Improving Outcomes for People Living With Unrelieved Neuropathic Cancer Pain - Understanding the Epidemiology, Patient Experience and Optimal Clinical Trial Design: The INCEPT Mixed Methods Project

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A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

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Certificate of original authorship

I, Jessica Lee, declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Faculty of Health at the University of Technology Sydney. This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

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Table of contents

List of tables

List of figures

Abstract

Aim

The INCEPT Project aimed to describe the impact of unrelieved neuropathic cancer pain and to identify opportunities to improve the outcomes of people living with this condition.

Methods

Phase I involved a cohort study of pain in the last week of life for Australians with cancer receiving palliative care, and a qualitative systematic review describing the experience of people with neuropathic cancer pain. Phase II sought to explore ways to better develop a solution framework for the evaluation of pharmacological interventions for people living with neuropathic cancer pain. It included a systematic review of sodium channel blockers for cancer pain, and a pilot randomised controlled trial of lidocaine infusion with an embedded semi-structured interview sub-study of trial feasibility and acceptability. Mid-study and end-study meta-inferences integrated the results.

Findings

Distress from unrelieved neuropathic cancer pain is commonly experienced by palliative care patients living with cancer. While pain is present in some people of all cultural and socioeconomic backgrounds and all tumour types during the last week of life, its prevalence varies. Tumour characteristics, and spiritual and social context may explain some of this variation. Future research on the experience of neuropathic cancer pain must reflect the diversity of demographic and tumour factors of people with pain at the end of life.

Unrelieved neuropathic pain is a complex experience with significant impact on the lives of people living with cancer. The experience is influenced by many factors, including the nature of the pain, spiritual and social context, information provision, functional impact, the patient–provider relationship, and self-efficacy. While some

factors are intrinsic and some are modifiable, more research is required to leverage these opportunities to improve neuropathic cancer pain management.

A continuous subcutaneous infusion of lidocaine of up to 2 mg/kg/hr was tolerated and has potential to improve outcomes for people living with unrelieved neuropathic cancer pain. Its impact is influenced by multiple domains. A clinical trial of extended continuous subcutaneous infusion of lidocaine is feasible, acceptable to and valued by people living with advanced cancer, including those receiving palliative care.

Utilising a patient-centred care framework to design clinical trials for people living with unrelieved neuropathic cancer pain may enhance recruitment, retention, intervention effectiveness, and interpretation of trial results. Incorporating consumer perspectives from trial inception to implementation can align clinical trial design with the five dimensions of patient-centred care and their influencing domains.

Abbreviations

AE	Adverse Event
AKPS	Australia-modified Karnofsky Performance Status
CALD	Cultural and Linguistically Diverse
CIPN	Chemotherapy-Induced Peripheral Neuropathy
EAPC	European Association for Palliative Care
ECG	Electrocardiogram
EQ-5D-5L	EuroQual-5 Domains-Five Level
GRAMMS	Good Reporting of A Mixed Methods Study
IASP	International Association for the Study of Pain
INCEPT	**I**mproving Outcomes for People Living with Unrelieved **N**europathic **C**ancer Pain: Understanding the **E**pidemiology, **P**atient Experience and Optimal Clinical **T**rial Design
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale
LiCPain	Lidocaine for Neuropathic Cancer Pain trial
NAS	Numeric Analogue Scale
NMDA	N-methyl-D-aspartate
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PCOC	Palliative Outcomes Collaboration

RCT	Randomised Controlled Trial
REDCap	Research Electronic Data Capture
SAS	Symptom Assessment Scale
SD	Standard Deviation
SEIFA	Socio-Economic Indexes for Areas
TEAE	Treatment-Emergent Adverse Event
TIPN	Treatment-Induced Peripheral Neuropathy
UK	United Kingdom
US/USA	United States of America
VAS	Visual Analogue Pain Score

Glossary of terms

Adjuvant analgesics	Adjuvant analgesics include medications with a primary indication other than pain, which are used for analgesic effect.[1]
Mixed pain	Simultaneous neuropathic and nociceptive pain.[2]
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system.[3]
Nociceptive pain	Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.[3]
Pain	An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[4(p1977)]

Chapter 1 Introduction

1.1 Chapter preface

Neuropathic pain is common in people with cancer.[5] It significantly impacts function[6] and quality of life[7] and has a high societal cost.[8] Despite pain management being a cornerstone of good palliative care, some people with cancer continue to experience unrelieved pain.[9] Neuropathic cancer pain is more likely than other types of pain to respond poorly to treatment.[10]

There remains a paucity of high-quality evidence informing the management of people with unrelieved neuropathic cancer pain. This includes a lack of a sound understanding of the epidemiology and experience of people with neuropathic cancer pain. Many interventions have been poorly or never evaluated. Clinical guidance for the treatment of neuropathic cancer pain is often extrapolated from experience with similar populations, including people with non-cancer related neuropathic pain.

This chapter provides background to neuropathic cancer pain and its epidemiology, impact and management. A clinical vignette is presented to illustrate the scenario that this doctoral research was designed to address. The research aims and objectives are presented followed by an overview of the thesis.

1.2 Clinical vignette

The following vignette is based on the experience of several people cared for by the doctoral candidate. It illustrates the urgent need to improve management of neuropathic cancer pain, and provides insight into the clinical context that this doctoral Project aimed to inform.

Tuan is an 83-year-old retired shopkeeper. He lives with his wife and has three adult daughters, of whom he is exceedingly proud. He grew up in Vietnam, and migrated to Australia as a refugee. He and his wife almost always appear cheery and developed an instant rapport with the palliative care team (his wife explained that she always tries to find something in common with people she meets). They enjoy active recreation such as bushwalking together.

Tuan was diagnosed with metastatic pancreatic cancer and decided on best supportive care due to a fear of the potential adverse effects of chemotherapy. Tuan had a background of major depressive disorder, well controlled for over 20 years using escitalopram. He also had a history of diabetic peripheral neuropathy, osteoarthritis (worst in his right hip) and previous cervical spine surgery for chronic pain. He was initially well, and pleased that his lifestyle was unaffected by his health conditions.

In the weeks before his initial consultation, Tuan developed a dull gnawing epigastric pain that radiated to his back. He was uptitrated to 80 mg oxycodone modified release and 300 mg pregabalin per day prior to being admitted to hospital for a pain crisis and increasing ascites. For the first two weeks of his admission he was mostly bedbound due to pain while his medications were adjusted, including uptitration of his oxycodone and pregabalin, addition of methadone, dexamethasone and tapentadol, and insertion of an ascitic tap. He attempted to mobilise with the help of a physiotherapist, but experienced anxiety and panic attacks related to sudden onset of pain on movement. A coeliac plexus block was planned, and on the day after confirming this plan he experienced a significant reduction in pain and was able to walk to the bathroom independently, despite no changes in his analgesia. Tuan said later that he thought the hope that came from having a plan improved his mobility. Unfortunately, this improvement was short-lived and the celiac plexus block was ineffective.

Tuan was eventually discharged home after a six-week hospital admission. He was bedbound, so his youngest daughter took extended leave from work to assist with his care. However, after three days he returned to the clinic. His family were distressed because he had pain that didn't respond to his breakthrough medication, and experienced pain during personal care. They felt unable to meet his bed-based care needs, particularly after his daughter's chronic back pain flared up.

Tuan was eventually discharged to an aged care facility (a nursing home). His pain was better controlled at rest, but he was still unable to walk and continued to have three to four episodes of pain daily, which were controlled with breakthrough oxycodone. The oxycodone caused significant drowsiness, but Tuan decided that this was an acceptable trade-off for better pain control. He spoke frequently of the sense of loss he felt at being unable to care for himself and to engage in his former pastimes such as bushwalking, as well as the cancellation of a planned trip to Vietnam. Moving to the aged care facility caused significant financial distress to his wife and family, who also felt a sense of failure due to being unable to care for him adequately at home.

1.3 Background

1.3.1 Definition of key concepts

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[4(p1977)] Pain in people with cancer may result directly from the cancer, be caused by cancer treatment, and/or be unrelated to the cancer.[2]

Pain in people with cancer can be classified according to pathophysiology as neuropathic, nociceptive, or mixed neuropathic and nociceptive pain (mixed pain).[2] The IASP defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system,"[3] and nociceptive pain as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors."[3] Pain characteristics can be conceptualised as lying on a spectrum from neuropathic to nociceptive.[11] Neuropathic pain in people with cancer is commonly considered to include both purely neuropathic and mixed pain.[12, 13] Mixed pain has both neuropathic and nociceptive components.[13] Cancer-induced bone pain is commonly considered to have a neuropathic component,[14] and was considered to be mixed pain in this PhD research.

There is little consensus on the diagnosis of neuropathic cancer pain for research and clinical practice. For the purposes of the research described in this thesis, neuropathic cancer pain was defined as pure or mixed neuropathic pain due to cancer and/or cancer treatment.[13]

The IASP Special Interest Group on Neuropathic Pain recommends grading of neuropathic pain as possible, probable or definite neuropathic pain based on history, examination, and confirmatory tests, respectively.[15] This diagnostic approach may have limitations in people with cancer, particularly regarding the requirement for a "diagnostic test confirming a lesion or disease of the somatosensory nervous system explaining the pain."[15(p1601)] The European Association for Palliative Care (EAPC) and IASP have proposed a modified clinical diagnostic algorithm[12] which has good sensitivity and specificity.[16] It diagnoses a clinical hypothesis of neuropathic pain based on history and examination, and identifies probable or definite neuropathic pain based on the presence of a confirming history of relevant etiologic lesion from medical notes and/or diagnostic tests.[12] Some studies utilise screening tools to identify people with neuropathic pain.[17-19] Commonly used screening tools such as the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS)[20] assess a history of symptoms consistent with neuropathic pain, with or without a limited clinical examination.[19] The PhD research used the EAPC/IASP modified clinical diagnostic algorithm[12] to capture people who have probable or definite pure or mixed neuropathic pain due to cancer and/or cancer treatment, defining neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system."[3]

In this thesis, the term "participants" is used to refer to people with neuropathic pain who are involved in empirical studies. To refer to people living with neuropathic cancer pain, for brevity and clarity, the word "patient" is used in some sections.

1.3.2 Epidemiology of neuropathic pain in people with cancer

It is estimated that more than 14 million people globally develop cancer annually, with at least two thirds of those who have advanced cancer experiencing unrelieved cancer pain.[21, 22] A study of Australian patients receiving care from a specialist palliative care

service found 25% had severe or overwhelming pain and 83% had mild or worse pain.[23] It is estimated that approximately one third of people with cancer pain experience neuropathic pain.[5] A systematic review of prospective studies published up until 2015[5] found an overall pooled prevalence of neuropathic cancer pain of 31.2% in adults with cancer pain attending an oncology and palliative care setting, and a prevalence of 34.5% in those in an inpatient/hospice setting.[5]

Oh et al.[7] found that neuropathic pain in people experiencing moderate to severe cancer pain is more prevalent than in people who have mild pain (42.4% vs 27.1%). Other studies have found that neuropathic pain is independently associated with higher pain scores, and requires more days to achieve stable pain control than nociceptive pain.[24-26]

Other factors associated with poor cancer pain control in all cancers include "younger age, neuropathic pain, incident pain, psychological distress, addictive behaviour and initial pain intensity."[24(p2896)] In a cancer pain clinic study involving 317 patients, a positive association ($p<0.05$) was found between a higher pain score at the time of screening and the following factors:

- belonging to higher income and upper socioeconomic groups;
- a history of substance misuse;
- greater functional dependency;
- palliative status designation;
- primary head and neck, genitourinary or gastrointestinal cancer diagnosis;
- recent radiotherapy treatment;
- presence of neuropathic or mixed pain;
- presence of metastases; and
- use of more than one adjuvant analgesic medication.[26]

1.3.3 Impact of neuropathic pain in people with cancer

Neuropathic cancer pain has a powerful effect on patient wellbeing. In an international cohort of 1051 oncology and palliative care inpatients and outpatients with incurable cancer, it was found those with neuropathic pain had worse physical, cognitive and social function than those with nociceptive pain.[6] Similarly, Oh et al.[7] surveyed 2003 Korean cancer patients and found that those with neuropathic pain had worse quality of life and greater interference with daily living than those without.

The economic cost of suboptimally managed cancer pain is high.[8] Costs typically relate to increased and extended hospitalisation, greater care requirements at home,[27] adverse effects on mood and quality of life and function.[6]

Despite ongoing research, unrelieved cancer pain remains common. The European Pain in Cancer Survey found 58% of those receiving prescribed medicine reported inadequate pain relief.[9] The complexity of treating people with neuropathic cancer pain, with limited efficacy and inadequate prescribing of adjuvant analgesics, may contribute to high prevalence of unrelieved pain.[28] Adjuvant analgesics are medications with a primary indication other than pain, which are used for analgesic effect.[1]

1.3.4 The need for evidence in neuropathic cancer pain

In order to improve neuropathic cancer pain outcomes, it is necessary to improve our understanding of the nature and scope of the condition. The evidence base for neuropathic cancer pain, although growing, remains inadequate compared with the scope of this problem.[13] Current policy and practice are commonly adopted from those in use for non-cancer chronic neuropathic pain,[29] which may not be appropriate given the differences in these populations. It is known that people with cancer differ in several key ways from those with non-cancer chronic pain, and these differences affect their symptom management. The mechanism of neuropathic cancer pain is heterogeneous and may differ from that of non-cancer pain. Mechanisms include direct tumour compression or infiltration, paraneoplastic effect, and effect of cancer therapies.[30] Although long-term cancer survivorship is becoming increasingly common, the prognosis for many people continues to be measured in weeks, months or a few years.

This adds an additional dimension to the suffering caused.[31] The cancer and its treatment cause other morbidity that affect function and quality of life. Increasing understanding of neuropathic cancer pain and evaluation of interventions to improve neuropathic pain in people with cancer will improve the ability for clinicians and policymakers to manage this debilitating symptom.

1.3.5 Evidence gaps in neuropathic cancer pain

People with cancer often fear dying with pain.[32] Three population-level analyses of pain in the last week of life have demonstrated that unrelieved pain is present in the last week of life in up to 85% of people.[33-35] Only one of these studies[33] involved prospectively collected data, and included minimal evaluation of the associations of unrelieved pain in the last days of life.[36] Studies of pain across the cancer continuum have shown tumour type,[37] performance status,[38, 39] socioeconomic status[40] and cultural and linguistic diversity[41] may affect pain prevalence and severity. Little is known as to whether these factors are relevant to people who have pain in the last days of life.[37]

It is essential to understand the lived experience of people with neuropathic cancer pain in order to design, evaluate and implement effective interventions. To date, no systematic reviews have examined the experience of either neuropathic cancer pain or cancer pain. Systematic review of studies exploring the experience of chemotherapy-induced peripheral neuropathy[42] can inform the management of neuropathic cancer pain, but treatment-related pain makes up only 20% of all neuropathic cancer pain.[43] Therefore, it is important to understand the experience of people with neuropathic cancer pain directly due to the tumour.

It is likely that improving outcomes for people with unrelieved neuropathic cancer pain requires a multifaceted strategy.[44] This may include the development and implementation of improved approaches to pharmacological and non-pharmacological interventions, screening and assessment and health system design. First-line pharmacological therapies recommended by international guidelines for neuropathic cancer pain include opioids, antidepressants and anticonvulsants.[29, 45] Paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) are also often

recommended despite there being no high-quality evidence to support or refute their use.[29, 45] Corticosteroids, bisphosphonates and topical agents are recommended in specific situations such as acute nerve compression or inflammation, bone metastases, and to minimise systemic analgesic adverse effects.[29, 45]

There is little evidence guiding the management of patients for whom existing therapies are ineffective. Opioid manipulation (parenteral delivery, rotation, combination, methadone and buprenorphine), N-methyl-D-aspartate (NMDA) receptor antagonists (ketamine), cannabinoids and lidocaine[46-48] have been reported in the literature and guidelines as candidates. Lidocaine is an agent with little high-quality evidence available, yet is used internationally in clinical practice.[49] It is increasingly recognised that the pharmacological effect of medications cannot be evaluated in isolation, and that their effectiveness is affected by a complex web of internal (patient) and external (doctor, consultation, professional context and societal) factors,[50] best viewed through a patient-centred care framework.[51]

1.3.6 Need to improve outcomes for people with neuropathic cancer pain

To meet the needs of people with neuropathic cancer pain, new management approaches must be developed. In order to develop a solution framework for neuropathic cancer pain, it is necessary to characterise this population. This includes knowing who they are and the nature of their experience. It is important to pilot any interventions to ensure their acceptability among people with unrelieved neuropathic cancer pain, as well as confirm the feasibility of the trial design. Appropriate piloting is essential to ensure that the result is a true indication of effect.

1.3.7 Rationale for the INCEPT Project

The **I**mproving Outcomes for People Living with Unrelieved **N**europathic **C**ancer Pain: Understanding the **E**pidemiology, **P**atient Experience and Optimal Clinical **T**rial Design (INCEPT) Project was designed to address a crucial area of unmet need. Neuropathic cancer pain is common and debilitating. By identifying modifiable factors that can

improve the experience of neuropathic cancer pain and enhance the design and evaluation of pharmacological interventions, this Project aimed to improve outcomes for people with neuropathic cancer pain.

A pragmatic approach was required to conduct research into the characteristics of and outcomes for people living with unrelieved neuropathic cancer pain. Whenever possible, this Project generated evidence directly from people with neuropathic cancer pain. However, some secondary cancer pain data was used in order to expedite building the evidence base to improve outcomes for people with neuropathic cancer pain. Neuropathic cancer pain comprises around 30% of cancer pain.[5] Because neuropathic cancer pain is typically harder to treat and less responsive to existing therapies than nociceptive pain,[24-26] it was theorised to represent a greater proportion of unrelieved cancer pain.

1.4 Research overview

1.4.1 Research aim

To describe the impact of unrelieved neuropathic cancer pain and to identify opportunities to improve the outcomes of people living with this condition.

1.4.2 Research questions

- What is the prevalence of unrelieved pain at the end of life for people living with cancer?
- What are the experiences of people living with unrelieved neuropathic cancer pain?
- How can we most effectively evaluate pharmacological interventions for people living with unrelieved neuropathic cancer pain using lidocaine as an example?

1.4.3 Research objectives

The objectives of this Project were to:

- characterise the prevalence and associations of unrelieved cancer pain experienced by people seen by Australian palliative care services in the last week of life (*Study 1*);
- describe the experience of unrelieved pain in people living with neuropathic cancer pain (*Study 2*);
- understand how to most effectively evaluate pharmacological interventions for people living with unrelieved neuropathic cancer pain by;
    - evaluation and meta-analysis of current evidence for systemic sodium channel blockers for cancer pain *(Study 3)*
    - investigation of the feasibility of a clinical trial of a subcutaneous infusion of lidocaine for neuropathic cancer pain *(Study 4)*
    - understanding the patient and carer experience of having a subcutaneous infusion of lidocaine and participating in a pilot study of this intervention *(Study 5)*.

1.4.4 Project design

Based on the paradigm of pragmatism, a two-phase hybrid sequential mixed methods design was employed to answer the research questions.[52, 53] This doctoral Project builds on existing research in unrelieved neuropathic cancer pain and will inform future research. The INCEPT Project is composed of five studies and two meta-inferences undertaken in two phases, detailed in Table 1-1.

Table 1-1: A guide to the research phases and studies included in this thesis

Phase	Study	Title	Description	Chapter
Phase I: Impact of unrelieved cancer pain	Study 1	**Pain in the last week of life: a cross-section of Australians with cancer receiving palliative care**	An epidemiological study to determine the prevalence and patterns of moderate and severe cancer pain in Australian patients seen by a specialist palliative care service	Chapter 3
	Study 2	**Experience of neuropathic cancer pain: a systematic review**	A qualitative systematic review to identify the characteristics of people with neuropathic cancer pain	Chapter 4
	Mid-point meta-inference	***The impact of unrelieved neuropathic cancer pain***	*A mid-point meta-inference of Study 1 and Study 2*	Chapter 5
Phase II: Developing a solution framework	Study 3	**Lidocaine for cancer pain: a systematic review and meta-analysis**	A systematic review and meta-analysis of sodium channel blockers for cancer pain	Chapter 6
	Study 4	**Lidocaine for Neuropathic Cancer Pain (LiCPain): a pilot randomised controlled trial**	A double-blind randomised controlled pilot of subcutaneous infusion of lidocaine versus placebo for neuropathic cancer pain	Chapter 7
	Study 5	**Feasibility and acceptability of "LiCPain" pilot RCT: perceptions and experiences of people with neuropathic cancer pain receiving continuous subcutaneous infusion of lidocaine or placebo and their carers**	A qualitative patient and carer experience substudy of participation in the Lidocaine for Neuropathic Cancer Pain trial	Chapter 8
	End-point meta-inference	***Evaluating pharmacological interventions for people living with unrelieved neuropathic cancer pain***	*An end-point meta-inference of Study 3, Study 4 and Study 5*	Chapter 9

Phase I

Phase I commenced with a quantitative study (Study 1) of the epidemiology of cancer pain in Australia in the last week of life. To understand the potential explanations contributing to the results of Study 1, a systematic review of the experience of people with neuropathic cancer pain was conducted. Because neuropathic cancer pain is thought to contribute disproportionately to unrelieved cancer pain,[7, 28] the review (Study 2) focused on neuropathic cancer pain.

A mid-point meta-inference integrated the Study 1 and 2 data to understand the impact of unrelieved neuropathic cancer pain at both a population and individual level. This analysis was conducted to improve understanding of who is affected by neuropathic cancer pain, their experiences, and how to improve their outcomes.

Phase II

Phase II was designed to further explain the reasons why people with cancer continue to experience neuropathic pain. It involved exploring ways to improve the evaluation of pharmacological interventions for people living with unrelieved neuropathic cancer pain. Candidate interventions were reviewed, and the most promising selected for further investigation as an exemplar agent. To further inform this work, a systematic review and meta-analysis were undertaken to delineate the existing evidence for sodium channel blockers to relieve cancer pain (Study 3). This meta-analysis informed the design of a feasibility randomised controlled trial (RCT) of lidocaine for neuropathic cancer pain (Study 4) with an embedded qualitative sub-study (LiCPain) (Study 5). Study 5 sought to use the experiences of participants and carers on the LiCPain trial to explain the quantitative data from Study 4.

After the Phase II data were analysed separately, an end-point meta-inference was undertaken to determine how to better evaluate pharmacological interventions for people living with unrelieved neuropathic cancer pain in order to improve their outcomes.

1.4.5 Research outcomes

The specific intended outcomes of the research were:

- a description of the prevalence and associations of cancer pain in the last week of life in people seen by Australian palliative care services *(Study 1)*;
- synthesised systematic review findings describing the experience of unrelieved pain in people living with neuropathic cancer pain *(Study 2)*;
- integrated key findings describing the prevalence and experience of neuropathic cancer pain (*mid-point meta-inference*);
- an evaluation and meta-analysis of current evidence for systemic sodium channel blockers for cancer pain *(Study 3)*;
- determination of the feasibility of a subcutaneous infusion of lidocaine for neuropathic cancer pain *(Study 4)*;
- determination of the feasibility of a phase III trial of a subcutaneous infusion of lidocaine for neuropathic cancer pain *(Study 4)*;
- key themes about the patient and carer experience of subcutaneous infusion of lidocaine and participation in a pilot study of this intervention *(Study 5)*; and
- key findings describing how we can better evaluate pharmacological interventions for people living with unrelieved neuropathic cancer pain (*End-point meta-inference*).

1.5 Chapter summary

Some people experience unrelieved cancer pain despite first-line measures. A significant proportion of these people are likely to have neuropathic cancer pain. Current approaches to the treatment of neuropathic cancer pain are inadequate. More

evidence is required to understand the nature of the population of people with unrelieved neuropathic cancer pain and how to evaluate and implement new therapies for them.

Chapter 2 describes the methodology and underpinning conceptual framework and research paradigm for the PhD Project.

Chapter 2 Research design and methods

2.1 Chapter preface

Chapter 1 provided an introduction to the PhD research. It highlighted the need to improve outcomes for people who experience unrelieved neuropathic cancer pain and the scant evidence base about ways to improve management. It presented an overview of the research's aims, research questions, objectives, outcomes and component studies.

This chapter provides an overview of the research design, including the rationale for choosing a sequential mixed methods design, the underpinning conceptual frameworks, and the intended outcomes. The specific methodology for each study is presented in the relevant chapter. An outline of the positioning of the researcher and the reflexivity used in the qualitative aspects of the INCEPT Project is given. Finally, this chapter outlines considerations relating to ethical conduct and data management, with individual study considerations presented in the relevant chapter.

2.2 Conceptual frameworks

2.2.1 Importance of conceptual frameworks in research

Use of a conceptual framework guides research design, analysis and interpretation by illustrating the theoretical relationships among various factors affecting neuropathic cancer pain. Moreover, it aids conceptualisation of the complex phenomenon of pain.

2.2.2 Patient-centred care

This program of doctoral research employed the conceptual lens of patient-centred care because of the emphasis that approach places on the patients and their experiences. Patient-centred care seeks to involve patients in important healthcare decisions, respects their personal beliefs and values, and incorporates their needs and preferences in the delivery of care.[54] Patient-centred care acknowledges that the factors influencing the

patient experience extend beyond the disease or intervention to include other dimensions.[50]

There is no single accepted definition of patient-centred care, but an umbrella review by Grover et al.[51] identified common elements: patient individuality, engagement, empowerment, family/caregiver involvement and support, provider training and characteristics, respect, implementation through behaviour change techniques, biopsychosocial care, shared decision-making, communication, and a systems-level approach.

Mead and Bower[50] conceptualised patient-centred care as encompassing five dimensions: a biopsychosocial perspective, 'patient-as-person', sharing power and responsibility, a therapeutic alliance, and 'doctor-as-person'. These dimensions are influenced by many and varied elements, categorised as shapers, professional context influences, doctor factors, patient factors and consultation-level influences (Figure 2-1).[50]

Patient-centred care contrasts with the traditional biomedical model, in which illness is reduced to a physical entity to be treated with a standardised appropriate therapy and will always respond uniformly. It is widely recognised as a foundation of high-quality healthcare,[55] but implementation varies.[54] In the current research, the patient-centred care framework was used to understand and organise the factors found to influence patient-centred care. The term "patient-centred care" is used interchangeably with "person-centred care,"[51] and is used in this thesis to reflect the terminology in Mead and Bower's conceptual framework,[50] while acknowledging that each patient must be viewed as a whole person who exists outside the patient–doctor interaction.

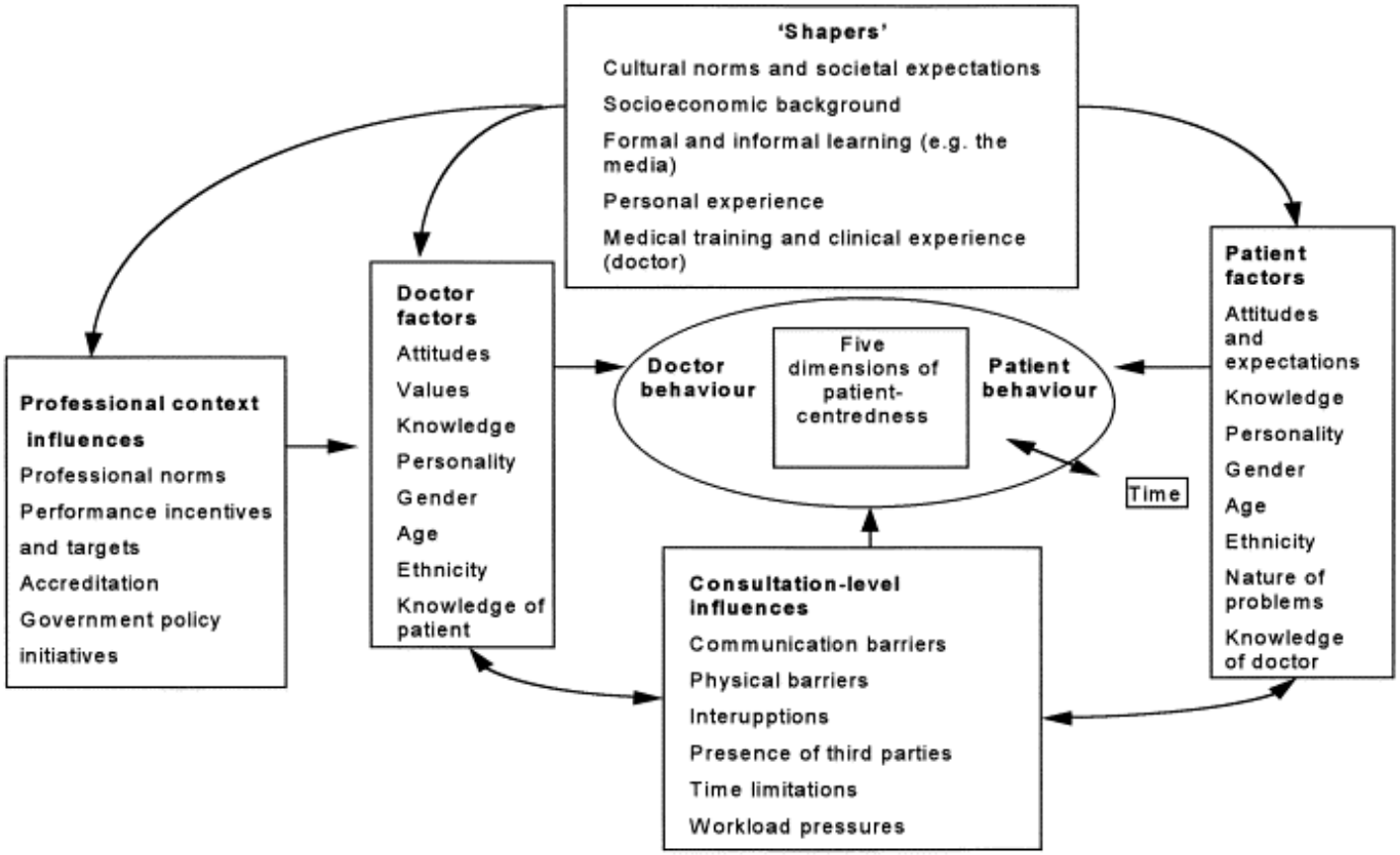

Figure 2-1: Domains influencing patient-centred care. Reproduced with permission from Mead 2000.[50(p1104)]

2.3 Mixed methods research design

Mixed methods research is an approach used to answer questions that require breadth and depth of understanding and corroboration.[56] It combines elements of both qualitative and quantitative research to gain a more comprehensive understanding of a research topic than using either method alone.[53, 57] An essential component of mixed methods research is the integration of data during the analysis to derive additional information and to respond to research questions that cannot be answered by quantitative or qualitative data alone.[53]

The research presented in this thesis was designed as a hybrid sequential mixed methods Project[53] in which there was mixing within a program of research across a closely related set of studies.[56] Hybrid designs are complex designs that draw on but do not follow one of the core designs of mixed methods research.[53]

2.3.1 Rationale for choosing mixed methods

Neuropathic cancer pain is a complex condition, and must be understood in the context of the patient as a whole person. This includes consideration of the biomedical characteristics of the pain and its response to management strategies, the two-way interaction between the pain and the person's psychosocial and spiritual characteristics, treating clinician characteristics, consultation factors and the societal setting.[58, 59] The expansive scope of factors that affect neuropathic cancer pain is increasingly recognised. Both quantitative (e.g., epidemiological) data and qualitative (e.g., people's experience) data are required to gain deeper insight and broader understanding of the needs of people with neuropathic cancer pain and design solutions to improve outcomes.

2.3.2 Need for a mixed methods design

Opportunities to improve outcomes for people living with unrelieved neuropathic cancer pain span many domains. Quantitative data collected in Study 1 were designed to delineate the prevalence and associations of unrelieved cancer pain at a population level. Qualitative data were required to understand the range of individual patient

experience and provide insight into the findings in Study 1, focusing on those with neuropathic cancer pain. In Studies 3, 4 and 5, the aim was to build on the quantitative results of Study 1 by selecting a novel treatment for neuropathic cancer pain and investigating the feasibility of an efficacy RCT of this treatment. The intention was to generate quantitative and qualitative data that explained why translational research has been unable to find ways to eradicate neuropathic cancer pain to date.

2.3.3 Mixed methods design for this Project

The hybrid sequential mixed methods design followed the six-step process outlined by Creswell.[60] It was determined that the research problem – unrelieved neuropathic cancer pain – required a mixed methods approach. Qualitative and quantitative data were collected using a hybrid sequential design,[53] with the intention that the qualitative data from Study 2 and embedded qualitative and quantitative data from Studies 3–5 would explain the quantitative results from Study 1, at the end of Phases I and II, through the use of joint display tables. Subsequently, meta-inferences were established from the data. This occurred within a patient-centred care conceptual framework. This process is illustrated in Figure 2-2 (adapted from Creswell[60(p209)]).

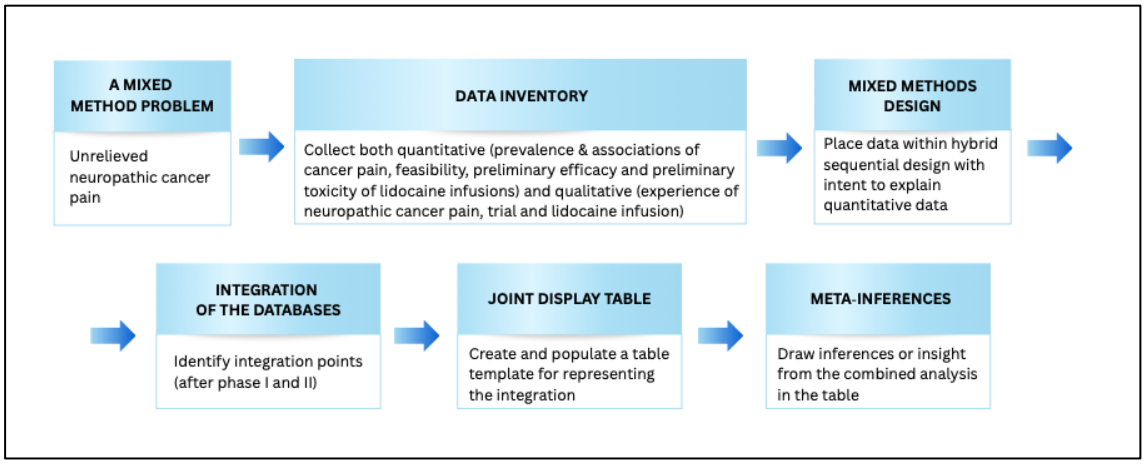

Figure 2-2: Mixed methodology process applied to the INCEPT Project.

Selection of a hybrid sequential mixed methods study design enabled the gathering of both quantitative and qualitative data and was based on the intent of the Project and

reflection on the procedures used to connect the datasets.[53] In this doctoral work, the intent was to explain the quantitative results from Study 1 using qualitative and quantitative data, and thereby understand how the experience of people with neuropathic cancer pain contributes to the prevalence of unrelieved cancer pain at the end of life, and how outcomes for this group can be improved through a better understanding of prevalence, experiences and evaluation of pharmacological interventions. The procedures involved were to use qualitative (Study 2 and 5) and quantitative data (Study 3 and 4) to explain quantitative results (Study 1). Qualitative data (Study 5) was collected after the intervention trial (Study 4) to explain the quantitative results from Study 4. Mid-point and end-point meta-inferences synthesised this data to answer the research questions.

The INCEPT Project was completed sequentially, albeit with some overlap in the start and finish times of the component studies to ensure the clinical trial (Study 4 and 5) could be completed within the time constraints of the doctoral program. The trial design drew on an existing body of literature describing the use of lidocaine infusions,[49] in addition to preliminary findings from the other studies undertaken within this research. Quantitative and qualitative data were given equal priority, with both providing unique perspectives on the problem of unrelieved neuropathic cancer pain.

The research phases, questions, methods and data types are displayed in Table 2-1.

2.3.4 Data integration across the INCEPT Project

The INCEPT Project's use of a mixed methods design was configured to improve understanding of the complexity of living with and managing unrelieved neuropathic cancer pain. Data integration is an essential component of mixed methodology and can occur in multiple dimensions of any study, including research design, purpose, data collection, analysis, interpretation and reporting.[61, 62] While each of the five studies stand alone, data integration and interpretation was required across the broader Project to gain a deeper understanding of the phenomena of unrelieved neuropathic cancer pain.

Table 2-1: Overview of research phases, questions, methods and data types

Study phase	Research question	Research objectives	Outcomes	Methods	Data type
Phase I: Impact of unrelieved cancer pain	What is the prevalence of unrelieved neuropathic pain at the end of life for people living with cancer?	To characterise the prevalence and associations of unrelieved cancer pain experienced by people seen by Australian palliative care services in the last week of life. *(Study 1)*.	A description of the prevalence and associations of cancer pain in the last week of life in people seen by Australian palliative care services *(Study 1)*.	Study 1: Cohort study	Quant
	What are the experiences of people living with unrelieved neuropathic cancer pain?	To describe the experience of unrelieved pain in people living with neuropathic cancer pain *(Study 2)*.	Synthesised findings describing the experience of unrelieved pain in people living with neuropathic cancer pain through systematic review and meta-aggregation *(Study 2)*.	Study 2: Systematic review and meta-aggregation	Qual
			Integrated key findings describing the prevalence and experience of neuropathic pain in people with cancer (Mid-point meta inference).	Mid-point meta-inference using joint display tables	Quant and Qual
Phase II: Developing a solution framework	How can we better evaluate pharmacological interventions for people	To understand how to better evaluate a novel pharmacological treatment for people living with unrelieved neuropathic cancer pain by:	An evaluation and meta-analysis of current evidence for systemic sodium channel blockers for cancer pain *(Study 3)*.	Study 3: Systematic review and meta-analysis	Quant

	living with unrelieved neuropathic cancer pain using lidocaine as an example?	1. Evaluation and meta-analysis of current evidence for systemic sodium channel blockers for cancer pain *(Study 3)*. 2. Investigation of the feasibility of a clinical trial of a subcutaneous infusion of lidocaine for neuropathic cancer pain *(Study 4)*. 3. Understanding the patient and carer experience of having a subcutaneous infusion of lidocaine and participating in a pilot study of this intervention *(Study 5)*.	Determination of the feasibility of a subcutaneous infusion of lidocaine for neuropathic cancer pain *(Study 4)*.	Study 4: Pilot randomised controlled trial	Quant
			Determination of the feasibility of a phase III trial evaluating a subcutaneous infusion of lidocaine for neuropathic cancer pain *(Study 4)*.	Study 4: Pilot randomised controlled trial	Quant
			Key themes describing the patient and carer experience of having a subcutaneous infusion of lidocaine and participating in a pilot study of this intervention *(Study 5)*.	Study 5: Embedded semi-structured interview study	Qual
			Integrated key findings describing how we can better evaluate pharmacological interventions for people living with unrelieved neuropathic cancer pain (End-point meta-inference).	End-point meta-inference using joint display tables	Quant and Qual

Integration during design

Data integration commenced at the design level with the use of a hybrid sequential design, in which each phase was planned to build upon the previous phase, followed by the merging of the data (Figure 2-3). Qualitative data from Study 4 was embedded within the clinical RCT in Phase 3. The understanding derived from Study 1 sought to inform Study 2, in order to increase our understanding of the experiences of people suffering cancer pain (particularly neuropathic pain) in the last week of life. Merging the Study 1 and 2 data during the mid-point meta-inference was designed to describe the prevalence and experience of unrelieved neuropathic pain for people living with cancer in order to inform a new intervention to be tested during Phase II.

The meta-inference to be undertaken at the end of Phase II was designed to show how to develop and evaluate pharmacological interventions for people living with unrelieved neuropathic cancer pain. Neither a purely quantitative or qualitative study could answer the complex questions posed in this doctoral research.

Integration during analysis, interpretation and reporting of this study was planned to use joint display tables to develop the mid-point and end-point meta-inferences. Joint display tables are a way to "integrate the data by bringing the data together through a visual means to draw out new insights beyond the information gained from the separate quantitative and qualitative results."[53, 62] Therefore meta-inferences in the form of theoretical statements were generated in this study using joint display tables to integrate and analyse the data collected.[61]

Meta-inferences are "overall conclusions drawn from the merging of qualitative and quantitative inferences that reveal unique insights which could not be achieved by either approach alone."[61(p2)]

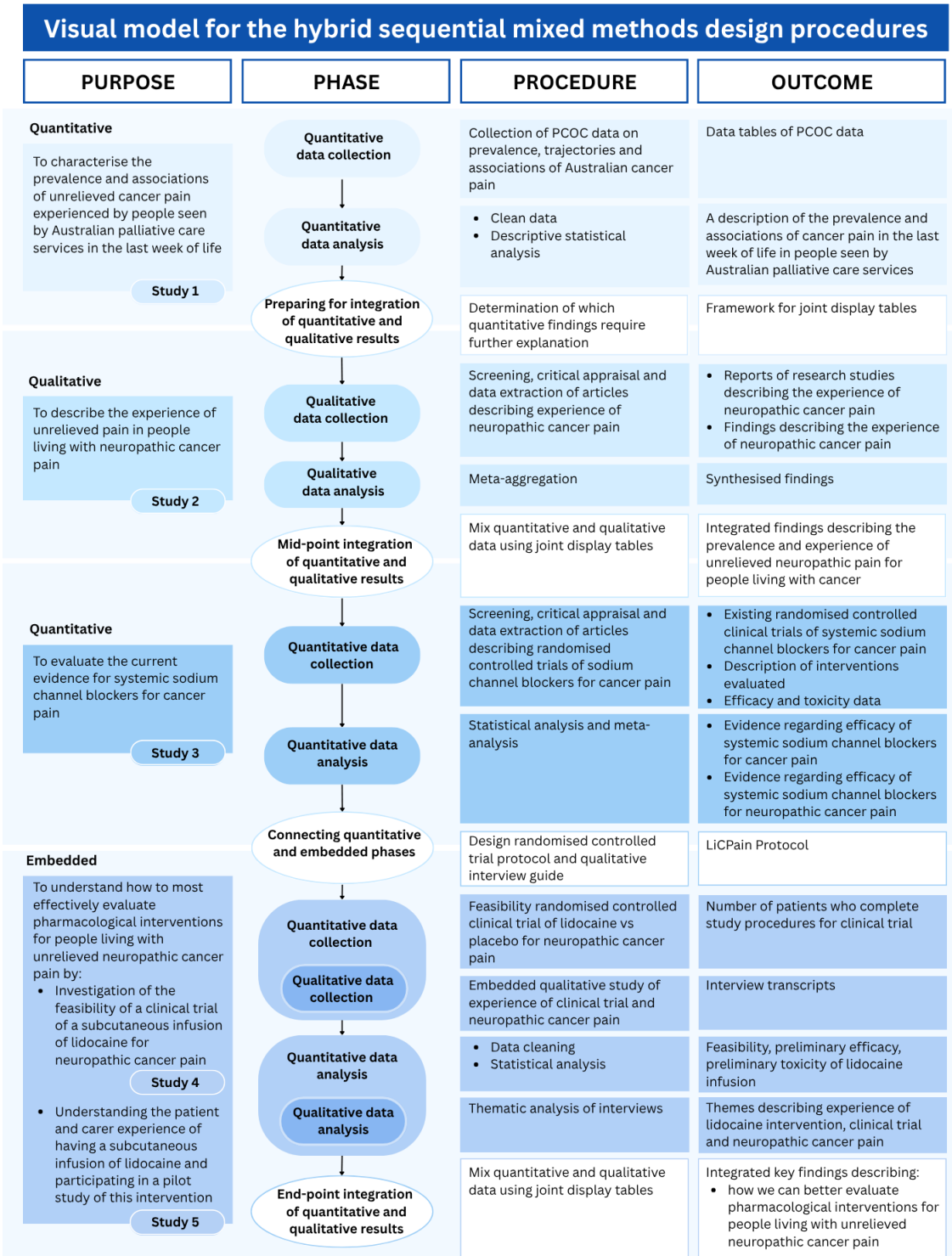

Figure 2-3:Visual model for the mixed methods sequential design procedures. Adapted from Fetters 2020.[63(p65)]

Integration during analysis

Meta-inferences can be categorised as global or specific, and include relational, predictive, causal and elaborative subtypes.[61] This research generated global meta-inferences in order to benefit future patients with neuropathic cancer pain. Global meta-inferences involve the extrapolation of findings to draw meta-inferences for diverse populations with similar characteristics.[61] Both elaborative and comparative meta-inferences were planned to be drawn from the data. Comparative meta-inferences offer a simple integrated account of the inferences drawn from each strand.[61] Elaborative meta-inferences are generated to offer new and latent insights into the studied phenomenon by going beyond the apparent meaning of the qualitative and quantitative inferences. These include careful consideration of the available contextual information while remaining rooted in the data.[61] For a phenomenon such as neuropathic cancer pain, for which there is substantial previous research to draw on from this and adjacent fields, an elaborative approach was selected so as to build on all current evidence.

