage the side effects three main strategies are suggested: the dose of the opioid can be reduced if possible while also maintaining efficacy of analgesia; the opioid can be changed to an alternative; or further medication can be added to manage the side effects of the opioid. It is often the final strategy that is used by clinicians and this approach results in polypharmacy with the risk of further side effects, drug-drug interactions and poor compliance with an increasing number of medications (Harris, 2008; Glare, 2006; McNicol, 2008).

Most authors and reviews on the topic suggest that patients become tolerant to the side effects over time and particularly if the opioid is titrated slowly to achieve optimum analgesia (McNicol, 2008). Constipation is the exception to this and is known to persist over time (Fallon, 1999). Different patient groups may find different side effects more or

less tolerable for example McNicol describes sedation as being more acceptable to cancer patients than those with non-cancer pain who are more likely to have an expectation of being able to drive and work. (McNicol, 2008)

4.4 Specific Opioid-Related Side-Effects

4.4.1 Nausea and vomiting

Nausea and vomiting are frequently attributed to morphine. In cancer patients particularly it is likely that multiple factors are contributing to the symptoms of nausea and vomiting and it can be difficult for the clinician to determine how much of the symptom is due to the opioid. Studies suggest between ten and 40% of patients on opioids will have nausea and that it is most frequent at opioid initiation and titration. (McNicol, 2008) Harris provides a clear summary of the pathophysiology of nausea and the various receptors involved in nausea and vomiting. The chemoreceptor trigger zone, cerebral cortex, gastrointestinal tract and vestibular apparatus all have a role in opioid-induced nausea and vomiting. (Harris, 2008; Lawlor and Bruera, 1998; McNicol, 2008; Laugsand, Kaasa, Klepstad, 2011; Smith and Laufer, 2014) The chemoreceptor trigger zone (CTZ) lies in the floor of the fourth ventricle. At this site the blood-brain barrier allows many toxins to cross from the systemic circulation and the CTZ is therefore directly stimulated by drugs and toxins. (Porreca and Ossipov, 2009) The cortex probably has a role in modulating nausea and vomiting based on patents previous experiences. The vestibular apparatus is also directly stimulated by the opioids. Mu, delta and kappa opioid receptors are all found in the inner ear. (Porreca and Ossipov, 2009)

Nausea and vomiting may also be due to biochemical abnormalities such as hypercalcaemia, raised intracranial pressure due to primary or secondary brain tumours, or due to the oncological interventions being used to treat underlying malignancy. Patients with non-malignant disease may experience nausea and vomiting as a result of the chronic

pain, following surgery or investigations, and as a side-effect of other drugs they are prescribed alongside the opioid.

In patients with chronic non-cancer pain gastrointestinal side effects are one of the most common reasons for discontinuing opioids (Porreca and Ossipov, 2009). The prevalence of nausea and vomiting in patients with non-cancer pain who are prescribed opioids varies from 10 to 50% (Porreca and Ossipov, 2009).

Haloperidol and metoclopramide are both frequently used first line in the management of opioid-induced nausea and vomiting. Given the multiple receptors involved it is not unusual to require more than one anti-emetic to control severe nausea and vomiting and non-pharmacological measures may also be helpful. (Harris, 2008; Lawlor and Bruera, 1998; McNicol, 2008; Laugsand, Kaasa, Klepstad, 2011)

In a systematic review of the "Management of opioid-induced nausea and vomiting in cancer patients" Eivor Laugsand and colleagues reviewed the available evidence with the stated objective of providing guidance on the use of anti-emetics. (Laugsand, Kaasa, Klepstad, 2011) They identified 56 papers which described the management of opioid-induced nausea and vomiting. Many of the studies identified were of limited relevance due to patient group for example patients prescribed spinal opioid or were of poor methodology for example small sample size or retrospective case note review. In many of the included studies the effect on nausea and / or vomiting was the secondary or even tertiary outcome of the study. Although there was some evidence to support the use of metoclopramide, tropisetron and olanzapine the evidence was not sufficiently to make recommendations on their use. Evidence is also lacking for the other strategies that are available for the management of opioid –induced nausea and vomiting in patients with cancer such as change of opioid and change of route of administration.

4.4.2 Constipation

Opioid-related constipation also occurs due to several mechanisms (Fallon, 1999, Choi and Billings 2002; Yuan and Foss 2000). Opioids cause delayed gastric emptying and reduced peristalsis. The tone of the ileocaecal valve and the anal sphincter tone are increased. There is evidence of disrupted defaecation reflex although this is probably most relevant in patients who are prescribed opioids and have pelvic malignancy. Patients are also likely to be on other constipating drugs such as anti-cholinergics and to be less mobile than previously due to pain or other co-morbidities. (Fallon, 1999; Choi and Billings 2002) Constipation in rats has been shown to occur at 25% of the opioid dose required to cause analgesia (Yuan and Foss, 2000). The combination of constipation, increased gastric reflux (due to delayed gastric emptying) and bloating are known as "opioid bowel dysfunction" (McNicol, 2008; Choi and Billings 2002; Becker, Galandi, Blum 2007) and are thought to occur in 25 to 50% of patients with cancer and 15 to 40% of those with non-cancer pain (McNicol, 2008). As constipation is unlikely to resolve with ongoing opioid therapy it is recommended that patients are commenced on regular laxatives (Harris 2008; McNicol, 2008).

Constipation can be distressing for patients and cause bloating, abdominal pain, nausea and vomiting (Choi and Billings, 2002). As well as the impact on the patient, the effect on healthcare services has been recognized with a need for nursing and medical time and sometimes hospital admission required to manage constipation. (Fallon, 1999)

There are opioid receptors in the gastro-intestinal tract but opioids also have a central role in mediating constipation via an effect on the autonomic nervous system (Yuan and Foss 2000) The opioid receptors in the gastrointestinal tract can be inferred to have an effect on gut function from the finding that loperamide – an opioid which does not cross the blood-brain barrier – can be used to manage diarrhoea. (Yuan and Foss, 2000) The presence of opioid receptors in the bowel provides a therapeutic opportunity and the use of peripherally acting opioid antagonists has developed. Prescribing a low dose of the opioid antagonist naloxone will reverse the gastrointestinal effects of the opioid without adversely affecting the analgesia. Methylnaltrexone is another opioid antagonist which has the additional

benefit of not crossing blood brain barrier so there is no risk of reduced analgesia effect. (Harris, 2008; Yuan and Foss 2002) It has been shown to reverse opioid induced slowing of smooth muscle in laboratory situations. (Yuan and Foss, 2000) There is evidence to support the role of the peripherally acting opioid antagonists in mediating constipation in those with cancer pain (Becker, Galandi, Blum 2007). In palliative care patients with an estimated prognosis of less than six months and who had not had a bowel movement for 48 hours, methylnaltrexone resulted in a bowel movement in approximately one hour with no loss of analgesia. (Gevirtz, 2007)

4.4.3 Other Opioid-Related Side –Effects

Respiratory depression and difficulty passing urine are usually associated with acute use or accidental overdose of opioids (Lawlor and Bruera 1998) and have not been considered further in this study. Opioid-induced itch is described by 1% of patients who are prescribed opioids. The use of spinal opioids causes pruritus to worsen. Itch is thought due to histamine release or activation of serotonin receptors. Dry mouth is a common side-effect and is also usually attributed to several different causes including opioids. Salivary gland pathology, post radiation damage and other drugs such as the anticholinergics are likely to be contributing. It seems the dry mouth may be due to an anti-muscarinic effect of opioids. Dry mouth appears to persist over time and the patient does not become tolerant. (McNicol 2008) Vanegas et al reported that in their experience methadone caused less dry mouth than morphine. (Vanegas et al, 1998)

There is no evidence to guide the management of myoclonus due to opioids. Most clinicians would try to reduce the dose if this could be achieved while maintaining pain control, alternatively a change of opioid may be required. Case reports and case series in the literature did not provide any conclusive evidence. (Stone and Minton, 2010)

Although opioid switching to manage the adverse effects of opioids is common in clinical practice there is little evidence to support this. While individuals may respond differently to a change of opioid it is also possible that the improved side effect profile is due to the placebo effect. (Dale, Moksnes, Kaasa, 2010)

4.5 Importance of Opioid Metabolites

Morphine is metabolized in the liver to several metabolites. The two most important metabolites are morphine-6-glucoronide (M6G) and morphine-3-glucoronide (M3G). Between 44 and 55% of morphine is metabolized to M3G and 9- 10% is metabolized to M6G. 8 – 10% of morphine is excreted unchanged in the urine (Andersen, Christrup, Sjogren 2003). M6G is the active metabolite which binds with the mu opioid receptor and is thought to contribute much of the analgesic effect of morphine. M3G does not bind at the mu opioid receptor (Faura et al, 1998) and its role in the clinical effects of morphine has been debated (Gretton et al, 2013; Andersen, Christrup, Sjogren 2003). It was previously thought to be responsible for the myoclonus and hyperalgesia although the evidence is mainly from animal studies and is not conclusive. (Andersen, Christrup, Sjogren 2003) In humans when there was an association between hyperalgesia, myoclonus, allodynia and M3G there was also a high concentration of the parent drug. (Andersen, Christrup, Sjogren 2003)

Morphine is also metabolized at extra-hepatic sites but these are of less significance. Extra-hepatic sites of metabolism include kidney, gastrointestinal tract and brain. (Andersen, Christrup, Sjogren 2003) Liver dysfunction causes a reduction in glucuronidation of morphine, although it seems likely that the extrahepatic sites of metabolism become more prominent in this situation, and thus prolonged action of the parent drug. In renal impairment morphine and its metabolites will accumulate. (Andersen, Christrup, Sjogren, 2003)

Several groups have studied the role of morphine and its metabolites in causing opioid side effects. The evidence is inconsistent though. In a systematic review published in 1998 Faura and colleagues reviewed 57 studies and based their conclusions on 1232 patients. Although the systematic review was based on a large sample size, the included papers were on the whole small studies. The mean sample size was just 12 patients with a range of one to 136 patients. The review highlights the difficulties in conducting the studies needed to explore the relationship between serum concentrations of morphine and its metabolites and opioid related side effects. (Faura et al, 1998)

Two more recent studies are discussed in more detail. They are based on larger samples and better define the clinical situation – a further flaw in other studies that have been published.

In 2003 Pal Klepstad published the findings of a study which recruited 300 patients the majority of whom (n = 263) were on oral morphine. The remainder of patients were on subcutaneous morphine or a combination of routes (n = 2). The median dose of morphine orally was 80 mg / 24 hours which was lower than the dose taken subcutaneously which was 110mg / 24 hours. The study divided patients into treatment failures and successes. The treatment failures were those patients with opioid-related side effects and inadequately relieved pain. The study did not find any association between level of pain, nausea, constipation or cognitive impairment and the concentrations of plasma morphine, M6G and M3G. (Klepstad et al, 2003) The authors recognize the difficulty in addressing the contribution of morphine and metabolite concentrations to both pain and adverse effects when there are so many variables contributing especially in cancer patients.

Sophie Gretton and her colleagues conducted a prospective study in 2013 and recruited patients with cancer related pain who were on oral morphine. On the basis of pain control and the presence of side effects they divided the group into patients who were responders and those who were non-responders. Blood was taken from the patients between two and four hours following a dose of morphine. They recruited 228 patients and analysed blood from 212 of those recruited. Although this study recruited larger numbers than many other

palliative care studies the number of patients with the side effects was very small. The authors suggested that central opioid effects are associated with a higher ratio of morphine metabolite to morphine ratio. However comments and conclusions on the association between morphine metabolite and morphine ratios are based on only seven patients with myoclonus and thirteen patients with severe confusion and / or hallucinations. Forty-two patients had severe drowsiness which represented 20% of the study group and are therefore more likely to represent real rather than chance findings. (Gretton et al, 2013)

The role of genetics in opioid-related side effects was explored in a study which was completed by 114 twin pairs. The twin pairs received intravenous alfentanil and then saline infusion (or vice versa) in a randomized double-blind placebo-controlled study. The authors found that respiratory depression, nausea and a disliking for the opioid were all inherited traits. Sedation, itch and a liking for the drug were all strongly associated within family units which may indicate inherited traits but may also be due to the twins having been exposed to the same environmental influences and experiences. Although the study is of direct relevance to the use of opioids in the acute setting for example in the perioperative setting this study shows that well conducted studies are possible to address the cause of opioid effects and to assess to what extent genetics determines how patients respond to opioids. (Angst et al, 2012; Fillingim, 2012)

Pharmacogenomic studies have identified some possible polymorphisms that may be contributing to the development of side-effects. These include genes which code for proteins involved in opioid receptor binding, transport of opioids and pathways of nausea and vomiting. (Smith and Laufer, 2014) However none of the pharmacogenomics is yet ready to translate into clinical practice.

4.6 Patient Acceptance of Opioids and Side effects

A qualitative study recruited eleven patients who were reluctant to increase the dose of opioid to improve management of their cancer pain and explored the reasons for the

reluctance. The patients were part of an earlier study evaluating a pain management intervention. Despite receiving education about their pain and the opioids the patients declined to take a higher dose. When the nurses who were delivering the education spoke with patients the interviews were recorded and transcribed. The research team recognised that within these interviews was a significant data which explained why patients did not always want to titrate their analgesia. The interviews were conducted as part of the education programme. They were therefore clinical interactions and not research interviews. The main reasons given were fear of addiction to opioids and previous personal history of misuse of prescription drugs, strongly held beliefs about drugs and previous experience of severe opioid-related side effects. Although the numbers were small and the interviews had been conducted with a clinical purpose which may have limited their research potential the themes extracted from the data are strong and clinically relevant. (Schmacher et al, 2002)

In a study which explored patient satisfaction with analgesia in acute pain secondary outcomes from a Randomised Controlled Trial were used. The methodology was one which could possibly be adapted for other palliative care research questions although there are intrinsic disadvantages for example the inability to explore fully some of the possible confounding factors. Although the patients had acute pain, the findings may still be relevant as the outcomes are about decision-making and acceptability of analgesia rather than the efficacy of the analgesic. The study showed that patients take into account several aspects when making decisions about analgesia including pain control and side effects of drugs. . The patients found the opioid-induced symptoms of nausea and fatigue were the least acceptable. (Jensen et al, 2004)

In a study designed to measure the acceptability of side effects to patients who have acute or chronic pain and require opioids to manage the pain Razmic Gregorian and colleagues also found that nausea, and in this study vomiting, were the least acceptable side effects to patients. Both professionals and patients placed significant value on the presence of side effects when choosing opioids to manage pain. In the study the patients with both chronic and acute pain had previous experience of opioid-related side effects and were experiencing two or more side effects at the time of the study. (Gregorian et al, 2009)

4.7 Methods

As in other parts of the study patients were recruited from three different clinical groups so that the prevalence of side effects in each group could be compared. Patients with chronic pain who were not prescribed a strong opioid were also recruited in order to provide a further comparison. Patients with cancer pain who were prescribed 60mg of morphine or an equivalent daily dose of an alternative opioid were invited to complete the assessments on up to three occasions. The majority of patients with chronic non-cancer pain who were prescribed an opioid and those who were not prescribed an opioid completed the assessment on two occasions. Patients with a history of substance misuse completed only one series of assessments.

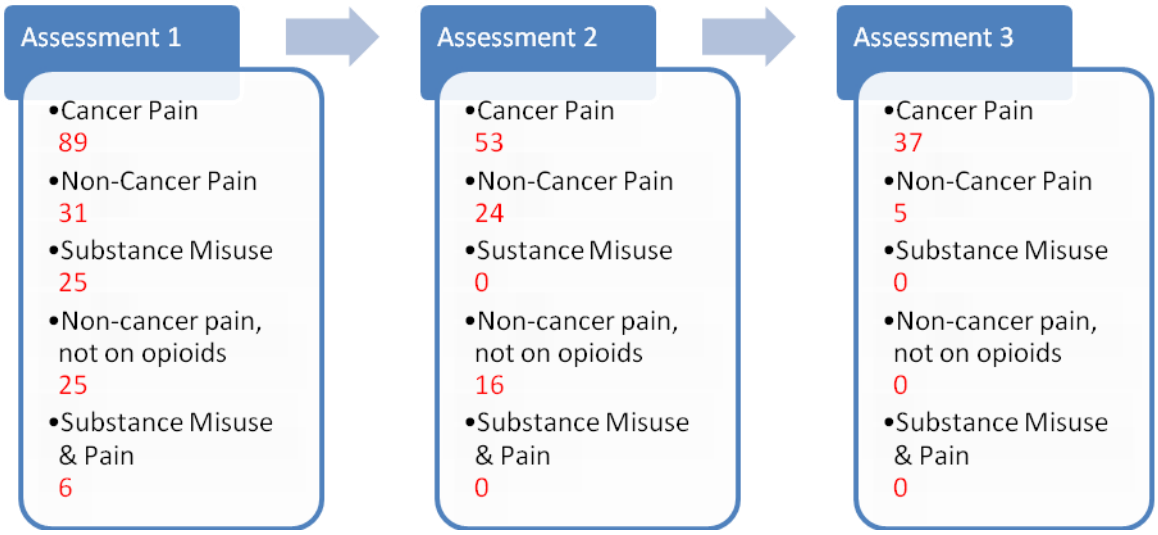
After providing information about their pain and opioid history patients were asked about the presence and severity of symptoms. Likert scales had been constructed for the purpose of the study. Patients were asked to reflect on the week prior to the assessment and record whether the symptoms had been present very often, quite often, occasionally, very rarely or never. Five statements asked the patients about the symptom using non-technical language. Many patients read and completed the scales themselves so it was important to describe the symptom rather than use technical names such as myoclonus or hallucinations. The results have been presented using the questions that were put to participants. The symptoms included were nausea, vomiting, dry mouth, myoclonus and hallucinations. A member of the research team was always with the patient to clarify questions as needed. Quintiles of opioid dose were used to enable a descriptive presentation of frequency of symptoms. The symptoms were further presented as a distribution of the frequency of each symptom according to dose increase or reduction. Spearman rank correlations were used to explore the possible association between opioid dose or titration of the opioid and the frequency of the side effect.

The patients then completed the questions about the presence and severity of constipation. The constipation score includes clear instructions for patients and again they are asked to think about the week prior to the assessment. There are three questions, each with statements from which the patient chooses the one they most identify with. Two of the

questions have three options and the third question has four possible answers. The questions are scored from zero to two or three and a maximum score of seven is obtained. A score of three or less signifies constipation. Patients were identified as constipated or not constipated after completion of the score. Basic descriptive statistics including mean, standard deviation and standard error were used to explore possible association between opioid dose and titration and constipation status.

4.8 Results

Figure 3: Number recruited in each patient group and the number of assessments completed by patients in each patient group



The presence of opioid related side effects was assessed at each time point in the study schedule. 178 patients were recruited and completed at least one set of assessments. The data for patients with substance misuse and chronic pain has been excluded from the analyses here due to the very small numbers recruited. The data for these patients has been presented separately in the chapter "Patients with Pain and a History of Substance Misuse".

Ninety patients completed two assessments. The numbers from the different patient groups who completed each assessment have been detailed in the chapter “Patient Characteristics”.

Table 12: Distribution of symptoms at assessment 1 by quintiles of dose in last 24 hours where n=147

		Never	Very rarely	Occasion-ally	Quite often	Very Often	All
	N	Percent	Percent	Percent	Percent	Percent	Percent
	Nausea						
Quintiles of dose in last 24 hours							
1	29	48	31	3	14	3	100
2	29	34	28	31	7	0	100
3	29	41	28	21	10	0	100
4	30	40	23	10	17	10	100
5	30	33	23	23	10	10	100
	Vomiting						
Quintiles of dose in last 24 hours							
1	29	76	10	14	0	0	100
2	29	76	17	7	0	0	100
3	29	79	17	3	0	0	100
4	30	73	7	10	7	3	100
5	30	50	20	20	10	0	100
	Dry mouth						
Quintiles of dose in last 24 hours							
1	29	14	3	31	31	21	100
2	29	10	14	24	10	41	100
3	29	14	7	21	24	34	100
4	30	23	7	10	10	50	100
5	29	21	7	31	17	24	100
	Myoclonus						
Quintiles of dose in last 24 hours							
1	29	59	10	17	14	0	100
2	29	45	14	14	24	3	100
3	29	38	14	31	10	7	100
4	30	30	13	20	13	23	100
5	30	27	3	37	23	10	100
	Hallucinations						
Quintiles of dose in last 24 hours							
1	29	93	0	3	3	0	100
2	29	72	7	7	10	3	100
3	29	72	14	7	3	3	100
4	30	60	10	17	3	10	100
5	30	80	3	17	0	0	100

There are 147 patients thus the first three quintiles each represent 29 patients, and last two quintiles represent 30 patients.

At the lowest doses of opioid represented by the first quintile 52% of patients reported nausea in the week prior to assessment. The percentage of patients reporting nausea remained at above 50% in all quintiles. At the highest doses of opioid 66% of patients reported nausea and 20% of patients reported nausea had been present either quite often or very often. It is interesting to note that the prevalence of nausea is similar in the three quintiles representing higher doses of opioid.

Overall the presence of vomiting is less than the presence of nausea in all quintiles of opioid dose. The percentage of patients reporting vomiting in the last week is highest in the final quintile. However there are still 20 to 50% of patients in each quintile reporting vomiting in the week prior to assessment representing significant symptom burden.

The percentages of patients reporting dry mouth are the highest of all symptoms documented. Between 70 and 83% of patients reported dry mouth at least occasionally in the week prior to assessment.

Myoclonus is present at least occasionally in 31% of patients in the lowest dose quintile and this rises to 70% of patients in the highest dose quintile.

Hallucinations are the least prevalent of all the symptoms. In the fourth quintile 10% of patients reported hallucinations very often. This was a higher percentage than reported hallucinations at the same frequency at the highest dose of opioid.

Table 13: Distribution of symptoms at assessment two by quintiles of dose in last 24 hours where n=74

		Never	Very rarely	Occasion-ally	Quite often	Very Often	All
	N	Percent	Percent	Percent	Percent	Percent	Percent
	Nausea						
Quintiles of dose in last 24 hours							
1	15	27	33	40	0	0	100
2	15	67	20	7	7	0	100
3	15	27	20	47	7	0	100
4	15	27	33	20	7	13	100
5	14	36	7	21	21	14	100
	Vomiting						
Quintiles of dose in last 24 hours							
1	15	67	27	7	0	0	100
2	15	80	13	7	0	0	100
3	15	67	20	13	0	0	100
4	15	53	27	13	0	7	100
5	14	50	14	21	7	7	100
	Dry mouth						
Quintiles of dose in last 24 hours							
1	15	7	20	33	13	27	100
2	15	13	7	20	13	47	100
3	15	7	7	27	27	33	100
4	15	7	13	20	27	33	100
5	14	14	21	14	14	36	100
	Myoclonus						
Quintiles of dose in last 24 hours							
1	15	53	13	20	0	13	100
2	15	53	13	13	7	13	100
3	15	33	20	20	20	7	100
4	15	33	13	33	20	0	100
5	14	21	36	29	14	0	100
	Hallucinations						
Quintiles of dose in last 24 hours							
1	15	73	13	7	0	7	100
2	15	93	0	7	0	0	100
3	15	87	0	13	0	0	100
4	15	80	13	0	7	0	100
5	14	71	14	7	7	0	100

The numbers in table 13 are much smaller than in table 12. Again they represent quintiles of opioid dose and are based on patients prescribed opioids for cancer and non-cancer pain and substance misuse. At assessment two, nausea is more frequent in four of the five quintiles than at assessment one. Dry mouth remains the most frequently reported symptom. Myoclonus has also persisted with 53% of patients in the fourth quintile reporting myoclonus at least occasionally and 43% of patients in the fifth quintile reporting the symptom at the same frequency. Hallucinations remain the least frequent symptom overall.

Table 14: Spearman rank correlations of opioid dose in last 24 hours at assessment 1 with side effects as measured on Likert scales at assessment 1 where n = 147

	Side effect	Correlation with dose in last 24 hours	P value
Cancer (N=89)	Nausea	0.003	0.974
Cancer (N=89)	Vomiting	-0.001	0.996
Cancer (N=89)	Dry mouth	-0.046	0.667
Cancer (N=89)	Myoclonus	0.252	0.017
Cancer (N=89)	Hallucinations	0.131	0.220
Non- Cancer pain (N=33)	Nausea	0.331	0.060
Non- Cancer pain (N=33)	Vomiting	0.406	0.019
Non- Cancer pain (N=33)	Dry mouth	0.198	0.269
Non- Cancer pain (N=33)	Myoclonus	0.004	0.982
Non- Cancer pain (N=33)	Hallucinations	0.142	0.431
Substance misuse (N=25)	Nausea	0.554	0.004
Substance misuse (N=25)	Vomiting	0.675	0.000
Substance misuse (N=25)	Dry mouth	0.249	0.240
Substance misuse (N=25)	Myoclonus	0.659	0.000
Substance misuse (N=25)	Hallucinations	0.142	0.499
All (N=147)	Nausea	0.155	0.060
All (N=147)	Vomiting	0.220	0.007
All (N=147)	Dry mouth	-0.026	0.752
All (N=147)	Myoclonus	0.278	0.001
All (N=147)	Hallucinations	0.125	0.132

In the results table 14 a positive correlation means worse symptoms with higher dose and a negative correlation means better symptoms with higher dose of opioid.
In the substance misuse group of patients there are the strongest correlations in particular between higher dose and more severe nausea, vomiting and myoclonus. These correlations are statistically significant.

In the non-cancer patients there is some correlation between higher dose of opioid and severity of nausea and vomiting reported by the patients but this is less than in the substance misuse group. Only the correlation between higher dose of opioid and vomiting is statistically significant however.

In the cancer patients there is least correlation between higher dose of opioid and severity of symptoms. Myoclonus shows the strongest correlation with opioid dose and this is statistically significant with a p value of 0.017.

When all the data was analysed together there are weak correlations between higher dose of opioid and severity of symptoms however two of the correlations are statistically significant – vomiting and myoclonus. Dry mouth is a negative correlation suggesting this symptom improves with higher dose of opioid.

Table 15: Spearman rank correlations of opioid dose in last 24 hours at assessment two with side effects as measured on Likert scales at assessment two where N=74

	Side effect	Correlation with dose in last 24 hours	P value
Cancer (N=50)	Nausea	-0.001	0.994
Cancer (N=50)	Vomiting	0.096	0.506
Cancer (N=50)	Dry mouth	-0.036	0.806
Cancer (N=50)	Myoclonus	0.156	0.279
Cancer (N=50)	Hallucinations	0.074	0.609
Non- Cancer pain (N=23)	Nausea	0.479	0.021
Non- Cancer pain (N=23)	Vomiting	0.399	0.059
Non- Cancer pain (N=23)	Dry mouth	0.078	0.724
Non- Cancer pain (N=23)	Myoclonus	0.047	0.832
Non- Cancer pain (N=23)	Hallucinations	-0.009	0.966
All (N=74)	Nausea	0.194	0.098
All (N=74)	Vomiting	0.221	0.059
All (N=74)	Dry mouth	-0.005	0.966
All (N=74)	Myoclonus	0.160	0.172
All (N=74)	Hallucinations	0.059	0.617

The "All patients" group includes the only patient with substance misuse to have had follow up assessments. Two patients had follow up assessments but had missing data from the Likert scales and are therefore excluded from this analysis (one patient with non-cancer pain and one patient with cancer pain).

In this analysis the strongest correlation between symptom severity and opioid dose is with nausea in patients with non-cancer pain. The Spearman rank correlation is 0.479 and is statistically significant with a p value of 0.021. As in the previous analysis dry mouth has a negative correlation with opioid dose but the correlation is weaker in this analysis.

Table 16: Spearman rank correlations of titration in last 7 days with side effects at assessment one as measured on Likert scales where n = 147 patients

	Side effect	Correlation with dose change between 7 days ago and last 24 hours	P value
Cancer (N=89)	Nausea	0.073	0.494
Cancer (N=89)	Vomiting	-0.093	0.383
Cancer (N=89)	Dry mouth	0.114	0.289
Cancer (N=89)	Myoclonus	0.041	0.703
Cancer (N=89)	Hallucinations	0.120	0.263
Non- Cancer pain (N=33)	Nausea	-0.023	0.901
Non- Cancer pain (N=33)	Vomiting	0.044	0.806
Non- Cancer pain (N=33)	Dry mouth	-0.056	0.758
Non- Cancer pain (N=33)	Myoclonus	-0.003	0.985
Non- Cancer pain (N=33)	Hallucinations	0.080	0.657
Substance misuse (N=25)	Nausea	0.155	0.461
Substance misuse (N=25)	Vomiting	-0.064	0.761
Substance misuse (N=25)	Dry mouth	0.281	0.184
Substance misuse (N=25)	Myoclonus	0.091	0.666
Substance misuse (N=25)	Hallucinations	-0.143	0.496
All (N=147)	Nausea	0.070	0.396
All (N=147)	Vomiting	-0.054	0.517
All (N=147)	Dry mouth	0.101	0.223
All (N=147)	Myoclonus	0.038	0.645
All (N=147)	Hallucinations	0.067	0.422

In the analysis above a positive correlation means an increased dose of opioid in the last seven days was associated with worse symptoms and a negative correlation means an increased dose of opioid in the last seven days was associated with better symptoms.

The analysis shows there is no clear correlation between recent titration of the dose of opioid and the severity of symptoms. The correlations are all very weak with values close to zero. None of the correlations achieve statistical significance though.

Some of the correlations are negative indicating the symptom actually improved when the dose of opioid increased. Several symptoms show negative correlation in the different patient groups. Only vomiting shows a negative correlation in the analysis of all patients together.

Table 17: Spearman rank correlations of opioid dose titration in the last 4 weeks with side effects as measured on Likert scales where n = 147

	Side effect	Correlation with dose change between 4 weeks ago and last 24 hours	P value
Cancer (N=89)	Nausea	-0.044	0.690
Cancer (N=89)	Vomiting	-0.047	0.669
Cancer (N=89)	Dry mouth	0.045	0.681
Cancer (N=89)	Myoclonus	0.044	0.685
Cancer (N=89)	Hallucinations	0.041	0.706
Non- Cancer pain (N=33)	Nausea	-0.033	0.854
Non- Cancer pain (N=33)	Vomiting	0.131	0.468
Non- Cancer pain (N=33)	Dry mouth	-0.062	0.734
Non- Cancer pain (N=33)	Myoclonus	-0.140	0.438
Non- Cancer pain (N=33)	Hallucinations	0.018	0.920
Substance misuse (N=25)	Nausea	0.033	0.877
Substance misuse (N=25)	Vomiting	0.012	0.954
Substance misuse (N=25)	Dry mouth	0.172	0.421
Substance misuse (N=25)	Myoclonus	0.201	0.336
Substance misuse (N=25)	Hallucinations	-0.164	0.433
All (N=147)	Nausea	-0.049	0.561
All (N=147)	Vomiting	-0.009	0.917
All (N=147)	Dry mouth	0.025	0.769
All (N=147)	Myoclonus	0.039	0.640
All (N=147)	Hallucinations	-0.021	0.805

In the analysis above a positive correlation means an increased dose of opioid in the last seven days was associated with worse symptoms and a negative correlation means an increased dose of opioid in the last seven days was associated with better symptoms.

All the correlations between titration of the opioid dose over the four weeks prior to assessment and the symptoms reported by the patients are weak. None achieve statistical

significance. Some of the correlations are negative. In the "All patient" group, nausea, vomiting and hallucinations are all negative associations but with values very close to zero indicating a weak relationship.

Table 18: Spearman rank correlations of opioid dose titration in the last 6 months with side effects as measured on Likert scales where n = 147

	Side effect	Correlation with dose change between 6 months ago and last 24 hours	P value
Cancer (N=89)	Nausea	0.143	0.337
Cancer (N=89)	Vomiting	0.050	0.741
Cancer (N=89)	Dry mouth	-0.090	0.548
Cancer (N=89)	Myoclonus	0.274	0.062
Cancer (N=89)	Hallucinations	-0.039	0.765
Non- Cancer pain (N=33)	Nausea	0.099	0.583
Non- Cancer pain (N=33)	Vomiting	0.148	0.410
Non- Cancer pain (N=33)	Dry mouth	0.037	0.837
Non- Cancer pain (N=33)	Myoclonus	-0.070	0.699
Non- Cancer pain (N=33)	Hallucinations	0.055	0.762
Substance misuse (N=25)	Nausea	-0.003	0.990
Substance misuse (N=25)	Vomiting	-0.072	0.749
Substance misuse (N=25)	Dry mouth	-0.041	0.857
Substance misuse (N=25)	Myoclonus	0.161	0.475
Substance misuse (N=25)	Hallucinations	-0.265	0.233
All (N=147)	Nausea	0.103	0.303
All (N=147)	Vomiting	0.045	0.656
All (N=147)	Dry mouth	-0.022	0.824
All (N=147)	Myoclonus	0.176	0.077
All (N=147)	Hallucinations	-0.053	0.600

In the analysis a positive correlation means an increased dose of opioid in the last seven days was associated with worse symptoms and a negative correlation means an increased dose of opioid in the last seven days was associated with better symptoms.

The correlations are generally weak with values close to zero. Several of the correlations are negative suggesting symptoms improved as the dose of opioid was titrated.

Table 19: Distribution of symptoms at assessment one by titration of opioid dose between 7 days ago and last 24 hours where n = 147

		Never	Very rarely	Occasion-ally	Quite often	Very Often	All
	N	%	%	%	%	%	%
Nausea							
Percent change 7 days to 24 hours							
Negative (dose decreased)	30	47	17	20	10	7	100
No change	91	38	31	16	11	3	100
Positive (dose increased)	26	35	23	19	15	8	100
Vomiting							
Percent change 7 days to 24 hours							
Negative (dose decreased)	30	67	17	13	3	0	100
No change	91	70	14	12	3	0	100
Positive (dose increased)	26	77	12	4	4	4	100
Dry Mouth							
Percent change 7 days to 24 hours							
Negative (dose decreased)	30	23	3	20	10	43	100
No change	90	17	10	26	21	27	100
Positive (dose increased)	26	8	4	19	19	50	100
Myoclonus							
Percent change 7 days to 24 hours							
Negative (dose decreased)	30	37	10	27	10	17	100
No change	91	44	9	26	15	5	100
Positive (dose increased)	26	27	19	12	31	12	100
Hallucinations							
Percent change 7 days to 24 hours							
Negative (dose decreased)	30	77	0	13	3	7	100
No change	91	78	8	10	3	1	100
Positive (dose increased)	26	65	12	8	8	8	100

The table show results of patients prescribed opioids for all reasons. Of the total patient group 30 patients had the dose of opioid reduced in the week prior to assessment. The patients still experienced symptoms despite opioid dose reduction. 37% of patients in this group reported nausea was present at least occasionally in the last week. 13% of patients reported vomiting; 73% reported dry mouth; 54% reported myoclonus and 23% reported hallucinations at least occasionally in the week prior to the assessment.

The opioid dose of 26 patients had been titrated in the week prior to assessment. The numbers of patients reporting symptoms at least "occasionally" are very similar in the two groups of patients i.e. those that had the dose increased and those that had a dose reduction. 42% reported nausea, 12% reported vomiting, 88% reported dry mouth, 55% reported myoclonus and 24% reported hallucinations.

The same analysis was carried out for two different historical time points. This aimed to provide a measure of the speed of change of the opioid dose and an attempt to differentiate between a rapid change of opioid and a slower change of opioid. For example if the dose of opioid is increased by 25% in a week this would be expected to have more impact on the patient than if the dose increased by 25% over 4 weeks or six months. From the data recorded it is not possible to know whether the opioid dose changed steadily or suddenly between any stated time points however the analysis provides an attempt at this.

Table 20: Distribution of symptoms at assessment one by titration of dose between 4 weeks ago and last 24 hours where n = 144

		Never	Very rarely	Occasion-ally	Quite often	Very Often	All
	N	**%**	**%**	**%**	**%**	**%**	**%**
Nausea							
Percent change 4 weeks to 24 hours							
Negative (dose decreased)	36	33	25	25	8	8	100
No change	69	42	29	13	12	4	100
Positive (dose increased)	39	41	23	21	13	3	100
Vomiting							
Percent change 4 weeks to 24 hours							
Negative (dose decreased)	36	69	19	8	3	0	100
No change	69	70	14	12	4	0	100
Positive (dose increased)	39	74	10	10	3	3	100
Dry Mouth							
Percent change 4 weeks to 24 hours							
Negative (dose decreased)	36	22	6	28	11	33	100
No change	69	14	7	20	25	33	100
Positive (dose increased)	38	16	11	24	13	37	100
Myoclonus							
Percent change 4 weeks to 24 hours							
Negative (dose decreased)	36	42	8	19	25	6	100
No change	69	42	10	29	13	6	100
Positive (dose increased)	39	33	13	21	15	18	100
Hallucinations							
Percent change 4 weeks to 24 hours							
Negative (dose decreased)	36	75	11	8	3	3	100
No change	69	75	4	16	4	0	100
Positive (dose increased)	39	77	8	3	3	10	100

The table shows the presence of symptoms by dose titration over the last four weeks. It includes results from 147 patients as some patients were relatively opioid naïve. A larger number of the patients have had the dose of opioid adjusted in the four weeks prior to assessment. 39 (27.1%) patients have had the dose increased from four weeks ago compared to 26 (17.7%) patients with a dose increase in the previous week. The numbers of patients reporting the symptoms remains similar to the previous table however. Dry mouth remains the most frequently reported symptom, hallucinations remains the least frequently reported. 41% of patients with a reduced opioid dose reported nausea at least occasionally, 37% of patients with an increased opioid dose reported nausea. 50% of patients with a reduced opioid dose reported myoclonus at least occasionally and 54% of those with an increased dose also reported myoclonus.

Table 21: Distribution of symptoms at assessment one by titration of dose between 6 months ago and last 24 hours where n = 102

		Never	Very rarely	Occasion-ally	Quite often	Very Often	All
	N	%	%	%	%	%	%
Nausea							
Percent change 6 months to 24 hours							
Negative (dose decreased)	36	50	25	14	6	6	100
No change	23	39	35	13	9	4	100
Positive (dose increased)	43	35	26	23	12	5	100
Vomiting							
Percent change 6 months to 24 hours							
Negative (dose decreased)	36	78	14	6	3	0	100
No change	23	70	9	17	4	0	100
Positive (dose increased)	43	72	14	5	7	2	100
Dry Mouth							
Percent change 6 months to 24 hours							
Negative (dose decreased)	36	19	6	17	22	36	100
No change	23	22	13	26	9	30	100
Positive (dose increased)	43	14	5	26	21	35	100
Myoclonus							
Percent change 6 months to 24 hours							
Negative (dose decreased)	36	42	11	31	8	8	100
No change	23	48	9	26	13	4	100
Positive (dose increased)	43	33	7	23	26	12	100
Hallucinations							
Percent change 6 months to 24 hours							
Negative (dose decreased)	36	78	6	11	3	3	100
No change	23	78	0	13	9	0	100
Positive (dose increased)	43	81	2	9	5	2	100

The table represents 102 patients. Not all patients in the study were on opioids six months prior to recruitment. The results show again the number of patients with symptoms. A minority of patients in each group were free of the symptom. Nausea was the most frequent symptom with at least 50% of patients in the three opioid titration groups reporting nausea in the week prior to assessment.

Table 22: Median symptom severity of symptoms in last 24 hours by regular drug at assessment one where n = 147

		Nausea	Vomiting	Dry mouth	Myoclonus	Halluc-inations
	N	Median	Median	Median	Median	Median
Drug						
Alfentanil	2	0.5	0.5	1.0	0.0	0.0
Buprenorphine	3	0.0	0.0	0.0	0.0	0.0
DHC	1	0.0	0.0	0.0	0.0	0.0
Diamorphine	1	1.0	2.0	2.0	3.0	2.0
Fentanyl	15	1.0	0.0	3.0	0.0	0.0
Hydromorphone	4	2.5	0.0	4.0	1.5	0.0
Methadone	21	1.0	0.0	2.0	2.0	0.0
Morphine	59	1.0	0.0	3.0	1.0	0.0
Oxycodone	40	0.0	0.0	2.0	2.0	0.0

The table shows the median values of the Likert scales for each of the drugs and indicates the frequency at which the patient experienced the symptom. A median of zero indicates the symptom had not been present in the last week. A median of 2.0 indicates the symptom had been present on occasion in the last week. A median of 4.0 indicates the symptom has been present “very often” in the last week. The most frequent symptom was dry mouth experienced by patients who were on hydromorphone. Dry mouth was the most frequent symptom experienced by patients on all the different opioids. Myoclonus appears to be the next most frequent symptom and was most common in patients who were prescribed diamorphine and methadone.

