Understanding opioid analgesic prescribing and cognitive adverse effects in older adults: a mixed methods study

Short title: Opioid prescribing and cognitive adverse effects in older adults

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PhD by Thesis

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Abstract

Background: Pain is prevalent in older adults (≥65). Opioids are used to manage moderate to severe pain, but older populations may be more at risk of adverse effects. Opioid-induced cognitive impairment can be distressing but evidence to inform our understanding is limited.

Aim: To understand opioid use in the pain management of older adults, how opioids impact older adults' cognition, and explore their experiences, perspectives, concerns, and information and support needs regarding these.

Methods: This study comprised two key components: (1) a systematic review to synthesise existing evidence on the impact of opioids on older adults' cognition and the assessments used to detect changes in cognition, and (2) a mixed methods study; comprising a cross-sectional survey and case note review to investigate opioid prescribing in community-dwelling frail older adults with chronic pain and their impact on cognition, and in-depth interviews to explore their experiences, perspectives and concerns of these aspects. Patient and Public Involvement was used to inform the mixed methods study, and refine study materials and interview topic guide.

Results: Limited evidence identified in the systematic review indicated that impairments were observed with higher mean opioid doses, and memory, attention, language and psychomotor function were worsened. Screening tools are rarely discriminatory enough to detect changes, and neuropsychological assessments are not feasible in clinical practice.

247 participants were recruited to the cross-sectional survey when attending an Integrated Care Centre for an assessment, and a case note review was conducted where medical record data was present. Qualitative interviews were conducted with a subset of 18 patient participants and their carers. A high prevalence of pain (>50%) despite treatment was observed. 51.8% were prescribed an opioid over the past year, with pain severity and number of medications being significantly associated with increased odds of an opioid prescription. The presence of opioid prescriptions were significantly associated with poorer health-related quality of life. *Insurmountable work* was required to manage chronic pain and cognitive adverse effects that impacted everyday life and emotional and psychological wellbeing. The challenges with accessing support led to a reduced sense of safety and security, and increased feelings of despair and isolation.

Conclusions: Pain remains a prominent issue for frail older adults despite treatment. Opioids are commonly prescribed and opioid-induced cognitive impairment is bothersome to older adults and their informal caregivers, and create insurmountable work. The importance of caring was essential to ensuring that patients felt safe and secure. Simple changes to patient-provider communication could improve pain management (e.g. provision of clear information, guided discussions to identify common adverse effects, ongoing support, and reviews).

Plain Language Summary

Background and aims of the research

Chronic pain is common among older adults (those aged 65 and above). Opioids can be used when people experience moderate to severe pain, loss of function and when other forms of pain medication have not provided suitable relief. However, these medications can have negative effects on cognition (e.g. memory) in older people. The impact of opioids on older adults' cognition is not well understood. This study aimed to learn more about opioid use for pain management in older adults, how opioids affect cognition, and older adults thoughts, experiences and concerns, and needs related to these matters.

Design and methods used

The research had two main parts: first, a review of existing evidence on how opioids affect cognition in older adults and the tools used to measure these effects; second, a mixed-methods study involving a face-to-face survey and medical record review with frail older adults living in the community, and interviews with a proportion of those recruited who had chronic pain and their family carers (where available). Members of the public were involved in developing the study materials and ensuring that the interviews focused on what was important to their experiences.

What was found?

The survey and medical record review involved 247 frail older adults who attended an Integrated Care Centre for a review of their health and social care needs. Interviews were completed with 18 of these older adults who had chronic pain, and their family carers (where available). It was found that despite treatment, many participants still experienced significant pain. Over half of them had been prescribed opioids in the past year, with pain intensity and the number of medications they were taking increasing the likelihood of opioid prescriptions. Those with opioid prescriptions had lower quality of life. The interviews showed that managing chronic pain and dealing with cognitive side effects from opioids was very challenging for older people and those that care for them, affecting their everyday lives and emotional well-being. Many faced difficulties in getting proper support, which led to feelings of insecurity, despair, and isolation.

What does this mean?

The research concluded that pain remains a major issue for frail older adults, and opioid use can be problematic due to its impact on cognition. Better communication between patients and healthcare providers, including clear information, discussions about potential side effects, ongoing support, and regular reviews, could lead to improved pain management.

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List of abbreviations

Acronym	Full term
6-CIT	Six-item Cognitive Impairment Test
AKPS	Australian Karnofsky Performance Status
CCG	Clinical Commissioning Group
CHCP	City Health Care Partnership
CFS	Rockwood Clinical Frailty Scale
CI	Confidence Interval
CIS	Critical Interpretative Synthesis
CNS	Central Nervous System
EQ-5D-5L	EuroQol-5D-5l
eFI	electronic Frailty Index
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GP	General Practitioner
HCP	Healthcare Professional
HRQoL	Health Related Quality of Life
HYMS	Hull York Medical School
ICC	Integrated Care Centre
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
IPOS	Integrated Palliative care Outcome Scale
IQR	Interquartile Range
MeSH	Medical Subject Headings
MMSE	Mini-Mental State Examination
NHS	National Health Service

NPV	Negative Predictive Value
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OME	Oral Morphine Equivalent
OR	Odds Ratios
PACE	Proactive Anticipatory Care Evaluation
PPI	Patient and Public Involvement
PPV	Positive Predictive Value
PRN	Pro re nata
QOF	Quality and Outcomes Framework
RCT	Randomised Controlled Trial
SD	Standard Deviation
UK	United Kingdom
VAS	Visual Analogue Scale
WHO	World Health Organisation

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Author’s declaration

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources, these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

Publications, other outputs and personal development

Peer-reviewed publications incorporated into this thesis

Pask S, Dell'Olio M, Murtagh FEM & Boland JW. The effects of opioids on cognition in older adults with cancer and chronic non-cancer pain: A systematic review. *Journal of Pain and Symptom Management*, 59(4): 871 – 93.

Additional peer-reviewed publications

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Dell'Olio M, Pask S, Seymour J & Reeve J (2019) What do the healthcare experiences of people with long-term conditions tell us about person-centred care? A systematic review. European Journal for Person-centred Healthcare, 7(4).

Conference presentations for this thesis

Pask S, Okoeki M, Khamis A, Johnson M, Murtagh FEM & Boland JW. 'Prevalence and patterns of opioids currently prescribed in community-dwelling older adults living with frailty.' Poster presentation on 6th – 8th October 2021, at the 17th World Congress of the European Association for Palliative Care [Online].

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Other conference presentations

Okoeki M, Wilson I, Harman D, Folwell A, Clark J, Boland JW, Pask S, Nwulu U, Elliott-Button H, Johnson M & Murtagh FEM 'Experiences of a novel Integrated Care Service for older adults at risk of severe frailty: an analysis of survey and interview data. Oral presentation, presented by Mabel Okoeki, 6th – 8th October 2021, at the 17th World Congress of the European Association for Palliative Care [Online].

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Personal development

Throughout the research project, I was able to develop knowledge of specific methods and advance wider research skills through structured training opportunities and learning 'on the job'. For more in-depth details on training and other academic activities undertaken during the duration of the thesis, see Appendix 1. These learning opportunities have helped to increase my knowledge of methodological approaches and improve transferable skills.

As someone with a non-clinical background working in health research, conducting this research and collaborating with key stakeholders throughout increased confidence in my expertise and role as a researcher, alongside service users and clinical partners.

Chapter 1: Introduction

The UK population aged 65 and over is projected to increase by 50% between 2016 and 2039.[1] With an ageing population, the prevalence of age-related health issues and associated burden is a major public health concern posing economic and social issues.[2-4] Older adults are living longer with more chronic conditions, multiple long-term conditions and frailty.[5-8] This population requires high levels of health and social care resources, including regular visits to general practice, as well as frequent and lengthier hospital stays.[9-11] Older adults often see several different healthcare providers, which makes continuity and coordination of care challenging.[9-11] To transform services for older adults requires coordinated care around their complex needs, rather than care based on single diseases.[11-15] Some healthcare professionals may attribute aspects of older people's experiences of illness as a normal part of ageing.[16-19] This characterisation of older adults' needs and experiences as 'normal' factors of ageing can significantly impact their independence and wellbeing.[11,19] More understanding and training on how to identify and address these complex healthcare needs is essential as the current system is not prepared for this growing population.[11,20]

Pain and pain management in older adults

Pain is a common but sometimes intractable symptom in older adults.[21-23] Chronic pain is estimated to be present in approximately 25% to 76% of community-dwelling older adults, with higher prevalence in residential settings.[24] Pain is often underestimated, underassessed and undertreated, as well as underreported in this population.[25,26] Older adults often experience different types and sources of pain simultaneously, which makes treatment difficult to balance.[21] Age-related physiological changes can also impact on pain management and how older adults respond to medication, due to changes in how medications are absorbed, distributed, metabolised and excreted.[27-29] Challenges are also present with managing multiple conditions, polypharmacy and complex reactions to treatment.[30] Chronic pain affects older adults' quality of life, psychological wellbeing and ability to self-care,[26] especially in older adults who are frail.[31] Pain management aims to improve function and quality of life, as complete pain relief may be an unrealistic aim.[21,29] Treatment plans preferably adopt both non-pharmacological and pharmacological approaches.[29,32,33]

Use of multiple medications

Older adults are prescribed multiple medications to manage various symptoms and comorbidities, and polypharmacy may seem unavoidable.[34,35] Polypharmacy can lead to an increased risk of adverse effects and poor outcomes, inappropriate prescriptions and combinations, issues with drug interactions, iatrogenic disease hospitalisation, costs and death.[30,36-38] Both appropriate prescribing and polypharmacy are a growing concern with older adults and pose challenges for clinical practice.[35,36,38] There needs to be an equilibrium between underuse of appropriate treatment in this population, and overuse of inappropriate medications.[39] 'Inappropriate medications' are characterised as unsuitable use of commonly used medications that have profound negative consequences on patient safety, and when their intended benefit is not achieved.[35,40] There is also reluctance to medicalise older age.[41,42] Older adults' beliefs about pain medications (e.g. fears of polypharmacy/ addiction) and perspectives on the demands of taking medications may influence achieving clinically meaningful adherence.[43-45] The risk of undertreatment in this population needs to be balanced against overtreatment.[36,39] It is important to identify those at most risk of harm and ensure that appropriate polypharmacy is achieved for effective use of medications.[44] Frequent reviews and optimising medication use by stopping unnecessary or inappropriate medications have been recommended to reduce potential harm, particularly when managing multiple medications and complex drug regimens.[45,46]

Opioid analgesic use to manage pain in older adults

Opioid analgesics can be used to manage moderate to severe pain in older adults and prescription rates in this population are rising.[47-51] Guidance has been produced to support the use of opioids with adults in clinical practice.[52-54] In particular, the World Health Organisation (WHO) three-step ladder has historically aimed to reduce cancer pain in adults by using an upward titration (based on effect and tolerability) from non-opioids, to opioids for mild to moderate pain (e.g. codeine), to opioids for moderate to severe pain (e.g. morphine) until pain relief is achieved alongside regular review.[25,54] This incremental approach is inexpensive, and has been found 70% to 90% effective in cancer pain management,[54] although there have been more recent challenges to reconsider the suitability of this three-step approach and its appropriateness with chronic non-cancer pain.[55-57] Nevertheless, there has been an increase in the prescribing

of opioid analgesics for patients with chronic non-cancer pain (including older adults).[48,49] Managing chronic non-cancer pain using opioids has led to overuse and adverse outcomes due to its complex nature.[58,59] Acute and end-of-life pain are easier to predict and have a more linear trajectory that may respond well to opioids.[58]

There is also a growing debate about the suitability of prescribing opioid analgesics in older adults,[48,49,51,59,60] as they may be more susceptible to adverse effects from analgesic medications and poor health outcomes.[26,51,61] Interventions that are commonly recommended by guidelines are not always supported by a robust evidence base.[62] An update of evidence-based guidelines for pain management in older adults emphasised the importance of considering non-pharmacological strategies, consideration of physiological changes and potential sensitivities to drugs, occurrence of adverse effects in relation to drug-disease and drug-drug interactions, route and timing of administration, and controlled initiation of drugs.[61] Clinicians are often encouraged to individualise and adapt prescribing with consideration to advances in modern practice,.[55-57] which is important to tailoring care but this may lead to inconsistencies and variations in approaches.

There are factors that can adversely impact opioid prescribing. Factors such as attitudes and societal factors, provider and patient concerns, and lack of understanding about opioids are still common issues.[42,63-66] The potential benefits of opioid analgesics are sometimes appreciated by patients, although there are concerns around becoming addicted.[63,66] There is also perceived stigma surrounding the use of opioids and what taking them means in terms of the seriousness of their condition.[66] These concerns are mitigated by the benefits of pain relief and quality of life.[66] Generally, non-opioid medications are considered the first port of call.[42,55] Healthcare providers have a responsibility for safeguarding, and in particular, may have concerns regarding opioid abuse.[42,64,65,67] The lack of clear guidance paired with the complexities of older adults experiences of pain impact the prescribing of opioid analgesics in this population.[42,64,67] Successful utilisation of opioids for pain management can be addressed by overcoming issues with routine assessment, and reasonable and individualised prescribing (with consideration to dose, administration, adverse effects and deprescribing, where needed and education).[26,68]

Adverse effects

Effective opioid therapy is partly dependent on balancing analgesic effectiveness and possible adverse effects.[69,70] In particular, it is important to recognise when pain is unlikely to be opioid-responsive.[29] Chronic opioid therapy may increase risk of adverse effects, which can affect a variety of systems; gastrointestinal, neurological, cardiovascular, pulmonary, urological, endocrinological and immune.[71-73] Adverse effects include constipation, cognitive impairment, respiratory depression and urinary retention, and can lead to discontinuation of use.[58,71,74] However, older adults can benefit in terms of pain relief as much as younger counterparts.[74] Adverse effects are common for all age groups but older adults are at greater risk due to multiple conditions and multiple medications.[72] These effects can often be managed by dose reduction, use of adjuvant pain medicines, use of other medications to manage symptoms induced by opioids, opioid rotation, and altering the route of administration.[72,75] More understanding is needed on the long-term safety and efficacy of opioid use with older adults, and to ascertain outcomes relevant to older adults taking opioids (e.g. risk of falls, daily functioning, cognition and quality of life).[74]

Opioid analgesics and cognitive impairment

Cognitive impairment has been more commonly researched in older adults receiving opioid analgesia in perioperative medicine or within the wider construct of adverse effects in those with chronic non-cancer pain or those receiving palliative care.[73,74,76,77] Reviews that have explored opioid-induced cognition explicitly have focused more broadly on adults with cancer and chronic non-cancer pain,[78-83] but not specifically older adults. There is a more limited understanding of the use opioid analgesics to manage chronic pain in community-dwelling older adults and cognitive adverse effects,[63,73,84] especially in those who are frail.[85] Impairment in cognitive function can lead to a reduced attention span, disorientation regarding time, restlessness, agitation, hallucinations and delirium; all of which can impact on patient and family carer quality of life.[86] The risk of opioid-cognitive impairment may effect clinicians' initiation of opioid therapy, and optimisation of use.[78] Opioid-induced cognitive impairment can be reduced by further understanding and recognition of the problem.[73] Strategies may be employed to help minimise the impact of cognitive effects (such as switching opioids)

but evidence is still limited, especially in a primary care setting.[73,86] More consideration to cognitive impairment has been called for in pain management and the use of major opioids in older adults.[74,84] This understanding will be able to guide clinical practice, and patient and carer knowledge.[78] Additionally, it is important that we further understand the complex relationship between cognition, opioids and pain in older adults.[78]

Impact of pain and pain management on those providing informal care and support

In the later stages of life, older adults can have a greater need for both formal and informal care, with greater functional dependence.[25,87] Informal care continues to increase with the growing number of older adults with advanced illness, with family members as providers of support.[87,88] Care is often provided at home in the community[89,90] and caring for patients with chronic pain can have an adverse impact on the family carers.[89] Carers often experience physical, emotional and financial burden.[89,90] A descriptive study demonstrated that 93% of family carers of patients with chronic pain exhibited one to six characteristics of caregiver strain.[91] Managing medication can be a key component of informal caregiving.[43,92-96] Challenges to managing medications included maintaining supplies of medication, making clinical judgements and communication with the care recipient and healthcare professionals.[92,95] These tasks also related to the patient's level of dependency.[92,95] Carers need support in managing pain relief for the patient.[91] To provide better support to carers, more understanding of these issues in relation to opioids is required.[92,94]

Summary

Opioid therapy is poorly understood in the context of managing chronic pain in older adults,[59,73,74,84] and remains a concern for patients, informal caregivers and health professionals.[63,64,94] Opioid-induced cognitive impairment affects initiation and continuation of treatment that could benefit older adults,[74,78] and significantly impacts their quality of life,[86] as well as their carers[92] but may be manageable or reversible.[72,75,86] To improve care and better understand opioid therapy and opioid-induced cognitive impairment in community care, it is important to explore opioid use in older adults in this care setting, and how cognition is affected, as well as capture the

impact, attitudes and beliefs, and wider concerns related to opioid therapy. Therefore, this study aims to understand opioid analgesic use in the pain management of older adults and the care received, how opioid analgesics impact older adults' cognition, and explore their experiences, perspectives, concerns, and information and support needs regarding these.

Chapter 2: Pain management in older adults and the role of opioid analgesics

2.1 Introduction

With an ageing population, any health problem that adversely affects the quality of life of older adults becomes increasingly salient.[4] Chronic pain is one of the most common conditions encountered by healthcare professionals, particularly among older adults (i.e. aged ≥65).[32] Pain is a complex and distressing problem that has consequences for the individual, their family and society.[10,97] These include emotional, psychological and financial consequences, in addition to the physical aspects that impact on basic physical activity and ability to complete daily activities.[97-103] However, there are several challenges with managing pain in older adults, including underreporting, underassessment and undertreatment.[23,25,29,32] Opioid analgesics are one possible treatment of pain, but their appropriateness for use in this population is often questioned.[49,104] This chapter will consider the challenges of conceptualising and understanding pain in this population, its prevalence and impact, and the challenges with managing pain, as well as the role of opioid analgesics.

2.2 Conceptualising and understanding pain

Pain is a ubiquitous experience and one that remains enigmatic in terms of its diagnosis, pathophysiology and treatment.[105,106] There are recognised challenges with drawing conclusions regarding the epidemiology of pain given the heterogeneity of research and varying approaches to understanding pain.[107] Since it is such a subjective phenomenon, it is important to understand certain challenges with conceptualising pain before considering the use of opioid analgesics in the pain management of older adults. This includes issues with definitions, terminology, and assessment and measurement of pain.

Pain can range widely in terms of severity and duration, and presents with varied pathophysiologic mechanisms and meanings that makes it challenging to provide a

succinct and precise definition.[108] It has generally been described as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage’ by the International Association for the Study of Pain (IASP),[109] which has provided a conceptual anchor and simplistic operational framework for healthcare professionals to understand the nature and management of pain.[108] This definition emerged alongside the Gate Control Theory of Pain, which introduced pain as ‘gating mechanism’.[105] Consequently, sensory, cognitive, affective, and motivational processes influence experience of pain.[105]

Neurosciences has considered chronic pain as changes with neural function (i.e. the neurophysiology of pain).[105,110] Chronic pain is therefore characterised as the brains response to noxious stimuli or nociception.[105] Nerve receptors that respond to an injury transmit information about damage or potential channels.[110] Receptors on nerves work by opening ion channels (otherwise known as gates) in the wall of the nerves.[105,110] Chronic pain can therefore be revealed in functional magnetic resonance imaging brain scans.[105]

However, pain and nociception are not synonymous, meaning that pain is not reduced to activity in the sensory pathways.[108] Chronic pain is a complex and multifaceted affective, cognitive, motivational, sensory and temporal phenomenon.[105,111,112] Over time, the affective, cognitive and environmental factors appear to have an increasing role in the maintenance of pain, emotional distress and functional disability.[112] More recently, the IASP definition has been updated to incorporate experiences that reflect actual and potential tissue damage,[108] which recognises that pain may sometimes be present without discernible damage. This definition enables the recognition of the multidimensional nature of pain (i.e. influenced by biological, psychological and social factors), whilst maintaining a practical approach, as well as maintaining focus on pain as an experience.[108]

This thesis will consider both pain that is currently experienced and ongoing pain, which is typically referred to as chronic pain or persistent pain. Whilst current pain is more easily established (i.e. at this moment),[113] there are a range of definitions that have

been proposed to describe ongoing pain. These include definitions that have been adopted in clinical practice[114,115] or applied in research,[116] although these may overlap. There has traditionally been a focus on duration of pain[117] or physiological aspects;[118] both of which have their own limitations (i.e. not accounting for pains multi-dimensionality or chronic pain from unknown causes). There is undoubtedly a challenge in providing a classification to cover all manifestations of pain.[119] This thesis will adopt the term 'chronic pain' to mean 'persistent or recurring pain lasting longer than three months',[119] which has commonly been applied in clinical practice,[120] national guidelines[121] and literature.[122] Additionally, this definition has been proposed in the new edition of the International Classification of Diseases (ICD-11),[119] which was a result of the work conducted to produce and update the classification of pain for use internationally (as described in the previous paragraph) and includes working subsets of chronic pain (such as chronic primary pain).[108] The ICD-11 definition is clear, succinct and easily operationalised (i.e. provides a systematic approach to pain that can be adopted clinically or within research).[119]

Classifying pain relies on the reporting and assessment of pain.[113] Several factors have been identified that complicate pain assessment in older adults,[123] which include underreporting and underassessment.[16,124] These factors then contribute to an undertreatment of pain, which comes with wider consequences and impact not only for the individual but their family, as well as the society that they are a part of.[113,123] Underreporting has been attributed to stoicism and viewing pain as a part of ageing or something that they have to learn to live with.[121,124,125] A small-scale study adopting a descriptive quantitative correlational design demonstrated that help-seeking behaviour was more common in women, with increasing age, a higher level of education, for those living alone and when severe pain was present.[125] These findings supported an extended literature review.[124] Nevertheless, further empirical investigation is needed to understand pain-related stoicism and its impact to help-seeking behaviour.[121,124]

Older adults often present with complex pain (with multiple aetiologies, for instance) and is commonly assessed by self-report,[121] as it is considered as the most accurate and reliable way to determine pain.[108] Pain can be described numerically (e.g. quantifying pain via scales) and/or descriptively.[113,126] There are several unidimensional (i.e.

Numeric Rating Scale and Verbal Descriptor Scale) and multidimensional (i.e. the Brief Pain Inventory Short Form and Geriatric Pain Measure) tools that may be suitable for assessing self-reported pain in older adults and are commonly adopted in literature.[113,126] Most unidimensional tools focus on pain severity or intensity, as well as the impact of pain.[113,126] Considering these aspects in isolation only presents part of the picture. Multidimensional tools allow for more comprehensive assessments (such as considering both pain severity and impact of pain on function or behavioural and psychological factors) but are used less frequently than unidimensional tools.[113,126] A comprehensive assessment of pain that integrates multiple approaches (e.g. self-report, physical examination, diagnostic testing and observation) has been considered useful in this population.[121,123] More routine comprehensive assessments of pain in this population are needed but infrequently occur.[123] Providers might not ask about pain despite regular and consistent assessment being seen as an important component of good pain management.[113,127]

The process of pain assessment in older adults should aim to obtain verbal and non-verbal self-report of pain.[113] However, self-report is not always possible in terms of communication issues or cognitive impairment.[113,121,128-130] Cognitive impairment has been recognised as one of the most prominent barriers to assessing pain, as it is assumed that those with impaired cognition are unable to respond to questions about or provide a self-report of pain.[113,127,129,131] Older adults' self-report may also be impacted by sensory impairments (such as visual or hearing impairments) and sociocultural factors.[113,121] However, there is evidence that these barriers do not always limit older adults' ability to self-report.[113,130] Informal caregivers may be able to support with self-report, confirm pain or provide a proxy report.[113,132] Studies support that proxy reports are a suitable alternative when self-report cannot be obtained,[130,132,133] but proxy reports should be interpreted with caution.[134]

2.3 Prevalence of pain in older adults and its impact

The occurrence of pain in older adults is common and prevalence estimates vary by the way pain is considered and assessed, as well as differences between studies (including the population and setting considered, type of study, methods used and date of

study).[4,24,98,122,135-138] The crude prevalence of older adults reporting any type of pain has been demonstrated to range from a low of 0% to a high of 93% in the literature.[24] Estimates of pain currently experienced by community-dwelling older adults also vary, ranging from 20% to 46%.[24] When considering pain severity, a prospective study showed that moderate to severe pain was experienced at baseline by 21.4% of older adults recruited.[139] This is supported by a cross-sectional study in the oldest-old across different settings of care (including at home with and without support), which found that 35.6% of participants had moderate to severe pain that impacted their daily activities on some level.[98]

Chronic pain is an issue for both developed and developing countries (ranging from 37.3% and 41.1%, respectively), and greater among women and older persons.[137] In the UK, a systematic review and meta-analysis of population studies estimated that chronic pain affects one-third to half of the population (corresponding to 28 million adults), a figure that is anticipated to increase in line with the ageing population.[122] When accounting for age, a trend of increasing prevalence is seen (i.e. 14.3% from young adults to 62% in those over 75 years of age).[122] Similarly, a 2017 health survey for England found that chronic pain was reported by 34% of all adults, ranging from 16% among young adults to 53% of older adults aged ≥75.[140,141] A further review found that chronic pain affects between 25% to 76% of older adults in the community.[24] Similarly, more recent evidence found that the prevalence of chronic pain ranged from 20.9% to 78.2%, albeit in different populations and settings (including the community), and with different definitions of chronic pain.[139,142,143] Despite the variation, the messages from the literature are consistent: pain is a common experience for all ages; there is an increasing prevalence of pain noted with advancing age; and older adults are more likely to experience pain. Therefore, alleviating or managing pain is a priority.

Older adults with chronic pain live with and are at risk of poorer health outcomes. As highlighted in Section 2.2, pain may be normalised as a part of ageing and this may reduce help-seeking behaviour.[19] Older adults often present with multiple sources of pain, which has been demonstrated to increase the risk of mortality.[144] Poorly managed pain is a significant cause of functional impairment, which is accompanied by reduced mobility, decreased socialisation, issues with sleep and slow rehabilitation.[145] It has

been recognised that such factors might be more impactful to older adults than their younger counterparts. For example, pain is likely to precipitate social isolation or feelings of loneliness in older adults,[146] which, in turn, can lead to increased symptoms (such as depression)[137,147] and increased cognitive impairment.[148] Additionally, older adults with chronic pain are more likely to experience falls.[149-151] Consequently, it leads to higher healthcare utilisation and costs, as well as increased risk of future hospitalisation.[10,145,152] Severe pain also impacts on quality of life.[152-154] It has implications for older adults daily lives and disrupts their ability to complete tasks.[99,139,155,156] This leads to adaptation with a number of daily tasks and stops certain tasks altogether, as well as presenting a challenge to people's notions of self.[155,156]

Pain also affects family and friends, as they may provide informal care (such as pain medication management and supporting daily activities), due to older adults' limitations and greater functional dependence.[157,158] All of which can lead to caregiver strain, including physical, emotional and financial burden.[91,95,157,159] There is an increasing need for informal care to enable older adults to remain at home.[160,161] A 'role reversal' with the care recipient has sometimes been described, where informal caregivers assumed responsibility for activities previously held by the recipient (such as domestic chores).[157] Determinants of caregiving overburdening include duration of caregiving and the recipient's dependency level.[89] Informal caregivers need support in managing pain relief, in particular, where multiple conditions are present and there are other regimens to consider.[61,90,91,96] Few studies have explored the experiences of informal caregivers supporting older adults with chronic pain living at home and in the context of primary care. To provide better support to carers, more understanding of these issues in relation to opioids is required.[92,94]

2.4 Challenges with pain management

Pain is a complex and multifaceted problem for older adults who form a reasonably large proportion of chronic pain sufferers.[25] There are several age-related changes that may impact on pain management.[26,32] This section will consider the specific parameters that make pain more challenging to manage in this population, in addition to the challenges identified in Section 2.2. This includes physiological changes, cognitive

decline, frailty, multiple conditions and polypharmacy, as well as attitudes, beliefs and concerns.