2.3.5 Design considerations

The mixed method design took account of various restrictions and factors such as sampling, implementing qualitative data collection, contradictory findings, researcher skills, and the length of time to conduct studies.[64, 65]

Sampling

In sequential design, where the intent is to explain quantitative data obtained in the first phase, the traditional approach for each subsequent phase is to select the same or a subset of participants from the initial phase.[64] In order to efficiently utilise existing data sources and minimise research waste and replication, participants were selected from the same population of people with cancer pain, but each study utilised a different sample of individuals. This was necessary due to the poor prognosis and frailty of people with advanced cancer and unrelieved pain, who are unlikely to be able to participate in multiple studies over a period of years.

Study 1 included Australians with cancer pain in the final week of life who died under the care of a specialist palliative care service. This analysis of a large national dataset of people experiencing pain in the last week of life, which may disproportionately include those with neuropathic cancer pain,[7, 28] enabled reliable population level data collection. Studies 2 and 3 included research involved international research participants with neuropathic cancer pain and cancer pain, respectively, and allowed evaluation of the global applicability of the project findings. The systematic review design of Study 3 allowed evaluation of only the studies of people with neuropathic cancer pain.. Study 4 examined Australians with neuropathic cancer pain across five specialist palliative care services while Study 5 included a subset of Study 4 participants and their carers. Studies 4 and 5 allowed for detailed evaluation of a group of people with neuropathic cancer pain, their response to participating in a clinical trial of lidocaine infusion and their experience.

This sampling strategy enabled both broad and deep exploration to improve understanding of people with unrelieved neuropathic cancer pain. These perspectives were brought together through the meta-inferences.

Implementing qualitative data collection

The sequencing of qualitative data collection, particularly the embedded semi-structured interviews (Study 5), was influenced by its intended use. In Study 5, data was collected after the trial (Study 4) to help explain the quantitative results. However, qualitative data was also collected in Study 2, before Study 4, in order to influence study design and enhance recruitment. Because Study 4 was a pilot study, the synthesised findings from the end-point meta-inference can inform future definitive trials.

Contradictory findings

Contradictory findings may emerge in mixed methods research.[64, 65] Discrepancies between studies were identified in the joint display tables utilised as part of the meta-inference, acknowledged and discussed.

Researcher skills

On commencing this program of work, the doctoral candidate (JL) had little experience in conducting mixed methods, quantitative or qualitative research. Developing sufficient skills in these methodologies concurrently was a substantial challenge,[66] but was achieved through formal and informal training as well as via collaboration with supervisors and other researchers. Formal supervision time with supervisors provided guidance and assistance to develop research skills. The candidate's supervisors had diverse research expertise encompassing quantitative (RCT), qualitative (interview) and mixed methods. The candidate's expertise increased throughout the course of the studies involved in the Project as well as a range of related research.

Length of time to conduct studies

The length of time required to conduct the five studies was a significant consideration. In particular, planning for recruitment of participants into the clinical trial commenced early in the Project. Preliminary analyses of Studies 1, 2 and 3 informed the design of the LiCPain trial, and analysis continued after the LiCPain trial began. Where appropriate, literature searches were updated to include more recent data.

2.4 Research paradigm

2.4.1 Positioning of the researcher

The candidate (JL) is a female, Australian-born ethnic Chinese palliative care physician and researcher. She provides direct clinical care to patients with neuropathic cancer pain in a metropolitan tertiary palliative care service in a consultative, inpatient and community setting. She is the research lead at this service, which includes leading the clinical trials unit that supported the operationalisation of the LiCPain clinical trial. She is involved in multiple research projects, in addition to her doctoral studies, which span a variety of palliative care areas. She contributes to service development and decision-making.

The candidate's non-research roles intersect with her PhD work in various ways. For example, some participants are also her patients. In addition, she and her service collect

data that contributes to the palliative outcomes collaborative dataset used in Study 1, meaning she has an intimate understanding of how the data represents patients at this site.

2.4.2 Philosophical assumptions

This research was grounded in a pragmatist worldview. Fundamental to pragmatism is the practical usefulness and consequence of ideas.[67] Research may be driven by the problem to be solved or question to be answered.[68] Pragmatism emphasises probability and identifies that errors can be rectified through further investigation.[67] This worldview matches the needs of health research to solve problems with the best evidence available.

2.4.3 Theoretical lens

The theoretical lens used in this Project was "complexity," as developed by Borgermans et al. in "A theoretical lens for revealing the complexity of chronic care." This lens has four major components: case (patient) complexity, care complexity, quality assessment complexity, and health systems complexity."[69] The complexity lens complemented the patient-centred care conceptual framework in guiding the research.

2.5 Ethical considerations

Ethical conduct was an essential component of the whole Project as well as the individual studies, and particularly those involving participants and their data. This Project was guided by the National Statement of Ethical Conduct in Human Research[70] as well as the core ethical principles of beneficence, non-maleficence, autonomy and justice.[71] Studies were approved by the University of Technology Sydney and the Sydney Local Health District Human Research Ethics Committee as required. Ethical considerations and details of the approvals for individual studies are presented at the end of the relevant chapter.

2.5.1 Core ethical principles

This doctoral Project was analysed with reference to the principles of beneficence, non-maleficence, autonomy and justice.[71] Beneficence involves acting in the patient's best

interest while non-maleficence emphasises avoiding harm.[71] This is important to consider in the design of research, as well as when recruiting a potential participant. Autonomy upholds patients' rights to make informed decisions about their own care or participation in research.[71] This required particular consideration in the INCEPT Project, because participants in Studies 4 and 5 were potentially in an unequal relationship with the researchers, due to being patients in the healthcare service running the trial. Justice focuses on fair and equitable distribution of healthcare resources,[71] which may include the time and energy of participants, research funding, clinician and investigator time. These core ethical principles were considered when deciding to undertake the research, as well as during its design and its individual studies.

The INCEPT Project was deemed important to undertake due to the high prevalence and severe impact of unrelieved neuropathic pain in people with cancer. The potential to improve outcomes for people with neuropathic cancer pain (beneficence) had to be balanced against the resources required to undertake the Project (justice) and burden to participants (non-maleficence). Designing and conducting a mixed methods research project comprising a clinical trial, systematic review and cohort study required significant financial and in-kind commitment from the investigators, mentors and organisations involved, as well as time and risk from the participants. These factors were judged to be outweighed by the potential benefit of the research for people with neuropathic cancer pain.

2.5.2 Data management

Data management encompasses the "generation, collection, access, use, analysis, disclosure, storage, retention, disposal, sharing and re-use of data and information"[70(p35)] related to the research. It is essential that data collected about research participants is managed in an ethical and secure manner. A research data management plan was developed for each study involving human participants (Studies 1, 4 and 5), with key components outlined in the methodology of the relevant chapter.

The identifiability of data refers to the ability to link data to an individual. It occurs on a continuum from non-identifiable to identifiable, and changed during the Project.[70] The

identifiability of data affected decisions on storage, with aggregate non-identifiable data stored on a secure institutional server. Data that could be reidentified was stored digitally on the secure platform REDCap, hosted through UTS, or as hard copy in a locked filing cabinet in a locked room at the relevant site according to the research governance approved data management plan. Identifiable data was stored only at the relevant site in hard copy or digital form. Data was transferred through secure approved channels. Great care was taken to ensure that data to be published was non-identifiable, especially in relation to the qualitative Study 5.

2.6 Reporting framework

The Project followed the Good Reporting of A Mixed Methods Study (GRAMMS) guideline, which includes the following prompts.[72] Locations of these items within the thesis are shown in parentheses.

- Describe the justification for using a mixed methods approach to the research question (Sections 2.3.1, 2.3.2).
- Describe the design in terms of the purpose, priority and sequence of methods (Section 2.3).
- Describe each method in terms of sampling, data collection and analysis (Sections 2.3.5, 2.3.6).
- Describe where integration has occurred, how it has occurred and who has participated in it (Section 2.3.4).
- Describe any limitation of one method associated with the presence of the other method (Section 2.3.6).
- Describe any insights gained from mixing or integrating methods (Chapter 5 and 9).

The GRAMMS reporting guideline was used to ensure comprehensive reporting of this mixed methods study. Reporting frameworks were used for each component study and are outlined in the relevant chapters.

2.7 Chapter summary

This mixed methods research, comprising five studies and mid-point and end-point meta-inference was grounded in a pragmatist worldview and informed by the patient-centred care framework.

Chapter 3 reports a study characterising the prevalence and associations of cancer pain in the last week of life (Study 1).

Chapter 3 Pain in the last week of life: a cross-section of Australians with cancer receiving palliative care

3.1 Chapter preface

Chapter 1 introduced the evidence gaps related to unrelieved neuropathic cancer pain and presented an overview of the doctoral Project's aims and research questions. Chapter 2 presented an overview of the methodology and study design of this two-phase hybrid sequential mixed methods program of research. The current chapter describes the epidemiology of unrelieved cancer pain experienced by Australians with cancer seen by a specialist palliative care service in the last week of life. This study was important in providing a better understanding of the population of people with unrelieved neuropathic cancer pain that interventions must target in order to improve outcomes.

The remainder of this chapter consists of an article prepared for submission to a peer-reviewed journal, formatted to conform to the rest of the thesis.

3.2 Pain in the last week of life: a cross-section of Australians with cancer receiving palliative care

3.2.1 Introduction

Pain affects up to 85% of people with cancer in their last week of life.[34] Despite their short prognosis, optimal pain control remains a priority. Freedom from pain is fundamental to good quality of life and is considered very important at the end of life by patients and families.[73]

Despite the high prevalence of the phenomenon, few studies have provided an in-depth evaluation of pain in the last week of life or explored any associated factors at a

population level.[36] Few data link age[74] and location of care[34] with the prevalence of pain in the last days of life. However, it is known that tumour type,[37] performance status,[38, 39] socioeconomic status[40] and cultural and linguistic diversity[41] affect pain prevalence and severity. Little is known about whether these factors affect pain-related distress in the last days of life.[37]

Quantitative data on the factors that correlate with moderate or severe distress from pain may health assist services to treat this population more effectively. Prospective, contemporaneously collected data allows the most accurate representation, with the aim of avoiding recall that may under- or over-estimate pain intensity.[37] Such data will help inform clinical responses and policies that more efficiently and equitably reduce pain for people with advanced cancer. Data from a diverse range of people is crucial to maximise generalisability.

The study reported herein was designed to produce a better understanding of the nature of moderate or severe pain distress in the last week of life for people with cancer seen by specialist palliative care service providers, and its relationship with other symptoms and demographic characteristics.

3.2.2 Material and methods

Design

This consecutive observational cohort study utilised secondary data from the Palliative Outcomes Collaboration (PCOC), a national quality improvement program.[75]

Objective

To estimate the proportion of adult Australians with cancer receiving specialist palliative care who experienced moderate or severe distress from pain in the last seven days of life.

Setting and subjects

The PCOC seeks to systematically improve palliative care patient outcomes. The PCOC dataset consists of sociodemographic and clinical assessment information at key time points, such as change in location of care or a clinical change requiring patient/family reassessment or modification of the care plan (phase change).[76] Data was collected from all consecutively admitted patients from most specialist palliative care providers (>200 metropolitan, regional and rural palliative care services) across Australia.[77] The database captures 25.1% of expected deaths nationally[78] and approximately 36% of all Australian cancer deaths.[79]

Inclusion criteria

All adults with a principal diagnosis of cancer who had at least one measurement of pain distress on the PCOC Symptom Assessment Scale (SAS) in the seven days before death, and who died between 1st January 2018 and 31st December 2022, were eligible for inclusion.

Proxy reporting was permissible if the person was unable to self-report. Rates of proxy reporting were not collected.

Data sources and variables

Demographic information. The preferred language and country of birth was collected as a measure of cultural and linguistically diverse (CALD) status. The Socio-Economic Indexes for Areas (SEIFA)[80] quintiles were based on the ABS Index of Relative Socio-Economic Disadvantage of the usual residence of the person based on their postcode. SEIFA quintiles were used, with quintile one being the most disadvantaged and quintile five being the most advantaged.[81]

Pain and other symptoms. Pain distress was collected on the PCOC SAS, a validated[82] patient-reported assessment tool by the clinician reviewing the patient at one or more key time points.[76] The PCOC SAS measures current distress from symptoms (rather than intensity of symptoms) on a scale from zero to 10, and collects eight commonly experienced symptoms for people with cancer. For this study, the analysis was limited

to four items: pain, difficulty sleeping, fatigue, and bowel problems with a clinically plausible rationale for correlating with pain.[82]

Performance status. Performance status was measured using the Australia-modified Karnofsky Performance Status (AKPS) scale.[76]

Potential confounding variables such as tumour type, performance status, socioeconomic status, cultural and linguistic diversity and co-existing symptoms were identified based on previous literature suggesting they impact pain prevalence and severity.[37, 38, 40, 41, 83]

Statistical methods

Data was anchored at death. Mild distress was defined as a score of ≥1 to ≤3 on the PCOC SAS, moderate as ≥4 but <8, and severe as ≥8.[76] Highest, lowest and last distress scores were evaluated for each person. Correlation between symptoms, and between distress from pain, performance status and time before death, were evaluated in relation to each assessment to account for individuals having multiple pain scores in the last week of life.

Data was analysed descriptively, with relationships between covariates explored using Pearson correlation coefficients. Chi-squared tests were used to compare between the category scores. All measurements for all patients were included in the analysis; no data was imputed. Analyses were conducted using SAS/STAT v9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics

This study was approved by the Human Research Ethics Committee of the University of Technology Sydney (HREC-ETH16-0809) and University of Wollongong (HE06/045).

Reporting guidelines

This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[84]

Table 3-1: Demographics of the PCOC cohort, 2018–22

		N	(%)
	Participants	71,750	(100)
Sex	Male	39,294	(54.8)
(n=71,707)	Female	32,413	(45.2)
Age at death (in years)	Mean	73.0	SD 12.9
	Median	74.0	IQR 18
Diagnosis	Lung	14,750	(20.6)
	Colorectal	7,683	(10.7)
	Other gastrointestinal malignancy	6,882	(9.6)
	Pancreas	5,952	(8.3)
	Haematological	5,114	(7.1)
	Breast	4,795	(6.7)
	Prostate	4,521	(6.3)
	Head and neck	3,636	(5.1)
	Gynecological	3,345	(4.7)
	Other urological malignancy	3,120	(4.4)
	Skin	2,376	(3.3)
	Unknown primary	2,201	(3.1)
	Central nervous system	1,554	(2.2)
	Bone and soft tissue	940	(1.3)
	Other primary malignancy	3,638	(5.1)
	Malignant – not further defined	1,243	(1.7)
Preferred language	English	64,116	(90.8)
(n=70,615)	Other than English	6,499	(9.2)
SEIFA	1 (most disadvantaged)	10,012	(14.0)
(n=71,431)	2	11,155	(15.6)
	3	15,005	(21.0)
	4	15,401	(21.6)
	5 (most advantaged)	19,858	(27.8)

3.2.3 Results

Demographic details

This study included 71,750 participants; just over half (55%) were male and the median (interquartile range – IQR) age was 74 (18) years (see Table 3-1).

Pain assessments

Within this cohort, 132,898 pain assessments were conducted over the participants' last 7 days of life. The mean (standard deviation – SD) number of pain assessments in the last week of life was 1.9 (1.0) per person. Seventy-six per cent of these pain assessments were conducted in an inpatient setting, and 24% in the community.

Distress from pain and associated symptoms in the last week of life

In the last week of life, 31% of participants in this study had at least one moderate or severe pain distress score, while 13% had moderate or severe pain distress at every timepoint reported. Just under 1 in 5 (19%) had a score reflecting moderate or severe pain distress as their last recorded pain score. Table 3-2 shows the highest, lowest and last pain, fatigue, difficulty sleeping, and bowel scores.

The median reported pain distress for all participants was 1.0 (IQR 0.0 to 3.0). There was a weak positive correlation between pain distress and fatigue ($r=0.31$), difficulty sleeping ($r=0.28$), and bowel problems ($r=0.25$; all $p<0.001$) (Figure 3-1).

Distress from pain and patient characteristics

The estimated proportion of participants who died in the inpatient setting which recorded at least one instance of moderate or severe pain distress during their last 7 days of life was 31.1% and was 28.8% in the community setting. The 95% confidence interval for the difference between the corresponding population proportions is (0.016, 1). Since this interval does not contain 0, we conclude that there is sufficient evidence to suggest that the population proportion of patients who die in the inpatient setting who experience moderate or severe pain in their last 7 days of life is higher than those in the community.

Moderate or severe pain was more common in participants with primary bone and soft tissue or prostate cancers, and less likely in those with central nervous system tumours (Figure 3-2).

Participants from non-English-speaking backgrounds, and those born outside of Australia, reported less distress from moderate or severe pain. There was no clear relationship between socioeconomic category (SEIFA) and incidence of moderate or severe distress from pain (Figure 3-3).

Table 3-2: Pain, sleeping, fatigue and bowel scores in the last 7 days of life

Symptom	SAS score	Highest score		Lowest score		Last score[a]	
		N	(%)	N	(%)	N	(%)
Pain	Severe	3778	(5.3)	968	(1.4)	1691	(2.4)
	Moderate	18150	(25.3)	8033	(11.2)	11673	(16.3)
	Mild	27576	(38.4)	23552	(32.8)	25254	(35.2)
	Absent	22246	(31.0)	39197	(54.6)	33132	(46.2)
	Total	71750	(100.0)	71750	(100.0)	71750	(100.0)
Difficulty Sleeping	Severe	1291	(1.8)	292	(0.4)	487	(0.7)
	Moderate	5838	(8.3)	1759	(2.5)	2617	(3.7)
	Mild	11290	(16.0)	5291	(7.5)	6326	(9.0)
	Absent	52386	(74.0)	63463	(89.6)	60993	(86.6)
	Total	70805	(100.0)	70805	(100.0)	70423	(100.0)
Fatigue	Severe	4137	(5.8)	1301	(1.8)	1997	(2.8)
	Moderate	16328	(22.9)	6760	(9.5)	8254	(11.6)
	Mild	18216	(25.6)	11613	(16.3)	11692	(16.5)
	Absent	32566	(45.7)	51573	(72.4)	48989	(69.1)
	Total	71247	(100.0)	71247	(100.0)	70932	(100.0)
Bowel Problems	Severe	1219	(1.7)	296	(0.4)	439	(0.6)
	Moderate	6195	(8.7)	1885	(2.7)	2653	(3.8)
	Mild	15084	(21.2)	6962	(9.8)	8298	(11.8)
	Absent	48537	(68.3)	61892	(87.1)	59252	(83.9)
	Total	71035	(100.0)	71035	(100.0)	70642	(100.0)

[a] The timing relative to death was not recorded

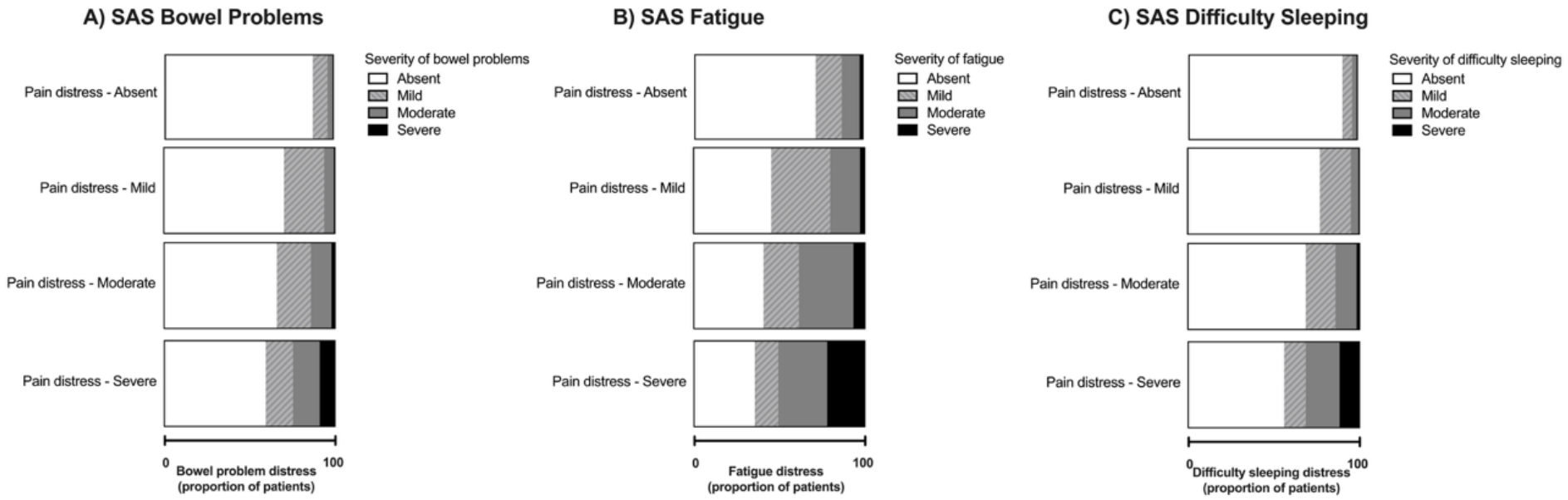

Figure 3-1: PCOC SAS pain distress by PCOC SAS distress from A) bowel problems, B) fatigue and C) difficulty sleeping

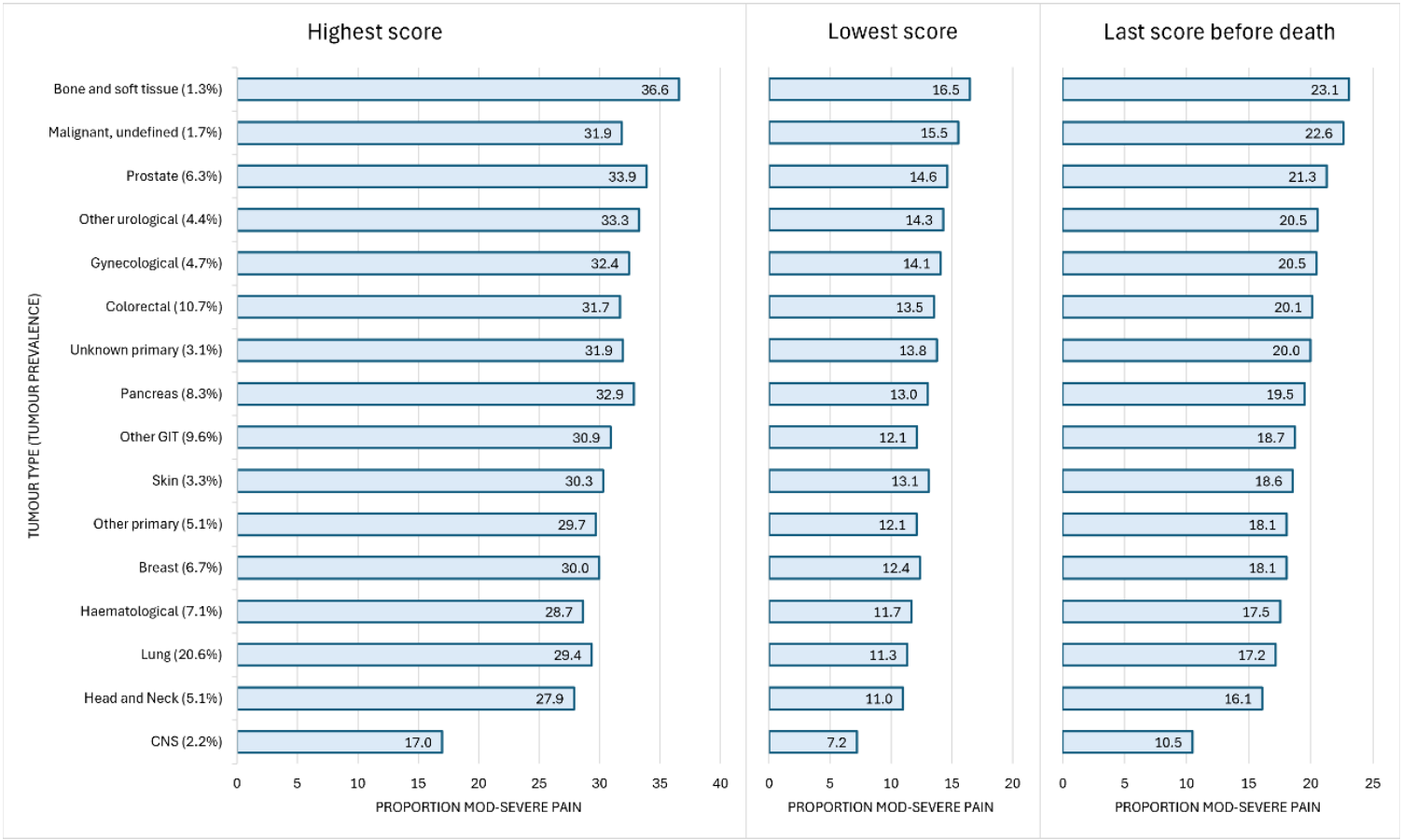

Figure 3-2: Pain distress (PCOC SAS) by tumour type

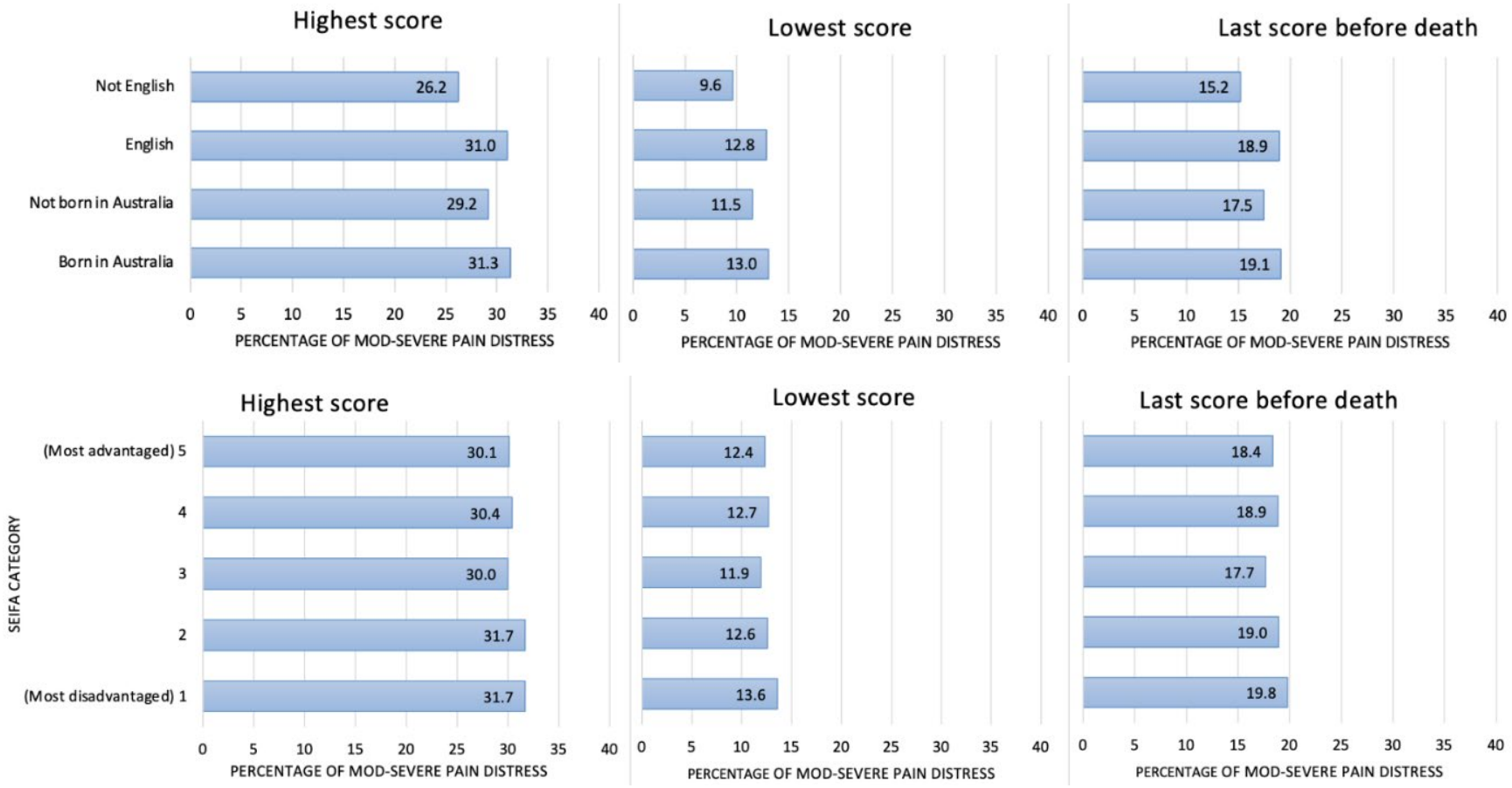

Figure 3-3: Pain distress (PCOC SAS) by sociodemographic factors

Change in distress from pain over the last week of life and performance status

As death approached, the proportion of participants with moderate or severe pain distress reduced (see Figure 3-4A). For participants with AKPS scores of 30 to 60 in the last week of life, the proportion with moderate or severe pain was approximately 25%, irrespective of the day on which the assessment was recorded in the last week of life. As AKPS scores declined, the proportion of people with moderate or severe pain also declined, from approximately 28% for AKPS 60 to approximately 11% for AKPS 10 (see Figure 3-4B).

There were too few people with AKPS ≥70 in the last week of life (n=583) to allow meaningful interpretation, so they are not included in Figure 3-4. A sensitivity analysis of the scores of those with AKPS scores of 10 found the proportion with moderate or severe pain distress was similar to that among all patients.

3.2.4 Discussion

Nearly one third of Australians with cancer receiving specialist palliative care in our study reported moderate or severe pain distress on at least one occasion in the last week of life, with 69% reporting any level of distress from pain. The proportion of people with moderate or severe pain distress reduced as death approached and their performance status dropped. Poorer performance status positively correlated with lower prevalence of distress. To our knowledge, this is the largest study of pain distress in patients receiving specialist palliative care with data derived from a national dataset, and one of only two studies globally evaluating prospectively collected data.[33]

In the other study, Seow et al. reported moderate or severe daily pain on the Resident Assessment Instrument for Home Care (RAI-HC) in 69% of people with cancer in home care one week prior to death[33] which is not directly comparable to pain distress on the PCOC SAS, an 11-point numeric rating scale. Retrospective clinician-reported data shows pain of any level in 79–85% of people with cancer in the last days of life[34, 35] and that 26% may remain unrelieved at the time of death.[85] This suggests that pain prevalence at any level may have lower rates in the last week of life for people referred to specialist palliative care services compared with all people with cancer. We found

poorer performance status in the last week of life is associated with less pain distress. Plausible explanations could include decreased movement and increased drowsiness in the last days of life.[86] Alternatively, this may be an artefact generated by the transition to proxy reporting for people unable to self-report due to declining performance status.

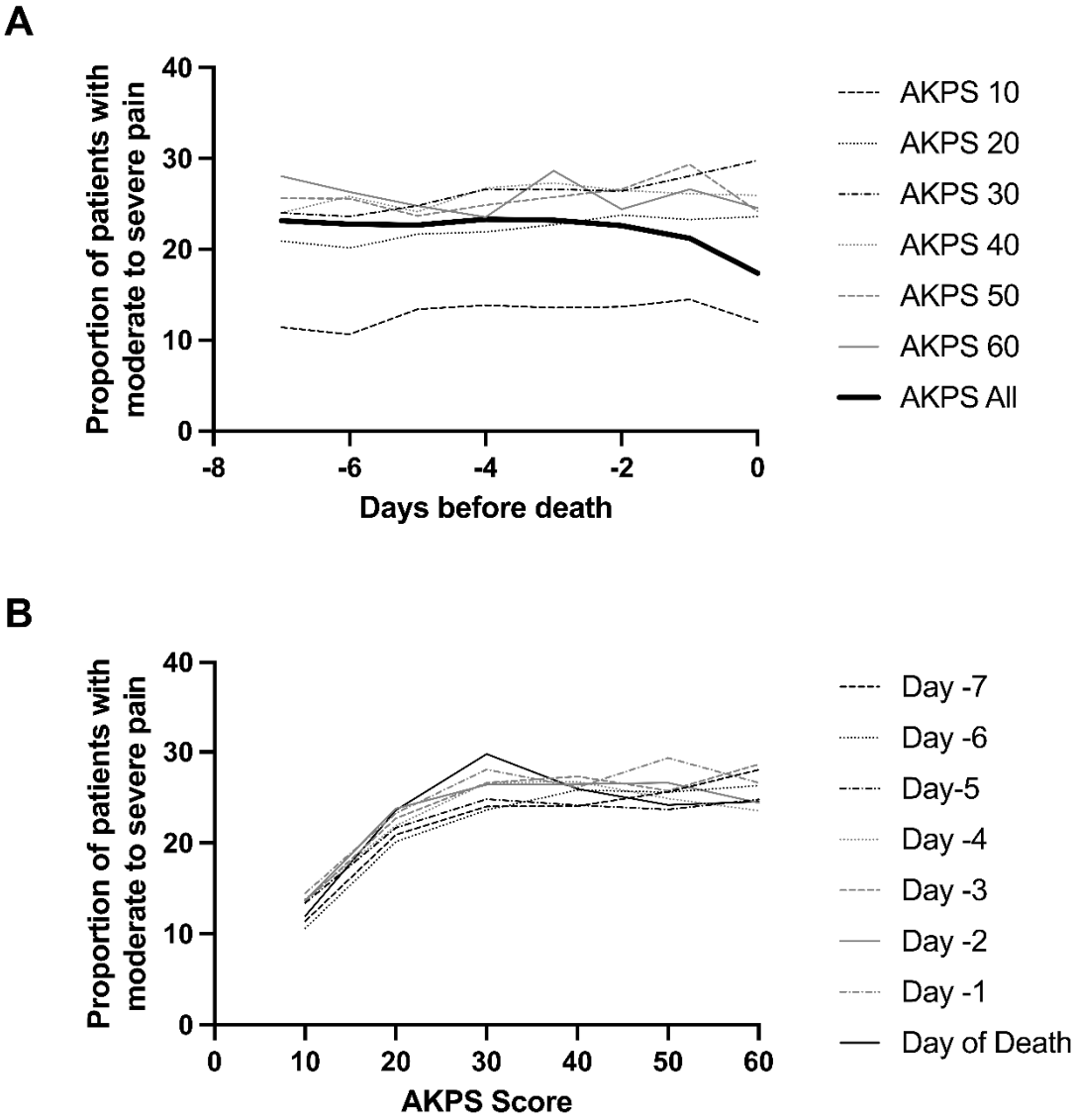

Figure 3-4: A) SAS Pain distress by AKPS and days before death B) Proportion of patients with moderate or severe SAS Pain distress by AKPS and days before death.

Note, the proportion of patients with moderate or severe pain with AKPS ≥ 70 are not presented, as there were too few patients with these scores for meaningful interpretation.

In 2019, 67.1% of all Australian cancer deaths were in hospital and 30.1% died at home or in residential aged care.[87] While the setting of data in this study is broadly reflective of deaths nationally, the skew towards hospital deaths in this study sample may reflect that this population required and had access to specialist palliative care, and may have been referred for the management of poorly controlled pain (or other symptoms). Based on our data, moderate or severe pain was experienced in a greater proportion of people who died in an inpatient setting compared with a community setting. This could represent moderate to severe pain creating a barrier to discharge for death at home or triggering admission in the last days of life. Services should consider interventions and practices which can enhance the capacity of community palliative care services to support people with moderate or severe pain requiring complex management.

People who were more likely to experience moderate or severe pain distress in the week leading up to death included those with comorbid fatigue, sleep and bowel problems and those with bone, soft tissue and prostate cancer. Better characterising these sub-groups may assist in identifying those who would benefit from early intervention, more timely conversations about symptom control priorities, and targeted pharmacological and non-pharmacological clinical trials to reduce unrelieved pain. However, it is important to note that pain was present in all groups evaluated. The presence of pain distress until death may partially reflect the 12–31% of the population with refractory chronic pain, predating cancer diagnosis, and which remains challenging to improve.[88] While some people choose to accept a level of pain either due to adverse effects of existing medication, personal or cultural beliefs, there is a discrepancy between the presence of pain and patient perception of poorly controlled pain.[33]

While it could be argued that the patients in our study reflect the best-case scenario, that is, people who are already under the care of specialist palliative care teams, for many their pain was still not well controlled. In the absence of agreed specialist palliative care referral criteria for people with life-limiting illnesses, it could be argued those who are referred have a greater symptom burden or intensity than those who are not. It is likely that those referred to specialist palliative care services experience better symptom control in the last weeks of life than those who are not referred.[89]

At a population level, the high proportion of people experiencing pain distress highlights the need for research and policy in this area. We need to understand what persistent unrelieved pain in the last days of life means to a person with cancer, the association between performance status and pain, and the correlation between patient and proxy pain scores. Better knowledge of all these topics would aid clinical decision-making.[90]

The lower reporting of pain distress by CALD populations is consistent with previous observations.[91] Whether this is due to cultural differences in expression of pain (given the PCOC assessment tools in use have not been culturally validated),[92] the use of interpreters, the presence of carers during assessment or a truly lower prevalence of pain is unknown. Further research is needed in this area.[91]

Strengths and limitations

Strengths of this study include the large cohort, which captured a high proportion of all Australian deaths in people with cancer over 2018–22. The description of associations of pain in the last week of life provides greater insight into the population who make up those with unrelieved moderate or severe cancer pain in the last week of life.

Our study had several limitations. Firstly, population datasets such as the PCOC dataset can leverage the power of a large number of participants to provide important epidemiological insights. However, they are limited in the number of aspects of pain which are characterised and the timepoints these are assessed. Interpreting a dataset with a variable number of assessment points for each participant is challenging, and has been addressed through the examination of highest, lowest and last scores before death. SAS measures self-rated pain distress and does not capture complexities such as pain intensity, nature, cause, incident pain, different pain types (including neuropathic pain) or multiple concurrent pains. This study captures only the last week of life, so the timing of pain onset is unknown. Clinical research is also necessary to understand the nuances of the pain experience which can then inform strategies to improve outcomes for people with cancer pain. Despite statistical significance of findings in this study, it is still necessary to consider the clinical significance.

Secondly, our study was confined to people seen by primarily specialist palliative care services.[86] Those with more complex pain and other symptoms may be referred to specialist palliative care services. We were unable to account for the impact of proxy reporting. Given the reduced level of consciousness of many people in the last days of life, in some cases proxy reporting was unavoidable. Nonetheless, there was a high inter-rater agreement between patient and proxy rated scores,[90] and given ~90% of patients remain able to participate in a conversation hours or days before death[34, 93] and sensitivity analysis excluding those with AKPS of 10 did not alter the overall findings, we believe that we captured clinically useful levels of pain distress in our study. People with palliative care and greater disadvantage, including Indigenous Australians, older people in aged care, people in prison and those with disabilities, were underrepresented in our study. It is unknown whether these groups lack access to specialist palliative care, although previous studies suggest this is the case.[94]

Despite these limitations, our findings are expected to be applicable to cancer populations supported by palliative care across metropolitan and regional Australia, as well as in similar high-income countries such as European nations, the United Kingdom and Canada.[95]

3.2.5 Conclusion

A substantial proportion of Australians with cancer experience moderate or severe distress from pain during the last week of life, despite specialist palliative care input. Understanding more about this group can improve the ability of clinicians and policymakers to predict and reduce pain in people with cancer. This will assist researchers to provide a range of solutions to improve pain outcomes at the end of life.

3.3 Ethical considerations

This cohort study utilised data initially collected for clinical and quality improvement purposes. After development of the analysis plan by the study investigator team, one investigator who was also the statistician for the data custodian analysed the data and provided this to the other investigators in an aggregated, deidentified form for further

analysis and interpretation. A waiver of consent was approved in line with the following criteria required by the Australian National Statement of Ethical Conduct in Human Research.[70(p21)] The research carried no more than low risk to participants, and the benefit of the research to improve understanding of the epidemiology of pain for people with cancer justified the risk of harm associated with not seeking consent. The risk of harm was low due to the deidentified and aggregated nature of the dataset. It was impracticable to obtain consent because all participants had died, seeking consent from the next of kin held potential to cause distress, and the database did not hold contact details for the participants who contributed data, with only the contributing institutions being able to link the data to the individual. There was no known or likely reason for thinking that participants would not have consented if they had been asked. Deidentification and aggregation provided sufficient protection of their privacy and data from this study was stored in secure, access restricted institutional network drives to further protect confidentiality. No commercial exploitation of the data was anticipated and the waiver was not prohibited by law.

All data was collected by the data custodian PCOC as part of routine clinical care and quality improvement. Data was provided to the investigator team in a deidentified form. No patient identifying features were provided. Individual palliative care services were not able to be identified.

Some members of the investigator team are members of the PCOC collaborative or services contributing data. They have access to data coded with a patient identifying number that could be traced to individual patients or services as part of their usual role. This information was not used as part of this Project, and was not made available to the remainder of the investigator team. Due to the aggregate nature of the data provided for this Project by the data custodian, identifying data were unable to be linked to this analysis.

3.4 Chapter summary

Chapter 3 presents a cohort study that identified a substantial proportion of Australians with cancer experiencing moderate or severe distress from pain during the last week of

life, despite specialist palliative care input. Moderate or severe distress from pain was seen in almost a third of people with cancer at least once during the last week of life. Moderate or severe distress from pain in the last week of life was most prevalent in people with primary cancer of the bone or soft tissue, and prostate cancer. Pain-associated distress scores reduced as death approached and performance status deteriorated. Pain was less frequently reported in people from CALD backgrounds.

A better understanding of the epidemiology of unrelieved pain at the end of life is an important first step towards improving pain outcomes for people with cancer. Population datasets such as the PCOC dataset can provide important insights into the epidemiology of cancer pain and leverage the power of a large number of participants. However, clinical research is also necessary to understand the nuances of the pain experience. Combining approaches may improve researchers' ability to provide a range of solutions to improve pain outcomes at the end of life.

Neuropathic pain is thought to be a significant contributor to unrelieved cancer pain.[28] It is present in around one third of people with cancer pain[5] and increases to 42% in people with moderate to severe cancer pain.[7, 28] Thus it is inferred that neuropathic cancer pain makes up a high proportion of people with moderate to severe pain in the last week of life. Understanding the lived experience of people with neuropathic cancer pain may help to explain why some pain remains unrelieved.

Chapter 4 reports a systematic review of scientific literature on the experience of people with neuropathic cancer pain.

Chapter 4 Experience of neuropathic cancer pain: a systematic review

4.1 Chapter preface

Chapters 1 and 2 introduced the research and its methodology. Chapter 3 described a cohort study of the burden of unrelieved cancer pain in the last week of life for people seen by a specialist palliative care service. The study found that almost a third of people with advanced cancer experience pain at least once in the last week of life and described the demographics of this group.