Table 23: Median severity of symptoms in last 24 hours by patient group at assessment 1 where n = 147

		Nausea	Vomiting	Dry mouth	Myoclonus	Halluc-inations
	N	Median	Median	Median	Median	Median
Cancer	89	1.0	0.0	3.0	1.0	0.0
Chronic non-cancer pain	33	1.0	0.0	3.0	2.0	0.0
Substance misuse	25	1.0	0.0	2.0	2.0	0.0

The table above shows the symptoms present in each of the different patient groups. Dry mouth is the most frequently present symptom. Patients with non-cancer pain have the most frequent symptoms with nausea, dry mouth and myoclonus all present. Myoclonus is also present frequently in all patient groups.

Table 24: Symptom frequency reported by patients in the week prior to assessment by patient group where n = 147

	Cancer pain	Non-cancer pain	Substance misuse
Nausea			
Never – Occasionally %	84.3	72.7	95.8
Quite/Very Often %	15.7	27.3	4.2
Vomiting			
Never – Occasionally %	97.8	87.9	100.0
Quite/Very Often %	2.2	12.1	-
Dry mouth			
Never – Occasionally %	46.1	33.3	70.8
Quite/Very Often %	53.9	66.7	29.2
Myoclonus			
Never – Occasionally %	76.4	72.7	66.7
Quite/Very Often %	23.6	27.3	33.3
Hallucinations			
Never – Occasionally %	93.3	90.9	91.7
Quite/Very Often %	6.7	9.1	8.3

The table above divides symptoms by patient group and frequency. Symptoms were divided into two groups representing the lowest three frequency options on the Likert scales or the highest two frequencies on the scales. In this table more patients with non-cancer pain had nausea more frequently than patients with cancer pain or substance misuse. Patients with substance misuse had nausea less frequently than either of the other two patient groups. Vomiting was less frequently experienced by either cancer pain or substance misuse patients. Dry mouth was the most frequently reported symptom in all patient groups. The symptom was still lower in substance misuse than in other groups. Less than 10% of patients in all three patient groups reported hallucinations either quite or very often.

Table 25: Symptom frequency in last week by opioid dose in last 24 hours at assessment one where n = 147

	MEDD dose in last 24h		
	Low	**Medium**	**High**
Less than two symptoms quite/very often (n)	24	58	25
Two or more symptoms quite/very often (n)	4	24	12
Less than two symptoms quite/very often (%)	85.71	70.73	67.57
Two or more symptoms quite/very often (%)	14.29	29.27	32.43

In this table the frequency of symptoms in all patients according to the morphine equivalent daily dose is presented. In this analysis a morphine equivalent daily dose of 60mg or less is regarded as low; between 60mg and 300mg is regarded as medium; and a dose of 300mg or greater is regarded as high. Most patients were on a medium dose of morphine (or equivalent dose of another opioid). At each range of morphine equivalent daily doses the majority of patients are experiencing less than two symptoms quite or very often. As the dose range increase from low through medium to high, the percentage of patients experiencing two or more symptoms quite or very often increases.

Table 26: Symptom frequency in last week by regular opioid drug in last 24 hours at assessment one where n = 147

	Less than two symptoms quite/very often		Two or more symptoms quite/very often	
	N	**%**	**N**	**%**
Alfentanil	2	100.0	0	0
Buprenorphine	2	66.7	1	33.3
DHC	1	100.0	0	0
Diamorphine	1	100.0	0	0
Fentanyl	9	60.0	6	40.0
Hydromorphone	1	25.0	3	75.0
Methadone	17	81.0	4	19.0
Morphine	43	72.9	16	27.1
Oxycodone	31	77.5	9	22.5

Patients on methadone seem to have a lower symptom burden than patients on other opioids with 17 (81%) of the patients reporting less than two symptoms present at the higher frequencies in the week prior to assessment. Patients who were prescribed fentanyl were more evenly spread in this table. Nine (60.0%) had less than two symptoms present at the higher frequencies, and 6 (40.0%) had two or more symptoms present at the higher frequencies. No patients on alfentanil, dihydrocodeine and diamorphine had two or more symptoms present at the higher frequencies.

Table 27: Morphine equivalent daily dose in the last 24 hours by constipation status for patients in different clinical groups and for all patients who were taking opioids where n = 147

Dose in last 24 hours								
		N	**Mean**	**SD**	**SE**	**Median**	**Minimum**	**Maximum**
	Constipation							
Cancer (N=89)	No	56	200.4	202.5	27.1	128	20	1120
	Yes	33	177.0	222.6	38.8	140	20	1120
Non-cancer (N=33)	No	21	371.9	540.3	117.9	200	56	2440
	Yes	12	295.0	379.9	109.7	188	25	1400
Substance misuse (N=25)	No	14	232.1	169.0	45.2	188	36	750
	Yes	11	641.4	427.7	129.0	525	80	1350
All	No	91	244.9	314.8	33.0	151	20	2440
	Yes	56	293.5	351.1	46.9	160	20	1400

Overall 56 (38.1%) of the patients were constipated. 11(44%) of patients with substance misuse were constipated compared to 12 (36.4%) of patients with non-cancer pain and 33 (37.1%) of those with cancer pain. There was no association between constipation and opioid dose. When the patient groups were combined P=0.39 on a t test. The mean difference in MEDD dose between those with & without constipation was 49, with a standard error of 56.

Table 28: Opioid titration in the last 7 days by constipation status for patients in different clinical groups and for all patients who were taking opioids where n = 147

% change 7 days to 24 hours								
		N	**Mean**	**SD**	**SE**	**Median**	**Minimum**	**Maximum**
	Constipation							
Cancer (N=89)	No	56	5.5	35.7	4.8	0	-38	200
	Yes	33	1.5	20.5	3.6	0	-33	100
Non-cancer (N=33)	No	21	1.1	14.8	3.2	0	-33	50
	Yes	12	-0.6	21.3	6.2	0	-44	48
Substance misuse (N=25)	No	14	32.7	143.1	38.3	0	-67	525
	Yes	11	-6.6	22.4	6.8	0	-67	24
All	No	91	8.7	62.4	6.5	0	-67	525
	Yes	56	-0.5	20.9	2.8	0	-67	100

Patients in the substance misuse group had the most significant dose titration.

There is no statistically significant association between titration of opioid dose in the week prior to assessment and constipation status. P=0.29 for t-test of mean difference (when the groups are combined)

Table 29: Opioid titration in the last 4 weeks by constipation status for patients in different clinical groups and for all patients who were taking opioids where n = 147

% change 4 weeks to 24 hours								
		N	**Mean**	**SD**	**SE**	**Median**	**Minimum**	**Maximum**
	Constipation							
Cancer (N=86)	No	55	15.3	44.2	6.0	0	-40	200
	Yes	31	5.1	33.4	6.0	0	-58	150
Non-cancer (N=33)	No	21	-3.0	18.9	4.1	0	-39	50
	Yes	12	-1.5	24.4	7.0	0	-57	48
Substance misuse (N=25)	No	14	99.4	205.9	55.0	0	-33	525
	Yes	11	13.2	63.2	19.1	0	-67	130
All	No	90	24.1	92.6	9.8	0	-40	525
	Yes	54	5.3	39.2	5.3	0	-67	150

Again it is the patients in the substance misuse group who have had the greatest change in opioid dose.

There is no statistically significant association between titration of opioid dose in the four weeks prior to assessment and constipation status. P=0.16 for t-test of mean difference (when the groups are combined)

Table 30: Opioid titration in the last 6 months by constipation status for patients in different clinical groups and for all patients who were taking opioids where n = 147

% change 6 months to 24 hours								
		N	**Mean**	**SD**	**SE**	**Median**	**Minimum**	**Maximum**
	Constipation							
Cancer (N=47)	No	28	133.6	369.1	69.8	22	-67	1900
	Yes	19	18.8	91.9	21.1	-10	-67	265
Non-cancer (N=33)	No	21	50.1	243.9	53.2	0	-64	1100
	Yes	12	63.8	146.1	42.2	17	-57	488
Substance misuse (N=22)	No	13	89.2	222.8	61.8	0	-67	525
	Yes	9	30.0	115.8	38.6	0	-67	317
All	No	62	96.0	301.6	38.3	0	-67	1900
	Yes	40	34.8	114.3	18.1	0	-67	488

When reviewing the last six months it is the cancer patients who have had the greatest change in opioid dose.

There is no statistically significant association between titration of opioid dose in the six months prior to assessment and constipation status. P=0.22 for t-test of mean difference (when the groups are combined)

Table 31: Constipation status by regular drug in last 24 hours at assessment 1

	Constipation		Constipation	
	No	Yes	No	Yes
	N	N	Percent	Percent
Drug				
Alfentanil	2	0	100.0	0
Buprenorphine	2	1	66.7	33.3
DHC	1	0	100.0	0
Diamorphine	0	1	0	100.0
Fentanyl	10	5	66.7	33.3
Hydromorphone	2	2	50.0	50.0
Methadone	12	9	57.1	42.9
Morphine	37	22	62.7	37.3
Oxycodone	24	16	60.0	40.0
All	90	56	61.6	38.4

Some of the drugs were only prescribed for very small numbers of patients making it difficult to draw conclusions. Fentanyl, methadone, morphine and oxycodone were the most frequently prescribed. Fentanyl appears to cause less constipation than the other drugs. Methadone appears to cause the most constipation. However a chi-squared test comparing rates of constipation between the four main drugs, Fentanyl, Methadone, Morphine & Oxycodone gives P=0.94, so the variation is not statistically significant.

4.9 Discussion

4.9.1 Summary of Main Findings

Patients were asked about the frequency of known opioid-related side effects in the week prior to assessment. Overall the patients are displaying clinically significant burden of side

effects from the opioids which have been prescribed. Hallucinations were the least common side effect. Dry mouth was the most common side effect in all patient groups ie cancer pain, non-cancer pain and substance misuse patients. Patients with non-cancer pain appear to have a higher side-effect burden than patients with either cancer pain or substance misuse.

Overall there were weak correlations between symptoms and opioid dose with myoclonus and vomiting being statistically significant. Patients with substance misuse showed a statistically significant correlation between opioid dose and nausea, vomiting and myoclonus. In the non-cancer group only vomiting was significantly associated with opioid dose. No correlation was observed between opioid titration and frequency with which the patients reported opioid-related side-effects. Titration over the seven days prior to assessment, four weeks and six months were all explored and no correlation was found. Patients reported similar levels of side-effects when the dose of opioid had been reduced as when it had been increased.

Constipation was common and 56 (38.1%) of the total study population were found to be constipated with a score of three or less on the constipation score. Patients with substance misuse were more likely to be constipated than other patient groups. There was no statistically significant association between dose and constipation. There was no association between titration of the opioid dose and constipation. This was explored at several time points prior to the assessment. In this study fentanyl was the least constipating of the opioids. Methadone was the most constipating. However there was not a statistically significant difference between the drugs.

4.9.2 Comparison with the Published Literature

In a study with some similarities to our own work Glare, Walsh and Sheehan recruited 42 patients who completed at least one assessment and thirty patients completed the assessments every week for four weeks. The patients were all known to the palliative

medicine team and had been on morphine for at least week at the time of recruitment. The authors of this study used a questionnaire designed to elicit the presence of opioid-related side effects. The median dose of morphine at the start of the study was 144mg per day with a range of 50 – 3600 mg / day. The authors calculated the point prevalence of the different side-effects based on the 30 patients who completed four questionnaires. 23 (77%) of the patients reported a dry mouth, 7 (23%) reported constipation, 13 (43%) reported myoclonus, 3 (10%) reported nausea and 1 (3%) reported hallucinations. There was a non-significant trend for nausea, dizziness and myoclonus to be worse with higher doses of morphine. In this group of patients nausea was usually mild and did not persist. Myoclonus was also usually mild and not persistent. The study benefits from the use of the specific questionnaire designed to identify all opioid-related side effects however it is limited by its duration of only four weeks. (Glare, Walsh, Sheehan 2006)

Although traditionally clinicians are most concerned about opioid-induced nausea and vomiting at the introduction of the opioid or when the dose is titrated a longitudinal study of patients in the USA found that for some patients the nausea and vomiting persisted. The data came from an open-label uncontrolled study which followed patients for up to three years. All patients were on modified release oxycodone for the management of non-cancer pain. The mean dose of oxycodone was 52.5 mg with a range of 10.0 to 293.5mg. Patients were managed according to local guidelines and their pain. The study imposed a few limitations on the management of patients, for example twice daily dosing only, and required an assessment every three months to collect study data. 44% of the 233 patients who enrolled in the study required dose titration within the first three months. The need for dose titration reduced with time. The incidence of side effects was greatest in the first three months of the study. Forty one (18%) of the patients discontinued oxycodone due to side effects. The incidence of constipation declined from 9.7% at one-three months to 3.2% at three- six months and declined further through the study. The incidence of nausea declined from 11.0% at one-three months to 4.2% at three- six months. However for a small number of patients the side-effects persisted over the three years of follow-up. (Portenoy et al, 2007)

The prevalence of opioid-related side effects in patients with a history of substance misuse and non-cancer pain who are prescribed methadone was discussed in a paper by Rhodin and colleagues in 2006. In a study of 48 patients dry mouth was reported by 19 (39.6%) patients, nausea by 10 (20.8%) and constipation by 9 (18.7%) of patients. The patients in this cohort more commonly experienced the less typical side effects of opioids including a combination of sweating, weight gain, fatigue, sedation and sexual dysfunction. (Rhodin et al, 2006)

As part of a study evaluating a pain management programme 174 patients with cancer and bone metastases were asked about their opioid use and experience of opioid-related side-effects. In this study constipation was much less prevalent in patients who were not on an opioid and most prevalent in those who were on regular opioid and using breakthrough doses. Nausea was more prevalent in patients who were taking regular and as required doses of opioid than regular opioid alone. In this study the opioid dose correlated with the severity of nausea, vomiting and constipation. (Villars et al, 2007)

"A systematic review of oxycodone in the management of cancer pain" published in 2011 found no evidence that oxycodone is more or less effective than morphine. The review also discussed a meta-analysis which had previously been published and found no difference in side-effect profile between the side-effect profiles of the two opioids. (King et al 2011) A similar review also published in 2011 found no significant differences between hydromorphone and morphine (Pigni, Brunelli, Caraceni, 2011). A review from the series compared transdermal opioids and oral morphine and found a reduction in constipation but no apparent benefit in terms of analgesia efficacy (Tassinari D et al, 2011).

In patients with advanced cancer the prevalence of nausea ranges from 11 to 78%, and the prevalence of vomiting in the same population is 7 to 49%. (Laugsand, Kaasa, Klepstad 2011) In cancer patients, opioid-induced nausea and / or vomiting is reported by up to 40% of patients (Laugsand, Kaasa, Klepstad, 2011). Our results also showed that nausea tended

to be mild indicated in our study by the patients reporting they had felt nauseous either very rarely or occasionally in the week prior to assessment. In our patient group myoclonus appeared to be more prominent. The myoclonus persisted over time and was present six to eight weeks later at assessment two. Hallucinations were the least frequent symptom in our patient group which is consistent with the findings of the other studies.

Laugsand et al looked at whether changing the opioid prescribed for patients with cancer pain and whether this had any impact on the nausea and vomiting reported. The conclusions were based on six studies only and all were of smaller sample size than this study. There was some evidence to suggest oral morphine caused more nausea than intravenous morphine or oxycodone either orally or intravenously. Changing to hydromorphone from morphine also resulted in an improvement in nausea. Methadone appeared to cause less nausea than transdermal fentanyl. The authors concluded that there was weak evidence to support a change of opioid from morphine to either oxycodone or hydromorphone in order to better manage patients with opioid-induced nausea. (Laugsand, Kaasa, Klepstad 2011) Porreca and Ossipov also commented there was some evidence that transdermal fentanyl causes less constipation than oral opioid in patients with non-cancer pain. (Porreca and Ossipov 2009) There is also a lack of evidence guiding the use of anti-emetics in patients with non-cancer pain. (Porreca and Ossipov 2009)

Constipation is recognised as one of the most frequent side effects of opioids with a prevalence of between 40% and 50% in patients with metastatic cancer who are prescribed strong opioids. (Choi and Billings, 2002) There are several factors which influence bowel habit in cancer patients and opioids are just one of the factors contributing. Choi and Billings suggested that opioids were accounting for approximately 25% of the constipation in frail patients. (Choi and Billings 2002)

In a study which recruited 50 patients with cancer who were referred to a specialist palliative care team 70% of the patients were constipated at the time of referral. Eight of the patients were not an opioid at the initial assessment. With the use of laxatives the

number of patients who were constipated at four weeks reduced to 26%. With findings similar to our results, the published study did not show any correlation between opioid dose and constipation. Instead it was the frailer patients who had the more resistant constipation. (Fallon and Hanks, 1999) Other authors have suggested a relationship between opioid dose and constipation. (Choi and Billings 2002) The published study used the same constipation score as this study. (Fallon and Hanks, 1999) The authors also reported that at six months twelve of the 50 patients were still being followed up. Of these 12 patients, four were prescribed an opioid but were not constipated and were not requiring a laxative and a further six of the 12 were prescribed a laxative were on a strong opioid and were not constipated. The authors concluded that morphine dose and constipation are not correlated and that the patients' performance state better predicts the development of resistant constipation. (Fallon and Hanks, 1999)

In a prospective survey of 100 hospice in-patients 47 patients had experienced visual hallucinations within the four weeks prior to assessment. Of the patients who described recent hallucinations 28% experienced hallucinations several times a week and 25% had hallucinations every day. The study explored the type of hallucination and found that 43% of patients saw a person either on waking or on going to sleep. The hallucinations were twice as likely to occur in patients who were sleepy or confused. Patients with hallucinations were more likely to be on opioids than the patients who were not prescribed opioids with an odds ratio of 4.45 although the author noted the wide confidence interval of the odds ratio. (Fountain 2001).

Porreca and Ossipov quoted a study from the UK which recruited general practitioners (GPs). 74% of the 569 GPs who completed the survey thought the side-effects of the pain medication prevented adequate pain control of non-cancer pain (Porreca and Ossipov 2009). They also quoted another study which suggested that patients with opioid-related side-effects may feel their doctor does not understand how best to manage their pain (Porreca and Ossipov 2009).

4.10 Conclusions

The findings of this study are consistent with the published literature in showing that patients who are prescribed strong opioids have a significant burden from opioid-related side effects. Nausea and constipation are frequently reported by patients despite long-term opioid use. There was no correlation with opioid titration or with morphine equivalent daily dose.

Although the small number of patients who were prescribed some of the drugs for example alfentanil makes it difficult to draw conclusions on the data regarding specific opioids this study benefits from a larger sample size than most of the literature. However this study has other advantages over many of the published studies. The data provides direct comparison between three clinically distinct patient groups and over a longer time period than many studies have done previously.

These data help inform a proactive management plan for different patient groups taking opioids. These side effects can impact significantly on quality of life and discussion with patients and relatives is key to ensuring clinicians are fully aware of the extent to which the patient is experiencing side effects and that the most appropriate and effective management plan is decided.

CHAPTER 5: THE EFFECT OF OPIOIDS ON COGNITIVE FUNCTION

Outline of chapter:

- Defines cognitive function and explains how impaired cognitive function can impact on the patient.
- Definition of delirium with an outline of the prevalence, presentation, causes and management of delirium.
- Considers the impact of opioids on cognitive function in patients with cancer pain and non-cancer pain.
- Describes the use of the Addenbrooke's Cognitive Examination -Revised in a population with pain.
- Demonstrates that significantly more morbidity due to cognitive impairment is detected when using the ACE-R.

5.1 Hypothesis

Opioids affect cognitive function and this differs between patient groups who are prescribed opioids for different indications.

5.2 Aims

- To assess the cognitive function of patients who are prescribed opioids for different indications
- To compare the cognitive impairment between the different groups
- To explore possible factors which may contribute to impaired cognitive function including opioid drug, opioid dose and the effect of titration of the opioid
- To describe the use of the ACE – R in a group of patients with pain or substance misuse and who are prescribed opioids.

5.3 Definitions of Cognitive Function

> "Cognitive function has been described as the brain's acquisition, processing, storage and retrieval of information." (Moriarty, McGuire, Finn 2011)

> "The term "executive function" is used as an umbrella for various complex processes and sub-processes. Most attempts to define executive function resort to a list of examples (such as task-switching, planning) or that other useful umbrella "working memory", which reflects the fact that executive function is by no means a unitary concept." (Elliott, 2003)

Cognitive function is a complex process involving memory, attention, visuospatial awareness, language and fluency. When any aspect of cognitive function is impaired it will adversely impact on the patient. For example if the patient's language is impaired it will affect their ability to converse with their family, can cause frustration when they cannot find the words to express themselves, can cause them to become socially isolated rather than face people with whom they find it hard to communicate. When memory and attention are affected patients can find it difficult to be involved in discussions with family or health professionals and there may be safety concerns about how they will manage medications or being on their own at home. Many authors have commented that impaired cognitive function leads to impaired quality of life. As such it is important to consider the prevalence and presentation of impaired cognitive function and the possible reasons for the impairment. For some patients the impairment may be wholly or partially reversible. In this chapter there will be a description of some of the factors that can impact on cognitive function in cancer patients and then a more systematic consideration of the impact of opioids on cognitive function.

Cognitive function can be affected by several neuropsychiatric disorders for example age-related cognitive decline, delirium, dementia and affective disorders. Differentiating between the causes relies on a comprehensive history from the patient and obtaining a collateral history from their carers and other health professionals. The importance of recognising delirium lies with the potential for reversibility if any of the causes can be found and the need to manage the symptoms of delirium which can cause distress for both

the patient and their family. Age associated cognitive decline is separate to any disease related cognitive impairment. Intelligence traits are present from early life and are still relevant in later life. They must be taken into account when assessing cognitive function and the assessments of cognitive function are therefore best done over time rather than at a single time point (Deary et al, 2009; Michaud, Burnand, Stiefel 2004). It is a change in cognitive function that is important rather than any individual result.

5.3.1 Definition of Delirium

Delirium is a term often used interchangeably with acute confusion or acute confusional state in the literature. Delirium is a clinical diagnosis which is defined as:

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for delirium is as follows[-]:

> "Disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness."

> "Change in cognition (eg, memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a preexisting, established, or evolving dementia."

> "The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day."

> "There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause."

5.3.2 Delirium and Palliative Care

The prevalence of delirium in palliative care populations varies with the patient group studied. For example in a review of patients admitted to a general cancer hospital Doriath and colleagues found that 11.8% (95% confidence interval: 9.7 – 14.2%) of patients were acutely confused (Doriath et al, 2007). However in a review article Centeno found the prevalence can be between 26% and 44% of patients with "terminal cancer" admitted to either hospital or hospice. (Centeno, Sanz, Bruera 2004) There was wide variation amongst the included studies in terms of diagnostic criteria, care setting, age and timing of study which is likely to explain this spread of prevalence. The lack of consistency in definition is not limited to delirium and was discussed in the introduction when considering research in palliative care more generally.

Delirium may present as hypoactive, hyperactive or mixed forms. The patient may be quiet, still and withdrawn or can be restless, agitated and hallucinating. All forms of delirium are distressing for the patient but there is more risk of the hypoactive from being overlooked by professionals. (Centeno, Sanz, Bruera 2004; Michaud, Burnand, Stiefel 2004) The patient may be disorientated in time, place or person. Hallucinations or sleep disturbances may be apparent.

When delirium is present it can make it harder to assess the patient and gain an understanding of the other symptoms which they may be experiencing for example pain, nausea, shortness of breath. There are several tools available which can help assess the patient, particularly with respect to pain and in a discussion paper Mary Wheeler provides a useful summary of them. (Wheeler 2006)

Delirium may be caused by hypoxia, biochemical abnormalities such as hypercalcaemia or hyponatraemia, sepsis or drugs. The presence of intracerebral pathology including metastatic disease or recent haemorrhage can cause delirium. Many drugs have been implicated and examples include opioids, steroids, benzodiazepines and anticholinergic drugs. (Michaud, Burnand, Stiefel 2004) Serotonin toxicity is an increasing problem in

palliative care and is probably not always recognised. Cancer affects serotonin levels and when drugs which also increase serotonin levels in the blood for example anti-depressants are prescribed there is a risk of serotonin toxicity. The features include hyperreflexia, clonus, agitation, anxiety and altered mental state. (Dvir and Smallwood 2008; Isbister and Buckley 2005)

Chemotherapy drugs are increasingly implicated in cognitive impairment and as such warrant particular consideration.

5.4 Chemotherapy-induced cognitive impairment

Cognitive impairment in cancer patients who received chemotherapy is recognised in a growing body of literature. Increasing recognition of cognitive impairment after chemotherapy is in part due to the increased survival of patients after chemotherapy. Given the increasing numbers of people who will be diagnosed with cancer during their lifetime and that there are new interventions which will continue to improve survival rates cognitive impairment is set to become a significant concern for those in oncology and palliative medicine. (Argyriou et al, 2011; Simo et al, 2013)

Chemotherapy-induced cognitive function is also called “chemobrain” and “chemo-fog”. It occurs during treatment with chemotherapy and can persist long after the treatment has finished (Argyriou et al, 2011). The prevalence of chemobrain in studies varies between 14% and 85%. It has been reported to last between two and ten years after the chemotherapy has been completed. (Argyriou et al, 2011; Hodgson et al, 2013). Females who have been treated for breast cancer appear to be the most commonly affected patient group. Other patient groups most commonly affected are those who have been treated for lung, prostate and ovarian tumours. (Argyriou et al, 2011) In one study a third of patients had cognitive impairment before chemotherapy was commenced (Hodgson et al, 2012). The type of chemotherapy and the duration of the treatment most likely to cause chemobrain remain unknown. (Cheung, Chui, Chan, 2012)

In a review in 2011, Argyriou and colleagues discussed that the aetiology of chemobrain is largely unknown but probably due to a combination of factors. Many of the chemotherapy drugs cannot cross the blood-brain barrier normally, however there is some genetic variation in permeability and there may be a genetic susceptibility to chemobrain. Other chemotherapy drugs can cross the blood-brain barrier, for example 5-fluorouracil, and thus there is a risk of direct neurotoxicity. Hormone changes related to cancer treatment including reduced oestrogen and testosterone levels can also affect cognitive function adversely. (Argyriou et al, 2011)

Emotional distress, fatigue and hormonal therapies have all been recognised by authors as confounding factors. (Argyriou et al, 2011) Opioids and other drugs used for the management of other side effects of chemotherapy and the sequelae of a cancer diagnosis have not been mentioned as possible confounders in the chemobrain literature. As with other clinical situations including the impact of opioids on cognitive function there is no consensus on the most appropriate method of testing cognitive function in order to assess and support patients with chemobrain. Subjective assessments tend to report more severe cognitive impairment than the objective measures of psychological performance. (Jansen 2013) This may reflect "real life" ie the subjective assessments reflect more closely the difficulties patients have in everyday functioning. Alternatively the subjective assessments may be more affected by anxiety or depression than the objective measures.

The importance of cognitive impairment that predates chemotherapy and therefore should not be wrongly attributed to chemotherapy is discussed by several authors (Hodgson et al, 2012; Schagen et al, 2014; Vardy and Tannock 2007). It may be that some of the cognitive impairment attributed to chemotherapy is due to other cancer related factors. Opioids may have a part to play but none of the studies reviewed reported on the patients' use of opioids or other analgesia.

Patient reports of cognitive impairment within qualitative research studiesreveals the impact of the cognitive impairment on patients. (Kohli et al, 2007; Von Ah et al, 2013; Myers 2013) Von Ah and colleagues interviewed 22 patients with breast cancer who were

between one and twelve years post treatment. The patients were aware of the change in cognitive function during their chemotherapy but more concerned with other side effects at the time for example nausea. The cognitive impairment was more important to them when the other side effects had either subsided or been appropriately managed. They appeared to recognise the chemotherapy as the cause of the cognitive impairment. (Von Ah et al, 2013) In contrast a review by Myers (Myers, 2013) found that not all patients had identified chemotherapy as the cause of their impaired cognitive function. Some were fearful of dementia as the cause. Patients in this review described withdrawing from social situations, adverse effect on work and the development of coping strategies. (Myers, 2013)

5.5 Effect of Opioids on Cognitive Function in Patients with Cancer Pain

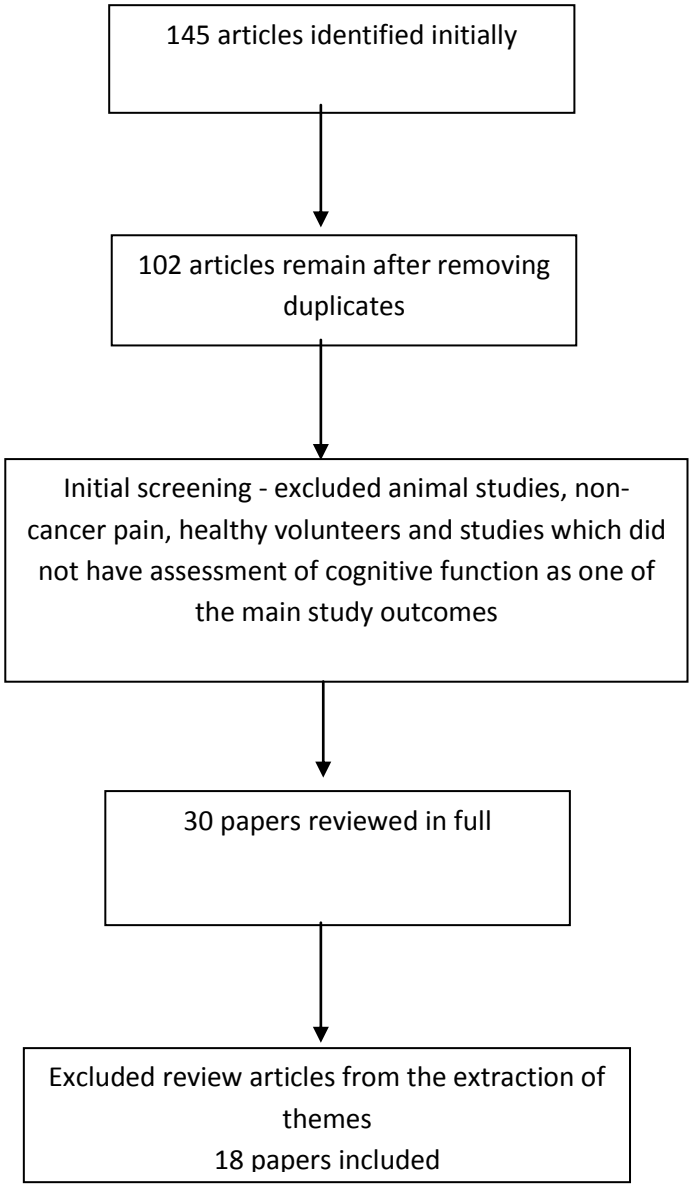
The published literature about the effects of opioids on cognitive function of patients with cancer pain is reviewed in this section. The numbers of confounding factors which are also likely to impact on cognitive function in this patient group make it difficult to evaluate well.

A literature search was carried out using the OVID database. The search was carried out within Medline (1946 – 2014), Embase (1947 – 2014) and Health and Psychosocial Instruments (1985 – 2014). The table below shows the search strategy used. Words in columns were combined using the Boolean term OR; words in rows were combined using the Boolean term AND. The papers obtained in the literature search and the process of including and excluding papers for the literature review are shown in the chart below.

Table 32: Search strategy used to identify papers for the literature review regarding the effects of opioids on the cognitive function of patients with cancer pain

Opioi$ Opiat$ Morphine Oxycodone Methadone Hydromorphone	Cancer Malignan$	Cogniti$ Function$

Figure 4: Papers identified for the literature review regarding the effects of opioids on the cognitive function of patients with cancer pain



5.5.1 Summary of Main Themes from Literature Review

Aspects of importance across all the studies have been extracted and presented in a series of tables in order to provide comparison across the studies.

The papers included in the review provide data on patients from across the world. Patients have been recruited who are attending outpatient clinics and who are hospice in-patients. It is likely that the care setting from which they have been recruited is of relevance to the outcomes of assessment. It is likely that hospice in-patients are frailer than those attending an oncology outpatient clinic particularly in countries where a poor prognosis is a requirement for admission to hospice.

In general the studies are small. The two large studies (Andreasson et al, 2012; Kurita et al, 2011) are both based on the European Pharmacogenetic Opioid Study (EPOS). Kurita and colleagues presented the results of the cognitive assessments of 1915 patients representing a significant achievement. The patients were recruited from 17 centres in 11 countries so it is likely that the number of investigators involved has introduced inter-observer bias. This large study also lacked follow-up data so although there is a wealth of data collected at a single point it is difficult to extrapolate to clinical settings.

There was a lack of longitudinal data in most of the studies. Most of the studies rely on single assessments of cognitive impairment in order to draw conclusions. While there may be some validity in this approach for studies exploring the effect of breakthrough doses of opioid, the results of studies aiming to explore the effects of regular or long-term opioids on cognitive function are open to question if they rely on a single assessment. Bruera et al (Bruera et al, 1989) presented 2 days of data; Clemons et al reviewed their patients for two weeks and up to three weeks for some (Clemons, Regnard, Appleton, 1996). Maddocks and McNamara also presented data over a two-week period (Maddocks et al, 1996; McNamara, 2002).

Vainio in 1995 used tests that were specifically designed for the assessment of driving- highly relevant to the research question being explored (Vainio et al, 1995). Other authors used specific tests of psychological function. Some of the tests require special training or equipment in order to apply and interpret the test appropriately. Indeed some of the studies had psychologists as part of the research team. The use of such tests inevitably limits the relevance to clinicians who wish to apply the results of the studies within busy clinical practice.

Five of the eighteen studies outlined did not report on the presence of other symptoms that could be attributed to opioids for example nausea, vomiting, sedation or dry mouth. Failure to report on the side effects of opioids takes the cognitive function assessments out of clinical context.

The studies took different approaches to exploring the impact of opioids on cognitive function. Some of the studies measured the serum concentration of morphine and its metabolites and looked for possible correlation between the concentrations and cognitive impairment. Some of the studies screened a cohort of patients for the development of delirium. The majority of the papers recruited patients who were on opioid and assessed their cognitive function and looked for possible contributory factors to cognitive impairment in the opioid history. Some went on to switch to an alternative opioid or route and to look for possible change in the cognitive impairment as a result of the intervention. These studies address highly relevant research questions as these are situations which clinicians face every day and questions which patients ask.

Table 33: Table which shows the features extracted from the studies exploring the impact of opioids on cognitive function in cancer patients

Author, Date	Andreassan, 2012	Ashby, 1997	Bruera, 1991	Bruera, 1989
Care Setting, Country	Majority in-patients, some out-patients, 17 centres in 11 European countries	Hospice in-patients, Australia	In-patients, specialist palliative care unit, Canada	Unclear on setting, Canada
Number of Patients	450 patients	36 patients	4 patients	40 patients
Method of Assessing Cognitive Function	MMSE (score < 23 = cognitive failure)	Clinical diagnosis	Mini-mental state questionnaire	Finger tapping, arithmetic, reverse memory of digits, visual memory
Control Group	Grouped according to CYP2D6 genotype	No comparison group	No	Two groups – stable opioid dose and following opioid titration
Opioid	Oxycodone	Morphine MEDD 20 – 600mg, median 110mg	Hydromorphone	Morphine, oxycodone, hydromorphone and codeine
Other Symptoms Assessed	Nausea, tiredness	Nausea, vomiting, confusion	No	Pain, nausea, drowsiness, confusion, depression and activity
Longitudinal Assessment	No	No	Only regarding presence of hallucinations	2 consecutive days
Timing of Opioid and Assessment	Serum oxycodone measured at "trough level" ie prior to routine dose	No fixed time after morphine dose	No fixed time, all patients were requiring opioid titration	Assessment 1: immediately before opioid Assessment 2: 45 minutes after opioid
Impact on Cognitive Function	None found Median MMSE scores for 2 groups were 28 and 29	9 / 36 had confusion but also had increased creatinine level	Hallucinations with no other change in cognitive function	Titration of opioid associated with drowsiness and impaired cognitive function

Table 34: Table which shows the features extracted from the studies exploring the impact of opioids on cognitive function in cancer patients

Author, Date	Clemons, 1996	Gagnon, 2000	Gaudreau, 2006	Kamboj, 2005
Care Setting, Country	In-patients and out-patients, UK	In-patient unit, Canada	Hospital patients, Canada	In-patients and out-patients, UK
Number of Patients	29 recruited	89 patients	114 patients	14 patients
Method of Assessing Cognitive Function	Multiple measures including adult reading test, logical memory test, reaction time, grammatical reasoning test	Confusion Rating Scale and Blessed Memory Concentration Test	Nursing Delirium Screening Tool	Multiple Objective and subjective measures
Control Group	Healthy volunteers and patients with cancer pain not taking opioids	No	No	Crossover study, placebo arm
Opioid	Morphine	Information lacking re opioid and method of conversion to MEDD	Multiple opioids, MEDD presented	Instant release opioid
Other Symptoms Assessed	Alertness, anxiety, pain, depression, concentration, clearheadedness	No	No	Dry mouth, anxiety and depression, pain
Longitudinal Assessment	Yes – 2 weeks follow up, some participants up to 3 weeks	Yes – screened three times / day until death	Yes – mean 16 days	No
Timing of Opioid and Assessment	1.5 hours after instant release morphine, 4 hours after modified release morphine	Not known	Not stated	45 minutes after administration of either instant release opioid or placebo
Impact on Cognitive Function	Yes. Seen in grammatical reasoning test, alertness and stroop colour-word test	Prevalence of delirium varied apparently with MEDD	Delirium more frequent with MEDD > 90mg	Impaired memory

Table 35: Table which shows the features extracted from the studies exploring the impact of opioids on cognitive function in cancer patients

Author, Date	Klepstad, 2003	Kurita, 2008	Kurita, 2011	Maddocks, 1996
Care Setting, Country	Hospital in-patients	Cancer and pain out-patients, Brazil	In-patients and out-patients, 11 European countries	Hospice in-patients, Australia
Number of Patients	300 patients	26 patients	1,915 patients	19 patients recruited only 13 patients completed study
Method of Assessing Cognitive Function	Mini-mental state examination	Mini-mental state examination and others	Mini-mental state examination	Clinical assessment of cognition
Control Group	No	No	No	No
Opioid	Morphine, stable use	Multiple opioids, MEDD used for comparisons	Multiple opioids, MEDD used for comparisons	Oxycodone
Other Symptoms Assessed	EORTC-QLQ	Beck Depression Inventory	EORTC – QLQ –C30,	Nausea and vomiting, itch
Longitudinal Assessment	No	Yes – of depression	No	Yes – 6 days
Timing of Opioid and Assessment	No consistent timing	Not stated	Not stated	At commencement of oxycodone infusion, after 24 hours with no dose change, after 6 days
Impact on Cognitive Function	No association between serum morphine and morphine metabolites and cognitive function	No association between MMSE score and opioid found but other tests suggested impairment	Impaired cognitive function associated with MEDD > 400mg (compared with MEDD < 80mg)	Reduction in delirium when change to oxycodone from morphine

Table 36: Table which shows the features extracted from the studies exploring the impact of opioids on cognitive function in cancer patients

Author, Date	McNamara, 2002	Morita, 2002	Sjogren, 2000	Sjogren, 1989
Care Setting, Country	Hospice in-patients, UK	Hospice in-patients, Japan	Hospital out-patients, Denmark	Hospital in-patients, Denmark
Number of Patients	19 patients	8 patients	130 patients	14 patients
Method of Assessing Cognitive Function	Cognitive function drug research assessment, DSM – IV criteria for delirium	Presence of DSM – IV criteria for delirium	Continuous reaction time, finger tapping test, paced auditory serial addition task	Continuous reaction time
Control Group	No	No	Yes – 5 groups according to pain, opioid and performance status	Yes – healthy controls
Opioid	Morphine changed to fentanyl	Morphine infusion	Multiple opioids, MEDD used	Multiple opioids changed during study to epidural opioid
Other Symptoms Assessed	Nausea, vomiting, constipation, myoclonus and dizziness	No	Pain, sedation	Pain, sedation
Longitudinal Assessment	Yes – 14 days	No	No	Before and after initiation of epidural morphine
Timing of Opioid and Assessment	Patients on transdermal opioid	Patients on continuous morphine infusion	Consistent time of day	Time between last opioid dose and testing included in analysis
Impact on Cognitive Function	Change to fentanyl led to improved concentration, working memory and speed of memory	Patients had increased morphine metabolites seen after delirium developed	Long – term opioid treatment did not seem to adversely affect the tests of neuropsychological function	No change in continuous reaction time with change of route of opioid

Table 37: Table which shows the features extracted from the studies exploring the impact of opioids on cognitive function in cancer patients

Author, Date	Vainio, 1995	Wood, 1998
Care Setting, Country	Out-patients, Finland	Hospice in-patients, Australia
Number of Patients	49 patients (7 patients did not complete)	18 patients
Method of Assessing Cognitive Function	Psychomotor tests designed for assessment of professional drivers	National adult reading test, Williams delayed recall test, immediate memory for digits, trail making test
Control Group	Yes – 24 patients on morphine, 25 patients not on opioid	No
Opioid	Morphine	Morphine
Other Symptoms Assessed	No	No
Longitudinal Assessment	No	No
Timing of Opioid and Assessment	Tests started 90 minutes after taking modified release opioid	Not stated
Impact on Cognitive Function	Balancing ability with closed eyes was the only test affected significantly by morphine	Impaired concentration and attention, delayed recall and conceptual tracking

5.5.2 Critical Review of Included Studies

Bruera, Schoeller and Montejo described a series of four patients who had visual hallucinations which were attributed to opioid. (Bruera, Schoeller, Montejo 1992) The case series is interesting as the hallucinations appeared without other features suggestive of the central side effects of opioids or delirium. Three of the patients responded to a change of prescribed opioid and the introduction of haloperidol. There were no other apparent drug causes and biochemical abnormalities were excluded. The authors therefore concluded the opioid was responsible. However the response may have been due to the haloperidol and the change of opioid did not necessarily contribute to the benefit seen. A case series of four patients, although well described, can only be of interest and not conclusive.