2.4.1 Attitudes, beliefs, concerns and knowledge

As highlighted in Section 2.2, attitudes and beliefs may account for patients decision-making in pain management.[61,125] This includes misconceptions, fears and concerns, personality, and cultural and religious beliefs.[29,162] The belief that pain should be accepted or hidden is a re-occuring theme with older adults.[121] They may perceive pain to be untreatable or medications as a last resort, and may hold negative attitudes towards medication or other interventions.[29,43,163] Whilst, medications may also be perceived as necessary.[164,165] Anxieties about becoming addicted to pain medication may also impact adherence.[166] There can also be concerns about masking disease progression or a loss of independence.[29] The attitudes, beliefs and concerns of informal caregivers are also important and may impact pain management.[121] It is also essential to consider health literacy,[167,168] as limited understanding may complicate older adults ability to meaningfully adhere to pain management.[169] Healthcare providers should consider attitudes, beliefs and concerns, as well as knowledge and understanding of pain management.[61] Tailoring information to meet patient needs would enhance effectiveness.[170]

2.4.2 Physiological changes

Ageing is accompanied by significant physiological changes that may not only alter response to and experiences of pain but also the pharmacokinetics and pharmacodynamics of drugs.[27-29] Age-related physiological changes can impact different systems, including gastrointestinal, liver, cardiac, renal and nervous systems.[29] Additionally, older adults may experience loss of body fat, body water and muscle.[29] Normal ageing may therefore be associated with pain homeostenosis (i.e. reduced ability to effectively respond to chronic pain stressors because of limited biological, psychological and social reserves).[28]

Pharmacokinetics refers to the steps the body takes to convert the drug and enable its excretion,[171,172] essentially, how drugs move within the body.[172] This includes how drugs are absorbed, distributed, metabolised and excreted.[172] Multiple factors contribute to this change, including, but not limited to, reductions in body weight, changes in renal excretion and liver enzyme function.[4,29] Pharmacodynamics considers how the drug interacts with the body (such as its biological and physiological response) and the observed effect of what the drug does to the body.[171] In terms of pharmacodynamics, older adults are deemed to be more sensitive to certain medications, such as those that affect the central nervous system.[30]

The evaluation and treatment of pain in this population needs to consider the multiple factors that potentially contribute to pain homeostasis and, in turn, pain-related disability.[28] This includes careful consideration to the drug classes used, route of administration and dose prescribed.[29,30]

2.4.3 Cognitive decline

Age-related cognitive decline is characterised by deterioration of higher cortical function (such as thinking, reasoning, comprehension and language).[173] It ranges from mild deficits that are not clinically detectable to dementia.[174] Cognitive decline can result in various health problems (including risk of developing dementia and increased mortality) and lead to a lower quality of life.[174-176] Prevalence of global cognitive impairment in community-dwelling older adults is estimated to be between 5.1% and 41%, with a median of 19%.[177] In the UK, cognitive impairment has been estimated to impact 18.3% of older adults living in the community and women in particular.[178]

As discussed in Section 2.2, the evaluation of pain depends on cognitive ability, and there may be challenges with underreporting, accuracy of or ability to self-report and undertreatment. Pain has also been classed as more than a purely sensory experience and one that involves cognitive processing.[179] Cognition has been described as the acquisition, processing, storing and retrieving of information.[180] It is an important component of the subjective experience of pain that requires evaluation, learning, recall and decision-making.[181] Evidence has suggested a bi-directional relationship between

the neural systems involved in cognition and pain,[182] although, the understanding of how pathophysiology and the mechanisms of cognitive impairment are associated with chronic pain and its treatment remains limited.[131]

A population-based cohort study of elderly patients showed a significant relationship between chronic pain and long-term cognitive decline when controlling for age, gender, education, comorbidities, depression and analgesics drugs.[183] Though, the presence of chronic pain was only assessed at baseline and not assessed at follow-ups but could perhaps be inferred from measures of activities of daily living.[183] In contrast, a systematic review and meta-analysis using pooled data from longitudinal studies found no significant association between chronic pain and risk for cognitive decline in community-dwelling older adults.[148] However, two of the included studies found that higher levels of pain are associated with cognitive decline/impairment in comparison to lower levels of pain.[184,185] Further research is needed exploring the role of high levels of chronic pain and its implications for treating pain, and whether it could be a modifiable factor for reducing the risk of cognitive decline in older adults.[131,148,183-185]

Cognitive decline may also impact the way older adults take pain medication. A cross-sectional study demonstrated that just under a third of community-dwelling older adults with dementia reporting pain either rarely or never took medications for pain.[130] This may support the evidence of undertreatment in this population, as those with cognitive impairment in Alzheimer's disease or related dementias had a lower likelihood of using over-the-counter pain medication or have a regular intake of pain medication prescriptions.[129]

2.4.4 Frailty

Frailty is a syndrome that, like chronic pain, increases in prevalence with age and is multifaceted.[29,186,187] There is a lack of consensus regarding an operational definition of frailty.[188] It is often characterised by decreases in physiological reserve and diminished resistance to stressors (i.e. homeostenosis) that cause difficulty with maintaining equilibrium (i.e. homeostasis),[188] as well as an increased risk of dependency and death.[189,190] Pain-related consequences have similarities to those found in older adults

with frailty,[191] in that, they may have reduced ability to effectively respond to the stress of chronic pain.[28,192]

Approaches to how frailty is operationalised and identified are broadly underpinned by one of two models, including the phenotype model[190] and the cumulative deficits model.[193] The phenotype model proposes that frailty is a physiological syndrome that has five core clinical presentations (i.e. weight loss, exhaustion, low energy expenditure, slowness and weakness).[190] The presence of any three of these characteristics suggests that the person may be living with frailty.[190] In particular, the model sees frailty as overlapping with comorbidities and disability but also distinct from these.[194] In contrast, the cumulative model attempts to assess a person's overall health by counting deficits (such as symptoms and diseases) and using this as a marker for frailty.[193]

Chronic pain has been suggested to contribute to deteriorating functional outcomes and frailty.[191,195] A review found that older adults that report pain are more likely to be frail, although conclusions regarding the direction of the association were not drawn (i.e. whether pain or frailty was the precursor).[8] A subsequent systematic review and meta-analysis of longitudinal studies demonstrated that chronic pain is a risk factor for developing frailty.[196] Frailty is also associated with a higher prevalence of analgesic use[197] and higher levels of inappropriate prescribing.[198] It has been proposed that chronic pain should be integrated into the frailty construct (described in the previous paragraph) to allow for a better understanding of frailty and how to best improve care for patients with or at risk of pain and frailty.[191]

2.4.5 Multiple conditions and polypharmacy

Chronic pain is commonly experienced across a wide range of long-term conditions.[199] In particular, a high prevalence of multiple conditions has been observed in older adults with chronic pain receiving care at home.[39] The presence of multimorbidity has been demonstrated to increase linearly with age,[5-7] although with a substantially earlier age of onset.[7,12] Additionally, the burden of complex multimorbidity (i.e. presence of at least three chronic conditions that affect at least three body systems) has increased across

England.[7] Generally, multiple conditions are more pronounced in women, those who are less educated and those with lower income.[5-7] Those with a wide range of long-term conditions are at higher risk of experiencing a greater degree of chronic pain.[199,200] Specific diseases and disease combinations are also related to chronic pain.[201]

These considerations pose specific challenges for healthcare and challenge the single-disease framework that has commonly been adopted in healthcare, and supports the move towards more integrated care.[12-15] The healthcare costs associated with elderly chronic pain patients in primary care may increase over time, mainly due to hospitalisation.[10] Healthcare costs are independently associated with the number of conditions, in addition to, chronic pain.[10] Therefore, chronic pain is an important factor in the consideration of managing patients with long-term conditions or multimorbidity, and vice versa.[199]

The use of several medications simultaneously (i.e. polypharmacy) is also common in community-dwelling older adults with multiple conditions (including chronic pain).[36,39] There are many definitions for polypharmacy but one of the most commonly employed is the number of medications exceeding a numeric threshold (such as five medications or more).[35] However, this descriptive approach has been criticised in terms of its arbitrary cut-off[202] and not accounting for specific comorbidities and the appropriateness of treatment.[203] Clinical consequences of polypharmacy in the elderly, as well as adverse drug events, drug interactions and medication non-adherence lead to increased healthcare costs.[38] Drug regimens for those on multiple medications are increasingly complex and can potentially be harmful, especially for older adults and those living in more deprived areas.[46] Therefore, those with polypharmacy are likely to benefit from regular review and prescribing optimisation.[46] Clinical guidelines are also important in improving the healthcare received by those with long-term conditions but recommendations can lead those with multiple conditions to rapidly accumulate medications and drive polypharmacy.[204] Medication-related problems that could impact the safety of drug treatment in this population result from drug interactions, overprescribing and underuse.[39] Redesigning practice to address problematic polypharmacy could help to reduce other complex issues within medical practice, such as chronic pain.[205]

2.4.6 Interconnectivity of cognitive decline, frailty, multiple conditions and polypharmacy

One clear narrative that came from reviewing the literature are the challenges associated with managing pain in community-dwelling older adults. There are recognised connections between cognitive decline, frailty, multimorbidity and polypharmacy. Frailty and multimorbidity are interrelating complex syndromes and untangling these concepts is challenging.[206,207] Frail older adults may also be at higher risk of cognitive issues than non-frail older people.[208] Polypharmacy is also associated with cognitive decline and frailty.[209] Additionally, the anticholinergic burden of multiple medications is associated with cognitive decline and dementia.[210] The presence of frailty has also been linked to adverse drug reactions, inappropriate prescribing and polypharmacy in older adults.[211-213] Multiple conditions and polypharmacy are associated with an advancing loss of resilience and impaired homeostasis, which has implications for frailty.[214] Careful reviewing of medication regimens is needed.[213] The electronic Frailty Index (eFI) or other frailty measures might be useful in identifying signs of frailty and in predicting polypharmacy in older adults.[213]

2.5 Approaches to pain management

The management of chronic pain in older adults remains an important clinical challenge and further understanding is needed regarding appropriate approaches,[215] especially for those with frailty.[85] Many non-pharmacological (including non-invasive, surgical and interventional treatments) and pharmacological (including opioids and non-opioid analgesics) treatments are available for managing chronic pain. An update of evidence-based guidelines for pain management in older adults, following a review of evidence since 2010 and consensus approach, emphasised the importance of considering non-pharmacological strategies, physiological changes, potential sensitivities to drugs, occurrence of adverse effects in relation to drug-disease and drug-drug interactions, route and timing of administration, and controlled initiation of drugs.[61]

An individualised multimodal approach to pain management is needed to manage the complex pain experienced by older adults and should consider both non-pharmacological and pharmacological treatments.[29,32,33] Non-pharmacological approaches include alternative therapies (such as physiotherapy), surgical and other interventional techniques, social care and self-management strategies.[29,216] Pharmacological treatments include opioid analgesics, non-opioid analgesics or a combination.[26,216] Older adults with multiple types of pain are likely to be on more than one form of analgesia.[51,217,218]

2.5.1 Alternatives to pharmacological treatment

A need for evidence-based strategies for the management of pain that address the biopsychosocial and environmental nature of the problem has been identified, which includes non-invasive nonpharmacological treatments and the durability of their treatment effects.[219] Therapies that focus on patients' bodies and minds have demonstrated some benefit for managing chronic pain and are cost-effective.[220]

A systematic review update on non-invasive nonpharmacological treatment for chronic pain largely supported their earlier report; namely that exercise, rehabilitation delivered by multidisciplinary professionals, acupuncture, cognitive behavioural therapy, mindfulness and massage were most consistent in improving function and/or pain beyond the course of treatment for common pain conditions (e.g. low back pain, neck pain and osteoarthritis).[219,221] Evidence is still sparse; studies often had small sample sizes and evidence assessing effects beyond 12 months after completion was limited.[221] Effect sizes were small for both function and pain. Data on harms from these types of interventions was limited but no evidence suggested serious harm form any of the interventions that were studied.[221]

These findings have also been supported in community-dwelling older adults. A systematic review demonstrated that non-pharmacological methods of managing pain in this group were effective in lowering pain levels.[222] This included acupressure, acupuncture, guided imagery and Thai Chi. Although, the application of certain interventions (such as acupuncture) needed to be maintained at regular intervals to

sustain pain reduction, as well as being considered an intervention that cannot be implemented by older adults themselves when in pain.[222] Again, a limited number of articles were identified on a diverse number of interventions, with limited in-depth investigation of individual interventions.[222] Overall, there appears to be some benefit from non-pharmacological interventions but further understanding is needed about the effectiveness of specific interventions and sustainability, as well as how they might be combined with pharmacological approaches.

2.5.2 Pharmacological approaches

For the purpose of this thesis, attention will be focused on opioid analgesics, as a pharmacological approach. Primary care is often the first point of contact for people suffering with chronic pain, and analgesics are one of the tools adopted by general practitioners.[223] There is increasing recognition that pharmacological approaches need to be improved.[104] Deficits in dosing patterns and appropriateness have been observed in older adults receiving care at home.[224] Diagnoses may influence the prescribing of pain medications and there can be challenges with receiving medications when pain is severe.[225] There are also specific concerns around the long-term safety of analgesic use in older adults, as well as their efficacy in managing pain.[25,26,104] Chronic pain and the use of pharmacological approaches may accelerate or increase risks of negative health outcomes in older adults.[19,107,215,226]

Pharmacological approaches to cancer pain management traditionally centre on using the oral route where possible (i.e. by mouth), ensuring that doses are delivered at regular intervals (i.e. by the clock) and that it is guided by the WHO ladder.[21] The three-step analgesic ladder was proposed by the WHO to guide pharmacological decision-making in cancer pain.[54] This strategy has since been modified to improve its application towards other types of pain (such as non-cancer pain).[55-57] Clinicians have also been encouraged to tailor prescribing, with the guidance depending on individual patients and reflecting advances in modern practice.[55-57]

The first step of the analgesic ladder for mild cancer pain includes paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), with or without adjuvant therapy (e.g.

tricyclic anti-depressants and anti-convulsants).[55,216] Paracetamol is often favoured in the management of mild to moderate pain because of its safety profile,[32] but less so for cancer patients using opioids for moderate to severe pain.[62] It is not associated with significant adverse effects, although overdose can cause hepatotoxicity.[32] NSAIDs can be effective but have established gastrointestinal, cardiovascular and renal risks that increase with age.[32]

Opioid analgesics are introduced on the steps on the analgesic ladder (with or without adjuvants), starting with opioids for mild pain, and increasing in strength.[55] It is recommended that the lowest possible dose be adopted initially, with an aim to review and amend as needed, to avoid adverse effects.[29,32] Opioids can be a tolerable and effective analgesic for different types of pain, although most commonly used to manage cancer pain.[23] There is limited evidence to support the long-term use of opioids, especially in older adults with chronic non-cancer pain.[227-229] In selecting an opioid, it is important to consider liver and renal functions, other medications and ability to consume the preparation.[23] Codeine, hydrocodone and tramadol are considered for milder pain.[55] Whilst fentanyl, methadone, morphine, oxycodone are considered for more severe pain.[55] Opioids can be administered by a number of enteral (e.g. by mouth) and parenteral preparations (e.g. transcutaneously via the skin), with varying times of onset depending on route.[23] Opioid formulations can be short-acting and immediate-release or long-acting and sustained release.[23]

2.6 The role of opioid analgesics in pain management

Opioids are more commonly used to manage cancer pain[23] and it is recognised that not all pain is opioid-responsive.[230,231] Evidence suggests that opioids may provide some benefit in managing chronic non-cancer pain, but the magnitude of its impact is likely to be small.[231,232] Yet, opioids are increasingly prescribed in older adults.[49] There is limited evidence in methodologically flawed studies with small samples supporting the long-term use of opioids in older people with chronic non-cancer pain to inform our understanding.[232] More research around the efficacy of opioids in pain reduction, physical function, as well as psychosocial wellbeing is needed.[232] Chronic non-cancer pain in older adults may ideally be managed by non-pharmacological approaches

alongside non-opioid analgesics, as well as a multi-disciplinary approach.[60,68] Guidance indicates that low doses of opioids can be used where patients have moderate to severe pain, loss of function and non-opioid analgesics have not provided adequate relief.[23,68] However, there are no clear recommendations regarding specific agents, initial dosing or monitoring parameters.[85]

Opioid prescribing increases with age.[47,49,50] The high prevalence of opioid prescribing in older adults means that it is important to monitor and evaluate treatment (such as initiation and continuation),[49] and identify potential risk factors.[47,48,50,233-235] Especially as the use of opioids has been linked to a higher risk of all-cause mortality, cardiovascular events and fractures.[236,237] Studies exploring the risk factors of receiving an opioid prescription found that in addition to older age, being widowed, depression, deprivation, and reporting poor physical health are also risk factors.[47,50] In particular, older age, presence of multiple conditions, larger practice sizes, rurality and deprivation are associated with either increased high-dose prescribing rates or long-term opioid use.[48,238] More specifically, predictors of opioid prescribing/use in older populations include ethnic background, number of chronic conditions, pain severity, perceived mental health, functional limitations, smoking status and region,[233,234] although, there may be limited application to other patient groups and countries due to differences in health systems.

In terms of opioid type, codeine is one of the most commonly prescribed opioids to adults (aged ≥18) without cancer across the UK, with a 5-fold increase in prescriptions between 2006 and 2017.[48] An observational study in older adults demonstrated an increase in the prescribing of buprenorphine and fentanyl.[49] There was also a decrease in prescribing noted with tramadol,[49] which perhaps reflects more cautionary prescribing as it may cause mental confusion.[59] Buprenorphine, fentanyl, morphine and oxycodone are often favoured for use in older adults,[239] as well as transdermal formulations and controlled-release oral dosage to improve convenience.[239] In summary, opioid prescribing changes with increasing age in terms of frequency, nature and duration despite the higher potential of harm.[49] A large number of contextual factors may influence the way opioids are prescribed to manage chronic pain in older adults.[235] Further understanding of influential factors is still needed, especially from a patient-,

provider- and system- perspective within the context of multiple conditions and treatment burden.[235] There is also limited evidence exploring opioid prescribing in those who are frail.[85]

Several studies have assessed and theoretically modelled general practitioners' experiences in opioid prescribing in primary care,[64,65,240,241] albeit predominantly focussed on adults generally and chronic non-malignant pain. Structurally, the act of prescribing opioid analgesics could be influenced by micro-, meso-, and macro- factors, as summarised in Table 2.1.[64] Toye and colleagues consider challenges to managing chronic non-cancer pain.[240,241] Additionally, they further dissect the complexity of decision-making at the level of the healthcare professional in regards to opioid prescribing and present a conceptual framework.[241] The decision to prescribe is not clear-cut. They propose that it depends on balancing the potential positive and adverse effects for the individual, ambivalence towards regulations and guidance, and potential non-clinical judgements made about the patient (including intra- and inter- personal factors).[241] The ideal aim is to minimise pain but there are concerns around the use of opioids and expressed social responsibility to protect patients.[241] Additional concerns were identified in relation to older adults due to the possible severity and impact of adverse effects.[241] Other studies found similar issues and considerations to opioid prescribing.[64,65]

Table 2.1 Summary of potential factors that could influence general practitioner analgesic prescribing[64]

Factor level	Description
Micro factors: patient-specific clinical considerations *Influences at a practice level setting*	- Aetiology, severity and progression of the pain. - Potential risks and benefits associated with prescribing analgesic and adjuvant medications (i.e. the risk-benefit analysis; comparing the efficacy of the medication with potential adverse effects).
Meso factors: local guidance, accessing secondary or consultant care and cultural perceptions of the GP role *Local and regional influences*	- Continuity of care across different settings - Access to and support from services (including multi-disciplinary care or specialist services) - Geographical proximity to specialist services
Macro factors: national and international context *National or international influences*	- Availability of information and guidance, as well as keeping up-to-date with treatment developments. - Clinical knowledge and understanding of pharmacotherapeutic management, including guidelines and formularies. - Lack of specific guidance on prescribing for chronic non-cancer pain.

From a patient perspective, analgesics are regarded as an important method for managing pain and are useful when other interventions are more challenging to access.[63] Internal and external factors that inform perceptions and experiences of analgesics have been identified from older adults accounts.[63] Internal influences on analgesic use include pain severity, perceived efficacy of the analgesics, adverse effects, and concerns about addiction or dependence. External factors include the views of their family members, as well as access to and interactions with healthcare professionals.[63] However, these older adults were identified via an organisation that aims to support those living with chronic pain.[63] Experiences may differ for those with a less formal route of support. Other studies have identified similar experiences and barriers,[165,242-245] although they were not focused towards the experiences of older adults[242-245] or on medications generally.[92,165] The role of family members in the management of pain in older adults and their medication has often been identified in literature,[63,92,96,157,242,246,247]

but remains relatively unexplored in the context of managing chronic pain and opioid use at home.

2.7 Summary

Understanding the prevalence of pain and the specific challenges faced with managing pain in this population is important, especially with the ageing population. This chapter has argued that pain is a prominent issue for older adults and that individual multidimensional approaches to understanding pain are needed. It has also recognised the challenges with managing pain, as well as the role of opioids and the factors that may influence decision-making regarding their use. To improve the care delivered, requires a clearer understanding of opioid use in older adults managing chronic pain at home, especially for those that are frail.

Before opioid use can be further explored in the frail older population, it is important to consider opioid-induced cognitive impairment in greater detail, and what is already known about this adverse effect. Chapter 3 considers, in-depth, what is meant by an adverse effect, how opioid-induced cognitive impairment is characterised and potential ways it can be measured, as well as its impact.

Chapter 3: Opioid-induced cognitive impairment

3.1 Introduction

As discussed in 2.6, opioid analgesics may lead older adults to experience adverse effects.[248] Older adults may be at greater risk of adverse effects than their younger counterparts due to multiple conditions and medications.[72] Common adverse effects include cognitive impairment, constipation, respiratory depression and urinary retention, and can lead to discontinuation of use and may shape decision-making regarding treatment.[58,63,71,74] These adverse effects impact neurological, gastrointestinal, cardiovascular, pulmonary, urological, endocrinological and immune systems.[71-73] Common central nervous system adverse effects are reduced or impaired cognition, delirium, hallucinations and sedation.[71,86] Effectively managing opioid therapy is partially dependent on balancing analgesic effectiveness and possible adverse effects.[69,70] Greater understanding of opioid-induced cognitive impairment is needed to improve older adults experiences of using opioids and their impact (e.g. cognition, daily functioning, and quality of life).[74] First, it is important to consider what is meant by an 'adverse effect'. Second, opioid-induced cognitive adverse effects are characterised. Lastly, the impact of opioid-induced cognitive impairment is considered.

3.2 Terms and definitions for unwanted effects

Medications, prescribed to benefit patients, are also capable of causing unwanted effects.[249] The terms 'adverse effect' and 'side effect' are used interchangeably in the literature to describe these unwanted effects, although they have slightly varied definitions. An 'adverse effect' is defined as encompassing all unwanted effects that seem to be associated with treatment and can be attributed to some pharmacological action of a drug.[249] Whilst, the term 'side effect' is characterised as an 'unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug' (p. 5).[250] However, this definition also encompasses effects that may be beneficial or tolerated rather than harmful, although not the main aim to the treatment (e.g. using an antidepressant to manage neuropathic pain may have benefits for depression).[251] It has been argued that the term 'adverse effect' is preferable as it does not make assumptions about mechanism

(e.g. dose), and avoids ambiguity and chances of misclassifying effects (i.e. as desirable).[249] Therefore, this thesis will predominantly adopt the term ‘adverse effect’.

3.3 Characterising opioid-induced cognitive impairment

3.3.1 Cognitive function and cognitive domains

Cognition can be characterised by cognitive domains,[252] which include memory, executive function, attention and concentration, language and verbal skills, processing speed, perception, sensation and motor skills.[131] These major cognitive parameters are depicted in Figure 3-1 and are formed of subdomains that reflect component ability processes.[131,252] The nature of these domains is largely agreed upon but there are inconsistencies across both clinical and research literature.[252] Inconsistencies usually exist in the broader domains as they may include multiple component processes.[252] This includes disputes about whether such processes belong in more general domains (such as executive function) or simpler domains (such as processing speed).[252]

Figure 3-1 Cognitive domains adapted from Khera and Rangasamy (2021)[131]

Note. Adapted from *Cognition and Pain: A Review* [Image] by Khera T. and Rangasamy V. (2021), Frontiers in Psychology (https://doi.org/10.3389/fpsyg.2021.673962). CC BY 4.0.

Memory is one of the most complex cognitive domains.[252] Memory conceptually consists of several storage systems that are essential for interpreting information from the environment to short-term memory, and subsequently into long-term memory.[131] Executive functioning includes neuropsychological processes that support complex cognitive functions, such as reasoning and decision-making.[131,252] Attention and concentration is a multidimensional construct that is commonly divided into two global subdomains, including selective attention and sustained attention.[252] Concentration tends to fall under sustained attention.[252] Attentional skills have executive functioning components.[252] Language and verbal skills include the ability to comprehend language and access to semantic memory to enable the identification of objects and respond to verbal instructions.[252] Processing speed refers to cognitive processing assessments that

necessitate the rapid performance of tasks (ranging from simple to complex).[252] Sensation refers to a person's ability to detect a stimulus in one of the five sensory modalities (including touch, sight, hearing, smell and taste).[252] Whilst, the ability to recognise a stimulus falls under the domain of perception.[252] Motor skills refer to a range of motor activity, from fine motor abilities (such as dexterity and reaction time) to more global skills (such as balance).[252]

3.3.2 Cognitive function and opioid analgesics

Opioid analgesics can induce central nervous system adverse effects that lead to several neurological deficits.[86,253] This includes impact to lower-level consciousness (such as drowsiness, sedation and distrubance with sleep).[86,253] Thinking processes and reactions may also be affected, including impaired attention, disorienation regarding time, memory, psychomotor impairment, restlessness, delirum, hallucinations, dreams and nightmares.[86,253] Additionally, opioids may have direct toxic effects to neurons and potentially cause hyperalgesia (i.e. increased sensitivity to pain) and tolerance.[86,253] There is heterogeneity in the effects experienced and defining the nature of opioid-induced cognitive impairment is challenging due to its subjectivity.[83,253] There are also methodological challenges, in that, it is difficult to replicate findings and findings are often inconsistent.[83,253] As discussed earlier in this section, how cognitive domains are conceptualised and assessed also vary.[252]

Disruption to cognitive function has been well-investigated in relation to opioid analgesics.[253] Adults with cancer and chronic non-cancer,[79-83] as well as postoperative[76] and outcomes of opioid use in chronic non-cancer[84] have been the focus of primary evidence and literature reviews. Analgesic use in community-dwelling older adults has been associated with dizziness and light-headedness, as well as unsteadiness on their feet and constipation.[254] The most commonly observed adverse effects in a systematic review of opioid prescribing in older adults related to the central nervous system.[85] Opioid-induced cognitive adverse effects in older adults is clearly an issue but understanding around this topic is limited,[51,72,248] especially for those living in the community and those with frailty.[85,254]

3.3.3 Diagnosis and attributing causality

Cognitive adverse effects of opioids can mimic diseases or conditions that occur naturally (e.g. dementia) or have a variety of other causes (including other medication and anticholinergic burden, health conditions or attributed to ageing).[249,251,253,255] This leads to challenges with identifying cognitive adverse effects, as well as determining whether the effect could be due to the opioid analgesics.[249] The probability of causation of a suspected adverse effect can be deduced from aspects such as timing and pattern recognition.[249]

The relationship between the use of an opioid analgesic and the occurrence of an adverse effect may help in attributing causality.[249] There are several elements that can be considered in relation to time, such as whether the adverse effect occurs or worsens when the dose is introduced or a steady-state dose is increased.[249,256] Time-dependent adverse effects may occur more or less immediately or may be delayed.[256] Adverse effects may be experienced initially or they may persist during the opioid therapy.[256] The adverse effect may be resolved by withdrawing the medication or may be lessened by partial withdrawal (i.e. reduced dose).[249,256] The pattern of the adverse effect may also fit the pharmacologic pattern of an opioid analgesic.[249] Pattern recognition should consider the frequency of the effect and how it is associated with the opioid.[249]

Guidance to assess the strength of an association between a cause and effect has been developed by Bradford Hill and highlights certain criteria that need to be considered before conclusions regarding causation can be made.[256] This includes the strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy (see Table 3.1).[256-258] Although, these guidelines are not designed to understand adverse effects or intended to be rigid criteria for determining causation, they have been widely applied in a range of contexts.[256-258]

Table 3.1 Summary of the Bradford Hill criterion of causation[257]

Criteria	Description
Strength of association	This criterion reflects that the larger an association is, the more likely it is to be causal. An important aspect is considering the definition of a 'strong' association. Traditionally, this has referred to the magnitude of an association, although statistical significance is the accepted benchmark.
Consistency	The concept of consistency refers to the ability to replicate the cause and effect.
Specificity	This implies that associations are more conceivable in terms of causality when they are specific.
Temporality	The exposure must precede the outcome and there must be a temporal progression between the two to allow for causal inference.
Biological gradient	The presence of a dose response implies that an association is more likely to be causal.
Biological plausibility	This criterion implies that the incidence of the outcome is related to the biological pathways.
Coherence	This is similar to the criterion of biological plausibility, in that the cause and effect should be logical and make sense in the context of the information available about the cause and effect.
Experiment	Causal associations that are evidenced from experimental manipulation allow for a strong support for causal inference.
Analogy	This refers to where similar effects are produced by equivalent interventions.

3.3.4 Measuring opioid-induced cognitive function

Opioid-induced cognitive impairment is usually measured objectively using cognitive function measures or subjectively using self-report or clinical judgement.[131,253] In research, studies have often determined and measured the impact of opioid analgesics on cognition using screening tools and neuropsychological assessments.[79-83] Screening tools provide a structured assessment of opioid-induced cognitive impairment.[253] There are screening tools that have been specifically designed to explore opioid-induced adverse effects (such as the Pasero Opioid-Induced Sedation Scale and Numerical Opioid Side Effect) and more general screening tools that have been designed to detect age-related cognitive impairment (such as the Mini-Mental State Examination; MMSE).[81,253] Whilst, neuropsychological assessments target the subdomains of the

larger constructs that are presented in Figure 3-1, usually measuring one or more distinct abilities.[131,252] However, there are recognised challenges with screening tools and neuropsychological assessments. They can lack the sensitivity to detect clinically meaningful changes in cognition or may be difficult to apply in clinical practice.[79-81,253] Additionally, there is limited understanding of what tools might be the most useful in older adults.

Clinically, the assessment of cognitive effects and sedation needs careful history and examination, and examination of mental status.[253] Self-report is not commonly adopted in the literature as it does not allow for a standardised approach[79-81] and self-report is identified as an invalid proxy for neuropsychological tests in healthy adults.[259] Adverse effects, as previously highlighted, may be attributed to other causes.[256] Related to this, other factors that might impact self-report include unawareness and hesitancy to report such effects or complacency that only safe medications are prescribed.[256] Older adults appear to disregard some adverse effects from medication; fewer adverse effects are self-reported compared to those clinicians observed.[260] The self-report of adverse effects may be improved by simple approaches, such as presenting a prompt list of adverse effects.[261] However, this has only been explored in patients with multiple myeloma.[261]

3.4 Impact and management of opioid-induced cognitive impairment

The avoidance of unfavourable cognitive outcomes is an important focus of opioid therapy and research.[63,85] Adverse effects can have consequences for quality of life.[253,261] Broadly, adverse effects from medication are associated with increased pain-related activity interference in adults with chronic pain, meaning greater reductions in daily activities even after controlling for changes in pain severity.[262] More specifically to older adults, a qualitative study of analgesic use in chronic non-cancer pain highlighted that sedation is one of the most distressing adverse effects from strong opioid analgesics.[63] The sedation caused by the analgesia impacted daily function, although this was only mentioned by one participant.[63] For some, adverse effects meant that they discontinued use of the pain medication despite experiencing pain relief.[63] Another qualitative study that considered adverse effects of chronic pain medications found that patients (including older adults) characterised the risks and benefits of

medications in two temporalities: present quality of life and risks in terms of future health.[263] Present impacts included changes to social lives and their living conditions and this study echoed the concerns regarding cognitive function.[263] Among the pharmacists interviewed, adverse effects impacting a patients quality of life were usually considered a lower priority in comparison to those impairing physical health.[263]

A survey demonstrated that patients with complex care needs and informal caregivers are largely concerned about adverse effects, interactions between medications and medication errors.[93] Although, the age range captured within this survey is unclear.[93] Adverse effects from medications not only impact older adults' views of medication value but also their informal caregivers.[264] Informal caregivers play an important role in gathering information about medication, including collecting information about potential adverse effects and drug interactions.[96] This involves monitoring the occurrence of adverse effects and following up with providers to modify medications as necessary.[96] Informal caregivers often notice adverse effects or other health issues before they are detected by healthcare providers, and could be influential to treatment decisions.[96]

3.5 Summary and rationale for thesis

This chapter considers what is meant by an adverse effect, as well as how opioid-induced cognitive impairment is characterised and its potential negative impact on quality of life. There are several challenges to identifying opioid-induced cognitive impairment that may mean it goes undetected or unmanaged, which can add to an otherwise complex experience of pain and pain management in this population.

Altogether, Chapter 2 and Chapter 3 have identified that there is increasing evidence of the poorer health outcomes experienced by older adults managing chronic pain, especially when treatment leads to adverse effects. Experiences of pain, opioid analgesics and opioid-induced cognitive impairment appear to impact decision-making regarding pain management, as well as the lives of patients and their informal

caregivers. There is also limited access to sources of support and differing priorities to healthcare professionals about pain management.

In summary, these background chapters have identified the need for the research to better understand how care and services could be improved, which this thesis proposes to address. This includes a limited understanding of the role of opioid analgesics in the management of chronic pain in older adults and their impact to cognition, especially for those who are frail and managing pain in the community, and improving understanding of what would work best to identify opioid-induced cognitive impairment in this population.