This chapter describes the experience of people with unrelieved neuropathic cancer pain and it's impact in order to explore the reasons why pain often remains unrelieved at the end of life. This takes the form of a systematic review of qualitative literature on the experience of people with neuropathic cancer pain which was conducted and reported according to the Joanna Briggs Institute methodology for systematic reviews of qualitative evidence. A team of investigators conducted this systematic review under the leadership and oversight of the PhD candidate (JL), with substantial support from research assistant IAD in data extraction and assessment of methodological quality.

4.2 Experience of neuropathic cancer pain: a systematic review

4.2.1 Introduction

Significance

Understanding the experience of people with neuropathic cancer pain is critical for improving outcomes for people with palliative care needs who have unrelieved pain. Effective interventions and policy must be informed by the lived experience of patients due to the complexity of neuropathic cancer pain. Neuropathic and mixed cancer pain

are present in 39.1% of people with cancer pain.[43] Rates of inadequate relief of cancer pain despite treatment of up to 83% have been reported in the literature.[9, 23]

Definition

As noted earlier (Section 1.3.1), the IASP defines neuropathic pain as pain due to a lesion or disease of the somatosensory nervous system, and nociceptive pain as caused by noxious stimuli to tissue or viscera.[3] Pain characteristics can be conceptualised as lying on a spectrum from neuropathic to nociceptive.[11] Neuropathic pain in people with cancer is commonly found as part of a mixed pain syndrome;[96] it may result directly from the tumour (64%), its treatment (20%), and/or be related to the presence of cancer (3.5%).[43] It may also be unrelated to the cancer or its treatment.[43] No authoritative international bodies define neuropathic cancer pain. For the purposes of this review, neuropathic cancer pain is defined as pain due to the tumour, related to the tumour and/or cancer treatment or unrelated to the cancer, and may be found in isolation or as part of a mixed syndrome.

Gaps in evidence base

Despite an increasing amount of research in this area, to date no systematic reviews have examined the experience of either neuropathic cancer pain specifically or cancer pain generally. A thematic synthesis of studies of chemotherapy-induced peripheral neuropathy (CIPN) found it is an unclear experience, a less important risk than disease progression, impacts on quality of life and is a feature of cancer survivorship.[42] Treatment-related pain only causes up to 20.3% of neuropathic cancer pain, so it is important to understand the experience of other types of neuropathic cancer pain including pain caused by the cancer itself. Reviews have described assessment and management[97-99] and shown ethnicity impacts the experience of cancer pain.[100]

Role of this study and significance

This study examined qualitative evidence about the experience of neuropathic cancer pain in order to inform future interventions to manage neuropathic cancer pain. Disparate studies of populations of patients with neuropathic cancer pain, utilising

different methodologies, were aggregated to provide data that applies to populations globally.

This information should inform the design and implementation of strategies to reduce the high rates of unrelieved neuropathic cancer pain and its significant impact on individual quality of life and societal structures. Neuropathic pain is independently associated with higher pain scores,[24, 26] more days to achieve stable pain control[24, 26] and greater requirement for opioid and adjuvant analgesics. Neuropathic cancer pain reduces patient wellbeing severely, causing worse physical, cognitive and social function than nociceptive pain.[6] The economic cost of suboptimally managed cancer pain is high, due to increased and extended hospitalisation and greater care requirements at home.[6, 8, 27]

4.2.2 Overview and objective

The objective of this study was to describe the experience of unrelieved pain in people living with neuropathic cancer pain and identify its impact. This qualitative systematic review sought to identify and synthesise the characteristics of these individuals. The work drew insights from the voices and lived experience of people with neuropathic cancer pain.

4.2.3 Methods

Design

A systematic review was undertaken using the Joanna Briggs Institute methodology for systematic reviews of qualitative evidence.[101] It was reported according to the ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ) statement.[102]

The Joanna Briggs Institute methodology involves a meta-aggregation approach to qualitative evidence synthesis. Meta-aggregation has pragmatism as its philosophical foundation.[103] It seeks to synthesise all types of qualitative evidence to develop synthesised findings that answer the research questions and generate meaningful insights and recommendations to inform practice.[104]

Review questions

- What is the experience of people with unrelieved neuropathic cancer pain?
- What is the impact of unrelieved neuropathic cancer pain?

Search method

A search was conducted in MEDLINE, PsycINFO, AMED, Embase, CINAHL, Scopus and Cochrane between 6 and 22 April 2020 from inception to search date. Primary terms for the search were "neoplasms", "oncology", "neuralgia" and related terms, with a "qualitative" filter. Search terms and filters were tailored to each database as required. The full search strategy can be found in Appendix B. Reference lists of included reports and relevant systematic reviews and meta-analyses identified in the search were examined for additional eligible research.

Inclusion criteria

Participants

Studies that included adults with cancer and neuropathic pain related to the cancer or its treatment were included. Studies were reviewed if they included participants with neuropathic pain or treatment-induced pain, or if the participants described neuropathic features of pain.

Phenomenon of interest

The phenomenon of interest was the experience of neuropathic pain due to cancer or its treatment. Participants' experiences were used to characterise features of people with unrelieved neuropathic cancer pain and its impact.

Context

Studies conducted in any setting – inpatient, outpatient, community, oncology or palliative care – were included.

Types of studies

The review considered English-language studies that focused on qualitative data, collected using designs such as phenomenology, grounded theory, ethnography and action research. Descriptive qualitative studies that describe the experience or describe the effects of the experience were also included.

Exclusion criteria

Reports describing protocols and ongoing studies were excluded. Studies reported in abstract form were excluded if the full reports could not be obtained from the corresponding authors.

Study selection, data extraction and management

Search results were imported into Endnote X7 software,[105] duplicates were removed, and the remaining records exported into Covidence systematic review software.[106] Two members of the review team independently applied eligibility criteria and examined title and abstracts. The reviewers documented reasons for exclusion of reports after examination of full text versions. Disagreements about inclusion and exclusion were discussed to resolve any discrepancies, with a third reviewer consulted when required.

Assessment of methodological quality

Two independent reviewers (JL and IAD) critically appraised eligible studies for methodological quality using the standard Joanna Briggs Institute Critical Appraisal Checklist for Qualitative Research.[104] The checklist has 10 questions that represent criteria concerning study methodology, methods, and findings; research ethics; and researcher influence on the research.

1. Is there congruity between the stated philosophical perspective and the research methodology?
2. Is there congruity between the research methodology and the research question or objectives?

3. Is there congruity between the research methodology and the methods used to collect data?
4. Is there congruity between the research methodology and the representation and analysis of data?
5. Is there congruity between the research methodology and the interpretation of results?
6. Is there a statement locating the researcher culturally or theoretically?
7. Is the influence of the researcher on the research, and vice versa, addressed?
8. Are participants, and their voices, adequately represented?
9. Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?
10. Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?

Possible responses to the questions are "yes," meaning clear evidence of criterion support, "no," meaning no evidence of criterion support, and "unclear," meaning some evidence of criterion support, but with detail or explanation missing. Any disagreements that arose between the reviewers was resolved through discussion or by a third reviewer. All studies, regardless of their appraised methodological quality, underwent data extraction and synthesis where possible.

Data extraction

Data extraction at the article level was conducted by IAD using Excel[107] with one other reviewer (JL) providing input and oversight. Study characteristics including citation details were retrieved from studies. Findings were extracted by JL from each study and evaluated for credibility by JL. Findings are defined as "a verbatim extract of the author's analytic interpretation accompanied by a participant voice, fieldwork

observations or other data."[108] Findings were assessed as "unequivocal" if they were accompanied by a contextually rooted, detailed, rich and clearly associated illustration, "credible" if accompanied by an illustration lacking detail, richness or clear association with it, and "not supported" if the findings were not supported by the data or no data were provided.[104] Findings that were not supported were discarded.

Data analysis

Data analysis was commenced by JL and refined in an iterative process through meetings and discussion with MA, ML and JLP. Qualitative research findings were, where possible, pooled using JBI SUMARI with the meta-aggregation approach.[104] This involved the aggregation or synthesis of findings to generate a set of statements that represent that aggregation, through assembling the findings and categorising them on the basis of similarity in meaning. These categories were then analysed to produce a single comprehensive set of synthesised findings that can be used as a basis for evidence-based practice. If textual pooling was not possible the findings were presented in narrative form. Only unequivocal and credible findings were included in the synthesis. Final synthesised findings were reviewed to ensure consistency with the source papers by JL.

Development of ConQual summary of findings

The ConQual summary of findings uses the dependability and credibility of the findings to determine a ConQual score for each synthesised finding based on methodology by Munn et al.[108] Dependability and credibility of each finding was graded as high, moderate, low or very low by JL.

Dependability is "the extent to which consistent quality is achieved and can be established when the research process is logical, traceable and clearly documented."[104] It is established by counting responses to questions two, three, four, six and seven of the critical appraisal tool JBI-QARI. Studies are ranked as having high dependability if four or five of those responses are "yes," moderate if two or three responses are "yes," and low if zero or one responses are "yes." The synthesised finding may then be

downgraded from a starting level of "high" based on the aggregate level of dependability determined for each study contributing to the included findings.

Credibility is "the degree to which extracted qualitative findings are judged to have been interpreted in a plausible and accurate way that represents the illustration associated with it."[104(p87-88)] Credibility started at "high" and was downgraded one level if there was a mix of unequivocal and credible findings and three levels if there were no unequivocal findings. Unsupported findings were not included in the data synthesis.

4.2.4 Findings

Study inclusion

The search strategy identified 1711 records, of which 212 were duplicates. One hundred reports were screened for full-text review based on title and abstract. Sixty-eight reports were excluded, leaving 32; of these, 11 were published in abstract form only and no further details could be obtained despite contacting the authors. Three reports did not have any relevant findings. Eighteen reports describing 18 studies were included in the final analysis. The PRISMA diagram, adapted from Page et al.,[109] is shown in Figure 4-1.

Methodological quality

The critical appraisal assessment identified variability in methodological quality across studies. Studies were predominantly of moderate quality, with two thirds scoring "yes" on 7 or 8 appraisal criteria, but some scoring as low as 2 or 3.

Most study reports (n=14) did not document the philosophical paradigm used, making it difficult to determine congruity with methods, and were assessed as unclear. In addition, most reports provided insufficient information about researcher reflexivity.

Critical appraisal results

The critical appraisal results are presented in Table 4-1.

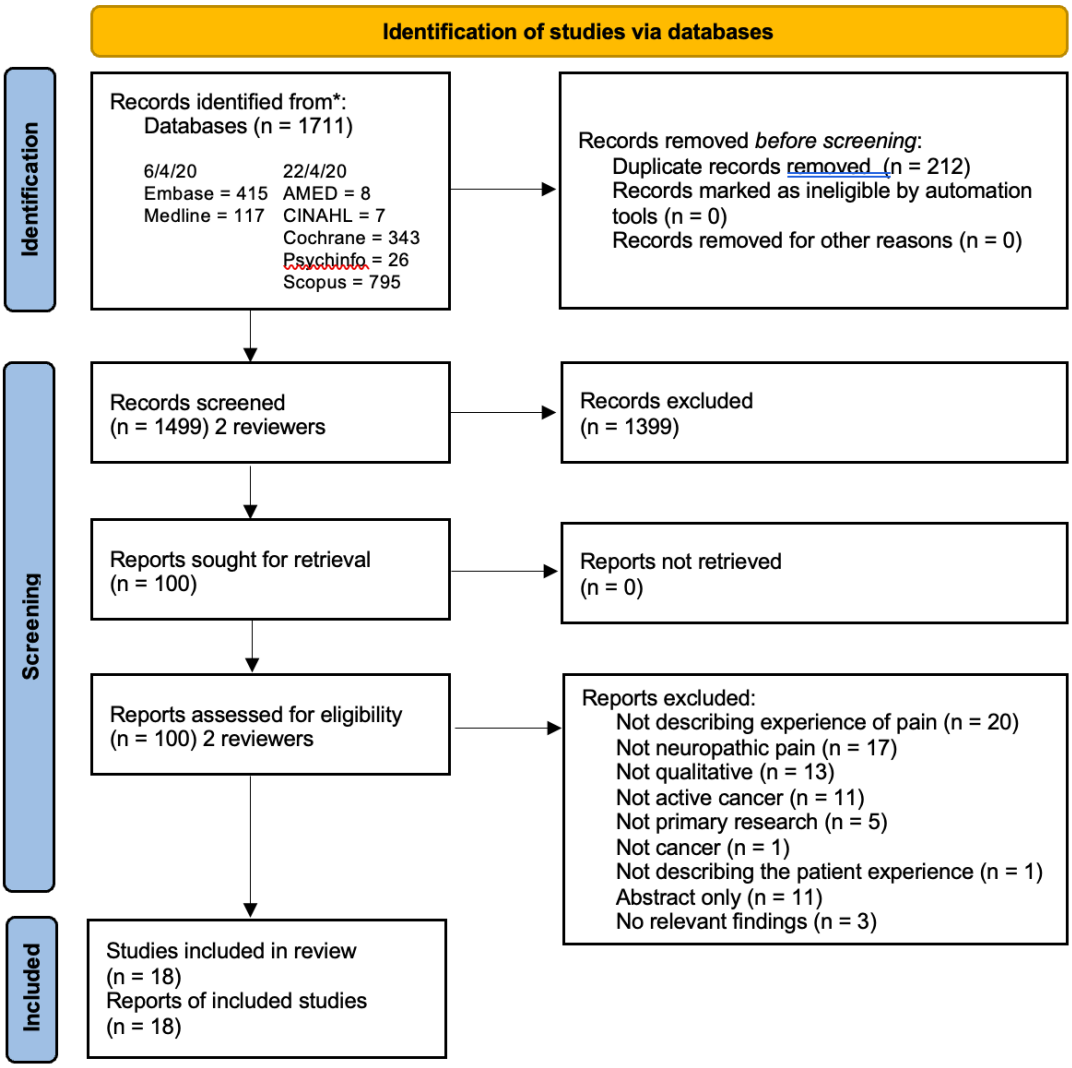

Figure 4-1: PRISMA flow diagram – experience of neuropathic cancer pain

Table 4-1: Critical appraisal assessment table: JBI-QARI critical appraisal instrument

	Critical appraisal question[#]									
Author, year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Bakitas, 2007[110]	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Beatty, 2008[111]	U	Y	Y	Y	Y	N	U	Y	Y	Y
Bennett, 2012[112]	U	U	U	U	U	N	N	Y	Y	Y
Cormican, 2018[113]	N	Y	Y	Y	Y	N	U	Y	Y	Y
Ekstedt, 2019[114]	U	U	U	U	U	N	N	Y	Y	Y
Gater, 2011[115]	U	Y	Y	Y	Y	N	N	Y	Y	Y
Hackett, 2016[116]	Y	Y	Y	Y	Y	U	N	Y	Y	Y
Haozous, 2011[117]	U	Y	Y	Y	Y	Y	Y	U	Y	Y
Hellerstedt-Borjesson, 2015[118]	U	Y	Y	Y	Y	N	N	Y	Y	Y
Juarez, 1998[119]	U	N	N	N	N	Y	N	Y	N	Y
Larsson, 2007[120]	U	Y	Y	Y	Y	N	N	Y	Y	Y
Loprinzi, 2007[121]	U	U	U	U	U	N	N	U	Y	Y
Padman, 2015[122]	U	Y	Y	Y	Y	N	N	Y	N	Y
Schumacher, 2002[123]	U	Y	Y	Y	Y	N	N	Y	N	Y
Schumacher, 2021[124]*	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Speck, 2012[125]	U	Y	Y	Y	Y	N	N	Y	Y	Y
Tofthagen, 2010[126]	U	Y	Y	Y	Y	N	N	Y	Y	Y

Williams, 2019[127]	U	Y	Y	Y	Y	U	N	Y	Y	Y

Y, yes; N, no; U, unclear

#Q1=Is there congruity between the stated philosophical perspective and the research methodology? Q2=Is there congruity between the research methodology and the research question or objectives? Q3=Is there congruity between the research methodology and the methods used to collect data? Q4=Is there congruity between the research methodology and the representation and analysis of data? Q5=Is there congruity between the research methodology and the interpretation of results? Q6=Is there a statement locating the researcher culturally or theoretically? Q7=Is the influence of the researcher on the research, and vice- versa, addressed? Q8=Are participants, and their voices, adequately represented? Q9=Is the research ethical according to current criteria or, for recent studies, is there evidence of ethical approval by an appropriate body? Q10=Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?

*Schumacher 2021 was published online ahead of print in 2019. The reference has been updated to reflect the final publication.

Characteristics of included studies

The characteristics of the 18 included studies, published between 1998 and 2019, are summarised in Table 4-2. The 18 studies were undertaken in Australia (n=3), the United States (USA) (n=10), United Kingdom (UK) (n=2), Europe (n=3) and Latin America (n=1, with some US content) in a variety of outpatient oncology and community settings. The methods used to collect data were interviews,[110, 112, 115-122, 125-127] focus groups[111, 113] and analysis of recorded interactions between study nurses and participants.[114, 123, 124] The three nurse-based studies were related, but involved different patient and investigator groups in evaluations of an intervention for pain management. The phenomena of interest in many of the studies related directly to the experience of pain. The remaining studies investigated a related phenomenon but produced data describing the experience of neuropathic cancer pain.

None of the studies focussed on neuropathic cancer pain in its entirety. Eight studies investigated chemotherapy-related or other treatment-related pain.[110, 112, 118, 121, 122, 125-127] Three studies examined patients with bone pain.[114, 115, 123] Seven studies looked at

cancer pain, and included participants who described classically neuropathic features or aetiologies of pain.[111, 113, 116, 117, 119, 120, 124]

Studies of treatment-related pain involved people with either mixed tumour types[110, 121, 126] or colorectal[112, 121] or breast[121, 125] cancers or myeloma.[127] Two studies[121, 126] specified a chemotherapy agent (Paclitaxel or Oxaliplatin). The other cancer pain studies examined populations defined by pain mechanism (bone metastases), [114, 115, 123] tumour type (breast cancer,[111] myeloma[113]), disease stage (advanced cancer,[116] end of life[120] or receiving outpatient treatment with good performance status[124]), or ethnicity (American Indian[117] and Hispanic[119] patients).

Synthesised findings

Four synthesised findings were drawn from this systematic review:

1. neuropathic cancer pain is multifaceted and must be considered in context of the whole person;
2. spiritual values and social context shape many people's experience of neuropathic cancer pain;
3. inadequate information, together with functional limitations, contribute to psychoexistential distress; and
4. people who develop a therapeutic patient-provider relationship and self-efficacy are better equipped to pursue and integrate a range of pain management strategies.

Subgroups were also analysed separately to determine whether the findings were affected by the nature of the populations studied.

Table 4-2: Characteristics of included studies

Authors	**Published Year**	**Title**	**Country**	**Method**	**Phenomena of interest**	**pain**	**Setting/context/culture**	**Participant characteristics and sample size**
Bakitas, M. A.	2007	Background noise: the experience of chemotherapy-induced peripheral neuropathy	USA	Interviews	Experience of chemotherapy-induced peripheral neuropathy	CIPN	Rural, National Cancer Institute-designated, comprehensive cancer center	Cancer patients (mixed cancer) (n=28)
Beatty, L., Oxlad, M., Koczwara, B., Wade, T. D.	2008	The psychosocial concerns and needs of women recently diagnosed with breast cancer: A qualitative study of patient, nurse and volunteer perspectives	Australia	Focus groups	Psychosocial concerns and needs of women with breast cancer	breast cancer, some had arm pain and numbness - no specifically stated neuropathic pain	Mixed	Australian women diagnosed with early-stage breast cancer as well as oncology nurses and volunteers who provide support services for women with breast cancer
Bennett, B. K., Park, S. B., Lin, C. S. Y., Friedlander, M. L.,	2012	Impact of oxaliplatin-induced neuropathy: A patient perspective	Australia	Interviews	Neuropathic symptoms in oxaliplatin-treated patients	CIPN	Hospital setting: Department of Medical Oncology, Prince of Wales Hospital	Patients with colorectal cancer (n=20)

Kiernan, M. C., Goldstein, D.								
Cormican, O., Dowling, M.	2018	Living with relapsed myeloma: symptoms and self-care strategies	Ireland	Focus groups	Symptoms and self-care strategies of relapsed myeloma patients	myeloma patients - some had peripheral neuropathy	Myeloma patients attending haematology centres	Relapsed myeloma patients (n=15) and carers (n=9)
Ekstedt, M., Rustoen, T.	2019	Factors That hinder and facilitate cancer patients knowledge about pain management: a qualitative study	Norway	Digitally recorded verbal interactions between the nurse and patients during coaching sessions	Pain management education	bone mets	Patients homes	Adult oncology outpatients (n=20)
Gater, A., Abetz-Webb, L., Battersby, C., Parasuraman, B., McIntosh, S.,	2011	Pain in castration-resistant prostate cancer with bone metastases: A qualitative study	USA	Interviews	Patient experiences of bone pain and impact on health-	bone mets	Eligible patients were recruited in the USA with the help of clinicians from two clinical practices and	Patients with castration-resistant prostate cancer and bone metastasis (n=17)

Nathan, F., Piault, E. C.					related quality of life		advertisements from a commercial recruitment agency	
Hackett, J., Godfrey, M., Bennett, M. I.	2016	Patient and caregiver perspectives on managing pain in advanced cancer: A qualitative longitudinal study	UK	Interviews (face to face)	Patients' and carers' experiences of advanced cancer pain and the processes to manage pain.	advanced cancer pain - many describe neuropathic features	Oncology outpatients in a tertiary cancer centre and a hospice	Patients with advanced cancer (n=21) and carers (n=16)
Haozous, E. A., Knobf, M. T., Brant, J. M.	2011	Understanding the cancer pain experience in American Indians of the Northern Plains	USA	Interviews (face to face)	Experiences of cancer pain	cancer pain - somatic and NP	Community setting	American Indians with both solid and hematologic malignancies (n=10)
Hellerstedt-Borjesson, S., Nordin, K., Fjallskog, M.-L., Holmstrom, I. K., Arving, C.	2015	Women with breast cancer: experience of chemotherapy-induced pain: triangulation of methods	Sweden	Interviews (face to face)	Impact of adjuvant chemotherapy-induced pain	chemotherapy -induced pain		Women with newly diagnosed breast cancer (n=16)

Juarez, G., Ferrell, B., Borneman, T.	1998	Influence of culture on cancer pain management in Hispanic patients	USA & Latin America	Interviews	Influence of culture on cancer pain management	cancer pain, many neuropathic descriptors	Community home-care agencies	Hispanic (Mexican and Central American) cancer patients (n=17)
Larsson, A., Wijk, H.	2007	Patient experiences of pain and pain management at the end of life: a pilot study	Sweden	Interviews (taped dialogue?)	Patient experience of pain and pain management	cancer pain - nociceptive and neuropathic	Pain unit	Cancer patients at the end of life treated by intrathecal pain management with an external pump (n=3)
Loprinzi, C. L., Maddocks-Christianson, K., Wolf, S. L., Rao, R. D., Dyck, P. J. B., Mantyh, P., Dyck, P. J.	2007	The paclitaxel acute pain syndrome: Sensitization of nociceptors as the putative mechanism	USA	Interviews	Paclitaxel-related acute pain syndrome	chemotherapy -induced pain	Outpatient chemotherapy unit	Oncology patients who were treated with paclitaxel and developed a subacute pain syndrome (n=18)
Padman, S., Lee, J., Kumar, R., Slee, M., Hakendorf, P., Richards, A., Koczwara, B.,	2015	Late effects of oxaliplatin-induced peripheral neuropathy (LEON)--cross-sectional cohort study of patients with	Australia	Interviews	Clinical impact of chronic peripheral neuropathy	CIPN	Patients treated at the Department of Medical Oncology, Flinders Medical Centre, were	Colorectal cancer patients who started oxaliplatin treatment at least 2 years prior to study commencement (n=25)

Kichenadasse, G., Sukumaran, S., Roy, A., Vatandoust, S., Karapetis, C. S.		colorectal cancer surviving at least 2 years					identified from pharmacy records.	
Schumacher, K. L., Koresawa, S., West, C., Hawkins, C., Johnson, C., Wais, E., Dodd, M., Paul, S. M., Tripathy, D., Koo, P., et al.	2002	Putting cancer pain management regimens into practice at home	USA	Audiotaped nurse/patient/family caregiver interactions during the three home visits, nurses' field notes, and nurses telephone logs	Experiences of cancer pain management	bone mets	Oncology outpatient centres	Adult oncology outpatients (n=52) and their caregivers (n=33)
Schumacher, K. L., Plano Clark, V. L., Rabow, M. W., Paul, S. M., Miaskowski, C.	2019	The experience of complex pain dynamics in oncology outpatients: a longitudinal qualitative analysis	USA	Audiorecorded intervention sessions and nurses' narrative field notes	Patients experience of cancer pain	Somatic and visceral pain, some patients also have bone pain or CIPN	8 outpatient oncology settings	Adult cancer patients who had pain (n=42)

Speck, R. M., DeMichele, A., Farrar, J. T., Hennessy, S., Mao, J. J., Stineman, M. G., Barg, F. K.	2012	Scope of symptoms and self-management strategies for chemotherapy-induced peripheral neuropathy in breast cancer patients	USA	Interviews	Self-management strategies for CIPN and to discriminate the CIPN symptom experience	CIPN	Rena Rowan Breast Center of the University of Pennsylvania	Breast cancer patients who experienced CIPN (n=25)
Tofthagen, C.	2010	Patient perceptions associated with chemotherapy-induced peripheral neuropathy	USA	Face to face interviews	Patient experience of CIPN and neuropathic pain	CIPN	Outpatient medical oncology practice	Cancer patients experiencing CIPN (n=14)
Williams, L. A., Garcia-Gonzalez, A., Mendoza, T. R., Haq, S., Cleeland, C. S.	2019	Concept domain validation and item generation for the Treatment-Induced Neuropathy Assessment Scale (TNAS)	USA	Interviews	Patient experience of treatment-induced peripheral neuropathy (TIPN)	TIPN		Patients with multiple myeloma, colorectal with TIPN who received bortezomib, oxaliplatin, or platinum–taxane combination therapy (n=32)

Synthesised finding 1: ***Neuropathic cancer pain is multifaceted and must be considered in context of the whole person.***

This synthesised finding was created from 22 findings in two categories (Table 4-3). Words used to describe pain included typical adjectives such as "shooting"[121] and unusual adjectives such as "like hot lava".[117] The anatomical location was used as a descriptor, but many patients stated that their pain could change location. Many descriptors were associated with other symptoms such as numbness[125] or nausea.[119] The aetiology of neuropathic pain in people with cancer included pain from the primary tumour,[111, 113] metastases,[114, 115, 123] and cancer therapies.[110, 112, 118, 121, 122, 125-127] Pain intensity was variable, both between and for individuals. Some studies categorised the pain people felt according to intensity or quality. Some pains were extremely severe or "crippling",[118] while others were manageable but "never completely goes away."[115] People were able to differentiate between the types of pains they experienced. Pain was one of a constellation of symptoms that affected participants and impaired their perceived ability to cope and quality of life.

Table 4-3: Synthesised finding 1

Finding		**Category**	**Synthesised finding**
CIPN could be kept in the background and was not the central focus of the participants' cancer experience except when it became severe	U	Characteristics of pain	*Neuropathic cancer pain is multifaceted and must be considered in context of the whole person* It may have different qualities and intensities
Severity and persistence of oxaliplatin-induced neurotoxic symptoms	U		
Patients were able to distinguish pain caused by bone metastases from other types of pain based not only on the location of the pain but also the intensity and temporal features of the pain including onset, frequency and duration	U		
Patients did experience some variation in the level of pain experienced	U		
Pain for some patients (n=5) was exacerbated by chemotherapy, and physical activities such as gardening, walking or standing. For other patients (n=4) there was no apparent cause for episodes of exacerbated pain	U		
Pain they experienced was manageable with analgesic medication such as acetaminophen and opioids, but never completely goes away	U		

Three distinct patterns of pain were discerned in patients' accounts, distinguishable in terms of complexity, severity, transiency and degree of perceived control over pain	U		and may occur in context of other pains, associated symptoms or comorbidities
Descriptors for neuropathic type pain included 'like lightening', electric shock, 'like hot lava', 'Needles', 'tingling', 'vibration'	U		
Three different categories crystallised: perception (A) of manageable pain, which allowed the women to maintain their daily lives; perception (B) of pain beyond imagination, whereby the impact of pain had become more complex; and perception (C) of crippling pain, challenging the women's confidence in survival	U		
Anatomic descriptors	U		
Words for pain/descriptors	U		
The most common adjectives used to describe the pain included "radiating," "shooting," "aching," "stabbing," and "pulsating"	U		
Occurred in changing locations	U		
The most commonly reported painful symptoms were burning, muscle aches, and sensitivity to cold	U		

The most common sensations reported by patients were numbness (23/30; 76.7%), pain (23/30; 76.7%) and tingling	U		
Participants reported a range of illness and treatment-related side-effects that impaired perceived ability to cope and quality of life, including fatigue and insomnia, numbness and pain (including lymphoedema), and malnutrition	C		
Other symptoms	U		
Co-occurring sources of pain	U	May have multiple pains, associated symptoms or comorbidities	
Complex pain dynamics	U		
Varying patterns of pain intensity	C		
The most frequent words used to describe the sensations of CIPN were “numbness,” “tingling,” and “painful”	U		
The most common sensations reported by patients were numbness (23/30; 76.7%), pain (23/30; 76.7%), and tingling	U		

U: unequivocal

C: credible

Synthesised finding 2: ***Spiritual values and social context shape many people's experiences of neuropathic cancer pain***

This synthesised finding (from 25 findings in four categories) identified multiple factors external to the patient and cancer that shaped the pain experience (Table 4-4).

Transcendental connection (commonly with "God," family or community) was important for many participants.

Pain contributed to isolation by impairing physical function and ability to engage in previously enjoyed social activities. It also differentiated the patient from others, amplifying isolation through the need to conceal pain to protect loved ones and protect their image. Stoicism was seen as an admirable cultural value in both Native American and Hispanic populations, but inhibited social connection for people with cancer pain. Coexisting with these isolating factors, in some cases pain was able to enhance connection, particularly in cases where the participant shared their pain experience with family.

The expression of pain was clearly intertwined with the meaning ascribed to it. This was perceived to be associated with disease progression or dying. Pain could act as both a distractor and a reminder of death.

Table 4-4: Synthesised finding 2

Finding		**Category**	**Synthesised finding**
Global disruptions and interference with activities of daily living; hobbies; and leisure, work, and family roles	U	Social isolation and connection	*Spiritual values and social context shape many people's experiences of neuropathic cancer pain* Transcendental connection, often with God, family, or community, was an important response to pain for many participants. Pain contributed to
Difficulty that participants had expressing how CIPN sensations felt	C		
Patients reporting impairments in daily functioning from a physical, emotional and social perspective (includes sleep, physical function, social activities)	U		
Social isolation was a far more disturbing result of cancer and cancer pain (subtheme of isolating within)	U		
Participants were wary of others in the tribe learning of the depth of their suffering	U		
Public suffering without appropriate stoicism would reflect poorly on their family or clan	U		
Participants would reach out and share their cancer experience with family members as a way of sharing the experience, in order to make connections	U		
Making connections with community and family provided important coping for a population that is economically, socially and physically isolated	U		
Power of spirituality to bring people together	C		
Socially, women experienced severe limitations in relation to what life had been like before treatment, and they turned down social invitations, gave up activities, and became withdrawn	U		
The pain resulted in their becoming isolated and reclusive; they disconnected from family and friends.	U		

Family very important	U		isolation by limiting physical and social activities, while stoicism further inhibited social connection
Tells Significant Other (spouse, caregiver)	U		
Behavioral expressions	U		
Tells God	U		
The coexistence of the need to reveal and conceal the pain experience	U		
Taught to Follow/Believe in God	U		
Some patients shared that it was “normal” to have pain when you have cancer and that you just have to be strong and endure the pain. They described that they were ashamed to ask for strong pain medications or tranquilizers. Others expressed guilt	C	Patient values impact expression of pain	
Stoicism was frequently cited as an important cultural value, one which had a deleterious effect on family and tribal connections	U		
Taught not to complain/stoic	U		
Escalating pain as well as change in type and/or source was perceived as indicative of disease progression, signifying that life was time-limited	U	Meaning of pain	
There was an insecurity regarding whether the pain had been caused by the treatment or was due to a worsening of the disease	U		
The experience of the pain is dreadful reminding the patient of the cancer and the uncertainty of the future	C		

Focus on pain and the possibility and hope of finding a new means of relieving it could also be a distraction from thoughts of death	U	Other patient priorities and concerns influence experience of pain (e.g., fear of death)	
Despite some patients having significant neuropathic symptoms, majority felt satisfied with their decision to receive oxaliplatin*	U		

Synthesised finding 3: ***Inadequate information, together with functional limitations contribute to psychoexistential distress***

This synthesised finding (from 20 findings in three categories) identified the impacts of pain on the patients' physical function and emotional wellbeing (Table 4-5).

Information provision was highly valued, but some people lacked adequate understanding of their illness, pain medication and management. People were not prepared for the severity or impact of neuropathic cancer pain. A lack of information about the future pain trajectory contributed to uncertainty, which in turn caused fear and distress. Neuropathic cancer pain impaired physical function in multiple domains, reducing patients' ability to complete activities of daily living and engage in social activities. The degree of impact varied. Functional impairment caused or coexisted with psycho-existential distress. However, it was noted the emotional response to pain could be harnessed for positive effect to give power to fight.

Table 4-5: Synthesised finding 3

Finding		**Category**	**Synthesised finding**
Information provision was of utmost importance to these patients	C	Inadequate information	*Inadequate information, together with functional limitations contribute to psychoexistential distress* Lack of education or understanding of
Patients had difficulty in seven areas when they attempted to put a pain management regimen into practice, namely: obtaining the prescribed medication(s), accessing information, tailoring prescribed regimens to meet individual needs, managing side effects, cognitively processing information, managing new or unusual pain, and managing multiple symptoms simultaneously	U		
Because of a lack of basic knowledge about their illness and of how their pain medication worked, patients made their own assumptions about the mechanisms	U		
Some patients had difficulties in understanding complicated explanations about pain medications and pain management and how to apply the information in their daily lives	C		
Awareness of CIPN was not always accurate, immediate, or straightforward	U		

Patients did not expect the neuropathy to affect their lives to the extent that it did	U		education together with uncertainty contributed to inadequate information provision. Functional impairment and its impact was significant. These factors both contributed to psychoexistential distress.
Of 19 patients, 12 did not recall being warned of CIPN. A number of those who were able to recall prior warnings felt the issue was inadequately emphasised	U		
The women retreated, felt that the future was very uncertain, became solely focused on survival, and greatly feared future treatments	U		
Never envisaged that the pain would be like this, and not knowing when it would end was described as unbearable	U		
Patients reporting impairments in daily functioning from a physical, emotional and social perspective (includes sleep, physical function, social activities)	U	Function and physical capacity	
Many patients described ongoing neuropathic symptoms, though the majority did not feel that neuropathy directly affected their daily function	U		
A minority of interviewees were unable to continue working, though most found they could continue their hobbies	U		
The reported impact of CIPN on participants' routine activities, functions, and behaviours varied, as did their approaches and adaptations to deal with the symptoms. Routine activities, functions, and behaviours impacted by CIPN symptoms included sleeping, driving, standing, walking, climbing stairs, loss of balance, opening containers,	U		

holding onto things, cooking, cleaning, flipping pages of paper, wearing certain shoes and jewelry, exercising, and socialising			
Patients described a variety of ways in which neuropathic symptoms interfered with manual dexterity, general activities, activities of daily living, driving, writing, picking things up, work, sleep, walking, hobbies, household duties, and exercise	U		
The effects of TIPN on normal functioning most often mentioned by patients were difficulty walking (14/30; 46.7%), difficulty using hands or fingers (11/30; 36.7%), problems with balance or falling (10/30; 33.3%), difficulty sleeping (6/30; 20.0%), and difficulty wearing or finding comfortable shoes (7/30; 23.3%)	U		
Peripheral neuropathy was considered to significantly impact on sensitivity to touch and overall quality of life	C		
They voiced feelings of frustration, depression, and loss of purpose as a result of having to give up enjoyable activities	U	Emotional impact	
Social isolation led to other side effects of disease such as depression (subtheme of isolating within)	U		
For the 75% of the sample who had a pain component, functional difficulties, fatigue, sleep disturbance, and mood effects were common sequelae	U		
Pain-evoked emotions also gave the women power to fight the pain (in women with manageable pain)	C		

Synthesised finding 4: ***People who develop a therapeutic patient-provider relationship and self efficacy are better equipped to pursue and integrate a range of pain management strategies***

This synthesised finding (from 25 findings in three categories) identified domains that could be targeted to optimise pain management.

The patient–provider relationship required continuity of care with the same provider as well as consistency between providers. People wanted action to address concerns. Continuity of care and the initiation of action led to trust and compliance.

Strategies to improve self-efficacy improved the ability to manage pain and empowered people to seek solutions to control their pain, including both conventional and complementary therapies. Information was sought from a range of sources, including other patients, lay people, traditional and conventional healthcare providers. Concerns about conventional medications included adverse effects and fear of addiction.

Table 4-6: Synthesised finding 4

Finding		**Category**	**Synthesised finding**
Continuity of care was paramount	U	Patient doctor relationship	*People who develop a therapeutic patient-provider relationship and self efficacy are better equipped to pursue and integrate a range of pain management strategies*
Information was collected and stored with little action taken in regard to the management of the actual problem	U		
When information from different sources was consistent, patients had the confidence to trust the advice	U		
Follows doctor's orders	U		
Diary complemented the coaching sessions by reminding the patients to maintain a regular schedule; it helped them to become aware of early signs and of the resources needed to efficiently manage their pain	U	Self-efficacy	
Categories of self-management strategies include the use of movement to reduce symptoms, attitude, and body awareness, logistics to simplify demands, and environmental change. Additionally, women reported using over the counter (e.g., Ibuprofen) or prescription medications	U		
Knowledge of how their body worked and awareness of their own weaknesses and strengths facilitated the patient's learning how to manage their pain	U		
Knowledgeable patients who took an active part in their own care had good control over their pain and knew what to do if they needed help	C		

Pain scales	U		Patients who develop a strong, trusting relationship with their healthcare providers and cultivate self-efficacy are more capable of managing their pain effectively. A positive patient-provider relationship fosters continuity of care, trust in medical advice, and adherence to
A number of self-care strategies to manage peripheral neuropathy and fatigue were shared in the groups, such as the use of heat and topical cream (capsaicin cream), gel soles, acupuncture, reflexology and alternative therapies in local cancer centres	U	Pain management and medication	
Provision of examples of how other patients in the same situation managed to control their pain increased the patient's hope and motivation to follow the nurse's advice	U		
Pain they experienced was manageable with analgesic medication such as acetaminophen and opioids, but never completely goes away	U		
Side effects of rescue morphine, in the context of intermittent pain, had the consequence that use was limited or stopped	U		
Relying on prayer and traditional medicine	U		
Family medicine woman	U		
Folk healers	U		
Beliefs about medications	U		
Advice from family/neighbours	U		
Advice from pharmacist	U		

Non-drug interventions	U		treatment plans, while self-efficacy empowers patients to actively engage in self-management strategies. These factors work together to enhance patients' ability to explore and integrate a variety of pain management approaches, including pharmacological, non-pharmacological, and alternative methods
Participants used cognitive processes such as minimizing, denying, or ignoring the symptoms...But some participants very consciously anticipated activities that would increase their symptoms and planned ahead	C		
Taking pain medications	U		
Fear of addiction	U		
Medication side effects	U		
Medication from Mexico	U		

Evidence for findings

Supporting quotes for findings and their assigned credibility and dependability are shown in Table 4-7. Included studies were colour coded by pain characteristics to support sub-group analysis.