Gaudreau et al recruited hospital cancer patients from an episode of delirium while they were in hospital. (Gaudreau et al, 2007) The episode of delirium regarded as the index episode was not necessarily their first episode therefore – it represented a convenience episode. The patients were followed up until they were discharged. Unfortunately the study is further flawed as the final data collected does not represent the outcome of the delirium. This study used the Nursing delirium Screening Scale which scores various aspects of delirium and results in a score from zero to ten where a score of greater than two indicates delirium. The study measured the NuDESC score three times each day. Any positive score was recorded as delirium. The study fails to provide any information on the duration of delirium. If the NuDESC score is positive on the subsequent day, the authors regarded this as a recurrent episode of delirium. A further flaw of this study is the failure to recognise that the interpretation of data does not distinguish between one episode of delirium lasting for ten days or ten daily episodes of delirium. They looked at specific doses and grouped the doses of the drugs above and below specific doses. Morphine was coded as above or below 90mg morphine equivalent daily dose. They found a statistically significant association between morphine dose greater than 90mg and delirium. The conclusion of this paper has to be tempered by the flawed assumptions described earlier.

Maddocks, Somogyi and colleagues wished to explore the hypothesis that a change of opioid can improve opioid-related delirium. They recruited 19 patients who had previously experienced morphine related delirium, however only 13 patients completed the study. The

patients were converted from morphine to subcutaneous continuous infusion of oxycodone and were monitored for features of delirium twice each day. All patients showed a reduction in delirium over the few days following the switch. The study is limited by the sample size, the lack of a validated tool and inter-observer bias given the number of observers involved in collecting the data (Maddocks et al, 1996).

Kamboj and colleagues conducted a very well thought through study which looked at the effect of instant release opioid on cognitive function. They developed their hypothesis from the traditional view that it is either initiation of opioids or a change in the dose of opioids that cause the side effects. They recruited 14 patients and included those with cancer and non-cancer pain, in-patients and out-patients and a variety of opioids which were given by three different routes. Although the premise of the study was good this heterogeneity in patients recruited makes it difficult to draw any meaningful conclusions as there are too many possible confounding factors that cannot be controlled for. They chose tests which had "ecological validity" which was another very positive aspect of the study. Ecological validity aims to ensure that tests are meaningful representations of real life. They used the Bond and Lader scales and the HADS. They found that instant release morphine causes impaired memory with a slight impairment in immediate recall and a more obvious impairment in delayed recall. The authors suggest that opioids have an effect on information retrieval and put forward the thought that instant release morphine

> "exposes the patients to cognitive "reserve capacity" limitations – already there due to cancer, age and background opioids" (Kamboj et al, 2005)

Klepstad explored whether serum concentrations of morphine or its metabolites M3G and M6G could be useful clinically. He recruited 300 patients who were in hospital and on a stable dose of morphine for at least three days prior to recruitment. They recruited 263 patients on oral morphine and 35 patients on a continuous subcutaneous infusion of morphine. A further two patients were receiving morphine by more than one route regularly. 91 patients were also requiring instant release morphine for breakthrough pain. The study found that morphine, M3G and M6G concentrations do not correlate with nausea, constipation or cognitive failure. The authors suggested that other factors were

responsible for example receptor properties and genetic variability in opioid pharmacology (Klepstad et al, 2003).

In a study published in 1989, Bruera and colleagues reviewed 40 patients with cancer and pain admitted to the hospital. There was no information on the reason for admission to hospital or the prescription of other drugs which could have influenced delirium although the authors stated that "none (of the patients) had evidence of other cause of delirium." The paper stated that 40 consecutive admissions were included but then excluded patients who were prescribed either a long-acting opioid or a continuous infusion of opioid. It was therefore unclear how the 40 patients were identified. The patients were divided into two groups. Twenty patients were on a stable dose of opioid and had no dose change for at least seven days. Twenty of the patients were on a dose of opioid which had been titrated by at least 30% in the three days or less prior to the assessment. Both groups then underwent the same series of tests on two consecutive days. The first test of the day was done immediately before the routine of dose of opioid and the second test was done 45 minutes after the routine opioid dose. Both groups had a reduction in pain and an increase in sleepiness after the opioid dose. Additionally finger tapping speed and an arithmetic test were impaired after the dose of opioid in the opioid titrated group. This study was limited by lack of information on other possible contributory factors and the small numbers recruited. The study is also limited by only recruiting patients on short-acting opioids and by the use of a battery of very specific psychological tests which may be less easy for clinicians to use in everyday clinical practice. The authors recognised some of the limitations of the study and felt that future work was needed to clarify the implications for informed consent, driving and involvement in making decisions. (Bruera et al, 1989)

Michael Ashby and colleagues conducted a study in Australia in 1997. Overall this is a very flawed study. The research team collected blood samples from 36 hospice patients at the same time as taking venous blood for other clinical analyses. Morphine, morphine -3-glucoronide and morphine-6-glucoronide were measured in the venous samples. There was no information on the patients recruited and how they were identified for the study. All the patients were on morphine for at least three days prior to being included in the study. There was no consistency about opioid usage and the timings of blood tests in relation to opioid

administration was not recorded. Overall the results suggested that the patients who experienced nausea, vomiting and impaired cognitive function may have done so as a result of renal impairment or accumulation of morphine metabolites. (Ashby et al, 1996)

In 2002 (Morita et al, 2002) another study was published which aimed to establish the impact of morphine metabolites on cognitive function. Although Morita's study was more robust than Ashby's study it still demonstrates clearly the problems in studying this area. The research team took samples of venous blood from patients who were on a continuous infusion of morphine – either subcutaneous or intravenous infusion - for at least 24 hours and in whom there was no evidence of cognitive impairment. It was not clear from the paper how it was decided that the patient had cognitive impairment. If delirium developed later in the patient's journey further blood samples were taken, this time within 24 hours of recognition of delirium. Of 258 patients admitted to the hospice, 131 patients were eligible ie were prescribed continuous infusion of morphine but the study only generated results for eight patients. All eight patients had delirium which was attributed to multi-organ failure on the basis of biochemistry results and recognised diagnostic criteria. The study suggested that morphine metabolites may accumulate in patients who do not have renal failure. Overall the study protocol did not seem well designed to address the hypothesis and role of morphine or metabolites in delirium. There was a risk that the levels of morphine and / or metabolites were fluctuating and that any findings were due to chance. Discussion was based on eight sets of results only and there was no consistency about relationship of initial sample to episode of delirium (Morita et al, 2002).

Sjogren and colleagues recruited 130 patients with cancer who were attending out-patient clinics. They excluded any patient with a poor performance status which clearly immediately limits the relevance of the findings of the study to many palliative care patients. The patients recruited were divided into five groups on the basis of performance status, pain and use of opioids. The patients completed a series of tests which included finger tapping test, Continuous Reaction Time (CTT) and Paced auditory serial addition task (PASAT). The tests assess non-specific cerebral function, vigilance and working memory respectively. The tests were chosen as they assess high order functioning and reflect information processing. The study showed that opioids did not affect the patients

functioning with the neuropsychological test. Patients with a lower performance status tended to have a slower CRT. When pain was more severe the patients performed less well on PASAT. The authors suggested that pain may have an arousal effect which helps patients function better. It is important to note though that 45% of all those recruited were unable to even complete the PASAT. As well as the exclusion of frailer patients and the use of specialised neuropsychological tests, the study is limited as there are no longitudinal data. The authors recognised this and stated:

> "It is well known that longitudinal studies in this population are difficult to conduct mainly because of a large number of drop-outs". (Sjogren et al 2000)

Two of the papers included in this literature review were drawn from the results of the European Pharmacogenetic Opioid Study (EPOS) which is a multi-centre study which has recruited patients from 17 centres in 11 European countries. Andreassen et al described a subgroup of the patients recruited for EPOS. Data on 461 patients who were taking oxycodone was extracted from the main study. This paper addressed very clearly stated research questions but was limited like so many of the papers by lack of follow-up and longitudinal data. Patients were grouped according CYP2D6 genotype and grouped according to speed of oxycodone metabolism ie extensive, poor or ultra-rapid metabolisers. 92% of those recruited were extensive metabolisers. The authors observed that CYP2D6 genotype affected oxycodone metabolism but not efficacy and that CYP2D6 genotype was not associated with opioid related adverse events including cognitive impairment as measured by the mini-mental state examination (Andreassen et al, 2012).

Another paper based on the EPOS study was written by Kurita et al in 2011. This paper analysed data on 1915 patients clearly benefitting from significant numbers recruited but again lacking longitudinal information. The EPOS study used the mini-mental state (MMSE) to measure cognitive function. MMSE scores of less than 23 out of 30 were taken to indicate definite cognitive impairment, scores of 24 to 27 to indicate possible cognitive impairment and scores of greater than 27 to indicate normal cognitive function. The authors found that poor performance status, increased age and short time since diagnosis (15 months) and lower MMSE scores were all associated. Overall one third of patients had

possible or definite cognitive impairment as indicated by a MMSE score of 27 or less. A morphine equivalent daily dose of 400 mg / day or greater was associated with a 1.75 times greater odds of having a low MMSE compared to a morphine equivalent daily dose of less than 80mg. Patients with breakthrough pain had 0.73 times lower odds of a low MMSE. The authors of this paper also highlighted the lack of cut-off scores for the more specialist neuropsychological tests to indicate clinically relevant cognitive dysfunction (Kurita et al, 2011).

McNamara conducted a small study which was published in 2002. The study explored whether changing patients to transdermal fentanyl would improve their cognitive function and other opioid related side effects. None of the results obtained were statistically significant but this was not surprising given the small sample size. Only 19 patients were recruited over a two year period and of the 19 recruited only nine completed the fourteen days of the study. Several of the patients who did not complete the study became too unwell or had an adverse event about which there was no detail. The patients were changed from morphine to transdermal fentanyl because of morphine toxicity. The patients reported an improvement in well-being that was not apparent to the researcher. The researcher did observe an improvement in drowsiness, working memory, attention and power of concentration. The small sample size and lack of completion of the protocol clearly limit the conclusions that can be drawn from the study (McNamara, 2002). Also of note is the rapid titration of fentanyl which would be unusual in most hospices. The transdermal fentanyl was titrated by 25 mcg / hour every 72 hours which would be considered too rapid by many clinicians.

Eighteen patients who were prescribed morphine and were hospice in-patients were recruited to assess their cognitive function on morphine. This study used the National Adult Reading Test to establish pre-morbid intellectual functioning and this showed that the patients were of average intelligence. However they showed an impaired ability to retain information and reduced ability on conceptual tracking test. There was a statistically significant correlation between immediate memory and attention and plasma morphine concentration. The patients in this paper were on lower dose of morphine than several of the other papers with a mean daily dose of 100 mg per 24 hours. (Wood et al, 1998) This

paper is of interest because the authors established the pre-morbid intellectual functioning and it was noted that the patients had not appeared confused to the clinical team but most had evidence of cognitive impairment on formal testing.

One of the key papers mentioned when discussing opioids and cognitive function was written by Vainio and colleagues in 1995. This paper addressed the safety of patients with cancer who are prescribed opioids to drive. The study used a battery of tests designed to assess professional drivers. Two groups were recruited for the study. Twenty four patients had cancer and were on twice daily sustained release morphine. The dose of morphine had been stable for at least two weeks. Also recruited were 25 patients with cancer but who did not have pain and were not prescribed opioids. Seven of the 49 patients recruited did not complete the tests due to either fatigue or problems with the equipment (Vainio et al, 1995).

> "However, we cannot ignore the tendency of the morphine group to show slower reaction times, make more mistakes, and process visual information and perform the motor sequences more slowly than the control group."……"In conclusion, long-term analgesic medication with stable doses of morphine does not have psychomotor effects of a kind that would be clearly hazardous to driving in traffic." (Vainio et al, 1995, pages 669, 670)

The two quotes from the paper appear at odds and it would seem there are risks when patients on morphine (and presumably other opioids) are driving.

All consecutive patients admitted to a hospice in Canada were screened for delirium using the confusion rating scale (CRS). Eighty-nine patients were followed from admission to the hospice until they passed away with a mean follow-up of 12 days. Patients who were positive for screening for delirium on CRS had the diagnosis confirmed or excluded using the Confusion Assessment Method. Of the 55 patients in the cohort who had a delirium only the dose of opioid prescribed was different from those who did not have a delirium. The patients had a higher morphine equivalent daily dose for regular analgesia ($p = 0.080$) and for their breakthrough pain ($p = 0.097$). (Gagnon et al, 2000)

In a pilot study exploring cognitive impairment in patients with cancer on opioids Kurita describes the assessment of two groups of patients (Kurita and de Mattos Pimenta, 2008). Fourteen patients who were prescribed opioids are compared to 12 patients who were not taking opioids. Only a small number of patients were recruited and attrition was high. The study aimed for three assessments over a month but only 13 of the patients recruited were able to complete all three assessments. The study assessed many aspects of cognitive function including attention, mental flexibility, concentration, working memory, short-term recall and long term memory. There was no difference found between the two groups recruited and no correlation between cognitive function and opioid dose. (Kurita and de Mattos Pimenta, 2008)

Clemons et al also found no difference in cognitive function between patients with cancer who were prescribed opioids and those who were not. There was a difference between the patients and healthy volunteers. This study was very small with only six patients in the cancer, not on opioids group and seven patients in the cancer and on opioids group. Although the study was well thought through it is possible that the findings are due to chance. The authors did not recognise this but did not consider that the results were biased due to recruitment only from a hospice in-patient population. (Clemons, Regnard, Appleton 1996)

Sjogren and Banning recruited fourteen patients with cancer pain who were on oral opioids and in whom there was to be a planned switch to epidural morphine because the patient was either experiencing inadequate pain control or unwanted sedation. (Sjogren and Banning 1989) Prior to cognitive function testing the patients were on a stable dose of opioid although fluctuations of 10% either way were allowed within this definition. This study used the continuous reaction time (CRT) and the patients reported their pain and sedation using a visual analogue scale. When the patients were changed to epidural opioid there was no statistically significant improvement in CRT and although the median VAS results for sedation and pain were lower there was an inevitable range and the results were not significantly positive. The study did not show significant with a change to epidural opioid but the sample size was small and there was no data to describe how long the

patients had been on opioid ie were they chronic opioid users? There were differences found between controls and patients CRT scores though (Sjogren and Banning 1989).

In 2003 Klepstad measured serum morphine, morphine-3-glucoronide and morphine-6-glucoronide concentrations and looked for possible correlations with symptoms. There was no correlation with the serum concentration of morphine or its metabolites and cognitive function, pain, nausea or constipation. The patients were only on a stable dose of morphine for 3 days and should have reached steady state however there was no consistency in timing between sample time and symptom assessment which may limit the conclusions. Some patients were using breakthrough analgesia and the analysis was repeated without these patients to all for the effect of breakthrough doses on stable dose. The authors suggest that it is not the concentrations of opioid or metabolite that are important per se and that receptor properties or intracellular pharmacodynamics is involved. The results and conclusions are in line with other authors. (Klepstad et al, 2003) This is an important clinical conclusion as we often see a time lag between reducing, stopping or switching an opioid and an improvement in cognition.

5.6 Effect of opioids on cognitive function in patients with non-cancer pain

In an industry- sponsored study designed to assess neuropsychological effects of opioids in patients with chronic back pain Jamison and colleagues provided data over a 180-day period. This represents the longest period of data collection identified in the literature. One hundred and forty four patients were included in this analysis and represented a subset of a larger study. All the patients had back pain and required opioids to manage their pain. The patients were prescribed either oxycodone with acetaminophen or transdermal fentanyl. They were prescribed the analgesia for 90 days and then crossed over to the other treatment. Only 68.8% completed the intended study assessments. Psychological performance was assessed using the trail making test and the digit substitution test. Together these tests are a useful indicator of fine motor speed, dexterity and reaction time. Unfortunately the trail making test is affected by age and also shows a practice effect. Both factors could have influenced the results. Although many of the patients showed

improvement in psychological function with improved concentration and hand-to-eye coordination, 16 - 25% of the participants showed deterioration in psychomotor function. The deterioration was linked to increased age and less pain at the start of the study. (Jamison et al, 2003)

In a study that recruited 40 non-cancer patients Sjogren and colleagues used the continuous reaction time, finger tapping test and paced auditory serial addition test to assess the neuropsychological function of patients who were on a stable dose of opioid. (Sjogren, Thomsen, Olsen 2000) The tests were chosen to reflect higher order functions and the ability to process information. Functioning in all the tests was impaired. The morphine equivalent daily dose was moderate with a range of 15 to 300mg and 12 of the patients were on methadone. Interestingly the study participants had a significant degree of anxiety and depression but no correlation was found between these morbidities and the ability to complete the neuropsychological tests. The authors suggested that there is a balance to be achieved between the effects of pain on arousal (ie increased) and concentration (ie decreased) and that the effects of the opioids are a part of this balance.

Tassain comments that the cognitive effects of opioids are less well studied in patients with non-cancer pain than in those with cancer pain. (Tassain et al, 2003) In a well-designed study Tassain and his colleagues sought to assess the effects of opioids on cognitive function in an observational study designed to reflect the realities of clinical practice. The participants of the study were opioid naïve but already on other forms of analgesia and anxiolytics or antidepressants as needed. Thirty two patients were identified and 28 consented for the study. The morphine was titrated to analgesic effect and the mean dose at 3 months was 62mg, at 6 months was 65mg and at 12 months was 72mg. Ten of the patients discontinued the morphine shortly after starting due to unacceptable side effects mainly constipation and sedation. Only 11 patients completed the final series of assessments at 12 months. The patients were required to complete a battery of assessments which measured mood, pain, quality of life, memory, attention and tests of fine motor speed and reaction time. The patients' pain responded to the morphine and there was no significant change in the cognitive function measures although there was some improvement in information processing. This study was useful as it approximates clinical

practice however the patients are on a relatively small dose of opioid and the numbers involved are very small. The number of patients who were unable to tolerate morphine represented a significant proportion of the study sample. (Tassain et al, 2003)

In a review article Chapman and co-authors recognised the importance of clarifying the effect of opioids on cognitive function. In healthy volunteers opioids have been shown to adversely affect motor speed even after one dose. Other studies have contradicted the finding and the balance between the effects of pain and opioids on arousal, anxiety and inhibition is discussed. The authors highlight the difficulties of comparing the findings from the studies which have been carried out due to the variation in outcome measures used. Inevitably given the available evidence the conclusion of this comprehensive review was that further research is needed to fully understand the role of opioids in cognitive functioning. (Chapman, Byas-Smith, Reed 2002)

In a review of the "extent of neurocognitive dysfunction in a multidisciplinary pain centre population" (Landro et al, 2013) the authors highlighted some key points. Cognitive impairment may be recognised by patients but not reported to a professional and when it is reported it may be wrongly attributed to anxiety or depression. In their study Landro and colleagues found that 20% of the patients had impaired cognitive function at baseline although it was not clear from the paper how many of this group were on pain medications. The difficulties in recruiting for this type of study were also clear – they recruited 73 patients from the total 123 patients who were screened. The research team used the everyday working memory questionnaire which assesses general memory and attention as well as several other measures of psychological function. They found that objective and subjective measures of cognitive impairment correlated. (Landro et al, 2013)

Kurita and colleagues recruited 49 patients after screening 137 patients. They used a battery of neuropsychological tests including the mini-mental state examination, trail making test, continuous reaction time. The patients recruited had been on opioids for many years (mean 6.8 years) and were on a moderate dose of opioid with a mean morphine

equivalent daily dose of 252mg / day. They found that a lower dose of opioid correlated with worse performance on the digit span test (Kurita et al, 2012).

5.7 Opioids and driving

Patients and professionals consider the question of whether it is safe to drive when taking strong opioids.

> "Safe operation of a motor vehicle is a learned activity demanding the complex interaction of physical, cognitive, perceptual skills and abilities." (Galski, Williams, Ehle 2000)

The ability to drive can maintain independence and quality of life and the implications of driving, if it is not safe to do so, are clearly significant. Despite this there is a lack of studies which address the question. In a review in 2012 Angela Mailis – Gagnon describes the inconsistencies in the conclusions drawn from the few studies that have been carried out and argues that previous reviews had not been able to safely conclude that patients on opioids are safe to drive. She argues that there many confounders such as concomitant medications, pain and sleepiness which are not properly allowed for in the analysis. The review identified only four studies which assessed driving or a driving simulator but these were limited not only by failure to address the confounders but also by the small sample size. The studies recruited 23, 16, 33 and 21 patients. Further bias was introduced by the recruitment of patients who responded to general calls to be involved. The recruitment of this self-selected group may indicate the recruitment of patients who were confident in their driving ability and those who knew they had difficulties decided to not be involved. (Mailis-Gagnon et al, 2012) Although recognising the lack of evidence regarding safety to drive an editorial by James Zacny argued that to preserve patients quality of life was the priority when the evidence was not conclusive (Zacny, 2006). He suggested putting the decision about driving back to the patient. In a structured review of the evidence Fishbain and colleagues also concluded that there was no evidence to support the restriction of

driving but recommended that patients should not drive for four or five days after the dose of opioid has been increased or if they ever feel sedated. (Fishbain et al, 2003)

In a study in 2005, Byas-Smith and colleagues evaluated the patients driving in the community and around an obstacle course. They only recruited 32 patients with a history of pain, 11 of whom were not taking opioids. The patients were experienced drivers with around 30 years' experience. Thirty of the 32 patients who agreed to take part were taking medication other than opioids which had the potential to impact on cognitive function. Also of note, the patients who volunteered for the study – only 15% of the initial patient group approached – were paid $75 (Byas-Smith et al 2005). In Galski's study (Galski, Williams, Ehle 2000) 16 patients were compared with 327 patients who had known cerebral compromise from a variety of causes including dementia, frail elderly and cerebrovascular accident. Small size and confounders make it difficult to draw any conclusions but the authors found no loss of visuospatial abilities in the patient group who were on opioids. However this group made more mistakes on tasks which rely on speed and accuracy together. It is also possible that the small number of participants from the population contacted represents a biased sample – those who knew they were having difficulties driving may have chosen to not become involved in the study (Galski, Williams, Ehle 2000).

5.8 Summary of the Literature

The literature regarding the effects of opioids on cognitive function is limited in particular by studies of small sample size and a lack of longitudinal data. The lack of clinically relevant and user accessible research tools limits the ability of the clinician to assess cognitive function in clinical rather than research settings. There is a need for a tool to assess cognitive function which can be used without specialist training, is not too onerous for the patient and has been shown to detect cognitive impairment in patients with pain or substance misuse and who are prescribed opioids.

5.9 Methods Specific to Effect of Opioids on Cognitive Function

Patients were recruited from three different clinical groups so that the impact of cognitive function could be assessed and compared between the groups. Patients with cancer pain who were prescribed 10mg of morphine (or an equivalent daily dose of an alternative opioid) completed assessments at one time point. Patients with cancer pain who were prescribed 60mg of morphine or an equivalent daily dose of an alternative opioid completed the assessments at two or three time points. Patients with chronic non-cancer pain who were prescribed opioid and those who were not prescribed opioid completed the assessment on two time points mainly. Patients with a history of substance misuse completed assessments at one time point only.

The Addenbrooke's Cognitive Examination-Revised (ACE-R) takes ten to fifteen minutes to complete. There are three versions available that have different names and addresses in each in order to prevent learning of the address on subsequent tests. The three versions are ACE-R A, B and C and they were used in that order at assessments one, two and three of the study. There are several questions for the patient to complete and the researcher or clinician scores each. The patient's responses to each of the questions can be recorded at the time and then the test can be scored at a later time. This avoids the patient being aware of scoring zero which could possibly cause them distress. The questions are clearly worded in order that there is no ambiguity for the patient and little chance of inter-observer bias due to more prompting within the question. Each question or small group of questions has the heading of the aspect of cognitive function that is being assessed. Each question has a maximum possible score that is written into a small box on the right hand side of the page. If the question was taken from the mini-mental state examination this is indicated by the presence of a shaded box also on the right hand side. The clinician can then add up the scores out of 30 or 100. Most of the questions are very straightforward to score for example "What is the day, date, month, year and season?" Each correct item scores one out of a possible total five for the question. Other questions such as the clock-drawing test require more consideration in order to ensure a consistent approach to scoring. A scoring sheet is available which provides helpful information on the scoring of each question.

The Addenbrooke's Cognitive Examination-Revised (ACE-R) provides a score out of one hundred that reflects five domains of cognitive function. The 30-point score of the mini-mental state examination can be extracted from the ACE-R and allows a comparison between the two tools. I compared the results of the two cognitive function tools in order to look for possible discrepancy in assessing cognitive function in our study groups. The five domains of cognitive function were explored in order to assess the domain which is most affected by opioids. The impact of opioid dose and opioid titration on cognitive function was explored using both Spearman and Pearson Correlation Co-efficients.

The table below has been constructed to show the different domains of cognitive function assessed by the two tests. It facilities a comparison between the two and highlights the extent to which the mini-mental state examination relies on assessment of attention and orientation and does not provide an adequate assessment of the other domains. For example the MMSE only provides a score out of three for memory and the ACE-R provides a score out of 26. The difference in scores comes directly from the very different number of questions in each of the two assessments.

Table 38: The table shows the different domains of cognitive function assessed by the two tests

Cognitive Domain	Mini-Mental State Examination	Addenbrooke's Cognitive Examination - Revised
Attention and Orientation	18	18
Memory	3	26
Visuospatial abilities	1	16
Language	8	26
Fluency	0	14
Total	30	100

The Bond and Lader analogue scales were used to provide a subjective measure of cognitive function. The Bond and Lader scales consist of sixteen 100 mm horizontal lines which are anchored at each end by a positive and negative aspect of an emotion. The patient is asked to place a vertical line across the horizontal line so that the intersection marks the degree to which they agree with the particular emotion. The Bond and Lader scales provide a subjective response to 16 individual emotions but they can also be grouped into four variables – mental sedation, physical sedation, calming effects and other feelings. The results of the analogue scales are presented and have been analysed to explore possible correlation between objective and subjective measures of cognitive function. Both Pearson and Spearman correlations have been provided. The Spearman correlation depends on the order or ranking of the values and does not assume consistent intervals. If the correlations show strong disagreement the research team would need to look for an extreme value that may be skewing the Pearson correlation.

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale. The HADS is widely used in many healthcare settings. There are fourteen questions – seven of which relate to anxiety and seven to depression. Each question is given a score from zero to three according to the response of the patient. The scores are not visible on the question sheet and some of the statements are inverted in order to reduce the risk of patients simply ticking the same box for each statement. The statements have been carefully constructed to reflect colloquial statements for example “butterflies in the stomach” which should be familiar descriptors to many patients and provide illustration to statements that could otherwise be hard to interpret.

Pain and interference due to pain were assessed using the Brief Pain Inventory. The Brief Pain Inventory starts with questions which identify the patient’s pain as more than an “everyday pain” and identifies the pain using a body chart. Patients are then asked for four scores which reflect the severity of the pain in the 24 hours prior to the assessment – the worst, best and average pain scores and to provide a pain score at the time of completing the assessment. The BPI goes on to ask seven questions which reflect the interference by the pain on various activities. Again this reflects the 24 hours prior to the assessment. From

the two different groups of questions, two scores are obtained. These are the mean pain severity score and the mean pain interference score.

Anxiety, depression and pain are all known to impact on cognitive function and therefore the scores of the ACE-R have been analysed with the scores from the Hospital Anxiety and Depression Scales and the Brief Pain Inventory to assess if there is any correlation and evidence of impact in these patient groups.

5.10 Results

Cognitive function was assessed at each time point in the study schedule. 178 patients were recruited and completed at least one set of assessments. The data for patients with substance misuse and chronic pain has been excluded from the analyses here due to the very small numbers recruited. The data for these patients has been presented separately in the chapter "Patients with Pain and a History of Substance Misuse".

Ninety patients completed two assessments. The numbers from the different patient groups who completed each assessment have been detailed in the chapter "Patient Characteristics".

Figure 5: Number recruited in each patient group and the number of assessments completed by patients in each patient group

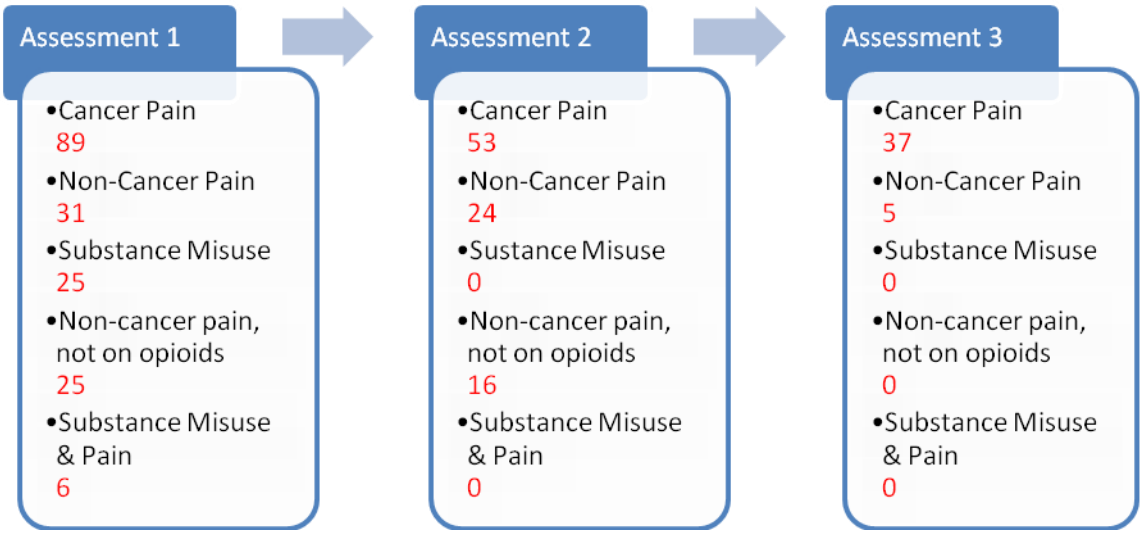


Table 39: Cognitive impairment as assessed by ACE-R vs MMSE at assessment 1

		ACE-R		
	MMSE	**< 85**	**>=85**	**All**
Cancer	Definite (<=23)	14	0	14
	Possible (24-27)	19	2	21
	None (>=28)	17	37	54
	All	50	39	89
Non-cancer pain	Definite (<=23)	1	0	1
	Possible (24-27)	4	3	7
	None (>=28)	4	21	25
	All	9	24	33
Substance misuse	Definite (<=23)	5	0	5
	Possible (24-27)	4	0	4
	None (>=28)	4	10	14
	All	13	10	23
Non-cancer pain, Non-opioid	Definite (<=23)	1	0	1
	Possible (24-27)	3	2	5
	None (>=28)	2	17	19
	All	6	19	25
All	Definite (<=23)	21	0	21
	Possible (24-27)	30	7	37
	None (>=28)	27	85	112
	All	78	92	170

Table 42 shows a comparison of cognitive function scores obtained when using the Addenbrooke's Cognitive Examination – Revised (ACE-R) compared to the Mini-Mental State Examination (MMSE). In table 42 it can be seen that 50 (56.2%) of the 89 patients with cancer pain had impaired cognitive function as measured by the ACE-R. When the MMSE was used to assess cognitive function only 35 (39.3%) patients were found to have globally impaired cognitive function. In the chronic pain patients who were prescribed opioids 9 (27.3%) patients out of the total 33 patients had impaired cognitive function on the ACE-R; 8 patients (24.2%) had impairment detected by the MMSE. In the group of patients with substance misuse the ACE-R detected cognitive impairment in 13 (56.5%) out of 23 patients; the MMSE detected cognitive impairment in nine (39.1%) patients. In the group of patients with chronic pain who were not prescribed opioids there are six

(24.0%) patients with impaired attention out of the total 25 patients. In this group of patients both tools detected the same prevalence of cognitive impairment.

Table 40: ACE_R subscales and MMSE at assessment 1 where n = 170

Attention impairment as assessed by ACE-R vs MMSE

		Attention		
	MMSE	**< 17**	**>=17**	**All**
Cancer	Definite (<=23)	14	0	14
	Possible (24-27)	8	13	21
	None (>=28)	2	52	54
P value 0.002	All	24	65	89
Non-cancer	Definite (<=23)	1	0	1
	Possible (24-27)	3	4	7
	None (>=28)	1	24	25
P value 0.046	All	5	28	33
Substance misuse	Definite (<=23)	5	0	5
	Possible (24-27)	2	2	4
	None (>=28)	1	13	14
P value 0.083	All	8	15	23
All	Definite (<=23)	21	0	21
	Possible (24-27)	17	20	37
	None (>=28)	4	108	112
P value <0.0001	All	42	128	170

Table 43 shows the results for attention which is one of the specific domains of cognitive function assessed by the ACE-R. The results show that patients may present a normal MMSE despite impaired attention. This is seen particularly in the cancer group where 24 patients had impaired attention detected by the ACE-R but only 14 patients had definite

cognitive impairment detected by the MMSE and a further 21 had possible cognitive impairment detected by the MMSE. The ACE-R is more accurate in assessing domains of cognitive function individually when compared to the MMSE in assessing cognitive function globally.

In patients with non-cancer pain there was less impairment of attention detected than in the cancer pain group. Five patients had impaired attention detected by the ACE-R and eight patients had possible or definite global cognitive impairment detected by the MMSE. In the substance misuse group eight patients had impaired attention and nine patients had global cognitive impairment detected by the assessments.

The findings were statistically significant when McNemar's test was applied to the results. P values are shown in the table.

Table 41: Memory impairment as assessed by ACE-R vs MMSE where n = 170

		Memory		
	MMSE	**< 19**	**>=19**	**All**
Cancer	Definite (<=23)	13	1	14
	Possible (24-27)	17	4	21
	None (>=28)	24	30	54
	All	54	35	89
Non-cancer	Definite (<=23)	1	0	1
	Possible (24-27)	5	2	7
	None (>=28)	4	21	25
	All	10	23	33
Substance misuse	Definite (<=23)	5	0	5
	Possible (24-27)	3	1	4
	None (>=28)	5	9	14
	All	13	10	23
Non-opioid, non-cancer	Definite (<=23)	1	0	1
	Possible (24-27)	2	3	5
	None (>=28)	3	16	19
	All	6	19	25
All	Definite (<=23)	20	1	21
	Possible (24-27)	27	10	37
	None (>=28)	36	76	112
	All	83	87	170

The results show that over half the patients with cancer pain had memory loss detected when the ACE-R was used. Fifty-four patients out of the total 89 patients had memory impairment in this patient group. When the MMSE was used 24 (44.4%) patients from a total of 54 patients would have had apparently normal cognitive function ie a normal MMSE score and the memory loss would have been missed. The proportion of patients with memory impairment was less in the group with non-cancer pain. In this group ten (30.3%) of the 33 patients had memory impairment with a preserved MMSE score. In the substance misuse group 13 (56.5%) of the patients had impaired memory. Fourteen (60.1%) patients had apparently normal cognitive function with the MMSE and only nine (39.1%) of the patients would have had their cognitive impairment recognised if the

MMSE was relied on. This is a lower proportion of patients with recognition of global impairment of cognitive function than the ACE-R is able to detect with specific memory loss.

Table 42: Fluency impairment as assessed by ACE-R vs MMSE where n = 170

		Fluency		
	MMSE	**< 8**	**>=8**	**All**
Cancer	Definite (<=23)	12	2	14
	Possible (24-27)	13	8	21
	None (>=28)	11	43	54
	All	36	53	89
Non-cancer	Definite (<=23)	1	0	1
	Possible (24-27)	0	7	7
	None (>=28)	1	24	25
	All	2	31	33
Substance misuse	Definite (<=23)	5	0	5
	Possible (24-27)	2	2	4
	None (>=28)	0	14	14
	All	7	16	23
Non-opioid , non-cancer	Definite (<=23)	1	0	1
	Possible (24-27)	1	4	5
	None (>=28)	0	19	19
	All	2	23	25
All	Definite (<=23)	19	2	21
	Possible (24-27)	16	21	37
	None (>=28)	12	100	112
	All	47	123	170

Patients in the cancer pain group have been shown to have reduced fluency. Thirty-six (40.4%) of the patients had reduced fluency in this group. In the non-cancer pain group fluency was much less affected and only two (6.1%) of the patients had reduced fluency. This low proportion was repeated in the group of patients with pain who were not prescribed opioids where two (8%) of the patients had reduced fluency. Interestingly in the

substance misuse group seven (30.4%) of the patients had reduced fluency and all the patients had possible or definite cognitive impairment on the MMSE.

Table 43: Language impairment as assessed by ACE-R vs MMSE where n = 170

		Language		
	MMSE	**< 21**	**>=21**	**All**
Cancer	Definite (<=23)	11	3	14
	Possible (24-27)	0	21	21
	None (>=28)	2	52	54
	All	13	76	89
Non-cancer	Definite (<=23)	1	0	1
	Possible (24-27)	0	7	7
	None (>=28)	0	25	25
	All	1	32	33
Substance misuse	Definite (<=23)	4	1	5
	Possible (24-27)	2	2	4
	None (>=28)	1	13	14
	All	7	16	23
Non-opioid, non-cancer	Definite (<=23)	1	0	1
	Possible (24-27)	0	5	5
	None (>=28)	0	19	19
	All	1	24	25
All	Definite (<=23)	17	4	21
	Possible (24-27)	2	35	37
	None (>=28)	3	109	112
	All	22	148	170

Language was the domain of cognitive function least affected in all groups of patients. Overall 22 (12.9%) of patients had impaired language abilities detected by the ACE-R. Patients in the non-cancer pain and non-cancer pain and not taking opioids groups were least likely to have reduced language abilities. Language was the domain of cognitive function most likely to be reflected by the MMSE. Seventeen (77.3%) of the 22 patients with impaired language abilities were in the possible or definite cognitive impairment groups when the MMSE was relied on.

Table 44: Visuospatial impairment as assessed by ACE-R vs MMSE where n = 170

		Visuo-spatial		
	MMSE	**< 14**	**>=14**	**All**
Cancer	Definite (<=23)	14	0	14
	Possible (24-27)	8	13	21
	None (>=28)	10	44	54
	All	32	57	89
Non-cancer	Definite (<=23)	1	0	1
	Possible (24-27)	2	5	7
	None (>=28)	3	22	25
	All	6	27	33
Substance misuse	Definite (<=23)	4	1	5
	Possible (24-27)	1	3	4
	None (>=28)	2	12	14
	All	7	16	23
Non-opioid, non-cancer	Definite (<=23)	1	0	1
	Possible (24-27)	3	2	5
	None (>=28)	0	19	19
	All	4	21	25
All	Definite (<=23)	20	1	21
	Possible (24-27)	14	23	37
	None (>=28)	15	97	112
	All	49	121	170

Visuospatial abilities can be seen to be impaired in the patient groups overall but particularly in the cancer pain group. Forty-nine (28.8%) of the total 170 patients had reduced visuospatial abilities. This was most pronounced in the cancer pain group where 32 (36.0%) of the group were affected. Despite the reduction in visuospatial abilities 54 (60.7%) of the 89 patients had apparently normal cognitive function when using the MMSE. In the non-cancer pain group six (18.2%) of the patients had reduced visuospatial awareness. Again this was a similar finding in the non-cancer patients who were not taking opioids. In this group four (16.0%) of the 25 patients had impaired visuospatial abilities.

Table 45: McNemar tests of agreement between impairment on ACE-R subscale and definite impairment on MMSE where n = 170

	Subscale				
	Attention	**Memory**	**Fluency**	**Language**	**Visuospatial**
	P	**P**	**P**	**P**	**P**
Group					
Cancer	0.002	0.000	0.000	0.655	0.000
Non-cancer	0.046	0.003	0.317		0.025
Substance misuse	0.083	0.005	0.157	0.317	0.317
Non-opioid	0.046	0.025	0.317		0.083
All	0.000	0.000	0.000	0.739	0.000

The table shows the McNemar tests of agreement between impairment on ACE-R subscale and definite impairment on MMSE. There was little impairment of language in any of the groups. The other domains of cognitive function however show significant disagreement between assessment on MMSE and assessment on the ACE-R subscales.