Chapter 4: Aims and objectives

4.1 Overall study aim

To understand opioid analgesic use in the pain management of older adults, how opioid analgesics impact older adults' cognition, and explore their experiences, perspectives, concerns, and information and support needs regarding these.

4.2 Objectives by study component

(1) Systematic review

- To identify, appraise and synthesise the evidence on the impact of opioids on cognition in older adults with chronic pain, and understand how opioid-induced cognitive impairment is assessed.

Research questions to address objective 1:

(1) What is the impact of opioids on cognition in older adults with cancer and chronic non-cancer pain?

(2) What screening and assessment tools have been used to detect and assess opioid-induced cognitive impairment, and how useful are they?

(2) Quantitative components

- To investigate opioid analgesic use to manage pain and the impact on cognition (including impact of opioid use on quality of life and functional status, and a description of opioid use), among older adults at risk of severe frailty.

Research questions to address objective 2:

(1) What proportion of participants ***self-reported*** being prescribed a pain medication at some point over the past year?
(2) What pain(s) do participants experience?
(3) What proportion of participants had an opioid prescription ***documented*** on their medical record at some point over the past year?
(4) What changes were made to participants' pain medications (including opioid analgesics) following a medication review at the Integrated Care Clinic (ICC)?
(5) What proportion of participants who report being prescribed a pain medication over the past year ***self-report*** being prescribed an opioid?
(6) What cognitive adverse effects were ***self-reported*** by participants who reported being prescribed a pain medication over the past year?
(7) Does health-related quality of life differ between those who ***self-reported*** cognitive adverse effects from pain medications over the past year and those that did not, and what factors are associated with self-reporting cognitive adverse effects?
(8) Does health-related quality of life differ between those with an opioid prescription ***documented*** on their medical record over the past year and those that do not, and what factors are associated with having an opioid prescription?
(9) What are the patterns of opioid prescribing over the past year?
(10) What are the differences between ***self-report*** and ***documented*** data regarding opioid prescriptions over the past year?

(3) Qualitative component

- To explore the experiences, perspectives and concerns of older adults and those that care for them regarding chronic pain, opioid analgesic use and cognitive adverse effects (including the challenges with managing pain, impact of chronic pain and opioid analgesics, and information and support needs).

Research questions to address objective 3:

(1) What are the experiences, perspectives and concerns of older adults and those that care for them, regarding chronic pain, opioid analgesics and cognitive adverse effects?

(2) What impact do chronic pain, opioid analgesics and cognitive adverse effects have on older adults and those that care for them?

(3) What information and support needs do older adults and those that care for them have regarding chronic pain, opioid analgesics and cognitive adverse effects?

Chapter 5: The effects of opioids on cognition in older adults with cancer and chronic non-cancer pain: A systematic review

5.1 Introduction

This chapter presents the first component of this thesis: a systematic review. It presents the rationale for conducting a systematic review, the methods used, and the findings and discussion of the systematic review to answer Objective 1 of this thesis: "To identify, appraise and synthesise the evidence on the impact of opioids on cognition in older adults with chronic pain, and understand how opioid-induced cognitive impairment is assessed". The following research questions were considered to address Objective 1, as presented in Chapter 4:

(1) What is the impact of opioids on cognition in older adults with cancer and chronic non-cancer pain?

(2) What screening and assessment tools have been used to detect and assess opioid-induced cognitive impairment, and how useful are they?

5.1 Article reference and acknowledgement

This systematic review was published in the *Journal of Pain and Symptom Management*, Volume 59, Pask S, Dell'Olio M, Murtagh, FEM and Boland JW, The effects of opioids on cognition in older adults with cancer and non-cancer pain: A systematic review, p. 871–93, Copyright Elsevier (on behalf of American Academy of Hospice and Palliative Medicine) (2019).[265] A copy of the publication can be found in appendices, which includes the background to the systematic review (see Appendix 2). The author accepted manuscript is presented in this chapter, with further elaboration in regards to the rationale and the methods. The results, discussion and conclusions remain the same.

5.2 Author contributions

I conceived the idea for this systematic review and developed the protocol, with guidance from my supervisors (Jason Boland (JB) and Fliss Murtagh (FM)). I also developed the search strategy with advice from Fiona Ware, the Academic Liaison Librarian at the University of Hull. I performed screening for all records returned in the search, selection of relevant papers and data extraction for all included studies, with Myriam Dell'Olio (MD) acting as a second reviewer for 100% of the screening and data extraction. I conducted the narrative synthesis, with advice from Professor Ivana Markova (Professor and Clinical Consultant of Neuropsychiatry from the University of Hull) on the synthesis and summary of screening tools and neuropsychological assessments. I wrote the manuscript as first author. All authors provided critical comment, which I addressed and incorporated into the final published manuscript.

5.3 Rationale

There are age-related parameters that may lead to increased risk of adverse effects in older adults (as presented in Chapter 2 and Chapter 3). Opioid analgesics can induce central nervous system adverse effects; all of which can impact on older adults and their informal caregiver's quality of life.[86] However, this remains understudied in older adults. Existing reviews have predominantly focused on cancer and chronic non-cancer pain in adult populations,[79-81] without focusing on older populations. Where older adults have been the focus of reviews, these have concentrated on postoperative cognitive impairment[76] or outcomes associated with opioid use (including the prevalence of all adverse effects) in chronic non-cancer pain.[74,84]

Cognitive adverse effects can present in a variety of ways and can be assessed using a number of tools.[253] This includes the use of formal assessments (such as screening tools and neuropsychological assessments) and self-report.[131,253] Systematic identification and assessment of cognitive impairment could be useful in guiding opioid therapy. However, there is little consensus around which screening tools and neuropsychological assessments are effective in identifying opioid-induced cognitive impairment and which cognitive domains are affected.[79-83] Given the specific age-related parameters and

approaches adopted in existing reviews, it is important to consider and understand both the impact of opioids on cognition and how they might best be identified and assessed in older populations to improve the delivery of pain management in clinical practice.

There are a number of primary studies that have explored how opioid analgesics have impacted older adults' cognitive function using formal assessments. However, most of these studies had small sample sizes and adopted different tools or assessments to assess impact. This limits the generalisability of their findings. This body of evidence has not previously been synthesised, and in doing so allows for broader conclusions on the cognitive effects of opioid analgesics on older adults to be drawn. Therefore, the aim of this systematic review chapter is to identify, appraise and synthesis the:

i) Evidence on the impact of opioids on cognition in older adults with cancer and chronic non-cancer pain.

ii) Screening and assessment tools that have been used to detect and assess opioid-induced cognitive impairment, and to discuss their usefulness for identifying cognitive issues in older adults.

5.4 Methods

The protocol for this systematic review was prepared according to Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[266,267] and registered with PROSPERO (CRD42018092943) prior to screening and data extraction.[268] The systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidance.[269]

5.4.1 Search strategy

Careful consideration was given to search terms to ensure breadth in the returned results from the search. Search terms were identified and developed from existing reviews. Free text terms for searching titles, abstracts and key words were combined with database-specific MeSH terms that reflected the following broad topics; [opioids] AND [cognition] AND [older adult population] (see Appendix 2 for an an example of the full

search strategy). Concepts and their related search terms were kept broad to ensure inclusivity of all possible studies. For example, scoping searches demonstrated a limited number of studies focusing on frail older adults, which has later been supported by another systematic review.[85] Focusing on frailty within this aspect of the thesis might have limited the understanding of existing evidence.

MEDLINE, EMBASE and PsycINFO (via Ovid), CINAHL Plus (now CINAHL Complete, via EBSCO), Cochrane Central Register of Controlled Trials in the Cochrane Library (via Wiley), Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index, Emerging Sources Citation Index, Conference Proceedings Citation Index – Science and Conference Proceedings Citation Index – Social Science & Humanities), ProQuest and OpenGrey databases were searched from inception to December 2018. No electronic limits were applied to database searches. The reference lists of relevant systematic reviews and SP's EndNote library were screened to identify further studies that may not have been identified in the database searches.

5.4.2 Study selection

The studies returned from the search were imported into EndNote™ X8[270] and duplicates were removed. Titles and abstracts were screened for inclusion by two authors (SP and MD) independently in duplicate. For articles that potentially met inclusion criteria on title and abstract, SP and MD then assessed full-texts for eligibility. Disagreements between the two authors at all stages were resolved through discussion with a third reviewer (JB). Inclusion and exclusion criteria are outlined in Table 5.1 and then described in further detail following the table.

Nine authors were contacted to obtain the full-text when not available (n=3) or where the paper lacked information to confirm eligibility (n= 3) or further detail for clarification was requested (n=3), with a response rate of 44.4% (n=4). One author responded regarding the request for the full-text. One author responded and provided their dataset to confirm whether it met the eligibility criteria in terms of sample age. Responses were received from two authors that provided clarification on aspects of their

papers (i.e. differences between groups of interest, strategy for determining the original indication for opioid use, and clarifying the type of pain experienced by participants).

Table 5.1 Inclusion and exclusion criteria

Study characteristics	Include	Exclude
Population	Older adults aged ≥65 with cancer and/or chronic non-cancer pain (including an overall mean age of ≥65, a mixed population with at least 50% aged ≥65 or a clear subgroup analysis reporting on participants aged ≥65)	Populations where substance misuse, psychiatric illnesses, neurocognitive/neurodegenerative diseases (e.g. Alzheimer's) and brain injury are present or studies that only consider healthy older adults.
Exposure and assessment	Studies exploring opioid use where screening tools and/or neuropsychological assessments have been used to detect opioid-induced cognitive impairment.	Studies that consider recreational use and perioperative use of opioids, that aim to block the effects of opioids or that use opioids for antitussive relief, diarrhoea or use opioids not used within clinical practice.
	Studies exploring multiple medications effects on cognition, as long as opioids were included and a clear subgroup analysis was available.	Studies that use self-report assessment or a healthcare professional opinion of cognitive function.
Study design and publication type	Randomised controlled trials, quasi-experimental studies and observational studies, which had been published in peer-review or grey literature.	Case reports, reviews or systematic literature reviews, qualitative studies, opinion pieces, editorials, comments, news and letters.
Publication date, setting (including country or care setting) or language	Any	

Population

For the purpose of this review, older adults in this systematic review were defined by the chronological age of ≥65, as commonly adopted by most developed countries to describe older adults.[271,272] Populations with substance misuse or perioperative population were excluded as patterns of use may be different compared to cancer and chronic non-cancer pain.[273-275] Studies that had populations with mental health issues (e.g. depression) and neurocognitive/neurodegenerative disorders (e.g. dementia, Alzheimer's and (mild) cognitive impairment) were also excluded, as cognitive function may already be compromised before the consideration of opioids.[276,277]

Exposure and assessment

Studies that explored the use of opioid analgesics on cognition using formal assessments were included. If opioids were included as a subgroup amongst other medications, these were also included as long as there was a clear subgroup analysis and formal assessment of cognition was present. Where studies had focused on recreational use or abuse of opioids, as well as opioids used for perioperative pain were excluded, as different patterns of opioid usage were likely to be observed (type, duration and administration schedule).[273-275] Only a small percentage of perioperative older adults' are likely to continue opioid use for a longer term.[275] Studies that considered less formal and systematic approaches to measuring opioid-induced cognition were excluded (such as self-report, and clinical or carer opinion) to enable comparison with previous reviews.[79-83] Studies that used opioid antagonists to counteract opioid effects, opioids used for other purposes (e.g. antitussive relief or diarrhoea) or those not used in clinical practice were excluded.

Comparison

Studies with or without comparison groups were included.

Outcomes of interest

Primary outcomes included whether there had been any change to cognition after the use of opioids (no difference, improved or worsened), the screening tools used to

identify cognitive impairment (including outcome, and sensitivity and specificity, if available), and neuropsychological tests used to assess cognitive impairment (including the cognitive domain assessed, timing/schedule, and the outcome of the neurological assessment). Secondary outcomes included opioid use (e.g. type, dose, duration and route of administration) in the context of opioid-induced cognitive impairment and concurrent medications. Opioid-cognitive function and/or cognitive function-pain correlations were also considered, if available.

5.4.3 Data extraction and analysis

SP and MD extracted data using a structured extraction sheet (see Appendix 3), which had previously been pilot-tested. Data extraction was completed independently in duplicate. Data extraction forms were crosschecked for accuracy and missing data. Data collected included general information (author and year, type of publication, country of origin, source of funding and conflicts of interest), study characteristics (aim, study design, inclusion and exclusion criteria, recruitment procedures and study duration), participant characteristics (number of participants, source and setting of population, age, gender, disease characteristics, comorbidities and concurrent medications), how cognitive impairment was assessed (screening tools and/or neuropsychological assessments) and other outcomes collected, details of opioid treatment (type, dose, route of administration and length of use), statistical analyses used, the effect of opioids on cognition, limitations, and conclusions.

Quality was also independently assessed by SP and MD using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields (QualSyst) 14-item checklist for quantitative studies.[278] This was incorporated into the data extraction form. QualSyst was developed to provide set of standard criteria for simultaneously assessing the quality of varied study designs, as other tools have often been developed to assess specific study types (e.g. randomised controlled trials).[278] A summary score is calculated for each paper by dividing the total sum by total possible sum to provide an indicator of its level of quality.[278] In this systematic review, the reviewers used the calculated score to define the quality of papers as strong (score of

>0.80), good (0.71–0.79), adequate (0.50–0.70) or poor (<0.50) and did not exclude on account of poor quality, in line with other systematic reviews.[279,280]

A narrative synthesis was used, guided by Popay and colleagues.[281] A theory of how, why and for whom the intervention worked was not developed for this systematic review as previous reviews of a similar nature found variable effects on cognition after opioid use. An exploratory approach was used, with study design/methods, sample size, diagnosis, tools/assessments used, and opioid dose and length of use identified as factors to consider in the synthesis. Secondly, tabulation was used to develop a preliminary synthesis of included studies to aid interpretation of patterns across studies. Data regarding dose was transformed into oral morphine equivalent (OME) daily dose to enable dose comparison between studies. Thirdly, outcomes of tools and assessments were mapped against cognitive domains assessed to analyse similarities and differences across studies. Additionally, the cognitive outcomes were mapped against previously identified cognitive domains affected by chronic opioid use (namely cognitive flexibility, cognitive impulsivity and verbal working memory),[83] as well as 'additional' domains captured by the screening tool and neuropsychological assessments of included studies. Lastly, a critical reflection of the strengths and limitations on the robustness of the synthesis is included in the discussion.

5.5 Results

5.5.1 Study selection

A total 4,036 unique records were identified. Of these, 57 full-texts were screened and 10 were found eligible for inclusion (see Figure 5-1). For a summary of included studies see Table 5.2.

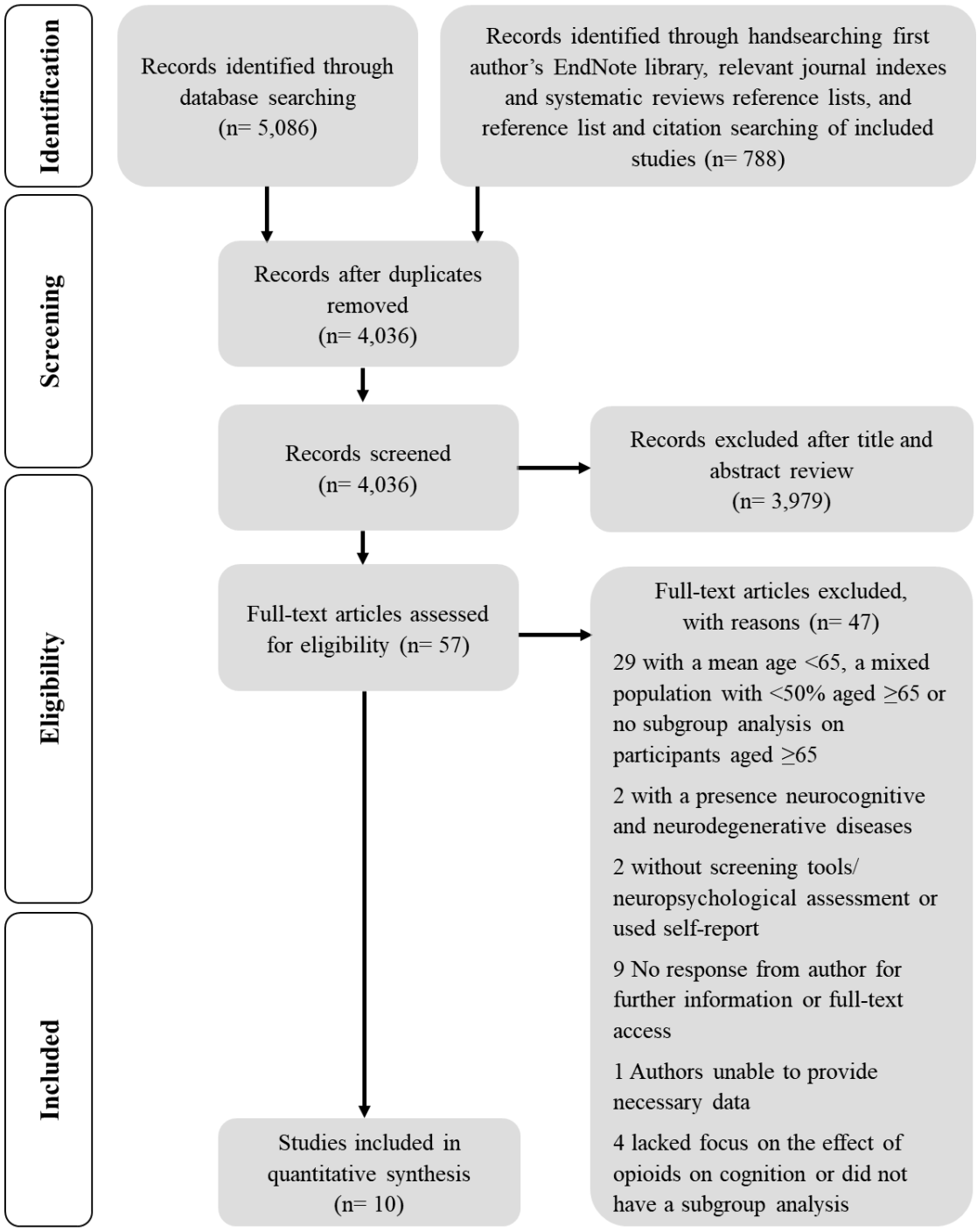


Figure 5-1 PRISMA flowchart

Table 5.2 Summary of included studies

Study and country	Design	Participants recruited; including diagnosis and age (mean age, range and/or % of ≥65)	Setting	Opioid type and oral morphine equivalent daily dose (OME; range)	Tools and assessments	Quality score
1. Clemons et al. (1996) *UK*	Quasi-experimental	29 participants (64.5; 51.7% aged ≥65); Group 1**:** 16 healthy participants (65.4), Group 2: 6 advanced cancer patients not taking opioids (62.8) and Group 3: 7 advanced cancer patients taking opioids (61)	Hospice (Inpatient/ outpatient)	Controlled release morphine sulphate or morphine sulphate solution 104.3mg (50 – 200mg)	GRT, LMT, NART, RT, SCWT	Adequate (0.55)
2. Corsinovi et al. (2009) *Italy*	Randomized, single blind, controlled	154 participants with persistent osteoarthritis-related pain; Group 1: 52 participants taking Oxycodone (79.2), Group 2: 52 participants taking Codeine (77.1), Group 3: 50 participants on conventional therapy (77.1)	Nursing home	Immediate release oxycodone 32mg* Immediate release codeine 11.5mg*	MMSE	Strong (0.93)
3. Gianni et al. (2011) *Italy*	Observational (Prospective cohort)	93 participants with osteoarthritis-related pain (79.1)	Multicentre (Ambulatory)	Buprenorphine 60 – 95mg	MMSE	Good (0.77)
4. Guerriero (2016) *Italy*	Observational (Longitudinal prospective cohort)	60 participants with moderate to severe chronic non-cancer pain (81.7)	Rehabilitation centre	Prolonged-release oxycodone 34.8mg*	MMSE	Strong (0.91)
5. Kamboj et al. (2005) *UK*	Double-blind, placebo-controlled, cross-over	14 participants; 12 (85.7%) with cancer pain and 2 (14.3%) with chronic back pain (65.2)	Palliative care unit (Inpatient/ Outpatient)	Sustained release opioid 190.7mg (30 – 800mg) Immediate release morphine 21.4mg (5-100mg)	PR, VFT, TMT, FT, DS, MST, TST, EC, ECD	Strong (0.82)
6. Karp et al. (2006)	Observational (Cross-sectional survey)	57 participants with non-cancer diagnoses (76.1) Opioid use present in 27 participants	Older adult pain management program	Not reported	MMSE, D-KEFS TMT, DSST, ILT	Adequate (0.55)
7. McNamara et al. (2002) *UK*	Observational (Single-centre, non-comparative, open label)	19 participants with cancer pain (65.7)	Hospice	Fentanyl 120mg (60 – 1080mg)	CDR	Good (0.73)

Summary of studies continued						
Study	**Design**	**Sample; including diagnosis and age (mean age, range or % or ≥65)**	**Setting**	**Opioid type and oral morphine equivalent daily dose (OME; range)**	**Tools and assessments**	**Quality score**
8. Pappagallo et al. (1994) *USA*	Observational (Longitudinal survey)	20 participants with postherpetic neuralgia (72.2)	Pain treatment centre	Slow release morphine 47.1mg (15 – 90mg) Compounded slow release oxycodone 55mg (15 – 90mg) Hydomorphone 64mg Methadone 100mg Overall OME dose 54.4mg	MMSE	Adequate (0.68)
9. Puustinen et al. (2011) *Finland*	Observational (Longitudinal population-based)	565 participants, including cancer and non-cancer diagnoses (70.5) Opioid use present at baseline (N= 9), follow-up (N= 43) and at both time-points (N= 3). Opioid users had arthritic diseases.	Municipality of Lieto	Codeine, dextropropoxyphene, ethylmorphine and dextromethorphan. Dose not taken into account.	MMSE	Strong (0.86)
10. Raja et al. (2002) *USA*	Double-blind, placebo-controlled, crossover	76 participants with postherpetic neuralgia (71)	Referrals and advertisements (Centre not clearly acknowledged)	Controlled-release morphine 91mg (15 – 225mg) Methadone (alternative to morphine) 150mg	MMSE, GPT, HVLT, SST	Strong (0.93)

Abbreviations: *CDR* Cognitive Drug Research computerised assessment, *D-KEFS TMT* Delis-Kaplan Executive Trail Making Test, *DS* Digit Span Test, *DSST* Digit Symbol Subtest, *EC* Elevator Counting, *ECD* Elevator Counting with Distraction, *FT* Finger Tapping Test, *GPT* Grooved Pegboard Task, *GRT* Grammatical Reading Test, *HVLT* Hopkins Verbal Learning Test, *ILT* Incidental learning tests, *LMT* Logical Memory Test, *MMSE* Mini-Mental State Exam, *MST* Map Search Test, *NART* National Adult Reading Test, *PR* Prose Recall, *RT* Reaction Time, *SCWT* Stroop Colour-Word Test, *SST* Symbol Substitution Task (Wechsler Adult Intelligence Test – Revised), *TMT* Trail Making Task, *TST* Telephone Search Test and *VFT* Verbal Fluency Test

*Opioid combined with acetaminophen (Corsinovi et al. 2009) and naloxone (Guerriero et al. 2016).

5.5.2 Study characteristics

Included studies were conducted in the United Kingdom (n=3), Italy (n=3), United States of America (n=3) and Finland (n=1). All studies were published in English. The studies comprised of three randomised controlled trials,[282-284] six observational[285-290] and one quasi-experimental design.[291] Four studies adopted the use of comparison groups to: (i) determine the efficacy of opioid use versus conventional therapy,[282] (ii) assess the difference between central nervous system (CNS) medication users and controls (with opioid subgroup analyses),[290] (iii) determine the difference between opioid users and non-opioid users[287] and (iv) investigate whether opioids or the disease itself had an impact on cognition.[291]

5.5.3 Population and settings

A total of 1,087 participants were included in the 10 studies. Changes to cognition from opioid use were explored by two studies in older adults with cancer pain,[288,291] six studies in older adults with chronic non-cancer pain[282,284-287,289] and two studies that included both.[283,290] Across nine of the ten included studies,[282-289,291] 44 participants had cancer pain, 462 participants had chronic non-cancer pain (predominantly osteoarthritis and postherpetic neuralgia) and 16 participants were healthy controls. In Puustinen et al. (2011), diagnoses were only available for 156 CNS medication users and 243 CNS medication non-users of the 565 recruited. This included both cancer and non-cancer diagnoses. However, participants who were taking opioids only had diagnoses of painful arthritic diseases.[290]

Study settings varied; two were conducted at a hospice (with one including both inpatients and outpatients).[288,291] The other studies were conducted within a municipality (i.e. single urban area)[290] as well as a multi-centre ambulatory services,[285] nursing home,[282] palliative care unit (inpatient and outpatient),[283] pain treatment centre,[289] an older pain management program[287] and rehabilitation centre.[286] One study did not clearly specify a study setting but recruited participants through GP referral/advertisements.[284]

5.5.4 Tools and assessments used to identify changes to cognition

A summary of the screening tools and neuropsychological assessments used to identify and assess changes to cognition from opioid use (including a description, cognitive domains assessed and outcomes of the tests) can be found in Appendix 2.

5.5.4.1 Type and combination

One screening tool and twenty-one neuropsychological assessments were used to identify changes to cognition from opioid use. Five studies[282,285,286,289,290] adopted the use of a screening tool (i.e. MMSE) in isolation and five studies[283,284,287,288,291] used a combination of neuropsychological tests. The MMSE was the most used instrument across all studies. Studies using neuropsychological assessments to assess cognition adopted different combinations of assessments. Clemons et al. (1996) stated that the National Adult Reading Test was resistant to the effects of drugs, whilst the Stroop-Colour Word Test was likely to give an indication of changes to cognition from opioid use.[291] Kamboj and colleagues (2005) also acknowledged that the Prose Recall Test would be sensitive to opioid-induced recall impairments.[283] The Cognitive Drug Research (CDR) computerised assessment used by McNamara and colleagues[288] was developed to assess effects from novel compounds on cognitive function, in both volunteers and patients in clinical drug development.[292] Other studies did not discuss the tools/assessments relevance to detect opioid-induced cognitive impairment.

5.5.4.2 Administration

The timing of screening tool and neuropsychological assessment administration varied across studies. Most studies provided limited description around when tests were administered (80%, n=8).[282,284-290] Those that provided more detailed information about administration generally provided timings in terms of hours or minutes after taking opioids to ensure that opioid plasma levels were at their peak and/or that the timing of tests remained consistent at each visit.[283,291] Nine of the ten studies measured cognition at baseline but follow-up periods ranged from 2 weeks to 52 weeks. Karp and colleagues (2006) conducted neuropsychological assessments within 2 weeks of

recruitment to minimise effects of newly prescribed treatments on the assessment outcomes.[287]

5.5.4.3 Cognitive domains

Fourteen cognitive domains were covered by the tool and assessments. Cognitive domains captured include attention, cognitive flexibility (including verbal and non-verbal fluency), concentration, language, memory (both short-term and long-term, as well as speed of memory retrieval), orientation, pre-morbid IQ, psychomotor function, psychomotor sedation, psychomotor speed, reaction speed and reasoning.

5.5.4.4 Changes to cognition

There were mixed effects of opioids on cognition in older adults with cancer and chronic non-cancer pain. Four studies (112 participants taking opioids),[283,287,288,290] demonstrated a change in cognition from opioid use when comparing the effects of morphine with a matched placebo[283], switching opioids[288] or between those who received opioid treatment and a control group comparison.[287,290] Control group comparisons consisted of non-opioid users (n=27),[287] and those using no CNS medication (n=384) and non-users of corresponding medications (n=556).[290] In six studies (233 participants taking opioids), no changes to cognition were observed from baseline to follow-up between groups[282,291] or in a cohort of participants.[284-286,289] Sixteen healthy controls and six advanced cancer patients not taking opioids,[291] and 33 participants receiving conventional therapy (i.e. acetaminophen, NSAIDs, COX-2-Inhibitor) not taking opioids[282] were used as control group comparisons. In four of the ten included studies, exploring changes to cognition from opioid use was the primary outcome,[283,284,290,291] however, in six studies it was a secondary outcome.[282,285-289]

5.5.4.5 Mapping cognitive domains and outcomes to opioid use in older adults

As discussed above, studies assessed cognitive function using either a screening tool in isolation or a combination of neuropsychological assessments covering 14 cognitive domains. The screening tools and neuropsychological assessments used have been

mapped against these different cognitive domains (see Appendix 2). Of the three cognitive domains identified by Baldacchino and colleagues,[83] the screening tool and neuropsychological tests of included studies all captured verbal working memory, whilst none captured cognitive impulsivity. Cognitive flexibility was captured by three studies.[283,287,291] Delayed recall/long-term memory was the most common 'additional' domain covered by included studies, followed by attention, language, orientation, concentration, psychomotor function, psychomotor speed, memory retrieval speed, pre-morbid IQ, psychomotor sedation, reaction speed and reasoning.