Table 4-7: Evidence for findings

Studies	Finding	Illustration	Page	Credibility	Dependability	Draft category	Synthesised finding
Bakitas 2007	CIPN could be kept in the background and was not the central focus of the participants' cancer experience except when it became severe	"I still have trouble trying to figure out when to listen to the pain, and how to interpret the pain, and when to just tune it out. When I get kind of loud noise from down there, I've kind of learned to just not listen to it.''	326	Unequivocal	Moderate	Characteristics of pain	1. Neuropathic pain is multifaceted and must be considered in context of the whole person.
Bennett 2011	Severity and persistence of oxaliplatin-induced neurotoxic symptoms	No improvement over the past 12 months	2962	Unequivocal	Low		
Gater 2011	Patients were able to distinguish pain caused by bone metastases from other types of pain based not only on the location of the pain but also the intensity and temporal features of the pain including onset, frequency and duration	It's so different, because it's very intense.	4	Unequivocal	Moderate		

Gater 2011	Patients did experience some variation in the level of pain experienced	Mine varies quite a bit. It goes from hardly any pain at all to severe’	5	Unequivocal	Moderate		
Gater 2011	Pain for some patients (n = 5) was exacerbated by chemotherapy, and physical activities such as gardening, walking or standing. For other patients (n = 4) there was no apparent cause for episodes of exacerbated pain	"the third day after chemo,...every bone in my body from my ankles to my head was in pain" "I just got up in the morning, the pain was there"	5	Unequivocal	Moderate		
Gater 2011 (duplicate)	Pain they experienced was manageable with analgesic medication such as acetaminophen and opioids, but never completely goes away	I control it somewhat with this medication	4	Unequivocal	Moderate		
Hackett 2016	Three distinct patterns of pain were discerned in patients’ accounts, distinguishable in terms of complexity, severity, transiency and degree of perceived control over pain	I feel like I've had to bite on something to stop me screaming. It's… like being stabbed.	713	Unequivocal	Moderate		

Haozous 2011	Descriptors for neuropathic type pain included “like lightning,” “electric shock,” “like hot lava,” “needles,” “tingling,” “vibration”	"It's mostly the heat. Burning. … like a lightning. Or a needle"	407	Unequivocal	High		
Hellerstadt 2015	Three different categories crystallised: perception (A) of manageable pain, which allowed the women to maintain their daily lives; perception (B) of pain beyond imagination, whereby the impact of pain had become more complex; and perception (C) of crippling pain, challenging the women’s confidence in survival	I cried on and off, even though I’m not the one to get scared, thinking that this just as well might be the end, because I could not take it anymore, and that’s so unlike me.	36	Unequivocal	Moderate		
Juarez 1998	Anatomic descriptors	‘The pain runs all the way through my arm, the entire arm, to the shoulder.’’	266	Unequivocal	High		
Juarez 1998	Words for pain/descriptors	I get a little pain like a burning pain that makes me feel bad, it hurts	266	Unequivocal	High		

Loprinzi 2007	The most common adjectives used to describe the pain included “radiating,” “shooting,” “aching,” “stabbing,” and “pulsating”	“radiating,” “shooting,” “aching,” “stabbing,” and “pulsating.”	400	Unequivocal	Low		
Schumacher 2019	Occurred in changing locations	“It’s all about where your pain is, and this last couple of weeks it’s been the esophagus.”	3	Unequivocal	Moderate		
Tofthagen 2010	The most commonly reported painful symptoms were burning, muscle aches, and sensitivity to cold	"ice cold" "walking on hot coals"	E25	Unequivocal	Moderate		
Williams 2019	The most common sensations reported by patients were numbness (23/30; 76.7%), pain (23/30; 76.7%), and tingling	Sometimes it’s like somebody’s taking a hammer and just hitting my feet.	1025	Unequivocal	Moderate		
Beatty 2008	Participants reported a range of illness and treatment-related side-effects that impaired perceived ability to cope and quality of life, including fatigue and insomnia, numbness	It's like laying on your arm and it s gone dead, and you wake up and sort of go “where is it?”	335	Credible	Moderate	May have multiple pains, associated	

	and pain (including lymphoedema), and malnutrition					symptoms or comorbidities	
Juarez 1998	Other symptoms	I feel like my stomach, like nausea, unpleasant, like that. Then I feel a lot of phlegm in my throat, and then kind of dizzy.	266	Unequivocal	High		
Schumacher 2019	Co-occurring sources of pain	"all over the map" … included bone metastases, radiation therapy, oral chemotherapy, other medication adverse effects, golf, yard work, and biopsy of a new lesion	4	Unequivocal	Moderate		
Schumacher 2019	Complex pain dynamics	I certainly experience certain types of pain. A lot of times I have both pains. If I have a complex pain, I'll take both of those [referring to his pain medications].	5	Unequivocal	Moderate		

Schumacher 2019	Varying patterns of pain intensity	Sustained decrease, waxing and waning, spikes, temporary relief, and unchanging	4	Credible	Moderate		
Speck 2012	The most frequent words used to describe the sensations of CIPN were “numbness,” “tingling,” and “painful”	“numbness,” “tingling,” and “painful.”	2435	Unequivocal	Moderate		
Williams 2019 (duplicate)	The most common sensations reported by patients were numbness (23/30; 76.7%), pain (23/30; 76.7%), and tingling	Sometimes it’s like somebody’s taking a hammer and just hitting my feet.	1025	Unequivocal	Moderate		
Hackett 2016	Escalating pain as well as change in type and/or source was perceived as indicative of disease progression, signifying that life was time-limited	Everything I think is connected to my cancer, so when I get pain in an area I think this is it.	715	Unequivocal	Moderate	Meaning of pain	2. Spiritual values and social context shape many participant's experience and expression of
Hellerstadt 2015	There was an insecurity regarding whether the pain had been caused by the treatment or was due to a worsening of the disease	I think it was the feeling that made me frightened, that it might come back, and that ruined a bit of the rest of the time.	36	Unequivocal	Moderate		

Larsen 2007	The experience of the pain is dreadful reminding the patient of the cancer and the uncertainty of the future	“The pain was enormous. I have never had such strong pain before. Here I am now in my wheelchair, and this wasn't what I had had in mind for my life."	14	Credible	Moderate		neuropathic cancer pain.
Hackett 2016	Focus on pain and the possibility and hope of finding a new means of relieving it could also be a distraction from thoughts of death	I’ll be honest … i’ve not told Eliza … she’d get carried away. Since I started on this cancer drug, I’m pretty sure in myself that my back pain has reduced.	716	Unequivocal	Moderate	Other patient priorities, concerns influence experience of pain (e.g., fear of death)	
Padman 2015	Despite some patients having significant neuropathic symptoms, majority felt satisfied with their decision to receive oxaliplatin	I'm alive, I've seen my grandson born, and what's a bit of pain in the feet	865	Unequivocal	Moderate		
Ekstedt 2019	Some patients shared that it was “normal” to have pain when you have cancer and that you just have to be strong and endure the pain. They described that they were ashamed	I feel a bit, like sinful in some way, I mean when I sort of beg for it, then maybe he or she is thinking ‘Oh, that’s the way it is,’ like I’m awfully eager to get myself some drugs.	757	Credible	Low	Patient values impact expression of pain	

	to ask for strong pain medications or tranquilizers. Others expressed guilt						
Haozous 2011	Stoicism was frequently cited as an important cultural value, one which had a deleterious effect on family and tribal connections	When asked to whom participants would disclose their pain or suffering, many responded that they would tell no one or that they would tell only a very close family member, and only if they felt that family member could do something immediate to help them endure the pain. (not a quote)	408	Unequivocal	High		
Juarez 1998	Taught not to complain/stoic	‘‘My mother, even if she felt bad, really bad, she almost never said anything. That’s why sometimes I endure the pain.’’	265	Unequivocal	High		
Bakitas 2007	Global disruptions and interference with activities of daily living; hobbies; and leisure, work, and family roles	‘‘Discomfort is only a 3 or 4, but as far as complicating my everyday activities it’s a 7 or 8	327-8	Unequivocal	Moderate	Social isolation and connection	

Bakitas 2007	Difficulty that participants had expressing how CIPN sensations felt	‘‘funny,’’ ‘‘strange,’’	327	Credible	Moderate		
Gater 2011 (duplicate)	Patients reporting impairments in daily functioning from a physical, emotional and social perspective (includes sleep, physical function, social activities)	‘[Bone pain] prevents me from doing many things that I would do, or would like to do, and normally would do, but I don’t do.’	6	Unequivocal	Moderate		
Haozous 2011	Social isolation was a far more disturbing result of cancer and cancer pain (subtheme of isolating within)	White people, they don’t care. They don’t care if you drive around in a cart. But Indians, they are hesitant to try those. It’s just cultural I guess. We have clans that tease each other. We wouldn’t see me do this. It keeps the people from doing things like that.	407	Unequivocal	High		
Haozous 2011	Participants were wary of others in the tribe learning of the depth of their suffering	‘Here on this reservation you can’t just talk to anybody, because they really like to talk. They backstab you’.	408	Unequivocal	High		

Haozous 2011	Public suffering without appropriate stoicism would reflect poorly on their family or clan	I only do that in the confines of my room because I don't want people to see me doing that because they might think I'm going off my rocker or something	408	Unequivocal	High		
Haozous 2011	Participants would reach out and share their cancer experience with family members as a way of sharing the experience, in order to make connections	I expect him to be more sympathetic	408	Unequivocal	High		
Haozous 2011	Making connections with community and family provided important coping for a population that is economically, socially and physically isolated	I really like the environment when everybody comes as one, and it makes you feel real good.	408	Unequivocal	High		
Haozous 2011	Power of spirituality to bring people together	I believe in God and for some reason he wants me to have this cancer for reason and to get help	408	Credible	High		
Hellerstadt 2015	Socially, women experienced severe limitations in relation to what life had been	I couldn't even walk the dog.	36	Unequivocal	Moderate		

	like before treatment, and they turned down social invitations, gave up activities, and became withdrawn						
Hellerstadt 2015	The pain resulted in their becoming isolated and reclusive; they disconnected from family and friends	I couldn't do anything; I couldn't even talk to people.	36	Unequivocal	Moderate		
Juarez 1998	Taught to follow/believe in God	''My mom always told me, 'One has to be subject to what the Lord says for your life, you have to...whatever it is. If you're suffering, however much you're suffering, the Lord wants it that way.' ''	265	Unequivocal	High		
Juarez 1998	Family very important	My brother is here with me, he came from Mexico just to be with me. If I was alone the world would cave in on me, right now.''	265	Unequivocal	High		
Juarez 1998	Tells significant other (spouse, caregiver)	I tell my husband that I have pain, to bring me water to take my	266	Unequivocal	High		

		pills. He tells me when you have pain tell me don't keep it to yourself					
Juarez 1998	Behavioral expressions	When I have pain I just lock myself up, and I don't say anything. My family knows that when I don't talk, I'm in pain.''	266	Unequivocal	High		
Juarez 1998	Tells God	When I have pain I tell God, the one who is invincible.	266	Unequivocal	High		
Larsen 2007	The coexistence of the need to reveal and conceal the pain experience	I have to be strong in front of my family because I feel like they suffer more than I do. I keep the pain to myself and when they are away, after they have gone, I have to make up for the pain that I've had during their presence.	15	Unequivocal	Moderate		
Bakitas 2007	For the 75% of the sample who had a pain component, functional difficulties, fatigue,	I think the combination of not really being able to function physically in	327	Unequivocal	Moderate	Emotional impact	3. Inadequate information,

	sleep disturbance, and mood effects were common sequelae,	the way I was used to, got to me and affected my mood.					together with functional limitations contribute to psychoexistential distress
Haozous 2011	Social isolation led to other side effects of disease such as depression (subtheme of isolating within)	[I] used to walk to the corral, hook up the truck, and do every day things. Simple tasks. Now just to get up from the bed. ..I guess, what do you call it? Depression? It goes with the pain. I get depressed.	407	Unequivocal	High		
Hellerstadt 2015	Pain-evoked emotions also gave the women power to fight the pain (in women with manageable pain)	I do it anyhow, the pain won't stop me; I get power from going and visiting my workmates.	35	Credible	Moderate		
Tofthagen 2010	They voiced feelings of frustration, depression, and loss of purpose as a result of having to give up enjoyable activities	I just get discouraged and down and…'cause I was always a doer.	E25	Unequivocal	Moderate		
Cormican 2011	Periphearl neuropathy was considered to significantly impact on sensitivity to touch and overall quality of life	It means I can't do the things I normally did properly.	1715	Credible	Moderate	Function and physical capacity	

Gater 2011	Patients reporting impairments in daily functioning from a physical, emotional and social perspective (includes sleep, physical function, social activities)	[Bone pain] prevents me from doing many things that I would do, or would like to do, and normally would do, but I don't do.	6	Unequivocal	Moderate		
Padman 2015	Many patients described ongoing neuropathic symptoms, though the majority did not feel that neuropathy directly affected their daily function	I don't have any trouble with the knitting or writing.	865	Unequivocal	Moderate		
Padman 2015	A minority of interviewees were unable to continue working, though most found they could continue their hobbies	I was a photographer, I've had to give it up.	865	Unequivocal	Moderate		
Speck 2012	The reported impact of CIPN on participants' routine activities, functions, and behaviors varied, as did their approaches and adaptations to deal with the symptoms. Routine activities, functions, and behaviors impacted by CIPN symptoms included sleeping, driving, standing, walking,	I had pain and itchiness and numbness in my hands that was distracting and at meetings I would have to hide my hands under the table if I was going to rub my hands to make them feel better. Um, and for that matter getting dressed for	2437	Unequivocal	Moderate		

	climbing stairs, loss of balance, opening containers, holding onto things, cooking, cleaning, flipping pages of paper, wearing certain shoes and jewellery, exercising, and socializing	work, putting jewelry on was difficult… I had to switch watches because there was one watch that was difficult for me to put on.					
Tofthagen 2010	Patients described a variety of ways in which neuropathic symptoms interfered with manual dexterity, general activities, activities of daily living, driving, writing, picking things up, work, sleep, walking, hobbies, household duties, and exercise	Both the combination neuropathy and the sciatic nerve problem forced me to close my medical practice.	E25	Unequivocal	Moderate		
Williams 2019	The effects of TIPN on normal functioning most often mentioned by patients were difficulty walking (14/30; 46.7%), difficulty using hands or fingers (11/30; 36.7%), problems with balance or falling (10/30; 33.3%), difficulty sleeping (6/30; 20.0%), and difficulty wearing or finding comfortable shoes (7/30; 23.3%)	I couldn't think about walking barefoot on anything…. Any type of carpet, mat, anything of that sort, it was off limits…. My feet were highly sensitive, and it was debilitating because you really didn't feel like walking anywhere.	1025	Unequivocal	Moderate		

Bakitas 2007	Awareness of CIPN was not always accurate, immediate, or straightforward	Just my imagination.	326-7	Unequivocal	Moderate	Inadequate information	
Bennett 2011	Patients did not expect the neuropathy to affect their lives to the extent that it did	Much much worse than she imagined they would be.	2962	Unequivocal	Low		
Cormican 2011	Information provision was of utmost importance to these patients	I went to my own GP and told her [what drugs she was taking] and she was looking at the books and this and that. (Patient speaking about taking a new medication)	1717	Credible	Moderate		
Ekstedt 2019	Because of a lack of basic knowledge about their illness and of how their pain medication worked, patients made their own assumptions about the mechanisms	When I feel better I skip the pills because I don't want to, um, trigger my system.	758	Unequivocal	Low		
Ekstedt 2019	Some patients had difficulties in understanding complicated explanations about pain medications and pain management and how to apply the information in their daily lives	One patient reported that he/she set the alarm clock for 4 AM to exactly follow the advice to take medication at regular intervals, without	757	Credible	Low		

		reflecting that this disturbed his/her night sleep (not a quote)					
Hellerstadt 2015	Never envisaged that the pain would be like this, and not knowing when it would end was described as unbearable	That night I was scared. I didn't really know where it would end. I felt why did this happen now, is this the end?	36	Unequivocal	Moderate		
Hellerstadt 2015	The women retreated, felt that the future was very uncertain, became solely focused on survival, and greatly feared future treatments	I lay in bed, just lay there with my eyes closed and had those kind of dark thoughts. I can't do it again; this is the last time, I won't do it again!	36	Unequivocal	Moderate		
Padman 2015	Of 19 patients, 12 did not recall being warned of CIPN. Some who recalled prior warnings felt the issue was inadequately emphasised	I was informed about it, but maybe it wasn't stressed enough.	865	Unequivocal	Moderate		
Schumacher 2002	Patients had difficulty in seven areas when they attempted to put a pain management regimen into practice, namely: obtaining the	We were a little bit shocked that our doctor hadn't given us that basic information.	374	Unequivocal	Moderate		

	prescribed medication(s), accessing information, tailoring prescribed regimens to meet individual needs, managing side effects, cognitively processing information, managing new or unusual pain, and managing multiple symptoms simultaneously						
Bakitas 2007	Participants used cognitive processes such as minimizing, denying, or ignoring the symptoms... But some participants very consciously anticipated activities that would increase their symptoms and planned ahead	I roll with it, there isn't much you can do.	329	Credible	Moderate	Pain management and medication	4. People who develop a therapeutic patient-provider relationship
Cormican 2011	Self-care strategies to manage peripheral neuropathy and fatigue were shared in the groups, such as the use of heat and topical cream (capsaicin cream), gel soles, acupuncture, reflexology and alternative therapies in local cancer centres	You get several different things there and it's free.	1716	Unequivocal	Moderate		and self efficacy are better equipped to pursue and integrate a range of pain

Ekstedt 2019	Provision of examples of how other patients in the same situation managed to control their pain increased the patient's hope and motivation to follow the nurse's advice	Yeah, I understand, they can't manage it without taking medication	756	Unequivocal	Low		management strategies.
Gater 2011	Pain they experienced was manageable with analgesic medication such as acetaminophen and opioids, but never completely goes away	I control it somewhat with this medication	4	Unequivocal	Moderate		
Hackett 2016	Side effects of rescue morphine, in the context of intermittent pain, had the consequence that use was limited or stopped.	O I thought well if I can stop taking that and it cures the nightmares, I would rather have the pain.	716	Unequivocal	Moderate		
Haozous 2011	Relying on prayer and traditional medicine	I pray a lot. There's traditional medicine, I believe in it, too.	408	Unequivocal	High		
Juarez 1998	Family medicine woman	My grandmother was one of those old medicine women. Everybody went to her so she would tell them what remedy to take.	265	Unequivocal	High		

Juarez 1998	Folk Healers	My family wants me to go back to my country to consult a folk healer.	265	Unequivocal	High		
Juarez 1998	Beliefs about medications	My feeling has always been, that you start taking stuff (medications)after a while it becomes normal to you, and you continue doing it every time something happens. So I just try to heal through my own body.	265	Unequivocal	High		
Juarez 1998	Advice from family/neighbors	My neighbor told me, “Take this herb, brew it and you’ll see how well you’ll get.”	265	Unequivocal	High		
Juarez 1998	Advice from pharmacist	My husband went to the pharmacy in Tijuana to ask for medicine and the pharmacist recommended cat’s claw and now I’m taking it.	265	Unequivocal	High		

Juarez 1998	Non-drug interventions	My husband gives me a massage with snake oil, when my legs hurt and the pain goes away.	267	Unequivocal	High		
Juarez 1998	Taking pain medications	Now I realized that whether I like it or not, I have to take at least my pain medications because there is no way I can go around with that much pain day and night. You have to accept the reality.	266	Unequivocal	High		
Juarez 1998	Fear of addiction	I told him [doctor], 'No I just don't want to get like that, like on drugs, I don't want to.	266	Unequivocal	High		
Juarez 1998	Medication side effects	I try not to take the morphine because it upsets my stomach a lot.	266	Unequivocal	High		
Juarez 1998	Medication from Mexico	My son-in-law brought me this cream (bee cream) from Guadalajara, it's very good for the pain.	266	Unequivocal	High		

Cormican 2011	Continuity of care was paramount	And you go see the doctor and you may be seeing the six months man [doctor on rotation] you may as well be seeing your Granny and she's dead this 50 years ...	1717	Unequivocal	Moderate	Patient doctor relationship	
Cormican 2011	Information was collected and stored with little action taken in regard to the management of the actual problem	I don't think that, they [doctors] don't want to know about side effects much. That they never, they asked me once or twice about my feet like. But they offered me nothing.	1717	Unequivocal	Moderate		
Ekstedt 2019	When information from different sources was consistent, patients had the confidence to trust the advice	I've figured out that no matter which doctor it is… and now I've been at three hospitals … it's exactly the same.	756	Unequivocal	Low		
Juarez 1998	Follows doctor's orders	I always take whatever dose is prescribed. That's what I take.	266	Unequivocal	High		

Ekstedt 2019	Diary complemented the coaching sessions by reminding the patients to maintain a regular schedule; it helped them to become aware of early signs and of the resources needed to efficiently manage their pain	I think it's been really useful because it forced me to sit down and think a bit about how I had been feeling. And then I know why I've gone from a 10 to a 3.	756	Unequivocal	Low	Self-efficacy	
Ekstedt 2019	Knowledge of how their body worked and awareness of their own weaknesses and strengths facilitated the patient's learning how to manage their pain	It’s pretty intense when it comes along, but then it’s gone again in a tenth of a second. I learned to sort of just sit still for the short time it lasted	757	Unequivocal	Low		
Ekstedt 2019	Knowledgeable patients who took an active part in their own care had good control over their pain and knew what to do if they needed help	I ask questions, and then I get answers.	757	Credible	Low		
Juarez 1998	Pain Scales	When I have pain I tell the nurse by number.	266	Unequivocal	High		
Speck 2012	Categories of self-management strategies include the use of movement to reduce	I think what worked for me was really trying to listen to what I	2436	Unequivocal	Moderate		

	symptoms, attitude, and body awareness, logistics to simplify demands, and environmental change. Additionally, women reported using over the counter (e.g., ibuprofen) or prescription medications	thought my body was telling me it needed.					
Bakitas 2007	Minimize or use an apologetic tone as they described their symptoms as though they did not want to sound as if they were complaining		327	Unsupported	Moderate		Unsupported
Cormican 2011	Many were hopeful that their experience of peripheral neuropathy would improve over time			Unsupported	Moderate		
Cormican 2011	Carers, in particular, reported discrepancies in the information their relative received from different healthcare professionals.	Only supported by carer quotes.	1717	Unsupported	Moderate		
Ekstedt 2019	Fears of death, the loss of control, and becoming dependent on drugs occupied	I thought that if you started taking analgesics, your body would	758	Unsupported	Low		

	many patients' thoughts and controlled their actions	eventually sort of get so used to them that you would always have to.					
Gater 2011	A constellation of symptoms of which bone pain, fatigue and low energy were predominant			Unsupported	Moderate		
Gater 2011	End-of-dose failure, defined as pain that occurs at the end of the timeframe in which pain medication is intended to be effective, was commonly experienced by patients			Unsupported	Moderate		
Hackett 2016	Severe, persistent pain adversely affected mood and inability to secure relief exacerbated sense of loss of control			Unsupported	Moderate		
Hackett 2016	Sense of helplessness at their inability to relieve pain			Unsupported	Moderate		
Hackett 2016	Being unable to do 'normal' things affected wellbeing			Unsupported	Moderate		

Hackett 2016	Sensory experience contributed to low mood as did inability to do things they enjoyed, exacerbating powerlessness and despair			Unsupported	Moderate		
Haozous 2011	Physical distress from pain was distressing (subtheme of Isolating within)		407	Unsupported	High		
Haozous 2011	Pain had the obvious result of causing participants to limit activities (subtheme of isolating within)		407	Unsupported	High		
Haozous 2011	Mobility became an important contributor to social isolation (subtheme of isolating within)		407	Unsupported	High		
Juarez 1998	Forgets to take pain medications	If I'm asleep, my daughter does not wake me up to take the pills.	266	Unsupported	High		

Green = treatment-related pain, purple = mixed neuropathic and nociceptive pain, blue = bone pain

Subgroup analysis

Studies were divided into three groups post hoc based on pain characteristics and colour coded in Table 4-7. Those with treatment-related pain such as CIPN were coded green, those where the studies included neuropathic and nociceptive pain were coded purple, and those with bone pain, which has mixed neuropathic and nociceptive mechanisms were coded blue. No differences were found in the synthesised findings for each subgroup analysis, and participants from each group contributed to all findings (see Table 4-7).

ConQual findings

The ConQual summary of findings is presented in Table 4-8.

Synthesised Finding 1 was synthesised from 22 findings from 13 studies of low (n=2), moderate (n=9) and high (n=2) dependability. Dependability was downgraded one level due to most findings (73%) having moderate dependability. There was a mixture of low (n=2), moderate (n=16) and high (n=4) dependability among the study findings. Credibility was downgraded one level due a mixture of credible (n=2; 9%) and unequivocal (n=20; 91%) study findings. The final ConQual score was downgraded two levels for dependability (n=1) and credibility (n=1) from high to low.

Synthesised Finding 2 was synthesised from 25 findings from nine studies of low (n=1), moderate (n=6) and high (n=2) dependability. Dependability was unchanged due to a most findings (52%) having high dependability. There was a mixture of low (n=1), moderate (n=11) and high (n=13) dependability among the study findings. Credibility was downgraded one level due a mixture of credible (n=4; 16%) and unequivocal (n=21; 84%) study findings. The final ConQual score was downgraded one level for credibility (n=1) from high to moderate.

Table 4-8: ConQual summary of findings

Title: Experience of neuropathic cancer pain: a qualitative systematic review **Population:** Adults with cancer and neuropathic pain related to the cancer or its treatment **Phenomenon of interest:** People's experience of neuropathic pain due to cancer or its treatment **Context:** Any setting, including inpatient, outpatient, community, oncology and palliative care.				
Synthesised finding	**Type of research**	**Dependability**	**Credibility**	**ConQual score**
Neuropathic cancer pain is multifaceted and must be considered in context of the whole person	Qual	Moderate (downgraded 1 level)	Moderate (downgraded 1 level)	Low (downgraded 2 levels for dependability and credibility)
Spiritual values and social context shape many people's experiences of neuropathic cancer pain	Qual	High (Unchanged)	Moderate (downgraded 1 level)	Moderate (downgraded 1 level for credibility)
Inadequate information, together with functional limitations contribute to psychoexistential distress	Qual	Moderate (downgraded 1 level)	Moderate (downgraded 1 level)	Low (downgraded 2 levels for dependability and credibility)
People who develop a therapeutic patient-provider relationship and self-efficacy are better equipped to pursue and integrate a range of pain management strategies	Qual	High (Unchanged)	Moderate (downgraded 1 level)	Moderate (downgraded 1 level for credibility)

Synthesised Finding 3 was synthesised from 20 findings from 12 studies of low (n=2), moderate (n=9) and high (n=1) dependability. Dependability was downgraded one level due to most findings (80%) having moderate dependability. There was a mixture of low (n=3), moderate (n=16) and high (n=1) dependability among the study findings. Credibility was downgraded one level due to a mixture of credible (n=4; 20%) and unequivocal (n=16; 80%) study findings. The final ConQual score was downgraded two levels for dependability (n=1) and credibility (n=1) from high to low.

Synthesised Finding 4 was synthesised from 25 findings from 8 studies of low (n=1), moderate (n=5) and high (n=2) dependability. Dependability was unchanged due to most findings (52%) having high dependability. There was a mixture of low (n=5), moderate (n=7) and high (n=13; 68%) dependability among the study findings. Credibility was downgraded one level due a mixture of credible (n=2; 8%) and unequivocal (n=23; 92%) study findings. The final ConQual score was downgraded one level for credibility (n=1) from high to moderate.

4.2.5 Discussion

Lived experience demonstrates that people with neuropathic cancer pain may experience inadequate pain control due to the complexity of the experience, which must be understood within the broader context of the whole person, including their spiritual and social values. Inadequate information and functional limitations may contribute to psycho-existential distress, affecting the person's pain experience. Protective factors may include a strong patient–provider relationship and developed self-efficacy.

Neuropathic cancer pain degrades patient wellbeing severely, causing worse physical, cognitive and social function than nociceptive pain (based on quantitative patient reported outcome measures).[6] This is the first known study to synthesise qualitative data describing the experience of neuropathic cancer pain; it reinforces the impact of multiple domains on a person's pain experience.

Social and spiritual connection is of utmost importance to palliative care patients from a variety of cultures.[128] This study shows that neuropathic cancer pain can both enhance and hinder that social connection. Social isolation is negatively associated with pain

interference[129] and is an important modifiable factor.[130, 131] In the included studies, spirituality is intertwined with the pain experience, supporting previous findings that higher levels of spiritual wellbeing are associated with lower intensity of neuropathic cancer pain.[132] Despite spirituality being understood as a core component of palliative care, research on the impact of spiritual interventions on cancer pain is scarce,[133] but some studies have shown they have the potential to improve cancer pain.[133] The relationship between spirituality and neuropathic cancer pain is an important target for further research.

Psychological distress has been shown to interact with pain perception in adults.[134, 135] The included studies showed that uncertainty about pain trajectory and management caused by lack of information contributed to distress and reduced patients' ability to manage their pain. This is consistent with existing evidence showing general uncertainty in cancer is associated with worse psychological health.[136] Functional impairment was common and associated with distress, loss, social isolation and poor quality of life; this phenomenon has been widely reported in neuropathic cancer pain literature.[7] Interventions to meet information needs and improve functional capability may improve the pain experience.

This qualitative study supports the quantitative evidence showing that the quality of the patient–provider relationship, characterised by empathy and trust, is critical in facilitating effective pain management and improving patient satisfaction.[137] Higher self-efficacy is associated with better pain outcomes and lower levels of pain-related distress.[138] These domains should be explored more thoroughly to find ways to improve outcomes for people with neuropathic cancer pain.

Strengths and limitations

This is the first known systematic review of the experience of people with neuropathic cancer pain. Its findings are directly and immediately relevant to policy and practice, demonstrating the need to incorporate the whole person into the management of neuropathic cancer pain. Its transparent reporting enables readers to draw additional conclusions as required to fit their individual situations.

A major limiting factor of this review was the paucity of studies explicitly describing the experience of purely neuropathic pain caused by cancer; instead, the studies were directed at CIPN, bone pain and mixed pain. This likely relates to the fact that people with cancer often have more than one form of pain.[139] Included studies of mixed pain did not define the number of people with neuropathic pain, therefore while these studies included people with neuropathic pain, some of the experiences contributing to the findings may have been from people without neuropathic pain. Although sensitivity analysis showed the same themes were relevant when studies involving each subgroup were excluded, further research specifically focussing on the experience of neuropathic pain due to cancer itself would add to our understanding of neuropathic cancer pain. Development of internationally accepted consensus criteria for inclusion of people with neuropathic cancer pain in research and clinical trials would aid the ability to compare results and apply results to clinical decision making.

The dependability and credibility of the findings was limited by the reporting of the contributing studies. In particular, many reports lacked statements describing the researcher and how reflexivity was addressed. This limitation is common in qualitative research[140] and could be improved through increased adherence to reporting guidelines.

Recommendations for practice, policy and research

The synthesised findings from this review lead to recommendations for practice, policy and research. They are categorised as grade B (weak recommendation, JBI grading)[104] because the underlying data is of low to moderate quality and further research on neuropathic cancer pain is needed.

Impeccable history taking may assist clinicians to identify neuropathic cancer pain and implement targeted management strategies. Clinicians should recognise that a person's spiritual and social context may shape their experience and expression of neuropathic cancer pain. Clinicians should consider how to meet the information needs of people with cancer who have or at risk of developing neuropathic pain. Multidisciplinary teams should be involved in care of people with neuropathic cancer pain in order to reduce functional limitations and psycho-existential and spiritual distress. Clinicians should

consider how to harness the patient–provider relationship to increase the impact of management strategies for people with neuropathic cancer pain.

Qualitative research on the experience of people with pure neuropathic pain directly caused by the tumour should be undertaken to determine whether the findings presented herein also apply to this group, who are underrepresented in this review. Interventions that strengthen self-efficacy could be developed and tested to identify ways to improve outcomes for people with neuropathic cancer pain. Research is needed to determine whether interventions deigned to improve the pain experience can reduce the number of people who have unrelieved neuropathic cancer pain.

4.2.6 Conclusion

This systematic review of qualitative data sought to produce a better understanding of why some people have unrelieved neuropathic cancer pain. Neuropathic cancer pain is multifaceted and must be considered in the context of the whole person. It varies in quality and intensity and often occurs alongside other pains, symptoms and/or comorbidities. Spiritual values and social context significantly shape the pain experience. Inadequate information and functional limitations contribute to psycho-existential distress. Developing a therapeutic patient–provider relationship and self-efficacy may equip individuals to pursue and integrate a range of pain management strategies. The full experience of neuropathic cancer pain must inform the design and implementation of effective pain management strategies at an individual and societal level.

4.3 Chapter summary

The qualitative systematic review presented in this chapter synthesised findings derived from the experiences of people with cancer and neuropathic pain. Its results highlight the complexity of neuropathic cancer pain and identify some personal domains that affect the experience of pain.

Chapter 5 reports a mid-point meta-inference of data from Study 1 and Study 2. It was designed to identify the prevalence and experience of unrelieved neuropathic pain for people living with cancer, and identify evidence gaps and inform the need for and design of the research in Phase II of the INCEPT Project.

Chapter 5 Mid-point meta-inference

5.1 Chapter preface

Chapters 1 and 2 introduced the INCEPT Project and described its mixed methods design. Chapter 3 presented Study 1, a cohort study that found that moderate or severe distress from pain occurred in 31% of people living with advanced cancer at least once during the last week of life, and described the characteristics of this population. These findings were expanded upon during Study 2, a systematic review of the experience of people with neuropathic cancer pain, as detailed in Chapter 4.

This chapter presents the mid-point meta-inference, which integrates the data from Studies 1 and 2 to inform the need for and design of Phase II of the research.

5.2 Objective

To understand the prevalence and experience of unrelieved neuropathic pain for people living with cancer and identify potential evidence gaps to be addressed.

5.3 Methods

A mid-point meta-inference was undertaken to improve our understanding of the experiences of living with advanced cancer and unrelieved neuropathic pain.

As detailed in Chapter 2, the mid-point meta-inference involved the integration of the quantitative epidemiological analysis of people with cancer who were known to a specialist palliative care service and had moderate or severe pain in the last week of life (Study 1) and the qualitative systematic review that sought to explain these results by examining the experience of people with neuropathic cancer pain (Study 2). Study 1's quantitative findings, along with the narrative synthesis of Study 2, were entered into a joint display table (Table 5-1) to enable visual linkage of data related to the same constructs, facilitate a deeper understanding of the patient experience and identify gaps in evidence about cancer-related neuropathic pain.

Table 5-1: Mid-study meta-inference joint display table

Domain	**QUAN – Study 1**	**QUAL – Study 2**	**Fit of data**	**Meta-inference**
Prevalence	Almost a third (31%, n=71,750) of Australians with cancer who received specialist palliative care experienced moderate or severe distress from pain at least once during the last week of life.	Evidence from people living with unrelieved neuropathic cancer pain (n=18 studies) in high-income countries (including Australia, Europe, UK and USA) suggests that neuropathic pain is multifaceted and must be considered in the context of the whole person. It may have different qualities and intensities and may occur concurrently with other pains, associated symptoms or other comorbidities.	Concordant	Distress from unrelieved neuropathic cancer pain is commonly experienced by palliative care patients living with cancer. While pain is present in some people of all cultural and socioeconomic backgrounds and all tumour types during the last week of life, its prevalence varies. Tumour characteristics, and spiritual and social context may explain some of this variation. Future research on the experience of neuropathic cancer pain must reflect the diversity of demographic and tumour factors of people with pain at the end of life.
	People from non-English-speaking backgrounds and those born outside of Australia were less likely to report distress when experiencing moderate or severe cancer-related pain.	Spiritual values and social context shape many people's experience and expression of neuropathic cancer pain.	Expansion	

	All socioeconomic groups reported pain in the last week of life.			
	Moderate or severe distress from pain in the last week of life was most prevalent in people with primary cancer of the bone or soft tissue (36.6%), and prostate (33.9%) cancer.	Unrelieved neuropathic cancer pain was reported by people with mixed tumour types, including colorectal, breast or myeloma.	Discordant	
Experience	Pain-related distress scores reduced closer to death, as the person's performance status deteriorated, and correlated with fatigue, bowel and sleep distress.	For people living with cancer-related neuropathic pain, a combination of functional limitations and sub-optimal information contributed to their psycho-existential distress of living with unrelieved neuropathic pain. Those who had established therapeutic patient–provider relationship and good self-efficacy were better equipped to pursue and integrate a range of neuropathic cancer pain self-management strategies.	-Expansion	Unrelieved neuropathic pain is a complex experience with significant impact on the lives of people living with cancer. The experience is influenced by many factors, including the nature of the pain, spiritual and social context, information provision, functional impact, the patient–provider relationship, and self-efficacy. While some factors are intrinsic and some are modifiable, more research is required to leverage these opportunities to improve neuropathic cancer pain management.

Findings from the integration of these distinct data sources included the prevalence and experience of people living with unrelieved neuropathic cancer pain, as described below.

Finding 1.

Distress from unrelieved neuropathic cancer pain is commonly experienced by palliative care patients living with cancer. While pain is present in some people of all cultural and socioeconomic backgrounds and all tumour types during the last week of life, its prevalence varies. Tumour characteristics, and spiritual and social context may explain some of this variation. Future research on the experience of neuropathic cancer pain must reflect the diversity of demographic and tumour factors of people with pain at the end of life.

Given that 31% of Australians cared for by a specialist palliative care service reported experiencing unrelieved cancer pain at least once during the last week of life (Study 1), opportunities to improve outcomes for this population exist. However, the type of unrelieved cancer pain experienced by Australians with palliative care needs is unknown. A better understanding of the nature of unrelieved cancer pain that this cohort experiences is critical to closing this clinical gap. Unrelieved neuropathic cancer pain for people with palliative care needs is a global problem (Study 2). People living with unrelieved cancer pain experience multiple kinds of pain, differing in aetiology, intensity and quality, so considering the multifaceted nature of their pain within a whole-person approach is key to improving their pain outcomes (Study 2).

While all socioeconomic groups with cancer experienced distress from pain in the last week of life, understanding why people from a non-English-speaking background or those born outside of Australia reported less distress from moderate or severe pain (Study 1) will facilitate equitable care.[91] Cultural differences in the experience and expression of pain that influence the reporting of pain distress could account for these differences, because spiritual values and social context shape many people's experience and expression of neuropathic cancer pain (Study 2).

Pain in the last week of life was most prevalent in people with primary cancer of the bone or soft tissue (36.6%) and prostate (33.9%) cancer (Study 1). These findings are discordant with the available data on the experience of neuropathic cancer pain in people with mixed, colorectal, breast and myeloma cancer (Study 2). Further research on the experience of neuropathic cancer pain should account for the varied socio-demographics of people with pain at the end of life.

Finding 2.

Unrelieved neuropathic pain is a complex experience with significant impact on the lives of people living with cancer. The experience is influenced by many factors, including the nature of the pain, spiritual and social context, information provision, functional impact, the patient–provider relationship, and self-efficacy. While some factors are intrinsic and some are modifiable, more research is required to leverage these opportunities to improve neuropathic cancer pain management.

Understanding the experience of people living with neuropathic cancer pain (Study 2), and the factors contributing to the being unrelieved, in part explains why nearly a third of people with cancer have unrelieved pain in the last week of life (Study 1). Neuropathic cancer pain is multifaceted, so considering it in the context of the whole person and how their spiritual values and social context may shape their experiences and expression of it is essential in designing feasible management strategies. Improving information provision and overcoming functional limitations can reduce psycho-existential distress, while a therapeutic patient–provider relationship and greater self-efficacy can equip people to pursue and integrate a range of pain management strategies.

Study 2 provided insight into the factors influencing the impact of neuropathic cancer pain. The information needs identified were varied and included information about medication, pain management, cancer pathophysiology, and expectations of pain and its trajectory. These insights are potentially modifiable targets for reducing the impact and prevalence of unrelieved neuropathic cancer pain.

The mid-point meta-inference expanded on Study 1 findings about the experience of cancer pain, including that pain-associated distress scores fall as death approaches and performance status deteriorates, and that pain distress correlates with fatigue, bowel and sleep distress. The complexity of pain suggests that many factors affect the individual experience. A patient-centred care framework can be used to organise and conceptualise the domains that clinicians must harness to improve outcomes for people with neuropathic cancer pain.

5.4 Discussion

These meta-inferences describe the prevalence of neuropathic cancer pain and the factors contributing to the experience of it. This meta-inference demonstrates how characterising people who have neuropathic cancer pain and understanding their experience can help clinicians provide patient-centred care, policymakers ensure sufficient and appropriate resources are available, and researchers identify opportunities to improve outcomes for people with neuropathic cancer pain.

The biopsychosocial perspective, a central dimension of patient-centred care,[50] takes into consideration the nature of the pain, psycho-existential distress and the spiritual and social context. The therapeutic alliance is highlighted in these findings in relation to the importance of the patient–provider relationship. Information provision and self-efficacy supports the sharing of power and responsibility.

These findings are similar to those from research involving people with non-neuropathic cancer pain living in regional Australia.[141] Although different domains of patient-centred care are highlighted in the current study, the findings are consistent with previous literature, which shows neuropathic cancer pain is common and has high impact.[6, 33, 34] Details about prevalence in cultural and socioeconomic groups have previously been reported only from small cohorts.[40, 41] Previous studies have not undertaken meta-inference of the quantitative (prevalence) and qualitative (experience) data about living with neuropathic cancer pain, which is why these findings represent valuable insights into the reasons for unrelieved cancer pain at the end of life.

5.5 Conclusion

Unrelieved neuropathic pain is common in people with cancer and has a severe impact on quality of life. Pain is present in all cultural, socioeconomic and tumour groups, but its prevalence varies. The experience of neuropathic cancer pain is complex and can influence the nature and delivery of patient-centred care. Key factors contributing to this influence include the type of pain, spiritual and social context, information provision, functional impact, patient–provider relationship and self-efficacy. Some factors are intrinsic and some are modifiable.

These findings highlight the urgent need to find strategies that reduce the prevalence and severity of unrelieved neuropathic cancer pain. It is important to understand why clinical trials to date have not found ways to eliminate neuropathic cancer pain. These findings identify that researchers seeking to develop and evaluate new interventions must consider the complexity of neuropathic cancer pain and the factors that may contribute to the person's experience.

5.6 Chapter summary

Collectively, the data presented in this chapter describe the characteristics of a representative population of Australians with unrelieved neuropathic cancer pain cared for by inpatient and community specialist palliative care services. The chapter describes how this Australian cohort is placed within the international context of the experience of people with unrelieved cancer pain in a range of settings. It confirms that more research is needed to improve management of unrelieved neuropathic cancer pain for this group of people.

Chapter 6 reports the systematic and narrative literature reviews undertaken to select, design and test a promising intervention for unrelieved neuropathic cancer pain.

Chapter 6 Choosing a candidate intervention

6.1 Chapter preface

Previous chapters described the prevalence and experience of people living with unrelieved neuropathic cancer pain. The mid-point meta-inference identified a need to find strategies that reduce the prevalence and severity of unrelieved neuropathic cancer pain and improve outcomes.

This chapter includes a review of candidate pharmacological interventions that could improve outcomes for people with unrelieved neuropathic cancer pain (Section 6.2). This is followed by a description of the characteristics of lidocaine (Section 6.3), a sodium channel blocker commonly used for cancer pain relief. A systematic review[142] published in 2019 in *Journal of Palliative Medicine,* a peer-reviewed scholarly journal with an impact factor of 2.2,[143] is presented in Section 6.4. This systematic review searched for articles on all forms of sodium channel blockers for cancer pain, but only trials of lidocaine were identified. The format and wording of the published article were changed to conform to thesis guidelines. Sections 6.5 to 6.7 describes additional literature which informs the design of the LiCPain trial.

Note that lidocaine is also known as lignocaine. Consistent with the international nonproprietary name,[144] "lidocaine" is used throughout this thesis.

Lee JT, Sanderson CR, Xuan W, et al. Lidocaine for cancer pain in adults: A systematic review and meta-analysis. *Journal of Palliative Medicine* 2019;22:326-334. DOI: 10.1089/jpm.2018.0257.

(citations: 46 (Journal of Palliative Medicine); Altimetric: 17)

6.2 Pharmacological management of neuropathic cancer pain

Several widely accepted interventions for managing neuropathic cancer pain exist. Some of these have been evaluated, and some researchers have inferred their benefit from other populations and via mechanistic reasoning.

The Australian Cancer Pain Management in Adults Clinical Guidelines[145] identify that management of cancer pain should encompass communication, pharmacological, non-pharmacological, anti-cancer therapy and interventional management. This candidate chose to focus on pharmacological interventions, while acknowledging that all intervention types are important and require further research.

Guidelines for cancer pain[29, 45, 145] state that antidepressants (serotonin norepinephrine reuptake inhibitors and tricyclic antidepressants) and anticonvulsants (gabapentinoids) should be used as adjuvant analgesics in combination with opioids to treat neuropathic components of pain. Paracetamol (acetaminophen) and NSAIDs are also recommended, despite no high-quality evidence to support or refute their use,[45, 145] as well as corticosteroids[29, 45] and topical agents[29] (lidocaine and NSAIDs). Bisphosphonates or denosumab may be used for bone pain.[29] Anti-cancer agents may be used in certain situations.[29] Opioids are recommended for neuropathic cancer pain, but with increasing awareness of the potential harms of opioids in an era when some people with cancer are living many years, alternatives are required.[44]

The mid-point meta-inference found that a proportion of people experience distress from cancer pain in the last week of life, despite being managed by a specialist palliative care service. It is expected that specialist palliative care clinicians would have high awareness of cancer pain guidelines,[146] although barriers to their implementation exist.[147] However, pain guidelines[29, 45, 145, 148] exhibit little consensus about management of people with persistent neuropathic cancer pain, despite the recommended agents. Therapies reported as having potential in certain situations include opioid manipulation (parenteral delivery, rotation, combination, methadone and buprenorphine), NMDA receptor antagonists (ketamine), cannabinoids and lidocaine.[46-48] The evidence, current use and clinical guidelines for each of these management strategies was evaluated and is summarised here.

Two phase III RCTs have demonstrated that ketamine is equivalent to placebo in neuropathic cancer pain[149] and cancer pain[150] respectively. Pain type (neuropathic or nociceptive) was not found to be a predictor of response.[150] While systematic reviews of ketamine for cancer pain reach conflicting conclusions,[151, 152] existing evidence

suggests another RCT of ketamine for unrelieved neuropathic cancer pain is a lower priority than an RCT of lidocaine.

Guidelines recommend against the use of cannabinoids as an adjuvant analgesic for cancer pain.[153] A 2023 Cochrane review concludes there is moderate-certainty evidence that oromucosal nabiximols and tetrahydrocannabinol (THC) are ineffective in relieving moderate-to-severe opioid-refractory cancer pain.[154] Of the included studies, only one evaluated CIPN, and found no statistically significant difference between nabiximols and placebo, although a responder analysis demonstrated five of 16 participants reported a two-point or greater reduction in pain.[155] Few articles[156-158] report the percentage of participants with neuropathic pain, and those that do reported 10–22% with neuropathic pain; no studies conducted subgroup analysis for neuropathic pain.

Little high-quality evidence is available about lidocaine, yet it is used in clinical practice internationally.[159-162] The National Comprehensive Cancer Network guidelines suggest that lidocaine infusion is useful for opioid-refractory cancer pain or cancer related neuropathic pain,[29] however the European Society for Medical Oncology and Australian Cancer Pain Management in Adults guidelines make no mention of lidocaine infusion.[45, 145] In the current research, lidocaine was chosen as a pharmacological agent worthy of further exploration, for reasons detailed in the following section.