Table 46: Distribution of ACE-R and MMSE by regular opioid drugs used in last 4 weeks where n =134

	Used in last					
	24 hours			4 weeks		
	N	Median ACE-R	Median MMSE	N	Median ACE-R	Median MMSE
Alfentanil	2	90	29	3	88	28
Buprenorphine	2	81	28	2	82	28
Dihydrocodeine	1	81	26	3	88	29
Diamorphine	1	83	28	1	83	28
Fentanyl	15	87	28	13	89	28
Hydromorphone	4	86	27	3	93	29
Methadone	19	87	29	18	85	29
Morphine	54	85	28	57	85	28
Oxycodone	36	87	28	32	87	29

The table shows little variation in the median ACE-R and MMSE by the different opioids which were prescribed. Alfentanil has a much higher median ACE-R at 24 hours than the other opioids however the result is from only two patients so it is not possible to draw any conclusions from this result. The numbers of patients on each opioid at the two time points are very similar suggesting that most patients were on the same opioid at the each time point and the data therefore suggests that cognitive impairment is not just a feature of the initiation of opioids.

Table 47: Distribution of ACE-R subscale scores by regular opioid drugs used in last 4 weeks

	Memory (max 26)	Attention (max 18)	Fluency (max 14)	Language (max 26)	Visuo-spatial (max 16)
	Median	Median	Median	Median	Median
24 hours					
Alfentanil	21	18	12	25	16
Buprenorphine	20	17	8	23	14
DHC	20	17	9	20	15
Diamorphine	16	17	10	25	15
Fentanyl	20	18	10	25	16
Hydromorphone	20	16	11	25	16
Methadone	20	18	10	25	15
Morphine	18	18	11	25	15
Oxycodone	19	18	9	25	15
4 weeks					
Alfentanil	20	17	10	25	15
Buprenorphine	19	18	9	25	12
DHC	20	17	9	25	15
Diamorphine	16	17	10	25	15
Fentanyl	20	18	10	25	16
Hydromorphone	23	17	11	25	16
Methadone	18	18	10	25	15
Morphine	18	18	10	25	15
Oxycodone	19	18	10	25	15

The results show that the median scores for each of the domains of cognitive function assessed by the ACE-R are similar for the different opioids prescribed. The maximum scores for each domain are shown in the heading of the table in brackets. Diamorphine has the lowest median score for the domain of memory. Methadone, morphine and oxycodone also have low median scores for this domain. The median scores for attention are similar across all the different opioids prescribed. Dihydrocodeine, buprenorphine and oxycodone have the lowest median scores for the domain of fluency. The results of dihydrocodeine and buprenorphine are based on very few patients though. It is the same two drugs which show impairment at the language subscale and again this result may to be a chance finding given the small numbers of patients involved. The median scores for the visuospatial domain are similar for all opioids except buprenorphine.

Table 48: Distribution of ACE-R subscale scores by regular opioid drugs used in last 4 weeks. (Cancer patients only)

	Memory (max 26)	Attention (max 18)	Fluency (max 14)	Language (max 26)	Visuo-spatial (max 16)
	Median	Median	Median	Median	Median
24 hours					
Alfentanil	20	18	9	24	15
Fentanyl	18	18	8	23	14
Hydromorphone	16	15	10	24	16
Morphine	18	18	10	24	15
Oxycodone	18	18	8	25	15
4 weeks					
Alfentanil	20	18	10	25	15
Buprenorphine	15	17	8	23	10
Fentanyl	18	18	8	25	14
Hydromorphone	18	16	10	25	16
Morphine	18	18	9	24	15
Oxycodone	18	18	9	25	15

The table above shows the median scores for each of the specific domains of cognitive function assessed by the Addenbrooke's Cognitive Examination-Revised. These results are for patients with cancer pain only. Although the medians appear slightly lower overall there is no significant difference between the cancer patients and the study patients as a whole. The results show there is no association between the opioid prescribed and the cognitive impairment.

Table 49: Correlations of cognitive scores at assessment 1 with total dose in last 24 hours

Variable	Correlation with dose	P
ALL PATIENTS ON OPIOIDS		
ACE_R	0.032	0.711
MMSE	-0.012	0.888
Memory	0.062	0.476
Attention	-0.113	0.196
Fluency	0.029	0.740
Language	0.083	0.342
Visuo-spatial	-0.025	0.777
CANCER PATIENTS ONLY		
ACE_R	0.122	0.280
MMSE	0.116	0.304
Memory	0.177	0.115
Attention	0.012	0.917
Fluency	0.085	0.448
Language	0.127	0.259
Visuo-spatial	-0.078	0.489

The results show the correlation between the scores obtained from assessing cognitive function and the total dose of opioid prescribed in the 24 hours prior to assessment. The correlations are shown for all patients in the study who were prescribed opioids and then separately for the patients with cancer pain. The opioid drugs and doses have been converted to the morphine equivalent daily dose (MEDD) to facilitate this analysis. None

of the correlations approach one, indicating there are no positive correlations. Dose of opioid does not appear to affect the cognitive function when assessed using the ACE-R.

Table 50: Correlations of cognitive scores at assessment 1 with titrations

Variable	Correlation with percent change 7 days to 24 hours	P	Correlation with percent change 4 weeks to 24 hours	P
ACE_R	0.056	0.520	-0.086	0.328
MMSE	0.029	0.744	-0.027	0.758
Memory	0.063	0.469	-0.048	0.585
Attention	-0.017	0.847	0.007	0.938
Fluency	0.018	0.833	-0.151	0.086
Language	0.071	0.417	-0.034	0.705
Visuo-spatial	0.043	0.627	-0.058	0.509

The table above shows the results of correlation between domains of cognitive function and opioid titration. The MEDD has again been used to facilitate the analysis. None of the correlations approach one indicating that there is no correlation between titration of the opioid and the degree of cognitive impairment as measured by the ACE-R.

Table 51: Correlation of ACE_R cognitive scores with Bond and Lader scales at Assessment 1

Assessment	Group	Variable	Pearson correlation with ACE_R	P	Spearman correlation with ACE_R	P
1						
	Cancer	Mental sedation	-0.149	0.186	-0.171	0.129
	Cancer	Physical sedation	-0.059	0.604	-0.150	0.186
	Cancer	Calming effects	-0.102	0.369	-0.115	0.311
	Cancer	Other feelings	-0.081	0.475	-0.134	0.237
	Non-cancer	Mental sedation	-0.034	0.856	-0.059	0.751
	Non-cancer	Physical sedation	-0.104	0.577	-0.100	0.593
	Non-cancer	Calming effects	-0.129	0.488	-0.154	0.409
	Non-cancer	Other feelings	-0.064	0.734	-0.117	0.530
	Substance misuse	Mental sedation	-0.728	0.000	-0.648	0.003
	Substance misuse	Physical sedation	-0.594	0.007	-0.635	0.003
	Substance misuse	Calming effects	-0.697	0.001	-0.703	0.001
	Substance misuse	Other feelings	-0.497	0.031	-0.449	0.054
	Non-opioid	Mental sedation	0.110	0.617	0.124	0.574
	Non-opioid	Physical sedation	-0.051	0.816	-0.060	0.786
	Non-opioid	Calming effects	-0.253	0.244	-0.260	0.231
	Non-opioid	Other feelings	0.024	0.915	-0.110	0.618

Table 52: Correlation of ACE_R cognitive scores with Bond and Lader scales at Assessment 2

Assessment	Group	Variable	Pearson correlation with ACE_R	P	Spearman correlation with ACE_R	P
2						
	Cancer	Mental sedation	-0.188	0.222	-0.176	0.252
	Cancer	Physical sedation	-0.030	0.846	-0.085	0.583
	Cancer	Calming effects	0.073	0.637	0.009	0.953
	Cancer	Other feelings	0.147	0.340	0.076	0.623
	Non-cancer	Mental sedation	0.009	0.968	0.095	0.692
	Non-cancer	Physical sedation	-0.285	0.223	-0.200	0.397
	Non-cancer	Calming effects	-0.197	0.406	-0.117	0.622
	Non-cancer	Other feelings	-0.006	0.718	-0.073	0.758
	Non-opioid	Mental sedation	-0.093	0.751	-0.093	0.751
	Non-opioid	Physical sedation	-0.169	0.564	-0.195	0.501
	Non-opioid	Calming effects	-0.160	0.586	-0.251	0.386
	Non-opioid	Other feelings	-0.016	0.957	-0.265	0.360

Table 52 shows the results of the Bond and Lader scales which have been grouped into the four classes of feelings. The data has been presented for each of the four patient groups and for the first two assessments. Only cancer patients had three assessments and the data are not presented here. The scores for each of the classes of subjective feeling have been correlated with the ACE-R score. Both Pearson and Spearman correlations have been used. Only the patients with substance misuse show any correlation between subjective and objective measures of cognitive function. This is statistically significant with both the correlations. The other patient groups do not show a correlation between objective and subjective measures.

Table 53 shows the correlation between the mini-mental state examination and the Bond and Lader scales. Again the data are presented for each of the four classes of subjective feelings and for two assessments. The patients with a history of substance misuse are the only patient group who show a correlation between objective and subjective measures of cognitive function. The correlation is present when both Spearman and Pearson correlations are used but is not as strong as the correlation with the ACE-R. The correlation between MMSE and subjective measures does not reach statistical significance.

Table 53: Correlation of MMSE cognitive scores with analogue scales at Assessment 1

Assessment	Group	Label	Pearson correlation with MMSE	P	Spearman correlation with MMSE	P
1						
	Cancer	Mental sedation	-0.146	0.198	-0.166	0.142
	Cancer	Physical sedation	-0.100	0.380	-0.223	0.047
	Cancer	Calming effects	-0.143	0.207	-0.099	0.383
	Cancer	Other feelings	-0.054	0.634	-0.080	0.483
	Non-cancer	Mental sedation	-0.059	0.754	-0.033	0.860
	Non-cancer	Physical sedation	-0.067	0.721	-0.015	0.935
	Non-cancer	Calming effects	-0.032	0.865	-0.063	0.736
	Non-cancer	Other feelings	0.023	0.904	0.029	0.876
	Substance misuse	Mental sedation	-0.649	0.003	-0.581	0.009
	Substance misuse	Physical sedation	-0.527	0.020	-0.435	0.062
	Substance misuse	Calming effects	-0.501	0.029	-0.525	0.021
	Substance misuse	Other feelings	-0.413	0.079	-0.346	0.147
	Non-opioid	Mental sedation	0.180	0.410	0.222	0.309
	Non-opioid	Physical sedation	0.033	0.880	0.123	0.576
	Non-opioid	Calming effects	-0.081	0.715	0.049	0.823
	Non-opioid	Other feelings	0.172	0.433	0.210	0.336

Table 54: Correlation of MMSE cognitive scores with analogue scales at Assessment 2

Assessment	Group	Label	Pearson correlation with MMSE	P	Spearman correlation with MMSE	P
2						
	Cancer	Mental sedation	0.055	0.722	0.034	0.827
	Cancer	Physical sedation	0.147	0.341	0.098	0.529
	Cancer	Calming effects	0.230	0.133	0.135	0.383
	Cancer	Other feelings	0.207	0.178	0.115	0.458
	Non-cancer	Mental sedation	0.223	0.344	0.179	0.450
	Non-cancer	Physical sedation	-0.010	0.968	0.012	0.961
	Non-cancer	Calming effects	0.008	0.974	-0.015	0.950
	Non-cancer	Other feelings	0.035	0.882	0.018	0.941
	Substance misuse	Mental sedation	.	.	.	.
	Substance misuse	Physical sedation	.	.	.	.
	Substance misuse	Calming effects	.	.	.	.
	Substance misuse	Other feelings	.	.	.	.
	Non-opioid	Mental sedation	-0.175	0.550	-0.238	0.412
	Non-opioid	Physical sedation	-0.268	0.354	-0.310	0.280
	Non-opioid	Calming effects	-0.125	0.671	0.005	0.987
	Non-opioid	Other feelings	-0.021	0.944	-0.076	0.795

Table 55: Correlations of ACE-R cognitive scores with analogue scales

Assessment	Label	Pearson correlation with ACE_R	P	Spearman correlation with ACE_R	P
1	Mental sedation	-0.190	0.019	-0.175	0.031
1	Physical sedation	-0.142	0.079	-0.176	0.029
1	Calming effects	-0.185	0.022	-0.218	0.007
1	Other feelings	-0.077	0.345	-0.148	0.067
2	Mental sedation	-0.059	0.605	-0.081	0.479
2	Physical sedation	-0.126	0.270	-0.130	0.253
2	Calming effects	0.030	0.793	-0.023	0.843
2	Other feelings	0.068	0.549	0.004	0.974

The table above shows there is no correlation between the ACE-R and the subjective measure provided by the Bond and Lader scales when all the patients are grouped together. None of the correlations approaches one which would indicate the two variables were correlated. The same results are shown in the table below which explores possible correlation between the MMSE score and the subjective measures. Again all patients have been grouped together.

Table 56: Correlations of MMSE cognitive scores with analogue scales

Assessment	Label	Pearson correlation with MMSE	P	Spearman correlation with MMSE	P
1	Mental sedation	-0.173	0.032	-0.124	0.126
1	Physical sedation	-0.151	0.062	-0.155	0.055
1	Calming effects	-0.155	0.055	-0.125	0.124
1	Other feelings	-0.035	0.672	-0.035	0.663
2	Mental sedation	0.106	0.352	0.047	0.681
2	Physical sedation	0.048	0.678	0.006	0.956
2	Calming effects	0.167	0.141	0.072	0.529
2	Other feelings	0.154	0.175	0.073	0.521

Table 57: Correlation of ACE_R cognitive scores with anxiety and depression scores (HADS) at assessment 1

Group	Variable	Pearson correlation with ACE_R	P	Spearman correlation with ACE_R	P
Cases with ACE_R=0 excluded					
Cancer	Anxiety	0.032	0.780	0.103	0.360
Cancer	Depression	-0.052	0.648	-0.054	0.634
Non-cancer	Anxiety	-0.117	0.562	-0.108	0.590
Non-cancer	Depression	0.002	0.990	0.022	0.913
Substance misuse	Anxiety	0.105	0.659	-0.044	0.855
Substance misuse	Depression	-0.273	0.245	-0.297	0.203
Non-opioid	Anxiety	-0.275	0.194	-0.238	0.263
Non-opioid	Depression	-0.142	0.508	-0.227	0.286

Table 58: Correlation of ACE_R cognitive scores with anxiety and depression scores (HADS) at assessment 2

Group	Variable	Pearson correlation with ACE_R	P	Spearman correlation with ACE_R	P
Cases with ACE_R=0 excluded					
Cancer	Anxiety	0.011	0.946	-0.064	0.682
Cancer	Depression	-0.090	0.571	-0.216	0.170
Non-cancer	Anxiety	-0.084	0.725	-0.039	0.869
Non-cancer	Depression	-0.186	0.447	-0.166	0.497
Substance misuse	Anxiety	.	.	.	.
Substance misuse	Depression	.	.	.	.
Non-opioid	Anxiety	-0.664	0.013	-0.523	0.067
Non-opioid	Depression	-0.218	0.453	-0.244	0.400

The tables above show the correlation of the ACE-R scores with the presence of anxiety and depression scores at assessment one and two. The four different patient groups have been presented. As before both Spearman and Pearson correlation co-efficients have been presented. None of the variables appears to correlate. Anxiety and the ACE-R score appear

to have some degree of correlation in the group of patients with pain who were not on opioids at assessment two however the number in this patient group are small so this may be due to chance. Substance misuse patients only had one assessment hence the lack of results at assessment two for this patient group.

Table 59: ACE_R and MMSE by HADS score over 15

	ACE_R		ACE_R		MMSE		MMSE	
	HADS Score		HADS Score		HADS Score		HADS Score	
	<=15	>15	<=15	>15	<=15	>15	<=15	>15
	Mean	Mean	Median	Median	Mean	Mean	Median	Median
Assessment 1								
Cancer	77.7	70.9	81	83	26.1	23.8	28	28
Non-cancer	83.7	89.3	90	91	26.9	28.8	28	30
Substance misuse	67.4	74.2	87	83	22.8	24.7	28	28
Non-opioid	85.5	87.5	92	90	27.3	28.6	30	29
All	79.6	77.3	87	85	26.2	25.5	28	28
Assessment 2								
Cancer	78.7	69.6	85	85	25.4	22.7	28	28
Non-cancer	72.2	82.3	90	90	23.2	26.2	29	28
Substance misuse	92.0	.	92	.	28.0	.	28	.
Non-opioid	94.2	81.0	95	93	28.8	25.7	30	29
All	79.5	76.8	90	88	25.4	24.6	29	28

The Hospital Anxiety and Depression score can also be used as a total score with a score of greater than 15 suggesting anxiety or depression. The patient group has been divided according to score on the HADS. The mean and median ACE-R and MMSE scores have then been given for each of the patient groups. There appears to be a difference between the mean ACE-R scores of those cancer patients who score greater than 15 on the HADS and those who score 15 or less. There also appears to be a difference between patients with

a history of substance misuse who score more highly on the HADS indicating anxiety and / or depression is present. The differences appear less clear when the MMSE is used to provide the objective measure of cognitive function. Both the mean and the median are reported because the distribution of the ACE-R is negatively skewed.

Table 60: Correlation of ACE_R cognitive scores with average pain (BPI) scores at Assessment 1

grp	Variable	Pearson correlation with ACE_R	P	Spearman correlation with ACE_R	P
Cases with ACE_R=0 excluded					
Cancer	Average pain (BPI Q4)	0.015	0.895	0.008	0.946
Cancer	Average pain interference score (BPI)	-0.101	0.452	-0.120	0.368
Non-cancer	Average pain (BPI Q4)	-0.233	0.200	-0.265	0.142
Non-cancer	Average pain interference score (BPI)	-0.043	0.822	-0.078	0.682
Substance misuse	Average pain (BPI Q4)	0.231	0.582	0.157	0.711
Substance misuse	Average pain interference score (BPI)	-0.275	0.655	-0.600	0.285
Non-opioid	Average pain (BPI Q4)	-0.268	0.205	-0.238	0.263
Non-opioid	Average pain interference score (BPI)	-0.378	0.082	-0.407	0.060

Table 61: Correlation of ACE_R cognitive scores with average pain (BPI) scores at assessment 2

grp	Variable	Pearson correlation with ACE_R	P	Spearman correlation with ACE_R	P
Cases with ACE_R=0 excluded					
Cancer	Average pain (BPI Q4)	-0.078	0.615	-0.084	0.588
Cancer	Average pain interference score (BPI)	-0.033	0.861	-0.109	0.567
Non-cancer	Average pain (BPI Q4)	-0.311	0.182	-0.294	0.208
Non-cancer	Average pain interference score (BPI)	-0.242	0.305	-0.118	0.621
Substance misuse	Average pain (BPI Q4)	.	.	.	.
Substance misuse	Average pain interference score (BPI)	.	.	.	.
Non-opioid	Average pain (BPI Q4)				
Non-opioid	Average pain interference score (BPI)				

The table above show the ACE-R scores of the patients in the different patient groups. Two questions from the brief pain inventory have been used to look for possible correlation between cognitive function as measured by the ACE-R and pain. The questions which have been used are the average pain severity score and the average pain interference pain score. It is demonstrated that in this study there is no association between pain and the score obtained on the ACE-R

5.11 Discussion

5.11.1 Summary of Main Findings

The use of the Addenbrooke's Cognitive Examination-Revised is more likely to detect cognitive impairment in our patient groups studied than the mini mental state examination. The higher detection of cognitive impairment was true for both the group as a whole and for the different patient groups recruited. The most noticeable difference was in the group of patients with cancer pain who were prescribed opioids, where 56.2% of patients had cognitive impairment detected by the ACE-R compared to 39.3% of patients with cognitive impairment detected by the MMSE. The disagreement between the two assessments of cognitive function was statistically significant when McNemar's test was applied. In the group of patients with non-cancer pain who were not prescribed opioids the two tests detected the same prevalence of cognitive impairment.

The results of this study showed that attention, memory, fluency and visuospatial awareness were all impaired. Language was not significantly affected in any of the patient groups. It is interesting to note that the MMSE relies mainly on attention and orientation in its assessment of cognitive function and yet it still failed to detect the same number of patients with cognitive impairment as the ACE-R.

Patients in the cancer and substance misuse groups had the greatest degree of cognitive impairment. The patients with cancer pain showed evidence of impaired cognitive function in all domains but particularly in the memory domain with 60.1% of patients exhibiting memory loss.

Possible correlations between cognitive function and the opioid prescribed were explored using the median values of the Ace-R and the MMSE. There was no evidence that

particular opioids have more impact on cognitive function however the sample sizes for some of the opioids were very small.

Possible correlations between the dose of opioid and the cognitive function scores were explored and the results showed no evidence of a correlation. Similarly there was no evidence to support the hypothesis that titration of the dose of the opioid contributes to cognitive impairment.

The objective and subjective measures of cognitive impairment did not correlate well in this study.

5.12 Bias and limitations

This study has provided longitudinal data however there are necessary gaps of time between assessments which will have limited the responsiveness of the data and lead us to rely on trends over time. The assessments we have used have been task-focussed and our study has this in common with other published work. While we have found a clinically relevant and accessible tool it remains a tool and may not adequately detect how patients function in everyday life. Qualitative research which was presented in chapter six of the thesis has furthered our understanding of this everyday functioning but further research could more specifically explore the issues for patients especially those who may also be trying to care for families or maintain employment while on opioids.

5.13 Comparison with Published Literature

5.13.1 Sample Size and Longitudinal Data

This study recruited 178 patients in different clinical groups. This sample size was larger than most of the published studies. Only Klepstad and the two papers based on data from the European Pharmacogenetic Opioid Study had larger sample sizes (Andreasson et al, 2012; Klepstad et al, 2003; Kurita et al, 2011) Klepstad recruited 300 patients but they were all hospital in-patients which may limit the relevance of the conclusions to other patients. The European Pain and Opioid Study recruited a very large number of patients but they were recruited in 11 different countries which must have introduced inter-observer bias to the results. In addition there may have been cultural variations in response to pain, interpretation of the questionnaires used (Kurita et al, 2011).

A further strength of this study is the longitudinal data that has been generated and the careful phenotyping of the patients. Gagnon (Gagnon et al, 2000) and Gaudreau (Gaudreau et al, 2006) both presented longitudinal data but most of the studies draw their conclusions from point prevalence and single assessments of cognitive function. The mean follow-up time in Gaudreau's study was 16 days which is significantly less than the follow-up time in our study where assessments were six to eight weeks apart and many of the cancer patients had three assessments. The nature of the multiple factors which can influence cognitive function especially in the cancer pain group mean there is almost certainly inaccuracy introduced by using only single assessments. For example if the patient was very fatigued on the day of the study.

In one of the few studies that provide longitudinal data, Tassain et al followed a small cohort of patients with chronic non-cancer pain over a 12 month period. This study is significant because patients were recruited when they were opioid-naïve and assessed prior

to commencing them on opioids. The numbers involved were small – only 28 patients were recruited and ten of these dropped out due to side effects or lack of benefit on their pain. These patients were asked to continue in the study in order to provide control data. Eleven patients on opioids continued to the 12-month assessment. The main side-effects causing patients to discontinue opioid were constipation and sedation. The researchers found no difference in memory, attention, verbal fluency and reaction time between the two groups and no apparent adverse effect from the introduction of opioid (Tassain et al, 2003).

Our study also derives strength from the recruitment of patients with cancer and non-cancer pain, a history of substance misuse and a history of chronic non-cancer pain but who were not on opioids. Completing the same research tools with the different groups of patients has enabled a useful comparison between different clinical groups which is not usually available in the literature.

5.13.2 Prevalence of cognitive impairment

The European Pharmacogenetic Opioid Study recruited 1915 patients who were prescribed opioids for the management of their cancer pain. Using the MMSE this study found that one in three of the patients had impaired cognitive function (Kurita et al, 2011). Although the sample size of the EPOS paper is much larger than our study the prevalence of cognitive impairment is quite similar. The MMSE detected impaired cognitive function in 39.3% of cancer patients, 24.2% of non-cancer patients and 39.1% of patients with a history of substance misuse. In his review of "Opioids and cognition in cancer patients" Lawlor referred to studies which had shown prevalence of cognitive impairment between 14 and 77% of patients (Lawlor, 2002) although the definitions of impairment varied and the highest prevalence was in patients who had a transient "impaired mental status" (Lawlor, 2002, page 1837). It is when the ACE-R was used in our study that the extent of the cognitive impairment was revealed however.

In a review of the published literature regarding the impact of opioids on the cognitive function of patients with chronic non-cancer pain Kendall and colleagues found generally poor quality studies and inconsistent findings. They recommended advising patients that opioids may adversely impact on cognitive function and that tests would be specific to the domains of cognitive function most likely to be affected. They recognised that the mini-mental state examination was probably not the most appropriate tool (Kendall et al. 2010).

In patients with substance misuse, Shane Darke and his colleagues found that patients who are on a maintenance programme perform less well than matched controls whether they were on methadone or buprenorphine maintenance (Darke 2012). Patients completed a series of tests which tested different cognitive domains including working memory, executive function and information processing speed. The authors felt the level of impairment may require additional help and support from clinicians when managing this group of patients (Darke 2012).

Importantly in their study in 1998 Wood and colleagues recognised that patients who appear cognitively intact with no evidence of sedation or confusion may still have impaired memory, attention and / or concentration (Wood et al, 1998). This finding, taken with our results about the prevalence of cognitive impairment, highlights the importance of screening for cognitive impairment in a systematic way rather than relying on gross assessment during clinical consultation.

5.13.3 Impact of Confounders on Cognitive Function

Possible correlation between the Addenbrooke's Cognitive Examination - Revised (ACE-R) and anxiety and depression as separate scores taken from the Hospital Anxiety and Depression Score was explored. No correlation was found in this study. When the HADS was used as a whole with a score above 15 indicating potential case of anxiety or

depression the ACE-R scores were less in those patients with a high score indicating anxiety and / or depression. This association was not detected by the MMSE.

Depression and cognitive impairment are both prevalent in patients with pain, both cancer and non-cancer pain (Brown, Glass, Park 2002) and it is difficult to separate them. Pain itself also affects cognitive function. Pain is known to adversely affect attention, the ability to form memories and reaction times (Moriarty, McGuire, Finn 2011).

5.13.4 Correlation between the objective and subjective measures of cognitive function

In this study there was no apparent correlation between the objective and subjective measures of cognitive function. The Bond and Lader analogue scales did not appear to be sensitive to the changes patients noticed in their cognitive function. The patients who were involved in the qualitative research were very aware of impairment in their memory and word-finding abilities and this was highlighted in the themes extracted from the transcribed interviews (see Chapter 6).

In a study published in 2013 Nils Inge Landro and colleagues recruited patients with chronic non-cancer pain who were attending a pain clinic in Norway. They highlighted that patients who discuss cognitive impairment with their pain specialist may find these symptoms are attributed to depression or anxiety and that the cognitive function is not fully assessed (Landro et al, 2013). The mean BPI score in this group was 6.2 which was higher than in our patient group. Interestingly Landro and his colleagues excluded the current pain score from the calculation of the mean pain severity domain of the Brief pain Inventory. In the published study they found:

> "About 20% of the patients presented neuropsychological problems that might influence daily psychosocial functioning in work settings demanding high degree of attentional control." (Landro et al, 2013, page 975)

47% of the patients exhibited a degree of cognitive impairment (Landro et al, 2013). The research team used specific tests of psychological function despite recognising that the reason patients are often not properly assessed is the lack of experience of clinicians with the specialist tests. They used a "Matrix Reasoning and Vocabulary" test and assessed psychomotor speed and attention using the Stroop test – ie the colour -word interference test. Furthermore in this published study the authors used the Everyday Memory Questionnaire and the objective and subjective measures were found to correlate (Landro et al, 2013).

In a series of studies in the late 1990's W. M. O'Neill and his colleagues used the Bond and Lader analogue scales. They used the scales to measure "alertness, calmness and contentment" (O'Neill et al, 1995, page 449) as part of the assessment of the impact of morphine, lorazepam, dextropropoxyphene and placebo on healthy volunteers. They found that morphine improved calmness and reduced alertness (Hanks et al, 1995; O'Neill et al, 1995; O'Neill et al, 2000). The authors of these studies found the Bond and Lader scales helpful for reasons which may reflect the differences between healthy volunteers and patients who are on long-term opioids for either pain or substance misuse. It may be that patients who are on opioids become accustomed to the calming and sedating effects of the opioids. It could also be that pain is having an arousal effect on the patient and counteracting the effects of the opioid (Kendall et al, 2010; Sjogren Thomsen, Olsen, 2000).

5.13.5 Specific cognitive domains affected

The results of this study showed that attention, memory, fluency and visuospatial awareness were all impaired. Patients appear to be aware of memory impairment (Landro et al, 2013). The Addenbrooke's Cognitive Examination – Revised (ACE-R) provides a more comprehensive assessment of memory than the Mini-Mental State Examination (MMSE) with a score of 26 out of 100 in the ACE-R relating to memory compared to just three out of 30 in the MMSE.

Using some of the specific neuropsychological tools can result in little cognitive impairment being revealed for example despite a comprehensive series of tests. Kurita and de Mattos Pimenta found that only two of the assessments revealed a difference in patients with pain and taking opioids compared to those with pain and not on opioids (Kurita and de Mattos Pimenta, 2008). They found a difference between the patient groups when assessing memory, attention and executive function (Kurita and de Mattos Pimenta, 2008). Similarly in a study which recruited patients with chronic non-cancer pain who were on oral opioids with a median morphine equivalent daily dose of 60 mg the authors found that attention, working memory and psychomotor speed were adversely affected in patients with pain who were on opioids (Sjogren, Thomsen, Olsen, 2000). While there may be issues with sample size in some of the studies and it is also recognised that cognitive impairment is multi-factorial and any impairment is unlikely to be attributable solely to opioids (see introduction to this chapter) it seems that the choice of tool is key. The discrepancy between the pathology detected by the two tools may be related to sample size or that the specific aspects of cognitive function affected are not well assessed by the MMSE.

5.13.6 Importance of Opioid and Route of Administration

Our results did not show an association between either the dose of the opioid or titration of the dose and the impact on cognitive function. Other studies have shown contradictory

results. In the paper based on the European Pharmacogenetic Opioid Study Kurita and her colleagues found that higher doses of opioids were associated with more significant cognitive impairment.

> "Patients receiving doses of morphine greater than 400 mg in 24 hours or the equivalent dose of an alternative opioid had 1.75 (95% CI, 1.25 to 2.46) times higher odds of having lower MMSE scores compared with those receiving daily doses less than 80 mg." (Kurita et al, 2011, page 1297)

Sjogren and Banning did not find any benefit when they changed patients from oral opioids to epidural opioid. The sample size was small though with just 14 patients. The patients recruited for the study were experiencing either unwanted sedation or inadequate pain control or both on oral opioids. As a group the patients gained little benefit from the change of opioid route (Sjogren and Banning, 1989).

In a study published in 1989, Eduardo Bruera showed that titration of the opioid was associated with a negative effect on cognitive function. He recruited twenty patients who were on a stable opioid dose and 20 patients who had a recent titration of opioid. He found adverse impact on memory, arithmetic tests, and visual analogue scales for sedation and nausea. The findings were statistically significant despite small numbers (Bruera, 1989).

5.14 Conclusion

We have used the Addenbrooke's Cognitive Examination – Revised to assess the cognitive function of patients from different clinical groups who are prescribed opioids. This is a tool which can be used by clinicians and does not rely on specialist psychological expertise to use it correctly. Using the ACE-R we have revealed the extent of cognitive impairment is greater than previously recognised when the MMSE has been relied on. We did not show an association between opioid dose or titration of the opioid which is consistent with some

of the published literature. Qualitative research revealed that patients are very aware of the cognitive impairment.

CHAPTER 6: HOW DO PATIENTS EXPERIENCE OPIOID TOXICITY?

Outline of chapter:

- Pain is prevalent in patients with cancer and is likely to be managed with opioids.
- Some patients will experience opioid toxicity which includes myoclonus, sedation, confusion, hallucinations and peripheral shadows.
- Qualitative description is a methodology which can be used to explore the patient experience of opioid toxicity.
- Opioid-induced hyperalgesia may be present with the symptoms of opioid toxicity. This has not previously been recognised.
- Patients also report significant impairment of cognitive function and covert self-management of the symptoms of opioid toxicity.

6.1 Aim

To explore the patient experience of an episode of opioid toxicity

6.2 Introduction

6.2.1 Opioid side effects and toxicity

Opioids have an essential role in the management of cancer and non-cancer pain but for some patients the side effects will outweigh the improvement in their pain. Opioid toxicity represents the more severe end of the spectrum of side effects and is a potentially distressing experience for both the patient and those who care for them. Studies have explored patients' views on being prescribed strong opioids but there has not been an attempt to explore the patient experience of opioid toxicity. This study provides the first description of the experience of patients with cancer pain who have previously been opioid toxic.

It is now well recognised that opioids have a role in the management of pain of patients with both malignant and non-malignant disease. Opioids are used at higher doses and at an earlier stage of disease than before. About 80% of patients with cancer will experience moderate to severe pain during their illness and for the majority of these patients the pain will be successfully managed using opioid analgesia. However some patients (10 – 30%) will not experience effective pain relief on strong opioids because analgesia is not adequate or the side effects of the medications limit adequate titration (Daeninck and Bruera, 1999; Cherny et al, 2001).

Patients vary in their experience of opioid side effects and the extent to which the side effects limit drug titration. Opioid side effects include nausea, vomiting, pruritus, constipation. Mild opioid toxicity may not be recognised by healthcare professionals or may not be reported by the patient. The effect of the opioids may only be recognised therefore when the patient develops severe opioid toxicity with myoclonus (muscle jerks), hallucinations, respiratory depression and marked confusion or cognitive impairment. Opioid switching to improve analgesia and minimise side effects is common but there is little evidence for its use (McNicol et al 2003; Dale et al, 2011)

6.2.2 Qualitative Research

"Qualitative research is an approach that allows you to examine people's experiences in detail, by using a specific set of research methods such as in-depth interviews, focus group discussions, observation, content analysis, visual methods, and life histories or biographies." Qualitative research is used to address the "How" and "Why" research questions. "It gives voice to the issues of a certain study population" and "provides depth, detail, nuance and context to the research issues" (Hennink M, Hutter I, Bailey A. Qualitative research Methods. Sage Publications 2011) It is not intended to be generalizable but it may be relevant or applicable to other patient groups.

Patients with advanced disease do not appear to find qualitative research too burdensome and responded positively when asked about participating in qualitative research. Gysels et al found that participants found being interviewed helpful as it allowed them to tell their story. This was therapeutic for the majority of participants when assessed after interviews conducted to address other research questions (Gysels, Shipman, Higginson, 2008)

In qualitative research researchers are active participants in the creation of data (Addington-Hall et al (ed) Research Methods in Palliative Care. Oxford University Press, 2009). Qualitative research requires an open mind. It should not be conducted with prejudice or pre-conceived ideas about what the patients may report. This can be challenging to the researcher who is already familiar with the literature on a particular subject and already has experience of managing patients with the symptoms or condition being investigated.

When conducting the interviews issues start to become apparent. The next interview explores the issue further and the interviewer askes more specific and probing questions in order to elicit more detail. Subsequent interviews follow the exploration and respond to new subjects and concerns as they are mentioned by participants. When no new information is being reviewed or elicited information saturation had been reached. Although there may be an instinct that suggests saturation has been reached this will only be confirmed once the data has been analysed.

Qualitative research differs from quantitative research in that it allows analysis of the data to start as soon as collection of data starts. This is a natural process as the researcher starts to process the data intuitively. The researcher will start to recognise keywords and phrases and to instinctively label these keywords as data. There is a benefit of one interviewer conducting all research interviews as this initial analysis allows subsequent interviews to draw out and explore whether themes discussed with one patient are of importance or relevance to other patients. Conversely if there is more than one interviewer they will almost certainly hear different cues while interviewing participants and this will lead to

different themes being explored. Involvement of more than one researcher has the potential to bring validity to the study.

Purposeful recruitment is valid in qualitative research. It is legitimate to actively seek those who have had a particular experience or fall into a particular group. The study was not looking at the prevalence of opioid toxicity but giving voice to those who had previously been opioid toxic. In this study we sought males or females who were aged over 18 years and who had a cancer diagnosis. The participants needed to be prescribed strong opioids and have been previously opioid toxic.

6.2.3 Qualitative Description

Qualitative description provides a rich description of an experience. "The final product is a description of informants' experiences in a language similar to the informants' own language." The aim is to sort and code the data and stay true to it. There is transparency of data in qualitative description that should be valued as there has been no attempt to infer or impose meaning, simply a description of the results (Neergaard et al, 2009; Sandelowski, 2000)

"Table 1: Analytic strategies in qualitative description (taken from Neergaard MA, Olesen F, Andersen RS et al, Proposed by Miles et al)

a. Coding of data from notes, observation or interviews
b. Recording insights and reflections on the data
c. Sorting through the data to identify similar phrases, patterns, themes, sequences and important features
d. Looking for commonalities and differences among the data and extracting them for further consideration and analysis
e. Gradually deciding on a small group or generalizations that hold true for the data

f. Examining these generalizations in the light of existing knowledge"

Several authors have argued the value of qualitative description is in its simplicity and the reporting of data in a very transparent way. There are no attempts to interpret the data or generate an underlying theory.

Sandelowski argues that qualitative description is a useful research method in its own right and does not need to be seen as a starter for other methods.

> "Researchers conducting qualitative descriptive studies stay closer to their data and to the surface of words and events than researchers conducting grounded theory, phenomenologic ethnographic or narrative studies. In qualitative descriptive studies, language is a vehicle of communication, not itself an interpretive structure that must be read. Yet such surface readings should not be considered superficial, or trivial and worthless. I intend the word surface here to convey the depth of penetration into, or the degree of interpretive activity around, reported or observed events. There is nothing trivial or easy about getting the facts, and the meanings participants give to those facts, right and then conveying them in a coherent and useful manner." (Sandelowski, 2000)

6.2.4 Consideration of other methodologies

Research questions that address individual experiences are best addressed through the interview method of data collection. Fieldwork approaches, which require a close interaction with participants and observation of behaviour over a period of time, were not appropriate to my research question. Individual interviews were chosen rather than focus groups as it would be challenging to bring together a group of patients who have malignant disease and are often attending oncology clinics, having chemotherapy or attending day hospice for the purpose of group discussions. It can be problematic to require this group of patients to travel at a particular time and date to a central location. In addition, I wanted to give voice to the individual and explore the individual's experience of opioid toxicity. It is easier to explore more sensitive issues on an individual basis rather than in a group

Therefore it was felt individual interviews were more appropriate (Addington-Hall et al (ed) Research Methods in Palliative Care. Oxford University Press, 2009).

Qualitative research covers several different methodologies including phenomenology, ethnology. There can be a pressure to make qualitative research fit a mould and generate a central theory. The pressure comes from comparisons between quantitative and qualitative research and the value of the different methodologies. For some studies this is appropriate but for others this forces the study into a new direction. The pressure can result from a tendency to view qualitative research as somehow inferior to quantitative research and researchers feel a need to overdo the methodology. This can be counter-productive. The research methodology should be appropriate to the research question and what is already known about the subject (Sandelowski, 2000; Mays and Pope, 2000) Qualitative description is a useful methodology for exploratory studies.

Accuracy of the data will be improved by comparing the recording and transcription of the interview. If the participant is able to read their own transcription accuracy will be further enhanced.

The use of quotes in qualitative research enables others to consider the data and the categories that have been generated. They can decide if the themes are applicable to their own patient group and whether the categories are appropriate given the data presented.

Reflexivity is "sensitivity to the ways in which the researcher and the research process have shaped the data collected." (Mays and Pope, 2000) Qualitative research both accepts and values the influence of a researcher on the "creation of research data" (Hennink, Hutter, Bailey. Qualitative Research Methods. 2011). In qualitative research the researcher interprets the data with a subjective view based on their own ideals and background and assumptions. (Hennink, Hutter, Bailey. Qualitative Research Methods. 2011) However it is reaching an understanding the experience from the participants' perspective that is

important. The researcher must reflect on the study and make it clear how participants' response to them may have influenced the study.

6.3 Method

6.3.1 Participant Selection

Participants were recruited who were part of the main study. While discussing the study and seeking consent for involvement participants were identified who had previously been opioid toxic. Others were identified to the researcher as having experienced opioid toxicity by the clinician who suggested they participate in the main study. Participants who had experienced hallucinations, myoclonus, sedation and peripheral shadows were invited to take part in the qualitative study. The diagnosis of opioid toxicity was made on the basis of the symptoms reported by the participant and on the resolution of symptoms coinciding with a reduction in the strong opioids prescribed. The diagnosis of an episode of opioid toxicity required both these aspects to be present before inclusion in this part of the study.

The aim of the project was explained to participants. The interview process was explained, including that the interview would be recorded and then transcribed. The use of quotes to illustrate themes was explained to participants and they were reassured they would not be identifiable from any quotes used. Written consent was obtained for the qualitative study.