5.5.5 Opioid treatment and concurrent medications

Opioids used varied across studies (see Appendix 2). Six studies[283-286,288,291] examined the use of one opioid only (including buprenorphine, fentanyl, morphine and oxycodone). Three studies[282,289,290] used more than one opioid (including: codeine, dextromethorphan, dextropropoxyphene, ethylmorphine, hydromorphone, morphine, methadone and oxycodone). Of which, two studies compared differences between drugs; including opioids in comparison to antidepressants[284] and between different opioids (oxycodone and codeine).[282] Whilst, one study included participants taking one of four opioids without comparison.[289] Oral administration of opioids was most common, followed by transdermal patch and syringe driver. Two studies did not report route of administration.[284,290] Karp and colleagues (2006) did not provide detail around the type(s) of opioids used or route of administration.[287]

OME daily dose across all studies ranged from 11.5mg to 190.7mg, with two studies not accounting for dose.[287,290] The length of use also varied from approximately 7 days to 72 weeks, with one study not accounting for length of use.[287] In studies that demonstrated no difference to cognition, mean OME daily dose ranged from 11.5 to 104.29mg,[282,284-286,289,291] excluding the 13 participants that were provided with 15mg methadone (150mg OME daily dose) due to adverse effects from morphine.[284] In studies that demonstrated a change to cognition, mean OME daily dose were 190.7mg over an 11.7 day study period,[283] 120mg – 240mg over a 14-day study period[288] and dose not taken into account when comparing baseline with a 7.6 year follow-up[290] or between opioid users versus non-opioid users, without consideration to dose or length of

use.[287] Pain relief was achieved at low daily doses of opioids in a number of studies without detriment to cognition.[282,284-286] Opioid switching also demonstrated improvements to patients' global assessment of wellbeing that were deemed clinically significant.[288] One study found that pain worsened along with general wellbeing, mood and concentration.[291]

The majority of studies provided some description around the use of multiple concurrent medications. Three studies reported that pain medications previously taken by patients were discontinued before study commencement.[282,284,285] However, Gianni et al. (2011) specified that medications were only stopped if they lacked efficacy.[285] Corsinovi et al. (2009) acknowledged that concurrent medications were taken at stable doses three weeks prior to the study and continued at stable doses.[282] Other studies detailed that rescue medication was provided for breakthrough pain but the authors did not clearly specify if any other medications were taken.[285,288] Three reported the use of concurrent medications taken by participants at the time of testing,[283,289,291] including opioids.[291] Puustinen et al. (2011) aimed to capture the use of any CNS medication but provided different subgroup analyses.[290] Two studies did not clearly report whether concurrent medications were taken.[286,287]

5.5.6 Risk of bias and reporting quality

The mean quality score for included papers was 0.77. There were three adequate-quality papers,[287,289,291] two good-quality papers[285,288] and five strong-quality papers.[282-284,286,290] Further detail can be found in Appendix 4. The randomised controlled trials demonstrated consistently high quality (strong; 0.82–0.93). Observational studies varied in quality, ranging from adequate to strong (0.55–0.91). The quasi-experimental study was adequate in quality (0.55). Two randomised controlled trials reduced chances of selection, performance and detection bias by using double-blind, placebo-controlled, randomised approaches.[283,284] Although, one did not provide detailed information around randomisation to treatment order and allocation concealment.[283] A single-blind approach lacked detail around random sequence generation and allocation concealment. However, chances of performance and detection bias were reduced by blinding the researchers to the intervention participants received.[282] Other included studies may be

susceptible to selection, performance and detection bias due to the absence of randomisation and blinding. All studies, where relevant, described attrition and exclusion from the analysis. Subject selection and sampling frames were not well-reported across most studies, along with power calculations to ensure whether the sample size was appropriate. Non-randomised studies often failed to control for confounding.[285-291]

5.6 Discussion

This systematic review builds on previous reviews[79-81,84,293] by focussing attention on the cognitive effects of opioids in older adults with cancer and chronic non-cancer pain. The current review also aimed to ascertain the screening and assessment tools used to identify changes to cognition from opioid use in this population. This complements recent systematic reviews and meta-analyses exploring the neuropsychological consequences of opioid use in adults with a chronicity of and/or dependent on opioid use[83] and long-term opioid use in adults with chronic non-cancer pain.[82]

5.6.1 Opioid-induced cognitive impairment in older adults with cancer and chronic non-cancer pain

Mirroring previous systematic reviews on the cognitive effects of opioid use in adults with malignant and non-malignant pain,[79-81] the current review found varied effects on cognition from opioid use, with six studies demonstrating no change to cognition from opioid use. Drawing together the findings from adult cancer populations[80] and chronic non-cancer populations,[79] an updated review indicated that there was either no difference or worsening cognition in adult cancer patients, and no difference or an improvement in cognition in chronic non-cancer populations.[81] In the current review, a non-comparative study exploring domains of cognitive function in an older adult population with cancer found that domains did not change (i.e. concentration, quality of secondary memory and psychomotor function) or improved (speed of memory retrieval and verbal working memory), although numbers were small.[288] In another study with a predominantly cancer population, changes to cognitive domains were either not present (i.e. psychomotor sedation or verbal working memory), improved (i.e. cognitive

flexibility), worsened (i.e. attention) or improved then worsened (i.e. psychomotor function) across the different neuropsychological assessments used,[283] although again, the sample was small. Whilst in a study that explored cognitive changes from long-term opioid use in chronic non-cancer patients (i.e. patients with painful arthritic diseases) via a subgroup analysis, there was a decline in cognitive function.[290] However, there was very few participants. Karp and colleagues (2006) found that opioid users experienced more difficulty with unprompted memory compared to opioid users, in those with non-malignant pain.[287] Nevertheless, the sample size and reporting around opioid use were limited. These findings contrast with previous reviews, with improvements to cognition detected in cancer populations and the decline of cognition in a chronic non-cancer population. However, methodological limitations, small sample sizes and variation in study design pose challenges to drawing definite conclusions from the included studies.

Dose increase was associated with impaired cognition in a previous systematic review.[81] There is no definitive definition of 'high dose' in scientific literature;[294] UK guidance states that the risk of harm increases at doses above 120mg/day without increased benefit.[52] Changes to cognition in the current review were mostly observed in studies that adopted the use of higher mean opioid doses (i.e. 120mg – 190.7mg OME daily dose).[283,288] However, Puustinen and colleagues (2011) demonstrated changes to cognition from long-term use of opioids, although dose was not taken into account.[290] Karp and colleagues (2006) also found that unprompted memory was impaired in those who used opioids compared to those that did not, without taking dose into consideration.[287] A number of studies found that low doses of opioids were a valid treatment for moderate to severe chronic pain without any associated cognitive impairment.[282,284-286,289] Although, some studies considered to have a low mean dose demonstrated some wide ranges in dose, including higher doses.[284,285,289] Transient improvements to short-term memory and memory retrieval speed were also observed after switching from morphine to fentanyl.[288] Potential benefits of opioid rotation and opioid switching[295] and the usefulness of fentanyl in comparison to morphine[296] were also recognised in excluded studies. However, a multi-national study on the prevalence and predictors of cognitive dysfunction in adult cancer patient demonstrated no difference in cognitive effects between three commonly used opioids (fentanyl,

morphine, and oxycodone).[297] Although, this study used the MMSE, which may not have been sensitive enough to capture subtle differences to cognition. Overall, the type of opioids assessed and the doses used across studies varied greatly.

The previous reviews commented on the methodological weaknesses of studies assessing cognitive function in cancer and chronic non-cancer populations.[79,81,298] The weaknesses identified were the use of non-randomised and non-controlled study designs, lack of suitable control groups as well as issues around the cognitive effects of pain itself, polypharmacy, and other confounders impacting on cognitive outcomes. These issues were also recognised within the current review. Studies that adopt a controlled design are thought to be of the highest quality.[81] This review did not restrict by controlled design or study quality as there is limited evidence in this population and we aimed to be inclusive of all possible studies. Kendall et al. (2009) highlighted that changes to cognition varied between study designs.[79] They found no difference to cognition or an improvement in RCTs and non-controlled comparative designs and no difference or worsened cognition in observational studies. Due to the limited number of included studies in this review and the small number of studies that detected a change in cognition, as well as the variety of study designs adopted, it was not possible to determine the role of study design in patterns of changes to cognition from opioid use. There are also challenges around the appropriateness of study design in this older adult population, such as long-term exposure to harmful effects of medications.[181,290,299]

Impaired cognition is frequently associated with the pain or disease experience.[202] The use of an appropriate control group is considered important as the use of healthy volunteers does not account for the effects of pain or the disease itself.[81] An ideal control group would include older adults eligible for opioid therapy but not receiving the treatment.[81] The prolonged use of a placebo or not providing suitable treatment could pose ethical issues but such methods can be beneficial if they adopt sound methodological considerations.[181,283,299] One included study used older adults with advanced cancer not taking opioids and healthy volunteers as control groups to determine the impact of opioids and the disease itself on cognition.[291] However, the reporting of group differences in study outcomes were vague and differed between the results and discussion sections of the paper; making it challenging to interpret the

impact of the disease itself and from the use of opioids. The control groups in the other studies consisted of conventional therapies without use of opioids,[282] those not taking CNS medications or non-users of corresponding medications[290] and older adults not taking opioids (and unclear if they are eligible for opioid therapy).[287] Therefore, the control groups adopted in other studies did not best reflect controlling for appropriate risk factors in the context of opioid-induced cognition. Other included studies did not adopt a control group, although, two studies used participants as their own controls in cross-over designs.[283,284]

Older adults commonly take several concurrent medications.[30] Older adults' cognition is susceptible to polypharmacy and anticholinergic burden from the use of multiple medications.[300,301] A longitudinal cohort study evaluating the combined use of multiple CNS medications (including opioids) in healthy older adults, excluded from this review, indicated that the combined use of CNS medications, particularly at high doses, were associated with cognitive decline in healthy older adults[302] We acknowledge that medications for a number of medical conditions may also impact on cognition. The cognitive effects of opioids from included studies are difficult to determine due to differences in or lack of controlling for the use of multiple medications in a number of studies,[282-284,287,288,290,291] as well as unclear/poor reporting.[285-287] This may explain some of the variability in the cognitive outcomes of included studies. By controlling for medications prior to study commencement or during, a better understanding of baseline cognition and opioid impact can be gained. Other confounding factors, such as degenerative cognitive impairment associated with age, should also be considered. Most included studies had signs of severe cognitive impairment or dementia (usually assessed by MMSE score) as an exclusion criterion.[282-287,289,290]

More understanding around the effect of opioids on cognition in older adults with cancer and chronic non-cancer pain is still needed. Currently, there is a small number of studies available. The limitations of current evidence, due to the heterogeneity of results and methodological approach, suggest that we need a more standardised approach, with clearer reporting.

5.6.2 Screening tools, neuropsychological assessments and cognitive domains

There are a wide variety of screening tools and neuropsychological assessments available but there is little consensus around a standardised approach to identifying and assessing changes to cognition from opioid use.[79,81,298] In particular, there is limited understanding of which tools and assessments may distinguish clinically meaningful changes to cognition in older adults with cancer and chronic non-cancer pain. Determining which tool(s) and/or assessment(s) are appropriate in this population could provide an accurate way to detect changes to cognition over time and inform adjustments to treatment.[79,291]

The MMSE was the only screening tool identified and was predominantly used across included studies. The MMSE was designed for use with patients with dementia and is commonly used to assess cognitive function.[303,304] Despite wide acknowledgement in the literature that the MMSE lacks sensitivity to detect minor changes to cognition, it is still predominantly used as reasonably quick to administer and engrained in clinical practice.[77,305-307] A significant association between cognitive decline (including attention, language, orientation and both short- and long-term memory) and opioid used was demonstrated in an observational longitudinal study included in the current review using the MMSE.[290] However, the small number of participants using opioids and issues with adjusting for some risk factors (e.g. alcohol use) limits the interpretation and generalisability of these findings to other elderly populations. A large longitudinal study, using self-reports of cognition, explored the relationship between opioids on clinical outcomes for patients receiving palliative care, it found that opioid use was not related to worsened cognition in an adjusted analysis.[308] Although, the authors acknowledged that the low cognitive symptom scores could have been due to the exclusion of low MMSE scores (i.e. ≤24) and that the included sample represented a group with lower risk of cognitive deterioration.[308] Other included studies in this review that adopted the MMSE did not detect a difference. Evidence supports the use of other, more nuanced, brief screening tools subsequently developed to detect mild changes to cognition in older adults compared to the MMSE.[303,309,310] The use of alternative screening tools has been recognised in substance misuse research, including opioid misuse.[78,79,81,311,312]

Neuropsychological effects from opioid use are well-documented.[79,81-83,253,298] Neuropsychological assessments can detect subtle changes to cognition from opioid use.[313] However, we do not know if performance on neuropsychological tests relate to clinically relevant effects or recommendations.[83,253,313] The single measure focus of neuropsychological tests (e.g. attention) is problematic in drawing conclusions around cognitive impairment from opioid use,[253] as multiple domains appear to be affected. The included studies that adopted neuropsychological tests used multiple assessments to assess different cognitive domains. The Incidental Learning Tests (i.e. free recall), Prose Recall Test, Trail Making Task and subtests of the CDR computerised assessment detected changes to cognition.[283,287,288] The use of multiple assessments may be challenging in clinical practice, as this would take significantly more time to perform.[314] Tools to detect opioid-induced cognitive impairment in a primary care setting need to be comprehensive, easy to administer within a short time frame, valid and reliable.[78]

A better understanding of the cognitive domains that are affected by opioid use in this older adult population could lead to the use of or development of a more suitable assessment tool and a clearer definition of what constitutes opioid-induced cognitive impairment. Baldacchino and colleagues (2012) identified cognitive flexibility, cognitive impulsivity and verbal working memory as important cognitive domains in adults using opioids chronically.[83] A more recent systematic review and meta-analysis found that long-term opioid use in adults reduced attention compared to other treatments that targeted the central nervous system.[82] All studies in the current review assessed verbal working memory; with one detecting an improvement using the CDR micro-computerised assessment[288] and one finding a decline to cognitive performance using the MMSE in this domain.[290] Cognitive flexibility was only measured in three studies and assessed with five different neuropsychological assessments;[283,287,291] with only the Trail Making Task (Task B-A) detecting an improvement in this domain.[283] Attention was also found to be affected in a longitudinal population-based study that screened cognition using the MMSE.[290] There are concerns regarding the ecological validity of neuropsychological assessments, in that, there is a lack of agreement around the constructs that some tests aim to measure, leading to difficulties in interpreting the outcome.[315] This may contribute to the varied findings across studies. Practice effects

are also a recognised characteristic from completing multiple assessments, where test performance may be attributed to increased familiarity.[316] Out of the included studies that conducted multiple assessments,[282-286,288-291] two discussed practice effects, whilst only one study controlled for them.[284] Therefore, practice effects may have had influence over the cognitive outcomes.

None of the existing screening tools and neuropsychological assessments of included studies are suitable to evaluate all cognitive domains.[317] Other domains that demonstrated cognitive change in the current systematic review included delayed episodic memory, language, orientation and psychomotor function. How we define opioid-induced cognition in older adults may need to consider additional cognitive domains (i.e. delayed recall/long-term memory and psychomotor function). However, due to the methodological designs of the studies, small sample sizes and populations included, there could be some noise around cognitive effects from opioids, such as issues of pain, the disease itself and the use of appropriate control groups. There may also be other cognitive domains to consider that have not been captured in the included studies. Limited reporting of the timing of administration may have also hindered understanding of whether the tools and assessments would detect a change in cognition due to opioids (e.g. ensuring opioid plasma levels were at their peak).[291]

Driving is a complex task that requires a range of cognitive skills (such as attention and executive functions), visuospatial skills, motor ability, and multisensory perception.[318,319] Previous reviews explored the impact of opioids on driving ability in adults with cancer and/or chronic non-cancer conditions as part of their assessment of opioid-induced cognitive impairment.[79,80,293,320] The findings from these systematic reviews are limited due to the scarce number of studies available, as well as the absence of clinically relevant information and appropriateness of tests to assess cognition and driving ability amongst chronic pain populations in terms of clinical practice and everyday tasks.[80,293] Studies assessing driving ability were considered within the current review, however, studies were not eligible for inclusion as study populations were under 65 years of age.

Clinically, opioid neurotoxicity in older adults often presents itself as sedation, confusion, as well as hallucinations, mood disorders and cognitive impairment.[84,253] The screening tool and neuropsychological assessments of included studies in this systematic review do not capture issues with some cognitive adverse effects, like hallucinations, and may not detect sedation and confusion in a clinically meaningful way. Yet, these are considered clinically important adverse effects[253,321,322] as well as impactful on patient wellbeing.[323]

5.6.3 Strengths and limitations

This systematic review was guided by the PRISMA Protocol checklist[266,267] to ensure that the protocol development and reporting were robust. Multiple search engines were searched (inclusive of language, publication status and publication date) to enable the identification of all possible literature. Another strength was our exclusion of studies where cognitive function may already be compromised either by existing health conditions (e.g. patients with dementia) or where patterns of opioid use were likely to differ (e.g. perioperative use or substance misuse).

There were several potential limitations. Studies that relied on self-report or clinical opinion, which may be of interest in clinical practice, were not included. However, the focus on formal screening tools and neuropsychological assessments allowed for ease of comparison with previous reviews. Another limitation was defining an older adult population. We used a chronological age of 65 and over; as commonly adopted by most developed countries and for providing a suitable cut-off value for inclusion.[271,272] We recognise that some included participants could be less than 65 and that chronological age does not account for individual patient characteristics/responses to prescribed medications.[324] Most included studies consisted of chronic non-cancer pain populations, which may limit the generalisability of findings to cancer pain populations. Additionally, some studies may have been underpowered, as they explored changes to cognition from opioid use as a secondary outcome. This review adopted the QualSyst tool to assess study quality, as it allowed for the standardised, empirically grounded, assessment of a variety of study designs.[278] However, it lacked the ability to identify specific biases, which may have led to inflated quality grades of included studies.

Overall, the methodological issues, small sample sizes and poor reporting in the included studies limits how we can interpret the effects from the opioids on older adults' cognition and the interpretation of the review findings. Therefore, this review does not make recommendations or implications for practice that go beyond the scope of the included evidence.

5.6.4 Implications for practice

This review highlights the absence of a standardised approach to assessing opioid-induced cognitive impairment in older adults with cancer and chronic non-cancer pain, and how current approaches adopted in research studies lack suitability. Therefore, the use of formal screening tools and neuropsychological assessments of opioid-induced cognitive impairment cannot replace clinical judgement and identifying clinically meaningful adverse effects, such as hallucinations. The use of formal screening tools should be seen as a guide to support clinical decisions. The MMSE does not appear to be discriminatory towards cognitive effects from opioid use. The use of a brief, more nuanced, screening tool that assesses attention, language, orientation, psychomotor function, and verbal working/short-term and delayed episodic memory may be beneficial in practice compared to neuropsychological assessments in detecting opioid-induced cognitive impairment in this older adult population, as less time consuming to administer. However, an appropriate tool requires further assessment.

5.6.5 Recommendations for future work

This review has observed changes to some cognitive domains from opioid use in older adults with cancer and chronic non-cancer pain. In particular, attention, language, orientation, psychomotor function, and verbal working/short-term and delayed episodic memory were worsened. Due to the small number of primary studies available and their limitations, future research should focus on determining the cognitive domains affected in this older adult population. Future primary research studies in this area should consider adopting cognition as a primary objective, larger sample sizes, clearer reporting around opioid use (type, dose, route of administration and length of use) and provide more detail around the administration of screening tools and

neuropsychological assessments used. This would also require determining the validity and reliability of existing screening tools and neuropsychological assessments to detect clinically meaningful changes, and other clinically important adverse effects not captured by current tools and assessments. The value of other screening tools, other than the MMSE, to detect cognitive change from opioid use in older adult populations with cancer or chronic non-cancer pain requires investigation.

5.7 Conclusions

The findings of this systematic review suggest effective pain relief may be achieved at low daily doses, with less impact to cognition. Changes to cognition (including both improvements and impairments) were predominantly observed in studies with higher mean opioids doses (120mg–190.7mg OME daily dose). Attention, language, orientation, psychomotor function, and verbal working/short-term and delayed episodic memory were worsened by opioid use. As neuropsychological assessments are too cumbersome for use in clinical practice, a more nuanced brief screening tool with consideration to the cognitive domains identified may be beneficial. The MMSE does not appear discriminatory enough. A better understanding of cognitive impairment caused by opioids in this population could be used to inform adjustments to pain treatment and the benefit-risk balance of opioid use.

5.8 Summary

The main findings from this chapter include:

- There are a limited number of studies exploring the impact of opioids on cognitive function via the use of formal assessments in older adults with cancer and chronic non-cancer pain, especially within a primary care setting.
- There were no papers identified that focused on frail older populations.
- Pain relief may be achieved with low daily opioid doses, and with less impact to cognition.
- Changes to cognition were predominantly observed in studies with higher mean opioid doses.

- The cognitive domains of attention, language, orientation, psychomotor function, and verbal working/short-term and delayed episodic memory were worsened by opioid use.
- Screening tools did not appear to be discriminatory enough to detect opioid-induced cognitive impairment, and neuropsychological assessments are too cumbersome for use in clinical practice.

The next chapter presents the methodological considerations regarding the other main component of this thesis, which is the mixed methods study. The mixed methods study expands on the findings from this systematic review and aims to address the gaps that are presented in this chapter (i.e. limited understanding of opioid use to manage pain in community-dwelling frail older adults and their impact to cognition).

Chapter 6: Methodology

6.1 Introduction

This chapter presents the methodological considerations for the quantitative and qualitative components of this study. First, an overview of the study is presented. Second, reflections on the philosophical considerations, as well as the conceptual and organisational lens through which this research is viewed. Third, a justification of the chosen research design is provided and considerations relating to the methods used (including the study population and data collection). Full methods are detailed in Chapter 7.

6.2 Study overview

This mixed method study addresses the thesis objectives and includes; data from a cross-sectional survey and case note review are used to describe pain, opioid use and cognitive adverse effects in the study population (Objective 2); in-depth qualitative interviews with a sub-set of the cross-sectional survey/case note review population to explore experiences, perspectives and concerns from older adults and their informal caregivers of these phenomena, as well as identify information and support needs (Objective 3). Together, these address the overall aim of this thesis.

6.3 Considerations in relation to philosophical and theoretical approaches

Various influences were considered in relation to this research, including the underlying philosophical foundations and existing theoretical frameworks relating to the phenomena under study.

6.3.1 Philosophical considerations

The use of both quantitative and qualitative methods in this study were predominantly determined by the research problem and questions. Therefore, the pluralistic and

practical paradigm of pragmatism was adopted.[325-327] Pragmatism lends itself to investigating a phenomenon using multiple perspectives and is orientated to 'what works', as well as real-world practice.[326,328] It recognises the value of combining different methods to provide more depth and breadth than one method on its own in answering specific research questions, rather than focusing on epistemology and ontology.[328] Specifically, this study aims to understand *how* opioid analgesics are used in the pain management of older adults at risk of severe frailty (i.e. an electronic frailty index of >0.36)[329] and the *impact* on cognition, as well as to explore experiences, perspectives, concerns regarding these. Describing the prevalence and patterns of pain, opioid prescribing and cognitive adverse effects via a quantitative approach was deemed necessary to understand the *how* and to summarise the *impact*. However, to further understand how opioids are used in practice and their impact to everyday life requires more than a positivist approach. Understanding experiences, perspectives and concerns regarding these issues is best addressed via a qualitative approach. Exploring these issues qualitatively adds depth to the quantitative data and allows for the consideration of real-world solutions to improve experiences of pain management in this population. In summary, using a pragmatic approach by adopting quantitative and qualitative approaches allows for the complexity of measuring pain, opioid use and associated cognitive adverse effects, and exploration of these from a patient and informal caregiver perspective. It also means that areas of convergence, divergence and discrepancy can be identified between the two datasets.

6.3.2 Theoretical considerations

6.3.2.1 Theoretical frameworks in mixed methods research

Theoretical frameworks can provide conceptual and organisational structures in which to consider a programme of research.[326] They can help to order or bring together observations from separate investigations, as well as, assist in summarising and connecting findings into an accessible and coherent structure to guide our understanding of phenomena (i.e. the what and why).[330] Therefore, theoretical frameworks could assist in navigating mixed methods research, where studies may consist of concurrent or sequential investigations, as well as facilitate the integration of methods used and act as

a map to understanding the phenomena. However, there is no widely accepted approach to the use of theoretical frameworks to guide inquiry in mixed methods research.[331]

A theoretical framework shares a common meaning across different research approaches but varies greatly in the way they are applied in quantitative and qualitative research.[326,332] In quantitative research, theoretical frameworks are used deductively (i.e. testing an existing theory), whilst qualitative research adopts an inductive approach (i.e. developing a theory).[326] Therefore, it can be questioned how mixed methods research might combine these procedures. Creswell and Plano Clark (2018) highlight that mixed methods researchers approach to adopting theory in their study can reflect a hypo-deductive testing framework (i.e. using key variables identified by the theory to develop hypotheses/questions that can be tested with the data, and subsequently, supported or refuted by the theory), an inductive-interpretative approach (i.e. adapting a preliminary framework into a modified newly configured theory as the data are analysed), or both.[326] The adaptation of a preliminary framework can be actioned in two ways within the inductive-interpretative approach; (1) *fully-theory informed inductive study design* (i.e. a theory or multiple theories are used to inform the research lens and create a framework that explains how the theory shapes the research questions) or (2) *theory-informing inductive data analysis* (i.e. the researcher waits until data analysis to determine which theories will inform data interpretations).[326]

6.3.2.2 Choosing an approach to theoretical frameworks

This thesis adopted an inductive-interpretative approach, and the theory or theories that will inform data interpretation will be determined at the analysis stage. Understanding the main concepts of interest may require multiple theoretical frameworks due to the multi-faceted nature of this research project. Existing theoretical frameworks appear to range from the broader determinations of chronic pain to narrower or mechanistic theories of factors influential to decision-making regarding pain management (including adverse effects). This section considers possible theoretical frameworks that could provide a foundation and interpretative lens for this thesis, from the more high-level view to those focusing on more specific aspects of chronic pain, opioid analgesic use and adverse effects (see Figure 6-1).

Figure 6-1 Diagrammatic representation of the range of theoretical frameworks

6.3.2.2.1 Broader theoretical frameworks

In their discussion around moving towards a sociology of pain, Bendelow and Williams (1995) highlight how theories of pain have traditionally been over-medicalised and biomedically orientated in both diagnosis and treatment.[111] Theories have often focused on understanding pain as a sensation that can be rationally and objectively measured. However, pain is an '*everyday'* experience that requires both a medical narrative, as well as others, including phenomenological and sociological.[111] To bring the meaning and understanding of pain into a fuller focus, the use of narratives to explore beliefs and individual responses to pain (i.e. pain as a lived experience) is essential, as well as, understanding the socio-cultural shaping of pain.

One of the most common theoretical approaches to understanding the multifaceted nature of chronic pain is the biopsychosocial model. Originally developed by Engel, the model proposes that in addition to biomedical dimensions of illness, other social, psychological and behavioural factors should also be considered.[333] The biopsychosocial model provides a 'blueprint' to aid clinical practice and research.[333] This model was later developed by Gatchel and colleagues, translating the model to the experience of chronic pain.[334,335] More recently, Miaskowski and colleagues adapted the biopsychosocial model of chronic pain to older adults (see Figure 6-2).[336] They recognised the specific challenges to managing older adults pain and aimed to better understand the factors that contribute to the development of chronic pain in this population using the biopsychosocial model as a conceptual guide.[336]

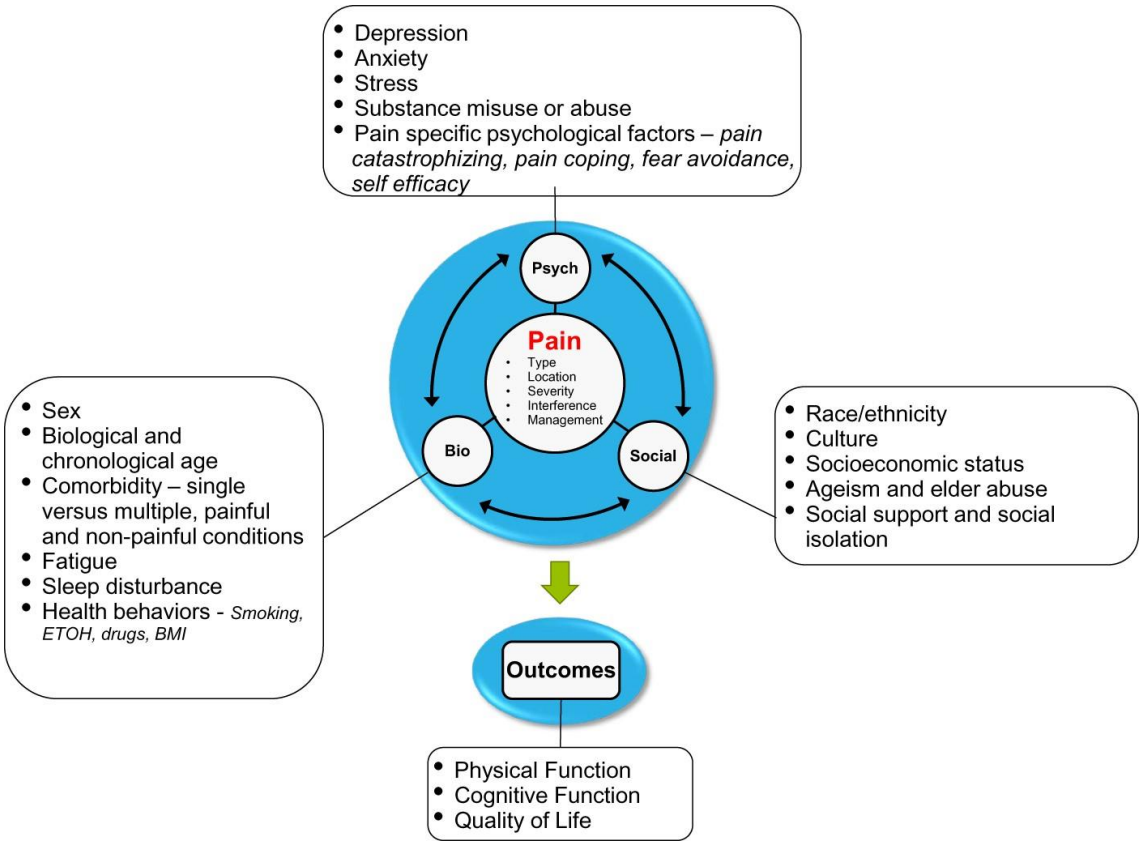


Figure 6-2 A conceptual framework for understanding chronic pain in older persons by Miaskowski et al.[336]

Acknowledgement. Created by Miaskowsi C, Blyth F, Nicosia F, Haan M, Keefe F, Smith A and Ritchie C. A Biopsychological Model of Chronic Pain for Older Adults, Pain Medicine, 2020, 21(9), p.1794, by permission of Oxford Univeristy Press.

This model provides a holistic approach to understanding the factors that cause chronic pain to guide its assessment and management.[336] It recognises the multiple causes of pain, rather than reducing to only biological factors.[336] Cognitive function is also a consideration of this model (as one of the main outcomes).[336] Although, this is concerning the impact of chronic pain, rather than opioid analgesics. Additionally, there is limited discussion around opioid analgesics in the biological, psychological and social domains. The model, although holistic and multi-dimensional, does not give great consideration to the lived experiences but more to the determinants of chronic pain and how these relate to the outcomes of physical function, cognitive function and quality of life. Although social influences are considered, it is more of a patient-focused model and does not consider the impact of caring for someone with chronic pain. The process

the authors used to select the literature to inform their model is also unclear, so there may be additional factors that have not been captured. However, the authors acknowledge that this model is still in development and requires further research to understand chronic pain more clearly in older adults (such as the causal relationships).[336]

Another theoretical framework that was developed in relation to managing chronic illness that may apply to chronic pain is the 'illness trajectory framework'.[337-339] It is based on years of studying problems of managing chronic illness within different settings (such as home). This framework was developed via unstructured in-depth interviews with 60 couples using the sociological concept of *illness trajectory* (i.e. the course of an illness, the related work and its impact).[337-339] Chronic illness was seen as something that needed to be examined in the context of the encompassing life.[339] In 1985, Corbin and Strauss presented the concept of *'work'* involved in managing chronic illness at home.[338] This included what work was done, how the work was done (or not done), by whom, under what circumstances and with what consequences and problems.[338] They identified three main lines of work, which included *illness work, everyday life work and biographical work*.[338]

Illness-related work refers to the tasks that were seen as necessary to manage chronic illness, including: regimen work, preventing and managing crises, symptom management and diagnostic-related work.[338,340] Biographical work involves defining, and maintaining identity and their concept of 'self', as disruption to a person's biography can occur due to losses that may arise during the course of an illness and the person's ability to come to terms with these.[338] Biography refers to the life course that develops around a continuous stream of experiences and leads to a unique identity.[339] Four biographical processes were acknowledged, including: contextualising (i.e. incorporating illness into ongoing life), coming to terms (i.e. adjusting and accepting the illness and its consequences), restructuring their self-concept and recasting their biography (i.e. giving new direction to their biography).[339] Another aspect of trajectory management included everyday work that occurs in the context of everyday life, in which illness-related and biographical work occur.[338] The management of everyday living requires the completion of certain tasks. Corbin and Strauss also present the

concept of ‘management context’ that consisted of the structure of process (i.e. the context in which managing illness takes place fluctuates and changes) and reciprocal impact (i.e. the management of each line of work will impact the other if and when it changes).[338] Therefore, obtaining a state of equilibrium is challenging and may be short-lived.