6.3 Characteristics of lidocaine

Lidocaine is thought to reduce pain by blocking tetrodoxin-resistant sodium channels, which control the propagation of nerve impulses in both neuropathic and nociceptive pain.[163] Additional proposed mechanisms include a reduction in sprouting of noradrenergic sympathetic fibres in dorsal root ganglia after injury,[164] reducing inflammation[165] and inhibiting protein kinase C, which blocks NMDA receptors.[166] These mechanisms may account for lidocaine's prolonged effect beyond the immediate duration of infusion. Its metabolites are thought to block the glycine transporter 1, increasing concentrations of glycine, the major inhibitory neurotransmitter.[167]

Lidocaine is eliminated primarily by hepatic metabolism, which appears to be limited by liver perfusion.[168] Hepatic failure and cardiac failure reduce lidocaine clearance.

Clearance of the active metabolite glycinexylidide is affected by renal function.[169] Steady state is achieved after 3–4 hours of continuous infusion.[168] The half-life after intravenous bolus is 1.5 to 2 hours, longer in the elderly (up to 2.5 hours), in hepatic and cardiac failure.[170]

Lidocaine may provide analgesic benefit with fewer neurocognitive side effects than alternatives in the palliative care setting. Its mechanism of action is biologically plausible and targets pathways that have not been investigated previously in this patient population. It is also likely to be cost effective because it is relatively inexpensive, and better cancer pain management will reduce health system costs. Subcutaneous lidocaine also offers a therapeutic option for cancer patients who are unable to swallow or cannot tolerate side effects or other anti-neuropathic medications – a group with few adjuvant analgesic options.

Data supports lidocaine as a promising safe agent in neuropathic cancer pain, warranting study in robust RCTs. Observational studies[160, 161] have found over 80% response to continuous lidocaine infusion in cancer pain without significant adverse effects.

6.4 Lidocaine for cancer pain in adults: a systematic review and meta-analysis

6.4.1 Background

Internationally, use of lidocaine infusions to treat cancer pain differs by centre.[159, 162] There is wide variation in recommendation for use. European Society of Medical Oncology clinical practice guidelines[171] and UpToDate,[172] a clinical decision support resource[173] identify a role for systemic lidocaine to treat cancer pain in selected patients. National Comprehensive Cancer Network and Australian Cancer Pain guidelines recommend against use or make no mention.[174, 175]

Existing systematic reviews do not adequately inform use of lidocaine or other sodium channel blockers in cancer pain. Reviews published in 2005 and 1998 on systemic local anaesthetic agents in neuropathic and chronic pain respectively[176, 177] concluded there

was little or no evidence in cancer pain. Since then, a large positive pilot study[178] of 50 participants has been published. Review of lidocaine in older adults[179] suggested possible benefit for lidocaine infusion, but excluded the three studies contributing to the recommendations in neuropathic and chronic pain.[176, 177] This systematic review provides an updated summary and analysis of the literature informing use of lidocaine infusions to treat cancer pain.

Improving evidence-based practice in cancer pain is crucial. More than fourteen million people develop cancer worldwide each year, with at least two thirds of those who have advanced cancer experiencing pain.[21, 22, 180] Despite significant advances, cancer pain remains poorly controlled. The European Pain in Cancer Survey found 58% of patients receiving prescription medicine reported inadequate pain relief at least several times a week.[9] A high proportion of patients are not responsive to opioids and require adjuvant analgesics.[181] It is also becoming increasingly recognised that opioid use has limitations particularly as cancer pain becomes more prevalent and more chronic.[182] The most common adjuvant therapies are anticonvulsants and antidepressants, however the evidence for their efficacy in cancer pain is variable and in many patients not tolerated due to toxicity.[183]

Lidocaine is a unique agent which has demonstrated level I benefit in non-malignant pain.[176, 177] It offers a different toxicity profile to that of opioid analgesics and other adjuvant therapies, is one of few adjuvant analgesics which can be given parenterally, and is thought to act via different mechanisms to other analgesics, all features which are desirable in some clinical situations.

6.4.2 Objective

The objective was to assess the effects of systemic sodium channel blockers on cancer pain in adults, review the dose protocols for administration and assess toxicity.

This review included lidocaine, mexiletine, tocainide and flecainide, however only studies on lidocaine met inclusion criteria.

6.4.3 Design

Protocol

This report was completed according to PRISMA guidelines. The full protocol is available from trial registry PROSPERO.[184]

Eligibility criteria

Randomised controlled studies including crossover studies were included for narrative review and meta-analysis. Observational studies, case reports and case series were excluded. Eligible studies included participants older than eighteen years with a portion of participants having pain from cancer. Studies investigating perioperative and periprocedural pain were excluded where lidocaine infusion was given only during or immediately after the procedure. Studies considered one or more of lidocaine via intravenous or subcutaneous route, or mexiletine, flecainide or tocainide via oral route; delivered at a site distant to the pain locus. All comparators including placebo and active control were considered. Studies considering regional nerve blockade, topical, tumescent, epidural and intrathecal administration of lidocaine were excluded. Outcome measures were chosen to reflect guidelines from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials on reporting chronic pain trials, which recommend a range of standardised outcomes be included.[185] No similar guidelines exist for cancer pain. The primary outcome measure was substantial benefit (defined as at least 50% pain reduction). Secondary outcomes were moderate benefit (at least 30% pain reduction),[185] mild pain post infusion (less than 30/100mm on VAS),[186] mean change in pain score, patient global impression, quality of life, adverse event withdrawal and serious adverse events.

Information sources and search strategy

Four electronic databases were searched: The Cochrane Central Register of Controlled Trials (on 5th September 2016), MEDLINE (1946 to 5th September 2016), EMBASE (1974 to 2nd September 2016), LILACS (1982 to 5th September 2016). Grey literature was searched through CARESEARCH and OpenGrey on 5th September 2016. EAPC congress abstracts from 1990 to 2016 were handsearched. The reference lists of all

eligible trials, key textbooks, and previous systematic reviews were searched for additional studies. The lead authors of all included trials were contacted for further information and any unpublished studies. The Australian manufacturer of each intervention was contacted for any unpublished trials. The MEDLINE search strategy is outlined in Table 6-1 and the authors can be contacted for the full search strategy.

Table 6-1: MEDLINE search strategy

1	(lignocaine or lidocaine).mp. or exp lidocaine/
2	(systemic* or intravenous* or subcutaneous*).mp.
3	1 and 2
4	mexiletine.mp. or exp Mexiletine/ or flecainide.mp. or exp Flecainide/ or tocainide.mp. or exp Tocainide/
5	3 or 4
6	palliative.mp. or exp Palliative Care/ or hospice.mp. or exp Hospices/ or terminal care.mp. or exp Terminal Care/ or terminally ill.mp. or exp Terminally Ill/ or cancer.mp. or neoplasm.mp. or exp Neoplasms/ or (tumour or tumor).mp. or oncol*.mp. or exp Medical Oncology/ or exp Radiation Oncology/ or malignan*.mp.
7	pain.mp. or exp Pain/ or neuropathic pain.mp. or neuralgia.mp. or exp Neuralgia/ or cancer pain.mp.
8	5 and 6 and 7

Data extraction

One author (JL) ran the electronic database and other searches and excluded duplicates. Two authors (JL, MA or CS) screened results and read the full manuscript of potentially eligible studies to assess for inclusion. Two authors (JL, MA or CS) independently assessed study quality and extracted data using a standard form. Missing data was sought from the lead author. Studies which were not published in English were evaluated through contacting the lead author or translation of the methods and results

sections. Disagreements were resolved by discussion and consultation with a third author.

Data items

The data items about the study collected were eligibility criteria, study design, number and gender of participants, age, setting (inpatient or outpatient), country, diagnostic criteria, study arms and outcomes. The results collected included the number of participants in each arm, number of missing participants, change in pain score, duration of relief, adverse effects and whether they were prospectively sought. Where there was more than one time-point, the pain scores immediately before and after the infusions were used.

Risk of bias in individual studies

Methodological quality of studies were assessed using the "risk of bias" domain-based evaluation by Jadad.[187] Selection bias including random sequence generation and allocation concealment, performance bias, detection bias, attrition bias, reporting bias and risk of carry-over were assessed. Each domain was judged low risk, high risk or unclear risk, with appropriate supporting quotes.

Synthesis of results plan

The primary outcome measure was the relative benefit (risk ratio) with 95% confidence interval of treatment compared with placebo to achieve substantial benefit (at least 50% pain reduction).

Secondary outcomes were based on recommendations in chronic pain studies.[185] Dichotomous data was used to calculate relative benefit (risk ratio) with 95% confidence interval of treatment compared with placebo. This was done for moderate benefit (at least 30% pain reduction) and 'mild post infusion pain' (less than 30/100mm on VAS). Continuous data was used to determine the difference in post-infusion pain score between treatment and placebo groups. Data which was reported as a visual analogue scale was converted to a numeric rating scale from zero to ten, as these have been shown to correlate closely.[188] Crossover trials were treated as though they were parallel group. Missing standard deviations were imputed by calculating the correlation

coefficient of other studies.[189, 190] Individual patient data available in table and graph form was extracted and analysed. The I^2 statistic was used to quantify the heterogeneity.[191] This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error.

Risk of bias across studies and additional analyses

A funnel plot was graphed to assess the risk of publication bias. Sensitivity analysis was performed to consider the effect of choices made in statistical analysis.

Data analysis

Revman 5.3 software was used for statistical analysis.

6.4.4 Results

Study selection

The PRISMA diagram (Figure 6-1) summarises the study selection process. One study was evaluated by contacting the lead author and the methods and results of six studies were translated to English. One letter[192] described two studies, both excluded. One randomised controlled trial[193, 194] which was reported twice, was excluded due to high risk of bias. One randomised controlled trial published as a conference abstract[195] was excluded due to insufficient information despite efforts to contact the authors.

Study characteristics

The five randomised controlled trials found were of intravenous lidocaine and are described in Table 6-2.[178, 196-199] Four were crossover trials of intravenous lidocaine compared with placebo. The fifth trial[199] compared intravenous lidocaine infusion with dexmedetomidine infusion in palliative care patients with neuropathic pain refractory to opioids. A total of 80 participants were included in the placebo comparator and 16 in the dexmedetomidine comparator groups.

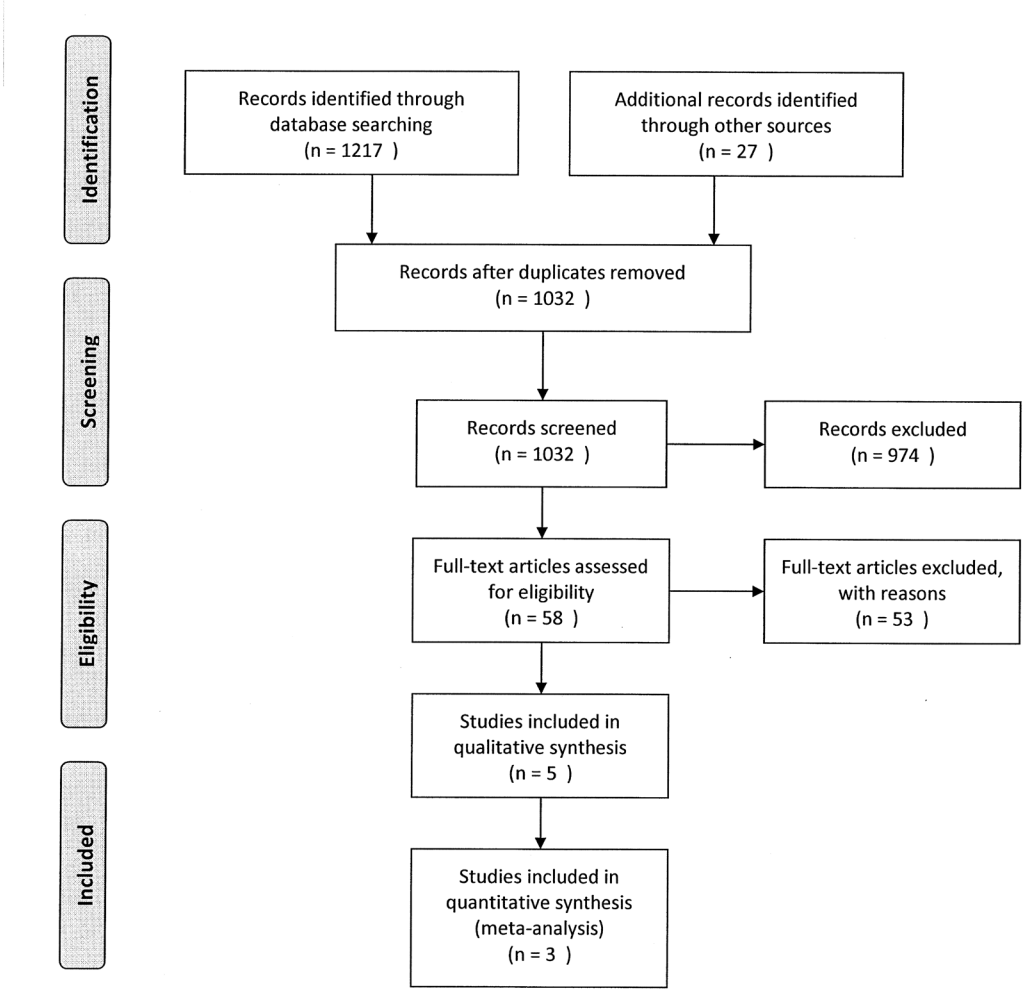

Figure 6-1: PRISMA flow diagram – lidocaine for cancer pain

The reported primary outcome measure was visual analogue pain score (VAS) on a scale of 0-100mm in four studies,[32-35] and numeric analogue scale (NAS) on a scale of 0-10 in one study.[178] It was measured immediately before and after infusion in all studies. It was also measured at a number of other time-points before and during the infusion and for up to 14 days after. Other outcome measures included patient global impression of change,[178, 196] number of rescue analgesic medications,[178, 196, 199] duration of pain relief,[178] reduction of more than 15mm on VAS[197] and sedation.[199]

Table 6-2: Included randomised controlled trials

Study	Design	n	Age	Disease	Study arms	Results	Adverse events
Bruera 1992	RCT - crossover	11[1]	54±17	Neuropathic cancer pain	Lidocaine 5mg/kg iv over 30mins VS Placebo	No significant difference on VAS 30mins post infusion [lidocaine 34±26 vs placebo 33±25]. No significant difference in rescue medications used.	- No significant adverse events with either placebo or lidocaine. - Not documented whether prospectively assessed.
Carrillo-Torres 2015	RCT - parallel	16	22-85	Neuropathic pain, hospice (15 cancer)	Lidocaine 3mg/kgIBW iv over 60mins VS Dexmedetomidine	No significant difference on VAS during or after infusion. Significantly more rescue medication used in lidocaine group.	-significantly more sedation in dexmedetomidine group

Elleman 1989	RCT - crossover	10	51 (30-67)	Cutaneous allodynia in cancer patients	Lidocaine 5mg/kg iv over 30mins VS Placebo	No significant difference in reduction of >15mm on VAS (p=0.99)	- 1 patient: mild transient drowsiness - - Not documented whether prospectively assessed.
Sharma 2009	RCT - crossover	50	67 (34-91)	Opioid-refractory cancer pain	Lidocaine 2mg/kg iv 20min bolus + 2mg/kg over 1 hour VS Placebo	Mean magnitude of decrease in pain score on NAS after lidocaine was 6.34 ± 1.73 vs after placebo 2.30 ± 2.40 (P < 0.0001)	- 52% adverse events after lidocaine, 36% after placebo. p<0.2 - 12 experienced ≥2 adverse events after lidocaine, 2 after placebo. P<0.006. - 1 patient required termination - tinnitus, perioral numbness, sedation, lightheaded, headache
Sjogren 1989	RCT - crossover	10	60 (44-68)	Bone metastasis pain	Lidocaine 5mg/kg iv over 30mins VS Placebo	No significant difference in average pain score in week after (p = 0.3438)	- nil - Not documented whether prospectively assessed.

[1]1 not evaluable. RCT – randomised controlled trial, VAS – visual analogue scale, PGIC – patient global impression of change, NAS – numeric analogue scale, iv – intravenous IBW – ideal body weight

Risk of bias within studies

In the placebo comparator group the risk of bias was not clearly documented in several domains, particularly selection,[197, 198] performance,[196-198] detection[196-198] and attrition[178] bias (Table 6-3). As four trials were of cross-over design, the risk of carry-over bias was added to the assessment tool. In the dexmedetomidine comparator trial[199] there was a high risk of attrition bias and an unclear risk of selection bias. It was attempted to contact authors to clarify data.

Table 6-3: Risk of bias

Bias	Bruera 1992	Carrillo-Torres 2015	Elleman 1989	Sharma 2009	Sjogren 1989
Random sequence generation (selection bias)	'A random pair block allocation technique was employed'	'simple table randomization'	'randomised investigation'. Method of randomisation was not documented.	'pre-sealed envelopes numbered in a random order' 'random number table'	'randomised'. Method of randomisation was not documented.
Allocation concealment (selection bias)	'after ... consent was obtained, patients were randomised'.	'solution … number assigned … prior to randomization'	Method of allocation not documented.	'opened immediately before infusion'	Method of allocation not documented.
Blinding of participants and personnel (performance bias)	'double blind'. Method of blinding was not documented.	"triple blind" 'patients did not know…drug' Randomisation and preparation by one researcher, administration and data collection by another researcher, independent statistician.	'randomised in a double blind crossover investigation'. Method of blinding was not documented.	'pre-sealed envelopes... opened... by a research coordinator who prepared the solutions for infusion by a study nurse'	'double-blind'. Method of blinding not documented.
Blinding of outcome assessment (detection bias)	'double blind'. Method of blinding not documented.	'collection of results by associate…without knowledge'	'double blind crossover'. Method of blinding not documented.	as above	'double-blind'. Method of blinding not documented.

Incomplete outcome data (attrition bias)	'1 was not evaluable; sepsis developed... 24 hr after the placebo'	Non-responders were not assessed post-infusion **(HIGH risk of bias)**	no missing outcome data	'12 opted out of the study after one infusion'	All patients completed all arms of the trial.
Selective reporting (reporting bias)	All stated outcomes were reported.	protocol was 'endorsed by the ethics committee…'. Stated outcomes were reported.	Results were reported as partial or complete relief, which were not predefined.	All stated outcomes were reported.	All stated outcomes were reported.
Other bias	No other bias noted.	No other bias noted.	No other bias noted.	No other bias noted.	No other bias noted.
Risk of carry-over	'if patients experienced significant pain relief, the treatment was not repeated until recurrent pain was felt'	N/A	'the second infusion as not given before the pain had returned to pretreatment level'	'baseline pain scores and duration of evaluation were similar"; temporal difference between the two infusions is more than the maximum duration of pain relief'	'the second infusion was given only after the analgesic effect had ceased'.

Legend: Low risk of bias | Unclear risk of bias | High risk of bias (labelled)

Publication bias

An asymmetric funnel plot was found due to two studies lying outside the 95% confidence interval (Figure 6-2).

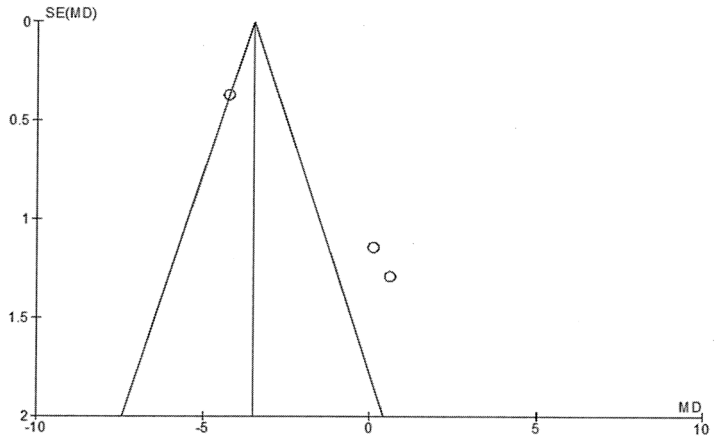

Figure 6-2: Funnel plot for publication bias

Results of individual studies

Sharma et al[178] demonstrated benefit of intravenous lidocaine infusion 2 mg/kg over 20 minutes then 2 mg/kg over 60 minutes for opioid refractory cancer pain. This was a crossover trial of 50 participants. The groups had similar pain scores at baseline (mean lidocaine 8.48, placebo 8.68). The mean duration of pain was 9 months. He found significant ($p<0.0001$) reduction in pain score after lidocaine infusion (6.34±1.73) compared with placebo (2.30±2.40). The mean time to onset of maximum analgesic effect after initiating the infusion was earlier after lidocaine (40±16.28 mins) than placebo (74.80±33.39 mins $p<0.001$) and the duration of pain relief longer (9.34±2.58 days after lidocaine vs 3.82±1.87 days after placebo). More patients had substantial pain relief (>50%) in the lidocaine (82%) than the placebo arm (16%). Significantly more patients reported a subjective decrease in analgesic requirements (64%vs 30% $p=0.0012$) and an objective reduction in rescue medications used (1.45±0.20 vs 1.76±0.25 per day $p=0.01$) after lidocaine compared with placebo.

Three studies demonstrated no significant difference in pain score after lidocaine and placebo infusions.[196-198] These studies evaluated lidocaine infusion 5 mg/kg over 30 minutes.

Bruera et al[196] evaluated 10 participants with neuropathic cancer pain. Pain intensity at baseline was 37/100 before lidocaine infusion and 39/100 before placebo. There was no difference in pain intensity at any timepoint from 10 minutes after infusion start, to day two.

Elleman et al[197] evaluated 10 participants with cutaneous allodynia in cancer. The mean pain score at baseline was 43/100 before lidocaine and 42/100 before placebo. Pain had been present a mean of 38 months (median 23.5, range 11-120 months). Two participants had a reduction in allodynia immediately after lidocaine, defined as >15mm on 100mm VAS. Three participants had a partial reduction after placebo.

Sjogren et al[198] evaluated 10 participants with bone metastases pain. Mean pain score over one week at baseline was 54/100. There was no significant difference in the change in average pain during the week before and after the infusion. Five patients experienced more than 10mm pain relief one hour after the infusion of lignocaine and two experienced more than 10mm pain relief after placebo.

The study comparing lidocaine 3 mg/kg over 60 minutes with dexmedetomidine[199] found no significant difference between the two arms in visual analogue score during the infusion.

Meta-analysis of results

Three of the studies evaluated a similar intervention, all compared with placebo and published data pertaining to the outcomes of this review. Individual patient pain score data was provided for two of these studies, allowing manipulation to address the outcomes of this review. The random effects model was used to estimate the effect size, because although the populations and trials were considered similar enough for meta-analysis, they are not homogeneous.[200]

Primary outcome – substantial (at least 50%) pain relief

Meta-analysis of the primary outcome was possible in two crossover trials of lidocaine infusion compared with placebo with total 60 participants. It demonstrated significant improvement in the number of participants who gained substantial pain relief with lidocaine (Figure 6-3), defined as ≥50% reduction in pain in the post infusion score compared with the pre-infusion score. The risk ratio was 3.29 with a 95% confidence interval of 1.41 to 7.70 (p=0.006, I2=33%). The quality of the evidence for substantial pain relief is moderate because there were only two studies with a small number of participants.[201]

Secondary efficacy outcomes

Four secondary outcomes were able to be analysed: the proportion of participants with moderate or better pain relief (Figure 6-4), with mild pain after the infusion (Figure 6-5), the global impression of change (Figure 6-6) and the post infusion pain score (Figure 6-7). These did not demonstrate any significant difference between lidocaine and placebo. Quality of life was not measured in any study.

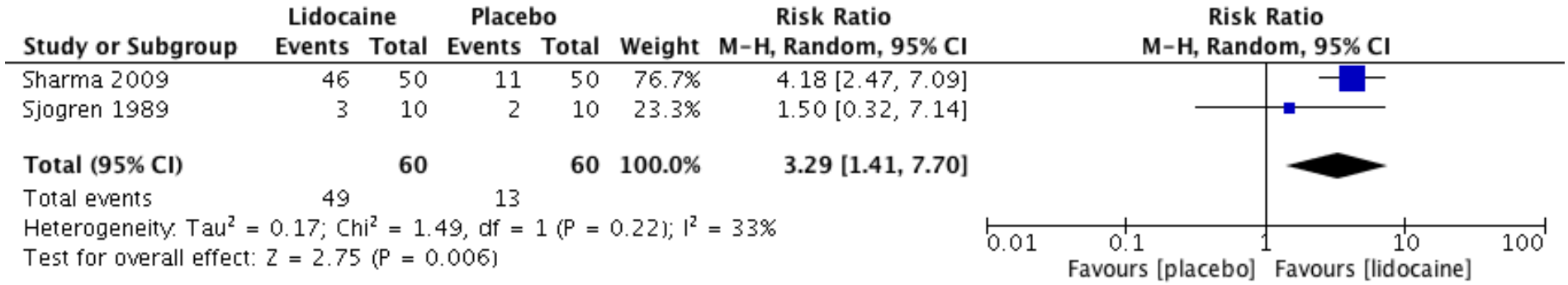

Figure 6-3: Substantial pain relief

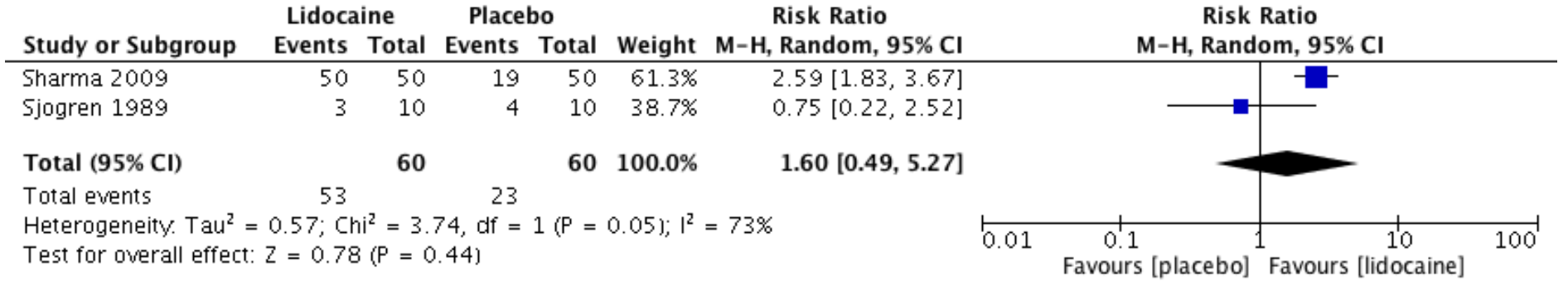

Figure 6-4: Moderate or better pain relief

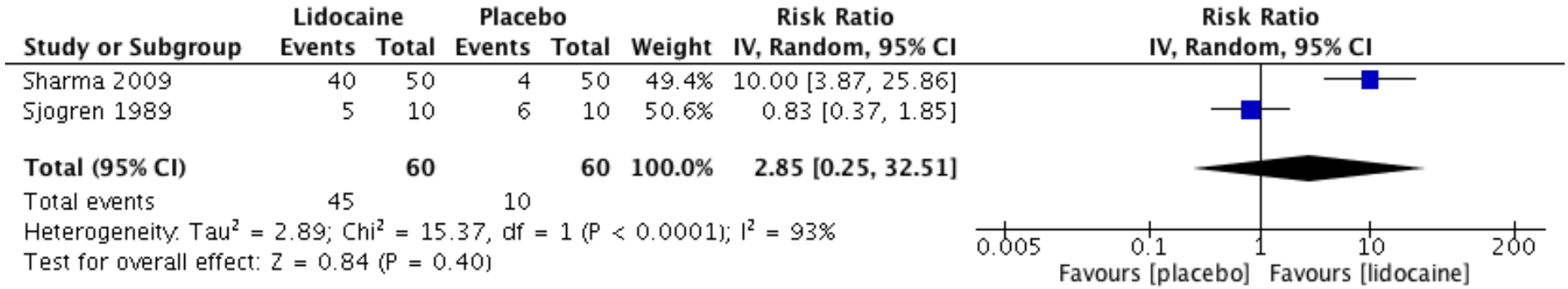

Figure 6-5: Mild pain post infusion

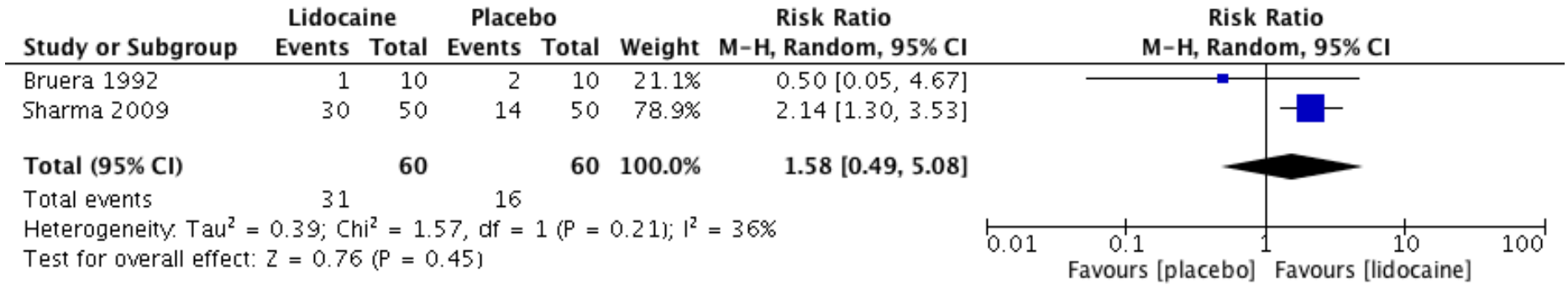

Figure 6-6: Patient global impression of change

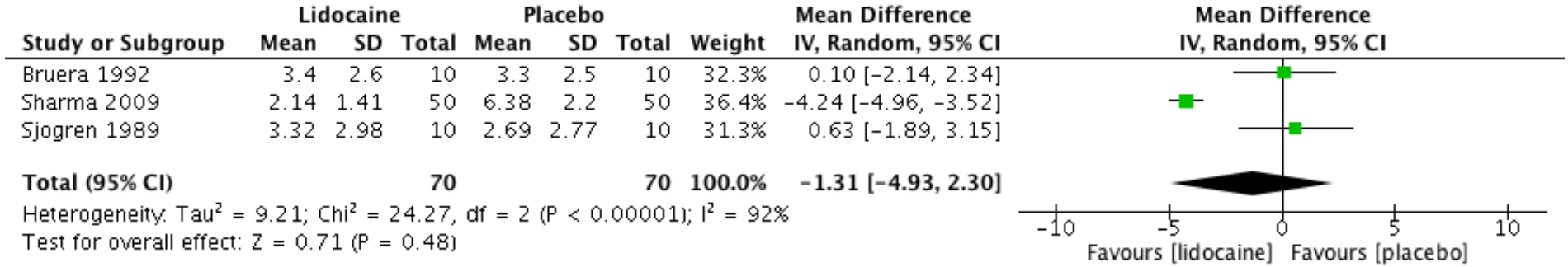

Figure 6-7: Post infusion pain score

Adverse events

Adverse events were prospectively sought in only two trials.[178, 199] In Sharma et al,[11] side effects noted were perioral numbness, sedation, light-headedness, tinnitus, and headache. There was a non-significant ($p<0.2$) increase in the number of patients experiencing at least one side effect after lidocaine (52% vs 36%). There were significantly more patients experiencing two or more side effects after lidocaine (24% vs 4% $p=0.006$). One patient required termination of infusion due to tinnitus, sedation and perioral numbness. The severity of side effects was not documented. Torres et al[35] found the dexmedetomidine group had greater sedation. The remaining trials did not clearly document the rate of adverse effects in the placebo group. One trial[198] reported that 4 patients out of 10 had transient adverse events after lidocaine infusion including drowsiness, nausea, circumoral parasthesia, euphoria, and confusion. One trial[197] reported that one patient experienced mild but transient drowsiness during and immediately after the infusion.[197]

6.4.5 Conclusions

Meta-analysis of pooled data in 60 patients identifies that there may be a benefit for lidocaine infusion of four to five mg/kg over 30 to 80 minutes compared with placebo for greater than 50% reduction in cancer pain. However, there is limited data contributing to this comparison, and it contrasts with the lack of significance found in secondary outcomes. Based on the current available evidence, lidocaine infusion could be considered in refractory cancer pain where agents with level one evidence are ineffective. In many centres, this may require a change in practice. Current guidelines should reflect this. Further research into this promising, potentially opioid sparing therapy is crucial.

Use of the random-effects model gives a relatively greater weighting to the data from Bruera et al[196] and Sjogren et al,[198] and less weighting to data from Sharma et al[178] compared with a fixed effects model. This contributed to the lack of significance in secondary outcomes. This has an impact in the analysis of results in this study because only three studies are suitable for meta-analysis, and the largest study gives opposite

results to the other smaller studies. This approach was chosen because the populations in the studies are heterogeneous. It is widely accepted as the statistical model most likely to reflect the true effect in a heterogeneous population.[200] However, it is important to recognise that this choice affects interpretation of the data. An alternative approach is to provide only descriptive data of individual studies, however this is problematic because readers are still prone to draw conclusions about summary effect which may be erroneous. In this case, narrative review would lead many readers to assume a stronger level of evidence for lidocaine, based on the largest, most recent, positive study. This may have underpinned current recommendations for lidocaine, highlighting the importance of this review and the need for more evidence to determine the true effect.

Use of systemic lidocaine infusion in other situations may inform research and clinical practice in cancer pain. There is level one evidence for lidocaine in all-cause neuropathic pain, acute renal colic and critical limb ischemia.[176, 179, 202] The evidence base for intraoperative lidocaine infusion is rapidly changing.[203, 204] Its use in cancer is a specific type of intervention for which the outcomes are different and warrant studies designed specifically to evaluate these outcomes of interest. In addition, these trials should consider looking at the impact of intraoperative lidocaine on longer term outcomes of chronic pain.

In examining the detail in this systematic review, preliminary opportunities to further explore lidocaine infusion for cancer pain are identified. The study by Sharma et al[178] included participants with significantly higher baseline pain scores than the other studies (8.6 vs 3.7-5.4/10). Lidocaine preferentially blocks nerves with a higher frequency of stimulation, and may be more effective in severe pain. Participants in Sharma et al[178] had had pain for a shorter period than in Elleman's[197] study, and the pain types in all the studies was different. The duration of infusion was longer in Sharma et al[178] than the other protocols. This could provide time for lidocaine to change neurological structure.[164] However it still provided analgesic benefit of only nine days. Could a different infusion protocol provide more lasting benefit? Identified randomised controlled trials test only a short infusion over up to 80 minutes. No randomised

controlled studies evaluate a continuous infusion which observational studies[159-161] strongly suggest has benefit and is used in clinical practice.[205]

Adverse effects were more common in the lidocaine group than placebo, but there were no serious adverse events due to lidocaine. One participant required cessation of the infusion, with resolution of symptoms. Thus it appears that lidocaine infusion is relatively safe, however comprehensive prospective assessment for adverse effects should be an integral feature of future trials.

Meta-analysis of included trials challenges common interpretations of the evidence base. Given the high proportion of people suffering unrelieved cancer pain, further research is urgently needed.

6.5 Neuropathic pain sub-group

In Sharma et al.'s study, 18% of participants had neuropathic cancer pain, 52% mixed pain and 30% nociceptive pain.[178] Of the remaining studies, three evaluated lidocaine infusion in people with neuropathic cancer pain,[196, 197, 199] while one study involved people with bone metastasis pain. This informs the PhD candidate's Lidocaine for Neuropathic Cancer Pain trial (LiCPain) trial which included people who had pain with a neuropathic component, including mixed pain and bone metastases pain.

6.6 Systematic review update

Since the systematic review presented in Section 6.4 was published in 2019,[142] an additional randomised double-blind placebo controlled crossover trial was published.[206] Hawley et al. compared two subcutaneous infusions of lidocaine, 10 mg/kg over 5.5 hours at least one week apart, with placebo for chronic cancer pain. This was only effective in two of 25 participants. Blood levels were lower than expected, and the authors hypothesised that insufficient dose contributed to the lack of effect.[206]

6.7 Design of intervention to be trialled

The approach in the LiCPain trial differed from previous RCTs in both cancer and neuropathic pain, which only gave short infusions of intravenous lidocaine over periods

of up to six hours.[176, 206, 207] Although these trials were very promising, their primary endpoints were pain during or shortly after the infusion, and the measured durability of response was a few days at most. Sharma et al. gave patients with neuropathic cancer pain 4mg/kg intravenous lidocaine (lignocaine) over 80 minutes and detected a mean reduction in pain score of 6.3 out of 10, compared to a reduction of only 2.3 in the placebo group; this reduction lasted a mean of 9.3 days.[178] Tremont-Lukats[207] found that a six-hour infusion of 5mg/kg/h intravenous lidocaine provided relief from peripheral neuropathic pain for six hours after cessation of the infusion. In contrast, a retrospective chart review by Schwartzman[208] found that a five-day intravenous infusion for chronic regional pain syndrome resulted in an average improvement in responders of 3.2 months.

Due to the short half-life of lidocaine, an extended continuous infusion was delivered in the LiCPain trial in order to achieve a steady state. The study aimed to provide preliminary evidence of a more durable effect with continuous infusion than bolus dosing. Continuous infusion is used in clinical practice.[159, 160, 209] A 72-hour infusion was chosen to allow adequate time to titrate to the appropriate dose for each patient and measure pain response while on the optimum dose. It was hypothesised that the extended duration of infusion compared with bolus dosing would allow more time for change in the neurological structural and biochemical system and lead to better and more durable analgesia.

Subcutaneous administration was chosen to reduce the burden in the palliative setting;[210] it is a common approach in clinical palliative care practice;[211-213] and allows broad generalisability given the ease of subcutaneous administration. Patients prefer subcutaneous to intravenous medication delivery if the efficacy is equivalent.[210] A subcutaneous butterfly is quicker to insert, less painful, has lower rates of dislodgement, blockage and cellulitis, and can remain in situ for longer than an intravenous cannula. It requires minimal training and can easily be managed in a community setting.

Four studies[159, 160, 214, 215] of subcutaneous lidocaine infusion suggested that it is effective in 48 to 87% of patients. However, the three largest studies[159, 160, 215] were retrospective, which may bias the effectiveness results.

6.8 Chapter summary

This chapter describes the systematic and narrative literature reviews underpinning the selection and design of the continuous subcutaneous infusion of lidocaine evaluated in the LiCPain trial.

Chapter 7 reports the quantitative component of the LiCPAIN trial.

Chapter 7 Lidocaine for neuropathic cancer pain: a pilot randomised controlled trial

7.1 Chapter preface

Chapters 1 and 2 describe the background and methodology to the INCEPT Project. Chapters 3 to 5 describe the prevalence and experience of people with neuropathic cancer pain. Chapter 6 describes the evidence for pharmacological treatment of neuropathic cancer pain, with a focus on lidocaine infusion. It reports a systematic review which found that short lidocaine infusion produced a greater than 50% reduction in cancer pain compared with placebo. No RCT evidence was found for extended continuous subcutaneous infusion of lidocaine, but observational studies of use in clinical practice report response rates of up to 87%.

This chapter describes research into the feasibility of conducting a definitive clinical trial of continuous subcutaneous infusion of lidocaine for neuropathic cancer pain. It discusses design approaches for RCTs of lidocaine in neuropathic cancer pain.

This chapter contains a protocol paper and a final results paper for the LiCPain trial (Study 4). These manuscripts were published in February 2023 in *BMJ Open* and July 2025 in *Journal of Pain and Symptom Management*, respectively. The articles are formatted to conform to thesis guidelines.

Lee J, Currow D, Lovell M, et al. Lidocaine for Neuropathic Cancer Pain (LiCPain): study protocol for a mixed-methods pilot study. *BMJ Open* 2023;13:e066125. DOI: 10.1136/bmjopen-2022-066125.

(citations: 1 (BMJ Open); Altimetric: 5)

Lee JT, Lovell MR, Ritchie M, et al. Lidocaine for Neuropathic Cancer Pain (LiCPain): A Pilot Randomized Controlled Trial. *J Pain Symptom Manage*. 2025;70(3):267-277.e6. doi:10.1016/j.jpainsymman.2025.05.015

(citations: 0; Altimetric: 2)

7.2 Lidocaine for Neuropathic Cancer Pain (LiCPain): study protocol for a mixed-methods pilot study

7.2.1 Introduction

Unrelieved cancer-related pain remains a pressing problem, with current treatments being unsatisfactory.[9] Patients with neuropathic cancer-related pain are significantly more likely to receive strong opioids and adjuvant analgesia, have a reduced performance status and report worse physical, cognitive and social functioning.[6]

Neuropathic cancer-related pain is thought to require multi-modal pharmacological therapy, with adjuvant analgesics such as anticonvulsants and antidepressants together with opioids. However, level I evidence for adjuvants in cancer-related pain is limited.[216] The efficacy seen in clinical practice is variable[217, 218] and treatment is often associated with harms.[183] Both opioids and gabapentinoids carry risk of misuse, abuse and diversion which is increasingly recognized to impact people with cancer.[219, 220] There is currently no 'gold standard' medication to manage neuropathic cancer-related pain.

Lidocaine offers an innovative approach to manage this challenging clinical problem.[142] This medication aims to provide analgesic benefit without significant psychoactive side effects, unlike alternatives such as opioids where this may limit dose escalation. Lidocaine's mechanism of action is biologically plausible and targets pathways not previously investigated in this patient population.[163-166]

Systemic lidocaine can be administered as an intravenous or subcutaneous bolus, short or extended infusion. We define an extended infusion as lasting greater than 24 hours. Lidocaine is also likely to be cost-effective, as better cancer-related pain management is likely to reduce health system costs due to reduced unplanned hospital readmissions, hospitalisations, emergency department and medical attendances and shorter inpatient stays.[221, 222] Moreover, subcutaneous lidocaine offers a therapeutic option for people

with cancer who cannot swallow or tolerate the side effects of other anti-neuropathic medications.

Data support lidocaine as a promising, safe agent in this setting, warranting further evaluation in robust, randomised controlled trials. Three observational studies have found 67% to 87% response to continuous subcutaneous or intravenous lidocaine infusion in cancer pain or palliative care patients.[160, 209, 215] A 2015 Cochrane review found that lidocaine as a bolus dose or a short infusion is safe and more effective than placebo in treating chronic, non-cancer neuropathic pain,[176] as well as better than placebo for early post-operative pain.[223] A meta-analysis[142] of bolus intravenous lidocaine 4-5 mg/kg over 30-80 minutes versus placebo in cancer pain showed a significant benefit for >50% reduction in cancer pain but not other outcomes. A single phase III randomised controlled trial[206] of subcutaneous lidocaine in cancer pain has evaluated the infusion of 10 mg/kg lidocaine over 5.5 hours and found no effect on pain, which may have been related to the sub-therapeutic serum concentration in all but two participants out of 33 randomised. Studies have shown lidocaine may have an effect beyond the duration of infusion.[178, 224]

Despite the use of extended, continuous subcutaneous infusion of lidocaine over days in clinical practice,[225] there are no randomised controlled trials evaluating subcutaneous lidocaine infusions of greater than six hours duration for the treatment of unrelieved neuropathic cancer-related pain.

This mixed-methods pilot aims to determine the feasibility of undertaking an international-first definitive phase three randomised double-blind parallel-arm trial to evaluate the efficacy and safety of a continuous subcutaneous infusion of lidocaine for neuropathic cancer-related pain. The pilot will provide important safety data and help inform the methodology of a definitive trial, including testing proposed outcome measures, recruitment strategy, randomisation process and patient acceptability of the methodology to ultimately provide a signal of whether this treatment should be further investigated.

This paper complies with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations for protocol reporting,[226] and the study will report against Consolidated Standards of Reporting Trials guidelines.[227]

7.2.2 Objectives

The primary objective is to determine the percentage of participants who complete the study intervention. This will be calculated by the number of participants in both arms who complete the study medication and procedures from day 1 to 4 as a percentage of the total number of participants randomised.