Only participants for whom the episode of opioid toxicity had already resolved were recruited. It would not have been appropriate to recruit those who were still experiencing opioid toxicity as it is likely that their capacity would be impaired or that they were distressed with the symptoms they were experiencing.

At the time of inclusion in the main study therefore participants were identified who had previously been opioid toxic. Participants needed to meet the inclusion criteria for the main study. They had a cancer diagnosis, aged 18 years or over and had a prognosis of at least three months. They had been prescribed and were taking a strong opioid. The interview was conducted at a different time to the completion of other study assessments where possible and unless the patient preferred otherwise. This was done to avoid tiring the participant.

Appropriate ethical permission had been granted and research and development approval was in place.

The safety of the researcher was considered and the lone worker policy was adhered to.

It was made clear to participants at the point of informed consent that if there were ongoing symptoms or features that suggested opioid related side effects these would not be managed by the researcher but contact would be made with the appropriate health professional to arrange review of the patient and instigate a management plan.

6.3.2 Data Collection

Semi structured interviews were undertaken with a question schedule which was drafted before recruitment commenced. As data emerged the questions were refined and became more detailed and structured. This is a recognised and valid part of data collection in qualitative research. When writing the interview guide open questions were formulated and language was chosen which was non-technical and understandable by participants.

Recruitment continued until saturation was considered to have been reached and that interviews were not revealing any new data or themes. The decision that saturation had been reached was confirmed at the time of data analysis.

The recorded interviews were transcribed not by the interviewer but by a colleague experienced in transcription of qualitative data. There was a short time interval between recording and transcription which enabled the researcher to review previous interviews. This allowed familiarity with the data to develop and learning from the conduct of interviews to take place. Transcription of the interviews by the researcher would have contributed further to immersion in the data however due to time constraints and the number of patient assessments required for the study as a whole it was not possible for the primary researcher to also undertake transcription. It was felt that familiarity with the data would result from the relatively small number of interviews and non-use of coding software.

Anonymity of the participants has been ensured by the use of numbers rather than any identifiable data.

6.4 Analysis

Six of the seventeen interviews were initially read and codes developed. The codes were modified as data analysis progressed. Deductive and inductive codes were produced. Inductive codes are those which emerge from the data and are derived from the language of the participants. Deductive codes come from the researcher's familiarity with the published literature and in this study the clinical phenomena being researched. Deductive codes are used to inform the development of the interview questions. The interviews were read several times and the researcher became immersed in that data in order that codes start to emerge. Words were underlined and the interviews annotated. Initial thoughts were noted and the data was questioned and interrogated to find the underlying meaning. Codes

were named and defined. To ensure validity a co-researcher has reviewed a sample of the interviews and the coding has been agreed between the two.

The purpose of the analysis was to explore the research question. The results must be grounded, that is, supported by the data and having come from the data. Transparency is ensured by the use of quotes.

The first reading of the transcribed interviews was quite passive but some codes were generated. Active reading and a search for meaning in the interviews revealed many more codes. These were refined and merged and then the codes were compared and categorized to produce themes.

Saturation was confirmed on completion of the data analysis. Once coding had been completed and agreed by both researchers involved in the coding the themes were explored. Both researchers agreed that no new codes or themes were emerging from the interviews conducted most recently. The codes were starting to repeat.

6.5 Results

Although the main study was open to patients who were prescribed opioids for non-cancer pain or substance misuse, the qualitative research part was open only to those with cancer pain. All the patients who were identified as eligible and were approached to take in the qualitative research were interested in participating.

Several key themes emerged from the data. There is significant impact on the participants and their family with rich description of impaired cognitive function and of altered pain experience. Participants describe the strategies that helped them to cope with the symptoms

of opioid toxicity. Participants were very accepting of the side effects that the opioids caused them.

6.5.1 Patients recruited

Seventeen participants were recruited and semi-structured interviews conducted. Eight participants were female and nine were male with an age range of 45 – 68 (mean 55.7) years. The characteristics of the participants recruited are described in table 2. The patients had a variety of primary tumours. Breast cancer was the most common primary malignancy. Lung and multiple myeloma were the next most frequent diagnoses. These three diagnoses accounted for ten of the patients malignancies.

All those who were approached to participate in this part of the study consented to be involved. All interviews were conducted by the same researcher (the author) and all but two of the interviews were conducted in the patient's own home. The interviews generated between 11 and 42 pages of transcribed text each with a mean length of text of 24.6 pages.

Table 62: Characteristics of the participants recruited to explore their experience of opioid toxicity where n=17

Patient ID	Age, Sex	Primary malignancy	Metastases present
Patient 1	51, M	Lung	Bone, Lung
Patient 2	45, F	Breast	Bone, Lung, Nodes
Patient 3	66, F	Ovary	Bowel, Omentum
Patient 4	45, F	Breast	Bone, Nodes
Patient 5	60, M	Prostate	Bone
Patient 6	59, F	Ovary	Omentum
Patient 7	51, F	Breast	Bone, Liver
Patient 8	60, M	Chronic Lymphocytic Leukaemia	
Patient 9	51, F	Lung	Nodes
Patient 10	62, M	Multiple Myeloma	
Patient 11	48, F	Colorectal	Omentum, Nodes
Patient 12	53, M	Lung	Lung
Patient 13	52, M	Multiple Myeloma	
Patient 14	61, M	Multiple Myeloma	
Patient 15	68, M	Prostate	Bone
Patient 16	58, F	Breast	Bone, Nodes
Patient 17	57, M	Bladder	Lung, Nodes

Table 63: Opioid History prior to Episode of Toxicity where n = 17

Patient ID	Opioid, Route, Dose	Duration of episode	Associated with changes in opioid?
Patient 1	Morphine, oral, 90mg bd	Symptoms present over 3 months	Associated with titration
Patient 2	Oxycodone , oral, 80mg bd	Symptoms present for six weeks	Associated with dose titration
Patient 3	Oxycodone, CSCI, 20mg	Symptoms present for 3 weeks	Associated with initiation and titration of opioid
Patient 4	Fentanyl, TD, 75mcg/hour	2 weeks	Associated with addition of adjuvant analgesic
Patient 5	Morphine, oral,100mg bd	Intermittent	Associated with use of multiple breakthrough doses
Patient 6	Morphine, oral, 30mg bd	Few weeks	Started chemotherapy
Patient 7	Morphine, oral & hydromorphone, oral, 24mg bd	Months	Opioid being titrated
Patient 8	Oxycodone, oral, 15mg bd	24 hours	No change in opioid or other factor identified
Patient 9	Morphine, oral, 30mg bd	Few weeks	Titration of opioid
Patient 10	Oxycodone, oral, 80mg bd	Weeks	Titration of opioid
Patient 11	Morphine, oral, 40mg bd	Few days	Dose of opioid titrated
Patient 12	Morphine, oral, 30mg bd	Few weeks	At initiation of opioid therapy
Patient 13	Patient unable to recall	6 – 8 weeks	Patient unable to recall
Patient 14	Morphine, CSCI, dose not known	24 hours	No change in opioid or other factor identified
Patient 15	Oxycodone, oral, 160mg bd	Few days	Associated with trial switch to morphine
Patient 16	Morphine, oral, 120mg bd	Worsening features over 3 months	At initiation of opioid
Patient 17	Oxycodone, oral, 20mg bd	Few days	Associated with titration to oxycodone 30mg bd

Table 63 shows that most patients were on morphine or oxycodone when they developed features of opioid toxicity. The patients were on very moderate doses of opioids. Not all patients were able to recall the dose of opioid that was associated with toxicity. The table also shows that although some patients sought help quickly others persevered with their symptoms for weeks or months before asking for advice.

Table 64: The site and nature of the pain experienced where n = 17

Patient ID	Site of Pain	Number of Pain Sites	Nature of Pain
Patient 1	Arm	1	Neuropathic
Patient 2	Knees, ankles, back	3	Bony
Patient 3	Lower limbs	2	Mixed
Patient 4	Arm	1	Neuropathic
Patient 5	Pelvis, knee, lower leg	3	Bony, some neuropathic
Patient 6	Abdominal	1	Visceral
Patient 7	Back	1	Bony
Patient 8	Coccyx	1	Neuropathic
Patient 9	Chest wall	1	Mixed
Patient 10	Back, shoulders	2	Musculoskeletal
Patient 11	Abdomen and perineum	2	Visceral and neuropathic
Patient 12	Chest	1	Mixed
Patient 13	Back, hips	3	Bony and neuropathic
Patient 14	Lower back	1	Bony
Patient 15	Lower limb	1	Mixed
Patient 16	Neck and arm	1	Neuropathic
Patient 17	Back	1	Neuropathic

Table 64 shows the variety of sites at which patients had pain. Six of the seventeen patients had more than one site of pain. Eight patients had neuropathic pain and four of the patients described a mixed pain.

6.6 Themes extracted

6.6.1 Impact of side effects on Person

Participants described the return to normality after being debilitated with the episode of opioid toxicity. They described with amazement how much more they could now achieve for example making lunch for friends or going shopping. One participant admitted she had thought "2010'll not exist for me" and "When am I gonnae start feeling okay?" (Participant 3)

Participants recalled a difficulty when others saw them and noticed the side effects. For example one man would fall asleep in the bathroom and his wife would find him there. Others were concerned what strangers would think if they saw them in the street and they either had myoclonus or memory loss. One participant described not wanting to see other people because she didn't have the energy or interest for conversation. She felt guilty that she was unable to respond to people's kindness.

Myoclonus was one symptom that caused distress due to the potential for danger. For example hot drinks and pans of hot food were spilt. Participants made efforts to modify their activities to keep themselves and others safe however this was limiting for those who lived alone or were on their own for long periods during the day.

One participant described feeling too affected by the drugs to really feel able to participate in decision making. Altered cognitive function and poor memory also caused distress.

"Because the patient sometimes is too spaced out on their own situation to really take in what's coming….." (Participant 10)

There were limitations on abilities due to the side effects. For example hobbies were no longer possible. Crossword completion and enjoyment of crafts such as card making and knitting was limited by the myoclonus. Participants were anxious about driving even though they had not all been specifically advised to stop driving. Some participants regulated their driving themselves. One participant avoided the use of breakthrough opioid during the day in order to be able to keep driving.

"And if I'm driving I'm not allowed to the other one (indicated breakthrough opioid) anyway seemingly… so I don't touch that one unless it's at night and I know I'm no going to be driving" (Participant 12)

Another participant described recognising she was not safe to drive. "Because when I was on the morphine, the, well most of the time I didn't drive, cos I knew I wasn't safe to drive, cos ma head felt fuzzy, and… no, it just wasn't, know like, I wasn't as alert as I should be, know, like, so I knew I couldn't drive. But I've been driving now on the methadone" (Participant 7). This participant recognised an improvement in herself and returned to driving.

Only one of the participants felt the side effects had been of benefit. She described being an observer rather than a participant whilst on higher doses of morphine and she felt this had allowed her some "space" from everything else.

"And I think, oh that's something I forgot to say when I was on the morphine erm…high dosage and I'd come off it that was what friends have said I seemed to be a spectator…. to their visit and the events and not a participant and when I went down to the 10mg more than one of them on different occasions had said you're more involved em…whereas before you seem to.. the visit happened to me." (Participant 6)

6.6.2 Impact on the participant's family

The impact of side effects on the friends and family of the participants was reflected upon by several of the participants. Participants recognised that witnessing some of the symptoms of opioid toxicity must have been distressing for those that care about them. For example one participant reported that nausea and vomiting had been prominent symptoms and she was concerned that the distressing symptoms would be a lasting memory for her young children. For participants who lived alone family members still needed to support them. One participant (participant 3) recalled her friend's distress when he could not contact her by telephone despite calling seven times in one hour because she had been too sleepy to respond to the telephone.

Participants reflected on the physical and emotional impact of the episode of opioid toxicity, recognising that carers became physically exhausted with providing care. Hallucinations and sleep disturbance due to the opioid meant that carers often had broken sleep too. Family members were called upon to help manage the physical symptoms due to the strong opioids. For example, one participant recalled falling asleep whilst shopping with her daughter. She needed to lie down in the changing room of a shop until she was able to travel home. At times when hallucinations were prominent, family members were called upon to provide reassurance when these had been frightening and to help distinguish reality from hallucinations.

> "Because as in that necessarily as in I was keeping her awake, but as in, what I say, there was a couple of points where I really jumped and she was frightened in case maybe I done something to myself…." (Participant 1)

Carers had a responsibility for the medication. They were often the ones administering the medication whilst also retaining responsibility for recognising the side effects and seeking help from a healthcare professional in order to better manage the pain and side effects. One participant declined to read the information leaflet provided with the medication and delegated all responsibility to his partner.

Participants relayed that carers had their own anxieties about the symptoms and possible causes. One participant felt that symptoms of opioid toxicity that caused distress to his wife would limit his use of strong opioids more than his own experience. Another participant knew that his wife was fearful for him because of the side effects she was witnessing.

6.6.3 Altered Cognitive Function

The impact of the opioid on cognitive function was of great importance to the participants. Participants described forgetfulness and altered behaviour. They were very aware of their poor memory. The cognitive impairment described included a slowing of mental function for example being less able to do simple mathematics, disorientation in time and a difficulty in differentiating real from unreal. Memory loss was a source of concern for those who experienced it. This impacted on conversations. Conversations were also described as "wandery" rather than straightforward. Participants clearly described forgetting midway through a sentence what they were trying to say.

> "….anything people told me I just forgot right away and then they'd say to me later on, "Remember I told you that." (Participant 13)

The memory loss affected their ability to give a clear history when attending for out-patient review. For example one participant had forgotten about headaches she had been experiencing and therefore failed to report a potentially significant symptom.
One participant was able to describe very clearly that it was his short-term memory that was affected but another participant was unable to recall names of those people that had been known for a long time. There was immediacy to the memory loss and an inability to retain information even for a few minutes.

The participants described the use of coping strategies to help manage the memory loss including the use of a whiteboard to write memos, reliance on partner, keeping notes and

copies of documents. The impact of the memory loss on family members was outlined. For example participants relied on family members to give information when attending appointments, to remember information given to them.

There was difficulty in social situations. The participants became frustrated with being able to communicate their needs due to an inability the words or recall names of people or objects. One participant described very slurred speech which resolved when the opioids were reduced and word-finding difficulties.

> "It was difficult to find the words, find the words I was looking for and er… that was probably why I was it was coming out slurred because I was finding it difficult to find the wards I was looking for…I was getting quite annoyed with that aye….I'd tend to just stop speaking.." (Participant 17)

The altered cognitive function was of great concern to participants. They felt it reflected badly on them as a person and were concerned how others perceived them. They were also concerned about the implications of impaired cognitive function and whether there was underling dementia.

> "….because you begin to wonder if you (participant laughs) you're hanging on to your facility [sic] …. Yeah, it reflects back on you a little more than the other ones do, you know." (Participant 5)

> "I have to write everything down, everything, absolutely everything……because I just completely and utterly forget…." (Participant 9)

6.6.4 Altered Pain experience

An altered pain description was reported by six of the seventeen participants. One participant described a pain all over which was felt as a dullness in the body. This resolved as the opioids were reduced.

"..…I felt my whole body kin' o' sore and tired." (Participant 3)

Other participants described a sensitivity of their skin such that they experienced pain when someone touched the skin over their back and their clothes felt painful against their skin. Other participants noted altered skin sensitivity and a prickly heat feeling. These changes resolved when the dose or type of opioid that had been prescribed was changed.

"My skin was quite sen…is almost, not like, well almost, like a prickly heat feel…" (Participant 5)

"I'll say "I cannae wear that hooded top cause it's too sair……..I can't keep my dressing gown on because it feels like a ton weight" (Participant 9)

"I was sensitive to things yes I think…. the bedding I didn't….mum gave me a blanket and there was no way I could take the blanket…… I don't think I liked rough textures" (Participant 6)

"It was a weird sensation, it was as if you had pins and needles …… it was like nerve endings or something, you know." (Participant 2)

Participants were also aware that the pain was not resolving despite escalation in their opioid doses and that the rescue medication was not resolving the pain when they took it.

"The pain oh well see I had the pain when I was on the lower dose and he gave me a higher dose to kill all the pain but to me at the time it didnae kill the pain…" (Participant 12)

6.6.5 Acceptance of drugs and side effects

Participants described some very difficult experiences due to opioid toxicity however opioids were still viewed as an essential part of their pain management. Although they would be wary of future changes in the dose of the opioids and the possibility that the risk / benefit ratio would shift, none of the patients had approached healthcare professionals to discontinue their opioid medication or to seek an alternative. There was a general acceptance that the severity of their pain was such that opioids were required.

"And with the side-effects I would've just said, right I'll just deal with the side-effects….I definitely wouldnae have stopped taking it…. Because I was in so much pain that I would've took anything that was going" (Participant 2)

"No I just put up with it aye, aye just part of the parcel know what I mean...." (Participant 12)

Potential changes in the dose of the opioids were a source of anxiety for many. The symptom that had been most prominent for them became the focus of that anxiety. For example if nausea had been severe there was a concern that nausea would become overwhelming. If hallucinations had been prominent there was a fear about the return of these.

"……is just the feeling that the side effects are going to take over and I don't feel well enough to do things…and everyday, everyday tasks…..and just be with the family so that's what really puts me off when they keep upping the drugs and not being able [to] just feel normal…."

Some participants highlighted they felt more confidence when a specialist in palliative medicine managed their pain rather than a general healthcare professional. They voiced how well supported they felt by their usual medical team but felt that they did not have the expertise to manage their pain with strong opioids. Confidence in their abilities was maintained for other aspects of symptom control.

Some participants had an expectation of a particular side effect but their own experience was felt to be worse than they had expected.

> "…and I just thought oh well I'll probably end up with nausea or the usual ones but I wasn't expecting the hallucinations like that and that really scared me……" (Participant 4)

One participant described his expectation of opioid-related side effects and medical error.

> "But my old brain was telling me that, I mean they are strong drugs that you're giving me and you know there is risk so you know I don't think I really need to be told that sort of thing. I would expect that something might happen and you can't get it right all the time." (Participant 14)

6.6.6 Control

Control was mentioned in several different contexts. Participants described the need to be in control over aspects of their pain management. For example being able to choose which analgesia to use at a particular time or for a particular type of pain was reported positively.

Coping with memory loss was also important in taking control. Keeping notes, informing spouses of information and appointments all help to keep the patient involved and in control.

An involvement in discussions over the titration of analgesia would give control to participants. One participant highlighted that if side effects had been included in the discussion about his analgesia he could have made different (and informed) decisions about changing dose of his opioid.

Understanding the reason for taking other prescribed drugs and the safe limit within which to adjust these was also felt to be helpful. For example, participants could adjust the dose of their aperient if experiencing opioid- induced constipation.

A lack of information when introducing opioids left the patients feeling out of control. Knowledge of the possible side effects that strong opioids may cause and knowing who to contact if the side effects occurred helped to put the participant back in control.

> "I think I'm more aware of the side-effects now and I'd speak out sooner" (Participant 7)

> "That's the point that somebody hadn't said you know we're giving you these extra tablets and that but you could go in and if you start to go into that stop it immediately… and then I would've done that but nobody told me anything at all so I just kept on taking them like a monkey" (Participant 13)

Control was also mentioned when discussing driving and the need to feel mentally in control enough to drive. One participant avoided taking rescue doses of opioids when she knew needed to drive and then took the medication later. Another participant adjusted the dose of her opioids herself and decided to take an asymmetric dose of her long-acting opioid. She took control of the side effects she was experiencing by reducing her morning dose. Balancing the dose and side effects put her back in control of her situation.

> "But I was trying to avoid the ones that made you sleepy obviously for driving…. And then once I got home then I would take them sort of when I got home later on in the afternoon and then later on in the evening so I wasn't going anywhere else if I fell asleep on the couch well that's fine…" (Participant 4)

> "…as soon as I could, as soon as I got all the side effects and things I was trying to get away with the three and to see if that still stopped the pain erm… what I found was that if I took three in the morning and four in the evening it wasn't so bad cause I'd be sleeping in the evening so it still got rid of the pain during the night so I could handle, I could handle that cause it was only when I was awake that I was worried…about any side effects." (Participant 11)

When describing an episode of severe nausea and vomiting which was due to opioids, one participant found the loss of control extremely distressing.

> "I felt like I was out of control, I have no control, they had no control [her family] and they were helpless to help me…" (Participant 4)

6.6.7 Coping Strategies

Humour was one of the coping strategies used to cope with the episode of opioid toxicity. For example falling asleep in the supermarket queue was described with laughter. Hallucinations were shared with family members.

Practical solutions to manage the memory loss were described by several participants. These included writing down messages while on the telephone, involving spouse or partner in giving information to health professionals and decision-making. Avoidance of certain activities was another strategy adopted to manage the symptoms. For example avoiding carrying hot drinks or plates of food, and avoiding taking breakthrough doses when they needed to drive.

Having enough information and knowing who to contact when problems arose helped patients cope with managing their opioids generally. They had often not known whom to contact during the episode of opioid toxicity and it had therefore persisted longer than necessary.

A degree of familiarity with a symptom also helped people cope with a particular symptom. For example if something had been experienced previously it caused less anxiety than a new symptom. New symptoms generated anxiety when the cause was unknown. There was anxiety in case it may be due to the cancer and in particular whether it represented disease progression.

6.6.8 Future changes

One participant had experienced symptoms particularly while on one opioid. Resolution of the symptoms had come when he changed drug as well as dose. His usual medical team had asked him to go back to the original strong opioid and he had agreed to this to see if it would improve his pain. However he experienced the same severe side effects again. Participants had a great deal of faith in their usual medical team and a willingness to try their suggestions. The severity of the pain often dictated a "try anything" approach.

A few participants reflected that not everyone has the same experience with drugs. They recognised that there was something individual about the response to strong opioids.

There was a general acceptance of the need to take strong opioids to manage their pain. The pain was such that they couldn't tolerate it without the medication.

There was also a general anxiety amongst participants that if the dose of their opioid were increased again they would experience side effects from the opioids. They expressed

concern about this. This was not universal though – one participant described a more relaxed and trusting attitude.

> "I trust everybody so I'll do what I've got telt and that's it." (Participant 16)

> "…sometimes you get a wee bit sort of apprehensive of, you know, if they say they are going to up the drug…cause I always think, oh, going to up the drug. What's going to happen, is it going to make me feel worse or is it going to start again or is something else going to happen that I don't know about. So it does make me feel a wee bit kind of anxious about it…" (Participant 4)

6.7 Discussion

6.7.1 Summary of main findings

This study provides the first description of the patient experience of an episode of opioid toxicity. Several themes have emerged from the data that may be helpful for professionals managing other patients who are prescribed strong opioids.

Participants were clearly able to describe an altered pain experience that suggests opioid induced hyperalgesia. The altered pain experience and a sensitivity of the skin were described along with other symptoms of opioid toxicity. The symptoms resolved when the other symptoms of opioid toxicity resolved. It is important to question patients about altered pain when assessing their opioids.

Participants tried to self-manage their symptoms and were keen to be involved in decision-making about the management of their pain. Participants understood the need to achieve a balance between the benefits that strong opioids have for their pain and the side effects that may occur. The participants in the study were interested in the side effects of opioids and

in helping minimise the adverse effects for other patients. However none of the participants sought advice on possible alternatives to systemic opioids. There was covert self-management by the participants rather than active engagement and involvement by the healthcare professionals.

Carers as well as participants felt the burden of side effects. They had responsibility for administering the medication which caused the participant to be less well, for seeking medical support and involvement in making decisions.

6.7.2 Comparison with published literature

Several authors have reported that patients link with pain with disease progression and may be anxious about reporting the pain or accepting morphine. (Schumacher et al, 2002; Flemming, 2009; Reid, Gooberman-Hill, Hanks, 2008; Coyle, 2004; Blake et al, 2006) In 2002 the barriers questionnaire was revised by a team in the USA. (Gunnarsdottir et al 2002) The original questionnaire identified barriers to adequate pain management including fear of addiction and tolerance, concern over side effects, fatalism, a feeling that patients should "be good" and not distract their doctor, a fear of injections and a perceived link between pain and disease progression. The questionnaire needed to be revised as it is now recognised that pain and disease progression are often linked and this is not always a misconception. Also much fewer drugs are given by injection when managing pain and the likelihood is that other routes will be available. In revising the questionnaire the authors found that the patients still fear addiction to painkillers and are concerned about side effects. They also still believe that "good" patients are those who do not complain about pain. The questionnaire was validated in patients with cancer and the results are therefore very relevant to patients in this study.

In 2008 Reid and colleagues conducted a qualitative research study exploring participants' views on commencing strong opioids. The study was also part of a larger quantitative study comparing the management of cancer using a traditional three-step analgesia ladder

with a new two-step approach. They approached 29 potential participants and 18 took part (Reid, Gooberman-Hill, Hanks, 2008). In the study described here all those approached were interested in participating.

The study identified four key themes with a link between themes of "morphine as the last resort". The participants described an association between increasing pain and concern that the cancer was progressing which was also voiced by participants in this study. They had faith in healthcare professionals, particularly those who took time with them and appeared knowledgeable. The impact of pain on the participant and their carers was of importance. In contrast this group of patients thought morphine would cause loss of function and hasten death. In this study participants viewed the side effects as causing loss of function.
Schumacher and colleagues used pain management autobiographies as a tool to explore and demonstrate patient barriers to the use of opioids. They recruited patients with cancer who were part of a pain management programme and who were reluctant to take analgesia despite poorly controlled pain. Patients were reluctant to take opioids if they had previous experience of side effects which had been unpleasant which correlates with our results. Patients also had some long held beliefs about opioids and the best way to manage to their own pain for example using as little analgesia as possible. (Schumacher et al, 2002)

Coyle interviewed seven patients with cancer over a period of time with between two and six interviews with each patient. The patients interviewed felt that pain "was a reminder of progression of disease and the imminence of death". However without previous experience of opioid toxicity this group of patients wanted their opioids to be increased to guarantee a peaceful death when they were at the end of life (Coyle, 2004)

In a study exploring the experiences of patients who were prescribed strong opioids for non-cancer pain Blake et al described four major themes - the impact of pain, attitudes to strong opioid medication, coping strategies and the relationship with the General Practitioner. Although these patients had non-cancer pain there were still some similarities in the thoughts expressed about opioids in particular the importance of a healthcare professional who could support them, in this case their general practitioner. Chronic pain

had placed limitations on their abilities and caused them to become socially isolated. They did not have the same experience of side effects but were concerned about disease progression as were the patients in this study (Blake et al, 2006)

In a study in 2010 Gregorian and colleagues looked at the trade-off between side effects and pain relief which patients were prepared to accept. They also looked at the trade- off from the physician's perspective. They recruited patients with acute and chronic pain. Both patients and physicians regarded nausea and vomiting as the most unacceptable side effects. Patients were more likely than the physicians to accept some drowsiness if they had better pain control. Some of the patients who completed this theoretical modelling study had previously experienced the side effect they were being asked about and some patients had no prior experience. There was no other significant difference in the two groups. The patients in this study were anxious about the recurrence of side effects which they had previously experienced. They expressed anxiety about opioid dose changes in the future (Gregorian et al, 2010). It may be that cancer patients are also experiencing side effects of their oncology treatments and that the opioid related side effects are the ones that they feel should be managed well or avoided by the professional. Future work would explore why cancer patients appear to feel differently about the trade-off.

Impaired cognitive function was noted by patients who participated in a study 2007. The authors reviewed 595 cancer patients who were having active cancer treatments. These patients also reported memory and concentration problems. The conclusions of this study were that the cognitive impairment was probably due to the oncology treatments however the analysis did not include analgesia. This study comments on the presence of the impairment at the start of the treatment. It may be that drugs had some part to play in the clinical presentation. It may also be that cancer itself affects cognitive function. (Kohli et al, 2007)

Von Ah explored "the impact of perceived cognitive impairment" using a qualitative research methodology (Von Ah, 2013). Questionnaires were posted to 25 women who had cognitive impairment following chemotherapy. Interviews were conducted and the data

was analysed using qualitative description. Memory loss was highlighted as the main concern of the women recruited. Other aspects of concern were "speed of processing, attention and concentration, language, and executive functioning." The participants reported feeling slower than usual or "foggy". Word-finding difficulties were described. All those recruited had breast cancer. The women spoke of the impact their cognitive impairment had on their families and the distress it caused themselves. 60% of the women in the study felt there had been adverse stress on a close relationship. Again the cognitive impairment had been assumed to be due to the chemotherapy but there is no evidence of consideration that opioids have contributed. An important finding of this study was that most of the women did not discuss the cognitive impairment with a professional and those that did discuss the impairment did not receive much support. The most helpful response received was that of "validation" ie an explanation that the concerns were justified and had a cause. There were many similarities between this study and the results of the qualitative research I undertook including the methodology.

The importance of patient involvement in decision – making has been debated widely and the variation in the degree to which patients wish to be involved has been recognised (Blake et al, 2006; Say and Thomson, 2003). More specifically Cheatle and Savage discussed the need to consider informed consent when commencing opioids (Cheatle and Savage, 2012) They highlighted some of the barriers to effective pain management including fear by the clinician of the associated risks including side-effects and diversion. Some specialists in chronic non-cancer pain are using opioid treatment agreements. Opioid treatment agreements encourage information-sharing and establish goals of treatment. Goals of treatment are decided and may include improvement in pain, increase in activities, aspects of mood and involvement with social activities. It may be that some of the participants in the study would have welcomed opioid treatment agreements and the information and involvement in decision-making that results. However Cheatle and Savage argued that the use of opioid treatment agreements may promote the view of opioids as risky.

Much of the literature on opioid-induced hyperalgesia (OIH) is from three groups – healthy volunteers, opioid addicts on methadone maintenance programmes, and patents receiving

opioids at the time of surgery. Authors have described an alteration in the pain with the pain becoming less well defined in site and nature as OIH develops. The literature on OIH in cancer patients is limited to case reports and small case series. (Lee et al, 2011; Fishbain et al, 2009; Angst and Clark, 2006;) In the chapter exploring opioid induced hyperalgesia a series of case studies are outlined. The studies have all been published and postulate opioid-induced hyperalgesia as the cause of the patients' symptoms. All the patients had cancer pain and most of them were on very high doses of opioids. Rapid titration was also a prominent theme. The patients in this study describe altered pain and hypersensitivity with much milder symptoms of opioid toxicity than the patients in the published literature. The patients in this study were on much more moderate doses of opioids and rapid titration to very high doses was not a feature. It may be that OIH is present in milder cases of opioid toxicity than has previously been recognised.

6.7.3 Reflexivity

Qualitative research interviews are often thought of as very similar to clinical interviews by novice researchers. This is due to not recognising the different purposes of the interview. The clinical interview needs to find an answer, often within a time limited consultation, that fits a recognised pattern ie to provide a diagnosis. The research interview is not constrained by time and should allow the patient to express their views in whichever direction makes sense to them. (Mays and Pope, 2000)

As a novice qualitative researcher, this research approach was not instinctive. It was initially difficult to detach from searching for facts and simply allow information and meaning to emerge. The transcription of the first interview revealed the interview had been too closely related to a medical history. Attention was paid to changing the conduct of the interview to enable a freer flow of information and allowing the participant to direct the conversation whilst still addressing the agenda.

Field notes were not recorded. This was also due to the newness of this research methodology. The presence of a more experienced qualitative researcher may have enhanced the depth of interviews and made it possible to record field notes. The presence of two researchers at each interview was not possible due to resource limitations. If field notes had been recorded additional data may have been available through non-verbal cues and the noting of emotional responses.

In palliative medicine it could be argued that the two interviews are closer than in other specialties as palliative medicine clinicians often have much more time to spend with the patient and allow then to tell their story in the order they wish. Palliative medicine clinicians enable their patient to prioritise their symptoms and needs in any order they wish and help find solutions to problems that suit the patient. We are more used to practicing an individually tailored approach to medicine.

The interviews were mainly conducted in the participant's homes. This was done in order to inconvenience the participants as little as possible. It is possible that the place in which an interview is conducted shifts the boundaries and power balance between interviewer and participant. In their own home the participant should feel more in control of the situation and in a position of natural power. This should enable them to voice their opinions more freely. None of the participants stated that they had found the home visit intrusive or to the detriment of their participation in the study. All those who participated in the study valued the chance to be involved.

There is potential for bias in qualitative research as with quantitative research. The researcher and participant will both be influenced by the nature of the researcher as a doctor and a specialist palliative medicine whether this influence is explicit or not. This can be further compounded if the doctor is part of the patient's usual medical team, even if they are not the responsible clinician or directly involved in the patient's usual medical care. There may be the perceived need for loyalty to the patient's usual medical team and a

perceived idea that they should reflect this in the thoughts they share during the semi structured interview.

It can be very difficult to record and observe without also finding oneself in the role of doctor. This was easier when other medical teams were responsible for the care of the patient and was more difficult when the researcher was assumed by the patient to have some influence or responsibility for their medical care. This was not always so and I tried to make it explicit at the start of the participants recruitment to the study and again before commencing the qualitative interviews.

It may also be that the researcher was part of the palliative medicine team that has successfully managed the participant's symptoms. This can engender a respect and loyalty from the patient that alters their responses as research participant. There is a bias that successful management of symptoms brings to the study.

6.7.4 Future work

"Respondent validation" (Pope and Mays, 2000) is a technique to enhance quality of the research. Pope and Mays suggest that those who participated in the study review the findings and their comments are included in the results. Although this would enhance quality it would not have been feasible with this patient group due to the length of time to recruit all seventeen participants. By the time recruitment and data analysis was completed unfortunately some of those recruited early in the study had passed away. It may be possible though to show the findings to a similar patient group and ask them to reflect on the findings and whether they recognise the views expressed.

The patients recruited were those who had experienced an episode of opioid toxicity. This had been successfully managed and the patients were under the care of specialist palliative care teams who were addressing any unresolved symptoms. It would be interesting to see

how the themes identified through analysis of qualitative interviews with participants with unresolved symptoms or opioid related side effects compared to those with well managed symptoms and who were no longer experiencing opioid related side effects. The need to assess capacity and ability to give informed consent may make this very challenging though.

Ethical approval was not sought to seek the views of carers of patients who had previously been opioid toxic. The study revealed some of the burden on carers and it would be interesting to explore this further. It would also be interesting to see if there were any differences between those with cancer and non-cancer pain who have previously been opioid toxic.

Field notes were not recorded during this study. Non-verbal cues are therefore not available for inclusion in the results. They may have added further depth to the data.

The use of pain management programmes for patients with cancer would be an interesting area to explore given that the participants were already developing coping strategies and using covert self-management techniques. Attendance at such a programme may empower them further.

6.7.5 Conclusion

The published literature has not previously revealed the impact of opioid toxicity on the patient and their family. It is the first time that the impact of an episode of opioid toxicity and in particular the effect of opioids on cognitive function, have been described. This is the first study to describe the altered pain and sensation that may be experienced along with the symptoms of opioid toxicity and that most likely represents opioid-induced hyperalgesia. The opioid-induced hyperalgesia is present with much milder symptoms of opioid toxicity and more modest doses of opioid than have been described in the literature. Participants engaged in covert self-management and developed coping strategies to manage the symptoms. This covert self-management could be the basis of future work to help empower the patient and adopt a more patient-centred approach.

CHAPTER 7: CHARACTERISATION OF OPIOID INDUCED HYPERALGESIA

Outline of Chapter:

- The pre-clinical and clinical evidence for the existence of opioid-induced hyperalgesia (OIH) is discussed
- A detailed review of the description of opioid-induced hyperalgesia is presented
- The findings of quantitative sensory testing in patients with cancer pain, non-cancer pain and substance misuse are described
- These findings are compared with published literature to help better define the clinical presentation of OIH.

7.1 Hypothesis

Patients who have pain and who are prescribed opioids will have different sensory thresholds when compared to healthy volunteers and those who have a history of substance misuse.

7.2 Aims

The specific aims of this part of the study were to:

- Establish the prevalence of features suggestive opioid-induced hyperalgesia
- Compare the sensory processing of patients with cancer and non-cancer pain with other groups of patients

- Characterise the clinical presentation of opioid-induced hyperalgesia in order to provide guidance in making the diagnosis for clinicians.

7.3 Opioid-induced Hyperalgesia and Tolerance

Recently there has been evidence that suggests the effect of the opioid is not maintained over time. There are two possible reasons why the analgesic effect of the opioid may lessen over time – tolerance and hyperalgesia. It can be difficult to distinguish opioid-induced tolerance from opioid-induced hyperalgesia particularly in the context of pain due to advanced cancer. In patients with advanced cancer it may be that their pain has worsened and therefore unrelated to the opioids. Opioid-induced tolerance requires a higher dose of opioids to manage the pain. Opioid-induced hyperalgesia "results in a paradoxical increase in atypical pain that appear to be unrelated to the original nociceptive stimulus." (DuPen 2007).

> "Hyperalgesia represents increased sensitivity to pain, whereas tolerance may reflect decreased sensitivity to opioids." (DuPen, 2007)

When the two opioid-related phenomena are not recognised it is not possible to manage patients' pain well. Opioid-induced hyperalgesia may be misdiagnosed as uncontrolled pain or generalised distress leading to inappropriate management with further escalation of opioid doses or the addition of anxiolytics or sedatives to relieve the patient's distress.

7.4 Opioid Physiology

The pathophysiology of pain was briefly outlined in the introduction. In this chapter the focus is primarily on opioid physiology and the mechanisms thought to underpin the development of OIH.

There are three groups of opioids prescribed for the management of pain and they have an effect by "modulating the endogenous opioid system." (Levac, 2001) The initial division of exogenous opioids is made on the basis of chemical structure. The endogenous opioids are the dynorphins, enkephalins, endorphins and endomorphins. For the purpose of this chapter the focus will be on the role of opioids in pain management but opioids also have an effect on gastrointestinal motility, temperature regulation, mood and respiration amongst others. (Levac, 2001)

Opioid receptors are found throughout the central nervous system including the hypothalamus, rostral ventromedial medulla and spinal cord dorsal horn. (Hutchinson, 2011) In the peripheral nervous system opioid receptors are found on nociceptors and in the spinal cord interneurons. (Stein, 2013) Analgesia results from both peripherally and centrally located opioid receptors. (Lee, 2014)

All the opioids are mu agonists and derive most of their clinical benefit from this activity. Other opioid receptors have also been identified – these are the opioid-like receptor 1 (ORL-1), delta and kappa receptors. In addition there are seven subtypes of mu receptor. The opioids all have varying affinity for the receptors and their subtypes which goes some way to explain why individual patients may respond better to particular opioids either in terms of analgesia or a better side effect profile. (DuPen, 2007) Genetic polymorphisms affect receptor structure and are a further component of the inter-individual variation. Genetic polymorphisms are discussed further in the chapter "Future work".

Morphine receptors are G-protein coupled receptors. When the opioid binds to the receptor the G-protein is activated and reduces cyclic adenyl phosphatase (cAMP), which in turn causes suppression of sodium and calcium channels and a reduction in the hyper excitability of the neurones involved in the pain pathway. Analgesia is the result. (DuPen, 2007)

The mechanisms underlying opioid tolerance are not well elicited. It is known that G-protein and the opioid receptor can uncouple after prolonged exposure to opioids. Beta–arrestin 2 regulates the uncoupling and lack of beta-arrestin 2 results in longer opioid-induced analgesia. (Levac, 2001) It is also possible for G-protein to switch to a pronociceptive protein so that analgesia is no longer the result of the sequence put in motion by the administration of the opioid. (DuPen, 2007)

Endocytosis of the opioid receptors by cells appears to have role in regulating receptor function. The endocytosis can be down-regulated and one study has shown that if patients don't have the down-regulator they cannot develop tolerance to opioids. Alternatively endocytosis may be important in preventing the development of tolerance by facilitating the replacement of opioid receptors with new ones that may avoid the uncoupling of the G-protein or G-protein switch described above. (DuPen, 2007)

Within the Central Nervous System (CNS) opioids are further involved in signalling and pathways. They have roles beyond the neuronal pathways of pain and have signalling roles in the immune system. Astrocytes form the blood-brain barrier, regulate cerebral blood flow, can detect the need for repair of nerves and help provide the nutrients and precursors of neurotransmitters that the central nervous system requires. In addition astrocytes express opioid receptors and appear to have a key role in maintaining opioid homeostasis. If the astrocytes respond to local or general changes in the nervous system this can impact on pain pathways. Microglia are specialised macrophages that are found in the CNS and respond to acute tissue damage. Toll-like receptors are an integral part of their ability to respond quickly. Once microglia have responded to an acute tissue injury they remain active and are able to respond more quickly if there is subsequent damage. (Hutchinson, 2011) Toll-like receptor 4 is expressed by microglia and has been shown to have a role in sepsis and it responds to substances released from damaged cells. It appears that Toll-like receptor 4 is able to detect the presence of opioids and transmit a signal within the CNS based on their presence. (Hutchinson, 2011) Toll-like receptor 4 is involved in the development of allodynia, hyperalgesia and neuropathic pain and is therefore of significant interest to researchers trying to unravel the pathophysiology of opioids which leads to opioid-induced hyperalgesia.