This theoretical framework focuses on the lived experiences of both the patient and their spouse within the home context, and could be applied to chronic pain. Pain can influence how lived space and time are organised, as well as, relations with others and ourselves.[341] Other studies have adapted this framework to help understand experiences of cancer survivorship and the work related to medication regimen.[342,343] This framework allows for the consideration of the problems patients and their informal caregivers may face managing chronic pain at home, as well as the work and complex interactions between these. The concepts presented in this theory are developed from interviews with patients and their spouses and there may be limitations to how these lines of work are applied to other types of caring relationships and for those who live alone. There may also be potential of over-conceptualising experiences of pain as ‘types of work’ and this may mean that other aspects of the experience may be missed.

6.3.2.2.2 Narrower theoretical frameworks

Medication-taking behaviour (including compliance, adherence and concordance) is an important aspect to consider, and may be influenced by adverse effects (as discussed in Section 2.6). Horne and colleagues (2005) provide a conceptual map to guide policy-makers, clinicians and health services research in relation to these three aspects using a Perceptions and Practicalities Approach framework.[344,345] This framework offers a straightforward framework to guide development and appraisal of interventions to promote adherence.[345] It focuses on how the individual interacts with their specific treatment, and considers how *motivation* and *ability* are essential to adherence.[345] Additionally, it presumes that although there are intrinsic and extrinsic factors in play, their effect on adherence to treatment is likely to manifest through addressing motivation and ability.[345]

In its development, Horne and colleagues considered a range of theoretical frameworks that are relevant to medication adherence, which include social cognition models that have been developed to explain how people initiate and sustain actions to preserve or improve their health status.[344] In particular, the widely adopted Common-Sense Model of Self-Regulation explains the processes by which people recognise, process, respond/navigate and monitor information or stimuli relating to a health threat.[346] There is evidence to support that the Necessity-Concerns Framework could be used to operationalise this social cognition model to explain nonadherence to medication.[347] The Necessity-Concerns Framework proposes that medication adherence is influenced by the persons implicit judgement of whether it is needed and concerns about the potential adverse consequences.[348] The Perceptions and Practicalities Approach – based on an extended Common-Sense Model – has been used to understand the various factors that may influence older adults adherence to analgesia.[63] This approach demonstrates the value of combining theoretical frameworks to understand a particular issue and help to provide a more comprehensive understanding. Although, overall, the main focus of this framework is on what drives decision-making behaviour.

The theories presented and described in this section will be revisited at the analysis stage and consideration will be given as to whether any of the theoretical frameworks provide an interpretative lens to view the data.

6.4 Considerations in relation to research design and approach

6.4.1 Possible approaches for this study

Several design approaches could be used to describe and explore the role of opioid analgesics in pain management and associated cognitive adverse effects in older adults at risk of severe frailty. In this section, three possible approaches are discussed and consideration is given regarding their appropriateness to address the aim of this thesis and corresponding objectives (see Chapter 4: Aims and objectives). These approaches include survey design, case note review and qualitative inquiry.

6.4.1.1 Cross-sectional survey

One approach to investigating opioid analgesic use in pain management and attributed cognitive adverse effects is via survey methodology. Cross-sectional surveys are commonly used to collect quantitative data in health and social sciences research[349] and in mixed methods approaches.[350] A cross-sectional survey design is an appropriate method for obtaining descriptive information from a large sample at a single time point.[350] It allows researchers to ask the same specific questions regarding a phenomenon to participants on a large scale. If a large enough sample is obtained, this can help build a comprehensive picture of patterns and trends, which produces replicable and potentially generalisable findings (as long as the sample is representative of a larger population).[351]

Surveys are also useful as a primary step, in that they allow us to understand attitudes, beliefs and what people do.[352] Although, they can lack detail or depth related to the phenomena under question (e.g. reasons behind behaviour).[353] Creswell and Hirose (2019) describe how survey data can be developed through and supported by more open-ended approaches (e.g. qualitative interviews).[350] With surveys, it is also possible to measure associations with pain, opioid use and cognitive adverse effects.[50,98,224,354] The demographics and other information collected via this method can help in understanding associated factors, and regression modelling can be used to explore how factors may interact with and influence phenomena.[355,356] However, it is challenging to determine, in detail, why an association may exist or how certain factors influence pain, opioid use or cognitive adverse effects. Practically, there are also weaknesses to consider. This includes limitations to the length of the survey,[357] especially in an older population and within certain settings. Open-ended items can also result in vague answers, reflect variation in verbal ability and are time-consuming to analyse.[357] There could also be reactive effects, such as social desirability (where participants provide socially desirable responses instead of choosing responses that reflect their true feelings).[357,358] Other challenges that may impact survey completion in relation to this population are discussed in Section 6.5.

Overall, this method was deemed suitable over other methods (e.g. randomised controlled trial, cohort or case-control studies), as descriptive information was required to: understand the topics in question, identify potential participants for qualitative interview, compare self-report and medical record data and inform the line of enquiry within the qualitative component. Additionally, this study did not seek to evaluate an intervention/treatment or determine whether a specific exposure was related to an outcome, as this was beyond the scope of this thesis (e.g. funding, timing and ethical considerations).

6.4.1.2 Case note review

The second approach is a case note review. A case note review is a quantitative method that is conducted retrospectively, where data originally collected for other reasons is analysed.[359] The investigation of existing data for secondary analysis has proved useful across multiple disciplines,[360,361] including healthcare research.[359,362-364] Medical records are often a primary source of clinical data in health research.[359] A case note review allows for access to routinely collected information on electronic medical records to understand sample characteristics (e.g. comorbid conditions), history of pain and medication(s) prescribed to manage pain.[48] One main advantage to this approach is that it enables the collection of clinical data with relative ease.[359] Additionally, data can be collected within a shorter time frame and with comparatively lower costs to other methods.[359,363] However, the primary limitations of this approach are that the data may be incomplete, potentially inaccurate (i.e. inaccurately reported or recorded) or missing, as not originally collected for research purposes.[359] In particular, if the topic investigated is not routinely or systematically reported, such as chronic pain and pain management.[113] These limitations can be minimised by verifying interpretation of data in the medical record, adopting a standardised approach (e.g. a case record form), and piloting or checking for consistency in approaches to data collection and entry.[359]

The purpose for using a case note review of medical records in this study would be twofold. One reason is to reduce the burden on survey participants by extracting relevant information that may be challenging to obtain via the survey method (e.g. opioid prescriptions over the last year).[365,366] The second reason is to obtain information

that would enable comparison with the patients self-reported data, as captured on the survey (e.g. self-reported opioid use over the last year compared to whether they were prescribed opioids for use within the last year).[367] In summary, using a case note review was seen as acceptable to answering some of the research questions of this study but not all (see Section 4.2). It allows for the extraction of clinical information supplementing the patients survey responses.[368]

6.4.1.3 Qualitative enquiry

The third approach is qualitative enquiry, which allows for an in-depth exploration of pain, opioid use and cognitive adverse effects from multiple perspectives. Qualitative approaches are commonly used in this area, including older adults.[63,242-244] In contrast to the other two approaches described above, it is possible to delve deeper into the complexities of pain (as multiple sources of pain are often experienced in this population),[121] the challenges with and processes of pain management (including opioid use), as well as exploring in-depth the experiences of cognitive adverse effects related to opioids. Qualitative research predominantly focuses on the study of a group of individuals that share experiences (for the purposes of depth rather than breadth).[369] Findings are concentrated on contextual significance to the particular phenomenon being studied.[369] Therefore, the main purpose of qualitative research is not to produce generalisable findings but potentially transferable findings to other populations of frail older adults.

Several qualitative approaches could have been used in this study, such as observation or group discussion.[357] However, the interview method was considered most appropriate for methodological and practical reasons. Observation has some advantages over an interview method, including directly observing naturally occurring behaviours and understanding the context in which behaviour occurs.[357,370] Group discussions can also be advantageous, as they can generate discussion around abstract and conceptual topics that can be illuminated by social norms, explore how people talk about an issue within group interaction and allow for differences within the group to be captured.[357,370] They are particularly useful in attitudinal research, as well as for creative thinking, and discussing solutions and strategies.[370] Observation was not suitable for this study as it

was not feasible to observe patients and informal caregivers experiences of pain, pain management and adverse effects, nor would it have necessarily provided an understanding of perspectives and concerns, as well as identify information and support needs related to these. Although, participant observation may have been appropriate for understanding communications between patient and healthcare professionals in relation to pain and pain management (including prescribing opioid analgesics) in primary care. Focus groups were also not chosen as they provide less opportunity for a detailed generation of an individual account and concentrate on the interaction between participants to illuminate the research issue;[357] understanding pain and pain management requires more in-depth accounts situated within personal history and experience.

In-depth semi-structured interviews are widely used to generate detailed individual or joint accounts of complex issues (e.g. decisions, impacts) from which the research phenomenon is located.[370] However, this method also comes with its own limitations. One aspect that can potentially limit or undermine in-depth qualitative interviews has also been considered one of its strengths; the interviewer-interviewee relationship. The interaction between the interviewer and interviewee shapes the data that is generated.[370] Bias may be present in the interview, as a social interaction between the interviewer and interviewee, which has an interviewer-led agenda. This interaction may be influenced by personal characteristics (e.g. age), personal beliefs or value and other factors (e.g. stereotyping, misinterpretation).[371] In line with this, a potential for power imbalance in the interviewer-interviewee relationship has also been considered as having an influential role, that is, when inhabiting the role of the '*interviewer*' may enable or disable the autonomy of the interviewee in the interview.[372,373] Furthermore, the interview method relies on the retrospective reconstruction of personal history and memory; reporting of events may be affected by recall bias (i.e. problems remembering accurately).[374] Additionally, pain and the emotions experienced by the person may also affect the saliency of recalling some memories over others.[375,376]

Overall, there is limited understanding about the complex relationship between pain, opioid use and cognitive adverse effects, especially from the perspectives of older adults and their informal caregivers managing chronic pain at home. Therefore, a qualitative

study may help to develop a theoretical framework in which to consider these and guide clinical practice and future research. As highlighted above, a limitation of qualitative research is that findings may be transferable to other contexts, but it is not possible to generalise beyond the study population in the same way as quantitative research.[374]

6.4.1.4 Reflexivity and bias

It is generally understood that a researchers background and position will have an impact on the choice and angle of investigation, the methods chosen and the conclusions drawn.[377] Reflexivity is the process of systematically attending to the context of knowledge construction at every stage of the research process. In particular, the role and effect of the researcher.[377] Therefore, it is important to critically review one's own actions when conducting research. It is also useful, within this, for researchers to consider their own background, and possible unconscious biases and preconceptions. I, therefore, exercise my own reflexivity throughout this study to minimise or recognise the potential biases that I may bring. I have completed training in Good Clinical Practcice (GCP), quantitative and qualitative data collection and have worked on a number of different research projects with a variety of individuals with different health conditions. I have a background in psychology and health psychology, and an interest understanding peoples experiences of health and illness. My own experiences of pain and its management as a young, white female may differ to those from different patient groups. However, my experiences and training have helped me to listen in an objective manner, appreciate and understand experiences through someone elses narrative, and be aware of the steps needed to address my potential biases.

Consideration is also given to the risk of researcher bias at different stages of the research project. Bias refers to deviations from the 'truth' in the data collected, analysis of the data, and interpretation and publication that may lead to the presentation of false conslusions.[378] Biases can be both intentional and unintentional,[378] and it is important to recognise that bias exists in research studies.[377] This helps to minimise the impact of potential biases and develops a critical reflection of the research findings. Therefore, bias is not necessarily eliminated but accounted for.[377] The involvement of the researcher is particularly pronounced for qualitative research.[377,378] Additionally, pain

by its very nature is subjective (as discussed in Section 2.2). Considerations given to my actions and reflexivity throughout this research are listed below by thesis component:

- Systematic review: This includes the development of a protocol to allow for transparency in decision-making, with review from supervisors. The use of a second reviewer through the different stages of screening studies for inclusion and exclusion allows for a second, independent opinion. This helps to ensure that the decisions made are appropriate and help account for reporting bias (i.e. where studies or outcomes are reported based on significant findings) and selection bias (i.e. where criteria have not been clearly outlined and may restrict the inclusion of studies).[379]
- Quantitative cross-sectional survey and case note review: Participants are invited to participate on a voluntary basis and to provide informed consent. Processes are adapted to enable those who wish to participate (see 6.4). Participants can complete the survey themselves, however, it can also be completed by a family member or a researcher. A predetermined database is used for data entry and developed collectively by three PhD students and the Project Manager. Meetings and discussions are used to determine consistency in approaches to entering data and minimising potential bias. Proforma is also used for data extraction from medical records. A list of common adverse effects (following a question asking participants to freely recall adverse effects) and case note review data for opioid prescriptions are used to help minimise recall bias.
- Qualitative component: Participants are given the fullest opportunity to share their views and experiences. Although I have had my own experiences with chronic pain, I acknowledge that I may not be able to specifically identify with the patient population recruited. However, I am able to understand and appreciate their experience by empathetically listening to their story. Field notes are adopted to record my own thoughts and opinions regarding interviews and can be used as a reference during analysis. My early interviews will be reviewed with my supervisors to enable reflection on my approach up to that point and how future interviews could be approached. The reflexive approach to analysis recognises that analysis is not about accuracy or agreement (such as comparing

double coding) but about developing thinking and challenging assumptions.[380] Themes are interrogated and discussed with supervisors.

6.4.2 Mixed methods research

In isolation, none of the methods described above can answer the overall aim of this thesis. Researchers have circumvented such issues by adopting a mixed methods approach.[326,327,381] Mixed methods research is recognised as a "third methodological movement", following on from quantitative or qualitative research alone, which comprises the mixing of practices from these other two methodologies.[326] There is a longstanding debate regarding the use and value of using mixed methods, and whether quantitative and qualitative approaches can or should be combined.[326,327,381,382] Methodological purists argue that quantitative and qualitative methods are based on mutually exclusive philosophical and methodological assumptions, and given the lack of common ground between them, precludes them from being combined.[383,384] Whilst, methodological pragmatists believe that there is considerable value in combining methods, as neither method is sufficient alone to develop a complete analysis.[327,385]

Quantitative research is more widely understood as 'an approach for testing objective theories by examining the relationship among variables' (p. 4).[385] Variables can be measured (characteristically using validated instruments) and data can then be analysed using statistical procedures.[385] Whilst qualitative research is neither uniformly nor distinctly defined.[386] Multiple definitions of qualitative research are presented and are shaped by various factors, including the purpose/focus, epistemological stance, or the process and context of data collection.[387] Qualitative research is perhaps best understood as an approach that adopts 'an interpretative approach to data collection and analysis, that is concerned with the meanings that people attach to their experiences of the social world and how people make sense of that world' (p.2),[386] rather than a narrower definition. It comprises a wide range of qualitative methods for data collection and analysis, including descriptive forms of data (i.e. text or visual) and explains these via interpretative analytical methods.[386] However, the boundaries between quantitative and qualitative methods are not entirely separate from one another, and research could be

viewed along a continuum.[327,388] Additionally, scientific inquiry can draw from both deductive and inductive frameworks.[327]

Greene (2007) suggests that the purpose of a mixed methods line of enquiry is to enable 'multiple ways of making sense of the social world, and multiple standpoints on what is important' (p. 20).[327] Therefore, knowledge regarding pain, opioid use and cognitive adverse effects can be obtained from multiple approaches. Mixing different methods aims to avoid some of the limitations of individual methods and to harness the strengths of each method to address the research problem, if well designed.[326,381] Some research questions may be largely accessible to either quantitative or qualitative methods, whilst other research questions may be better addressed using methods from both approaches.[326] The mixing of methods helps to understand the complexity of the phenomena under scrutiny[389] and means that each approach can compensate for the other's weaknesses.[327] It is supported by the *compatibility thesis*, where combining quantitative and qualitative approaches is seen as appropriate in many research settings and not fundamentally different.[327] Specifically, combining both these forms of data and using them synergistically provides the most complete and comprehensive picture of complex problems and one that would not be possible with just a single method.[326,390]

In line with this, it can be used for exploring and identifying areas of convergence, divergence and discrepancy. Combining methods enables the assessment of the credibility of inferences made from each approach. Additionally, it allows us to obtain divergent and incongruent views of the same phenomenon.[327] A mixed methods approach can also be useful in informing various stages of a research project. Some researchers focus on more practical strategies, where the combination of quantitative and qualitative approaches can be described in the context of timing.[391,392] The priority (i.e. equal or dominant) and sequence (e.g. concurrent or sequential) of quantitative and qualitative components are defining features.[391,392] This allows for development (i.e. questions for one strand of research emerging from another strand) or expansion (i.e. explaining results that have been derived from a previous strand) of findings.[327]

Mixed methods research does come with its own challenges. The feasibility of developing, collecting and analysing two different types of data can be an issue – in

particular, whether there is sufficient time and resources available.[326] This requires careful consideration at the design stage to optimise the data collection process, ensuring that the approach is getting the most out of the data and considering how components will interact. Additionally, Tashakkori and Teddlie present the concept of *'minimum level of competency'*, in which those conducting a mixed methods study should have the skills and expertise to meet the full spectrum of research methods.[327] There can also be the issue of data collection burden, especially if the quantitative and qualitative data are collected from the same individuals.[393] The differences between the knowledge claims and interpretative frames of reference does also raise a number of considerations, including terminology, philosophical and theoretical frameworks adopted, the reasons and values for adopting both quantitative and qualitative approaches and approaches to analysing and integrating findings efficiently.[326,327] The benefits of using a mixed methods approach to describe and explore pain, opioid use and cognitive adverse effects in older adults outweigh the challenges of this approach, and on this basis, mixed methods are adopted here.

6.4.3 Mixed methods in this study

Mixed methods research in this study is defined as 'research in which the investigator collects and analyses data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study or a program of enquiry' (p. 4).[394] Pragmatism is commonly aligned with this approach, as it supports the use of multiple methods to inform the research problem under study (with primary importance given to the research question) and is orientated to 'what works'.[326] This overlaps with a general characteristic of mixed method research, otherwise referred to as *methodological eclecticism*, where the most appropriate techniques are selected and used synergistically to investigate a phenomenon of interest more thoroughly.[327]

The design of this study is driven by the research problem. It was felt that this would best be answered using a cross-sectional survey and case note review to describe pain, opioid use and cognitive adverse effects, and an accompanying qualitative study to further explore these. The rest of this section considers how these components could best be combined to describe and explore the phenomena under study. There are

numerous mixed methods typologies available that support researchers in classifying the way in which research methods may be combined.[326] As mixed methods research has matured and developed as an approach, the numerous typologies have also evolved. Creswell and Plano Clark's most recent classification attempts to simplify the various classifications available and present three core designs, including the convergent design (i.e. data collected simultaneously), the explanatory design (i.e. quantitative data informs/is explained by subsequent qualitative data) and the exploratory design (i.e. qualitative data informs the quantitative component).[326] As touched on in section 6.4.2, another useful way to conceptualise mixed methods designs is in terms of the timing of components (i.e. concurrent versus sequential), the dominance of its components (i.e. equal versus dominant), and the way in which the methods interact. These will be discussed in turn below in relation to this study.

6.4.3.1 Timing

The quantitative components and qualitative component are implemented concurrently and data are collected from the same participants, which corresponds to a convergent design.[326] Since pain and pain management are not expected to be entirely stable constructs,[131,395,396] the richest data could be obtained if pain, opioid use and cognitive adverse effects expressed by individuals could be directly explored. Additionally, adherence to medication in older adults can be poor and there may be discrepancies between how older adults are prescribed medications and how they actually take them.[169,397] Therefore, a case note review aids understanding of how opioids are prescribed, whilst qualitative interviews enable further insight into how they are actually used. This also ties into the concept of recall; older adults may feel burdened by recalling pain medication used over a long time period and there may be inaccuracies with their recall, especially as time goes on.[366] The saliency of memories recalled over others might also be impacted by the pain and emotions experienced by the person.[375,376]

As this study recruited from an older population who are at risk of severe frailty with varying health problems (including chronic and acute issues), it was considered that the same participants would be less likely to be available to participate in both phases of a

sequential study. Using different participants in different phases may have weakened the inferences that could be drawn from the data, as pain, opioid use and cognitive adverse effects are unique to the individual and their family. Therefore, a convergent design enables stronger inferences to be drawn from the data and more robust conclusions.

Other considerations concerning the design include timing and resources (i.e. developing quantitative and qualitative components, ethical approval, and collecting and analysing two types of data).[326,327] Sequential designs allow the second component to be conducted based on what was learned from the first (corresponding to explanatory and exploratory designs), although this requires a longer study period and sustained resources.[326] This study and its components are embedded within a service evaluation; meaning that there is sufficient time and resources for conducting the case note review and qualitative interviews concurrently (see Chapter 7 for further details). Timelines also need to align with the wider project and access to the recruitment site as per ethical approval.

6.4.3.2 Dominance

Describing overall pain, opioid use and cognitive adverse effects are considered equally as important as exploring these in more depth. Therefore, both strands are given equal emphasis. This can also be described as a QUANT + QUAL design.[326] The cross-sectional survey and case note review provide context for the interviews and quantify pain experienced, opioid prescribing patterns and cognitive adverse effects. The in-depth interviews, undertaken in a sub-sample of survey participants, allow for deeper exploration of these and add the informal caregiver perspective. The two components address different aspects of the phenomena addressed within the research question; the qualitative interviews provide essential data that expand and supplement the findings beyond the inferences of the cross-sectional survey and case note review. The combination of methods enables a more comprehensive answer to the research question than what could be provided by any individual method in isolation. Therefore, they are equally valued in answering the research problem and contributing towards understanding the wider picture.

6.4.3.3 Interaction and integration

Consideration of how methods interact with one another is central to mixed methods research, otherwise referred to as integration.[326] As discussed by Creswell and Plano Clark (2011), integration can occur at different stages of the research process, including: the design, data collection, data analysis and with interpretation of the findings.[398] This study uses the same participants for both quantitative and qualitative data collection, therefore, it is seen as beneficial to integrate the methods as closely as possible to ensure that the depth and breadth of the data are captured. In particular, it is important to integrate methods at the stage of data analysis and interpretation as this is the intention of the convergent design.[326] Integration at this stage intends to develop the results and interpretation of results beyond the analysis of the separate components; expanding understanding and ensuring that results and interpretations are comprehensive, validated and confirmed.[326] In this study, the interaction and integration between methods occur at the following stages:

(1) Data collection and sampling phase: Participants in the cross-sectional survey are sampled for qualitative interview based on relevant characteristics (see Section 7.5.4). Additionally, survey answers and data extracted as part of the case note review (i.e. data collected at an individual level before analysis) are used to inform the line of enquiry in interviews.

(2) Analysis phase: The merging of data within the convergent design can be actioned in one of two ways to accomplish the *intent of integration*, including comparing the two data sets or transforming one data set and conducting further analyses.[326] For the purpose of this study, common phenomena across the data sets will be identified and analysed via a side-by-side comparison, noting where data confirm, diverge or expand on one another. Differences will be interpreted and resolved. Further details on the approach to integrating data in the analysis phase are provided in Section 7.6.

(3) Interpretation phase: Findings from each method are triangulated; considering how the confirming, diverging and expanding results provide insights to the research problem.

Figure 6-3 illustrates the mixed methods design of this study, highlighting where methods interact. As highlighted above, this study utilises a convergent design, as presented in Creswell and Plano Clark's typology of core designs, where the quantitative components and qualitative component are conducted in parallel.[326]

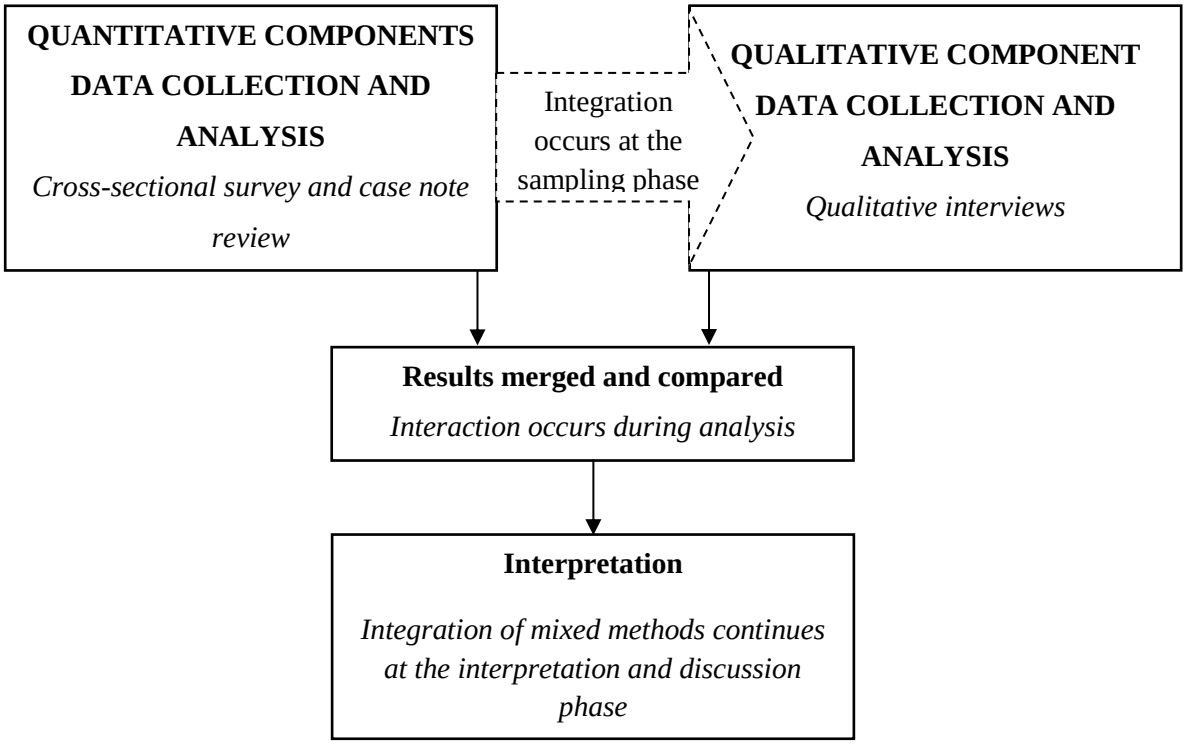


Figure 6-3 Detailed diagrammatic representation of study components

6.5 Considerations in relation to the study population and data collection

This study explores pain, opioid use and cognitive adverse effects in older adults at risk of severe frailty; methodological implications to this are discussed below.

6.5.1 The impact of health-related issues

Older adults can experience multiple health problems that can lead to challenges with successful recruitment and retention in research, which can be mitigated through planning, good practices and balanced solutions.[399,400] Common health concerns

include, but are not limited to, frailty, severe pain, acute illness, multiple health conditions (such as cardiovascular disease or diabetes), shortness of breath, hearing and/or visual impairment, and becoming easily fatigued.[399] These are important factors to consider regarding the study population.[85,399] Inattention to these areas has an impact on ageing-related research and may lead to bias in recruited participants.[399] Recruitment success has been linked to face-to-face contact and cultivating relationships with community-based organisations.[401]

In this population, it was important to consider their capacity to participate, as cognitive impairment is a predominant issue in older adults.[402,403] Cognitive issues may impact understanding of research, provision of informed consent and their ability to participate.[399] To exclude all potential participants with any form of cognitive impairment may bias the study sample. This study included older adults with cognitive impairment as long as they were considered to have the capacity to provide informed consent. The timing of introducing the study and how it is communicated are considered. Additionally, enlisting knowledgeable family or friends, as appropriate, is considered a useful way to support the involvement of older adults. For further details regarding capacity and consent in this study, see Section 7.4.3.2.

Health-related issues might impact willingness to participate, completion of practical tasks and following up with participants regarding interviews (such as difficulty reading study materials and performing written aspects),[401] especially when data is collected from the same individuals. Therefore, it is essential to consider the balance between gathering sufficient study data to address the research aim, as well as a cross-sectional survey and interview topic guide that can be completed without undue burden. For both of these, the use of succinct sections are useful to produce a design that works with fatigue or pausing for rest breaks. Large print copies would be made available on request. Additionally, participants would be supported with issues of manual dexterity and are able to verbally communicate with the researchers to complete study documentation and use a proxy to sign on their behalf for consent. These aspects were reviewed by local community groups to achieve this balance (see Section 7.7).

A case note review was also used to reduce the burden on study participants, especially around the more specific details of opioid prescribing (see 7.4.3.4). Flexibility during the research process is used to support patients to participate, if they were willing. This included considering an alternative time to complete the survey if they are not able to complete this during their visit (as long as consent is obtained on the day) or rescheduling/cancelling interviews if needed. Another limitation to multiple health concerns relates to the interpretation of results, ensuring that confounding factors are considered and interrogated so as not to overreach the findings from this research and acknowledge the complexities of researching within this population.

6.5.2 Social and cultural considerations

There are also social and cultural considerations in relation to the study population and data collection.[401,404] As in the context of managing pain, health-literacy is also important to consider in research.[404] The presentation of study materials needs careful consideration, and how these are read and comprehended.[405] The language and concepts presented need to be easily understood and accessible to participants (such as the terminology used).[406] For example, adverse effects are more commonly known as side effects.[407] Using more simple and general terms may aid understanding. The level of trust in research and its perceived importance are also potential barriers to participation.[408] These can be managed by providing enough information to potential participants to understand who is conducting the research and the impact of the findings.[408]

6.6 Summary

This chapter has argued the reasons for and advantages of using a pragmatic approach and mixed methods design to meet the demands of the research question, given its complexity. This approach provides more depth and strength of inference, as well as exploring areas of convergence, divergence and expansion. A flexible approach to recruitment is considered essential to enable potentially severely frail population to participate in research.

This chapter has also considered the methodological challenges surrounding the study population and data collection, as well as the theoretical frameworks that might be best to understand opioid analgesic use in the pain management of older adults, how opioid analgesics impact older adults' cognition. The next chapter outlines the research methods used in this study in detail.

Chapter 7: Methods

7.1 Introduction

This chapter discusses the specific methods used to collect data for the quantitative and qualitative components of this thesis, based on the methodological considerations described in Chapter 6. The first section of this chapter places this thesis in context by describing the overall design and the larger programme of research the thesis data collection was situated within; the Proactive Anticipatory Care Evaluation (PACE). Subsequent sections detail the study setting, and the approaches for the quantitative and qualitative components (including the study sample, data collection and analysis). The overall design was a mixed methods approach, however, at some points, details of the components are discussed separately for clarity.