The secondary objectives are to evaluate other aspects of feasibility; preliminary efficacy, harms, health outcomes, and health service utilisation; and the pathophysiology of subcutaneous lidocaine infusion. Specific aims and objectives can be found in the protocol on the Australian New Zealand Clinical trials Registry (ANZCTR).[228]

7.2.3 Methods and analysis

Trial design

We propose a mixed-methods pilot study to determine the feasibility of a definitive phase III trial which would evaluate the efficacy and safety of a continuous subcutaneous infusion of lidocaine for neuropathic cancer-related pain.

This feasibility study will comprise:

- A phase II double-blind randomised controlled parallel-group pilot of subcutaneous infusion of lidocaine versus placebo over 72 hours for neuropathic cancer-related pain.
  Descriptive quantitative data will provide important feasibility data about trial procedures, recruitment, preliminary efficacy, safety and health service use.
- A pharmacokinetic sub-study of subcutaneous lidocaine.
  Pharmacokinetic data will inform the definitive study and confirm extrapolation from existing data to this subcutaneous infusion regimen.

- A descriptive qualitative sub-study of patient experience of the intervention. Semi-structured interview data will inform the design of a definitive trial.
- A descriptive qualitative sub-study of informal carer experience of the intervention. Semi-structured interviews will generate understanding of the experience of the intervention and caring for a person with cancer-related neuropathic pain. The perspective of informal carers is essential to inform the provision of holistic care and is likely to impact recruitment to a definitive study.

The three sub-studies will be undertaken in a subset of consenting patients. Methods and analysis plans for these will be fully reported together with publication of the results in accordance with relevant reporting guidelines.

Patient and Public Involvement

The investigator team includes a consumer (BN) with lived experience both as a person with cancer as well as carer, who has been involved in study design and drafting of participant materials. The consumer will be involved in analysis and interpretation of data obtained.

Setting

Data will be gathered from five palliative care inpatient units in Sydney, Australia. Participants must be inpatient for the 72 hours of the study. The study is sponsored by the University of Technology Sydney. The study will be coordinated by the IMPACCT trials coordination centre (ITCC). Scientific endorsement was provided by Cancer Symptom Trials.[229]

Study population

Inclusion and exclusion criteria are listed in Table 7-1.

Table 7-1: Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**

• Age 18 years or more
• Capacity to provide informed consent
• Ability to complete study assessments and comply with the study procedures
• Participant is willing to be an inpatient for the duration of the trial
• Pain related to cancer or its treatment with an worst pain score of 4 or greater on an 11-point (0-10) numerical rating scale in the past 24 hours
• Patient's cancer may be solid tumour or haematological
• Neuropathic component to pain which the clinician assesses to meet the International Association for the Study of Pain criteria for neuropathic pain which is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system"[230] OR has a score of 12 or greater on
	• Previous adverse reaction to lidocaine (lignocaine) or other amide-type local anaesthetics such as prilocaine, mepivacaine or bupivacaine
	• Use of systemic lidocaine (lignocaine) infusion for analgesia within the four weeks prior to study entry at a dose greater than or equal to 1 mg/kg/h intravenous or subcutaneous
	• Liver failure (Child class B or C, likely due to hepatic impairment)
	• Renal failure (estimated Glomerular Filtration Rate <15ml/min/1.73m^2)
	• Cardiac comorbidity deemed a contraindication by the treating clinician including
	  ○ Symptomatic cardiac failure (New York Heart Association class II or greater[231] within the past year
	  ○ heart block (first, second or third degree) at any time in the past

the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS).[20] Mixed neuropathic/nociceptive pains are included as well as cancer induced bone pain which is considered to have a neuropathic component.[14] • An adequate trial of opioid medication defined as titration to the maximum tolerated dose as limited by adverse effects or titration to at least a dose of 30 mg/day oral morphine equivalent, for at least 24 hours *or* inability to tolerate opioids (eg due to allergy) • An adequate trial of at least ONE adjuvant analgesic defined as titration to the maximum tolerated dose as limited by adverse effects or titration to at least a dose of Amitriptyline 37.5 mg, Duloxetine 30 mg, Gabapentin 900 mg, Pregabalin 150 mg, Venlafaxine 60 mg or equivalent, for at least 24 hours *or* inability to tolerate any adjuvant analgesic listed above (eg. due to comorbidity, medication interaction or previous adverse effects) *or* inability to take oral medications (as determined by the treating clinician eg due to dysphagia)	ten years. Participants managed with a permanent pacemaker are not excluded. o Stokes-Adams syndrome • Cardiac abnormalities at time of screening o bradycardia less than 60 beats per minute at rest whilst awake o systolic blood pressure less than 100 mmHg or greater than 160 mmHg sitting o unstable angina or myocardial ischemia o atrial or supraventricular tachycardia greater than 100 beats per minute at rest • Seizure episode within the past 4 weeks • Fluctuating level of consciousness or delirium as determined by the treating team • Acute porphyria • Current use of medications which may interact with lidocaine or impact

or expected poor absorption of oral medications (as determined by the treating clinician, eg due to vomiting) • Stable regular adjuvant analgesics, opioids, cannabinoids, antidepressants, anticonvulsants, benzodiazepines, paracetamol, non-steroidal anti-inflammatory drugs and steroids for 24 hours. Transdermal opioids must have had stable dosing for 48 hours due to the extended time to reach steady state. Short acting breakthrough opioid may be used as required.	its metabolism:[232] propranolol, phenytoin, amiodarone, metoprolol, nadolol, St John's Wort, donepezil, cimetidine, flecainide, fluvoxamine, dihydroergotamine, vernakalant, saquinavir, dronedarone, amprenavir, lopinavir, propofol, arbutamine, atazanavir, succinylcholine, dasabuvir, paritaprevir, cobicistat, hyaluronidase, delavirdine, fosamprenavir, etravirine, ombitasvir, quinidine, disopyramide, procainamide, tocainide, mexiletine, propafenone, encainide, moricizine, bupropion, telaprevir, penbutolol, rapacuronium, nevirapine, nitrous oxide, cisatracurium, indinavir, ritonavir • Participants who have participated in a clinical study of a new chemical entity within the four weeks prior to study entry • Pregnant or breastfeeding

Inclusion and exclusion criteria were chosen with safety as first priority, aiming to limit participation by patients with unpredictable lidocaine pharmacology while still reflecting the diversity of the population who may benefit from this intervention. Participants are required to have a trial of opioid and non-lidocaine adjuvant analgesia unless otherwise contraindicated as the existing evidence for these therapies, while limited, is stronger than for the intervention. Minimum doses for inclusion were chosen based on studies by Reis-Pina et al,[233] Caraceni et al,[234] Mercadante et al;[235] with a 25% threshold of total daily maximum dose of adjuvant agents as defined by Dworkin et al.[236]

Study intervention

The intervention is described in Table 7-2.

Table 7-2: Intervention

Intervention
Participants will be randomised to receive the intervention or placebo, with both treatment arms receiving best practice standard of care. 1. **Lidocaine Hydrochloride 10%w/v (3000 mg/30ml)** 2. **Placebo: Sodium chloride 0.9%** The appropriate dose of interventional product or identical volume of placebo will be diluted in sodium chloride 0.9% to the volume of the syringe driver(s). Sites use existing Niki T34 syringe drivers which allow a maximum of either a 30mL or 50mL syringe. The syringe holds 30mL of interventional product, however the maximum syringe driver capacity is less than this. If required, two syringe drives may be used. All study drugs will be prescribed as a continuous subcutaneous infusion to be changed every 24 hours of the intervention period. There will be up to two dose modifications during the treatment period, at 24 hours and 48 hours, unless toxicity requires a dose reduction. All doses will be rounded to the nearest 100 mg.

The continuous subcutaneous infusion of lidocaine/placebo will commence on day 1 at 1 mg/kg/h (maximum 120 mg/h).

The patient will be assessed for efficacy and toxicity on days two and three between 0.5 and 4 hours prior to the infusion change time. The dose for the next 24 hours will be charted according to the following algorithm:

The dose will be increased by 0.5 mg/kg/h every 24 hours to a maximum of 2 mg/kg/h or 120 mg/h (whichever is lower).

Exceptions:

If the patient's average and worst pain score in the last 24 hours is ≥3/10, the dose will remain the same

If there is any new or increased toxicity, this will be managed according to the protocol, which may include treatment of the symptom, dose reduction or cessation of infusion

After 72 hours (on day 4), the infusion will be ceased.

All medications will be charted on the standard inpatient medication chart and will be signed off by nursing staff according to local protocol.

Concomitant care

Best practice standard of care will include continuation of prescribed analgesic or potentially analgesic medications (without further dose change) in both arms of the study, and additional opioid use as required by the patient for breakthrough pain. Due to the fluctuating nature of neuropathic cancer-related pain, and the high psychosocial distress that accompanies a diagnosis of cancer, it would be unethical to deny this population access to breakthrough medication (typically an opioid). If a participant becomes unable to tolerate medications, equivalent substitutions may be made.

Rationale for dose schedule

The intervention schedule has been devised to maximise the likelihood of benefit while minimising the risk of adverse events. The commencing dose, dose increments, and maximum doses are within the doses where efficacy has been seen in other settings, and where reported toxicity is infrequent as outlined below.

Weight-based dosing will be used as lidocaine pharmacokinetics are influenced by body size.[237]

The effect of lidocaine is dose-dependent.[207, 238] Therefore, it is proposed to increase the dose if optimal analgesic benefit has not been obtained. Adverse effects are also likely to be dose-related, and severe reactions are often preceded by somnolence and paresthesia.[239]

Selection of starting dose (mg/kg), increments, and maximal doses of lidocaine are limited by the fact that there are no prospective interventional trials evaluating an extended continuous infusion of lidocaine for pain. The longest randomised controlled trials were by Hawley[206] who evaluated 10 mg/kg subcutaneous lidocaine over 5.5 hours and found no effect on cancer pain and Tremont-Lukats[207] who randomised 32 patients with neuropathic pain to placebo, 1, 3 or 5 mg/kg/h intravenous infusion of lidocaine over six hours and found a benefit of lidocaine 5 mg/kg/h after four hours, which lasted a further six hours. Blood pressure, heart rate, ECG readings as well as adverse effects were monitored throughout both trials. No serious adverse events were reported.

Available pharmacokinetic data have also been considered in deciding the optimum dose schedule, although lidocaine serum concentrations do not always correlate with toxicity, as cases of toxicity are found at serum concentrations within the presumed ‘therapeutic range’. Most of the pharmacokinetic data for lidocaine is from intravenous studies in which bioavailability is 100%.[168] The bioavailability of subcutaneous lidocaine, the route being used in this study, is dependent on the vascularity of the site, and is likely to be less than intravenous administration. In a horse model, when compared to administration of an equivalent intravenous lidocaine dose, a subcutaneous

lidocaine dose may take ten times longer to reach a maximum concentration which is nearly three times lower.[240]

Physical signs of toxicity are more likely seen at lidocaine serum concentrations above 6 to 10 µg/ml, and serious adverse effects are rare below 5µg/ml.[168] Adverse effects typically follow a progression with mild adverse effects such as numbness, tinnitus, lightheadedness, dizziness, confusion and visual disturbance at lidocaine serum concentrations around 3-8µg/ml, nausea and vomiting, severe dizziness, decreased hearing, tremors and changes in blood pressure and pulse at serum concentrations 8-12 µg/ml and drowsiness, confusion, muscle twitching, convulsions, loss of consciousness, cardiac arrhythmias and cardiac arrest at serum concentrations greater than 12µg/ml.[241]

Pharmacokinetic data are available from a study by Ferrini[242] who reported a case series of six patients with cancer pain. Infusions were continued until death, for up to 240 days. Two patients were given intravenous lidocaine at 10-48mg/h intravenously and returned concentrations from 2-9.3µg/ml. Four patients were given lidocaine 32-80mg/h subcutaneously, and lidocaine serum concentrations were 1.3-3.3µg/ml. Schwartzman[208] found that when intravenous lidocaine infusion was given for complex regional pain syndrome at 88mg/h, plasma concentrations were between 1.1-4.4µg/ml, but at 120mg/h, 3 out of 49 patients had plasma concentrations between 5.1-6.1µg/ml. Mild self-limiting adverse effects were found at 120 to 144 mg/h. Serum lidocaine concentrations were obtained in a subset of the study by Thomas[209] of intravenous lidocaine at a dose of 1-2mg/kg bolus followed by 1mg/kg/h, which found a mean lidocaine serum concentration of 5.1µg/ml and standard deviation of 2.9µg/ml.

Several case series describe other lidocaine dose ranges used in clinical practice for analgesia. Brose[214] gave three patients with cancer pain randomised boluses of lidocaine 4mg/kg, fentanyl or normal saline. This was followed by a subcutaneous infusion of lidocaine 100-160mg/h for 3 weeks to 6 months with good analgesia and no attributable adverse effects. Blood concentrations ranged from 1.3µg/ml to 5µg/ml. In two patients, recurrent pain was associated with lidocaine blood concentrations under 2µg/ml. Amikura[160] gave 32 patients with neuropathic cancer pain lidocaine with an average maintenance dose of 38mg/h (range: 8-60mg/h) for 5 to 158 days, and 87.5%

experienced significant pain relief. Seah[243] reported 23 hospice patients with a median subcutaneous lidocaine dose of 0.65mg/kg/h. Thomas[209] conducted a retrospective chart review of 82 consecutive hospice patients as above which found 82% had a major response and 8% had a partial response of their pain.

Because of limited prospective data for extended continuous infusions of lidocaine in cancer-related pain or neuropathic pain populations, the following data from randomised controlled trials evaluating perioperative pain was also considered. Swenson[244] found that, with a dosing regimen of intravenous lidocaine 2mg/minute for patients under 70kg and 3mg/minute for patients over 70kg, several patients had potentially toxic plasma concentrations. This regimen was changed to 60mg/h and 120mg/h, respectively. Herroeder[245] found that an intravenous infusion of 120mg/h did not produce any plasma concentrations above 5μg/ml. These patients were monitored, and no adverse effects were observed. Kuo[224] found 3 patients in the intravenous lidocaine group developed intermittent bradycardia at doses of 3mg/kg/h.

After considering the above data, a starting lidocaine dose of 1 mg/kg/h was chosen. This dose is unlikely to cause serious adverse effects given experience in previous trials. In addition, the infusion will be delivered subcutaneously, which is likely to have less bioavailability and systemic absorption than the intravenous infusions used for cardiac stability. Nonetheless, rigorous monitoring (including vital signs, ECG readings and structured symptom assessment for adverse effects) will occur to detect and manage potential adverse events as soon as possible. Lidocaine dose titration up to 2mg/kg/h will allow for individual response, with patients remaining on the minimal dose required for adequate analgesia. Although appearing to have better efficacy and lower risks of serious adverse events in a non-cancer population, higher doses would need to be used with caution in the cancer population, who may have a higher rate of frailty and comorbidity. Therefore, a maximum dose of 120mg/h (regardless of the calculated weight-based dose) will be imposed to limit the risks from higher dose infusions[208, 244].

Outcomes and data collection

The primary outcome is the rate of completion of study procedures and medication use from day 1 to day 4. A completion rate of 80% or more of randomised patients will be considered feasible, while a completion rate of 60% or less will be considered unacceptable.

The secondary feasibility outcomes are the number of eligible participants who are consented to and randomised within the first 18 months from the lead site opening, recruitment:screening ratio, completion:screening ratio, rate of complete data sets, and time taken to complete the study measures at the main daily assessment. Other secondary outcomes measure preliminary efficacy, toxicity, health outcomes and health service utilisation associated with the intervention, and the relationship between lidocaine serum concentration and dose/efficacy/toxicity.

Table 7-3 shows the primary and secondary outcomes.

Table 7-3: Primary and secondary outcomes

<table>
<tr><th colspan="2">Primary outcome and measure</th></tr>
<tr><td colspan="2">The primary outcome is the completion rate of the study medication and procedures from day 1 to day 4. A completion rate of 80% or more of randomized patients is considered feasible and a completion rate of 60% or less is considered unacceptable.</td></tr>
<tr><th colspan="2">Secondary outcomes</th></tr>
<tr><td>Feasibility
• The number of eligible participants who are consented and randomized within the first 18 months from the lead site opening
• Recruitment to screening ratio
• Completion to screening ratio: the ratio of participants who complete all study medication and procedures from day 1 to day 4 compared to number of patients screened
• Completion of data. A rate of greater than 80% of randomized participants with complete data set is considered feasible</td><td>Preliminary Efficacy
Exploratory efficacy outcomes will include the following.
• The proportion of participants who have an improvement from baseline to day 4 in:
- Average pain of 1 point or more on the BPI-SF
- Worst pain of 2 point or more on the BPI-SF (moderate clinically important difference)
- Average pain of 2 point or more on the BPI-SF
- Worst pain of 4 points or more on the BPI-SF (major clinically important difference)
- Average pain of 4 points or more on the BPI-SF
- Worst pain to be reduced to ≤3 on the BPI-SF
- Average pain to be reduced to ≤3 on the BPI-SF</td></tr>
</table>

• Acceptability of subcutaneous lidocaine (lignocaine) or control infusion and study design to participants and carers (sub study) • Impacts of the intervention relevant to participants and carers (sub-study) • Time taken to complete study measures at the assessment prior to dose change	- Arithmetic mean of worst, least, average and now pain of 1 point or more on the BPI-SF - Number of breakthrough pain medications used - Burning (superficial) spontaneous pain of 1 point or more on the Neuropathic pain symptom inventory (NPSI) - Pressing (deep) spontaneous pain of 1 point or more on the NPSI - Paroxysmal pain of 1 point or more on the NPSI - Evoked pain of 1 point or more on the NPSI - Paresthesia/Dysesthesia of 1 point or more on the NPSI
Preliminary Toxicity • Prospectively sought adverse events with the likelihood of relationship to intervention	• Global impression of change measured on a 7-point scale • Mean change in worst pain on BPI-SF • Mean change in average pain on BPI-SF • Proportion of participants who achieve their personalized pain goal • Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 OR those who have unchanged pain but a reduction in number of breakthrough medications used in the last 24 hours - Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 AND breakthrough medication use which is unchanged or reduced in the last 24 hours - Cumulative responders for all changes in worst pain score on BPI-SF on day 4
Pathophysiology • The median dose at study completion • The relationship between serum lidocaine (lignocaine) level at steady-state and continuous subcutaneous infusion dose (sub-study) • Preliminary relationship between serum lidocaine (lignocaine) level and efficacy and toxicity (sub study)	
Preliminary Quality of Life and Health Services Utilization • Completion rate of EQ-5D-5L(generic)	

• Arithmetic mean of the seven items assessing interference on the BPI-SF on day 4 compared with baseline; this mean can be used if more than 50%, or four of seven, of the total items have been completed on a given administration • Total RUG-ADL score on day 4 compared to baseline • Lidocaine (lignocaine) and analgesic medication costs • Management of adverse effects, e.g. investigations, additional clinician review, medications • Inpatient stays (length of stay, AR-DRG), excluding pharmacy costs	- Cumulative responders for the proportion of participants who have a reduction in worst pain score of 1 point or more on day 2, 3 and 4 - The proportion of responders, defined by a 1-point reduction in worst pain at day 4, who have a continued response at day 9, 15 and 29 will be calculated for each group. Subgroup analysis will be performed to evaluate the following for potential as biomarkers of response to lignocaine - patients who have never had an adjuvant therapy vs patients who have not been on the maximal doses listed in appendix. - patients who are on minimal, moderate and large doses of morphine (<60, 60-200, >200 mg/day) - patients who have severe pain (≥7/10) and moderate pain (4-6/10) - patients with allodynia

Table 7-4 provides an overview of the data collection tools used in this study. SPIRIT Figure 1[226] published in Lee et al.[49] describes the tools and data collected at each study time point. The systematic adverse effects screening assessment is shown in Table 7-5. Participants will be reviewed face-to-face daily from baseline to day 4 in the four hours before intervention dose change, then by telephone during follow up. The protocol provides specific guidance for management of drug specific side effects including dose reduction, cessation and increased frequency of review depending on the severity and risk of the symptom.

Table 7-4: Overview of study instruments

Instrument	Details
Eligibility and demographic	
Leeds assessment of neuropathic symptoms and signs (LANSS)	Seven item scale including sensory description and examination. Score of 12 or greater has 85% sensitivity that neuropathic mechanisms likely contribute to the patient's pain[20]
Charlson Comorbidity Index (CCI)	Score composed of major comorbidities weighted to reflect risk of death[246]
Non-pharmacological management	Use of patient education, pain diary, physiotherapist, occupational therapist, psychologist, music therapist or other complementary therapy to improve pain management collected from medical record or participant recollection. Recommended by guidelines[174]
Efficacy assessments	
Brief Pain Inventory – Short Form (BPI-SF)	Validated 9-item tool based primarily on 0-10 numeric rating scale assessing pain intensity and impact.[247] Question 7 omitted to reduce participant burden as medication information collected by study staff
Worst pain	Numeric rating scale from 0 to 10 of worst pain in the last 24 hours

Average pain	Numeric rating scale from 0 to 10 of average pain in the last 24 hours
Neuropathic Pain Symptom Inventory (NPSI)	12 item questionnaire covering the domains of superficial and deep spontaneous pain, paroxysmal pain, evoked pain and paresthesia/dysaesthesia. Validated to assess neuropathic pain[248] and may detect treatment effect[230]
Personalised pain goal	Patients asked to describe on a 0-10 scale the level/intensity of pain that will allow the to achieve comfort in physical, functional, and psychosocial domains[249]
Medications	Regular opioid and adjuvant analgesics recorded Breakthrough medication formulation, route of administration, frequency prescribed, number taken during the prior 24-hour period
Health and service use outcomes	
EuroQual-5 Domains-Five Level (EQ-5D-5L)	Validated tool measuring five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) of health-related quality of life with relevant population norms[250-252]
Global impression of change	Seven-point scale regarding participant perception of change in overall status since study commencement; graded from ‘very much worse’ to ‘very much improved’

Australia-modified Karnofsky Performance Status (AKPS)	Validated scale measuring performance status from 100 (normal) to 0 (dead)[253]
Resource Utilisation Group Activities Daily Living (RUG-ADL)	Four-item scale measuring patient motor function for activities of daily living including bed mobility, toileting, transfers and eating,[254] of most value when AKPS is less than 60[255]
Australian Refined Diagnosis Related Group (AR-DRG)	Groups inpatient stays into clinically meaningful categories of complexity that consume similar amounts of resources[256]
Toxicity	
Adverse effects	Documented using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0[257] terminology with indication of severity, likely causality, and action taken. Vital signs, electrocardiogram (ECG), and structured toxicity assessment will aid this. These will be measured in a full assessment daily. An additional focused toxicity screen will occur three hours after dose changes to improve safety.

Table 7-5: Adverse effect screening assessment

Symptom	**Yes**	**No**
Fatigue, somnolence, lethargy, depressed level of consciousness, delirium, hallucinations		
Paraesthesia, circumoral paraesthesia		
Seizure, tremor		
Light headedness, dizziness, presyncope, syncope, headache, blurred vision, throat tightness		
tinnitus		
Ataxia, dysarthria		
Depression, anxiety, euphoria		
Palpitations		
Chest pain		
Cardiac failure, pedal edema		
Review vital signs: bradycardia less than 60 beats per minute at rest, awake systolic blood pressure less than 100mmHg or greater than 160mmHg tachycardia greater than 100 beats per minute at rest oxygen saturation less than 88% on room air respiratory rate less than 8 breaths per minute		
Review ECG: arrhythmia, conduction disorder		
Dyspnoea, cough, wheezing		
Anaphylaxis		
Injection site reaction (check site)		
Nausea, vomiting, constipation		
Pruritis		

In the pharmacokinetic sub-study, timed blood sample collection will occur daily, 20 to 24 hours after commencing of the lidocaine infusion. Samples will be analysed using a validated HPLC assay[258] to estimate lidocaine and metabolite concentrations.

Sample size and recruitment

Based on an acceptable completion rate of 80% and an unacceptable completion rate of 60% the sample size is 36 participants. Fleming's two-stage design[259] will be used. This calculation generates a range of values. A mid value has been selected taking into consideration is whether sufficient feasibility data has been collected to inform a future phase III study. The null hypothesis that the true response rate is 0.6 will be tested against a one-sided alternative. In the first stage, 17 patients will be accrued. If there are 10 or fewer responses in these 17 patients, the study will be stopped for futility. If there are 15 or more responses in 17 patients, the study will be stopped and the null hypothesis rejected. Otherwise, 19 additional patients will be accrued for a total of 36. The null hypothesis will be rejected if 25 or more responses are observed in 36 patients. This design yields a type I error rate of 0.05 and power of 0.8 when the true response rate is 0.8. A maximum of twelve participants will be recruited to the pharmacokinetic substudy. Participants will be invited to participate on admission to the palliative care unit and during regular screening at each site. Regular promotion of this study to clinicians at this site is designed to improve recruitment. Advertising posters may be placed in clinical areas.

Allocation

At each centre, potential participants will be sequentially allocated an ID number. The REDCap (Research Electronic Data Capture) randomisation tool will be used to facilitate randomisation. REDCap is a secure web application for building and managing online surveys and databases.[260] Random allocation tables will be created by the trial statistician and uploaded into the REDCap Project. Treatment for each participant will be allocated according to a block randomisation schedule in a 1:1 ratio. The site investigator or delegate will enrol participants. To maintain the blind, the site pharmacist will consult the online REDCap tool to randomise.

Blinding

Treatment allocation will not be disclosed to participants, study staff or, treating clinicians. All investigators except the collaborative national manager and statistician will be blinded. The study medication and placebo will be packed into identical syringes and labelled by an accredited pharmaceutical packaging facility holding a license to manufacture therapeutic goods for clinical trials. All medicine packs will be prepared by the unblinded site clinical trial pharmacist according to the randomisation schedule. The ward nurse or study nurse will load the syringe driver from the dispensed study medications. A nursing record of administration will document study medication administered and discarded. Used syringes will be disposed on the ward.

Unblinding will only be done in cases of emergencies where knowledge of the code will have consequences for clinical decision making.

Data management

Deidentified study data will be collected on paper worksheets and then entered onto and managed on REDCap database. All identifiable data (master list, consent forms, pathology reports, copies of medical record) will be filed separately to the worksheets and stored securely as set out in Good Clinical Practice guidelines.[261] Data will be stored for 15 years, then destroyed.

Statistical and data analysis methods

The study completion rate will be calculated by the number of participants in both arms who complete the study medication and procedures from day 1 to 4 as a percentage of the total number of participants randomised. A rate that has a confidence interval including 80% and excluding 60% will be considered feasible.

The number of eligible participants who are consented and randomised within the first eighteen months from the lead site opening will be documented. Thirty-six patients will be considered satisfactory. Study chronology will be adjusted if the study requires a break for operational reasons. The number of patients randomised as a percentage of the patients screened will be calculated. The data completion rate will be calculated. A rate of greater than 80% of patients with a complete data set will be considered satisfactory.

The mean and range of time taken to complete study measures will be calculated for the major assessment point prior to dose adjustment.

Descriptive statistics will be used to calculate the proportion of participants with improvements in preliminary efficacy measures. A cumulative responder graph for all changes in the worst pain score on BPI-SF on day 4 will be plotted. Sub-group analysis will be performed to evaluate potential biomarkers or responses. Missing data will be imputed where possible by carrying forward the last available measurement. The rate of adverse effects will be tabulated. A preliminary economic analysis will describe the direct cost of treatment, health services use and health-related quality of life measured using the EQ-5D-5L. A comparison of the interference of the subscale on BPI-SF and RUG-ADL between arms will also be conducted.

In the pharmacokinetic sub-study concentration-time data will be used to estimate the steady-state concentration (Css) of lidocaine the maximum observed concentration (Cmax) and the time to the Cmax. Css will be correlated with pharmacological effects of lidocaine.

Monitoring

Adverse events and serious adverse events will be reported using a secure online reporting system to enable study wide reporting and reviewed by an independent medical monitor. The role of the medical monitor[262] is to provide oversight and review of safety reports. Serious adverse events will also be reported to the relevant human research ethics committee.

Ethics and dissemination

Participant safety is paramount and will be carefully monitored. Standardised assessments for adverse effects are built into the trial protocol. The trial will be conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice Guidelines.[263]

Obtaining consent for this study will be a process of information exchange between the study staff, the potential participant and any other person the potential participant believes should be included in the discussion. The participant information sheet will be

used as a basis for the discussion, which will cover all procedures, benefits, burdens and side effects expected or possible during the study. No compensation is provided to participants.

Findings will be published in peer-reviewed journals and presented at local, national, and international conferences. This study will be considered suitable to progress to a phase III study if there is a completion rate where the confidence interval includes 80% and excludes 60%. Quantitative and qualitative data will be synthesised in an iterative process with the investigator team. Recommendations generated from the data synthesis will inform the design of a subsequent phase III study.

The protocol and Patient Information and Consent Form have been approved by Sydney Local Health District (Concord) Human Research Ethics Committee 2019/ETH07984 and University of Technology Sydney ETH17-1820.

Trial status

The current study protocol is version 3.0 dated 1 June 2022 Recruitment commenced 13th May 2019 and is expected to be completed by June 2023. Recruitment and trial operation have been impacted by Covid-19.

7.2.4 Discussion

This Project provides crucial feasibility data for a program of work that aims to improve the management of unrelieved neuropathic cancer-related pain and influence clinical practice. Unrelieved neuropathic cancer-related pain is highly prevalent, with a significant impact on the patient, carer, healthcare system, and society.[6] Continuous subcutaneous infusion of lidocaine for cancer-related pain is a promising intervention that has been prospectively investigated only rarely and inconclusively in small-scale randomised controlled trials with a short infusion duration. Lidocaine is currently used variably in clinical practice with a scant evidence base. Data generated by this work will directly lead to a recommendation to clinicians in the Australian Cancer Pain guideline recommendations[174] and support clinicians to provide the best evidenced-based neuropathic cancer-related pain management.

7.2.5 Declarations

Ethics approval and consent to participate

The protocol and Patient Information and Consent Form have been approved by Sydney Local Health District (Concord) Human Research Ethics Committee 2019/ETH07984 and University of Technology Sydney ETH17-1820. Protocol amendments are communicated by email and regular trial site meetings and trial investigator meetings after approval by the relevant ethics and governance committees.

7.3 Lidocaine for Neuropathic Cancer Pain (LiCPain): a pilot randomised controlled trial (final report)

7.3.1 Introduction

There is urgent need for improved interventions to manage neuropathic cancer pain. Pain with a neuropathic component affects up to 39% of people with advanced cancer, despite advances in treatment[43]. People with neuropathic cancer pain are significantly more likely to receive strong opioids, anticonvulsants, and antidepressants yet have worse physical, cognitive and social function[6].

New management strategies are required to reduce the impact of neuropathic cancer pain. There is level one evidence for systemic lidocaine infusion to improve chronic neuropathic pain[176]. However, despite its use in clinical practice[159-161, 215], few randomized controlled trials have evaluated systemic lidocaine in people with advanced cancer[142, 206]. The evidence to date is inconclusive on the benefit of systemic lidocaine in this population. Systematic review shows a signal of benefit for a short intravenous infusion of lidocaine[142]. A randomized controlled trial of subcutaneous lidocaine given over 5.5 hours was inconclusive[206], possibly due to subtherapeutic doses. To our knowledge, there are no randomized controlled trials evaluating an extended continuous infusion of lidocaine, however observational studies show benefit of infusions between 1 and 240 days[159, 160, 242, 264].

The purpose of this trial was to determine the feasibility of conducting an adequately powered randomized controlled trial of continuous subcutaneous infusion of lidocaine versus placebo in palliative care patients with neuropathic cancer pain.

7.3.2 Methods

Design

This pilot study comprised a phase II double-blind randomized controlled parallel group pilot of subcutaneous infusion of lidocaine hydrochloride or placebo over 72 hours for neuropathic cancer-related pain, a pharmacokinetic substudy, and a qualitative substudy of patients' and carers' experiences.

The trial and pharmacokinetic substudy are reported here according to the Consolidated Standards of Reporting Trials extension for randomized pilot and feasibility trials Checklist[265]. In-depth details are included in the published protocol paper [49] and the Australian New Zealand Clinical Trial Registry (ACTRN12617000747325), with summarized methods presented here. The qualitative substudy will be reported subsequently.

Ethics

All participants provided written informed consent. This study was approved by the Sydney Local Health District (Concord) Human Research Ethics Committee 2019/ETH07984 and the University of Technology Sydney ETH17-1820. A major protocol amendment was undertaken dated June 2022, which included reducing the analgesic pretreatment and expanding the definition of neuropathic cancer pain to include those who meet the International Association for the Study of Pain (IASP) definition of neuropathic pain[266].

Population

Participants were recruited from five palliative inpatient units in Sydney, Australia, between July 2019 and January 2024. The units comprised a total 107 beds and approximately 2500 new admissions per year. Key inclusion criteria were neuropathic cancer pain with a worst pain score ≥ 4 out of 10 on the Brief Pain Inventory-Short

Form, and an adequate trial of opioid and adjuvant analgesia. Neuropathic pain was defined as a Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale score ≥ 12 or meeting the IASP definition for neuropathic pain. Pain was related to cancer or its treatment. Key exclusion criteria were liver failure, chronic kidney disease stage V, cardiac failure, heart block, cardiac ischemia, Stokes-Adams syndrome, heart rate and blood pressure abnormalities, seizure, delirium and medications which interact with lidocaine (see also Supplementary Table 1).

Potential participants were invited to take part upon admission to the palliative care unit and during regular screening at each site.

Intervention

Participants were randomized 1:1 to receive the intervention or control, with both treatment groups receiving best practice standard of care. Intervention: Lidocaine hydrochloride 10% w/v (3000 mg/30 mL) diluted in sodium chloride 0.9%; Control: Sodium chloride 0.9%.

Study drugs were prescribed as a continuous subcutaneous infusion titrated every 24 hours to effect and adverse effects. The dose started at 1 mg/kg/hour (maximum 120 mg/hour). The participant was assessed for efficacy and toxicity on days 2 and 3, and the dose was increased by 0.5 mg/kg/hour every 24 hours to a maximum of 2 mg/kg/hour or 120 mg/hour (whichever is lower) unless the pain was well controlled, or toxicity was present. The dose remained the same if the patient's average and worst pain score in the last 24 hours was ≤3/10 on the Brief Pain Inventory (BPI-SF). A new or increased toxicity was managed according to the protocol, which could include treatment of the symptom, dose reduction or cessation of infusion. After 72 hours (on day 4), the infusion was ceased.

Concomitant care

The best practice standard of care included continuation of prescribed continuous and breakthrough analgesic (without further dose change) in both groups of the study.

Outcomes

The primary outcome was the proportion of study medication and procedures completed ('non-missing data'). Baseline data was collected on day 1. Efficacy, toxicity and serum concentration were collected on days 2, 3 and 4 with followup data collected on days 8, 15 and 29. The ideal (100%) 'non-missing data' was defined as having completed study medication and procedures on a daily basis by assigning a '1' for all completed assessments; and a '0' for incomplete assessments, or where the participant had withdrawn or ceased the infusion, from baseline to day four. This total was expressed as a proportion of the maximum score of 42. A 'non-missing data' proportion of more than 80% was considered feasible, while a confidence interval which included 60% was considered unfeasible. This outcome was chosen to ensure that participant fatigue and clinical instability would not be a barrier to completing this trial.

Secondary outcomes included the feasibility of conducting the trial, preliminary efficacy, toxicity, health outcomes and health service utilization associated with the intervention, and the relationship between lidocaine serum concentration and dose/efficacy/toxicity (Supplementary Table 2 and Supplementary Table 3).

Sample size and recruitment

Fleming's two-stage trial design was used to determine the sample size based on an acceptable completion rate of 80% and an unacceptable completion rate of 60%[49]. This calculation generates a range of values. A mid-value was selected taking into consideration that sufficient feasibility data is required to inform a future phase III study. The null hypothesis was that the true completion rate is 0.6 was tested against a one-sided alternative. In the first stage, 17 participants were accrued. As there were 15 or more responses (participants with a completion rate where the confidence interval included 80% and excluded 60%) from 17 participants, the study was stopped and the null hypothesis rejected. If there were 10 or fewer responses in these 17 patients, the study was to be stopped for futility. If there were between 10 and 15 responses, 19 additional patients would have been accrued for a total of 36. This design yielded a type I error rate of 0.05 and power of 0.8 when the true response rate was 0.8.

Blinding and allocation

All participants, study staff, clinicians and investigators except the sponsor national manager and statistician were blinded. Treatment for each participant was allocated in a 1:1 ratio.

Pharmacokinetic sampling and analysis

Participants in the pharmacokinetic substudy had steady-state blood samples collected at baseline (Day 1) and between 20-24 hours after dose titration. Samples were frozen at -80°C then transported at 4°C to the laboratory. Samples were analyzed using a validated high performance liquid chromatography (HPLC) assay [258] to estimate lidocaine and metabolite concentrations.

Data analysis

The primary analysis was conducted on a modified intention to treat basis, that is according to the participants' randomization for participants who received at least one dose of study treatment. Safety analysis was conducted according to the allocation for all participants who received at least one dose of study treatment.

The analysis was repeated in the per protocol set which comprised of all participants who received 72 hours of study treatment; according to the participant's actual allocation.

Pharmacokinetic data were reported using descriptive statistics. Categorical data were summarized using proportions and compared between treatment groups using risk ratios and Pearson's chi-squared tests. Continuous outcomes were described using mean and standard deviation for normally distributed data, and medians, maximum and minimum for non-normally distributed data. Between groups comparisons were conducted using generalized linear models. Unless otherwise stated, results are presented as mean (standard deviation).

7.3.3 Results

Demographics

Seventeen participants were randomized from 124 screened (Figure 7-1). The mean age of participants was 64.1 (11.2) years, mean weight 70.8 (23.3) kg and 77% were female. The mean worst pain score at baseline was 7.8 (1.2), with a mean daily oral morphine-equivalent regular opioid use of 189.2 (160.6) mg (Table 7-6).

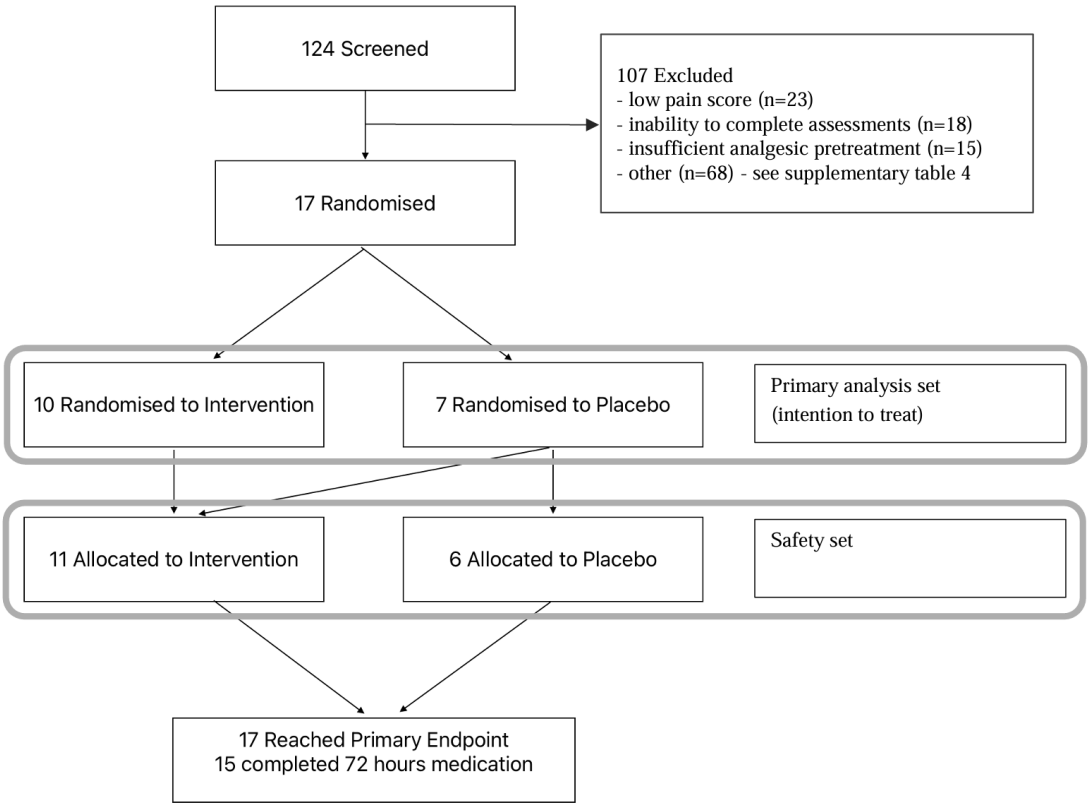

Figure 7-1: CONSORT diagram

Table 7-6: Participant demographics

Characteristic	**All n=17**	**Randomization Lidocaine n=10**	**Randomization Control n=7**	**P value**
Age, years mean (SD)	64.1 (11.2)	64.9 (11.0)	62.9 (12.3)	0.73
Sex: female (%)	13 (77%)	8 (80%)	5 (71%)	0.68
Weight, kg mean (SD)	70.8 (23.3)	61.4 (14.9)	84.1 (27.7)	0.045
Primary Cancer (%)				
Colorectal	5 (29%)	4 (40%)	1 (14%)	0.25
Breast	5 (29%)	2 (20%)	3 (43%)	0.31
Lung	4 (24%)	2 (20%)	2 (29%)	0.68
Other gastrointestinal	1 (6%)	0	1 (14%)	-
Other urological	1 (6%)	1 (10%)	0	-
Metastatic sites of cancer				
(%) Bone	11 (65%)	7 (70%)	4 (56%)	0.59
Lymph nodes	8 (47%)	6 (60%)	2 (29%)	0.20
Lung	5 (29%)	4 (40%)	1 (14%)	0.25
Liver	5 (29%)	3 (30%)	2 (29%)	0.95
Other	3 (18%)	2 (20%)	1 (14%)	0.76
Charleson Comorbidity Index mean (SD)	7.2 (2.2)	7.2 (2.1)	7.2 (2.5)	0.96
Interpreter required (%)	2 (12%)	1 (10%)	1 (14%)	0.79
Usual language: English (%)	13 (77%)	8 (80%)	5 (71%)	0.68
Worst pain in 24 hours prior to baseline from 0-10 mean (SD)	7.8 (1.2)	8.1 (1.4)	7.3 (1.1)	0.21
Average pain in 24 hours prior to baseline from 0-10 mean (SD	5.5 (1.8)	5.5 (1.5)	5.6 (2.4)	0.94
Leeds Assessment of Neuropathic Symptoms and Signs ≥12 (%)	8 (47%)	6 (60%)	2 (29%)	0.20

Baseline oral morphine equivalent, mg mean (SD)	189.2 (160.6)	199.7 (188.1)	174.2 (123.6)	0.76
Baseline oral morphine equivalent				
≥200mg		3 (30%)	2 (29%)	0.95
60-200mg		3 (30%)	4 (57%)	0.26
≤60mg		4 (40%)	1 (14%)	0.25
Baseline RUG-ADL mean (SD)	4 (4-10)	7.4 (4.5)	6.0 (3.5)	0.50
AKPS mean (SD)	50(11.2)	48.0 (12.3)	52.1 (9.5)	0.40
Other pain management exposure				
Patient education (%)	9 (53%)	4 (40%)	5 (71%)	0.20
Pain diary (%)	4 (24%)	3 (30)	1 (14%)	0.45
Physiotherapy (%)	10 (59%)	6 (60%)	4 (57%)	0.91
Occupational therapy (%)	7 (41%)	5 (50%)	2 (29%)	0.38
Psychology (%)	4 (24%)	2 (20%)	2 (29%)	0.68
Music therapy (%)	1 (6%)	1 (10%)	0 (0%)	-

Feasibility of completion and recruitment

Prescreening data identified that the most common reasons for exclusion were low pain severity (<4/10 worst pain on BPI-SF), inability to complete study assessments and inadequate analgesic pretreatment (Supplementary Table 1, Appendix C). Fourteen percent of screened participants were consented. It took 54 months to reach the sample size. The study was formally placed on hold for seven months due to COVID-19, with a staggered return of sites after this. Two sites were added in 2020 and 2022.