Endogenous opioids are released in response to painful stimuli and activation of the pain pathways from nociceptor to cerebral cortex.

> "Inflammation of peripheral tissue leads to increased expression, axonal transport and enhanced G-protein coupling of opioid receptors in DRG (dorsal root ganglia) neurons." (Stein, 2013)

The endogenous opioids are released from leukocytes in response to stress, cytokines and bacteria. Further inhibition of the pain pathways occurs in the spinal cord where opioids and Gamma amino butyric acid (GABA) act to reduce the excitatory ascending pain signal.

7.5 Evidence of Opioid-Induced Hyperalgesia

There have been several reviews considering opioid-induced hyperalgesia (OIH) and its relevance to clinical practice. The authors have differing views and there are some who do not feel there is sufficient evidence to consider OIH to be an important clinical phenomenon (Fishbain et al, 2009). The conclusion of the review conducted by Fishbain and his colleagues was that the evidence of OIH in humans was inconsistent and they favoured acute tolerance to opioids rather than OIH as the explanation for study findings.
Bannister and Dickenson published a very comprehensive review in 2010 in which they outlined the mechanisms which may underpin the development of OIH (Bannister and Dickenson, 2010). They draw attention to the ability to extrapolate from animal studies into human models due to the lack of significant variability in the structure of the mu opioid receptor.

Three main pathways are thought to be involved in the development of OIH. The dorsal horn of the spinal cord is the anatomically most important region in its development (Chu et al, 2008).

Central sensitisation occurs in the spinal cord and represents a "hypersensitivity of the spinal cord to nociceptive inputs from the periphery" (DuPen, Shen, Ersek, 2007, page 116). The normal response to pain becomes exaggerated in the presence of central sensitisation. NMDA (N-methyl –D –aspartate) is thought to protect against the development of OIH (Lee et al, 2011). Central sensitisation and therefore opioid-induced hyperalgesia do not develop if the NMDA receptors are antagonised (Colvin and Fallon, 2009; Silverman, 2009). In animal studies the concomitant use of ketamine and opioid at the time of procedure resulted in less thermal hyperalgesia for the four days after the procedure (Tompkins and Campbell, 2011) Authors who have suggested ketamine as a means of managing OIH are utilising the protective effect of NMDA (Chu, Angst, Clark, 2008).

Spinal dynorphin levels are thought to play an important role in the development of OIH. Levels of dynorphin increase after administration of opioids and this in turn causes an increased release of excitatory peptides. The increased release of the peptides causes increased stimulation of the nociceptors (Lee et al, 2011). Dynorphin is a kappa-opioid antagonist and also has non-opioid actions. Studies have suggested that increased levels of dynorphin enhance the nociceptive response (Vanderah et al, 2001)

The third pathway which has gained interest and support for its involvement in the development of OIH is the "activation of facilitative descending pathways from the RVM" (Lee et al, 2011, page 148) (RVM, rostral ventromedial medulla). Activation of these pathways is thought to enhance the processing of pain by the nociceptors. The descending pathways exist in a state of equilibrium which is affected by the administration of opioids over time. The opioids cause an increase in the excitatory pathways and a reduction in the inhibitory pathways and an overall move to excitation (Bannister and Dickenson, 2010; Vanderah et al, 2001).

The injection of anti-inflammatory drugs into the intrathecal space reduces OIH. The role of spinal inflammation in the development of OIH is a further area of interest to basic science researchers (Chu, Angst, Clark, 2008).

The evidence for OIH in humans comes from three patient groups. Patients who are on methadone maintenance programmes have been shown to have an increased sensitivity to cold induced pain (Lee at el, 2011). Angst and Clark outline further studies in support of OIH in this patient group (Chu, Angst, Clark, 2008; Angst and Clark, 2006). It does seem to be a sensory specific modality in this group of patients. Pain in response to electrical or mechanical stimuli is near normal (Chu, Angst, Clark, 2008).

There has been some work to suggest patients who are given very high doses of opioids as part of general anaesthesia for surgical procedure may have greater intensity of pain after the procedure (Lee at el, 2011). However there have also been several studies refuting this (Chu, Angst, Clark, 2000). Although the studies recruited patients with a well-defined clinical phenotype, the numbers are small. In healthy volunteers there is a suggestion of multiple sensory modalities being affected including heat-induced pain and mechanically-induced pain (Chu, Angst, Clark, 2000).

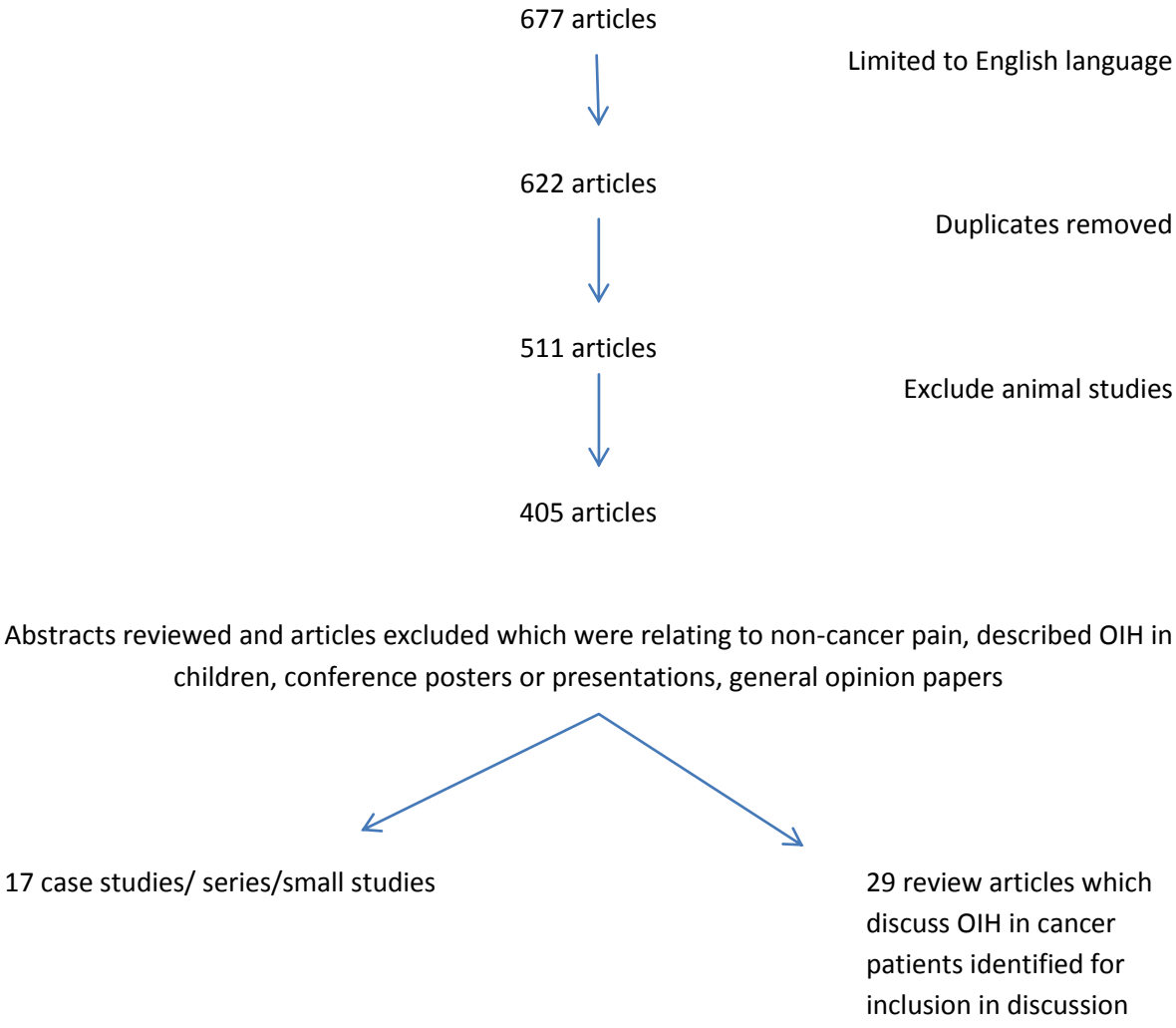
Case studies support the suggestion that OIH is part of the spectrum of opioid toxicity and this is discussed further in the section on OIH in patients with cancer pain. There have been similar case reports of patients with chronic non-cancer pain developing generalised allodynia, sometimes associated with myoclonus, at very high doses of opioids (Angst and Clark, 2006). The patients responded to reduction of the opioid dose and / or an opioid switch.

In healthy volunteers who have been given opioids as part of research studies have shown an increased sensitivity to cold-induced pain (Lee at el, 2011). However the studies of healthy volunteers may represent hyperalgesia precipitated by acute opioid withdrawal rather than OIH.

7.6 Opioid-induced Hyperalgesia in Palliative Medicine

A literature search was carried out using Ovid Medline (1946 to 2014) and Embase 1947 to the present. The search was conducted using the key words opioid$ or opiate$ or morphine or oxycodone or fentanyl or methadone and hyperalgesia or paradoxic$ pain or allodynia or increased pain and cancer pain or palliative care or palliative medicine or terminal care.

Figure 6: Articles identified of relevance to literature search regarding opioid-induced hyperalgesia in palliative medicine



7.6.1 Summary of Papers Included in Review

Initially seventeen papers were identified which discussed opioid-induced hyperalgesia in cancer patients. On reviewing the full text it was evident that the clinical symptoms in some cases were that of severe opioid toxicity without hyperalgesia. These papers were therefore excluded from this review. Further papers have been identified from the reference lists of the initial papers. Data has been extracted from the papers and is presented in table 1.

All the patients included in this review had a cancer diagnosis. There were many different tumour sites and pathologies. Eight (57.1%) of the fourteen patients were male. The ages ranged from 31 to 76 years with a median age of 52.9 years.

7.6.2 Opioid prescribed

The opioids most frequently prescribed by specialist palliative care were all implicated in the development of OIH ie morphine, oxycodone, hydromorphone and methadone. Morphine was the most frequently prescribed opioid at the time the features suggestive of OIH developed. Nine of the patients were prescribed morphine initially; some patients were on a combination of opioids. The opioids were prescribed by different routes including oral, transdermal, intravenous and intrathecal routes.

Seven patients were receiving very high doses of opioids. One of the patients had been given an acute overdose of fentanyl. The opioids had been significantly titrated in nine of the patients. The time course of titration was short (two to four weeks) in many of the cases described.

7.6.3 Clinical presentation

Ten of the cases outlined had an increase in pain, allodynia or generalised pain described in combination with other features of opioid toxicity. There were descriptions of myoclonus, hallucinations, sedation, tremor, miosis, delirium, nausea and vomiting. Four patients had escalating pain coinciding with escalating opioid doses but had no features of opioid toxicity described.

7.6.4 Other factors

Two patients had a significant history of anxiety and depression and depression, anger and benzodiazepine misuse. A further patient was recognised to be very distressed. It is possible that these diagnoses affected the presentation of pain and response to opioid.

Radiotherapy had been given to two patients as part of the management of their pain and disease shortly before the symptoms of OIH and opioid toxicity developed.

7.6.5 Management of opioid induced hyperalgesia

Dose reduction of the opioid was important in the management of the majority of patients. Two patients did not have a significant dose reduction; one of these patients had a further episode of the symptoms suggestive of OIH. The only patient for who dose reduction and / or opioid switch was not the major factor in managing their OIH was the patient who had given the wrong dose of fentanyl. As expected this patient required naloxone as the primary intervention. In two patients the dose of opioid was reduced by a factor of 100.

Eight patients had an opioid switch. Seven patients were switched to methadone. Three patients had more than one opioid switch.

7.6.6 Theory postulated by authors

The presence of hyperalgesia and allodynia in patients who were opioid toxic was reflected upon by the authors of each of the papers. Rapid titration phase and ultra-high doses of opioids were both identified as likely to have contributed. Methadone was postulated as important to the management, alongside an opioid reduction, as it is the only opioid that has an antagonist effect at the NMDA receptor.

Failure to recognise pain as a multidimensional experience was also thought to have contributed to the development of OIH in one of the cases. The opioids had been titrated rapidly with the intention of relieving pain but the extent of the patient's severe distress and anger at her cancer diagnosis and limited prognosis had not been recognised.

The patient who received a significant overdose of fentanyl was noted to have features of central excitation which responded to naloxone. Naloxone would not be expected to relieve these features in patients who receive doses of opioid higher than required for their pain over a prolonged period.

7.7 Summary of Clinical Evidence from Patients with Cancer Pain

These case reports provide a clear link between rapid titration of opioids and the development of hyperalgesia as part of the clinical picture of opioid toxicity. The authors were able to provide a description of worsening pain with increasing doses of opioids. It can be difficult to recognise this link when managing a patient's overwhelming pain but the authors have provided real clarity.

The patients who had received radiotherapy had further reason for their opioid requirements to change. The radiotherapy may have caused an improvement in their pain and therefore rendered them more vulnerable to opioid toxicity.

The presence of psychological distress was significant for one of the patients. Another patient also had a history of anxiety and depression. The authors recognised her spiritual and psychological pain and providing support from the multi-professional team was instrumental in relieving her pain.

Two other case series have also been published but there was not sufficient clinical description to extract themes for the tables. In one series (Sjogren et al, 1993) eight cancer patients were described who developed hyperalgesia whilst on treatment with intravenous morphine. Seven of the eight patients had neuropathic pain due to direct tumour invasion of nerves. Four of the patients also had myoclonus. The authors suggested that the neuropathic pain and the use of morphine rather than other opioids had contributed to the development of the hyperalgesia.

In a further series also by Sjogren (Sjogren et al, 1998) six patients were described – four of the patients had malignant disease. There was scant clinical description but when the patients developed features which suggested opioid-induced hyperalgesia the levels of morphine -3-glucoronide (M3G) were found to be higher than expected. The authors suggested this as an interesting finding but recognised that without clear "normal values" for M3G concentration and without full clinical descriptions the conclusions were limited.

These case reports provide a compelling argument for the relevance of OIH in patients with cancer pain. They demonstrate a link between rapid titration and ultra-high doses of opioids and the development of hyperalgesia. The patients had features suggestive of OIH and symptoms of opioid toxicity suggesting that OIH may form part of the spectrum of opioid toxicity.

While we continue to rely on anecdotal evidence for the existence of OIH in cancer patients it is difficult to guide those who prescribe opioids, and the patients who take them, as to which opioids are most likely responsible, when to be cautious about the titration phase and how best to manage OIH.

Much of the literature published on opioid-induced hyperalgesia is based on small studies and some papers are contradictory. No research group has yet studied OIH in a cancer population in a systematic way. Studies that have been done have tended to focus on single measures or outcomes and there has not been a comparison of comprehensive longitudinal data gathered in different patient groups. A longitudinal study of patients with cancer pain will provide the answers to some of these questions.

Table 65: Included papers with themes extracted exploring opioid-induced hyperalgesia in patients with cancer pain

Author, Publication year	Demographic details	Opioid prescribed	Clinical presentation	Management of OIH	Other relevant factors	Theory postulated by authors
Lawlor et al, 1997	52,F Recurrent renal cell carcinoma	Morphine; PO and IV; 28,800mg MEDD	Generalised hyperalgesia, constipation, myoclonus, hypoactive – agitated delirium, cognitive impairment, hallucinations, tonic seizure	Opioid dose reduced by a factor of 100. Changed to methadone. Multidisciplinary support. Resolution of symptoms over subsequent 6 days	Past history of depression, anger and benzodiazepine misuse	Failure to recognise the other dimensions of pain ie psychological and spiritual distress resulted in escalation of opioid doses
Wilson and Reisfield,2003	39, M Testicular cancer. L2 bony destruction with compromise of thecal sac	Morphine, IT; 86,000mg MEDD	Escalating pain despite escalating doses of opioid. Alert and lucid	Reduction of IT morphine by factor of 100. Improvement of pain 6 hours after opioid reduction		Opioid induced hyperalgesia with "a near absence of analgesia from ultra-high dose opioid therapy"
Fainsinger and Bruera, 1995	68, M Multiple myeloma, bone disease	Transdermal fentanyl and morphine, PO; MEDD 4800mg at max	Escalating pain despite escalating doses of opioid. Agitation, myoclonus, hallucinations	Reduction of opioid and several opioid switches. Pain control achieved on methadone, MEDD 300mg		Opioid tolerance had developed. Symptoms due to high M3G concentrations

Table 66: Included papers with themes extracted exploring opioid-induced hyperalgesia in patients with cancer pain

Author, Publication year	Demographic details	Opioid prescribed	Clinical presentation	Management of OIH	Other relevant factors	Theory postulated by authors
Okon and George, 2008	76, F Locally advanced leiomyosarcoma of uterus	Fentanyl, IV PCA; 200 mcg / hour	Hypersensitive to light touch on lower limbs, delirium, hallucinations, distress, intermittent sedation	Fentanyl initially reduced by third, further reductions until fentanyl discontinued on day 5. Symptoms settled over 24 hours		Although moderate dose of fentanyl was administered there had been a rapid titration phase. Fentanyl accumulation may also have contributed
Davis, Shaiova, Angst, 2007	54, M Hepatocellular cancer, spinal cord compression	Oxycodone PO; Converted to methadone PO	Myoclonus, generalised burning pain, sensitivity to light touch and clothing, delirium	Oxycodone converted to methadone, dose reduction of methadone and introduction of ketamine. Symptoms resolved over 1 week	Presented 3 weeks after radiotherapy	Escalating doses of methadone resulted in OIH

Table 67: Included papers with themes extracted exploring opioid-induced hyperalgesia in patients with cancer pain

Author, Publication year	Demographic details	Opioid prescribed	Clinical presentation	Management of OIH	Other relevant factors	Theory postulated by authors
Vorobeychek et al, 2008	56,M Squamous cell lung cancer, spinal metastases	Initially morphine, then fentanyl TD plus oxycodone PO plus morphine PCA; Then hydromorphone PCA >50,000mg MEDD	Pain escalating over a 4 week period; sedation, fatigue, weakness, severe pain, nausea and vomiting	Hydromorphone dose reduced by 40 – 50%; and changed to methadone. Symptoms resolved over 4 days	Recent radiotherapy	OIH postulated as scan did not show significant disease progression and symptoms improved with reduced opioid dose and introduction of NMDA antagonist
Mercadente et al., 2010	48, M Sarcoma in chest wall, metastatic disease	Fentanyl TD titrated from 3.6g / day to 12g / day in 2 weeks	Severe pain despite escalating opioid doses; myoclonus	Changed to methadone and dose reduced by a factor of 100. Pain controlled by day 6		OIH due to opioid dose escalation

Table 68: Included papers with themes extracted exploring opioid-induced hyperalgesia in patients with cancer pain

Author, Publication Year	Demographic details	Opioid prescribed	Clinical presentation	Management of OIH	Other relevant factors	Theory postulated by authors
Bruera and Pereira, 1996	62,M Adenocarcinoma of stomach; advanced intra-abdominal disease	Overdose of fentanyl iv. Received 5000mcg in 1 hour (50x usual dose)	Acute confusion, hallucinations, tremor, myoclonus, hyperalgesia of limbs, sweating, miosis	Naloxone iv administered; symptoms resolved after 2-3 mins; symptoms recurred and further naloxone bolus and infusion needed		Acute opioid overdose causes central excitation which responds to naloxone and contrasts with chronic opioid overdose which causes central excitation which is not responsive to naloxone
Juba, Wahler, Daron, 2012	43, F Metastatic non small cell lung cancer	Morphine 200mg / day; previously on fentanyl TD	New generalised pain 2 weeks after starting morphine, pain on light touch; allodynia and hallucinations with second episode	Changed to oxycodone tds with hydromorphone prn; symptoms resolved over 1 week. Symptoms recurred when hydromorphone use increased. Changed to fentanyl PCA and symptoms resolved over 3 days	Anxiety and depression also	Opioid rotation enabled excretion of metabolites of causative opioid. OIH is due to metabolites.

Table 69: Included papers with themes extracted exploring opioid-induced hyperalgesia in patients with cancer pain

Author, Publication Year	Demographic details	Opioid prescribed	Clinical presentation	Management of OIH	Other relevant factors	Theory postulated by authors
Mercadente et al, 2003	54, M Lung cancer with thoracic metastases 47, M Hepatocarcinoma	Fentanyl, TD Morphine; iv; changed to methadone and morphine combination	Worsening pain, whole body hyperalgesia, confusion, agitation followed titration of methadone Titration of opioid was followed by whole body pain with no other adverse effects	Trial of ketamine bolus was not helpful; required sedation and intrathecal bupivacaine Intrathecal catheter was placed and bupivacaine and morphine infused	Poor compliance with treatment previously, severe psychological distress	Opioid-induced hyperalgesia due to escalating opioid doses Opioid-induced hyperalgesia due to escalating opioid doses
Sjogren, Jensen, Jensen, 1994	19,F Gliosarcoma 55, F Metastatic breast cancer 68, F Metastatic breast cancer	Morphine; PO Morphine; PO; then methadone then to morphine again Morphine; PO	Whole body allodynia, myoclonus "Skin burning" Allodynia	Opioid switch significant dose reduction Changed to ketobemidone Changes to sufentanil subcutaneous infusion		Opioid-induced hyperalgesia due to very high opioid doses Opioid-induced hyperalgesia Opioid-induced hyperalgesia

7.8 Methods

Patients were recruited from the different clinical groups that have been outlined previously in order to provide comparison between the groups. The different patient groups were – patients with cancer pain, patients with chronic non-cancer pain, patients with a history of substance misuse, patients with non-cancer pain and co-morbid substance misuse, and patients with non-cancer pain who were not on opioids. In addition healthy volunteers were recruited to provide comparison with the population from which the patients had been recruited rather than normal data from other countries.

Patients who were on 60 mg of morphine or an equivalent dose of another opioid were eligible to complete more than one series of assessments. Patients with a history of substance misuse were asked to complete just one series of assessments.

The opioid history was completed in detail at the first assessment providing information about the use of opioids in the six months prior to the assessment. At the subsequent assessments the opioid history was updated if there had been any changes to the opioid or dose prescribed.

Patients were asked to complete the Self-Completed Leeds assessment of Neuropathic Symptoms and Signs (S-LANSS). The S-LANSS tool asks patients seven questions about the nature of their pain and helps to distinguish neuropathic pain from other pain types. Patients answered questions regarding the presence of pins and needles or tingling, altered sensation and colour change at the site of their pain. Each question is given a score and if the total score is 12 or greater it suggests the pain is neuropathic in origin. The validation of the S-LANSS was discussed in the methods chapter.

Quantitative sensory testing provides a functional assessment of the peripheral nervous system. The patients were asked to compare the different sensations between the index and control site. For each sensory modality tested they were asked to describe the sensation as

increased, significantly increased, reduced, significantly reduced, no difference or not detected.

The quantitative sensory testing was carried out in a consistent manner and all researchers involved ensured they used the same language for each assessment and as other members of the research team.

The quantitative sensory testing (QST) was carried out with the patient relaxed and comfortable. The thermal rollers were at the correct temperature before the QST commenced to avoid any delays or the need to change the order of the testing. Each of the sensory modalities was explained separately and documented in the case report form.

A soft brush was gently applied to the skin at both index and control sites and the patient was asked to describe the sensation as indicated above. The patient was also asked to give the sensation a pain score from zero to ten. A cool roller at a temperature of 25^0 was applied next followed by a warm roller at 40^0. The rollers are applied to the skin and the same questions are asked as for the brush.

Von Frey filaments are calibrated so that they apply a consistent force to the skin. The filaments are numbered from three to 19.

The filaments are placed on the skin and the handle is depressed just enough to bend the filament. Starting at the filament which applies the lowest force the researcher moves through the filaments until the patient is just able to detect the force applied. The number of the filament is then recorded as the detection threshold. The patient is asked to give a pain score from zero to ten and then the sequence of testing each filament in sequence continues until the patient reports the force applied causes pain. The number of this filament is recorded as the pain threshold and a pain score is recorded.

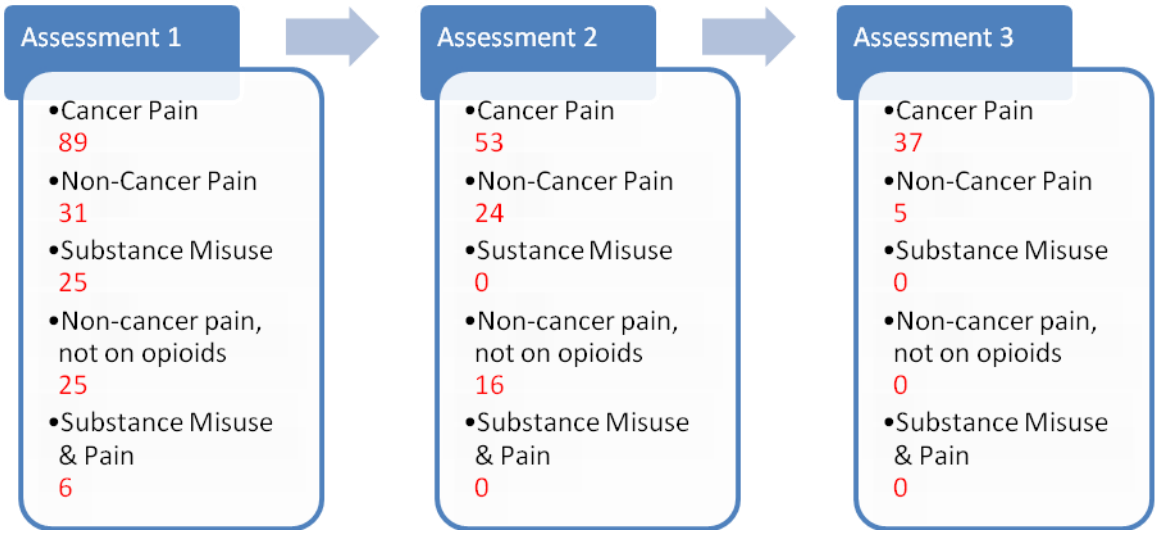
Pinprick sensation was tested at both index and control sites. Patients were asked if they could detect the pinprick and whether it caused them any pain. A test for wind-up was the final stage of the quantitative sensory testing. The pin was used to cause several skin pricks in quick succession. If severe pain resulted, wind-up was present and a pain score was attributed.

In order to facilitate the statistical analysis of the detection and pain thresholds the filament numbers are converted to a force applied according to the manufacturers calibration chart. The chart has been included as Appendix L.

The findings of the quantitative sensory testing have been explored using descriptive statistics to explore possible correlations between sensory processing and either the opioid prescribed or recent titration of the dose. Possible correlations between the presence of pain and the type of pain ie cancer or non-cancer pain and the patients' sensory processing were also explored. The data from healthy volunteers were compared with data from the control site of the patients.

7.9 Results

Figure 7: Number recruited in each patient group and the number of assessments completed by patients in each patient group



The tables below show the results of the quantitative sensory testing. The results are presented by patient group, opioid prescribed and opioid titration for each of the sensory modalities explored.

Table 70: Thermal thresholds reported by patients at index and control sites where n = 164 at assessment 1 and n = 88 at assessment 2

	N (%)
Assessment 1	
Index cool response	
Decrease	23 (14.0%)
No change	71 (43.3%)
Increase	70 (42.7%)
Index warm response	
Decrease	39 (23.8%)
No change	71 (43.3%)
Increase	54 (32.9%)
Assessment 2	
Index cool response	
Decrease	17 (19.3%)
No change	34 (38.6%)
Increase	37 (42.0%)
Index warm response	
Decrease	21 (23.9%)
No change	39 (44.3%)
Increase	28 (31.8%)

The thermal thresholds at the index site of all patients are shown above. At assessment one 23 patients (14.0%) described a decreased response when the cool threshold was tested and 70 patients (42.7%) described an increased response to the same stimulus. At assessment one a larger number of patients (n=39, 23.8%) reported a reduced response to the warm stimulus and 54 patients (32.9%) reported an increased response to stimulus.

At assessment two, 17 patients (19.3%) reported a reduced response to cool stimulus and 37 (42.0%) patients reported an increased response to the same stimulus. The number of patients reporting altered response to warm stimulus also increased at assessment two. Twenty-one patients (23.9%) reported a reduced response and 28 patients (31.8%) reported and increased response.

Table 71: Thermal thresholds at assessment no. 1 by patient group where n = 159

Index cool response		
Cancer	Decrease	8 (9.5%)
	No change	37 (44.0%)
	Increase	39 (46.4%)
Non-cancer	Decrease	8 (25%)
	No change	10 (31.3%)
	Increase	14 (43.8%)
Substance misuse	Decrease	1 (5.7%)
	No change	12 (63.2%)
	Increase	6 (31.6%)
Non-opioid	Decrease	5 (20.8%)
	No change	9 (37.5%)
	Increase	10 (41.7%)
Index warm response		
Cancer	Decrease	11 (13.1%)
	No change	42 (50.0%)
	Increase	31 (36.9%)
Non-cancer	Decrease	14 (43.8%)
	No change	9 (28.1%)
	Increase	9 (28.1%)
Substance misuse	Decrease	2 (10.5%)
	No change	10 (52.6%)
	Increase	7 (36.8%)
Non-opioid	Decrease	11 (45.8%)
	No change	7 (29.2%)
	Increase	6 (25.0%)

The table above provides further details of the thermal thresholds in each patient group. In the substance misuse group, the majority of patients had normal threshold responses to the cool stimulus. In both the cancer and non-cancer pain groups a significant proportion of patients had an increased response to the cool stimulus.

Table 72: Thermal thresholds at assessment no. 2 by patient group where n = 88

Index cool response		
Cancer	Decrease	8 (16.3%)
	No change	20 (40.8%)
	Increase	21 (42.9%)
Non-cancer	Decrease	6 (26.1%)
	No change	8 (34.8%)
	Increase	9 (42.9%)
Substance misuse	No change	1 (100.0%)
Non-opioid	Decrease	3 (20.0%)
	No change	5 (33.3%)
	Increase	7 (46.7%)
Index warm response		
Cancer	Decrease	10 (20.4%)
	No change	25 (51.0%)
	Increase	14 (28.6%)
Non-cancer	Decrease	6 (26.1%)
	No change	9 (39.1%)
	Increase	8 (34.8%)
Substance misuse	Decrease	1 (100.0%)
Non-opioid	Decrease	4 (26.7%)
	No change	5 (33.3%)
	Increase	6 (40.0%)

The responses to the cool stimulus do not appear to have changed much between assessment one and two in any of the patient groups. There is only one patient in the substance misuse group though. The responses to the warm threshold appear to have changed significantly in those patients with non-cancer pain and those patients with non-cancer pain who are not on opioids when assessments one and two are compared. There are smaller changes seen at assessment two in the cancer pain group. Between the assessments the percentage of patients in the non-cancer group who have a decreased response to the warm stimulus has reduced from 43.8% to 26.1% with an increase in the percentage of

patients who had either no change or an increased response. The same pattern was seen in the patients who were not on opioids but had chronic non-cancer pain.

Table 73: Thermal thresholds at assessment no. 1 by regular drug where n = 129 and the most frequently prescribed drugs are shown

Index cool response		
Fentanyl	Decrease	1(6.7%)
	No change	5(33.3%)
	Increase	9(60.0%)
Methadone	Decrease	2(10.0)
	No change	12(60.0%)
	Increase	6(30.0%)
Morphine	Decrease	8(14.3%)
	No change	26(46.4%)
	Increase	22(39.3%)
Oxycodone	Decrease	6(15.8%)
	No change	14(36.8)
	Increase	18(47.4%)
Index warm response		
Fentanyl	Decrease	1(6.7%)
	No change	6(40.0%)
	Increase	8(53.3%)
Methadone	Decrease	3(15.0%)
	No change	12(60.0%)
	Increase	5(25.0%)
Morphine	Decrease	10(17.9%)
	No change	29(63.0%)
	Increase	17(34.7%)
Oxycodone	Decrease	10(26.3%)
	No change	13(34.2%)
	Increase	15(39.5%)

Fentanyl has the largest proportion of patients with an increased response to the warm stimulus. Patients who were prescribed methadone were most likely to report no change in their response to warm threshold. Patients who were prescribed morphine and oxycodone either reported no change or an increase in response to the warm stimulus with a small number of patients who were prescribed each drug reporting a decreased warm response.

Similar patterns were seen when patients were asked to describe their response to the cold stimulus. Again patients who were prescribed methadone were most likely to have no change in their response to the warm stimulus. Patients who were prescribed morphine also were most likely to have no change in the description of the warm stimulus.

Table 74: Change in temperature thresholds by mean change in morphine equivalent dose (MEDD) between assessments 1 and 2 where n = 88

	Change in 24 hour MEDD					
	N	**Mean**	**SD**	**SE**	**Min**	**Max**
Change in cool response						
Reduced	25	0.2	60.7	12.9	-120.0	139.5
Same	42	7.9	61.4	11.2	-120.0	200.0
Elevated	21	-7.1	76.9	18.1	-160.0	205.0
All	88	1.6	64.8	7.7	-160.0	205.0
Change in warm response						
Reduced	18	4.2	54.1	12.7	-120.0	110.0
Same	54	-0.6	70.2	11.2	-160.0	205.0
Elevated	15	2.4	68.4	19.8	-120.0	180.0
All	87	1.2	65.2	7.8	-160.0	205.0

The table shows the patients divided into three groups according to the change in their response to the cool stimulus between assessments one and two. The responses were either reduced, the same or increased between the two assessments. “N” shows the number of patients in each group. There is a very wide range of opioid dose changes as shown by the

maximum and minimum values. The mean changes are very small with large standard deviations.

The same information is also presented for the patients description of their response to the warm threshold.

Table 75: Temperature thresholds at the index site by mean opioid titration from 7 days ago & from 4 weeks ago at assessment 1 where n = 164

		Dose change (%) from 7 days ago			Dose change (%) from 4 weeks ago		
	N	Mean	Min	Max	Mean	Min	Max
Index cool response at assessment 1							
Decrease	23	-6.4	-33.3	0.0	-8.4	-57.1	40.0
No change	71	9.6	-66.7	525.0	31.6	-66.7	525.0
Increase	70	1.4	-44.4	66.7	9.1	-52.0	200.0
Index warm response at assessment 1							
Decrease	39	-1.8	-33.3	50.0	-1.9	-57.1	80.0
No change	71	8.9	-66.7	525.0	23.9	-66.7	525.0
Increase	54	0.9	-44.4	66.7	18.4	-28.6	200.0
All	164	4.0	-66.7	525.0	16.8	-66.7	525.0

The table shows the patients divided into three groups according to the change in their response to the cool stimulus between assessments one and two. The responses were either reduced, the same or increased between the two assessments. “N” shows the number of patients in each group. There is a wide range of opioid dose changes and these ranges are greater over the longer time period. The mean changes are very small with large standard deviations.

Table 76: Brush Response at the index site for all patients in the study where n = 163

Assessment 1	
Decrease	40(24.5%)
No change	97(59.5%)
Increase	26(16.0)
Assessment 2	
Decrease	16(18.2%)
No change	61(69.3%)
Increase	11(12.5%)

In the study group as a whole at assessment one and two the majority of patients reported a normal response to the brush stimulus.

Table 77: Brush response at the index site by patient group and assessment where n = 158 at assessment one

Assessment 1		
Cancer	Decrease	17(20.2%)
	No change	56(66.7%)
	Increase	11(13.1%)
Non-cancer	Decrease	9(29.0%)
	No change	13(41.9%)
	Increase	9(29.0%)
Substance misuse	Decrease	5(26.3%)
	No change	12(63.2%)
	Increase	2(10.5%)
Non-opioid	Decrease	8(33.3%)
	No change	13(54.2%)
	Increase	3(12.5%)
Assessment 2		
Cancer	Decrease	5(10.0%)
	No change	40(80.0%)
	Increase	5(10.0%)
Non-cancer	Decrease	5(22.7%)
	No change	13(59.1%)
	Increase	4(18.2%)
Substance misuse	No change	1(100.0%)
Non-opioid	Decrease	6(40.0%)
	No change	7(46.7%)
	Increase	2(13.3%)

At assessment one the majority of patients in each of the different groups described an unchanged response to the brush at the index site. In patients with non-cancer pain and those with non-cancer pain who were not on opioids this majority was less than in the other two patient groups. Patients with non-cancer pain who were prescribed opioids had a more even distribution between those patients who described an increased and a decreased

response to the brush. In patients with non-cancer pain, not on opioids only a small minority had an increased response to the brush at the index side.

At assessment two, the majority of patients with cancer pain have an unchanged response to the brush at the index site with 56 patients (80.0%) reporting a normal experience. In the non-cancer pain group the same pattern is seen at assessment two and assessment one. In the group of patients who were on not on opioids but had chronic non-cancer pain there is again a more even distribution between those patients who had an unchanged response to the brush and those with a reduced response to the stimulus. A minority of two (13.3%) of patients in this group had an increased response.

Table 78: Brush response at assessment no. 1 by regular drug where the most frequently prescribed opioids are shown and n = 128

Fentanyl	Decrease	4 (26.7%)
	No change	6 (40.0%)
	Increase	5 (33.3%)
Methadone	Decrease	5 (25.0%)
	No change	13 (65.0%)
	Increase	2 (10.0%)
Morphine	Decrease	8 (14.5%)
	No change	44 (80.0%)
	Increase	3 (5.5%)
Oxycodone	Decrease	11 (28.9%)
	No change	16 (42.1%)
	Increase	11 (28.9%)

As in the previous tables where the results are presented by regular opioid prescribed, 15 patients were prescribed fentanyl, 20 patients were prescribed methadone, 55 patients were

prescribed morphine and 38 patients were prescribed oxycodone. The majority of patients who were on methadone reported no change in response to the brush. Patients who were prescribed morphine had the greatest majority (80%) of patients with an unchanged response to the brush.

Table 79: Von Frey detection thresholds in units of force (g) at index and control site by patient group where n = 140 at assessment one

		Detection threshold: index					Detection threshold: control				
		N	Mean	Median	Min	Max	N	Mean	Median	Min	Max
Assessment No											
1	Cancer	83	3.8	0.4	0	110	84	2.8	0.7	0	34
	Non-cancer	33	16.0	1.1	0	110	31	4.5	0.4	0	110
	Non-opioid	24	5.5	0.2	0	110	24	1.0	0.3	0	8
	All	140	7.0	0.4	0	110	139	2.9	0.4	0	110
2	Cancer	50	4.9	1.4	0	34	50	2.5	1.1	0	17
	Non-cancer	23	7.5	1.1	0	110	20	0.8	0.3	0	5
	Non-opioid	15	15.5	0.4	0	110	15	0.8	0.4	0	3
	All	88	7.4	1.1	0	110	85	1.8	0.4	0	17

The table above shows the detection thresholds at the index and control sites for patients with cancer pain, non-cancer pain and those patients with non-cancer pain who were not on opioids. The thresholds are given as forces in grams. At the index site patients with non-cancer pain had the highest mean detection threshold with a mean of 16.0 g. This is much higher than patients in the other groups. At the control site patients with non-cancer pain again had the highest mean detection threshold. At assessment two it is the patients with non-cancer pain who were not on opioids who had the highest mean detection threshold at the index site.

Table 80: Difference between index and control sites in Von Frey detection thresholds in units of force (g) by patient group where n = 138 at assessment one

		Detection threshold index - control				
		N	**Mean**	**SE**	**Min**	**Max**
Assessment No						
1	Cancer	83	1.0	1.4	-19	107
	Non-cancer	31	9.0	4.9	-5	110
	Non-opioid	24	4.6	4.5	-5	108
	All	138	3.4	1.6	-19	110
2	Cancer	49	2.4	1.1	-7	29
	Non-cancer	20	7.6	5.4	-1	108
	Non-opioid	15	14.7	9.8	-3	110
	All	84	5.9	2.3	-7	110

The table above shows the detection threshold at the index site minus the detection threshold at the control site. At assessment one it is the patients with non-cancer pain who had the greatest difference between sites. At assessment two it is the patients with non-cancer pain who were not on opioids. Patients with cancer pain had the smallest difference between thresholds at both assessments. In all patients together detection threshold are significantly difference between index and control sites. There is no significant difference between the sites in the different patient groups.

Table 81: Von Frey pain thresholds in units of force (g) at index and control site by patient group where n = 139 at assessment one

		Pain threshold: index					Pain threshold: control				
		N	Mean	Median	Min	Max	N	Mean	Median	Min	Max
Assessment No											
1	Cancer	82	46.4	24.0	0	110	84	49.6	24.0	0	110
	Non-cancer	33	49.6	24.0	0	110	31	39.9	17.0	0	110
	Non-opioid	24	35.2	12.7	0	110	24	29.6	12.7	2	110
	All	139	45.2	17.0	0	110	139	44.0	24.0	0	110
2	Cancer	50	47.3	24.0	0	110	51	41.7	24.0	1	110
	Non-cancer	23	54.8	34.0	0	110	21	66.2	110.0	0	110
	Non-opioid	15	33.9	5.1	2	110	15	29.1	8.3	1	110
	All	88	46.9	24.0	0	110	87	45.4	24.0	0	110

The table above shows the pain thresholds at the index and control sites for patients with cancer pain, non-cancer pain and those patients with non-cancer pain who were not on opioids. The thresholds are given as forces in grams. At the index site patients with non-cancer pain had the highest mean pain threshold and those patients with non-cancer pain who were not on opioids had a much lower threshold. At assessment one the mean pain threshold at the control site in patients with cancer pain was higher than at the index site.