7.2 Overall design

This thesis adopted a mixed methods approach to understand opioid analgesic use in the pain management of older adults at risk of severe frailty and related cognitive adverse effects in a primary care setting, comprising of a cross-sectional survey, case note review and qualitative interviews (as previously described, in more depth, in Chapter 6: Methodology). The research reported in this thesis formed a distinct component of and was embedded within a larger programme of research; PACE. For context, a summary of PACE and its aim are included in this section.

PACE was a non-randomised controlled study that evaluated a structured programme of work established in 2018 to redesign the care of older adults at risk of severe frailty in Hull (i.e. the community frailty pathway). I was part of the research team, alongside the Project Manager (Mabel Okoeki [MO]) and other PhD students (Helene Elliott-Button [HEB] and Ugochinyere Nwulu [UN]) responsible for developing the study protocol and materials, recruitment, consent procedures and data collection for PACE.

PACE aimed to assess the effectiveness of this proactive anticipatory multidisciplinary care intervention in improving overall quality of life and health outcomes for older

adults at risk of severe frailty. In addition, there was an embedded qualitative component to address broader issues relating to older, frail adults that provided an opportunity for myself and two other PhD students to further investigate use of pain medications and possible adverse effects (with focus to opioid analgesics and effects on cognition; my project), chronic breathlessness (HEB) and unintentional weight loss (UN) in this population. The evaluation was conducted concurrently alongside the running of the community frailty pathway service. PACE consisted of three components of data collection, including a longitudinal survey, case note review and qualitative interviews. The survey aimed to measure the impact of the intervention on patient wellbeing and quality of life from the patient perspective, as well as, identify participants for qualitative interview. This allowed me to include my own questionnaire to identify older adults who had used pain medications over the last year and experienced adverse effects (with focus to opioid analgesics and cognitive adverse effects) for qualitative interviews. Demographic and clinical data were also extracted from electronic medical records as part of the case note review. The qualitative interviews then focused on the experiences of the use of pain medication and possible adverse effects (my project), chronic breathlessness (HEB), and/or unintentional weight loss (UN), if applicable. The process is depicted in Figure 7-1.

The primary outcome of PACE was patient wellbeing, with secondary outcomes of functional status and health-related quality of life (HRQoL). These outcomes were measured at baseline, 2–4 weeks (first follow-up; following the intervention start) and 10–14 weeks (second follow-up; to assess longer-term outcomes of the intervention). PhD survey questions were only asked within the baseline survey to identify participants for qualitative interview. Those receiving the intervention were compared with a matched group of frail older adults recruited from primary care that were not due to receive the intervention until a later timepoint. Data collected in care home settings and from follow-up timepoints as part of the longitudinal survey (i.e. at 2–4 weeks and 10–14 weeks) did not directly relate to this PhD and are not described further. More detailed information about PACE can be found in the published paper.[409]

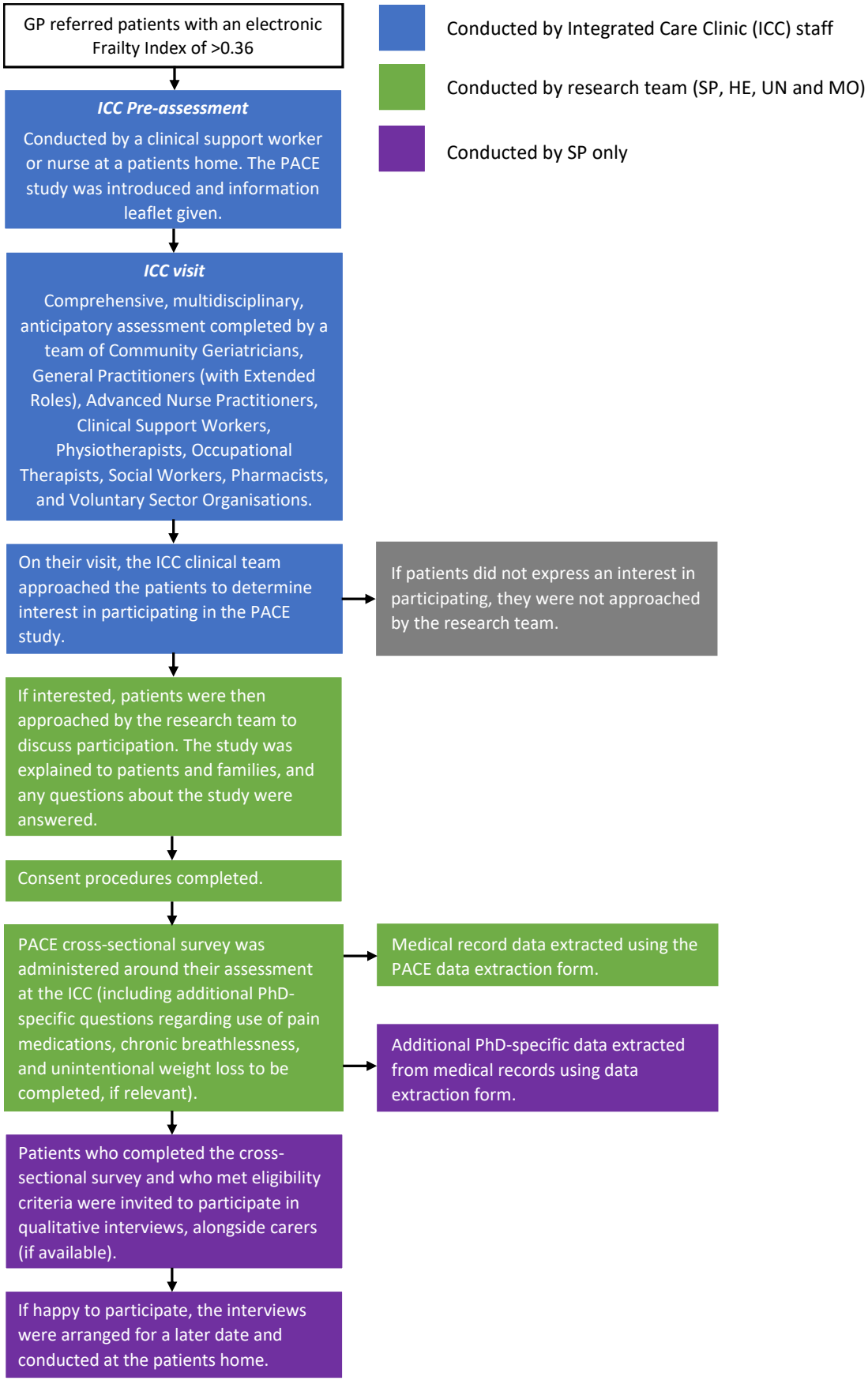


Figure 7-1 PACE patient journey flowchart

7.3 Setting and context

For context, a brief description of the re-design of the community pathway and integrated assessment are presented in Sections 7.3.1 and 7.3.2, respectively. This is followed by a summary of the setting in the context of this thesis.

7.3.1 The re-design of the community frailty pathway

The redesign of the community frailty pathway aims to support all older adults at risk of severe frailty who live in their own home within the Hull Clinical Commissioning Group (CCG) area. This service aims to identify all older adults at risk of severe frailty within the local population (approximately 3,100 across the Hull CCG area) that live in the community or care homes and referred by their General Practitioner (GP) using the electronic Frailty Index (eFI). The pathway delivers a new model of multi-disciplinary care, which is a standardised comprehensive anticipatory assessment and follow-up. They are invited to attend an integrated assessment at the Integrated Care Centre (ICC) or their care home, if a resident. If they agree, they receive a pre-assessment visit by a nurse or clinical support worker at their home or place of residence, and a date for integrated assessment is arranged.

7.3.2 The integrated assessment

The pathway involves multidisciplinary care provided by a team of General Practitioners with Extended Roles, Community Geriatricians, Physiotherapists and Occupational Therapists, Pharmacists, Social Workers, and selected members of voluntary sector organisations. The multidisciplinary team meet with the patient for an assessment, followed by a team discussion to develop and agree with the patient, an effective integrated and personalised care plan. The assessment also includes a review of the patient's medical records, medication and prescriptions review (and changes to medications where appropriate), a comprehensive geriatric assessment, secondary care (including appointments, investigations and procedures), clarification around follow-up actions, responsibilities and timescale, as well as the development of a personal care plan with patients.

7.3.3 Setting context for this thesis

Participants were recruited from the ICC in Hull. The population served by this centre and the service context are provided in Table 7.1. Recruitment from this setting ensured access to those at risk of severe frailty and enabled access to medical records for the case note review.

Table 7.1 Population served and service context for the ICC

Date service commenced	July 2018
Catchment area	Kingston upon Hull - Index of Multiple Deprivation Rank of Average Score (2019): 4th most deprived local authority in England (n=317 local authorities)[410] - Population age structure: 15.5% ≥65[411] - Diversity: 5.9% Black or minority ethnic residents[412]
Population served	Older adults at risk of severe frailty
Number of unique patients (July 2018 – August 2019)	4580 patients aged ≥65 Gender n (%) and average age: Male: 1875 (40.9%); 80.4 average years of age Female: 2705 (59.1%); 81.8 average years of age Population age structure of patients attending n (%): 65 – 69: 418 (9.1%) 70 – 74: 620 (13.5%) 75 – 79: 804 (17.6%) 80 – 84: 1040 (22.7%) 85 – 89: 977 (21.3%) ≥90: 721 (15.7%)
Multidisciplinary healthcare professionals	The pathway involves multidisciplinary care provided by: General Practitioners (with extended roles), Community Geriatricians, Advanced Nurse Practitioners, Clinical support workers, Physiotherapists and Occupational Therapists, Pharmacists, Social Workers, and selected members of voluntary sector organisations.
Integrated assessment	The multidisciplinary team meet with the patient for an assessment, followed by a team discussion to develop an effective integrated and personalised care plan to: (1) enable communication between the healthcare professionals and the delivery of the plan, (2) creation of maintenance and escalation plans, (3) involve specialist teams (e.g. respiratory) where required and (4) produce an advance care plan, where appropriate.

7.4 Quantitative components: Cross-sectional survey and case note review

7.4.1 Participants and inclusion criteria

Participants in this study were patients attending the ICC who had been referred by their GP due to a risk of severe frailty. The inclusion and exclusion criteria are listed in Table 7.2.

Table 7.2 Inclusion and exclusion criteria

Inclusion criteria
• Patients aged 65 and over • Identified at 'at risk' of severe frailty by their general practitioner, using the eFI (>0.36) • Are a resident of and registered with a general practice in Hull • Able to speak in English or are with an interpreter
Exclusion criteria
• Failure to meet the inclusion criteria

7.4.2 Sample size

Survey sample size is usually determined by the total size of the population being studied, the expected prevalence of the phenomena being studied, the margin of error and the distribution (or standard deviation).[349] However, the sample size of this thesis was determined by the PACE study and based on the minimum clinically important difference of the evaluations primary outcome (Integrated Palliative Outcome Scale (IPOS) total score; used to assess patient wellbeing), accounting for attrition at follow-up and propensity score matching between the intervention and control group participants.

7.4.3 Data collection

7.4.3.1 Participant identification and approach

A clinical support worker primarily introduced the study and provided an information leaflet when completing the pre-assessment visit at the patient's home to ensure that patients were aware of the research study. The pre-assessment usually occurred at least 24 hours prior to the patient attending the ICC. In some instances, the pre-assessment had been conducted before the PACE study commenced. Additionally, a few patients were fast-tracked to attend the ICC; meaning it was not possible to conduct a pre-assessment. Therefore, it was not possible to introduce the study to these patients prior to their attendance.

Potentially eligible patients were initially approached by a member of staff from the clinical team on attendance to the ICC to minimise potential participants from feeling coerced. At this point, they introduced or re-introduced the study, provided a copy of the information leaflet (see Appendix 3) and gained verbal consent for approach by a member of the research team. Large print formats of the information leaflet were also offered. If the patient expressed an interest in participating to the clinical team, a member of the research team then approached potentially eligible participants to discuss participation, answer any questions they may have, and provided time to consider whether they wished to participate. It was emphasised that participation was voluntary and that they could withdraw at any time from the study. Additionally, it was clearly indicated that participation would not impact on their integrated assessment and no incentives were offered (i.e. financial or otherwise).

7.4.3.2 Capacity and consent

As highlighted in Section 6.5.1, this study gave careful consideration to a participants' capacity to consent on an individual basis. The research team consulted with the clinical team and assessed capacity for consent, to determine the potential participants understanding of the study and willingness to participate, when applicable. If capacity was deemed to be present and the patient agreed to participate, then witnessed verbal consent (i.e. if unable to physically sign) or written consent was obtained. Capacity was

assumed unless demonstrated otherwise. If potential participants were deemed to lack capacity, they were not automatically excluded. In line with the Mental Capacity Act, their ability to provide informed consent was then assessed with consideration to the following: (1) could the individual understand the information provided about the study; (2) retain the information (even for a short time); and (3) use or weigh up that information and (4) communicate their decision. If these criteria were met, a personal consultee approach was then adopted, whereby a carer or family member provides written approval by signing a consultee declaration form, if it felt appropriate. This approach included a verbal explanation of the study and clarification of potential questions. Personal consultees could help participants to understand the study questions and, in some cases, provide proxy answers. Participants who provided consent (i.e. either the patient or a personal consultee) were given a copy of the information sheet to read and keep. Participants were asked to sign two copies of the consent form (see Appendix 4), one for their records and the research team retained the other.

For participants with capacity, consent was sought for (i) the use of clinical records, (ii) survey completion and (iii) to be approached about a qualitative interview, if relevant. For participants with impaired capacity, consent was only sought for (i) the use of clinical records and (ii) survey completion (which could be completed by a carer or family member). Personal consultees were not invited to interview if the patient had no capacity, as a dual perspective (i.e. patient and family carer) was sought. The consent procedure and survey completion were supported by a member of the research team. All participants were informed that they could withdraw at any time should they wish.

7.4.3.3 Overview of data collection measures

Table 7.3 presents an overview of the data collection measures used in the cross-sectional survey, as well as, data extracted from medical records as part of the case note review. These are then described in more detail in Sections 7.4.3.4 and 7.4.3.5.

Table 7.3 Overview of data collection measures

PATIENT/PROXY DATA (i.e. CROSS-SECTIONAL SURVEY)	
Category	**Measure**
Section 1: Symptoms and concerns	Integrated Palliative care Outcome Scale: 7-day version
Section 2: Quality of life	EuroQol 5D-5L
Section 3: Using medicines to manage pain	Including questions about experience of pain, pain medications prescribed at some point over the past year, concerns and problems with pain medications, communication with healthcare professionals regarding these.
RESEARCHER RECORDED DATA (i.e. CASE NOTE REVIEW)	
Data collection measures captured in the PACE data extraction form	
Category	**Measure**
Demographic characteristics	Age, gender, ethnicity, relationship/marital status, living situation, smoking status and postcode (to estimate the Index of Multiple Deprivation)[413,414]
Diagnoses	Diagnoses including comorbidities listed
Functional status	Australia-modified Karnofsky Performance Status
Patient health*	Pre-assessment questionnaire data (including questions regarding physical health, carer support received, falls, hospital admissions, number of medications, cognitive function, emotional function, home life, activities and daily living, social life and community)
Data collection measures captured in the data extraction form for this thesis	
Category	**Measure**
Medications and treatment*	Extracted from the ICC's pre-assessment questionnaire; additional questions regarding aspects of medication and treatment were extracted in addition to the number of medications extracted in the PACE data extraction form.
Changes to pain medications	Recommended changes to pain medications following the ICC assessment
Medications prescribed	Medications prescribed within the past 30 days (using prescription data)
Cognitive function	Clinical summary and 6-Item Cognitive Impairment Test
Anticholinergic burden score	Derived from the Anticholinergic Burden Calculator
Prescription data for opioid analgesics	Including prescription date, opioid analgesic name, route of administration, dose (units and frequency), quantity prescribed and reason for prescription (if available)
Frailty	Electronic frailty index and Rockwood Clinical Frailty Scale
Experience of pain	Summary of pain experienced, as assessed by ICC staff during the assessment

* The ICC developed a pre-assessment questionnaire to complete with patients at their home before they were due to attend their assessment. This data was based on the self-report of the patient

7.4.3.4 Cross-sectional survey

The cross-sectional survey consisted of three sections, and was designed to minimise patient burden and maximise response rate. As outlined in Table 7.3, the first two sections of the survey (including outcome measures assessing patient wellbeing and

quality of life) were intended to be completed by all participants recruited to the PACE study. The third section of the survey presented screening questions to identify participants for qualitative interview as part of this thesis. Therefore, participants were asked "Over the past year, have you been prescribed any painkillers?" If participants answered 'Yes' to this screening question, they then completed the questions within this section of the survey. This third section was designed to act as a screening tool for qualitative interviews, as well as determine older adults' experiences of pain and pain management (i.e. medications used to manage pain, such as opioids) to help obtain self-report data for comparison against medical record data. The full survey booklet can be found in Appendix 5.

7.4.3.4.1 Data collection measures

Data collection measures were selected with attention to the research aims and to manage methodological challenges (as discussed in Section 6.5). The measures needed to be brief to minimise research burden on patients who were at risk of severe frailty, as well as, fit around the delivery of the integrated assessment at the ICC. In addition, the measures within the initial sections of the survey needed to allow for both patient self-report and personal consultee proxy reporting; in case recruited participants lacked capacity. Sections one and two of the cross-sectional survey, to be completed by all participants, assessed patient wellbeing and quality of life using the following measures:

- The Integrated Palliative Care Outcome Scale (IPOS),[415] which is a widely used outcome measure that assesses patients' symptoms and concerns. It comprises of a three-factor structure addressing physical symptoms, emotional symptoms, and communication and practical issues. Seventeen items are scored on a 5-point Likert scale from 0 (best) to 4 (worst). It also includes free-text items about main problems and concerns, and additional symptoms to be specified and scored. Patients are asked to reflect on a timeframe of 3-days for inpatient settings or 7-days for ambulatory settings.
- The EuroQol EQ-5D-5L (EQ-5D),[416-419] which is a well-established and widely used measure for assessing generic HRQoL using five dimensions, including: mobility, self-care, usual activities, pain or discomfort, and anxiety or

depression. These dimensions are scored on a scale of 1 (best) to 5 (worst), where responses lead to descriptive 'value sets' (e.g. 11111 – No problems in any dimension). This descriptive system can then be converted to a 'utility' value for current health that can be weighted by patients and populations, which is anchored at 1 (full health) and 0 (dead). It also adopts visual analogue scale from 0 (i.e. the worst possible health imaginable) to 100 (i.e. the best health imaginable) to provide a self-rating of the participants health.

Both of these measures can be patient-completed or proxy-completed. Other existing tools for patient well-being are well validated but proxy-reported versions are less well-established.[420] Evidence on proxy-completed measures for HRQoL are more variable.[421,422] However, since 2008, the EQ-5D has been a preferred measure of HRQoL in England and can be weighed against the population.[423-425] Additionally, for participants who lack capacity, it is comparable in terms of other generic utility instruments, and the descriptive system is easy to complete.[426] The IPOS and EQ-5D are short, focused measures, that minimise research burden on participants. The IPOS and EQ-5D have been well-validated in populations with advanced illness and across a range of diseases, respectively.[415,417] In particular, the EQ-5D has also demonstrated validity and responsiveness when administered to older adults with multimorbidity and polypharmacy who were able to self-complete the measure.[427] They have been adopted in a range of different settings (including the community) and have been used successfully in cross-sectional studies.[415,417,428,429]

In addition to the measures described above, participants were asked an additional screening question "Over the past year, have you been prescribed any painkillers?" If the participant stated "Yes" to this question, they were then asked a series of questions. This third section of the survey needed to be brief and inform screening for qualitative interviews and collection of self-reported data. The EQ-5D and IPOS provided a more formal understanding of current pain on the day of recruitment[418] and within the week prior to recruitment[415] without having to use additional measures. In this section, patients were asked to summarise their experiences with pain severity over the past year in general (to match the opioid analgesic timeline), duration of their pain (as a way of identifying those with chronic pain – i.e. more than three months), types of pain

medications prescribed at some point over the past year (i.e. to establish prevalence and identify opioid analgesics), provided with an opportunity to self-report and freely recall adverse effects, followed by a prompt with a list of common adverse effects. Therefore, cognitive adverse effects were assessed in two ways, by an open response question (i.e. "Have your pain medicines caused you any problems (i.e. side effects)?", which was followed up by "If so, what problems have they caused?") This was followed by the list where they were prompted to select any relevant adverse effects. This approach was informed by a similar study in multiple myeloma patients.[261] Where participants self-reported both opioids and non-opioids analgesics, it was challenging to disentangle which adverse effect was attributed to each of these groups of pain medications as patients were not asked in relation to each pain medication. Additional questions were used to help the line of inquiry in the interviews, including: communication with healthcare professionals, concerns, adherence and changes to medication regimes, and frequency of medication review. Terms that older adults were more likely to recognise were adopted (such as 'pain medication' and 'side effect') and the description of visual and/or auditory hallucinations was simplified (see Appendix 5).

7.4.3.4.2 Data collection procedure and recruitment period

Survey data were collected, face-to-face, from participants who provided consent on attendance to the ICC. This was selected as the most practical method, given that the population were at risk of severe frailty and possibly needed assistance in completing the survey. Additionally, it enabled survey completion around the delivery of the integrated assessment. Therefore, completing the survey did not present a clinical issue for the patient and did not interfere with the integrated assessment.

Recruitment was planned to occur over six months at the ICC. Four researchers conducted data collection (Helene Elliott-Button (HE), Mabel Okoeki (MO), Sophie Pask (SP) and Ugochinere Nwulu (UN)) during the ICC's clinic hours (i.e. from 8:30am until the clinic ended, approximately 3pm). One or two researchers attended the ICC each day during the recruitment period. The researchers approached all patients who had indicated an interest in participating to the clinical staff and were deemed clinically appropriate to approach. In some instances, patients were not approached if the clinical

team felt the participant was too distressed or lacked capacity and had attended without a family member or friend. Study participants were recruited consecutively. A screening log was used to record information collected during visits (e.g. number of eligible/ineligible patients, not approached, did not attend or declined participation).

Once consent had been obtained, the survey was administered by one of the four members of the research team. Where participants had capacity, the survey could be completed by the individual on their own. If needed, a researcher or a family member/friend who accompanied them to the ICC could help them complete the survey. If participants completed the consent procedure but were unable to fill in the questionnaire on the day of their visit, a home visit was arranged at a subsequent date and time at the patient's convenience and within a few days of their visit. Where participants lacked capacity, the survey could be completed by a family member or friend who accompanied them to the ICC, with help from a researcher, if needed.

It was anticipated that participants would complete the IPOS and EQ-5D-5L questions, once consented (unless unable to due to emotional distress or time constraints). The additional questions regarding pain medication were only answered if relevant, as determined by the screening questions, to ensure patients would only answer additional questions if applicable. Where patient participants reported 'Yes' to more than one screening question (including pain medications, experiences of breathlessness or unintended weight loss), a flexible approach was adopted. This included: (i) completing all the relevant sections, if able, (ii) completing the section they deemed as most important or (iii) if one topic area was not meeting recruitment targets, participants would be encouraged to complete this section first, in case of fatiguing. Overall, patients were encouraged to only complete what they felt able to.

7.4.3.5 Case note review

For all participants recruited to the cross-sectional survey, a case note review was conducted to extract data from participants' electronic medical records using two data extraction forms. The data extraction proforma allowed for a systematic and consistent

approach. This section provides a summary of how the data extraction forms were developed, piloted, revised and implemented.

7.4.3.5.1 Development of data extractions forms

Several aspects were considered during the development of the data extraction forms, including the content and the process of how data would be extracted from medical records. Several demographic and clinical variables were collected as part of the PACE study. To avoid the duplication of data, the second data extraction form was used to collect additional items for the purpose of this thesis. The forms were designed to allow for a straightforward and logical approach to extracting data, with consideration of the platform the medical records were accessed from. The case note review aimed to reduce the length (i.e. the number of questions to be asked) of the cross-sectional survey administered to minimise the burden on study participants, as well as allowing for comparison between self-report and medical record data. The items in each data extraction form, outlined in Table 7.3, were chosen to help contextualise the patient group by describing their demographic and clinical characteristics, as well as their experience of pain and pain management (focusing on opioid use).

The proforma developed as part of the PACE study was led by the Research Associate (MO) and supported by SP and the two other PhD students (HE and UN) that formed the research team. A basic template of how medical records appear on SystmOne and the types of data available were provided by the City Health Care Partnership (CHCP) Project Support Manager to assist with the ordering of items. Additionally, ICC staff provided input regarding SystmOne. The second proforma developed for the purpose of this thesis was designed by SP. The development of the form was influenced by study objectives, comparison with self-reported data in the cross-sectional survey, discussions with supervisors and the data known to be available within the medical records.

7.4.3.5.2 Piloting data extraction forms

The forms were piloted to assess the feasibility of the proposed format. The PACE data extraction form was piloted in May 2019 with participants initially recruited to the

study, once approvals were in place to access participant data. The content and ordering of the items on the form were largely appropriate, due to the template being provided in advance. The CHCP Project Support Manager had also created an interface within SystmOne that mirrored the template (including shortcuts to the data required) to help with data extraction. Although, some demographic items (such as marital status) were not easily identified in the initial template. Additionally, medical diagnoses were described within both the journal pages of ICC assessment and appeared as Quality and Outcomes Framework (QOF) diagnosis icons. As a result, the interface was amended to ensure easier access of demographic information and medical diagnoses were sought from both places. The extraction form itself did not require changes to content or order, but was re-formatted to aid data extraction and minimise error (i.e. ensuring that question and answer boxes fit to the same page).

The second form, identifying additional items for this thesis, was piloted in May 2019 to inform qualitative interviews. The ordering of the items was revised to enable a more logical flow through the sections. Three items were also amended, which related to cognitive function, opioid analgesics prescribed and non-opioid analgesics prescribed (these are discussed in more detail below). Measures of frailty were captured as part of this form, as it was decided that comparing the eFI score (GP referral) and the Rockwood Clinical Frailty Score (CFS; on attendance to ICC) would be useful and formal data extraction for this form commenced at a later date. Although experience of pain was briefly reported on in the survey, a more detailed clinical assessment of participant's pain was extracted from the ICC summary. Lastly, anticholinergic cognitive burden was either documented on participants' medical records or could be calculated using the ACB calculator[430] based on the data extracted summarising other medications currently prescribed (i.e. within the past 30 days).

Cognitive function

Cognitive function was only captured by the pre-assessment questionnaire in the PACE data extraction form, using statements where participants agreed or disagreed with (e.g. "I have problems with memory, which affects my day-to-day life"). The second data extraction form captured other available data on cognitive function, which was assessed

on attendance to the ICC. This included the 6-item Cognitive Impairment Test (6-CIT) and a summary of the clinical assessment of cognition by ICC staff. The clinical assessment of cognition was categorised into three categories (i.e. no cognitive problems, some concern raised around cognitive function, evidence of cognitive problems).

Opioid analgesics prescribed

Originally, the name of the opioid prescribed, dose, route of administration, length of use and reason for prescribing were going to be used to characterise opioid use. This approach made it challenging to quantify how opioids were prescribed at some point over the past year (i.e. gaps in prescription history, calculating an average dose). However, opioid prescription data was only viewable on study commencement, once approvals were in place and informed consent had been obtained. Prescription data could only be accessed from the data recorded in the tabbed journal by the GP or within the community setting. SystmOne supports the sharing of medical information across different settings of care but requires the organisation that collected the data to give permission for access. Once participants were identified and referred by their GP, access to their medical data was usually provided to the ICC. Once it was clear what information was available, the approach was amended to reflect processes adopted in the literature.[431,432] This included recording any individual opioid prescription issued in the 12 months prior to the date of recruitment (i.e. date prescribed, name of opioid, route of administration (oral or transdermal patch), quantity provided and the reason for prescription, if available). These items allowed for the summary of the number of opioid analgesics prescribed, total number of prescriptions, total annual days' supplied and daily dose, as well as a comparison against self-report data regarding opioid prescriptions.

Non-opioid analgesics prescribed

Originally, the name and dose of non-opioid analgesic medication currently prescribed were planned to be recorded. This was not feasible in practice due to time restrictions; therefore, the names of these medications were recorded alongside other medications currently prescribed.

7.4.3.5.3 Final data extraction forms

A more detailed summary of the final measures for the data extraction forms that were briefly outlined in the overview of data collection measures in Table 7.3 are presented below. The final data extraction forms can be found in Appendix 6 (for PACE) and Appendix 7 (for this study).

Measures collected using PACE data extraction form

- Demographic characteristics: Age in years (derived from date of birth), gender, ethnicity, relationship/marital status, living situation and smoking status. These were obtained to describe the population and provide context for interpreting the findings regarding pain and opioid analgesic prescription data. Additionally, participants postcodes were used to determine the Index of Multiple Deprivation (IMD) quintile (from 1 being the most deprived to 5 being the least deprived).[413,414]

- Diagnoses: Diagnoses were extracted from the ICC summary and from QOF diagnosis icons. Diagnoses were obtained from these avenues to understand comorbidities, as ICD codes were unavailable. This was considered important as the number of comorbidities and comorbid burden are often associated with higher reports of pain, lower levels of activity and medication-related problems.[39,200]

- Functional status: The Australian Karnofsky Performance Status (AKPS) was used to assessed function. The AKPS is a modified tool from the Karnofsky Performance Status (KPS) measure (i.e. originally developed for inpatient oncology settings) and the Thorne modified KPS measure (i.e. a version of the KPS for community-based care), to allow for the assessment of functional status in all clinical settings of care (such as home).[433] The AKPS assesses overall performance status in three dimensions: activity, work and self-care. The measure results in a single score, ranging from 0 to 100%, based on ability to perform common tasks, with lower scores equating to poor function. The AKPS is validated in populations with advanced conditions and can be used to understand functional status in older adults.[429,433,434] Compared to other

performance measures, the AKPS was demonstrated to be superior, provided more categorical levels of performance or was considered easier to use in clinical encounters.[433]

- Pre-assessment questionnaire: This questionnaire was designed by the ICC and completed by a Clinical Support Worker with the patient in their home, prior to the patient attending the ICC. Patients are asked questions regarding: their physical health, care support received, hospital admissions, medication and treatment, cognitive function, emotional function, home life, activities of daily living/instrumental activities of daily living, and social and community needs. Data extracted for PACE included all areas mentioned above, except it extracted an more limited data from medication and treatment section (i.e. whether they take more than five medications a day and if so, how many).

Measures collected using the thesis data extraction form

- Medications and treatment: This included extracted information from the other questions from the pre-assessment questionnaire (mentioned above) on medication and treatment, which captured issues with getting, remembering, swallowing medications, as well as any concerns about or problems with adverse effects from medications.
- Changes to pain medications: All medications, including pain medications, were reviewed as part of the clinical assessment and medication review on attendance to the ICC (at the time of recruitment). This included recommendations to start, increase, decrease, stop or changes to repeat prescriptions, as well as reasons for the recommended change. Only changes made regarding pain medications (as identified by the reason given for the recommendation) were extracted. This included medications that are not recognised as an analgesic but were suggested in relation to pain management. As clinicians are encouraged to tailor prescribing,[55-57] the suitability of pain medications prescribed to older adults is an important issue, especially in reducing iatrogenic medication-related harm.[135,235,435] Therefore, it was important to consider recommended changes to opioid analgesics, and other pain medications that may be preferential to those currently prescribed.