The median time taken to perform eligibility visits was 85 minutes (range 20-300), baseline 75 minutes (range 20-160) and subsequent follow-up visits 40 minutes (range 20-175).

There was a 93% completion rate of study medication and procedures (95% confidence interval 88-98%). Complete data sets were available for 29% of participants, and 82% had a 90% complete data set. The most commonly missed items were vital signs (1 to 2 sets missing in 24 hours) and missed individual questions in the BPI-SF and Neuropathic pain symptom inventory (NPSI) at cessation.

Eighty-eight percent (n= 15) of all participants completed 72 hours of study medication (82% in the intervention group vs 100% in the control group).

Preliminary efficacy

There was no significant improvement in pain measure in the intervention compared with control group. The mean change in worst pain on the BPI-SF was –1.0 (1.25) in the intervention and –2.0 (2.77) in the control group (p=0.32). Other outcome measures are tabulated in Table 7-7 and Supplementary Table 2, Appendix C. Preliminary efficacy was also examined based on the per protocol set (Supplementary Table 3, Appendix C). This accounted for two participants who did not complete the intervention due to toxicity, one participant who was randomized to control but was allocated intervention; and one participant who was missing the BPI-SF on day four. Similar results were obtained in both sets.

Table 7-7: Efficacy measures

Outcome	Randomized: Lidocaine	Randomized: Control	Risk ratio	p value
From baseline to cessation		**Participants with improvement:**		
Number (%) of participants with improvement of	**N=10**	**N=7**		
Worst pain of ≥1 point on BPI-SF	6 (60%)	4 (57%)	1.05	0.91
Average pain of ≥1 point on BPI-SF	3 (30%)	5 (71%)	0.42	0.09
Worst pain reduced to ≤3 on BPI-SF	1 (10%)	3 (43%)	0.23	0.12
Number of breakthrough pain medications used	3 (30%)	2 (29%)	1.05	0.95
Number of participants with improvement of ≥1 point:	**N=9**	**N=7**		
Burning (superficial) spontaneous pain on NPSI (%)	3 (33%)	4 (57%)	0.58	0.34
Pressing (deep) spontaneous pain on NPSI (%)	2 (22%)	4 (57%)	0.39	0.15
Paroxysmal pain on NPSI (%)	4 (44%)	5 (71%)	0.62	0.28
Evoked pain on NPSI (%)	2 (22%)	4 (57%)	0.39	0.15
Paresthesia/Dysesthesia on NPSI (%)	3 (33%)	4 (57%)	0.58	0.34
Pain	**N=10**	**N=7**		
Worst Pain, median (min, max)	-1.00 (-3.00, 1.00)	-2.00 (-5.00, 2.00)		0.33
Average Pain, median (min, max)	0.00 (-3.00, 3.00)	-2.00 (-7.00, 1.00)		0.05

No. of breakthrough medications used, median (min, max)	1.00 (-5.00, 5.00)	1.00 (-2.00, 2.00)	0.95
Neuropathic Pain Symptom Inventory	**N=9**	**N=7**	
Total Intensity on Neuropathic Pain Symptom Inventory (out of 100)	2.00 (-17.00, 62.00)	-27.00 (-41.00, -1.00)	0.02
Burning (Superficial Spontaneous) Pain	0.00 (-9.00, 2.00)	-2.00 (-9.00, 6.00)	0.92
Pressing (Deep Spontaneous) Pain	0.00 (-5.00, 2.50)	-3.00 (-6.50, 0.00)	0.09
Paroxysmal Pain	-0.50 (-8.00, 0.50)	-1.00 (-10.00, 0.00)	0.59
Evoked Pain	1.17 (-3.33, 6.33)	-1.33 (-3.67, 1.67)	0.08
Paresthesia/Dysesthesia	0.00 (-2.50, 8.00)	-1.00 (-5.00, 0.00)	0.05
At cessation:			
Global impression of change (number)	**N=9**	**N=7**	0.31
very much improved	1 (11%)	0 (0%)	
much improved	1 (11%)	4 (57%)	
minimally improved	2 (22%)	2 (29%)	
no change	2 (22%)	1 (14%)	
minimally worse	0 (0%)	0 (0%)	
much worse	1 (11%)	0 (0%)	
very much worse	2 (22%)	0 (0%)	

Preliminary toxicity

The safety analysis set comprised of 11 participants in the intervention group and six participants in the control group. There were 37 treatment-emergent adverse events (TEAE) experienced during the trial from baseline to cessation, 29 in the intervention and 8 in the control group (Table 7-8). Overall, nine (82%) people in the intervention and four (67%) in the control group experienced one or more TEAEs (p=0.48). These included 'possibly, probably or definitely related' adverse events (AE) events in both groups.

The most common TEAEs for the intervention group were tremor (n=3), ataxia (n=3) and fatigue (n=3). No changes in electrocardiogram (ECG) were seen. Four participants in the intervention group and one in the control group had changes in vital signs. Grade 3 (severe) or worse TEAEs occurred in two participants in the intervention group and two participants in the control group. The remaining adverse events were mild or moderate. There were no serious adverse events reported while on the intervention. Three participants in the intervention and two in the control group had adverse events resulting in reduced or discontinued study infusion.

Adverse events during follow-up are tabulated in Supplementary Table 4, Appendix C. There were four serious adverse events of "neoplasm" leading to death: in the intervention group one occurred during follow-up and two were an incidental finding post-study; in the control group one death occurred during follow-up (p=0.62). There was one serious adverse event of "confusion" in the control group.

Table 7-8: Treatment emergent adverse events

		All events (n=37)		**Grade 3 or worse (n=4)**	
System Organ Class	Preferred Term	Allocated to lidocaine (n=11)	Allocated to control (n=6)	Allocated to lidocaine (n=11)	Allocated to control (n=6)
Total number of adverse events		29	8	2	2
Nervous system disorders	Tremor	3 (27%)	0	0	0
	Ataxia	3 (27%)	0	0	0
	Dizziness	2 (18%)	0	0	0
	Paresthesia	2 (18%)	0	0	0
	Somnolence	2 (18%)	0	0	0
	Lethargy	1 (9%)	0	0	0
	Movement Involuntary	0	1 (17%)	0	0
General disorders and administration site conditions	Fatigue	3 (27%)	0	2 (18%)	0
	Hyperhidrosis	1 (9%)	0	0	0
	Injection Site Reaction	0	1 (17%)	0	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	2 (18%)	0	0	0
	Sore Throat	1 (9%)	0	0	0
Eye disorders	Blurred Vision	2 (18%)	0	0	0
Cardiac disorders	Palpitations	1 (9%)	0	0	0
	Sinus bradycardia	1 (9%)	0	0	0
	Sinus Tachycardia	1 (9%)	0	0	0
Vascular disorders	Hypotension	1 (9%)	0	0	0
	Hypertension	1 (9%)	1 (17%)	0	1 (17%)
Musculoskeletal disorders	Myalgia	0	1 (17%)	0	0
	Back pain	1 (9%)	0	0	0
Gastrointestinal Disorders	Abdominal Pain	0	1 (17%)	0	1 (17%)
	Nausea	0	1 (17%)	0	0
Ear and labyrinth disorders	Tinnitus	1 (9%)	0	0	0
Psychiatric Disorders	Confusion	0	1 (17%)	0	0
Infections and Infestations	Fever	0	1 (17%)	0	0

Feasibility of collecting data to inform economic analyses

Collecting data on health outcomes and resources used to inform economic analyses was feasible, including counting the number and length of hospital admissions and intervention use. Completeness and outcomes are shown in Table 7-9. The median baseline utility value was 0.50 (range 0.03-0.96). Three participants were admitted for three or four days and one outlier for 127 days. The remainder ranged from 9 to 67 days. The cost of lidocaine at the lead site was AUD$2.37 per 500mg, giving a median medication cost of $31 for the duration of the intervention.

Table 7-9: Health outcomes, resource use and costs

	Complete data	**median**	**range**
Change in utility value (n=15)	88%	0.12	-0.34 to 0.36
Daily cost based on AR-DRG (AUD$) (n=16)	94%	1551.90	1246.19 to 1696.80
Length of stay (days) (n=17)	100%	23	3 to 127
Lidocaine use (mg) (n=17)	100%	6420	2000 to 8400
Change in RUG-ADL (n=17)	100%	0	-6 to 0
Change in AKPS (n=17)	100%	0	-20 to 20
Change in Pain interference (n=15)	88%	2.14	-1.14 to 5.00

RUG-ADL = Resource Utilisation Groups – Activities of Daily Living; AKPS = Australia-modified Karnofsky Performance Status; AR-DRG = Australian Refined Diagnosis Related Groups

Pharmacokinetic data

Two of the five participants who consented to the pharmacokinetic substudy were allocated to intervention. Figure 7-2 and Table 7-10 show total and unbound lidocaine concentration data.

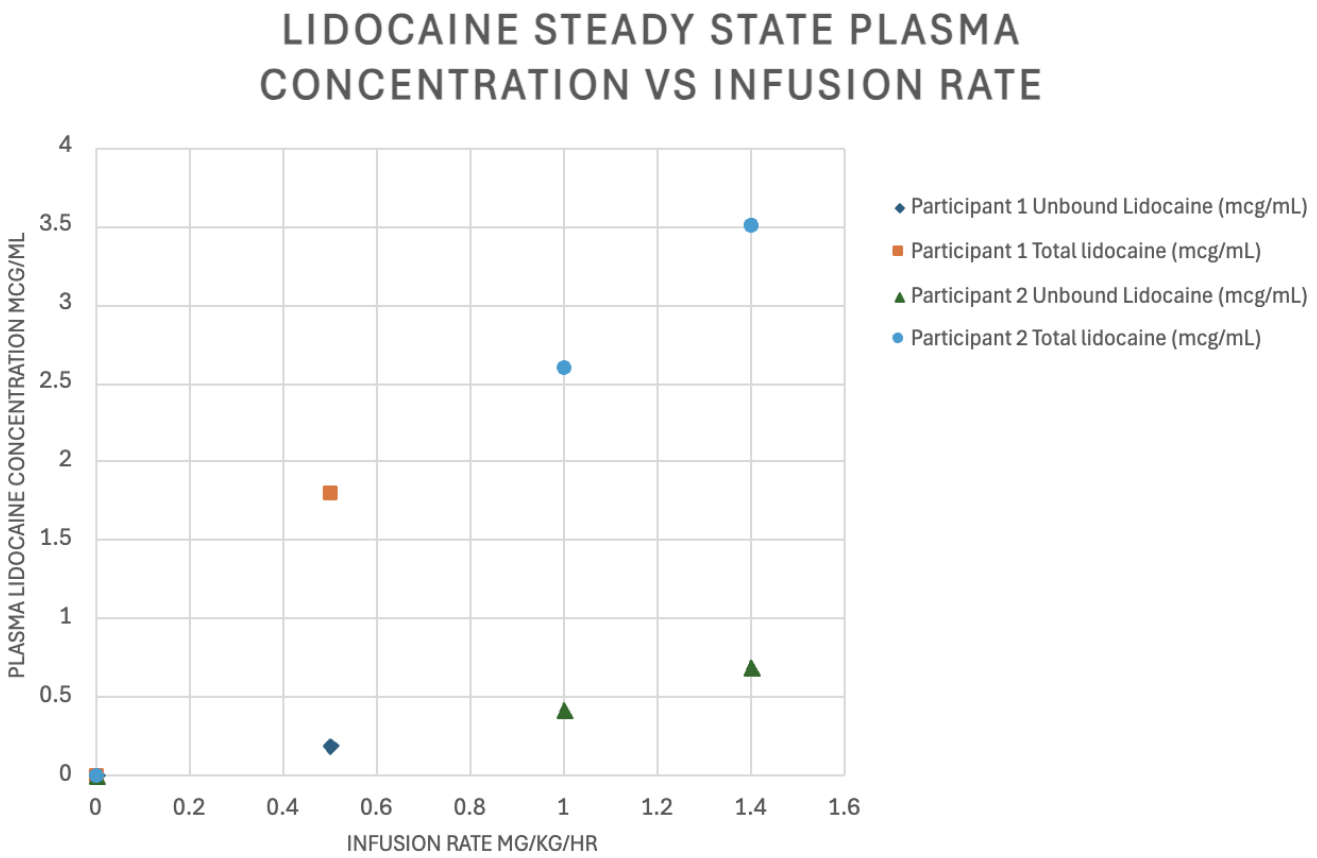

Figure 7-2: Pharmacokinetics of lidocaine in two participants

Table 7-10: Total and unbound lidocaine concentration data

Infusion dose for 24h prior (mg/kg/h)	Unbound lidocaine (mcg/mL)	Total lidocaine (mcg/mL)	Participant	Treatment Emergent Adverse Events
0	<0.05	<0.1	1, 2, day 1	N/A
0.5	0.18	1.8	1, day 4	Increase in tremor and paresthesia from grade one to grade two together with perioral numbness on day two. Dose reduced from 1mg/kg/h to 0.5mg/kg/h at 2100 on day two. Symptoms were resolved by assessment at 1100 on day three. Pharmacokinetic data for days two and three are missing.
1	0.41	2.6	2, day 2	Grade one hypertension up to 169/68mmHg, increased from baseline of 152/79mmHg.
1.4 (capped at 120mg/h)	0.68	3.5	2, day 3	Grade one ataxia and an increase in tremor and lethargy from grade one to grade two.
1.4	0.69	3.5	2, day 4	

Intervention exposure

Of those allocated to intervention, four were capped at 120mg/h, three reached 2mg/kg/h, and four had the dose reduced or ceased. The mean maximum dose in those who had a reduction in worst pain of ≥1 and received intervention was 1.5 (0.5) mg/kg/h compared with 0.9 (1.0) mg/kg/h in those who did not respond (p=0.25).

7.3.4 Discussion

To our knowledge, this is the only prospective Phase II randomized controlled trial (RCT) of an extended continuous subcutaneous lidocaine infusion. Other trials in people with cancer have investigated shorter subcutaneous [206] and intravenous [142] infusions of up to 5.5 hours. This study provides important feasibility data for a phase III clinical trial of extended subcutaneous lidocaine infusion. It provides systematically collected data informing lidocaine dosing and adverse effects in the clinical management of people with neuropathic cancer pain, adding to previous retrospective observational studies[159, 160, 215]. This study contributes significantly to the sparse literature prospectively evaluating subcutaneous infusions of lidocaine in people with neuropathic cancer pain.

Intervention feasibility

This study shows that it is feasible to complete a 72-hour infusion of subcutaneous lidocaine in people with neuropathic cancer pain, titrating daily from 1mg/kg/h to 2mg/kg/h with a maximum dose of 120mg/h. Eighty-eight percent of participants completed 72 hours of study medication. International use of lidocaine varies widely[264], and this study adds to the evidence that this dose algorithm could be used in clinical practice. However, clinicians should note that there is insufficient evidence to use continuous subcutaneous lidocaine infusions for neuropathic cancer pain. It should be considered if other evidence-based strategies are not suitable or in the context of a clinical trial. Any risk and benefit should be carefully assessed.

Few participants who consented to the pharmacokinetic study were randomized to intervention. Future trials might stratify for this sub-study. An open label

pharmacokinetic study with pain scores and toxicity correlation may further inform dosing. Consistent with other reported data[206, 215, 242], serum lidocaine levels during this subcutaneous infusion appear to be lower than reported for intravenous infusions for cancer pain[161, 208, 242]. The highest lidocaine level was 3.5mcg/mL which is well below the 5 mcg/mL threshold for serious adverse effects[168]. Therapeutic levels of lidocaine for pain are not well established, however these fall within the quoted ranges of 2.5-3.5 mcg/mL [206] and 1.5-5 mcg/mL[215]. Participant one had a lower level of 1.8mcg/mL, in keeping with the lowered dose of 0.5mg/kg/h, below the starting dose. Given the relative safety demonstrated, higher lidocaine doses could be cautiously evaluated.

This pilot study was not powered for efficacy, however, both groups demonstrated a reduction in pain, with both the response rate and magnitude greater in the control group. The control response rate of 57% in this study was higher compared to other cancer pain studies which found placebo response rates of up to 27%[267, 268]. Previous research has found that studies with blinded outcome assessor and concealed allocation have a higher placebo response[269]. Further research into whether specific features of this trial design, population or intervention contributed to the high placebo response may inform future cancer pain studies and delivery of the intervention.

Structured assessment found no significant difference in toxicity between lidocaine and placebo groups regarding the number of participants experiencing one or more TEAE or grade 3 or worse or serious AE. This study was not powered to compare AE between groups and caution is needed when interpreting this data to inform clinical practice. The rate of adverse events in both the intervention and control groups was higher than previously reported observational studies of extended subcutaneous lidocaine infusion[160, 161], and randomized controlled trials of shorter infusions[178]. Most adverse events in this study were of low severity. The most common were nervous system disorders. This study highlights the importance of daily structured clinical assessment and awareness of potential toxicities for early recognition of adverse effects for people on lidocaine infusions in both clinical practice and future clinical trials. Cardiac and vascular events noted such as changes in heart rate and blood pressure may not be of clinical significance. Many AEs, including those graded serious, occurred in the follow-

up or post-study phase, which may be expected in this population given their comorbidity and frailty, and are unlikely to be attributed to the intervention itself[270]. All participants who died were in the follow-up or post-study phase.

Despite daily monitoring, the lack of ECG changes suggests that it may be safe to conduct a future phase III trial at this dose with clinical assessment but without ECG monitoring. This is consistent with previous studies[162]. It is the first trial to prospectively record ECG in this population.

Trial design feasibility

Trial processes piloted were feasible for participants to complete with 93% completion of assessments and intervention, with the least compliance in vital signs and missed individual questions in the BPI-SF and NPSI at cessation. Key strategies to address this missing data may include limiting the collection of patient-reported outcomes to reduce the burden for participants and providing incentives for completeness of data collection[271]. Alternate methodological design such as the estimand framework could be considered to handle participants who cease the intervention or are lost to follow-up due to their underlying disease[272].

The slow recruitment rate of this study highlights the challenges in recruiting to clinical trials in inpatients with neuropathic cancer pain. These are reflected in trials with similar populations[7, 252, 273]. It was noted that in addition to the reasons captured in prescreening, many inpatients were not screened due to cognitive impairment or being too unwell to complete assessments. There were unpredictable extended periods of challenging recruitment at each site due to staffing vacancies, competing clinical priorities and inpatient service constraints. A phase III trial will require modification to the design and recruitment strategy to ensure it is able to be completed in a reasonable timeframe and budget. Modifiable factors may include inpatient requirements and level of pretreatment of analgesics. Using the IASP definition of neuropathic pain [266] allowed inclusion of participants with clinician diagnosed neuropathic cancer pain who did not meet the LANSS cutoff, reflecting decision-making in clinical practice. Assessments could be adapted to allow more unwell people to participate. A future trial may consider

evaluating this intervention in both neuropathic and non-neuropathic cancer pain, as in previous trials[178, 206]. Alternate study designs may more efficiently guide practice, especially those which integrate systematic collection of evidence of efficacy into routine clinical care or provide an incentive to the control group through standardization of best practice care in both arms or a waitlist control design. The high placebo response rates in this study may be a helpful recruitment aid to future randomized trials.

Health economic data was feasible to collect. This population had a relatively poor quality of life compared with the Australian general population[252, 273], similar to other studies of neuropathic cancer pain[7]. The cost of the inpatient stay is high compared to the drug cost. Use of the intervention as an outpatient would significantly reduce this cost.

Limitations

This study shows that the intervention is feasible in this population, however selection bias may have excluded frailer people from this evaluation. The inclusion criteria are narrow, limiting the generalizability of this study but can be modified. Safety data from this study and other recent studies [162, 206] may facilitate this. Covid-19 impacted the recruitment to this study directly due to clinical trial activity hiatus of up to two years and indirectly due to staff focus on clinical responsibilities, fewer research staff, reduced inpatient beds and increased reluctance for participants to be admitted to the hospital. Finally, the low uptake of the pharmacokinetic substudy limited the ability to correlate the clinical outcomes in these participants with a lidocaine level. Considering Hawley's recent study, there is concern whether the lower-than-expected serum levels could impact the preliminary efficacy.

7.3.5 Conclusion

This pilot RCT demonstrates that a randomized controlled phase III clinical trial of continuous subcutaneous infusion of lidocaine for neuropathic cancer pain is feasible, however the current design would require modification to improve recruitment rates. It provides important insights into the design of clinical trials of lidocaine for people with neuropathic cancer pain and identifies areas to optimize, such as recruitment. As the

only RCT to date of extended continuous subcutaneous infusion of lidocaine for neuropathic cancer pain, it adds to the evidence informing clinical use of lidocaine infusions, which are currently used in clinical practice allowing clinicians to better evaluate the risk and benefit.

7.4 Pragmatism in the LiCPain trial

The pilot LiCPain trial was designed to be as pragmatic as possible, informing the use of lidocaine infusions by providing evidence for adoption of the intervention into real-world clinical practice.[274] In an ideal pragmatic trial, the participants, setting and intervention delivery should reflect the usual conditions under which the intervention would be implemented.[275] During this trial it was identified that the participants did not reflect the demographics of people with neuropathic cancer pain in terms of their cultural and linguistic diversity and the presence of a neuropathic component of pain. The specific protocol amendments designed to rectify these trial design limitations are discussed below.

7.4.1 Culturally and linguistically diverse participants

The November 2020 amendment to allow inclusion of culturally and linguistically diverse participants was felt to be essential to reflect the 9.2% of people with distress from cancer pain in the last week of life (Study 1). Study sites reported that potential participants were excluded prior to the prescreening phase due to lack of English language ability. The importance of including CALD participants in clinical trials is recognised,[276, 277] and there are barriers to inclusion at a systemic and individual trial level.[277-279] Watson et al. identified language and consent as key factors on which to focus to improve participation of CALD communities in clinical trials.[276] Accordingly, the researchers modified the domains in order to make the LiCPain trial more accessible to CALD participants.

Validation of patient-reported outcomes

Ideally a trial would use validated translated patient-reported outcomes for all participants who speak a language other than English, because concepts may be

understood differently in translation. However, the small number of patient-reported outcomes and the wide range of possible translations necessitated a choice between the ideal outcome measures and inclusion of language groups. The LiCPain amendment added translated patient-reported outcomes where available, but allowed use of an interpreter if the preferred language or tool was unavailable, aligning with a pragmatic approach.

Consent

Informed consent was achieved via employing interpreters to administer the English language consent form. Interpreter details were recorded in the medical record. It is known that participants may not fully recall the informed consent discussion or may wish to refer to it later. Alternate strategies, not offered in this trial, include simplified consent forms[276] and audio-recording the consent discussion. Audio-recording may pose other barriers such as concern about misrepresentation or embarrassment at the sound of the participant's own voice,[280] which could be reduced by offering participants a choice and ownership of the recording. All participants should have the opportunity to review the written information form and share it with trusted carers or advisors if wished. Translation of the consent form was considered, but deemed impractical due to cost and uncertainty about which languages would be required.

Determination of language groups

Although the languages other than English most frequently used in the population served by the trial unit were known (Chinese, Arabic and Vietnamese),[277] at an individual level it was not possible to predict which language, or cultural variation of a language, otherwise eligible participants might speak. Across Australia, 22.3% of people speak a language other than English at home, but the top five such languages are spoken by only 7.5% of Australians.[277] It was decided the most equitable plan was to include these participants using an interpreter to assist them to complete measures not available in their language.

Future trials could consider using a structured toolkit[276] to design culturally inclusive clinical trials.

7.4.2 Determining neuropathic cancer pain

Neuropathic cancer pain was defined as pain with a neuropathic component that the clinician assessed met the IASP criteria for neuropathic pain ("pain arising as a direct consequence of a lesion or disease affecting the somatosensory system"[230] or with a score of 12 or greater on the LANSS).[20] Mixed neuropathic/nociceptive pain was included, as well as cancer-induced bone pain, which is considered to have a neuropathic component.[14]

This definition was broadened from the original (based purely on the LANSS score) to better reflect the real-world target population. This pragmatic approach improves the relevance of study outcomes to people with neuropathic cancer pain seen in clinical practice and better informs implementation of the results of a subsequent phase III trial. The LANSS score was noted by study teams to exclude a number of people with probable or definite neuropathic cancer pain; in particular, it was noticed to have low sensitivity for coeliac plexus pain which typically did not result in skin changes. This is consistent with a systematic review of neuropathic cancer pain studies which found that the median LANSS score for patients with clinically diagnosed neuropathic cancer pain was 12, which is the cut-off point for 'likely neuropathic pain'.[19(p770)] It is important to note that the LANSS is a screening tool rather than a diagnostic tool.[19(p770)]

Allowing clinician diagnosis of neuropathic pain aligned the inclusion criteria with the EAPC/IASP modified clinical diagnostic algorithm for neuropathic cancer pain.[12] This algorithm diagnoses a clinical hypothesis of neuropathic pain based on history and examination, which is divided into probable or definite neuropathic pain based on the presence of a confirming history of relevant etiologic lesion from medical notes and/or diagnostic tests.[12] LANSS screening together with other history and examination could be used to guide clinical assessment to make the diagnosis of neuropathic cancer pain. Further research to accurately identify neuropathic cancer pain will inform clinical trial design and clinical assessment.

7.5 Ethical considerations of the LiCPain trial

A comprehensive plan to ensure ethical conduct of the LiCPain trial (Studies 4 and 5) was approved by the Sydney Local Health District (Concord) Human Research Ethics Committee and ratified by the University of Technology Sydney Human Research Ethics Committee. Key components included informed consent, equity of inclusion, conducting research in a frail and fatigued population, equipoise, psychological safety and data management. All personnel involved in the clinical trial were required to have certification of good clinical practice training. This ensured they were aware of their roles and responsibilities in ethical conduct of the clinical trial, in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines.

Informed consent was obtained from every participant based on a written participant information and consent form, which was developed with input from clinicians and a consumer. All investigators were trained to offer participants the opportunity to engage a carer in the decision to participate.

Including people who spoke a language other than English involved extra difficulty (see Section 7.4.1), but was important to ensure equity of access and generalisability of results. Practical constraints prevented translation of the study materials, so healthcare interpreters were used to facilitate participation. The support from health districts varied, meaning only some recruitment sites could access interpreters. Patient-reported outcomes required validation for each new language administered and this could not be achieved for all outcomes in all languages. The ability to use an interpreter to assist the participant to complete the patient-reported outcome was a pragmatic decision chosen to facilitate inclusion despite budget and scientific limitations.

Inpatients with advanced cancer represent a particularly vulnerable population. They may have a prior relationship with the research team, which requires careful management using a third-party researcher and careful communication. Many participants fatigued easily, and the balance between collecting data and not causing burden was important to consider in study design.

All participants had pain, and care was required to ensure there was equipoise between the two arms, in particular for the control arm. The use of placebos is problematic in cancer pain trials.[268, 281] For people with unrelieved neuropathic cancer pain despite opioid and conventional adjuvant analgesics, there is currently no proven standard therapy.[13, 46, 47] An important component of the intervention was to allow continued breakthrough opioid dosing to ensure participants had the ability to manage the changing nature of neuropathic cancer pain.

Psychological safety is important in clinical trials, especially if participants are asked questions about distress, and in interview studies. Hence, a management plan for distress included immediate validation and support and escalation to the clinical team, which included multidisciplinary experts in psychosocial care.

A comprehensive data management plan, specifying means of ensuring privacy and security, was approved by the aforementioned ethical and governance committees.

7.6 Chapter summary

This chapter describes the methodology and results of the quantitative component of the LiCPain pilot RCT. It presents a discussion of key learning points which may help future researchers to undertake pragmatic trials in people with neuropathic cancer pain and clinicians prescribe and monitor continuous subcutaneous lidocaine infusions. Both intervention feasibility and trial design feasibility were evaluated in this trial. Future similar trials could increase the clinical relevance of results by giving greater priority to outcomes informing intervention feasibility. For example, stratification for pharmacokinetic substudy consent may have increased the useful data obtained.

This chapter demonstrates that a phase III RCT of continuous subcutaneous infusion of lidocaine for neuropathic cancer pain is feasible, and provides important insights into feasibility, population selection, recruitment and safety in order to optimise the design of future similar trials. Additional pilot studies may be considered to further evaluate design improvements, efficacy and safety of different dosing protocols.

Chapter 8 reports the qualitative results from the interview sub-study (Study 5) embedded in the LiCPain trial.

Chapter 8 Participant perspectives of the feasibility and acceptability of the LiCPain pilot RCT: an embedded semi-structured interview study

8.1 Chapter preface

This chapter provides a discussion of participants' and carers' experiences of the LiCPain trial through a thematic analysis of semi-structured interviews. Improving outcomes for people with neuropathic cancer pain requires the design and evaluation of novel interventions. In turn, this requires understanding the experience of people who participate in clinical trials for neuropathic cancer pain. Phillip et al. produced a framework for qualitative research embedded within clinical trials that can be used to refine study procedures and outcome measures, sample selection, the intervention design, and translation of results.[282] Their framework provided valuable guidance for using the experience of participants' study procedures, as well as their experience of the LiCPain intervention and its interaction with neuropathic cancer pain to inform the operationalisation of the LiCPain trial. A team of investigators conducted this qualitative analysis under the leadership and oversight of the doctoral candidate, with initial data coding and analysis by investigator EH and supervisors ML, JLP and MA.

This chapter contains a manuscript presenting the themes identified in the interviews from the LiCPain trial (Study 5), formatted to conform to thesis guidelines.

Lee JT, Agar M, Phillips J, et al. Feasibility and acceptability of "LiCPain" Pilot RCT: Perceptions and experiences of people with neuropathic cancer pain receiving continuous subcutaneous infusion of lidocaine or placebo and their carers. Submitted on 4th October 2025.

8.2 Feasibility and acceptability of the LiCPain pilot RCT: Perceptions and experiences of people with neuropathic cancer pain receiving continuous subcutaneous infusion of lidocaine or placebo and their carers

8.2.1 Introduction

Optimal clinical trial design and governance requires consumer contribution. Understanding participants' experiences in feasibility studies allows trial and intervention designs to be adapted to ensure that trials are feasible and solutions meet the needs of the target population. People with advanced cancer may have competing priorities and low capacity to engage in research design, so qualitative interviews allow the voices of this group of people to be heard.

Few extant studies of interventions for neuropathic pain in advanced cancer include a qualitative component; most collected data from cancer survivors or people with good performance status.[283-286] It is important to understand the experience of people with more advanced cancer living with neuropathic pain.

We conducted a pilot randomised controlled trial (RCT) of continuous subcutaneous infusion of lidocaine hydrochloride 10% w/v (3000 mg/30 mL) or placebo (sodium chloride 0.9%) over 72 hours in people with unrelieved neuropathic cancer pain. This qualitative study was embedded within the published pilot RCT[287] (ACTRN12617000747325).

8.2.2 Aim

To understand the experience of patients and carers participating in the LiCPain RCT and the acceptability and feasibility of the proposed trial design.

8.2.3 Methods

Study design

An exploratory descriptive qualitative[288] sub-study of participants and their carers in the LiCPain pilot RCT, using semi-structured interviews.

Setting

This study was conducted across five Australian palliative care inpatient settings with between 17 and 28 beds and 350 to 670 admissions per year, during 2019–24.

Participant selection and method of approach

All participants in the pilot double-blind randomised controlled parallel-group pilot and their carers were invited by the study nurse or investigator to participate in a qualitative interview at the time of consenting to the main study.

Sample size was determined by the pilot RCT recruitment pool. Data saturation was assessed during analysis, and it was felt that the data was of sufficient quality to allow generation of meaningful themes.[289]

Data collection

A single face-to-face or telephone interview was conducted with each consenting participant within two days of completion of the primary endpoint (day four to six) using a piloted semi-structured interview guide (Table 8-1 and Supplementary Table 5, Appendix D). Face-to-face interviews were conducted alone at the participant's bedside or in a quiet space on the ward. The interview was audio-recorded and transcribed verbatim by DeliverHealth, Inc and confirmed by JL. Field notes were not taken. Transcripts and findings were not returned to participants for checking due to the length of time between interview and transcription and the poor prognosis of the participants.

Table 8-1: Patient interview guide

Topic	Initial open questions	Possible probing questions
Overall study	How have you found being involved in this study?	What things did or didn't you like about being involved? Are there any changes you would recommend? Would you recommend this study to another patient? Why/Why not?
Feasibility of phase III	What concerns did you have about participating in this study?	Were there any things that may have stopped you from participating initially? What positives and negatives did you find from participating in the study? Did you worry about being in the placebo arm?
Specific components (if not already covered)		Using a syringe driver Subcutaneous route Hospitalisation Assessments Having other medications unchanged during the study
Translation to practice	Would you use this treatment if it was found to be effective?	What would make you more or less likely to try this treatment outside of a trial?
Pain experience	How has having pain affected you?	Are there any aspects of how pain affects you that we haven't assessed in this trial which you would like to discuss?

Research team and reflexivity

The research team comprised female and male Australian clinicians, academic researchers and a consumer. Interviewers were female registered nurses and a palliative care physician (JL) from the study team at each site, often with established relationships with participants from the trial or clinical care. Participants were aware of the purpose

of the study as discussed in the consent process, but not the researchers' personal motivations. The principal investigator was a female PhD candidate and admitting physician at the lead site with prior practical and theoretical experience in qualitative methodology, guided by experienced team members. Reflexivity was practised during design and analysis through reflection and collaboration.

Data analysis

Data were analysed following Braun and Clarke's reflexive thematic analysis approach.[290, 291] Thematic analysis[290, 291] was grounded in a pragmatist research paradigm.[292] Six steps were followed.[293]

- *Familiarisation with the dataset*. Interviews were transcribed by a professional transcription service. No field notes were taken. The interviews were reviewed (JL), and transcripts confirmed (JL) and deidentified (JL).
- *Coding*. Two researchers (JL and EH) initially coded the transcripts, with some transcripts having a third coder (JLP or ML). Data were coded into categories without fitting into a pre-existing coding frame or researcher preconception. Codes generated by the researcher were formatted into tables with relevant quotes using Microsoft Word.
- *Generating initial themes*. Codes were combined with other codes to form potential overarching themes and sub-themes (JL, EH) and refined (JL, JLP, ML, MA).
- *Developing and reviewing themes*. The themes were reviewed in relation to the coded extracts and the entire dataset (JL, JLP, ML, MA)
- *Refining, defining and naming themes*. Themes were further refined and named (full investigator team).
- *Writing up*. The initial draft report was written by JL and refined by all investigators.

Ethical considerations and reporting

This study was approved by the Sydney Local Health District HREC 2019/ETH07984. Written consent was obtained from each participant. The voluntary nature of

participation was emphasised, including participants' freedom to withdraw at any time. No incentives were offered. Reporting of this study adhered to the COREQ checklist.[294]

8.2.4 Results

Demographics

One hundred and twenty-four patients were screened to participate in the LiCPain pilot RCT. Of 17 participants randomised to the LiCPain trial, seven patients (P1–7) and one carer (C1) of an interviewed participant (P1) consented and contributed to the qualitative sub-study. Eight participants declined. One participant (patient) consented to participate but became too unwell, and another did not have a carer. The semi-structured interviews ranged in length from 15 to 60 minutes.

Interviewed patients were between 41 and 75 years old (median 70 years), and five were female. Their primary cancers were breast, colorectal, prostate or urological. All participants usually spoke English at home. The median worst pain score was 8 on a 10-point numeric rating scale (range 7–10) and the baseline oral morphine equivalent intake was 30 to 285 milligrams daily. Their median baseline Australia-modified Karnofsky Performance Status (AKPS),[253] which measures performance status on a scale from zero (dead) to 100 (normal, no complaints, no evidence of disease), was 40 (range 20–60).

Main findings

Three major themes were identified:

1) trial participation offered a sense of hope and purpose;

2) the impact of the intervention has multiple contributing factors; and

3) pain affects every aspect of life.

Theme 1: Trial participation offered a sense of hope and purpose

Sub-theme 1A: Altruism and legacy

Many participants identified their rationale for being in the trial as to help other people. Participant P2 wanted to be in the trial:

Just for the sake of helping out.

Taking part in this study matched with most participants' philosophy that:

...participating in research is for the good of all. (P3)

Study participation met their desire to continue learning as an individual and as a society.

> *I have a real thing about learning and what you need to do. And you know, that if I want to benefit from any of these sort of research things, then I need to also be a part of doing it ... If we don't actually participate, then we're not going to get any benefit from any of the changes; nothing is going to change. And in fifty years time, it'll still be exactly the same.* (P4)

Participants felt proud that they would leave a meaningful legacy. Participant P5 stated:

> *It's the future of medicine, you know. I mean it's us, but there's a lot of people that might be helped by it.*

Sub-theme 1B: Trial participation: a help or hindrance?

When deciding whether to take part in this trial, participants weighed the risks and benefits for themselves. Key concerns were the risk of side effects and the inconvenience of participating in the trial.

> *At the back of my mind, I was just thinking of the potential side effects. Because I am quite sensitive to medication, I didn't know how I would react.* (P3)

Participants balanced this concern with the hope that the trial would broaden their therapeutic options and relieve their pain, as well as provide the satisfaction of helping others. A carer said the following about her husband:

> *... when he was on the trial, I think it was a positive sign for him. He probably thought "This is it. This is something that's going to take away this dreaded pain."* (C1)

Sub-theme 1C: Monitoring and control can assuage uncertainty

Uncertainty about their clinical condition before, during and after the trial distressed some participants:

> *What is affecting me is driving here every morning thinking "what am I going to find?" Once I get here and see what's happening, then I just get on with it.* (C1)

Plans for close monitoring eased concerns about uncertainty and adverse effects. Participant P3 stated:

> *I was well monitored by [researcher]. So I was at ease after, like, a few hours of participating kind of knowing that I was monitored. If something happened, I was kind of in good hands.*

The importance of maintaining control was mentioned in multiple settings. Participants valued being in control of trial participation:

> *... so long as it wasn't going to increase the pain at all, and I knew that any time if it did, I could stop.* (P5)

Participants valued verbal and written communication about management plans. The carer described how a written plan on a whiteboard in the room contributed to a sense of control.

> *[it was helpful] to know what drugs were coming, what drugs were to be given at certain times, what we could do to ease.* (C1)

Sub-theme 1D: Acceptable despite frustrations

Most participants felt trial processes were "very easy" (P4) and overall had a positive experience.

> *I didn't have to involve myself too much, I just had to be the subject of examination. So I didn't feel that there was much work required from me other than providing any medical things I was feeling at the time.* (P1)

Some participants found the assessments "a little bit repetitive" (P2) and tiring:

> *It nearly wore me out.* (P5)

Participants did not worry about changes to usual management on the trial such as keeping medications unchanged.

Staff professionalism, organisation, flexibility and consideration for participants were valued:

> *I'm very thankful that the research staff were very flexible and would say, "come back here at two o'clock" or "go and take a break."* (P3)

Some participants found change in trial staff difficult. P6 said:

> *I find that my only difficulty with a team approach is that I'm talking to a different person each time.*

All participants stated they would recommend study participation to others in the future.

> *I definitely recommend the study for other people.* (P3)

Theme 2: The impact of the intervention has multiple contributing factors

Sub-theme 2A: Contextual factors

The perceived effect of the intervention had multiple dimensions that were unrelated to its pharmacological action, including hope and preconceptions.

Being on the trial affected the participants' mental state, which in turn affected their pain and function. Carer C1 noted her partner's pain was interrelated with his mood.

> *... it just seems the pain comes and goes ... it all depends [on] his mood.*

C1 believed the trial reduced her partner's pain and improved his functional capacity.

> *On the trial he was a lot more upbeat, can do things. And when the trial ended on Saturday, on Sunday he was just down and [feeling] pain and not able to do*

things. He couldn't feed himself, nothing. So maybe that was his way of thinking, oh well, something else is being taken away.

However, she felt that it was hard to determine the cause of his changes in pain because:

... every day is different with his pain. (C1)

Participants identified that their prior experience may have influenced how they felt. Participant P6 noted they were prone to getting side effects from medications:

My side effects were just a general giddiness that I tend to get with a lot of medications.

And that this experience may have contributed to the physical impact of the medication.

... unfortunately from almost sort of on the first day, the effects I felt caused my debilitation in the way that I suddenly – whether it was psychosomatic or not, I don't know – but I suddenly felt there were so many things I couldn't do without assistance. I couldn't get to the toilet, and prior to the trial, I could quite easily get to the toilet. (P6)

Sub-theme 2B: Intervention delivery

Aspects of the intervention delivery affected the likelihood of a participant wanting to use this intervention in future.

Some participants found the subcutaneous butterfly and syringe driver "not a problem at all" (P2). P4 said:

With the little dilly bag that it was in, it made it very easy. I could get up and go and sit outside in the sun, go for walks down the end of the ward.

While others found it awkward, saying:

... my shakiness and imbalance made me feel quite awkward at times with that, that I was going to drop the unit. I didn't feel confident with that. But as regards to the actual implants themselves, I soon forgot they were there. (P6)

A suggestion was to put the equipment in:

> *... a lighter handbag. Or something, you know, more easily detachable.* (P5)

Sub-theme 2C: Hospitalisation: a virtue or a vice?

Participants had mixed opinions about being hospitalised for the intervention. Frustrations about being in hospital included logistical problems (such as parking) as well as a lack of control.

> *I'm used to being at home on my own and sort of my day is nice and calm and quiet. And being interrupted all the time by different people coming in for different reasons – but that's hospital ... I want to sleep in my bed, and I want to get my drugs as soon as I want them, not to have that long wait.* (P4)

Other participants saw the benefits of being in the hospital as:

> *If you're in a safe environment, given your condition, et cetera, it's probably better to be in the hospital.* (P1)

Sub-theme 2D: Embrace the intervention if effective

Overall, most participants stated that they would use this medication if it was found to be effective.

> *I'll just definitely give it a go.* (P2)

Some participants qualified this statement, stating they:

> *... would like to see some sort of results from somewhere that says, you know, like there's a seventy per cent chance that this will work for you.* (P4)

Theme 3: Pain impacts every aspect of life

Sub-theme 3A: Pain impacts daily life

Pain impairs function not only by restricting movement, but by causing fatigue and hindering communication. This was expressed through sentiments such as:

... [pain] stop[s] you doing the stuff you want to do. (P7)

It's made me exhausted ... so tired you can't read. (P5)

I find it difficult to communicate when I'm in pain. (P6)

Pain was repeatedly described as affecting a person's whole life, with participants giving descriptions such as:

It steals my, I suppose, general wellbeing. (P6)

It affects my everyday life. (P3)

The impact of the limitation from neuropathic cancer pain was described as:

... overwhelming at times. (P6)

Sub-theme 3B: Impact on relationships

The participants' pain affected their relationships with friends and family by hampering their communication and ability to participate in activities. Participant P4 described how her experience was not understood:

You look at your friends and family, and there are some of them who understand and there are some of them who obviously don't. And who get very resentful for the fact that, you know, you're not able to do things; you're not able to keep up.

In particular, they claimed that others did not understand the changing nature and uncertainty of neuropathic cancer pain.

Now I'll say, "Look, I'll try," and that gets people's back up. It's, you know, "but you went to [friend's event] and you're not coming to mine." Yeah well, I didn't have pain that day. (P4)

Sub-theme 3C: Grief and loss

Participants spoke of the grief they felt when comparing their current situation to their previous condition. Participant P4 reflected how she was very healthy previously:

Until I got cancer, I'd never even had a headache. (P4)

She described her grief at the loss of her rich former life.

I can't be involved in a lot of the things that I used to be involved in. I've had to change the way I do things. It's made me change my whole life, my living, my working. (P4)

C1 also spoke of how her partner's pain affected her own quality of life.

It's very tough on somebody who is always on the go, and now it's just hospital and home and hospital room. I would like to take him there [to a café] to sit down and have lunch, and I can't do that ... Well we can't do any of that now.