Table 82: Difference between index and control sites in Von Frey pain thresholds in units of force (g) by patient group where n = 137 at assessment one

		Pain threshold index - control				
		N	**Mean**	**SE**	**Min**	**Max**
Assessment No						
1	Cancer	82	-1.8	4.2	-107	102
	Non-cancer	31	9.4	9.0	-107	109
	Non-opioid	24	5.6	5.1	-23	102
	All	137	2.0	3.3	-107	109
2	Cancer	50	7.0	4.8	-93	102
	Non-cancer	21	-8.7	14.1	-110	110
	Non-opioid	15	4.9	11.0	-86	102
	All	86	2.8	4.8	-110	110

The table above shows the pain threshold at the index site minus the pain threshold at the control site. At assessment one, patients with cancer pain had a negative mean reflecting the higher pain threshold at the control site than the index site. At assessment two, it is the patients with non-cancer who were not on opioids who had a negative mean.

Table 83: Visual Analogue Scores for the pain threshold detected using the Von Frey filaments where n = 141 at assessment 1

		Pain threshold VAS: index					Pain threshold VAS: control				
		N	Mean	Median	Min	Max	N	Mean	Median	Min	Max
Assessment No											
1	Cancer	84	2.3	1.0	0	10	85	1.9	1.0	0	10
	Non-cancer	33	2.3	1.0	0	9	32	2.4	1.0	0	8
	Non-opioid	24	2.0	1.0	0	7	24	2.0	1.0	0	6
	All	141	2.2	1.0	0	10	141	2.0	1.0	0	10
2	Cancer	50	2.1	1.0	0	9	51	2.3	1.0	0	10
	Non-cancer	23	2.2	1.0	0	8	21	0.8	0.0	0	5
	Non-opioid	15	2.3	1.0	0	8	15	3.1	3.0	0	8
	All	88	2.1	1.0	0	9	87	2.1	1.0	0	10

The pain scores range from the minimum to the maximum possible values on the visual analogue scales indicating some patients did not feel pain even at the strongest force exerted by the Von Frey filaments. The mean and median pain scores appear similar throughout the patient groups.

Table 84: Difference between index and control sites in Von Frey detection and pain thresholds in units of force (g) by regular opioid where n = 107 at assessment one

		Detection threshold index – control			Pain threshold index - control		
Assessment No	Drug	N	Mean	SE	N	Mean	SE
1	Fentanyl	14	0.4	1.0	14	-2.3	3.3
	Morphine	57	4.0	2.7	57	-4.7	5.5
	Oxycodone	36	3.9	3.1	35	10.6	7.6
2	Fentanyl	9	3.5	3.3	9	-13.4	18.8
	Morphine	34	5.7	3.3	35	8.4	6.8
	Oxycodone	22	1.5	1.0	23	-0.2	8.9

Fentanyl had the lowest mean difference between detection thresholds at the index and control sites. Oxycodone had the highest mean difference between pain thresholds at the index and control sites.

Table 85: Pearson correlations between dose change from assessment 1 to 2, and change in thresholds (index - control) between assessments 1 & 2 for cancer and non-cancer pain patients

		Correlation with dose change	P
Cancer	Detection threshold	0.285	0.052
	Pain threshold	0.165	0.267
Non-cancer	Detection threshold	-0.061	0.799
	Pain threshold	0.165	0.474
All	Detection threshold	0.195	0.113
	Pain threshold	0.154	0.210

Table 86: Comparison of Control results at assessment 1 with results for 102 healthy volunteers

Grp	Mean (SE) Detection Threshold	Mean (SE) Difference from Healthy volunteers	t ratio of difference	Mean (SE) Pain Threshold	Mean (SE) Difference from Healthy volunteers	t ratio of difference	Mean (SE) Pain VAS	Painvasdiff	t ratio of difference
Healthy volunteers	0.29 (0.05)		.	66.48 (4.55)		.	2.88 (1.43)		.
Cancer	2.78 (0.62)	2.49 (0.62)	4.01	49.62 (5.11)	-16.86 (6.84)	-2.46	1.91 (0.27)	-0.97 (1.45)	-0.67
Non-cancer	4.51 (3.53)	4.22 (3.53)	1.20	39.91 (7.89)	-26.56 (9.11)	-2.92	2.41 (0.47)	-0.47 (1.50)	-0.32
Substance misuse	0.48 (0.15)	0.19 (0.16)	1.18	60.83 (10.41)	-5.65 (11.36)	-0.50	1.13 (0.40)	-1.76 (1.48)	-1.18
Non-opioid	0.98 (0.39)	0.69 (0.39)	1.76	29.61 (7.85)	-36.87 (9.07)	-4.06	2.04 (0.37)	-0.84 (1.48)	-0.57
All	2.50 (0.74)	2.21 (0.75)	2.97	46.47 (3.63)	-20.00 (5.82)	-3.44	1.91 (0.19)	-0.97 (1.44)	-0.67

The table shows the mean detection thresholds using Von Frey filaments in healthy volunteers and then the difference between mean detection thresholds in healthy volunteers and the other patient groups. The table also shows the mean pain thresholds using Von Frey filaments in healthy volunteers and then the difference between mean detection thresholds in healthy volunteers and the other patient groups.

T ratios greater than two are unlikely to be due to chance. Pain thresholds are 'significantly' lower than healthy volunteers in the cancer, non-cancer and non-opioid groups, but detection thresholds are significantly higher in the patients with cancer pain and for all patient groups combined.

Table 87: Wind-up frequencies by patient group at assessment 1 where n = 50

Patient Group	Wind-up at Index Site	Wind-up at Control site
Cancer	8 (9.1%)	3(3.6%)
Non-cancer	13 (39.4%)	9 (27.3%)
Substance misuse	4 (16%)	N/A
Non-cancer pain, Non opioid	9 (36%)	4 (16%)

The table above shows the number of patients with wind-up in each patient group. At the control site which is a non-painful area it is surprising to note the number of patients who have wind-up. Nine (27.3%) out of 33 patients with non-cancer pain reported wind-up at the control area.

Table 88: Mean pain (VAS) of patients with wind-up detected at the index site by patient group and assessment at assessment 1

		Index		Control	
		N	Mean pain (VAS)	N	Mean pain (VAS)
Assessment	Patient group				
1	Cancer	8	2.5	3	0.3
	Non-cancer	13	4.6	9	3.8
	Substance misuse	3	3.0	N/A	N/A
	Non-opioid	8	2.5	4	1.1

Table 88 shows the mean pain visual analogue scale (VAS) of those patients who reported wind-up. The results are shown for each patient group and at each assessment. Patients were asked to score their pain from zero to ten. The mean pain VAS for those patients with non-cancer pain was 4.6 at the index pain site and 3.8 at the control site. The mean pain scores for patients in the non-cancer pain group were higher than the mean pain scores reported by patients in the other groups.

Table 89: Mean pain differences (Index minus Control) for patients with wind-up detected at the index site by patient group and assessment at assessment one

		Index	Control	Index minus Control
		Mean pain (VAS)	Mean pain (VAS)	Mean pain (VAS)
Assessment	Patient group			
1	Cancer	2.5	0.3	2.3
	Non-cancer	4.6	3.8	1.0
	Non-opioid	2.5	1.1	1.4
	All	3.4	2.2	1.5

Patients with substance misuse were excluded from this table of results as wind-up was only sought at the index site in that patient group. The table shows there is little difference in mean pain scores at index and control sites for those patients with non-cancer pain who detected wind-up. There is a greater difference between wind-up associated pain at the index and control sites for those patients with cancer pain.

Table 90: Mean pain (VAS) of index and control wind-up by regular drug at assessment 1 for patients with wind-up detected at the index site and who were prescribed one of the four most frequently prescribed opioids where n = 22

	Index		Control	
	N	**Mean pain (VAS)**	**N**	**Mean pain (VAS)**
Fentanyl	5	3.2	4	2.8
Methadone	4	3.8	1	3.0
Morphine	8	4.0	8	2.1
Oxycodone	5	4.6	5	1.8

The table above shows the number of patients who were prescribed the most frequently used opioids who detected wind-up at index and control sites. The mean pain score at the index site of patients who were prescribed oxycodone is higher than the mean pain score reported by patients prescribed other opioids. However at the control site the mean pain score of patients who were prescribed oxycodone is lower than the other corresponding scores for patients on other opioids.

Table 91: Wind-up frequencies at assessment 1, by patient group and most used regular opioid (last 24h) where n = 83 and only the four top opioids are shown

		Index Wind-up			Control Wind-up		
			D	N		D	N
Cancer	Fentanyl	.	2	6	7	.	1
	Morphine	1	1	39	25	.	16
	Oxycodone	1	4	29	17	.	17
	All	2	7	74	49	.	34
Non-cancer	Fentanyl	1	3	3	3	2	2
	Methadone	.	1	.	.	1	.
	Morphine	.	7	10	3	4	10
	Oxycodone	.	1	4	3	1	1
	All	1	12	17	9	8	13
Substance misuse	Methadone	.	4	16			
	Oxycodone	.	.	1			
	All	.	4	17			

The table above shows the number of patients who detected wind-up by opioid prescribed and in each patient group. In the cancer pain group oxycodone is the most frequently prescribed opioid in those patients who detected wind-up. In the non-cancer pain group morphine is most commonly associated with wind-up.

7.10 Summary of Main Findings

7.10.1 Wind-up

The most striking result is the presence of wind-up at the control site. Patients with chronic non-cancer pain were more likely than patients with cancer pain to have wind-up at the control site. Patients with wind-up were asked to score the pain from zero to ten and the mean pain score at the index site was 3.4 in all patient groups and 2.0 at the control site. In patients with cancer pain oxycodone was the opioid most often associated with wind-up at the control site. In patients with non-cancer pain morphine was the opioid most commonly associated with wind-up.

7.10.2 Thermal Thresholds

Patients with chronic non-cancer pain had altered thermal thresholds. This change appeared to be exaggerated when the patients were prescribed opioids to manage the pain. Patients with substance misuse were least likely to have altered thermal thresholds. Patients with cancer pain and non-cancer pain had either no change in thermal thresholds or an increase in both cool and warm responses. Patients who were not on opioids and had non-cancer pain showed an increased proportion of patients with reduced thermal thresholds and this was most pronounced at assessment two. Methadone was the opioid prescribed which appeared least likely to alter the patients' response to thermal thresholds. Fentanyl was the most likely to increase the response to the warm stimulus.

7.10.3 Brush Allodynia

Overall there was less consistency between patient groups in their response to the brush being applied to the skin. Patients with cancer pain were most likely to have an unaltered response to the brush. Patients with non-cancer pain reported an increased and decreased response in almost equal proportions. Patients who were prescribed morphine and methadone were most likely to have an unaltered response to the brush. Fentanyl was the opioid most likely to induce a change however the change was split between increased and decreased response.

7.10.4 Pain and Detection Thresholds

Patients with non-cancer pain had the highest mean Von Frey detection threshold and the greatest difference between detection thresholds at the index and control sites. Patients with non-cancer pain also had the highest mean pain threshold at the index site. Although the numbers are small there does appear to be a difference between the opioid. Fentanyl had a smaller difference between detection threshold at the index and control sites. The healthy volunteers had higher pain thresholds than any of the patient groups but were able to detect Von Frey filaments at lower forces than the patient groups.

7.11 Discussion

In a study comparing patients with pain but not on opioids and patients with pain Lucy Chen and colleagues found no evidence of mechanical hyperalgesia in any of the patient groups. They found heat-induced wind-up was present in patients with pain and on opioids but not in the other patient groups. They found a correlation between morphine equivalent daily dose and both the heat pain threshold and the presence of heat-induced hyperalgesia (Chen et al, 2009). The results of this study are very comparable to our own findings but

highlight the difficulties in comparing quantitative sensory testing results between studies when the parameters used are so different.

Wind-up at the control site indicated a significant proportion of patients in our study were developing central sensitisation. Central sensitisation occurs when normal inhibitory controls are reduced or stopped (Dickenson, 1995). This has been recognised in experimental studies in both animal and human models (Bannister et al, 2011). Thus the presence of the wind-up may be an early means of identifying patients at risk of developing OIH. Testing for wind-up is possible for clinicians in all care settings and requires no specialist equipment or training. The recognition of a hyper-excitable state is helpful in terms of making a diagnosis of hyperalgesia but it does not necessarily lead us to conclude the opioids are responsible. Our results suggest that pain and chronic exposure are both playing a role with overlap in patients who have chronic pain and are prescribed opioids.

In our patient groups there was also altered thermal sensitivity. 32.9% of the patients reported an increased response to the warm stimulus and this was maintained over time to the second assessment. Altered thermal thresholds have also been recognised in both animal and human models. Anne Vardanyan and colleagues discussed the role of the TRPV1 receptor in opioid-induced hyperalgesia. In a study involving rats with implanted morphine pellets they were able to demonstrate thermal and touch hypersensitivity in rats with TRPV1 receptor expressed and this was absent in TRPV1 knock-out mice. TRPV1 is known to play a role in inflammatory mediated pain and in the presence of inflammation the expression of TRPV1 increases. The ability to block the hyperalgesia with a TRPV1 antagonist further supports its importance in the OIH pathway (Vardanyan et al, 2009). Further weight was given to the role of the TRPV1 receptor by the findings of Rowan's work (Rowan et al, 2014). The altered thermal threshold was also demonstrated in patients with COMT val^{158}met polymorphism (Jensen et al, 2009) which is discussed in the chapter on future work.

Sensitivity to cold-induced pain has also been described and attributed to exposure to morphine. This has been demonstrated in methadone maintenance patients in particular (Compton et al, 2010; Cleeland et al, 1995). Again patients in our study groups described altered response to the cool stimulus with 42.7% describing an increased response to the cool roller.

In a study published in 2014 Wasserman and colleagues described a cohort of patients on long-term opioids and had persistent pain. They found that some patients who were on opioids had persistent pain and wondered if his clinical finding may indicate OIH or that the patients had a central pain which was less likely to respond to the opioids (Wasserman et al, 2014). One aspect that certainly warrants further exploration in our group is the presence of neuropathic features of the pain and whether there is any association between pain which is predominantly neuropathic and the development of the features of OIH.

Our results add to the published literature and provide valuable comparison between patient groups. The data are also provided at different time points which are of benefit. We have provided comparison between different patient groups which are highly relevant to clinicians. While there will be limitations on comparison due to different quantitative sensory testing protocols it will be possible for other research groups to compare our results to their own findings. Although our results are consistent with the literature in terms of altered thermal threshold we need to explore in more detail whether individual patients have both altered warm and cool sensory processing and whether it is the patients with altered thermal threshold who also have wind-up at the control site. When this further analysis has been carried out we will be much closer to defining the clinical phenotype of OIH.

CHAPTER 8: PATIENTS WITH CHRONIC NON-CANCER PAIN AND A HISTORY OF SUBSTANCE MISUSE

8.1 Hypothesis

Patients with chronic non-cancer pain and co-morbid substance misuse will have a different response to opioids. This will result in different opioid-related side effects and sensory thresholds when compared to patients who are taking opioids for the management of either chronic non-cancer pain or substance misuse.

8.2 Introduction

Much has been written about the risks of patients becoming addicted to opioids which have been prescribed for the management of their pain. Less has been written about the management of chronic pain in those patients with a current history of substance misuse. In an editorial in Pain in 2009 Alford highlighted the importance of knowing whether the patient had a history of substance misuse when managing chronic non-cancer pain. He called for specialists in pain management and addiction to work together to achieve the best outcomes for patients. As well as the need for vigilance when prescribing opioids for this group of patients he also highlights the altered and often increased pain responses that patients who are substance misusers display (Alford, 2009, Ballantyne and LaForge, 2007).

While it is important to be cautious of the risks involved when managing pain in patients with substance misuse, it would not be ethical to withhold analgesia from patients with chronic pain, including opioids where these are an appropriate therapeutic option. It should be noted however, that the risk/ benefit balance that needs to be considered before starting any patient on a strong opioid is different in this group of patients. Patients with a history of substance misuse will have a higher risk of iatrogenic dependence, but uncontrolled pain may be a stressor that can contribute to relapse.

8.2.1 Definition of Addiction

Physical dependence will occur after prolonged use of an opioid and is a physiological response to exposure. It will manifest with symptoms when the drug is withdrawn suddenly or the dose is significantly reduced. Symptoms are those covered by the short opioid withdrawal scale and will include yawning, sweating, abdominal pain and muscle aches. Physical dependence is not the same as, or a precursor for, addiction. The definition of addiction requires that the patient has a pre-occupation with the need to obtain the drug. Loss of control over the use of the opioid is important in both the development of addiction and in making the diagnosis (Lingford-Hughes et al, 2010). Portenoy (quoted in Hojsted and Sjogren, 2007, page 492) describes addiction as "a psychological and behavioural syndrome characterised by evidence of psychological dependence, and evidence of compulsive drug use, and/or evidence of compulsive drug use, and/or evidence of other aberrant drug-related behaviours."

There is a "spectrum of substance misuse behaviours" including harmful use and substance abuse (Lingford-Hughes et al, 2004). Methadone maintenance programmes are effective at keeping patients in management programmes, reducing the use of other non-prescription drugs, reducing patient involvement in crime and preventing drug related deaths (Lingford-Hughes et al, 2004).

"Addiction stems from the progressive adaptation of the brain to repeated exposure to drugs of abuse" (Lutz and Kieffer, 2013, page 473). Initially patients gain a reward from use of the drug whether this is an opioid, cannabis, or alcohol or another substance with potential for misuse. After the experience of reward the patient starts to seek the reward again and enters a cycle of reward, withdrawal and craving which deteriorates into addiction. The mu-opioid receptor is involved in the sensation of reward associated with opioids and it is possible that genetic variation in the mu opioid receptor affects responses to social behaviour which have also been implicated in the development of addiction.

Conversely the kappa receptor has been shown to block the experience of reward to both opioids and social experiences (Lutz and Kieffer, 2013).

Several brain areas are key in the addiction pathways and these include the nucleus accumbens, the orbitofrontal cortex and the amygdala. Dopamine is one of the main mediators involved in dependence developing. (Lingford-Hughes et al, 2010)

8.2.2 Drugs used to manage addiction to opioids

In the UK methadone and buprenorphine are the drugs most frequently used to maintain patients with substance misuse. Methadone is a synthetic opioid which binds at the mu opioid receptor which will relieve pain for four to six hours but will suppress withdrawal and craving for up to 36 hours due to a long half-life. Buprenorphine is also a synthetic opioid which is a partial agonist at the mu opioid receptor and has a ceiling effect which prevents the risk of respiratory depression if larger doses are taken. It dissociates slowly from the opioid receptor which gives the added benefit of a long duration of action. (Chapter 3, Pharmacology of medications used to treat opioid addiction in Center for Substance Abuse Treatment. Medication–Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005.)

8.2.3 Chronic Non-cancer Pain and Co-morbid Substance Misuse

Substance misuse exists with other psychiatric illnesses including depression, anxiety and psychosis. (Lingford-Hughes et al, 2004) Patients may also have physical health problems. Pain may be the reason patients seek opioids initially and pain can cause loss of physical

and social functioning that drives vulnerable patients to seek drugs as a means of coping and escape. (Trafton et al, 2004; Cicero et al, 2008)

It is difficult to ascertain the prevalence of chronic non-cancer pain in those with substance misuse as the patients may not engage with health services or their pain may not be recognised and there can be a tendency to over-diagnose prior to substance misuse (Weisner et al, 2009). However in 2012 a meta-analysis conducted by Fischer and colleagues provided an estimate of the prevalence of pain as 48% with the prevalence of anxiety as 16% and of depression 17%. It is noted that the prevalence of the diagnoses is in patients who are using prescription opioids illicitly and does not necessarily reflect the prevalence of co-morbidities in those patients who are enrolled in methadone maintenance programmes.

In a large study in the USA Constance Weisner and colleagues looked at data from two health plans and found that patients who were prescribed opioids for chronic non-cancer pain who also had a history of substance misuse were younger than other patients who were prescribed opioids. (Weisner et al, 2009) In another large study, Cicero and colleagues reviewed 1408 patients who were admitted for management of substance misuse. In this study there were many different substances used prior to admission for treatment. Patients were found to have significantly lower physical well-being across several domains including chronic pain, mental health and social functioning when compared to the national norms. In the study 45% of the patients reported that their first contact with opioids had been as part of the management of pain rather than as part of experimentation with drugs or seeking highs. This study neatly demonstrated the overlap of chronic pain and substance misuse. (Cicero et al, 2008)

The management of patients with chronic pain and a history of substance misuse relies on making an accurate diagnosis of all co-morbidities. It is important to obtain collateral history from family members and other health professionals where possible in case they have concerns about on-going use of other substances. Opioid contracts and written

treatment plans may also be helpful. (Wesson et al, 1993) Joint working between addiction and pain specialists is very important. It is likely that healthcare professionals will be wary of managing chronic pain in those patients with a history of substance misuse and there is a risk that adequate pain relief will be delayed. (Baldacchino et al, 2009)

8.3 Aims

The specific aims of this part of the study were to

- Establish the impact of opioids on the cognitive function of patients with chronic pain and substance misuse
- Compare the sensory processing of patients with chronic pain and substance misuse with the other patient groups.
- Compare the side effect burden of patients with chronic pain and substance misuse with the other patient groups.

8.4 Methods

Patients were recruited from a specialist clinic. After they had provided written consent they were asked to complete the research assessment on one occasion. Demographic data was collected and a detailed opioid history was obtained. Patients completed the same series of assessments as outlined in methods chapter. A detailed opioid history was taken and patients completed Likert scales which detailed the frequency of opioid-related side effects in the last week. The Brief Pain Inventory provided a measure of pain severity and the Self-completed Leeds Assessment of Neuropathic Symptoms and Signs provided an indication of the quality of the pain. Both objective and subjective measures of cognitive

function were used. Quantitative sensory testing provided information on the function of the peripheral nervous system.

8.5 Results

Only six patients were recruited with chronic non-cancer pain and a history of substance misuse. The patients in this group were all recruited from the specialist clinic in NHS Lothian at which patients are managed jointly by specialists in addiction and pain medicine. The clinic runs twice each month.

Table 92: Demographic details of the patients recruited with a history of chronic pain and substance misuse where n = 6

Patient Identification Number	Age, Sex	Pain Site	Pain Type
Patient 1	36, M	Lower abdomen	Mixed
Patient 2	41, M	Flank and inguinal region	Visceral
Patient 3	36, M	Neck, phantom arm pain	Muscular
Patient 4	22, M	Bilateral whole leg pain	Neuropathic
Patient 5	36, M	Back	Musculoskeletal
Patient 6	40, F	Forehead	Neuropathic

The patients were predominantly male with an age range of 22 to 41 years and a mean age of 35.2 years. There are several different types and sites of pain in the patient group.

Table 93: Opioid history and morphine equivalent daily dose (MEDD) of each patient with a history of chronic pain and substance misuse where n = 6

Patient Identification Number	Primary Opioid Prescribed	MEDD	Duration of Opioid Use
Patient 1	Dihydrocodeine	66 mg	10 years
Patient 2	Methadone	960 mg	Not stated
Patient 3	Methadone	1500 mg	12 years
Patient 4	Methadone	600 mg	1.5 years
Patient 5	Methadone	975 mg	8 years
Patient 6	Methadone	1050 mg	4 years

Methadone was the most frequently prescribed opioid in this patient group. The MEDD ranged from 66 mg to 1500 mg with a mean of 858.5 mg and a median of 967.5 mg. The duration of use ranged from 1.5 years to 12 years with a mean of 7.1 years and a median of 8 years.

Table 94: Use of adjuvant analgesics and non-pharmacological pain management techniques of each patient with a history of chronic pain and substance misuse where n = 6

Patient Identification Number	Adjuvant Analgesics	Non-pharmacological Interventions
Patient 1	Diclofenac, Methocarbamol	Acupuncture, Heat, Massage, Physiotherapy, Psychology, TENS
Patient 2	Gabapentin, Hyoscine butylbromide	Relaxation, Heat
Patient 3	No	Acupuncture, Massage, Aromatherapy, Reiki
Patient 4	Sodium Valproate, Gabapentin, Amitriptyline	Physiotherapy, TENS
Patient 5	No	Physiotherapy
Patient 6	Paracetamol, Ibuprofen	Acupuncture, TENS

Four of the six patients were also prescribed adjuvant analgesia and all the patients had engaged with non-pharmacological interventions as part of the approach to managing their pain.

Three of the patients had a co-existing psychiatric disorder – two patients had anxiety and depression and one patient had bipolar disorder.

Table 95: Median symptom severity scores and Number (percentage) of patients experiencing symptoms either very or quite often, or less frequently than this, in patients with a history of chronic pain and substance misuse where n = 6

	Median Severity of Symptom	N (%) of patients Experiencing Symptom Very / Quite Often	N (%) of patients Experiencing Symptom Occasionally / Never
Nausea	2.0	1 (16.7%)	5 (83.3%)
Vomiting	2.0	0 (0%)	6 (100%)
Dry Mouth	4.0	3 (50%)	3 (50%)
Myoclonus	1.0	1 (16.7%)	5 (83.3%)
Hallucinations	2.0	0 (0%)	6 (100%)

The table above shows dry mouth was the most frequent symptom in this patient group. The median symptom severity score for dry mouth was dry mouth. Nausea, vomiting and myoclonus were the most frequently reported symptoms in patients with a history of chronic pain and substance misuse.

Using the constipation score, three patients (50%) were constipated. Only one of the patients was prescribed a laxative.

Table 96: S-LANSS and Brief Pain Inventory Scores for patients with a history of chronic pain and substance misuse where n = 6

	S-LANSS Score	Brief Pain Inventory Scores	
Patient Identification Number		**Mean Pain Severity**	**Mean Pain Interference**
Patient 1	12	8.0	9.1
Patient 2	2	5.5	5.9
Patient 3	5	3.8	6.0
Patient 4	16	7.0	3.3
Patient 5	8	3.8	3.4
Patient 6	0	2.8	3.1

Two of the six patients scored 12 or greater on the S-LANSS indicating symptoms and signs consistent with neuropathic pain. The Brief Pain Inventory scores revealed the severity of the patient's' pain. The mean pain severity ranged from 2.8 to 8.0 out of 10, with a mean of 5.2. The mean pain interference ranged from 3.1 to 9.1 out of 10, with a mean of 5.1.

Table 97: MMSE and ACE-R scores for each patient with a history of chronic pain and substance misuse where n = 6

Patient Identification Number	MMSE Score	ACE-R Score
Patient 1	28	74
Patient 2	28	91
Patient 3	30	97
Patient 4	30	98
Patient 5	28	73
Patient 6	30	94

Cognitive function was assessed using the Addenbrooke's Cognitive Examination – Revised. Two of the patients had scores below 85 out of 100 indicating impaired cognitive function. All six patients had normal Mini-Mental State Scores.

Table 98: Thermal thresholds, brush response and presence of wind-up as detected by Quantitative Sensory Testing in patients with a history of chronic pain and substance misuse where n = 6

Patient Identification Number	Cool Response at Index Site	Warm Response at Index Site	Brush Response at Index Site	Wind-up at Control Site
Patient 1	Increased	Increased	Increased	No
Patient 2	Unchanged	Unchanged	Unchanged	Yes
Patient 3	Reduced	Reduced	Reduced	No
Patient 4	Reduced	Reduced	Reduced	No
Patient 5	Missing	Missing	Missing	Yes
Patient 6	Unchanged	Unchanged	Unchanged	No

One patient had missing QST data at the index site. Of the remaining five patients three had altered thermal thresholds and response to brush stimulus. Two of six patients had wind-up at the control site indicating sensitisation beyond the site of the pain.

8.6 Discussion

8.6.1 Summary of Main Findings

Only six patients were recruited with a history of chronic non-cancer pain and substance misuse. Recruitment for the study overall had been relatively straightforward however this

group of patients proved difficult to identify despite one of the research team being present at the specialist clinic.

Given the small number of patients recruited the pragmatic decision was taken to present descriptive results obtained for the patients. This has ensured transparency of findings.

The patients have varied pain histories. They are most frequently prescribed opioids and most of the patients have been on opioids for several years. Dry mouth and constipation were the most frequently reported symptoms. Two of the six patients had impaired cognitive function when assessed using the ACE-R. All patients had preserved cognitive function when assessed using the MMSE.

Four of the six patients have altered thermal thresholds and response to brush at the site of their pain on Quantitative Sensory Testing. Two patients had wind-up at the control site suggesting a general sensitisation.

8.6.2 Comparison with Other Patient Groups from this Study

Dry mouth is the most frequently reported symptom in all patient groups. The median severity is highest in patients with pain and a history of substance misuse but this is based on only six patients. The frequency of each of the symptoms appears very similar across the different patient groups. Constipation is more frequent in patients with substance misuse and a history of substance misuse than in other patient groups. The mean pain interference score in this group of patients is lower than in the other groups. As in other patient groups the ACE-R detected cognitive impairment which was not detected by the MMSE.

In this sample it was most common to have reduced sensitivity to cool and warm stimulus at the site of the pain. This is different to the other patient groups where a minority had reduced sensitivity to thermal stimuli.

8.6.3 Comparison with Published Literature

The patients had a significant side effect burden. In a study of 48 patients on methadone 39.6% reported dry mouth, 20.8% reported nausea and 18.7% reported constipation. The patents in this study were on a mean daily methadone dose of 99.5 mg which is a Morphine Equivalent Daily Dose of 746.3 mg ie slightly lower than the MEDD in this patient group. (Rhodin et al, 2006)

In a literature review published in 2013 Garland comments that altered working memory,

> "reduced cognitive flexibility and increased impulsivity in long-term opioid users" can be "compounded with those associated with chronic pain, may compromise the patient's ability to exert cognitive control needed to cope through non-pharmacological means, thereby inadvertently promoting dependence on opioids as a means of obtaining relief from pain."

(Garland et al, 2013) In this patient group it will not be possible to determine how much cognitive impairment is due to the opioids and how much is due to the substance misuse or other –co-existing psychiatric disorder. However cognitive impairment is to be expected in this patient group. The patients in this small sample have again shown the ACE-R to be superior to the MMSE in detecting cognitive impairment in patients who are prescribed opioids. (Karasz et al, 2004)

In a qualitative study which recruited 12 patients several themes emerged. Patients were already on methadone maintenance programmes but were not yet involved with pain management services. They described the severity of their pain and a subsequent loss of physical abilities which resonates with the patients in this study. The six patients in this study had a mean pain interference score of 5.1 reflecting the impact of the pain on their ability be active and carry out daily activities. Four (66.6%) of the six patients had a mean pain interference score greater than five which is almost the same as the findings of Rosenblum et al who found that 65% of patients with chronic pain who were in a methadone maintenance programme had a mean pain interference score of five or greater. The results in the paper were based on 143 patients. (Rosenblum et al, 2003)

Patients with a history of substance misuse have been shown to have reduced pain tolerance and report higher levels of pain in general and to thermal stimulus in particular. Patients with chronic pain who were identified as high risk for substance misuse had lower pain thresholds and higher pain ratings to mechanical and thermal stimuli which were not otherwise accounted for by variables which included age, sex or opioid use. (Edwards RR 2011) Patients with substance misuse have also been shown to have lower pain tolerance than healthy volunteers. (Compton et al, 2000) In this study only one of the six patients exhibited increased sensitivity at the site of pain but two of the patients had wind-up at the control site indicating sensitisation. In the qualitative study published by Alison Karasz in 2004 patients also described worsening of their pain which they had attributed to the methadone. The possibility that the quotes described opioid-induced hyperalgesia was not recognised or discussed by the authors. (Karasz et al, 2004)

8.7 Conclusions

Limited conclusions can be drawn from a sample of six patients. However this is a difficult patient group to recruit and there is little published literature on the burden of side effects and cognitive impairment which they may experience. The importance of using an assessment tool which assesses the relevant domains of cognitive function more fully have

been shown in this patient group and are consistent with the larger numbers recruited in the rest of the study. The Addenbrooke's Cognitive Examination appears to be superior to the Mini-Mental State Examination in detecting cognitive impairment. Two of the six patients had wind-up which may reflect general sensitisation due to opioids. A larger sample size would be needed to explore this finding and there may be benefit in conducting qualitative interviews with this patient group to explore their views on their pain and the effects of the methadone.

CHAPTER 9: FUTURE WORK

9.1 Summary of Main Findings

The results of this study are exciting and highly clinically relevant. In the context of increasing opioid use and increasing recognition of the potential complications the data presented here adds to our understanding of the adverse effects of opioids.

Patients who are prescribed opioids for the management of pain, either cancer or non-cancer related, and substance misuse experience opioid-related side effects. The results revealed the burden of the side effects. Our results were consistent with some published studies with persistent side effects over time and not just at initiation or titration of the opioid. Understanding that side effects are likely to be present over prolonged time periods helps clinicians take a more proactive approach. Ensuring opioid-related side effects are discussed and specifically sought during patient reviews should avoid patients feeling they must cope alone.

The prevalence of impaired cognitive function has highlighted a significant issue for patients and clinicians. The patients who participated in the qualitative interviews eloquently discussed the impact of the problem. They described the coping strategies they had developed to manage their memory loss and word-finding difficulties. Clinicians need to ask patients about their memory and ability to cope in everyday situations for example managing their medications. Patients may not volunteer information about memory loss. The perceived stigma of memory loss was clear from the qualitative interviews.

The qualitative interviews also revealed that patients are aware of altered pain sensation and sensitivity of the skin along with other features suggestive of opioid toxicity. This study is the first to recognise that opioid-induced hyperalgesia may be present and the

symptoms recognised by the patient. Taking a full and thorough history from patients who are on opioids could identify those with OIH.

The quantitative sensory testing revealed evidence of central sensitisation in patients who are on opioids. The central sensitisation was signalled by the presence of wind-up at a non-painful site. Thermal thresholds were altered which has been described in the literature previously. Detection thresholds were higher in patients with pain compared to healthy volunteers and pain thresholds were lower in the patients with pain.

We have made some progress to defining the clinical phenotype of OIH. Further analysis of the data collected will refine this further.

9.2 Bias and Limitations

There was no power calculation for this study. The decision was made at the start of the study after discussion with the statistician to recruit as many patients as possible but without a sample size calculation. This was felt to be an appropriate approach for an exploratory study. The number of patients recruited was 178 and many of them completed assessments at two or three time points which are a significant number especially in the palliative medicine patient population where patients are likely to become frailer during participation in a study.

The research team were all members of either specialist palliative care or chronic pain teams with both clinical and research roles. It may be that some of the patents under-reported symptoms and side-effects due to a loyalty to clinicians from the same team.

The study was conducted at several sites in Glasgow, Edinburgh and Forth Valley. The geography of the area and the number of patients recruited for the study required the involvement of several team members in conducting research assessments. This may have introduced observer bias particularly with the quantitative sensory testing. Other research tool used such as the Brief Pain Inventory and the Self-completed Leeds Assessment of Neuropathic Symptoms and Signs should have been more robust in terms of inter-observer bias. They rely on subjective responses from the patient but have still been shown to have validity.

It was difficult to recruit patients with chronic non-cancer pain who were not on opioids. Most patients were prescribed an opioid before being referred to the specialist clinic. It may have been easier to recruit this group of patients through primary care. Patients with a history of substance misuse were keen to participate in the study but were clear in their preference to complete the assessments whilst attending clinic. This was a practical arrangement as the assessments were only required at one time point for this patient group. Patients with chronic pain and a co-morbid history of substance misuse were the most challenging to recruit. They may have other health issues which preclude regular attendance at the clinic.

The majority of the patients were seen in their own home according to their preference. This probably contributed to a more comfortable environment for the patient. Many of the patients enjoyed participating in the study and reported they enjoyed the visits and valued the additional contact.

The time interval between study assessments was six to eight weeks. For patients with metastatic cancer there can be significant change in their well-being and medications during a period of weeks. Although a pragmatic choice the time interval will have affected our ability to detect changes in the study outcomes. The provision of longitudinal data has

affected the ability to detect smaller changes. It is also likely that during the time interval malignant disease progressed and the confounding factors changed.

Patients were asked about the presence of side-effects in the week prior to the assessment and this was recorded using the Likert scales. Many of the published studies have used side-effect severity as the outcome measure rather than frequency. This limits the ability to compare our results with the published literature. However the information does give a very meaningful description of the burden of side-effects. It is likely that patients will differ in their opinion of the relative importance of frequency and severity of side-effects and this opinion will have been affected by their own experience. It would have given even more depth and meaning if the history of both frequency and severity of opioid-related side-effects had been sought.

Overall patients were able to complete the assessments required by the study without difficulty. They did not find the study too burdensome and welcomed the chance to participate. Many patients commented on the first question of the Brief Pain Inventory which askes about "pains other than everyday aches and pains". Many patients found this question confusing. They lived with pain each day and for them even very severe pain had become part of everyday life.

Patients seemed to have the most difficulty when completing the Bond and Lader scales. Several of the patients needed support and clarification before being able to complete the scales. Patients appeared more familiar with the use of numerical rating scales which were used to record the pain severity at various times in the assessments for example during completion of the Brief Pain Inventory. If subjective measures of cognitive function were needed for future studies either numerical rating scales or verbal rating scales to assess specific aspects of cognitive function would be used. It may be that if the study had focussed on particular aspects of cognitive function – those that are most meaningful to patients in terms of everyday functioning –the results of the subjective measures of cognitive function would have had more meaning to the patients.

9.3 Future Work

There are still further explorations of the data that will clarify findings already discussed and help to refine the conclusions reached. There are many confounders for both the opioid-related side effects and the effect of opioids on cognitive function. The possible contribution of chemotherapy to the impaired cognitive function has not yet been explored. Another possible analysis of the data already collected could explore the impact of socioeconomic factors on the cognitive function of the patients for example. It would also be interesting to compare the affective component of the Brief Pain Inventory with the Hospital Anxiety and Depression Scale results and how they correlate with the Addenbrooke's Cognitive Examination and the Mini-Mental State Examination.

The prevalence of cognitive function revealed by the Addenbrooke's Cognitive Examination is fascinating. It is likely that the cognitive impairment is due to multiple factors including the opioids, other drugs such as anti-cholinergics, chemotherapy, pain and co-morbidities. However recognising the extent of the cognitive impairment is the first step. We have used an objective measure of cognitive function that does not require specialist training and was acceptable to patients. Future work would ideally recruit patients with cancer-related pain who are opioid-naïve and assess their cognitive function prior to introducing opioids. The project would have a flexible approach so that patients can be reviewed soon after changes in their opioids have been made. This future project would offer the responsiveness lacking in the current study. Due consideration would need to be given to the assessment of patients at times when they had needed a change in their opioids which implies an increase in pain (or breathlessness) as the pain itself may also impact on their cognitive function. Having identified the extent of cognitive function it would also be interesting to explore this further with patients through qualitative interviews. Some themes were highlighted during the interviews with patients who had previously been opioid toxic but exploring the cognitive impairment further with both patients and their main carers may help clinicians understand better how their patients cope.

Some of the patients in the study had a significant side-effect burden and were managing their symptoms, opioid-related side effects and pain covertly. This was highlighted by some of the participants in the qualitative part of the study. A project being considered is the introduction and evaluation of a pain management programme for patients with cancer-related pain in order to provide them with a better understanding of their pain, the drugs they have been prescribed, the management of the side effects and how to obtain further information and support.