- Medications prescribed: Medications 'currently' prescribed were also recorded; this was defined as any prescription issued within the 30 days prior to recruitment. This was used to summarise the total number of medications prescribed and polypharmacy, which have been identified as important in the context of opioid prescribing for pain in older adults.[235]
- Cognitive function: Comments regarding cognition as assessed on attendance to the ICC were extracted from the clinical summary. In some instances, the 6-CIT was also conducted on attendance to the ICC and were extracted where available. The 6-CIT has been designed to be a brief measure to assess global cognitive status in dementia.[436]
- Anticholinergic burden score: For some patient participants, anticholinergic burden was calculated on attendance to the ICC using the ACB calculator.[430] This tool was developed to aid clinicians with decision-making during medication reviews and offer more suitable alternatives with a lower anticholinergic burden.[430] It was based on multiple anticholinergic burden tables and where discrepancies exist, the higher score was chosen.[430] A score of three or more is associated with increased cognitive impairment. Where scores were not recorded on the patients visit during the pharmacist's review, SP used medications 'currently' prescribed (see 'Medications prescribed' above) were used to determine anticholinergic burden via the same calculator.
- Prescription data for opioid analgesics: Opioid use over the last 12 months (including date prescribed, name of the opioid, route of administration, dose (units and frequency), quantity prescribed and reason for prescription, if available).
- Frailty: Frailty was assessed using two measures. Using the eFI, GPs were expected to refer their patients who were at risk of severe frailty to the ICC (see Section 7.4.1). The eFI is a validated screening tool that uses routinely collected data within the patient's electronic medical record to identify their *risk* of mild, moderate and severe frailty.[329,437] It uses a cumulative deficit model where Clinical Terms Version 3 Read codes were mapped to 36 deficits (e.g., activity limitation or polypharmacy).[329] The eFI score is calculated using the presence or absence of individual deficits as a proportion of the total possible.[329] It has been implemented in primary care electronic health record systems (including

SystmOne) and is freely available to 99% of GPs across the UK.[329] As part of their assessment when attending the ICC, frailty was subsequently assessed using the CFS. The CFS is a 7-point scale, comprising: (1) very fit, (2) well, (3) well, with treated comorbid disease, (4) apparently vulnerable, (5) mildly frail, (6) moderately frail and (7) severely frail.[438] It considers items such as comorbidity, cognitive impairment and disability, and is based on clinical judgement.[438] There is no standard measure of frailty; however, the eFI formed part of the ICC's referral criteria and has the potential to identify vulnerable patients in primary care.[329,439] Additionally, the CFS is widely used in multiple settings, easily applied in clinical assessment and well validated.[438,440,441]

- Experience of pain: To avoid duplication of data and to minimise data collection burden, data collected as part of the clinical assessment by ICC regarding the pain participants experienced was extracted. This included using free-text data to create groupings of the types of pain experienced and then quantifying whether participants had reported either one type of pain or more during their clinical assessment.
- Other information (including reports of sensitivities to opioids and adverse effects experienced, when available).

The second data extraction form was aided by a list of opioids (including the generic, and common and uncommon brand names), see Appendix 8. The list was developed by using both the British National and Palliative Care formularies,[442,443] and reviewed by supervisors. A pharmacist from the ICC was also consulted to ensure that the list included commonly prescribed opioids from this setting and population.

7.4.3.5.4 Process of data extraction

The research team completed SystmOne training and were issued with National Health Service (NHS) Care Identity Service cards to enable access, as well as CHCP computer logins. Data were extracted at the ICC onto paper hard copies following obtaining consent and survey completion, which were then stored at the university in a locked filing cabinet. Data extraction as part of the PACE study was performed between May 2019 and September 2019 by SP and two other PhD students (HE and UN), whilst the

data extracted for this thesis was completed by SP between October 2019 and January 2020. For those participating in qualitative interviews, data was extracted before their interview date to provide more context and support the discussion. To minimise systematic errors and guide opioid data extraction, as mentioned above, a list of search terms for oral and transdermal patch opioid analgesics was developed.

7.4.3.5.5 Opioid analgesic prescription data

The basic prescription data (e.g. quantity and frequency) extracted from medical records needed to be converted meaningfully to summarise patterns of prescribing. Additionally, data was collected for different opioid types and it was important to consider how these could be compared. Opioid consumption can be expressed in numerous ways, such as cost or number of prescriptions.[444] Although, these variables can differ across regions and countries over time and may not be translated easily on an international level.[444] This has been addressed by the concept of 'Defined Daily Dose' (DDD), which is defined as 'the assumed average maintenance dose per day for a drug used for its main indication in adults'.[444] Although, this is a fixed unit of measurement and may not correspond to the recommended or 'Prescribed Daily Dose' (PDD).[444] PDD is defined as 'the average dose prescribed according to a representative sample of prescriptions'.[444] However, this will only give the average amount of the specific drug prescribed and does not consider differences in potency between drugs.[444] A useful addition to these concepts is 'Oral Morphine Equivalent' (OME), which is where the equianalgesic ratios are used to convert DDD to OME in milligrams.[445] The use of OME is commonly used in the literature and appears to be the optimal method for interpretation and comparison between different opioid types and geographical locations, and is therefore adopted in this thesis (see Table 7.4 for conversion rates).[446]

Table 7.4 Opioid analgesic equianalgesic ratio for conversion to OME daily doses, ordered by potency

Opioid analgesic and route	Potency	Oral Morphine Equivalent
Oral		***Equivalent to 10mg oral morphine***
Oxycodone	1.5	6.6mg
Morphine*	1	10mg
Codeine	0.1	100mg
Dihydrocodeine	0.1	100mg
Tramadol	0.1	100mg
Meptazinol	0.025	400mg
Transdermal patches		***Equivalent oral morphine (milligram per day)***
Buprenorphine 5, 10 and 20 mcg/h	2.4	12mg, 24mg and 48mg
Fentanyl 12, 25, 50, 75 and 100 mcg/h	2.4	30mg 60mg, 120mg, 180mg and 240mg

Note. *Morphine as a reference = 1. There are various conversion tables and rates reported for comparing opioid analgesic doses; thus, potency and the OME are variable. For the purposes of this thesis, oral morphine equivalent for orally administered opioid analgesic were guided by the British National Formulary[442] and the Faculty of Pain Medicine of the Royal College of Anaesthetists.[447] *Abbreviations: mcg/h* Micrograms per hour.

Other considerations to prescription data are presented in Table 7.5.

Table 7.5 Definitions for characterising opioid analgesic prescribing

Concept	Definition
Opioid prescribing period	This included considering two time periods, including: (1) over the past year (i.e. within the 365 days prior to recruitment) and those 'currently' prescribed an opioid (i.e. within the 30 days prior to recruitment).
Prescription type	Prescriptions were categorised into *regularly scheduled* and *pro re nata (PRN)* (i.e. as and when needed). - *Regularly scheduled* was defined as a prescription that is expected to be taken in its on a regular basis entirety (e.g. '30mg codeine four times daily'). This included prescriptions where a range in dose was present but no indication of 'as and when' or 'up to' (e.g. '30mg codeine, 1 or 2 tablets four times daily'). - *PRN* was defined as a prescription that is expected to be taken 'as and when' needed (e.g. '15mg codeine 2 tablets, 4 times daily, as needed' or '50mg tramadol, 1 or 2 tablets up to TDS').
Opioid preparation	Prescipriptions were labelled as either '*immediate release'* or '*modified/sustained release'*.

Total number of opioids prescribed	The total number of opioids prescribed across the opioid prescribing period were counted and totalled. This was also summarised by *prescription type*.
Route of administration	Oral and transdermal routes of administration were considered and summarised.
Daily dose in OME	OME daily dose was investigated in a number of ways, depending on the *opioid prescribing period* considered: - *Over the past year:* Dose was characterised in two ways, including: the *average daily dose* and *dose by the total days supply.* The *average daily dose* was calculated by summing the OME per prescription for each participant and dividing by 365 days. This allowed for comparison across participants. Whilst the dose by total days supply was calculated to understand the *'intended'* dose when prescribed; this was calculated by summing the OME per prescription by the days supplied (and reflected ranges in dose – i.e. minimum and maximum possible doses). - *Currently prescribed:* Calculated using the frequency and strength, and presenting minimum and maximum dose where a range is present. These were considered by *opioid type* (e.g. buprenorphine) and *prescription type*.
Days' supply	For opioids prescribed *over the past year*, the days' supply of opioids was also considered. This was calculated using the quantity provided, dose strength and frequency, as well as reflected variation in the number of days where a range in dose was present.

7.4.4 Data management and cleaning

7.4.4.1 Management of study documentation and data

Participant consent forms and other identifiable data (i.e. contact details) were retained and stored in a lockable filing cabinet in a secure office at the university, in accordance with the General Data Protection Regulations (GDPR), Data Protection Act (2018) and university policy. Participants were provided with a copy of their consent form, alongside one for their medical record. All participants were assigned a unique anonymised identification number on both paper and electronic records related to the study for anonymisation purposes. Completed surveys only captured identifiable information on the cover (such as the participant's name), which were detached and disposed of in confidential waste on storing at the University of Hull. Surveys were then only identifiable via their unique identification number and stored in the same manner

as described above. Although, the consent forms and other identifiable data were stored separately from the survey booklet.

Data from the cross-sectional survey and PACE data extraction form were entered by the research team (i.e. HE, SP and UN) into a predetermined database using Microsoft Excel 2016®[448] The Project Manager (MO) also assisted with data collection. SP was responsible for entering the additional data extracted for the purpose of this thesis. To minimise systematic errors with data entry, common approaches were adopted and the team met to discuss possible concerns with the interpretation of data. All members of the team were GCP trained and aware of confidentiality and secure research procedures. Although double entry is recommended for optimal data entry, data were not double entered, for reasons of time and resources.

7.4.4.2 Data cleaning

Data were cleaned prior to analysis. Once all data were entered into the database, the PhD researchers (HE, SP and UN) addressed any outstanding queries regarding data entry. Queries included correcting formatting where necessary and tabulating all individual variables, subscales and total scores to seek out-of-range entries were. The data were then complete for each PhD student to extract their relevant data and develop their own database. Following a process of variable selection, the relevant variables were then extracted into a separate database and case note review data were added to the Microsoft Excel 2016®[448] spreadsheet. Data were then transferred to IBM SPSS Statistics for Windows® (Version 27).[449]

Prescription data were entered into a separate Microsoft Excel 2016®[448] spreadsheet prior to entering them into the main database to aid conversion to OME. To minimise errors with calculating dose, formulas were developed to reflect opioid potency and applied. These were cross-checked manually for each opioid type to ensure accuracy. Opioid data was tabulated to seek any discrepancies or values that do not represent the expected potency adjustment.

7.4.4.3 Strategies to reduce missing data

7.4.4.3.1 Cross-sectional survey

Effort was made to avoid missing data, at both unit (i.e. missing questionnaires) and item (missing answers) level. The survey was either completed by the researcher on behalf of the patient or surveys that were self-completed were checked for errors, and amended where possible. Telephone contact and/or home visits were made to complete the survey when it was not possible to complete on attendance to the ICC. However, some missing data occurred due to participants having limited time to complete the survey, or they became unwell or distressed when answering some questions – and follow-ups to obtain information were not possible.

7.4.4.3.2 Case note review data

An important part of this study was a case note review of medical records. Some missing data was inevitable, for example, access to medical record data containing information regarding opioid prescriptions from the participant's general practice was not always granted. Additionally, the consistency of information recorded within medical records varied.

7.4.4.4 Management of missing data

Patterns of missing data, including the unit (i.e. the whole questionnaire) and item-level (i.e. missing answers), are described. Participants who did not complete the whole survey (including the section related to pain medications prescribed at some point over the past year) will be excluded from the overall analysis. For descriptive statistics, all remaining cases are included regardless of missing data. Where missing data is greater than 10%, the results of subsequent analyses are likely to be biased and excluding cases from the analysis if a single value is missing is discouraged.[450-452] Therefore, for inferential statistics, a complete case analysis was undertaken for levels of missing data below 10%. Statistical models were built using participants with complete datasets. Where more than 10% of data was missing, imputation was considered. Data were also assessed to determine if they were missing completely at random. A complete case

analysis is deemed as an acceptable approach to the multilevel logistic regression analyses, where data are deemed to be missing completely at random.[453]

7.4.4.5 Statistical analysis

Quantitative data were entered into Microsoft Excel 2016®[448] and transferred to IBM SPSS Statistics for Windows® (Version 27)[449] for analysis. Participants and non-participants were compared in terms of age and gender, using descriptive statistics (including frequencies and averages). Non-participants were defined as those who declined participation on researcher approach, did not have capacity or a personal consultee, were feeling to tired or unwell, were away during the study period or leaving the catchment area, or communication difficulties (e.g. able to speak English) (see Figure 8-1 and Table 8.3).

Descriptive statistics were proposed to present demographic and clinical data from the cross-sectional survey and case note review of medical records. Continuous data were summarised using mean, standard deviation, median, interquartile range and range. Categorical data was summarised using counts and percentages. Inferential statistics (Chi-square, Fisher's Exact test, Mann-Whitney U and a McNemar test) were used to compare differences between groups in relation to experiences of pain, quality of life (as measured by the EQ-5D), comparisons of demographic and clinical characteristics, and differences in self-report and medical record data.

Two binary logistic regressions were planned to explore potential predictors of the outcome variables presented in Table 7.6. There are multiple ways to consider the cognitive impact of opioid analgesics (as discussed in Chapter 5), however, it was not possible to assess cognition formally and self-report was the best approach to capture cognitive adverse effects. Additionally, this thesis wanted to understand the factors associated with the presence or absence of an opioid prescription. As the outcomes are binary in nature, with two categories, binary logistic regressions with a logit link function were conducted.

Table 7.6 Summary of outcome variables used in the binary logistic regressions

Outcome variable	Definition/description
Presence or absence of cognitive adverse effects	A binary outcome variable reported as 'Yes' or 'No' to summarise the presence of absence of any cognitive adverse effects attributed to pain medications at some point over the past year. This was determined from a list of common adverse effects and supplemented by a free-text question from the survey.
Presence or absence of an opioid prescription	A binary outcome reported as 'Yes' or 'No' to summarise the presence or absence of an opioid prescription at some point over the past year. This was determined using opioid prescription data that was extracted from participants medical records.

The number of candidate predictors proposed were restricted to increase the robustness and validity of the models. The candidate predictors were selected in advance based on subject knowledge; this included a review of the literature and consideration of clinical relevance (see Appendix 9 for more a more detailed description of the selection process and justification for selected candidate predictors for the final models). The distribution of candidate predictors was planned and transformations were proposed, where necessary. The final candidate predictors proposed are presented in Table 7.7, with details of how they are scored or categorised.

Table 7.7 Final candidate predictors

Presence or absence of cognitive adverse effects: Final candidate predictors
1. Sociodemographic characteristics: These were age and gender. Age (in years) was regarded as a continuous variable. Gender was male and female, with the male category acting as the reference category.

2. ***Average daily dose of opioid analgesics prescribed at some point over the past year:*** Daily opioid doses were converted in equipotent milligrams of oral morphine. Participant's doses over the past year were summed and divided by 365 (days) to determine average daily dose over the past year.
3. ***Anticholinergic burden score:*** Anticholinergic burden scores were assessed using the ACB calculator.[430] As a score of three or more is associated with increased cognitive impairment, participants scores were characterised as follows: scores of ≤2 and scores of ≥3. The reference category was 'scores of two or less'.
Presence or absence of an opioid prescription: Final candidate predictors
1. ***Sociodemographic characteristics:*** These included age and gender. Age (in years) is regarded as a continuous variable. Gender was male and female, with the male category acting as the reference category.
2. ***Pain:*** Pain was assessed using the IPOS; the pain item (i.e. 'Please tick one box that best describes how pain has affected you over the past week') from the list of physical symptoms was scored from 0 (Not at all) to 4 (Overwhelmingly). This was treated as an ordinal variable.
3. ***Depression:*** Depression was also assessed using the IPOS; the depression item (i.e. 'Over the past week, have you been feeling depressed?') from the emotional symptoms section was scored from 0 (Not at all) to 4 (Always).
4. ***Loneliness:*** Loneliness was assessed within the pre-assessment conducted by the ICC prior to attendance. Participants were presented with the statement 'I often feel lonely' and asked whether they agreed or disagreed.
5. ***Number of prescribed medications:*** This was calculated from medical record data and included all medications prescribed over the 30 days, and treated as a count variable.
6. ***Self-rated health:*** Self-rated health was expressed via the EQ-5D, participants were asked to rate their health on attendance to the ICC. This was scored from 0 (i.e. worst imaginable health status) and 100 (i.e. best imaginable health status).
7. ***Number of hospital admissions over the past year:***

Number of hospital admissions were assessed within the pre-assessment; 'How many time were you admitted to hospital over the last year?'. This was a count variable.
8. Functional status: Functional status was assessed using the AKPS, ranging from 0% (death) to 100% (normal with no complaints or evidence of disease).

7.5 Qualitative component: In-depth semi-structured interviews

This section presents the methods adopted to address Objective 3 outlined in 'Chapter 4: Aims and objectives', which was 'To explore the experiences, perspectives and concerns of older adults and those that care for them regarding chronic pain, opioid analgesic use and cognitive adverse effects (including the challenges with managing pain, impact of chronic pain and opioid analgesics, and information and support needs)'.

7.5.1 Study design

A qualitative study was conducted using semi-structured, in-depth, interviews.

7.5.2 Participant eligibility

Participants were eligible to participate if they met the following criteria:

- Consented to being approached for a qualitative interview on the cross-sectional survey.
- Self-reported experiencing pain for three months or more.
- Prescribed an opioid at some point over the past year (identified by self-report and confirmed using data extracted from medical records).
- Self-reported a cognitive adverse effect that was attributed to an opioid analgesic or a combination of pain medications (including an opioid analgesic).

If the participants had a family member or friend who provided some form of informal care related to pain or pain management, they were eligible to participate in an

interview (either separately or alongside the patient participant). Informal caregivers were either identified on attendance to the ICC or when telephoning the patient participant to discuss whether they wished to take part in an interview. People unable to speak sufficient English to contribute to an interview or did not have capacity to provide informed consent were excluded, as were those failing to meet the inclusion criteria.

7.5.3 Sample size and data saturation

In thematic analysis, as adopted in this thesis (see Section 7.5.8), concepts such as 'information power' are considered more useful than data 'saturation'.[380,454] Higher information power is thought to be obtained when the aim is narrow, the sample recruited is specific, an established theory has been applied to the data, the dialogue is unambiguous and in-depth, and analyses narratives from a small number of selected participants.[454] More participants are needed when each of these elements are approached 'broadly', as it is assumed that this increased breadth minimises information power.[454] Additionally, the concepts of data-, thematic-, code- and meaning- saturation are not consistent with the values and assumptions of thematic analysis.[455] Meaning is generated through the interpretation of data and not extracted from the data, and judgement about the number of data items or when to stop data collection is subjective and cannot be determined wholly in advance of analysis.[455] In summary, the concepts of sample size and data saturation are challenging for numerous reasons and cannot be conclusively achieved.[456]

Considering the elements of 'information power', the aim of the qualitative interviews was orientated to opioid analgesic use and opioid-induced cognitive impairment, but considered broader aspects of experiences, perspectives, concerns, and information and support needs. In line with this, the sample was specific and purposively sampled. Established theories have been presented (see Section 6.3.2.2) and are applied as appropriate to help understand the data. The topic guide was developed to aid meaningful discussion to address the aim, although concepts of pain, cognition and opioid analgesics may hold some ambiguity (such as participants knowledge and understanding of these concepts, see Section 2.4.1). These study-specific elements were also considered in the context of another study that held a similar aim but exploring

analgesia more generally in a broader aged sample (i.e. ≥50) applying a theoretical framework of adherence and thematically analysed recruited 28 participants.[63] Aside from the authors acknowledging that they reached data saturation,[63] the elements of their study were considered to be broader than that of this thesis. Therefore, aiming for a sample of up to 20 patient participants (and their informal caregivers, where available) should provide substantial 'information power'.

7.5.4 Sampling and recruitment

The interviews were introduced to participants on attendance to the ICC via the participant information sheet (see Appendix 3), and were asked whether they would be happy to be approached by a member of the research team regarding an interview at a later date. Once eligible participants had been identified from the cross-sectional survey using the eligibility criteria (outlined in Section 7.5.2), purposive sampling was used. Participants were sampled according to: gender and cognitive adverse effects experienced (to represent a range of and experience of one or multiple cognitive adverse effects). Purposive sampling aimed to minimise selection bias by selecting participants who matched certain criteria, such as a similar number of men and women and varying experiences of opioid-induced cognition. However, it is recognised that those willing to provide consent for the interview were a self-selecting group.

SP followed up with potential participants via the telephone, explained the qualitative component of the study, and answered any queries they had. If they were willing to take part, an interview was scheduled at a time and a place convenient to the participant. Informal caregivers were identified at this point or on attendance to the ICC, where available. On the day of recruitment and prior to data collection, SP introduced herself, summarised the study and participants were given a participant information sheet specific to the qualitative study (see Appendix 10). SP read the information sheet through with participants, if requested. All participants provided written informed consent (see Appendix 11) prior to being interviewed. The issue of informed consent was important to re-review at this stage, as interviews occurred after the cross-sectional survey (as discussed in Section 7.4.3.2).

7.5.5 Setting

The semi-structured, in-depth, interviews were undertaken in the place of each participant's preference (i.e. within their place of residence) and of convenience to the interviewee, and were situated in Hull.

7.5.6 Data collection

7.5.6.1 Topic guide development

Topic guides were developed to prompt and aid discussion in the interviews to ensure that key points were covered. These were based on the study objectives and areas of specific interest derived from the literature, as well as guided by quantitative data. Originally, interviews were designed to be conducted on an individual basis, to allow both patient participants and informal caregivers to provide detail without their narratives being shaped by one another. Therefore, individual topic guides were developed for both patients and informal caregivers. The topic guides were also discussed with supervisors (JB and FEM) and the wider PACE team, and modified following feedback. The topic guides were also reviewed by two local community groups (for further details see Section **7.8**) before being finalised. This helped to ensure the topic guide was clear and understandable for the intended population.

Prior to the commencement of the qualitative interviews, it was decided that providing participants with the option of sole or joint interviews would be more appropriate, after observing mixed attendance to the ICC. A joint topic guide was then developed based on the finalised patient and carer guides to aid the possible multiple interview structures (patient only, carer only and joint interviews). At the beginning, efforts were made to interview patients and carers alone, to reduce the influence on both parties' responses to the questions. In most interviews, this was not feasible, as patient participants often requested their spouse or other family member to be present.

The topic guides contained questions to: understand experiences of chronic pain and its impact, the circumstances in which opioids were initiated, alternative approaches to

managing pain, attitudes and concerns regarding opioids (prior to taking and after taking), adherence to taking opioids, whether they provided satisfactory relief, perceived adverse effects from opioid use (with focus to cognition) and impact on informal carers, care provided by the informal carers, communication with health professionals, and information and support needs for both the patient and informal carer (if present). The guide and order of the questions was flexible to allow for the emergence of relevant but unanticipated responses, and therefore, to the development of new prompts/questions for subsequent interviews. As the interviews progressed, items were iteratively added to the topic guide (see Appendix 12). The interviews were designed to last approximately between 45 minutes to an hour for individual interviews and from an hour to 1 hour and 15 minutes for joint interviews.

7.5.6.2 Interviews

All consent forms included consent to audio record the interviews. Data from the cross-sectional survey and case note review were reviewed prior to the interview and used to inform and aid the discussion during the interview (such as the opioid-induced cognitive adverse effects experienced and opioid analgesics prescribed over the past year).

With the nature of the study, participant comfort and emotional wellbeing were considered a priority. Refreshments were obtained prior to starting the interview and SP ensured that they were in their preferred seat. Participants were able to mobilise or adjust their 'usual' chair and pause the interview, if needed. Additionally, they were informed that they could stop the interview entirely or withdraw from the study (i.e. up until the point of transcription). Any time constraints the participant(s) had were confirmed prior to starting the interview. Despite the study being considered low-risk, there are unavoidable risks present when conducting research in the patients home and covering sensitive topics. To minimise risk of harm to the participants, consent was also obtained by the researcher to follow-up any issues causing distress to the clinical team at the ICC. Additionally, the researcher followed the lone worker policy as outlined by their research group.

Field notes were recorded the same day of interview to document initial thoughts and observations and reviewed iteratively. This supported the identification of recurring topics and additional lines of enquiry for future interviews to be considered. Field notes are considered a useful tool in qualitative research that provide detailed contextual descriptions.[457] Each interview was then transcribed verbatim. Field notes and early transcripts were critically reviewed with supervisors (JB and FM), to reflect on content, provide feedback and refine techniques.

7.5.7 Data management

Consent forms were stored in a secure and locked filing cabinet in an office at the University of Hull, in accordance with the GDPR, Data Protection Act (2018) and university policy. All participants were provided with a copy of their consent form for their own personal records. Participants were assigned with a unique identification number as part of the cross-sectional survey, which was also adopted for the purpose of the interviews. Informal cargivers were allocated the same number but with the letter 'C' to denote caregiver.

SP was responsible for all data collection and transcription. Interviews were recorded using an audio recorder (i.e. Olympus Digital Voice Recorder WS-853) and were immediately transferred to an encrypted memory stick and labelled using their unique identification number upon return to the workplace or home, and then deleted from the audio recorder. The interviews were transcribed verbatim and saved on the encrypted memory stick under their identification number. The interview content was anonymised, removing identifiable information (such as names, services and locations) and replacing with generic terms (such as 'daughter'). Anonymised transcripts were imported into NVivo (Version 12)®[458] for analysis and stored on a password-protected University platform. The audio recordings and transcripts were deleted from the encrypted memory stick once stored on the University password protect platform.

7.5.8 Analysis

7.5.8.1 Thematic analysis

Interviews were analysed using thematic analysis **as explicated by Braun and Clarke**, as it recognises that themes are produced by the researcher through meaningful and systematic engagement with the data.[380] It is suited to identifying patterns of meaning within qualitative data.[380] This approach to thematic analysis involves six phases. This begins with *familiarisation* of the data, moving on to a rigorous and systematic approach to *coding*, before starting to *generate initial themes* and *developing and reviewing themes.*[380] The final two phases include the *refinement, defining and naming of themes* and *producing a report of the findings*.[380] These phases are described in more detail in relation to the analysis of the study data in Table 7.8. These phases were used to guide the analysis and recognises that the phases are not clearly delineated or unidirectional, but more iterative and progressive (i.e. moving back and forth between the phases as thinking progresses).[380] Reflexivity is considered a fundamental characteristic of thematic analysis and involves critically reflecting on the role of the researcher and research practices on the phases of analysis.[380] Its theoretically flexible nature also supports the pragmatic and inductive-interpretative approach adopted in this thesis.[380]

Table 7.8 Summary of the thematic analysis in relation to this study[380]

Phase 1: Familiarisation with the dataset. Data were reviewed in-depth to ensure familiarity with the content of the interviews. This was completed through a process of immersion and involved reading and re-reading the data and corresponding field notes, as well as reviewing the audio files again. Brief notes were made, documenting analytic ideas and insights regarding the data.
Phase 2: Coding. The data were systematically worked through with a fine-grained approach. Segments of the data that were considered interesting, relevant or meaningful to the research aim were identified and code labels were applied. Codes were concise analytically-meaningful descriptions of specific single-meaning concepts; adopting a mixture of semantic (i.e. explicit surface level codes) and latent coding (i.e. conceptual or implicit codes). Codes were considered at the level of the individual (patient participants and informal caregivers) and joint meaning, where relevant.

Phase 3: Generating initial themes. The shared meanings and patterns across the dataset were then identified. Clusters of codes that appeared to share a core idea or concept that might provide a meaningful *'answer'* to the research questions were compiled. Themes were actively constructed and shaped by my knowledge and insights, as well as the research aim. As this stage, the themes describe the broader meaning attributed to the codes. Once potential themes were identified, all coded data relevant to this theme were collated.

Phase 4: Developing and reviewing themes. The initial fit of these potential themes against the data were assessed, ensuring that the themes make sense in the context of the coded extracts and the dataset as a whole. It was important to consider at this stage whether each theme presents a compelling 'story' and do all the themes collectively highlight the most important patterns across the data. The 'potential' themes were then either retained, restructured or discarded. The central organising concept of each theme was considered within the wider context of research and existing knowledge (such as the theoretical frameworks discussed in Section 6.3.2.2). These were discussed with my supervisors for sense-checking.

Phase 5: Refining, defining and naming themes. The analysis was then fine-tuned, ensuring that themes were clearly demarcated and were built around strong core concepts. Brief summaries of each theme were developed and further discussed with my supervisors.

Phase 6: Producing a report. An analytical process was adopted and started early on through the use of familiarisation notes and reflexive journaling, which was fed into the formal write-up as presented in Chapter 9: Qualitative component – Results. This involved weaving together the analytic narrative and vivid data extracts to address the aim of the research and answer the research questions.

7.5.8.2 Adaptation of theoretical frameworks

As outlined in Table 7.8, the potential themes were considered in relation to existing knowledge. The codes and themes identified as part of the inductive approach to analysis resonated with two of the theories presented in Section 6.3.2.2, which were the 'three lines of work' proposed by Corbin and Strauss[338] and Horne and colleagues model of adherence.[344,345]

The experiences of chronic pain and associated adverse effects from pain medication have been situated within understanding the impact to adherence and decision-making in prevention and management.[63] The broader context in which people and their families manage chronic pain and the associated 'work' is often lost. People experience their chronic pain journey (including adverse effects) with family members, and in the context of their lives and communities. The concept of chronic pain work extends not only to aspects of pain management and self-care to people with chronic pain and family carers, but to all aspects of their lives. This includes performing formal and informal roles, household and relationship maintenance, as well as reconstructing identity. Therefore, this analysis will combine the lines of work that people with chronic pain and their families undertake, as well as, the aspects that influence their management of pain. Exploration of the 'lines of work' means the close inspection of its many facets: the tasks involved, who does them, how, where, the consequences and problems involved, as well as the interplay.

7.6 Integration of quantitative and qualitative components

The integration of quantitative and qualitative approaches can occur at different levels (as discussed in Section 6.4.3.3). This section will focus on the analysis, interpretation and reporting of the different components of this study. This thesis has adopted a narrative and connecting approach, where the findings of the systematic review, quantitative cross-sectional survey and case note review, and the qualitative in-depth interviews are presented separately in their own chapters. This is then supplemented by an overall synthesis that was conducted in two stages: (1) a synthesis and discussion of the mixed method quantitative and qualitative results that draws overarching inferences between the data and (2) integrating the mixed methods findings with the systematic review findings, where relevant.