8.2.5 Discussion

Key findings

Our qualitative sub-study findings indicate that participation in the LiCPain trial provided a sense of hope and purpose for patients, revealing important insights into the complex nature of neuropathic cancer pain and its management. This finding aligns with a growing body of research identifying hope and altruism as key drivers in anti-cancer therapy clinical trials,[295-298] showing that these factors are also relevant in cancer pain trials. Our findings support other findings of the significant impact of cancer pain on every element of quality of life, including roles, relationships, wellbeing and even meaning and purpose.[299-301]

Patients found meaning and purpose in trial participation because it enabled them to create a legacy. Despite altruistic motivations, patients carefully evaluated the personal benefits of trial participation against the risks and burden. Patients' perceptions of anticipated burden affected their decision to participate.[286] In this study, altruism was a prominent theme, whereas in early-phase studies it is seen as a secondary driver of trial participation.[298] Participants expressed the importance of hope, including to be able to help future patients, leave a legacy and improve pain, concepts parallel to those of participants in early-phase studies who hope for a cure[296, 297] or to extend life.[298]

Research on participating in palliative care trials is predominantly confined to the evaluation of hypothetical participation in research, with few studies describing the experience of actual trial participation.[302-304] The extant studies identify similar themes of benefits for self and others. These findings demonstrate nuanced decision-making processes and highlight that clearly communicating risk management strategies in trial recruitment with patients living with advanced cancer can increase their sense of control, which is important for patients.

Contextual factors[305] contributing to a placebo response[306] are less well studied in cancer pain than chronic pain. Nonetheless, the impact of all components of the intervention – including the delivery, therapeutic alliance and patient factors, as well as the pharmacology of the medication – must be considered in both clinical practice and trial design.[307, 308] Our data suggests contextual factors such as participant beliefs about the benefit of the trial or sensitivity to medication influence the positive and adverse effects of an intervention.

Although the experiences described were specific to the LiCPain intervention, some aspects of delivery utilised in operationalising this trial are also used to provide clinical management in palliative care, such as hospitalisation or use of a subcutaneous syringe driver. Syringe driver redesign to reduce bulk and improve useability may improve acceptability, which is consistent with previous reports.[309] The participants' mixed perspectives on hospitalisation highlight the need for choice in delivery of care, which links back to the sub-theme of control.

Our findings emphasise the devastating impact of neuropathic cancer pain on multiple life domains, consistent with studies in cancer pain,[141] bone pain[115] and chemotherapy-induced peripheral neuropathy.[112, 118] Participants described pain as affecting physical function, communication, relationships, emotional wellbeing, and overall quality of life. They experienced grief at the loss of what used to be "normal" before living with neuropathic cancer pain, which has been reported in people with chemotherapy-induced cancer pain.[310] Few previous studies specifically examined the experience of neuropathic cancer pain, which is known to worsen physical, cognitive and social function more than nociceptive pain.[6]

Strengths and limitations of this study

This qualitative sub-study provides valuable insights into the experience and thought processes of people with advanced cancer participating in a neuropathic pain intervention trial. It gives voice to a vulnerable population often excluded from research due to their frailty, offering rare insights into their trial participation motives, intervention acceptability, and the profound impact of neuropathic cancer pain on daily life and relationships.

This data captures only a sample of potential participants in this trial, creating bias by capturing the views of those who chose to participate in the trial and again of those who chose or were able to participate in an interview. Cultural diversity was limited by the requirement to speak English. This may not fully reflect the true barriers contributing to recruitment difficulties or the experience of all people with neuropathic cancer pain.

The dual role of some interviewers as both researchers and treating physicians may have influenced the patients' and carer responses. Interpretations could not be verified with participants. These limitations should be considered when interpreting the results. However, given the paucity of data on people with advanced cancer undergoing neuropathic pain trials in palliative care, our results make a useful contribution to knowledge about their experiences and their likeness to those of similar populations.

Significance

Clinicians need to be cognisant of the value of trial participation and the self-efficacy it affords for many patients, as well as the importance of allowing them to determine whether to participate. Empowering patients to make this decision if they are eligible will improve recruitment.[311] The findings of this study may also help to improve future neuropathic cancer pain trial designs by highlighting the potential benefit of the trial to others in patient information and consent forms and other recruitment materials,[311] or in a certificate of appreciation.[312] Resources are available to assist in embedding this process in clinical design.[313] Finally, patients valued the analgesic benefit of the intervention and noted its positive impact on their psychological state.

8.2.6 Conclusion

This study found that people living with advanced cancer and neuropathic cancer pain derived hope and purpose from participation in the LiCPain trial. Contextual factors influenced the intervention's perceived effectiveness, emphasising the need for patient-centred trial and intervention design. Participants in clinical trials value having a sense of control, which can be enhanced by reducing uncertainty and minimising burden. Findings from this study can be used to refine the design of future clinical trials of interventions for neuropathic cancer pain. The substantial burden of pain for participants and carers highlights the urgent need for clinical trials of ways to improve outcomes for people suffering from unrelieved neuropathic cancer pain.

8.3 Chapter summary

This chapter presents the themes derived from a qualitative interview sub-study embedded within the LiCPain RCT. It was designed to produce a better understanding of how to develop and evaluate pharmacological interventions for people with neuropathic cancer pain. The themes represent primary data about the experience of people with neuropathic cancer pain, and support the findings of Phase I of the INCEPT Project.

Chapter 9 describes the conduct and results of the end-point meta-inference which integrated data from Studies 3, 4 and 5.

Chapter 9 Data integration, recommendations and conclusion

9.1 Chapter preface

The INCEPT two-phase hybrid sequential mixed methods Project was designed to determine the impact of unrelieved neuropathic cancer pain and identify opportunities to improve the outcomes for those affected. It employed a patient-centred care framework that placed the patients' experience and preferences at the centre of healthcare provision. It acknowledged that multiple domains (the biopsychosocial perspective, the "patient-as-person", sharing power and responsibility, the therapeutic alliance, and the "doctor-as-person") influence the five dimensions of patient-centred care: shapers, professional context influences, doctor factors, patient factors and consultation level influences.[50]

Chapter 3 presents an answer to the research question "What is the prevalence of unrelieved pain at the end of life for people living with cancer?" It describes a cohort study performed using a large administrative dataset of routinely collected pain assessments in people with cancer pain in the last year of life. It found that nearly a third of Australians with cancer who are seen by a specialist palliative care service experience pain at least once in their last week of life. Chapter 4 describes an exploration of the experiences of people living with unrelieved neuropathic cancer pain through a systematic review of qualitative studies. A mid-point meta-inference was conducted to integrate these findings and describe the prevalence and experiences of unrelieved neuropathic pain among people living with cancer.

Chapter 6 presents a discussion of lidocaine as a candidate pharmacological agent for pain relief, and a systematic review of sodium channel blockers that suggests lidocaine infusions are beneficial for cancer pain. Chapter 7 reports the methodology and quantitative results of the LiCPain study, a pilot RCT of continuous subcutaneous

infusion of lidocaine for neuropathic cancer pain. Chapter 8 describes an interview sub-study embedded in the LiCPain pilot.

This final chapter achieves the overall aim of the INCEPT Project by describing the impact of unrelieved neuropathic cancer pain and identifying opportunities to improve the outcomes of people living with this condition. It reports an end-point meta-inference of the data from Phase II (Studies 3, 4 and 5) viewed through the patient-centred care framework.[50]

9.2 End-point meta-inference

An end-point meta-inference was undertaken to integrate the data from Studies 3, 4 and 5 in order to answer the question "How can we better evaluate pharmacological interventions for people living with unrelieved neuropathic cancer pain?" The data fell into two domains: the role of lidocaine in the therapeutic pipeline of pharmacologic agents to improve outcomes for neuropathic cancer pain, and considerations for design of future trials of pharmacological agents such as lidocaine for neuropathic cancer pain (Table 9-1).

Table 9-1: Joint display table for the end-point meta-inference

Domain	**Quan – Study 3**	**QUAN – Study 4**	**Qual – Study 5**	**Fit of data**	**End-point meta-inference**
How can lidocaine contribute to the therapeutic pipeline of interventions which improve outcomes for people with neuropathic cancer pain?	There may be a benefit for lidocaine infusion of 4–5 mg/kg over 30 to 80 minutes compared with placebo for greater than 50% reduction in cancer pain. Lidocaine infusion could be considered in refractory cancer pain where agents with level one evidence are ineffective. No RCTs evaluate a continuous infusion which	Leveraging a patient-centred approach to neuropathic cancer pain, a clinical trial of extended continuous subcutaneous infusion of lidocaine was found to be feasible for a palliative care population. Rapid titration of lidocaine from 1 mg/kg/hr to 2 mg/kg/hr is tolerated for neuropathic cancer pain.	Participants consider multiple factors about the intervention whilst weighing up potential benefits/risks of participation.	Expansion	A continuous subcutaneous infusion of lidocaine up to 2 mg/kg/hr is tolerated and has potential to improve outcomes for people living with unrelieved neuropathic cancer pain. Its impact is influenced by multiple domains. A clinical trial of extended continuous subcutaneous infusion of lidocaine was feasible, acceptable and valued by people living with advanced cancer, including those receiving palliative care

	observational studies strongly suggest has benefit and is used in clinical practice				
What considerations are needed to design future trials of pharmacological agents such as lidocaine for neuropathic cancer pain?		Trial design modification is required to improve recruitment Regular structured clinical assessment, including for neurological symptoms, can facilitate the detection of adverse effects when administering lidocaine infusion	Participants consider multiple factors about the intervention whilst weighing up potential benefits/risks of participation While neuropathic cancer pain impacted every aspect of the person's life, opportunity to participate in clinical trials of new interventions offers hope and purpose	Expansion	Utilising a patient-centred care framework to design clinical trials for people living with unrelieved neuropathic cancer pain may enhance recruitment, retention, intervention effectiveness, and interpretation of trial results. Incorporating consumer perspectives from trial inception to implementation can align clinical trial design with the five dimensions of patient-centred care and their influencing domains

Finding 3

A continuous subcutaneous infusion of lidocaine of up to 2 mg/kg/hr was tolerated and has potential to improve outcomes for people living with unrelieved neuropathic cancer pain. Its impact is influenced by multiple domains. A clinical trial of extended continuous subcutaneous infusion of lidocaine is feasible, acceptable to and valued by people living with advanced cancer, including those receiving palliative care.

Important steps in the development of a therapeutic pipeline of pharmacologic interventions to improve outcomes for people with neuropathic cancer pain are the identification and design of a promising intervention followed by piloting of the intervention and the clinical trial design to evaluate its benefit. While the systematic review (Study 3) found that lidocaine infusion of 4–5 mg/kg over 30–80 minutes may produce greater than 50% reduction in cancer pain compared with placebo,[142] it identified no RCTs of an extended infusion of lidocaine for neuropathic cancer pain, despite benefit being reported in observational studies and from use in clinical practice.[159-162, 215] A pilot RCT (Studies 4 and 5) found that a clinical trial of extended continuous subcutaneous infusion of lidocaine of up to 2 mg/kg/hr over 72 hours for neuropathic cancer pain was feasible, suggesting that a phase III RCT could be conducted. However, recruitment was challenging, so design modification is required and may require piloting. Additional pilot studies may be warranted to further evaluate efficacy, safety and pharmacokinetic profile of different dosing protocols. The pilot RCT was acceptable and valued by participants, bringing benefits such as hope. Efficacy, toxicity and health economic measures were feasible to collect and will support sample size calculations for a future phase III trial. While this pilot RCT was not powered to determine efficacy , rapid titration from 1 mg/kg/hr to 2 mg/kg/hr was tolerated and acceptable for people living with neuropathic cancer pain. This informs clinicians, who may choose to administer lidocaine infusions when other, evidence-based strategies for managing unrelieved neuropathic cancer pain are unavailable.

The impact of lidocaine infusion for recipients has multiple contributing factors, reflecting the complexity of the experience of neuropathic cancer pain identified in the

mid-study meta-inference, and the understanding that the intervention comprises the medication as well as the delivery and supports around delivery. These can be better understood by viewing the intervention through a patient-centred care lens that acknowledges that the impact of pain is affected by not only the pharmacological action of the medication but other domains such as societal shapers like cultural norms, and patient factors like expectation of pain relief and adverse effects.[50]

Finding 4

Utilising a patient-centred care framework to design clinical trials for people living with unrelieved neuropathic cancer pain may enhance recruitment, retention, intervention effectiveness, and interpretation of trial results. Incorporating consumer perspectives from trial inception to implementation can align clinical trial design with the five dimensions of patient-centred care and their influencing domains.

Although the pilot RCT of lidocaine showed a full RCT was feasible (Study 4), the trial design required improvement in several aspects to increase recruitment rates and ensure that the included participants are representative of adults with neuropathic cancer pain. These findings are consistent with the mid-point meta-inference findings that the experience of neuropathic cancer pain is complex and influenced by both modifiable and intrinsic factors that can be conceptualised through the patient-centred care framework.

Consideration of the five dimensions of patient-centred care and the domains that influence them can support clinical trial design to improve recruitment and retention as well as enhance the effect of the intervention. The consumer voice, heard through the embedded qualitative Study 5 as well as the consumer investigator, guided these insights. For example, the use of verbal and written communication to enhance information provision and consistency of staff to support development of a positive relationship can support the therapeutic alliance dimension of patient-centred care. It can counter fears and uncertainty by giving the participants a sense of control (Study 5), which may relieve pain and encourage participants to consent to or remain in the trial.

The importance of hope and purpose, described in Study 5, ought to be harnessed to improve recruitment by ensuring the trial design and recruitment materials consider what benefits the trial can bring to the participant, both related to the potential for pain relief and indirect benefits such as the opportunity to leave a legacy or help future patients.

Patients' contexts, including their health, sociocultural factors and motivation, influence the dimensions of patient-centred care and trial results. For example, the prior experiences of the participant may influence the perceived effect and adverse effect of the interventions (the patient-as-person dimension). Hence, the candidate designed a more pragmatic trial in which the participants reflected the population of people with neuropathic cancer pain. The modifications included facilitating the recruitment of CALD participants and a broader group of people with probable or definite neuropathic cancer pain.

9.3 Summary of findings

The INCEPT Project findings met the aim of describing the impact of unrelieved neuropathic cancer pain and identifying opportunities to improve the outcomes of people living with this condition. These findings are depicted in Figure 9-1.

9.4 Discussion

9.4.1 Significance

The results presented in this thesis make a significant and original contribution to the evidence base about ways to improve outcomes for people living with unrelieved neuropathic cancer pain. Characterising unrelieved neuropathic cancer pain is crucial for developing effective strategies to meet the needs of the people with this condition, even in the last week of life.

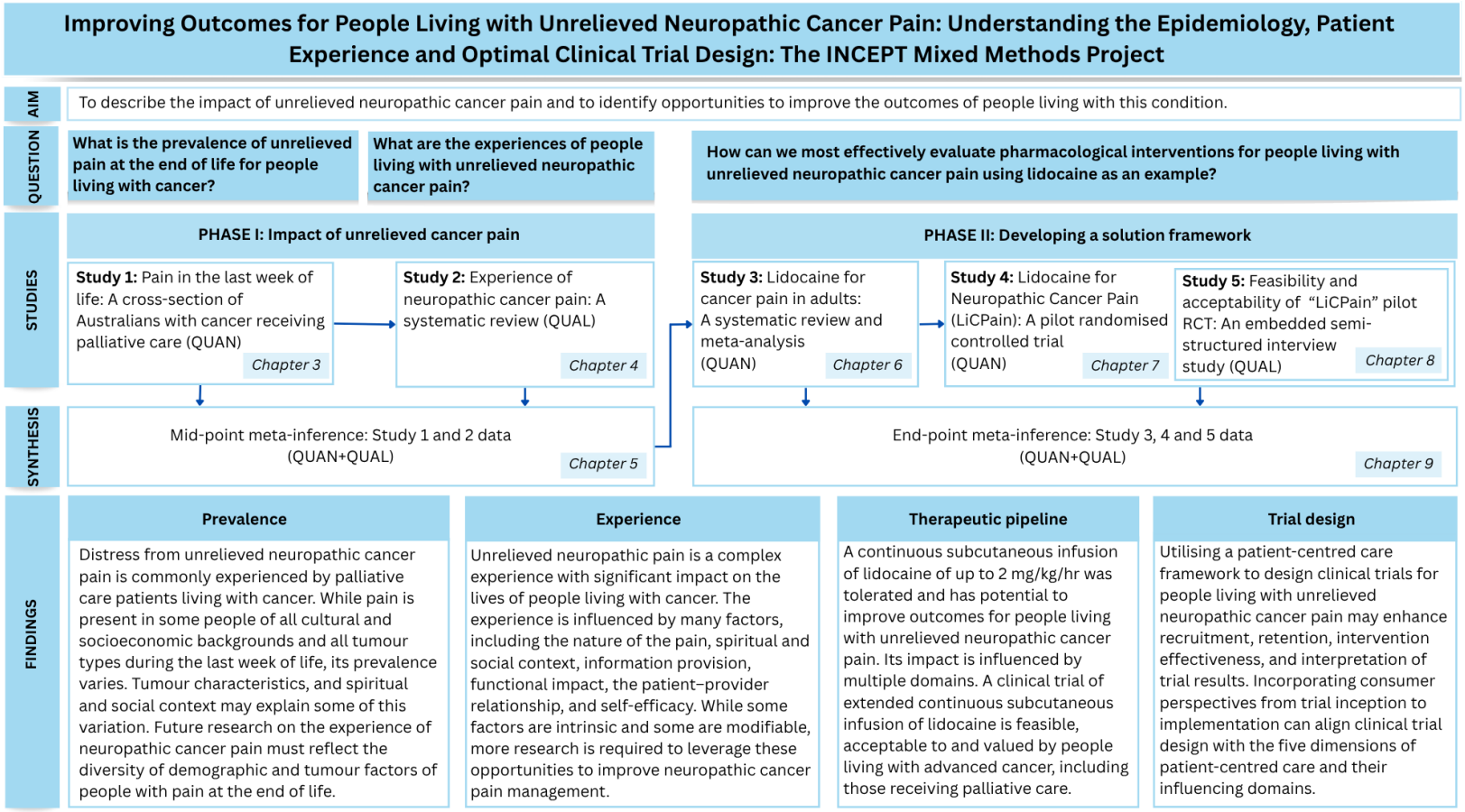

Figure 9-1: Overview of INCEPT Project and findings

The prevalence and associations of cancer pain in Australian patients seen by a specialist palliative care service (Study 1) have not been evaluated in such a robust manner previously. Pain does not occur in isolation, but is a symptom in patients with unique constellations of physical, psychosocial, functional and demographic characteristics. Understanding these factors will provide valuable insight into interventions that are likely to reduce pain effectively, and guide development of management strategies for neuropathic cancer pain in clinical practice, research and service development.

The INCEPT Project was one of the first studies to characterise people living with unrelieved neuropathic cancer pain, identify its impact based on the experiences of adults with cancer (Study 2), and evaluate sodium channel blockers for cancer pain (Study 3). The systematic review[142] of literature on lidocaine for cancer pain (Section 6.4) has been cited 56 times, including by the National Comprehensive Cancer Network international cancer pain management guidelines.[29] This highlights the relevance of lidocaine to the current scientific discourse and the urgent need for more definitive evidence about its role in managing neuropathic cancer pain.

The LiCPain feasibility study (Studies 4 and 5) was a global first, the only RCT of an extended infusion of subcutaneous lidocaine for neuropathic cancer pain over multiple days.[142, 206] It provided important insights into the conduct of clinical trials of lidocaine that can be applied to trials of other pharmacological agents for neuropathic cancer pain. It also provided robust safety data on the use of lidocaine, which can inform clinicians in its use for unrelieved neuropathic cancer pain, pending more definitive evidence.

The criticality of considering the patient perspective in the evaluation of pharmacological interventions for neuropathic cancer pain is increasingly acknowledged by the scientific community.[314] Adopting this approach extends patient-centred care (a widespread clinical practice in palliative care) to a traditionally positivist research culture, and recognises that the impact of an intervention for neuropathic cancer pain will be affected by the person's context.

The use of mixed methods to position a clinical trial for optimum implementation of results is an emerging practice[315] that streamlines the translational pipeline of evidence and maximises the use of valuable resources.

9.4.2 Recommendations for clinical practice

Clinicians should recognise that a person's spiritual and social context may shape their experience and expression of neuropathic cancer pain. They should consider how to meet the information needs of people with cancer who have or at risk of developing neuropathic pain and how to harness the patient–provider relationship to increase the impact of pain management strategies. Multidisciplinary teams should be involved in care of people with neuropathic cancer pain in order to reduce functional limitations and psycho-existential and spiritual distress.

Lidocaine infusion could be considered in refractory cancer pain where agents with level one evidence are ineffective. Dose schedules which could be used include four to five mg/kg over 30 to 80 minutes; or an infusion titrated daily from 1 to 2 mg/kg/h with a maximum dose of 120mg/h. Any risk and benefit should be carefully assessed. Daily structured clinical assessment may detect adverse effects such as neurological toxicity, however routine cardiovascular monitoring has not shown benefit.

Clinicians need to be cognisant of the value of trial participation and the self-efficacy it affords for many patients, as well as the importance of allowing them to determine whether to participate.

9.4.3 Recommendations for research

Further research is needed to find strategies that reduce the prevalence and severity of unrelieved neuropathic cancer pain at the end of life. Utilising a patient-centred care framework and incorporating consumer perspectives to design and evaluate interventions may enhance outcomes. Particular areas may include to clarify the association between performance status and pain, and the correlation between patient and proxy pain scores, to understand the drivers for differential reporting of pain in

CALD populations and understanding the experience of people who have pure neuropathic pain directly caused by cancer.

Researchers seeking to develop and evaluate new interventions must consider the complexity of neuropathic cancer pain and the factors that may contribute to the person's experience. Modifiable factors such as self-efficacy may be harnessed to improve neuropathic cancer pain management. Researchers should ensure that trial participants reflect the diversity of demographic and tumour factors of people with pain at the end of life.

Lidocaine is a promising intervention for improving the management of neuropathic cancer pain. A phase III trial, as described in the LiCPain RCT is feasible but will require modification to the design and recruitment strategy to ensure it is able to be completed in a reasonable timeframe and budget. This may include designing a more pragmatic trial with a population and trial procedures closely reflecting clinical practice, such as through participant selection and reduced trial burden. Further research into whether specific features of this trial design, population or intervention contributed to the high placebo response may inform future cancer pain studies and delivery of the intervention. Higher lidocaine doses could be cautiously evaluated, informed by further pharmacokinetic data.

9.4.4 Recommendations for policy

Provision of resources and policy framework to address neuropathic pain at the end of life in people with cancer is essential due to the significant impact of this experience.

Policy should ensure a patient centred approach to pain management. Facilitating outpatient use of lidocaine infusions if prescribed would improve the patient-centredness of care as well as reduce costs.

9.4.5 Strengths

The INCEPT Project has many strengths. Firstly, the robust design of the INCEPT Project and its component studies supports the utility of the results. Secondly, this Project was developed in collaboration with experts in the field of managing

neuropathic pain and other symptoms for people with advanced cancer, drawing on a wide range of expertise. Thirdly, the mixed methods and integration of data in the INCEPT Project allowed for insights that transcend the individual studies. Finally, this Project filled important gaps in the care of people with unrelieved neuropathic cancer pain, making important advances in the quest for ways to improve outcomes for this large group of people with poor quality of life and function.

9.4.6 Limitations

This doctoral Project was able to examine only a small portion of the many factors that contribute to unrelieved neuropathic cancer pain. Future work might capture a greater diversity and depth of experience of neuropathic cancer pain, such as through qualitative interviews exploring the experiences of people with pain caused by cancer itself, to compare to findings from people with pain related to the cancer. While it is expected that many of the lessons gleaned from the pilot RCT of extended infusion of lidocaine for neuropathic cancer pain will be transferable to other pharmacological and non-pharmacological randomised controlled trials, this requires further evaluation.

Another limitation of this Project was that a feasibility study cannot directly determine whether the agent being tested is effective. Future studies are required to progress the science around lidocaine for cancer pain toward translation. Improved recruitment through stratification or a larger sample size in the pharmacological sub-study may have added depth to the interpretation of the LiCPain trial results, increasing their applicability.

Finally, a pragmatic approach was used when determining the populations to be studied and the order of component studies in this mixed-methods doctoral Project. This was done in order to minimise research waste and complete this Project in the requisite timeframe. In some cases, preliminary findings were initially used to inform the next phase of the Project. A particular challenge was the assumption that the characteristics of people with cancer pain in the last week of life reflect those of people with neuropathic cancer pain. A future study describing the characteristics of cancer pain in the last week of life could confirm this.

9.5 Conclusion

Phase I of the INCEPT Project revealed the prevalence of unrelieved pain at the end of life for people living with cancer and the experiences of people with unrelieved neuropathic cancer pain. It integrated a cohort study of unrelieved cancer pain in people seen by a specialist palliative care service with a systematic review of studies of the experience of people with neuropathic cancer pain. It also included a qualitative synthesis of semi-structured interviews with people with neuropathic cancer pain enrolled in a clinical trial of continuous subcutaneous infusion of lidocaine. The following meta-inferences were made.

Distress from unrelieved neuropathic cancer pain is commonly experienced by palliative care patients living with cancer. While pain is present in some people of all cultural and socioeconomic backgrounds and all tumour types during the last week of life, its prevalence varies. Tumour characteristics, and spiritual and social context may explain some of this variation. Future research on the experience of neuropathic cancer pain must reflect the diversity of demographic and tumour factors of people with pain at the end of life.

Unrelieved neuropathic pain is a complex experience with significant impact on the lives of people living with cancer. The experience is influenced by many factors, including the nature of the pain, spiritual and social context, information provision, functional impact, the patient–provider relationship, and self-efficacy. While some factors are intrinsic and some are modifiable, more research is required to leverage these opportunities to improve neuropathic cancer pain management.

In Phase II of the INCEPT Project, the doctoral candidate examined a group of people with unrelieved neuropathic cancer pain and how to improve their outcomes. She sought ways to improve evaluation of pharmacological interventions for people living with unrelieved neuropathic cancer pain. This included completion of a systematic review and pilot RCT with an embedded qualitative sub-study of a novel intervention, subcutaneous infusion of lidocaine, for neuropathic cancer pain. Integration of the studies in Phase II of this doctoral Project identified the following meta-inferences.

A continuous subcutaneous infusion of lidocaine of up to 2 mg/kg/hr was tolerated and has potential to improve outcomes for people living with unrelieved neuropathic cancer pain. Its impact is influenced by multiple domains. A clinical trial of extended continuous subcutaneous infusion of lidocaine is feasible, acceptable to and valued by people living with advanced cancer, including those receiving palliative care.

Utilising a patient-centred care framework to design clinical trials for people living with unrelieved neuropathic cancer pain may enhance recruitment, retention, intervention effectiveness, and interpretation of trial results. Incorporating consumer perspectives from trial inception to implementation can align clinical trial design with the five dimensions of patient-centred care and their influencing domains.

These findings will support researchers and clinicians to work towards improving outcomes for people with neuropathic cancer pain. They demonstrate the need to understand neuropathic cancer pain within a patient-centred care framework, and use this to inform the design of interventions and clinical trials.

Appendix A Ethics approvals

Outlook

UTS HREC Approval - ETH16-0809

From Research.Ethics@uts.edu.au <Research.Ethics@uts.edu.au>
Date Wed 05/10/2016 17:15
To Jessica Lee <JessicaTsuann.Lee@student.uts.edu.au>; David Currow <David.Currow@uts.edu.au>; Jane Phillips <Jane.Phillips@uts.edu.au>; Meera Agar <Meera.Agar@uts.edu.au>; Melanie Lovell <Melanie.Lovell@uts.edu.au>; Research Ethics <research.ethics@uts.edu.au>

Dear Applicant

The UTS Human Research Ethics Committee reviewed your application titled, "Moderate and severe cancer pain in palliative care patients", and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct in Human Research (2007). I am pleased to inform you that ethics approval is now granted.

Your approval number is UTS HREC REF NO. ETH16-0809
Approval will be for a period of five (5) years from the date of this correspondence subject to the provision of annual reports.

Your approval number must be included in all participant material and advertisements. Any advertisements on the UTS Staff Connect without an approval number will be removed.

Please note that the ethical conduct of research is an on-going process. The National Statement on Ethical Conduct in Research Involving Humans requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at least annually from the date of approval, and at the end of the project (if it takes more than a year). The Ethics Secretariat will contact you when it is time to complete your first report.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of approval. If you require a hardcopy please contact Research.Ethics@uts.edu.au.

To access this application, please follow the URLs below:
* if accessing within the UTS network: https://rm.uts.edu.au
* if accessing outside of UTS network: https://remote.uts.edu.au , and click on "RM6 - ResearchMaster Enterprise" after logging in.

We value your feedback on the online ethics process. If you would like to provide feedback please go to: http://surveys.uts.edu.au/surveys/onlineethics/index.cfm

If you have any queries about your ethics approval, or require any amendments to your research in the future, please do not hesitate to contact Research.Ethics@uts.edu.au.

Yours sincerely,

Professor Marion Haas
Chairperson
UTS Human Research Ethics Committee

Contact: Sydney Local Health District Human Research Ethics Committee – CRGH
Concord Repatriation General Hospital (CRGH)
Concord NSW 2139
Telephone: *(02) 9767 5622*
Email: *crgh.ethics@sswahs.nsw.gov.au*

Our Ref:

CONCORD
REPATRIATION GENERAL
HOSPITAL

21 September 2017

Dr Jessica Lee
Palliative Care
CONCORD RGH

Dear Dr Lee,

Re: HREC/17/CRGH/151 CH62/6/2017-098
A multi-centre double blind randomised controlled trial of continuous subcutaneous lidocaine (lignocaine) for the management of neuropathic cancer pain - a feasibility study.

Thank you for submitting the above project for single ethical and scientific review. This project was first considered by the Sydney Local Health District Human Research Ethics Committee – CRGH at its meeting held on 29 June 2017. This Human Research Ethics Committee (HREC) has been accredited by the NSW Ministry of Health as a lead HREC under the model for single ethical and scientific review.

This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice.*

I am pleased to advise that the proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research* and final ethical approval has been granted.

The documents reviewed and approved include:

	IDENTIFICATION NUMBER	DATE
National Ethics Application Form (NEAF)	**Submission code AU/1/2ABD25**	**09/05/2017**
Protocol	**Version 1.3**	**17/09/2017**
Master Participant Information Sheet & Consent Form – Feasibility Study	**Version 1.3**	**17/09/2017**
Master Participant Information Sheet & Consent Form – Caregiver sub-study	**Version 1.3**	**17/09/2017**

The HREC has provided ethical and scientific approval for the following sites:

1. Concord Repatriation General Hospital

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at Concord Hospital until a Site Specific Application has been reviewed and approved and separate authorisation from the Chief Executive or delegate has been obtained

2. St Vincent's Hospital
3. Liverpool Hospital

Appendix B Full search strategy, Chapter 4

	Search Concept	**Medline database term**
1	Exp Neoplasms/	Exp Neoplasms/
2	Exp Medical oncology/	Exp Medical oncology/
3	Exp Radiation Oncology/	Exp Radiation Oncology/
4	Exo Haematology/	Exp Hematology/
5	Cancer*.mp	Cancer*.mp.
6	Neoplasm*.mp	Neoplasm*.mp.
7	Tumo?r*.mp	Tumo?r*.mp.
8	Oncol*.mp	Oncol*.mp.
9	h?ematol*.mp	h?ematol*.mp
28	**1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9**	
10	Exp neuralgia/	Exp neuralgia/
11	Exp somatosensorty disorders/	Exp somatosensory disorders/
12	Peripheral nervous system diseases/	Peripheral nervous system diseases/
13	Brachial plexus neuropathies/	Brachial plexus neuropathies/
14	Complex regional pain syndromes/	Complex regional pain syndromes/
15	Mononeuropathies/	Mononeuropathies/
16	Nerve compression syndromes/	Nerve compression syndromes/
17	Neuritis/	Neuritis/
18	Peripheral nerve injuries/	Peripheral nerve injuries/
19	Polyneuropathies/	Polyneuropathies/
20	Radiculopathy/	Radiculopathy/
21	Small fibre neuropathy/	Small fibre neuropathy/
22	Neuralgia.mp.	Neuralgia.mp.
23	Nerve pain.mp.	Nerve pain.mp.

24	Neurodynia.mp.	Neurodynia.mp.
25	Neuropathic.mp.	Neuropathic.mp.
26	(pain* adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp.	(pain* adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp.
29	**10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26**	
27	((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab. or interviews as topic/ or focus groups/ or narration/ or qualitative research/	
30	**27 and 28 and 29**	

Appendix C Supplementary data, Chapter 7

Supplementary Table 1: Prescreening failure reasons

Total screen failure 107	
23	Worst pain score not 4 or greater on 11-point rating scale
18	Inability to complete study assessments
15	insufficient analgesic pretreatment
8	Pain not related to cancer or its treatment
7	Does not want or not appropriate for admission
7	Prescribed beta blocker
5	Pain does not have neuropathic features
4	Liver failure or metastases
3	Abnormal vital signs
3	Patient or clinician did not want control group
3	Patient already on lidocaine infusion
3	Distress or anxiety
2	Cancer (solid or hematologic)
2	History of seizure
1	Patient declined - other
1	Limited access due to isolation
1	Taking mexiletine
1	On another clinical trial

Supplementary Table 2: All preliminary efficacy outcomes, randomized set (categorical values)

Outcome	**Randomized: Lidocaine**	**Randomized: Placebo**	**p-value**
From baseline to cessation	**Participants with improvement**		
Number (%) of participants with improvement of	**n=10**	**N=7**	
Worst pain of ≥1 point on BPI-SF	6 (60%)	4 (57%)	0.91
Worst pain of ≥2 point on BPI-SF	4 (40%)	4 (57%)	0.49
Worst pain of ≥4 point on BPI-SF	0 (0%)	3 (43%)	0.023
Worst pain reduced to ≤3 on BPI-SF	1 (10%)	3 (43%)	0.12
Average pain of ≥1 point on BPI-SF	3 (30%)	5 (71%)	0.092
Average pain of ≥2 point on BPI-SF	2 (20%)	4 (57%)	0.11
Average pain of ≥4 point on BPI-SF	0 (0%)	2 (29%)	0.072
Average pain reduced to ≤3 on BPI-SF	0 (0%)	4 (57%)	0.006
Number of breakthrough pain medications used	3 (30%)	2 (29%)	0.95
Proportion of participants who achieve their personalized pain goal	1 (10%)	3 (43%)	0.12
Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 OR those who have unchanged pain but a reduction in number of breakthrough medications used in the last 24 hours	6 (60%)	5 (71%)	0.63
Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 AND breakthrough medication use which is unchanged or reduced in the last 24 hours	3 (30%)	1 (14%)	0.45
Number of participants with improvement of ≥1 point:	**N=9**	**N=7**	
Burning (superficial) spontaneous pain on NPSI (%)	3 (33%)	4 (57%)	0.34
Pressing (deep) spontaneous pain on NPSI (%)	2 (22%)	4 (57%)	0.15
Paroxysmal pain on NPSI (%)	4 (44%)	5 (71%)	0.28
Evoked pain on NPSI (%)	2 (22%)	4 (57%)	0.15

Paresthesia/Dysesthesia on NPSI (%)	3 (33%)	4 (57%)	0.34
At cessation:			
Global impression of change (number)			0.31
very much improved	1 (11%)	0 (0%)	
much improved	1 (11%)	4 (57%)	
minimally improved	2 (22%)	2 (29%)	
no change	2 (22%)	1 (14%)	
minimally worse	0 (0%)	0 (0%)	
much worse	1 (11%)	0 (0%)	
very much worse	2 (22%)	0 (0%)	
Mean pain of ≥1 point on BPI-SF	5 (56%)	5 (71%)	0.52
From baseline to cessation	**Number of responses varied**		
Worst pain of ≥1 point on BPI-SF at day 8	1 (33%)	1 (20%)	0.67
Worst pain of ≥1 point on BPI-SF at day 15	0 (0%)	2 (40%)	0.44
Worst pain of ≥1 point on BPI-SF at day 29	0 (0%)	1 (33%)	0.5

Supplementary Table 3: All preliminary efficacy outcomes (per protocol set)

Outcome	**Randomized: Lidocaine**	**Randomized: Placebo**	**p-value**
From baseline to cessation	**Participants with improvement**		
Number (%) of participants with improvement of	**n=9**	**N=7**	
Worst pain of ≥1 point on BPI-SF	6 (67%)	4 (67%)	>0.99
Worst pain of ≥2 point on BPI-SF	4 (44%)	4 (67%)	0.4
Worst pain of ≥4 point on BPI-SF	0 (0%)	3 (50%)	0.018
Worst pain reduced to ≤3 on BPI-SF	1 (11%)	3 (50%)	0.095
Average pain of ≥1 point on BPI-SF	4 (44%)	4 (67%)	0.4
Average pain of ≥2 point on BPI-SF	3 (33%)	3 (50%)	0.52
Average pain of ≥4 point on BPI-SF	0 (0%)	2 (33%)	0.063
Average pain reduced to ≤3 on BPI-SF	0 (0%)	4 (67%)	0.004
Number of breakthrough pain medications used	3 (33%)	2 (33%)	>0.99
Proportion of participants who achieve their personalized pain goal	1 (11%)	3 (50%)	0.095
Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 OR those who have unchanged pain but a reduction in number of breakthrough medications used in the last 24 hours	6 (67%)	5 (83%)	0.47
Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 AND breakthrough medication use which is unchanged or reduced in the last 24 hours	3 (33%)	1 (17%)	0.47
Number of participants with improvement of ≥1 point:			0.64
Burning (superficial) spontaneous pain on NPSI (%)	3 (38%)	3 (50%)	0.64
Pressing (deep) spontaneous pain on NPSI (%)	3 (38%)	3 (50%)	0.53
Paroxysmal pain on NPSI (%)	4 (50%)	4 (67%)	0.64
Evoked pain on NPSI (%)	3 (38%)	3 (50%)	0.64
Paresthesia/Dysesthesia on NPSI (%)	3 (38%)	3 (50%)	0.26
At cessation:			

Global impression of change (number)			
very much improved	1 (12%)	0 (0%)	
much improved	1 (12%)	4 (67%)	
minimally improved	2 (25%)	1 (17%)	
no change	2 (25%)	1 (17%)	
minimally worse			
much worse			
very much worse	2 (25%)	0 (0%)	
Mean pain of ≥1 point on BPI-SF	6 (75%)	4 (67%)	0.73
From baseline to cessation			
Worst pain of ≥1 point on BPI-SF at day 8	1 (33%)	1 (20%)	0.67
Worst pain of ≥1 point on BPI-SF at day 15	0 (0%)	2 (40%)	0.44
Worst pain of ≥1 point on BPI-SF at day 29	0 (0%)	1 (33%)	0.5

Supplementary Table 4: All adverse events from baseline to day 29

	All events (n=63)		**Grade 3 or worse (n=12)**		**SAE (n=5)**	
System Organ Class / **Preferred term**	**Allocated to Lidocaine**	**Allocated to Placebo**	**Allocated to Lidocaine**	**Allocated to Placebo**	**Allocated to Lidocaine**	**Allocated to Placebo**
Total number of adverse events	43	20	7	5	3	2
Nervous system disorders						
Ataxia	3 (27%)	0	0	0	0	0
Depressed level of consciousness	2 (18%)	0	1 (9%)	0	0	0
Dizziness	3 (27%)	0	0	0	0	0
Headache	0	2 (33%)	0	0	0	0
Lethargy	1 (9%)	0	0	0	0	0
Movement involuntary	0	1 (17%)	0	0	0	0
Paresthesia	2 (18%)	0	0	0	0	0
Somnolence	3 (27%)	0	0	0	0	0
Tremor	5 (45%)	0	0	0	0	0
General disorders and administration site conditions						
Fatigue	3 (27%)	0	2 (18%)	0	0	0
Gait Disturbance	1 (9%)	0	0	0	0	0
Hyperhidrosis	1 (9%)	0	0	0	0	0
Injection Site Reaction	0	1 (17%)	0	0	0	0
Respiratory disorders						
Dyspnea	2 (18%)	0	0	0	0	0
Sore Throat	1 (9%)	0	0	0	0	0
Eye Disorders						
Blurred Vision	2 (18%)	0	0	0	0	0
Cardiac Disorders						
Palpitations	1 (9%)	0	0	0	0	0
Sinus Bradycardia	1 (9%)	0	0	0	0	0

Sinus Tachycardia	1 (9%)	0	0	0	0	0
Psychiatric Disorders						
Agitation	1 (9%)	1 (17%)	1 (9%)	0	0	0
Anxiety	1 (9%)	1 (17%)	0	0	0	0
Confusion	1 (9%)	1 (17%)	0	0	0	1 (17%)
Delirium	0	1 (17%)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Neoplasms	3 (27%)		3 (27%)	1 (17%)	3 (27%)	1 (17%)
Vascular Disorders						
Hypertension	1 (9%)	2 (33%)	0	2 (33%)	0	0
Hypotension	1 (9%)	0	0	0	0	0
Gastrointestinal Disorders						
Abdominal Pain	0	2 (33%)	0	1 (17%)	0	0
Constipation	1 (9%)	0	0	0	0	0
Nausea	0	1 (17%)	0	0	0	0
Musculoskeletal Disorders						
Back Pain	1 (9%)	0	0	0	0	0
Myalgia	0	1 (17%)	0	0	0	0
Arthralgia	0	2 (33%)	0	0	0	0
Ear and labyrinth disorders						
Tinnitus	1 (9%)	0	0	0	0	0
Infection and Infestations						
Fever	0	1 (17%)	0	0	0	0
Sepsis	0	1 (17%)	0	1 (17%)	0	0
Hepatobiliary Disorders						
Gallbladder pain	0	1 (17%)	0	0	0	0

Appendix D Supplementary data, Chapter 8

Supplementary Table 5: Carer interview guide

Topic	Initial open questions	Possible probing questions
Overall study	How have you found the experience of (name) being involved in this study?	What things did or didn't you like about (name) being involved? Are there any changes you would recommend? Would you recommend this study to another patient? Why/Why not?
Feasibility of phase III	What concerns did you have about (name) participating in this study?	Were there any things that may have stopped (name) from participating initially? What positives or negatives did you find from (name) participating in the study? Did you worry about (name) being in the placebo arm?
Specific components (if not already covered)		Using a syringe driver Subcutaneous route Hospitalisation Assessments Having other medications unchanged during the study
Translation to practice	Would you recommend this treatment if it was found to be effective?	What would make you more or less likely to recommend this treatment outside of a trial?
Carer experience	How has (name) having pain affected you?	Are there any aspects of how pain affects (name) that we haven't assessed in this trial which you would like to discuss?

Coding tree

Theme	Sub-theme	Codes
Trial participation offered a sense of hope and purpose	Altruism and legacy	• Reasons to recommend (future patients) • Value of participation
	Trial participation: a help or hindrance?	• Ease of participation • Concerns about participating (monitoring AE, potential AE)
	Monitoring and control can assuage uncertainty	• Monitoring of adverse effects (reassured by surveillance) • Uncertainty • Long-term management of pain
	Accceptable despite frustrations	• Experience with the study (positive/negative/neutral) • Attitude towards placebo • Assessments and questionnaires (positive feedback, flexible scheduling) • Recommend study
The impact of the intervention has multiple contributing factors	Contextual effects	• Attitude towards placebo • Adverse effects of use (e.g. drowsiness) • Effectiveness of intervention • Multifactorial pain management
	Intervention delivery	• CSCI device use (convenience, size, SC administration, walking with SD)

	Hospitalisation: a virtue or a vice?	• Hospital experience (inpatient stay)
	Embrace the intervention if effective	• Future considerations • Would use if effective • Attitude towards opioids
Pain impacts every aspect of life	Pain impacts daily life	• Impact on daily life • Description of pain
	Impact on relationships	• Pain not understood by friends or family
	Grief and loss	• Change in pain • Comparing self to others

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