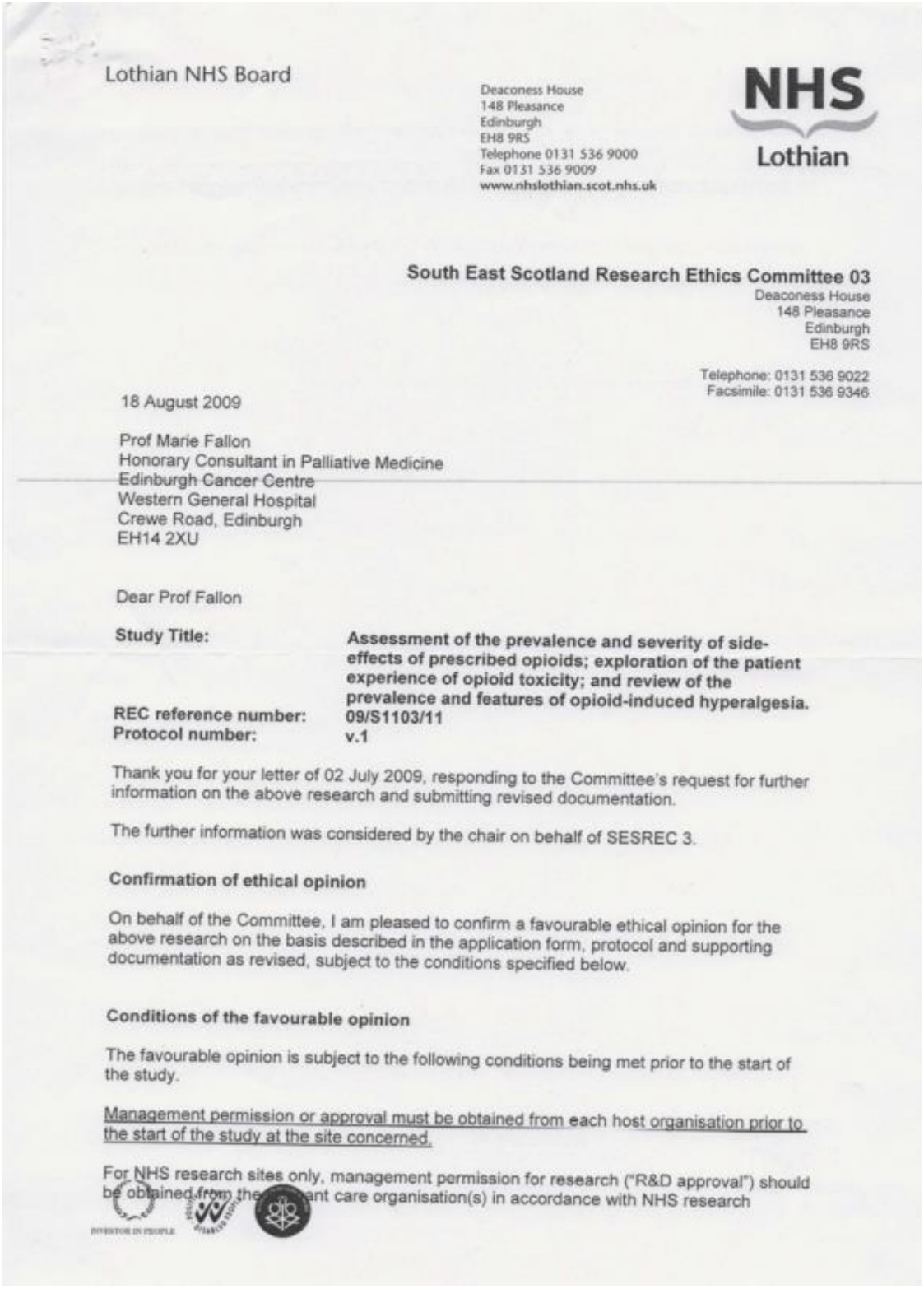
9.4 Impact of other Drugs on Cognitive Function

Patients with cancer and non-cancer pain are likely to be on several different medications. We are keen to explore the impact of these medications and will explore possible correlation between other medications and objective and subjective measures of cognitive function.

The drug burden index will be used to explore the possible role of other drugs. The index was developed to understand some of the risks to patients from the medications they are taking. The index takes into account the sedative effects and the anti-cholinergic side-effects of drugs. The index has been shown to correlate with physical frailty and poor function on a specific test of cognitive function – the digit symbol substitution test. We will explore how the drug burden index correlates with the Addenbrooke's Cognitive Examination and whether it helps separate the role of opioids and drugs from the other factors affecting cognitive function (Hilmer et al, 2007; Kouladjian et al, 2014).

APPENDICES

Appendix A



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18 August 2009

Prof Marie Fallon
Honorary Consultant in Palliative Medicine
Edinburgh Cancer Centre
Western General Hospital
Crewe Road, Edinburgh
EH14 2XU

Dear Prof Fallon

Study Title: **Assessment of the prevalence and severity of side-effects of prescribed opioids; exploration of the patient experience of opioid toxicity; and review of the prevalence and features of opioid-induced hyperalgesia.**

REC reference number: **09/S1103/11**
Protocol number: **v.1**

Thank you for your letter of 02 July 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered by the chair on behalf of SESREC 3.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the [illegible]ant care organisation(s) in accordance with NHS research

governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. *Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.*

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
C.V.	v.1	19 March 2009
C.V.	v.1	19 March 2009
C.V.	v.1	19 March 2009
GP/Consultant Information Sheets	v.1	02 March 2009
Questionnaire	v.1	08 March 2009
Questionnaire	v.1	08 February 2009
Letter from Sponsor		06 March 2009
Covering Letter		16 March 2009
Protocol	v.1	08 February 2009
Investigator CV		20 March 2009
REC application revised		17 March 2009
Correspondence		20 March 2009
Response to Request for Further Information		02 July 2009
Participant Information Sheet: PIS Srathcarron Hospice	2	02 June 2009
Participant Information Sheet: PIS Beatson	2	02 June 2009
Participant Information Sheet: PIS Univ of Edin	2	02 June 2009
Participant Consent Form: PCF Univ of Edin	2	02 June 2009
Participant Consent Form: PCF Strathcarron H	2	02 June 2009
Participant Consent Form: PCF Beatson	2	02 June 2009

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/S1103/11	**Please quote this number on all correspondence**

Yours sincerely

Dr Christine West
Chair SESREC 3

Email: joyce.clearie@nhslothian.scot.nhs.uk

Enclosures:

"After ethical review – guidance for researchers" *[SL-AR1 for CTIMPs, SL- AR2 for other studies]*

Copy to: *Elspeth Currie*
[R&D office for NHS care organisation at lead site]

Appendix B

Patient Information Sheet

Study Title: Opioid-induced side-effects and hyperalgesia

Explanation of the title

Opioids are strong painkillers which may be prescribed for different reasons including longstanding non-cancer pain and cancer pain. Opioids are a class of drug which include morphine and drugs similar to morphine. Methadone is another example of an opioid drug. It is sometimes prescribed for pain and sometimes to help people who have previously had a drug misuse problem.

All the strong painkillers can have side-effects. There is also a small risk that the painkiller can cause an increase in the type or severity of pain which is reported. This is known as opioid-induced hyperalgesia.

Some patients who have chronic pain but are not taking morphine or any of the drugs similar to morphine will also be invited to take part to help us understand the effects of the strong painkillers.

Introduction

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.
Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

This study is being done so that we can learn more about the side-effects and potential problems that can happen when people are prescribed strong painkillers such as morphine for their pain. Some of these problems affect only a very small number of people but it is still important that we learn as much as possible about the risks so that we can help those affected. For some people there is a chance that taking the strong painkiller will make their pain worse or change the type of pain they experience.

Why have I been invited to take part in the study?

You have been invited to take part in the study because you are on strong painkillers for your pain or other reasons. About 250 people who are taking morphine or drugs similar to morphine will take part in the study. Some people will also be asked to take part because they have experienced pain over a long period of time. The type of pain they experience may be different and it is likely there will be many different causes of the pain.

Do I have to take part?

It is up to you to decide. Before you decide to take part, please read this information sheet carefully. Ask us to explain anything that is not clear or if you would like more information about any part of the study. If you decide to take part, we will ask you to sign a consent form to show you have agreed to take part. You are **not** obliged to take part in this study; it is your choice whether you take part or not. If you do take part, you may change your mind and leave the study **at any time**. Leaving the study or not taking part will have **no** effect on your usual medical care and you will continue to be treated by your doctor(s) as before.

What will happen to me if I take part?

There are different parts to this study. You may choose to take part in one aspect of the study or you may be eligible for all three parts.

The first part of the study involves a single assessment of your pain and any side-effects you may be experiencing as a result of the painkillers you are taking. The assessment process is described below.

The second part of the study involves a more detailed interview for those people who have experienced more severe side-effects of the painkillers. The doctor who usually looks after you will let us know that you have had this experience. The interviews will be conducted on an individual basis and will be recorded. This should take no more than 60 minutes.

The third part of the study involves repeating the assessments (as described below) every 4 to 8 weeks. This will tell us if your pain is changing and whether this change could in any way be due to the painkillers you are taking. We can also review any side-effects you may be experiencing. If you are happy to be involved in this part of the study, we will continue to see you for a maximum of 18 months.

All patients who participate in the study will be asked if they would provide a blood sample or mouth swab. This will be stored and analyzed in the future to try and understand in more detail the link between genetics and side-effects of the drugs. You do not have to provide a blood sample even if you are helping with other parts of the study.

The assessment undertaken in the first and third parts of the study involves a series of questionnaires which should take no more than 60 minutes to complete. They will provide us with information on the type of pain you are experiencing and how the pain is affecting you generally for example your mood and intellectual functioning. We will also test the sensation in the skin at the site of your pain. This involves very briefly pressing fine plastic fibres and warm and cool rollers against your skin. Most of the tests are not uncomfortable, but if it produces a very mild discomfort, this shouldn't last for more than a few seconds.

The first part of the study is open to anyone who is taking strong painkillers such as morphine. The third part of the study is open to those who are taking more than 60mg of morphine each day (or an equivalent dose of another strong painkiller).

The detailed assessment of your pain is in addition to your normal treatment. The doctors looking after you will continue to manage your pain and to adjust your painkillers as

needed. This study does not affect the medication you can take for your pain.

What will I have to do?

If you decide to take part in the study we will ask that you complete the questionnaires and examination whilst you are attending the hospital for your usual clinic appointments or treatment.

What are the possible advantages and disadvantages of taking part?

We cannot promise the study will help you but the information we get from the study will help those who experience side-effects or a worsening or change in the type of pain as a result of taking strong painkillers. You will have a very detailed assessment of your pain on a regular basis and if there are problems we will contact your doctor who normally looks after your pain to make any necessary changes. The main disadvantage to you is the additional time that will be required to complete the study although we will make every effort to ensure this coincides with your routine visits to the hospital clinic and, if it is more convenient for you, a researcher can arrange to visit you at home.

What if there is a problem?

Any complaint about the way you have been dealt with during the study will be addressed. The detailed information on this is given in part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Information from the assessments you complete will be identified by your initials and a number, rather than by your name. All information will be securely stored. Occasionally regulatory authorities need to check that research is being done properly. In this case they may need to access your medical records.

If the information in part 1 has interested you please read the additional information in part 2 before making any decision.

Part 2

What if relevant new information becomes available?

If during the course of the study it becomes clear that you are someone who is experiencing side-effects of the strong painkillers or that the drugs are changing the pain you are experiencing, we will contact the doctors who usually look after your pain. They will arrange for any necessary changes to be made to your medications.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any point. Questionnaires that you have already completed will remain part of the study but you will not need to complete any further assessments. The researcher may suggest that you stop the study, for example if there is a change in your medical condition.

What happens if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (0141 211 3418/ 0131 777 3518). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Involvement of the General Practitioner / Hospital Consultant

We will inform your general practitioner and hospital consultant of your involvement in the study. They will receive a letter which explains the study and explains who they can contact if they have any questions.

What will happen to the results of the research study?

The results of the study will be published in journals and presented at conferences. There will be no way of identifying you in any of the publications. If you would like to be informed of the results of the study once it is completed we can explain them to you.

Who is organising and funding the study?

The Beatson Oncology Centre Fund (A registered charity) in Glasgow is funding the study. The study is being organised by a team of researchers who work in Glasgow and Edinburgh as part of the Edinburgh Translational Research in Pain Group.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, well-being and dignity.

Contact: Dr Ruth Isherwood (0141 211 3418)
Dr Suzanne Carty (0131 777 3518)

Thank you for taking the time to read this Patient Information Sheet.

Appendix C

Consent Form
4th November 2010 (Version 4)

Title of project: Opioid-induced side-effects and hyperalgesia.

Researchers:
Dr Ruth Isherwood, Senior Clinical Research Fellow
Dr Suzanne Carty, Advanced Pain Trainee
Dr Lesley Colvin, Consultant in Anaesthesia and Pain Medicine
Prof Marie Fallon, Consultant in Palliative Medicine
Dr Michaell Orgel, Consultant in Substance Misuse

Patient Identification Number for Trial: ……

Please initial each statement to confirm your consent.

1. I confirm that I have read the patient information leaflet and have had the opportunity to ask questions regarding this study. □

2. I understand that members of the research team will need access to my medical records as part of this study and I give permission for them to look at the records. I also understand that regulatory authorities may need access to my medical records where it is relevant to my participation in research. □

3. I agree to my GP and hospital consultant being informed that I am participating in this study and to them being contacted if it may improve the management of my pain. □

4. I understand that participation in the study is voluntary and that I am free to withdraw from the study at any time. If I withdraw from the study I understand that any assessments I have already completed as part of the study will remain in the study database. I understand that withdrawing from the study does not affect my medical care or legal rights. □

5. I consent to take part in the assessments described in the patient information leaflet.
   1.One series of assessments only as part of the study □
   2. Repeat series of assessments every 4 to 8 weeks as part of the study □

6. I understand that if I participate in the interview about my experiences of having side-effects of the strong painkillers (opioids), the interview will be recorded and transcribed ie a written copy will be made which will remain confidential. □

7. I understand that if I participate in the interview about my experiences of having side-effects of the strong painkillers (opioids), quotes from this interview may be used in publications or submitted thesis. I will not be identifiable from any quotes used. □

8. I agree to provide a blood sample or mouth swab which will be stored and analysed in the future to provide more information on the link between genetics and side-effects of the strong painkillers (opioids) □

…….	……	..……
Name of Patient	Date	Signature
…….	……	…….
Name of researcher taking consent	Date	Signature

Appendix D

Short Opioid Withdrawal Scale

Please put a tick in the appropriate box if you have suffered from any of the following conditions in the last 24 hours:

	None	Mild	Moderate	Severe
Feeling sick				
Stomach cramps				
Muscle spasms / twitching				
Feelings of coldness				
Heart pounding				
Muscular tension				
Aches and Pains				
Yawning				
Runny nose				
Insomnia / Problems sleeping				

Appendix E

ORAL Morphine Equivalency Factor	PO - By Mouth	SL - Sublingual	BC - Buccal	SC - Subcutaneous	IV - Intravenous IM - Intramuscular	CSCI - Cont. Subcut Inf.	TD - Transdermal	TM - Transmucosal	N - Nasal	ED - Epidural	IT - Intrathecal
C1 - Co-codamol 30/500	Divide by 6										
C1 - Co-codamol B1 8/500	Divide by 6										
C1 - Co-codamol B2 15/500	Divide by 6										
C2 - Codeine Phosphate	Divide by 8										
C3 - Co-proxamol	Divide by 8										
C4 - Dihydrocodeine	Divide by 10										
C5 - Tramadol	Divide by 13.3										
D1 - Alfentanil		MC		x30					MC		
D2 - Buprenorphine		x80					x2.1				
D3 - Diamorphine	x3			x3						MC	MC
D4 - Fentanyl		Divide by 20	Divide by 20				x3	Divide by 33	MC	MC	MC
D5 - Hydromorphone	x7.5			x25						MC	MC
D6 - Methadone	x7.5			MC						MC	MC
D7 - Morphine	x1			x2	x2	Divide by 2				MC	MC
D8 - Oxycodone	x2			x4							

KEY: 'MC' = drug can be given by this route but will require manual conversion for individual patients

Appendix F

The Presence and Severity of Symptoms

1. Please read and answer each question about symptoms that you may have noticed.
2. If you are experiencing the problem, please rate the severity of the problem.
3. Answer the questions while thinking about the last week.

	Very often	**Quite often**	**Occasionally**	**Very rarely**	**Never**
1. Have you **felt** sick or nauseated?	**4**	**3**	**2**	**1**	**0**
2. Have you **been** sick?	**4**	**3**	**2**	**1**	**0**
3. Does your mouth feel dry?	**4**	**3**	**2**	**1**	**0**
4. Have you noticed any jerking or twitching of your arms or legs (e.g. spilling drinks or whilst reading a book or whilst trying to go to sleep)?	**4**	**3**	**2**	**1**	**0**
5. Have you thought you have seen or heard anything that may not have been real or that seemed strange?	**4**	**3**	**2**	**1**	**0**

Appendix G

The Presence and Severity of Constipation

1. Please read the following questions about your bowel function.
2. Answer the questions while thinking about the last week.
3. Please tick the answer which best represents your bowel function in the last week.

1. How often have your bowels moved in the last week?	Twice less than usual □	As usual or once more or less than usual □	Twice more than usual □	
2. How easy has it been to move your bowels?	Difficult □	Normal □	Easy □	
3. What has been the consistency of your motions?	No motion □	Hard □	Normal □	Loose □

Appendix H

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":			
Most of the time □	A lot of the time □	Time to time, Occasionally □	Not at all □
I still enjoy the things I used to enjoy:			
Definitely as much □	Not quite so much □	Only a little □	Not at all □
I get a sort of frightened feeling like something awful is about to happen:			
Very definitely and quite badly □	Yes, but not too badly □	A little but it doesn't worry me □	Not at all □
I can laugh and see the funny side of things:			
As much as I always could □	Not quite so much now □	Definitely not so much now □	Not at all □
I feel as if I am slowed down:			
Nearly all of the time □	Very often □	Sometimes □	Not at all □
I get a sort of frightened feeling like "butterflies in the stomach"			
Not at all □	Occasionally □	Quite often □	Very often □
I have lost interest in my appearance:			
Definitely □	I don't take as much care as I should □	I may not take quite as much care □	I take just as much care as ever □
I feel restless as if I have to be on the move:			
Very much indeed □	Quite a lot □	Not very much □	Not at all □

Hospital Anxiety and Depression Scale (Continued)

Worrying thoughts go through my mind:			
A great deal of the time □	A lot of the time □	From time to time but not too often □	Only occasionally □
I feel cheerful:			
Not at all □	Not often □	Sometimes □	Most of the time □
I look forward with enjoyment to things:			
As much as I ever did □	Rather less than I used to □	Definitely less than I used to □	Hardly at all □
I get sudden feelings of panic:			
Very often indeed □	Quite often □	Not very often □	Not at all □
I can sit at ease and feel relaxed:			
Definitely □	Usually □	Not often □	Not at all □
I can enjoy a good book or radio or TV programme:			
Often □	Sometimes □	Not often □	Very seldom □

Appendix I

Brief Pain Inventory (Short Form)

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 everyday kinds of pain today?

1. Yes 2. No

2. 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

3. Please rate your pain by circling the one number 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

4. 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

5. 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

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

……
……

7.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

Brief Pain Inventory (continued)

8. 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

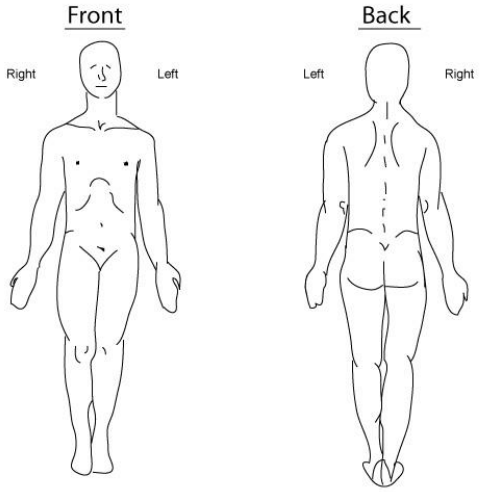
Appendix J

Quantitative Sensory Testing

Spontaneous pain score (0 - 10) ☐

Does the patient have an area with abnormal sensation? Yes ☐ No ☐

If yes, map area on paper. Mark index and control areas on chart below:



	Index area		**Control area**	
	Result	VAS	Result	VAS
Brush				
Rolltemp				
Cool				
Warm				
Von Frey filaments				
Detection threshold				
Pain threshold				
Pinprick (Record if not detected)				
Wind-up				

Key				
	No change	0	Decrease	3
	Increase	1	Significant decrease	4
	Significant increase	2	Not detected	5

Appendix K

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R

Final Revised Version A (2005)

Name :
Date of birth :
Hospital no. :

Addressograph

Date of testing: ...../...../.....
Tester's name: .....
Age at leaving full-time education: .....
Occupation: .....
Handedness: .....

ORIENTATION

➢ Ask: What is the	Day	Date	Month	Year	Season	[Score 0-5]
➢ Ask: Which	Building	Floor	Town	County	Country	[Score 0-5]

REGISTRATION

➢ Tell: 'I'm going to give you three words and i'd like you to repeat after me: lemon, key and ball'. After subject repeats, say 'Try to remember them because i'm going to ask you later'. Score only the first trial (repeat 3 times if necessary).

Register number of trials .....

[Score 0-3]

ATTENTION & CONCENTRATION

➢ Ask the subject: ' could you take 7 away from a 100? After the subject responds, ask him or her to take away another 7 to a total of 5 subtractions. If subject make a mistake, carry on and check the subsequent answer (i.e. 93, 84, 77, 70, 63 -score 4)

Stop after five subtractions (93, 86, 79, 72, 65). ....

➢ Ask: 'could you please spell **WORLD** for me? Then ask him/her to spell it backwards:

....

[Score 0-5]
(for the best performed task)

MEMORY - Recall

➢ Ask: 'Which 3 words did I ask you to repeat and remember?'

....

[Score 0-3]

MEMORY - Anterograde Memory

➢ Tell: ' I'm going to give you a name and address and I'd like you to repeat after me. We'll be doing that 3 times, so you have a chance to learn it. I'll be asking you later'

Score only the third trial

[Score 0-7]

	1st Trial	2nd Trial	3rd Trial
Harry Barnes	....	....	....
73 Orchard Close	....	....	....
Kingsbridge	.....	.....	.....
Devon	.....	.....	.....

MEMORY - Retrograde Memory

➢ Name of current Prime Minister .....
➢ Name of the woman who was Prime Minister .....
➢ Name of the USA president .....
➢ Name of the USA president who was assassinated in the 1960's .....

[Score 0 -4]

ATTENTION&ORIENTATION MEMORY

VERBAL FLUENCY - Letter 'P' and animals

➢ **Letters**

Say: 'I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. Are you ready? You've got a minute and the letter is P'

[Score 0 - 7] ☐

>17	7
14-17	6
11-13	5
8-10	4
6-7	3
4-5	2
2-3	1
<2	0
total	correct

➢ **Animals**

Say: 'Now can you name as many animals as possible, beginning with any letter?

[Score 0 - 7] ☐

>21	7
17-21	6
14-16	5
11-13	4
9-10	3
7-8	2
5-6	1
<5	0
total	correct

FLUENCY

LANGUAGE - Comprehension

➢ Show written instruction:

[Score 0-1] ☐ ☐

Close your eyes

➢ 3 stage command:
'Take the paper in your right hand. Fold the paper in half. Put the paper on the floor'

[Score 0-3] ☐ ☐

LANGUAGE - Writing

➢ Ask the subject to make up a sentence and write it in the space below:
Score 1 if sentence contains a subject and a verb (see guide for examples)

[Score 0-1] ☐ ☐

LANGUAGE

LANGUAGE - Repetition

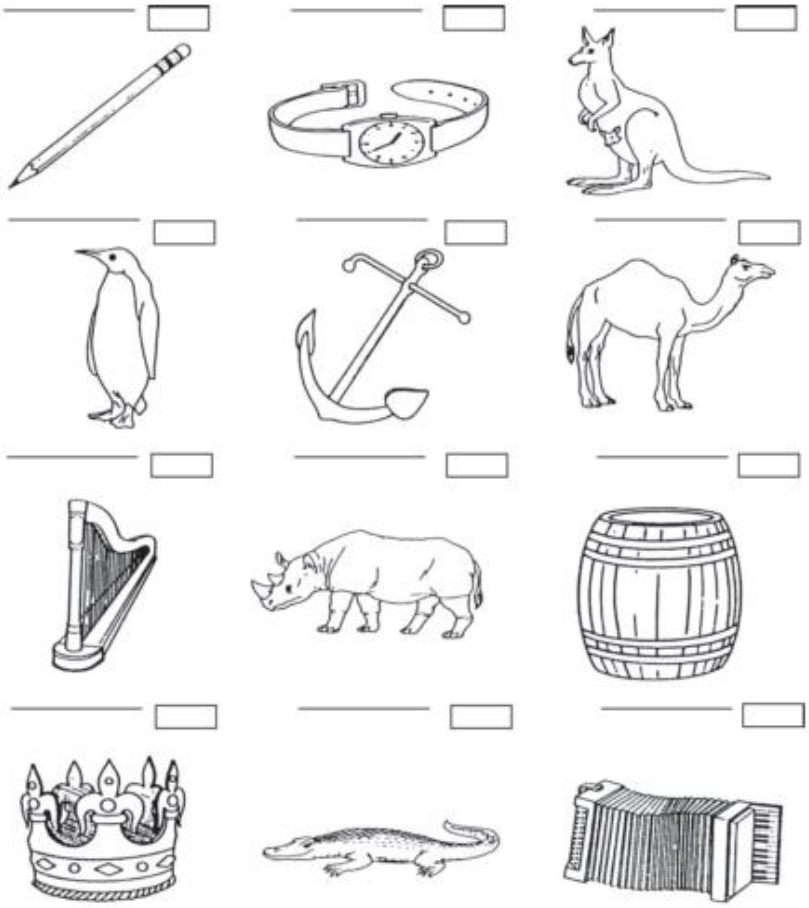
➢ Ask the subject to repeat:' **hippopotamus'; 'eccentricity; 'unintelligible'; 'statistician'**
Score 2 if all correct; 1 if 3 correct; 0 if 2 or less. [Score 0-2] ☐

➢ Ask the subject to repeat: **'Above, beyond and below'** [Score 0-1] ☐

➢ Ask the subject to repeat: **'No ifs, ands or buts'** [Score 0-1] ☐

LANGUAGE - Naming

➢ Ask the subject to name the following pictures: [Score 0-2] pencil + watch ☐☐



[Score 0-10] ☐

LANGUAGE - Comprehension

➢ Using the pictures above, ask the subject to: [Score 0-4] ☐

- Point to the one which is associated with the monarchy _____
- Point to the one which is a marsupial _____
- Point to the one which is found in the Antarctic _____
- Point to the one which has a nautical connection _____

LANGUAGE

LANGUAGE - Reading

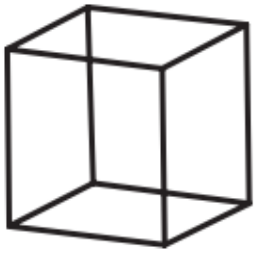
➢ Ask the subject to read the following words: [Score 1 only if all correct] [Score 0-1] ☐

sew
pint
soot
dough
height

VISUOSPATIAL ABILITIES

➢ Overlapping pentagons: Ask the subject to copy this diagram: [Score 0-1] ☐☐

➢ Wire cube : Ask the subject to copy this drawing (for scoring, see instructions guide) [Score 0-2] ☐



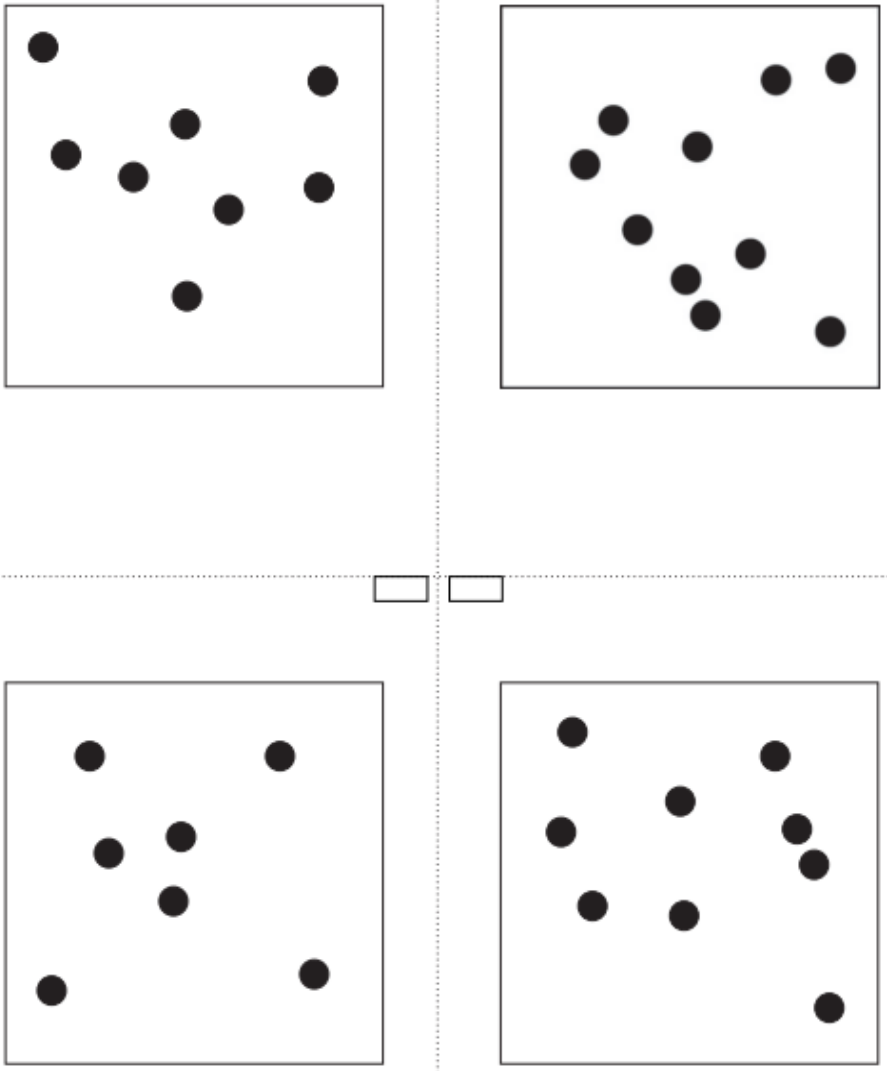
➢ Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (for scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct) [Score 0-5] ☐

PERCEPTUAL ABILITIES

VISUOSPATIAL

- Ask the subject to count the dots without pointing them

[Score 0-4]



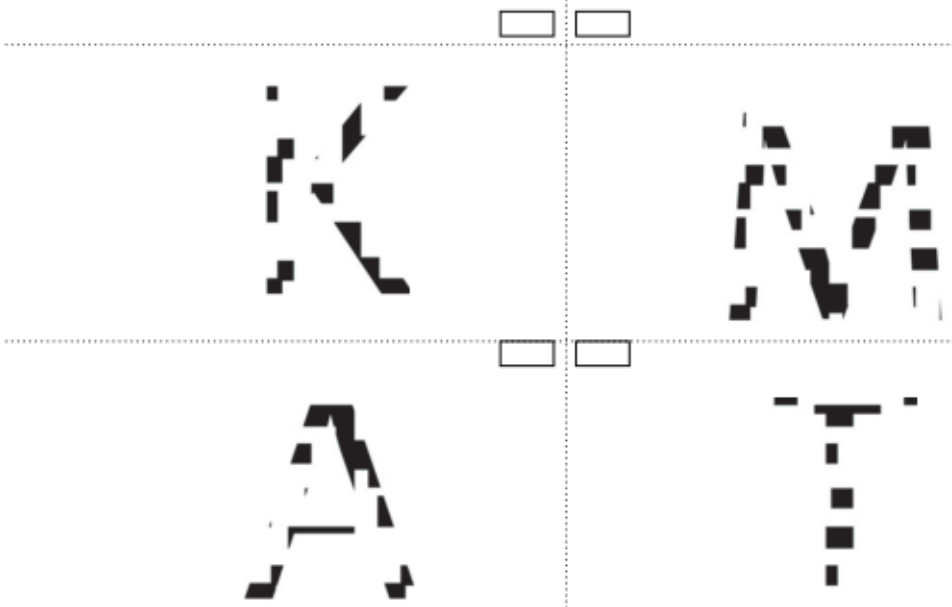
ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R

Final Revised Version A (2005)

PERCEPTUAL ABILITIES

➢ Ask the subject to identify the letters

[Score 0-4]



VISUOSPATIAL

RECALL

➢ Ask "Now tell me what you remember of that name and address we were repeating at the beginning"

[Score 0-7]

Harry	Barnes	....
73	Orchard	Close ....
	Kingsbridge	.....
	Devon	.....

RECOGNITION

➢ This test should be done if subject failed to recall one or more items. If all items were recalled, skip the test and score 5. If only part is recalled start by ticking items recalled in the shadowed column on the right hand side. Then test not recalled items by telling "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point which is added to the point gained by recalling.

[Score 0-5]

Jerry Barnes		Harry Barnes		Harry Bradford		recalled	
37		73		76		recalled	
Orchard Place		Oak Close		Orchard Close		recalled	
Oakhampton		Kingsbridge		Dartington		recalled	
Devon		Dorset		Somerset		recalled	

MEMORY

General Scores

SCORE

MMSE	/30
ACE-R	/100

Subscores

Attention and Orientation	/18
Memory	/26
Fluency	/14
Language	/26
Visuospatial	/16

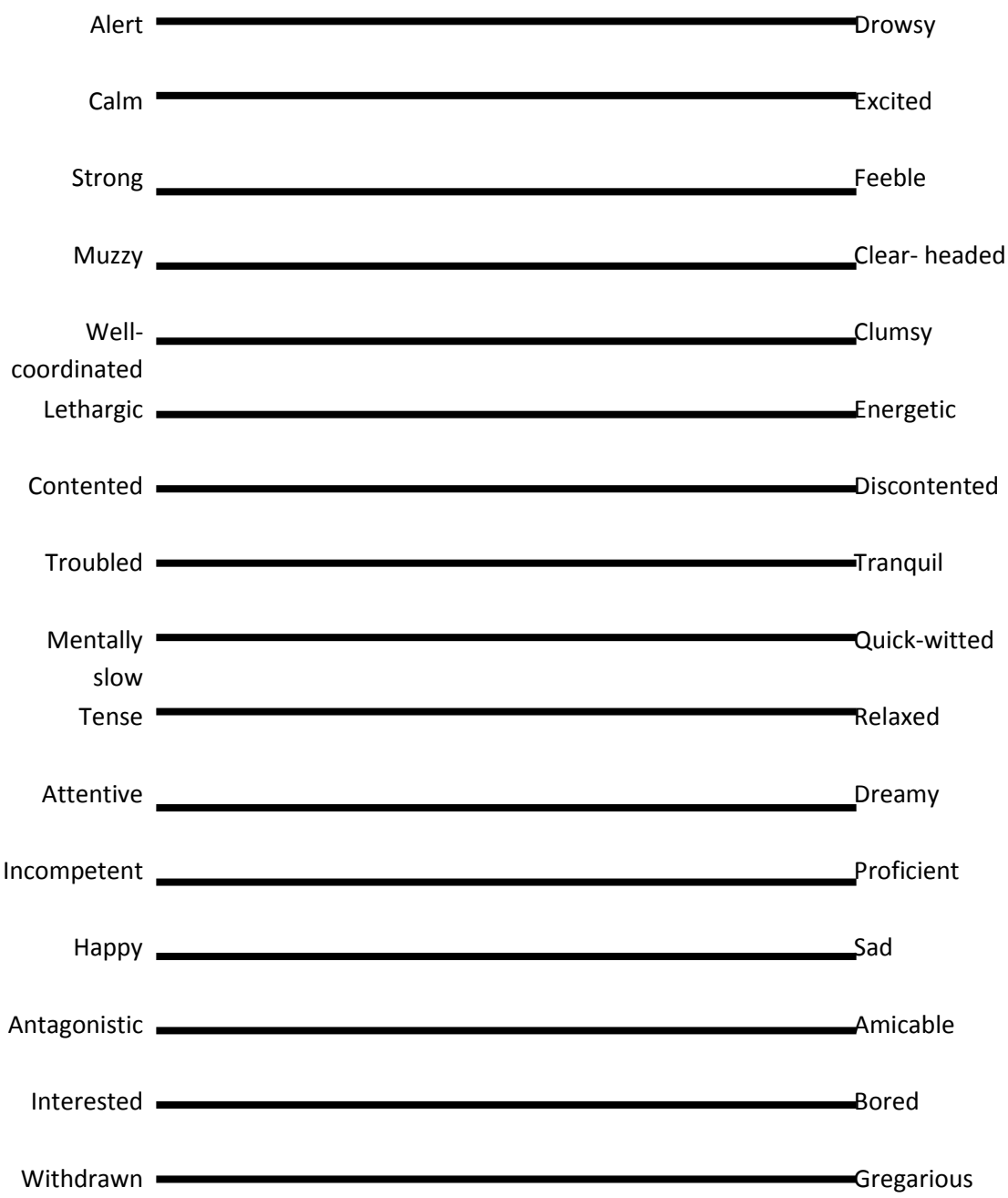
Normative values based on 63 controls aged 52-75 and 142 dementia patients aged 46-86

Cut-off <88 gives 94% senstivity and 89% specificity for dementia
Cut-off <82 gives 84% sensitivity and 100% specificity for dementia

Appendix L

The Use of Analogue Scales to Rate Subjective Feelings

1. Please rate the way you feel in terms of the dimensions given below.
2. Regard the line as representing the full range of each dimension.
3. Rate your feelings as they are at the moment.
4. Mark clearly and perpendicularly across each line.



Appendix M

THE NEUROPATHY TRUST
www.neurocentre.com carpe diem
Supporting people affected by peripheral neuropathy and neuropathic pain

THE S-LANSS PAIN SCORE Leeds Assessment of Neuropathic Symptoms and Signs (self-complete)

Dr Mike Bennett MD FRCP
Senior Clinical Lecturer in Palliative Medicine, St Gemma's Hospice and University of Leeds

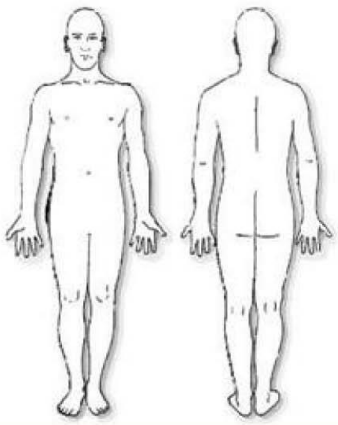
The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale has seven items consisting of five symptom items and two examination items. Usually, the examination items are done by a doctor but the modified version (the S-LANSS or self-report LANSS) allows people to do this themselves. The purpose of these scales is to assess whether the pain that is experienced is predominantly due to nerve damage or not. Both the LANSS and S-LANSS are scored out of 24; a score of 12 or more is strongly suggestive of neuropathic pain. Please note, however, that although the S-LANSS is a useful guide to the type of pain, it should only be viewed as an indicator, and not as a diagnosis. Always consult your doctor for a qualified opinion.

Read more … http://www.neurocentre.com/nep.php

NAME:_____ DATE:_____

- This questionnaire can tell us about the type of pain that you may be experiencing. This can help in deciding how best to treat it.

- Please draw on the diagram below where you feel your pain. If you have pain in more than one area, **only shade in the one main area where your worst pain is**.



• On the scale below, please indicate how bad your pain (that you have shown on the above diagram) has been in the last week where :'0' means no pain and '10' means pain as severe as it could be.

NONE 0 1 2 3 4 5 6 7 8 9 10 SEVERE PAIN

- Below are 7 questions about your pain (the one in the diagram).
- Think about how your pain that you showed in the diagram has felt **over the last week**. Put a tick against the descriptions that best match your pain. These descriptions may, or may not, match your pain no matter how severe it feels.
- Only circle responses that describe your pain.

1. In the area where you have pain, do you also have 'pins and needles', tingling or prickling sensations?

a) NO - I don't get these sensations (0)

b) YES - I get these sensations often (5)

2. Does the painful area change colour (perhaps looks mottled or more red) when the pain is particularly bad?

a) NO - The pain does not affect the colour of my skin (0)

b) YES - I have noticed that the pain does make my skin look different (5) from normal

3. Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this.

a) NO - The pain does not make my skin in that area abnormally sensitive (0) to touch

b) YES - My skin in that area is particularly sensitive to touch (3)

4. Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like 'electric shocks', jumping and bursting might describe this.

a) NO - My pain doesn't really feel like this (0)

b) YES - I get these sensations often (2)

5. In the area where you have pain, does your skin feel unusually hot like a burning pain?

a) NO - I don't have burning pain (0)

b) YES - I get burning pain often (1)

6. Gently rub the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?

a) The painful area feels no different from the non-painful area (0)

b) I feel discomfort, like pins and needles, tingling or burning in the (5) painful area that is different from the non-painful area

7. Gently press on the painful area with your finger tip then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?

a) The painful area does not feel different from the non-painful area (0)

b) I feel numbness or tenderness in the painful area that is different from (3) the non-painful area

Scoring: a score of 12 or more suggests pain of a predominantly neuropathic origin

SCORE_____

Appendix N

The SOMEDIC von Frey set consist of a specially designed case, containing 17 monofilaments, marked 3 to 19 and a built-in-thermo-hygrometer.

Manufacturing details for SENSELab monofilaments (hairs) are as follows:

Hair No	Diameter (mm)	Length (mm)	Nominal Force (g)	Pressure (g/mm2)
3	0.12	46	0.026	5
4	0.12	40	0.034	8
5	0.15	46	0.064	7
6	0.17	46	0.085	11
7	0.20	46	0.145	11
8	0.23	46	0.320	14
9	0.25	43	0.390	18
10	0.30	46	1.10	23
11	0.35	46	1.70	38
12	0.40	46	3.30	49
13	0.45	43	5.10	53
14	0.50	43	8.30	90
15	0.55	43	17.0	90
16	0.65	40	24	122
17	0.70	40	34	133
18	0.80	40	50	169
19	1.00	40	110	178

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