The integration of findings was achieved by using a modified Critical Interpretative Synthesis approach. Critical Interpretative Synthesis is a method that allows for quantitative and qualitative data to be integrated and synthesised through an interpretative process.[459] This approach draws on conventional systematic review

methodology while combining a traditional qualitative line of enquiry.[459,460] In particular, recognition is given to the interpretative process required to produce a synthesis based on the distinct forms of evidence.[459] It is increasingly used in systematic reviews that aim to synthesise both quantitative and qualitative evidence to understand a phenomenon.[460,461]

This thesis adapted the Critical Interpretative Synthesis method to, firstly, synthesise the mixed methods study findings, and then, further integrate with the systematic review findings using an integrative grid (see Table 10.1 in Chapter 10). Although presented together, these were treated as two distinct steps. Firstly, to allow inferences to be drawn from the quantitative and qualitative components of the mixed methods study in relation to the population recruited and the use of self-report to identify opioid-induced cognitive impairment. Followed by consideration of the insights gained from the systematic review, where more formal screening tools and neuropsychological assessments were a main focus. This aided a gradual zooming out of the data to consider the essential inferences at each stage, and bringing all the findings together. An alternative option would have been to present a separate chapter synthesising the mixed methods findings, and then a final discussion chapter incorporating the systematic review findings. However, this would have led to significant repetition, so to avoid this, the findings have been brought together as an integration and discussion chapter.

Table 10.1 presents the main components of the synthesis along the top of the table and the main phenomena listed down the left-hand side. This side-by-side comparison of findings presented a narrative summary where columns were populated with the main findings and meta-inferences (i.e. the overall conclusion, explanation or understanding) are brought together within the 'synthesis' and 'additional insights' columns. Discrepancies in the data were also considered.

7.7 COVID-19 impact statement

For the most part, the pandemic has had minimal impact on this thesis. Restrictions came in as data extracted from medical records were being double-checked to ensure

accuracy. Access to the ICC was restricted as the building was repurposed and staff were redeployed to respond to the pandemic. The University also introduced its own guidance for students to follow, which meant that all field work had to be completed by Friday 20th March. The planned work was completed within the timeframe, and ensured that opioid prescription data was captured correctly from the medical records. In some instances, it would have been useful tohave subsequent access to the survey hardcopies stored on campus to check against data entered into the database. However, this was achieved when resctrictions eased and only had temporary impact to data tidying and analysis.

7.8 Patient and public involvement

When designing and conducting patient-related research, it is essential to include the views and opinions of patients, their families and members of the public. Patient and public involvement (PPI) ensures that research is relevant and appropriate for those with lived experience of the phenomena under study, and has been central in my approach to this study and within my research career. PPI in this study occurred in phases to ensure that feedback on this study and study-related materials were deemed as acceptable, and identify areas for improvement.

PPI was implemented to review the questionnaire development and design, as well as supporting study documents for the PACE study. Feedback on study documentation was sought from the Engagement Manager for Patients and the Public from NHS Hull CCG (as involved in the development of PPI for the ICC) and an ICC PPI member. Overall, the survey and other study documents were deemed as appropriate. It was suggested that the language for one item on the IPOS addressing whether the patient was ‘at peace’ could be simplified to whether they felt ‘comfortable or settled’. Additionally, it was suggested that the 0 – 100 scale for how good/bad their health is today (as part of the EQ-5D-5L) was too large and would not be tangible to patients. As these questions came from validated measures, it was not possible to amend the items. However, the researchers administering the survey were aware that more explanation may be required in relation to these items. The additional questions around breathlessness, pain medications, and unintended weight loss were thought to be cumbersome if completing

all sections. However, they were reassured that patients would only complete these questions if relevant, as per the strategies to minimise burden. Minor amendments were also provided to improve the language and understandability of the one-page study introduction and participant information sheet. It was not possible to conduct a formal pilot study to determine the acceptability and feasibility within the ICC setting with the older adults, due to time constraints.

From my previous experience working as a Patient and Public Involvement, it is important to involve patients, families and members of the public in various stages and elements of the research. A sample topic guide had been submitted as part of the ethical review and the study protocol outlined that further PPI would be used to develop and refine the topic guides for the qualitative interviews for each PhD study. Two separate community groups were approached to gather views on whether the line of enquiry was understandable, including whether the aspects covered were considered to be important, the language was appropriate and accessible, and whether any changes were needed. I organised to attend the Trans Humber PPI Group at Castle Hill Hospital, Hull on the 19/03/2019 at one their regularly scheduled meetings for reviewing research. However, it was important to also obtain the views of older adults. I adopted a grass roots approach to engage with local groups and organised to attend a local older adult's support group at Sutton Reading Rooms in Hull on the 25/02/2019.

Across both groups, approximately 20 people were present and included people aged 65 and over. On reviewing the topic guide, the PPI groups advised that the line of enquiry covered aspects that were important to them and in understanding experiences of pain medication. The questions were found to be understandable but they advised on some areas that could be refined to ensure that questions were explicitly clear to interviewees in terms of the language used. The group of local older adults specifically offered insights into their own experiences of pain medication and the challenges they encountered with them. Topic guides were amended and discussed with supervisors before the final refinement. Slight alterations were also made to the topic guides as the interviews progressed, using an iterative approach.

7.9 Ethical approval

As this study involved collecting data from older adults at risk of severe frailty, formal ethical approval was required to ensure appropriate conduct and avoid unnecessary burden on potential participants and participants. Additionally, as participants were recruited from an NHS organisation; ethical approval was required from a UK NHS research ethics committee. The Health Research Authority (HRA) coordinates such applications and assess the feasibility of conducting the research at the participating NHS organisation. Formal ethical approval for this study was obtained from both the Hull York Medical School Ethics Committee at the University of Hull (Reference 1823) and the HRA (Reference 18/YH/0470). Site specific approval was also received from the CHCP CIC Research Approval Group (RAG). For ethical approval letters see Appendix 13.

7.10 The service evaluation and my contribution

Although this thesis was included within the PACE research programme and shared inclusion criteria with the larger PACE study, it was nevertheless a self-contained piece of mixed-methods research. I contributed to the design of PACE by co-writing the protocol and ethics application, and worked on all study processes, including the data collection schedule for baseline data and compiling the master site file.

The PhD used data collected at baseline from the ICC to investigate, in greater depth, an aspect of the PACE aim: 'to further investigate the use of pain medications and possible adverse effects (with focus to opioid analgesics and effects on cognition).' I contributed at every stage of this research as follows:

- Co-wrote the protocol and ethics application
- Contributed to the development and design of the baseline survey and medical record data extraction booklet; including conceiving, drafting and writing the section on pain medication use over the last year

- Conceived, drafted and wrote a separate data extraction booklet for additional items of specific interest to this PhD that were collected at a separate timepoint
- Conceived, drafted and wrote the interview topic guide
- Recruited participants to the study at the ICC care setting (and care homes), and undertook quantitative data collection alongside colleagues
- Conducted all of the qualitative interviews, including transcription
- Analysed and interpreted the data presented in this thesis

7.11 Summary

This chapter has described the specific methods used for this mixed methods study and how it was situated within a wider programme of research, followed by consideration of how the quantitative and qualitative components will be integrated. Additonally, it discussed how different stakeholders were involved in the shaping of the study documentation and ethical considerations. The next chapter presents the findings from the quantitative components.

Chapter 8: Quantitative components – Results

The results from this PhD are presented in the following chapters:

- Chapter 5: Systematic review on the effects of opioids on cognition in older adults with cancer and chronic non-cancer pain
- Chapter 8: Quantitative components – Results
- Chapter 9: Qualitative component – Results
- Chapter 10: Integration of findings

The results from the systematic review were presented first in a standalone chapter, and are followed by the quantitative components (i.e. the cross-sectional survey and case note review) in this chapter, which aims to address Objective 2 of this thesis: 'To investigate opioid analgesic use to manage pain and the impact on cognition (including impact of opioid use on quality of life and functional status, and a description of opioid use), among older adults at risk of severe frailty'. The demographic and clinical characteristics of participants are described, and the results are presented by the research questions developed to address Objective 2.

8.1 Description of sample

This section describes the study participants, including the characteristics of those who were identified, approached and recruited to the study.

8.1.1 Participant identification and recruitment

Recruitment was undertaken between the 30th April 2019 and 20th August 2019. Recruitment to the PACE study was completed within 4 months from study commencement due to good recruitment rates – therefore, recruitment took place over four months rather than 6 months. During the study period, 471 unique patients at risk of severe frailty were invited to attend the ICC and were potentially eligible for the

study; 435 were formally assessed for eligibility. 359 patients were identified as eligible for study inclusion, and of these, 250 participants consented to participate (i.e. 69.6% (250 of 359) of participants assessed as eligible consented). Figure 8-1illustrates the flow of participants through the assessment and recruitment process. The reasons patients were not assessed are documented in Table 8.1. Reasons for ineligibility and for refusal are documented in Table 8.2 and Table 8.3, respectively.

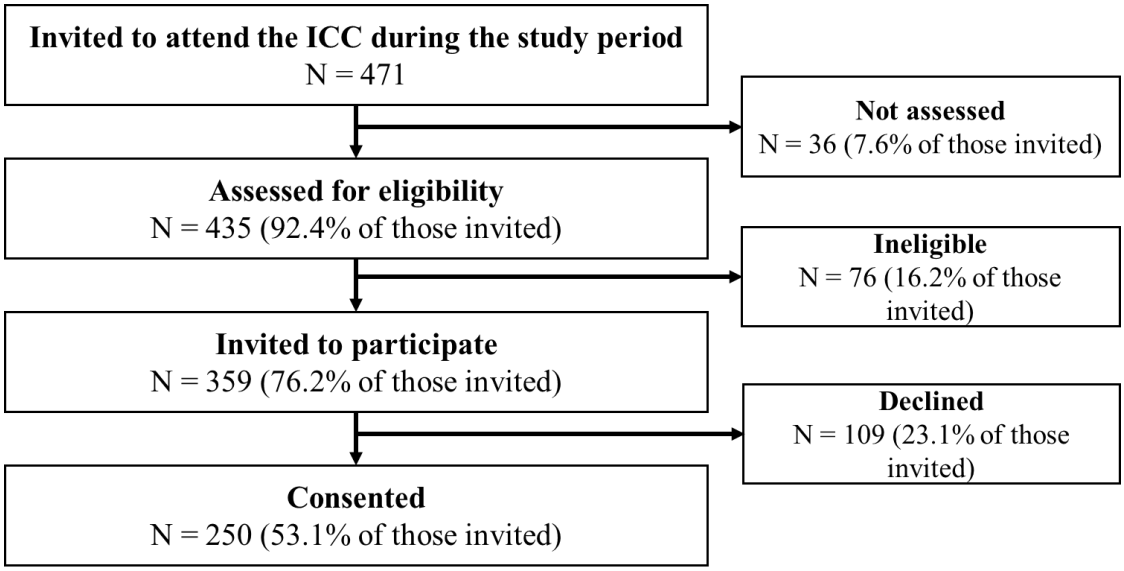


Figure 8-1 Recruitment flowchart

Table 8.1 Reasons patients invited to attend the ICC were not assessed for eligibility

	n	**%**
Left before they could be approached by a member of the clinical team regarding study	18	50.0
Did not attend their appointment	15	41.7
Recruitment target met	3	8.3
Total	**36**	**100.0**

Table 8.2 Reasons for ineligibility for participants who were assessed and found to be ineligible

	n	%
Under 65 years of age	33	43.4
Deemed clinically inappropriate for a researcher to approach	31	40.8
Reported no interest in being approached by a researcher on clinical introduction to the study	12	15.8
Total	**76**	**100.0**

Table 8.3 Reasons for refusal for patients who were eligible but did not consent to participate

	n	%
Declined to take part in study on researcher approach	87	79.8
Feeling too tired and/or unwell	6	5.5
Found to lack capacity on researcher approach and no personal consultee	4	3.7
Patient or family concerned regarding access to medical records	3	2.8
Communication difficulties	2	1.8
Demonstrated interest in study but left before consent and survey completed	2	1.8
Waiting on transport and concerned about time to complete survey	2	1.8
Away during study period	1	0.9
Moving out of the catchment area	1	0.9
Taking part in another study and unable to commit to another	1	0.9
Total	**109**	**100.0**

Basic characteristics of non-participants were collected for the purposes of the screening log; these were age and gender. Table 8.4 below compares these basic characteristics for participants and those who were identified as eligible but did not participate in the study. Characteristics were similar across participants and non-participants.

Table 8.4 Age and gender for participants and non-participants

	Participants (n=250)	Non-participants (n=109)
Age		
Mean (SD)	80.3 (7.4)	81.4 (7.6)
Median [IQR]; (range)	81 [75, 85]; (65 – 99)	82 (75, 86.5)
Missing n (%)	0 (0.0)	0 (0.0)
Gender n (%)		
Female	153 (61.2)	73 (67.0)
Male	97 (38.8)	36 (33.0)
Missing	0 (0.0)	0 (0.0)

8.1.2 Participant characteristics

Of the 250 participants who consented to participate in the PACE study, three participants were excluded for the purpose of this thesis, as they did not have a complete survey. Therefore, the sample size for this quantitative analysis is 247 participants. Nine participants lacked the capacity to consent for themselves; these participants were included in the study based on the approval of a personal consultee, as per protocol and ethics approval. The nine participants who lacked capacity provided data via a proxy respondent. Table 8.5 shows the demographic and clinical characteristics of participants.

Table 8.5 Demographic and clinical characteristics of the study population (n=247)

	***N* (%)**
Age	
Median [IQR]; (range)	81 [75 – 85]; (65 – 99)
Missing	0 (0.0)
Gender	
Female	151 (61.1)
Male	96 (38.9)
Missing	0 (0.0)
Ethnicity	
White	212 (85.8)
Mixed/Multiple Ethnic Groups	18 (7.3)
Black African/Black Caribbean/Black British	1 (0.4)
Missing	16 (6.5)
Relationship Status	
Married/Civil Partnership	119 (48.2)
Widowed	74 (30)
Divorced	14 (5.7)
Single	7 (2.8)
Separated	2 (0.8)
Missing	31 (12.6)
Living Situation	
Spouse/Partner	112 (45.3)
Alone	111 (44.9)
Other family	20 (8.1)
Other	1 (0.4)
Missing	3 (1.2)
Smoking Status	
Former smoker	111 (44.9)

Non-smoker	104 (42.1)
Current smoker	29 (11.7)
Missing	3 (1.2)
Index of Multiple Deprivation	
1 (Most deprived)	108 (43.7)
2	54 (21.9)
3	36 (14.6)
4	17 (6.9)
5 (Least deprived)	26 (10.5)
Missing	6 (2.4)
Capacity	
Yes	238 (96.4)
No	9 (3.6)
Missing	0 (0.0)
Comorbid groups	
Median [IQR]; (range)	4 [3 – 5]; (0 – 9)
Cardiovascular and circulatory conditions	233 (94.3)
Musculoskeletal conditions	128 (51.8)
Endocrine disorders	118 (47.8)
Kidney conditions	103 (41.7)
Respiratory conditions	94 (38.1)
Obesity	64 (25.9)
Gastrointestinal conditions	59 (23.9)
Malignancy	43 (17.4)
Eye, ear, nose and throat issues	41 (16.6)
Mental health issues	37 (15.0)
Cognitive decline issues	26 (10.5)
Neurological conditions	21 (8.5)
Pain issues	19 (7.7)
Dermatological conditions	17 (6.9)
Urological issues	17 (6.9)
Another comorbidity	15 (6.1)
Missing	0 (0.0)
Functional status (AKPS)	
Median [IQR]; (range)	70 [60 – 80]; (40 – 90)
90 (Normal activity, minor signs of illness)	16 (6.5)
80 (Normal activity requires effort, signs of illness)	63 (25.5)
70 (Cares for self, unable to carry on normal activities)	51 (20.6)
60 (Cares for most needs, requires some assistance)	70 (28.3)
50 (Considerable assistance and medical care required)	46 (18.6)
40 (In bed more than 50% of the time)	1 (0.4)
Electronic Frailty Index Score	
Fit	3 (1.2)
Mild frailty	7 (2.8)
Moderate frailty	55 (22.3)
Severe frailty	166 (67.2)

Missing	16 (6.5)
Rockwood Clinical Frailty Scale	
Median [IQR]; (range)	5 [5 – 6]; (1 – 8)
1 (Very fit)	1 (0.4)
2 (Well)	3 (1.2)
3 (Managing well)	12 (4.9)
4 (Vulnerable)	38 (15.4)
5 (Mildly frail)	99 (40.1)
6 (Moderately frail)	66 (26.7)
7 (Severely frail)	20 (8.1)
8 (Very severely frail)	1 (0.4)
Missing	7 (2.4)

Abbreviations: AKPS Australia-modified Karnofsky Performance Status, *SD* Standard Deviation, *IQR* Interquartile Range.

Participants had a median age of 81, and 151 (61.1%) were female. Most participants were white (85.8%), married or in a civil partnership (48.2%), and were mostly living with their spouse/partner (45.3%) or alone (44.9%). A large proportion of participants were former smokers (44.9%) or non-smokers (42.1%), with a small percentage recorded as current smokers (11.7%). In terms of relative deprivation, just over 40% of the participants fell in to the most deprived quintile of the IMD (i.e. 43.7% were in quintile 1).

The median number of comorbid groups per participant was 4. Cardiovascular and circulatory conditions were the most common amongst the comorbid groupings, affecting 94.3% of participants. The median functional status score (as determined by the AKPS) for was 70. Participants were referred to the ICC on the basis that they were identified as being ‘at risk’ of severe frailty by their general practitioner, using the eFI (i.e. a score of >0.36). Considering this, some participants referred to the ICC had lower eFI scores. Although, the majority of participants were identified as having a risk of severe frailty (67.2%). On attendance at the ICC, frailty was evaluated using the CFS, where less than 10% of participants were assessed as being severely frail or very severely frail.

Participants HRQoL was also considered and is presented below. The descriptive system of the EQ-5D-5L that comprises of five health dimensions (mobility, self-care,

usual activities, pain or discomfort and anxiety or depression) is presented in Table 8.6. Eleven participants reported a health profile of '11111' across all the domains (i.e. no problems reported). All other participants reported problems on at least one of the EQ-5D-5L dimensions. Among the 247 participants, there were 122 unique health profiles. Two patients were missing data from one dimension, meaning that it was not possible to determine a full health profile or global HRQoL score. Problems at the most severe (level 5) and next to worst (level 4) severity level for one or more dimensions were reported by 44 participants and 105 participants, respectively. Overall, most problems were reported in the 'mobility' dimension, where 63.6% of participants reported level 3 problems or worse. This was followed by problems in the 'pain or discomfort' (56.7%) and 'usual activities' (49.4%). Less problems were reported in regards to self-care (22.3%) and anxiety or depression (20.6%).

Table 8.6 Distribution of EQ-5D-5L dimension responses

Dimensions	**All participants (n=247)**
Mobility	
1 - No problems walking about	37 (15.0)
2 - Slight problems walking about	52 (21.1)
3 - Moderate problems walking about	72 (29.1)
4 - Severe problems walking about	72 (29.1)
5 - Unable to walk	13 (5.3)
Missing	1 (0.4)
Self-care	
1 - No problems washing or dressing	153 (61.9)
2 - Slight problems washing or dressing	39 (15.8)
3 - Moderate problems washing or dressing	35 (14.2)
4 - Severe problems washing or dressing	12 (4.9)
5 - Unable to wash/dress washing or dressing	8 (3.2)
Missing	0 (0.0)
Usual activities	
1 - No problems doing usual activities	77 (31.2)
2 - Slight problems doing usual activities	48 (19.4)
3 - Moderate problems doing usual activities	55 (22.3)
4 - Severe problems doing usual activities	39 (15.8)
5 - Unable to do usual activities	28 (11.3)
Missing	0 (0.0)
Pain or discomfort	

1 - No pain or discomfort	55 (22.3)
2 - Slight pain or discomfort	52 (21.1)
3 - Moderate pain or discomfort	76 (30.8)
4 - Severe pain or discomfort	52 (21.1)
5 - Extreme pain or discomfort	12 (4.9)
Missing	0 (0.0)
Anxiety or depression	
1 - Not anxious or depressed	141 (57.1)
2 - Slightly anxious or depressed	54 (21.9)
3 - Moderately anxious or depressed	29 (11.7)
4 - Severely anxious or depressed	15 (6.1)
5 - Extremely anxious or depressed	7 (2.8)
Missing	1 (0.4)

Abbreviations: EQ-5D-5L EuroQoL.

Participants were also asked to rate their health on the day of recruitment from 0 (i.e. worst health they can imagine) to 100 (i.e. best health they can imagine). The median self-rated health score was 60, with an interquartile range of 50 to 80 (see Table 8.7).

Table 8.7 Self-rated health on day of recruitment

Self-rated health using EQ-5D-5L VAS	All participants (n=247)
Median [IQR]; (Range)	60 [50 – 80]; (15 – 100)
Missing	0 (0.0)

Abbreviations: EQ-5D-5L EuroQoL, *VAS* Visual analogue scale

The health utility value represents current health, based on the five dimensions, where full health has a value of one and dead has a value of zero. The median health utility score was 0.67, with an interquartile range of 0.43 to 0.85 (see Table 8.8). Scores that equated to health that was worse than dead and full health were observed.

Table 8.8 Health utility scores of participants

Health utility score	All participants (n=247)
Median [IQR]; (Range)	0.67 [0.43 – 0.85]; (-0.18 – 1.00)
Missing	2 (0.8)

Scoring: Full health has a value of 1 and dead has a value of 0.

8.2 Results by research question

Figure 8-2 presents a summary of how participants from the study population were used to answer the research questions to address Objective 2 of this thesis.

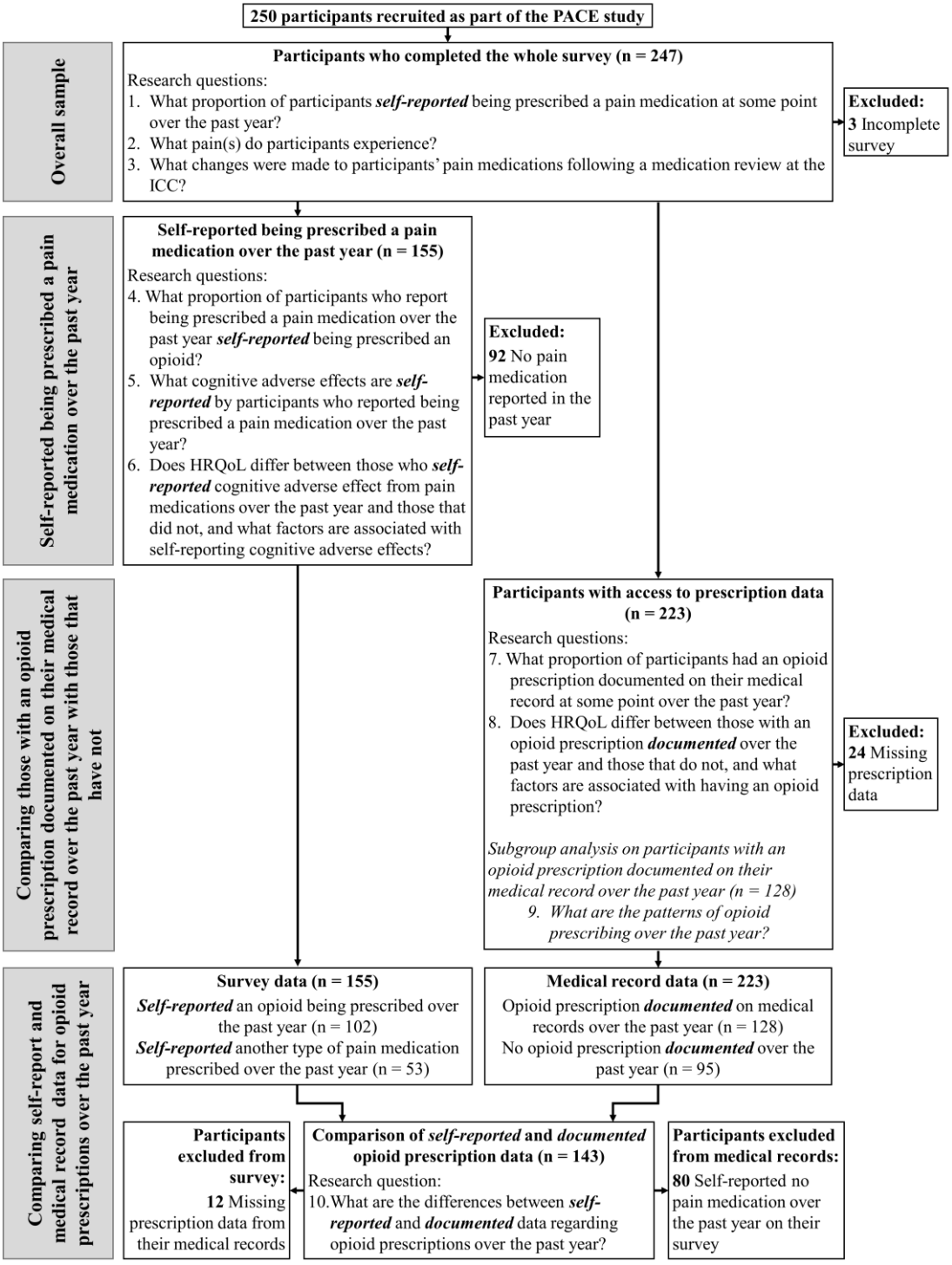


Figure 8-2 Summary of research questions and the relevant participants

8.2.1 Proportion of participants who self-reported being prescribed a pain medication at some point over the past year (Research Question 1)

Table 8.9 presents the proportion of participants who self-reported being prescribed a pain medication at some point over the past year. Of the 247 participants, over half (62.8%; 95% CI [56.8%, 68.8%]) self-reported being prescribed a pain medication.

Table 8.9 Proportion of participants who self-reported being prescribed a pain medication at some point over the past year

Pain medication prescribed at some point over the past year? n (%)	All participants (N=247)
Yes	155 (62.8)
No	92 (37.2)

8.2.2 Description of pain(s) experienced by participants (Research Question 2)

The following sections (8.2.2.1, 8.2.2.2, 8.2.2.3) provide a description of pain reported by participants, and compares those who self-reported being prescribed a pain medication at some point over the past year and those who have not. To allow for multiple comparisons, a Bonferroni correction[462] is used, so that a p-value threshold of 0.017 (0.05/3), rather than 0.05, is sought as the level of statistical significance.

8.2.2.1 Pain as a main problem or concern

Participants were asked to report their main problems and concerns over the past week (as determined by the IPOS); pain was reported as a main problem or concern by just over a third of all participants (see Table 8.10). The prevalence of pain as a main problem or concern was higher for those who self-reported being prescribed a pain medication over the past year (with the difference reaching statistical significance with the Bonferroni correction).

Table 8.10 Proportion of participants who self-reported pain as their main problem or concern over the past week

Pain as a main problem or concern over the past week n (%)	All participants (N=247)	Self-reported a pain medication being prescribed over the past year?		Pearson Chi-square test
		Yes (n=155)	No (n=92)	
Yes	85 (34.4)	63 (40.6)	22 (23.9)	χ^2 (2) = 13.75 **p = 0.001** Φ = .24[a] *n* = 247
No	116 (47.0)	73 (47.1)	43 (46.7)	
No problems or concerns stated	46 (18.6)	19 (12.3)	27 (29.3)	

Degrees of freedom are presented in brackets. Φ = effect size (Phi coefficient or Cramer's V).
[a]A significant difference with an effect size ≥ Cohen's definition of "small".

8.2.2.2 Self-report of pain

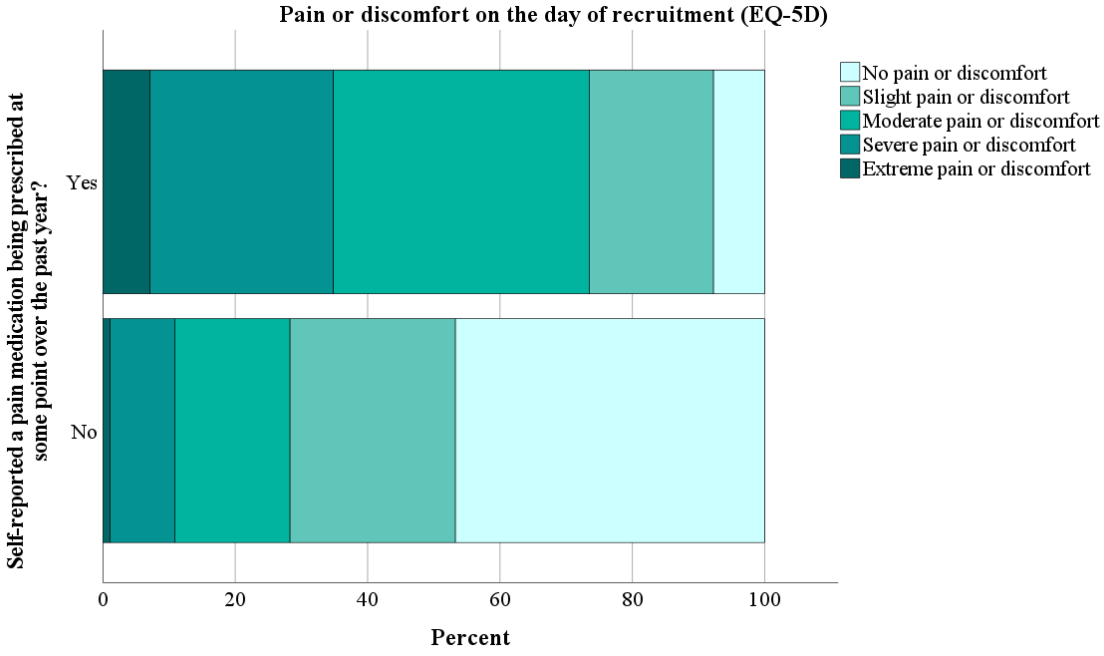
All participants self-reported pain in two ways on the cross-sectional survey; which sought pain on the day of recruitment (as assessed by the EQ-5D; "What best describes your pain/discomfort today?") and pain over the past week (as assessed by the IPOS; "How has pain affected you over the past week?"). Table 8.11 shows a high prevalence of pain amongst all participants, with moderate to extreme pain or discomfort on the day of recruitment reported by 56.8% of participants and moderate to overwhelming pain over the past week reported by 63.6% of participants.

A comparison between those who self-reported being prescribed a pain medication at some point over the past year and those who have not is also made in Table 8.11, and presented graphically in Figure 8-3. The distribution of the EQ-5D scores for pain and discomfort were different between the two groups (U = 3255.5, p = <0.013, *r* = -.47), with those that self-reported being prescribed a pain medication at some point over the past year having worse pain on the day of recruitment. The distribution of IPOS scores for pain were also unequal between the two groups (Mann-Whitney U test z = - 6.95, p = < 0.013, *r* = -.44), with those self-reporting being prescribed a pain medication being in worse pain over the past week. These differences in self-reported pain for both pain on day of recruitment and over the past week are highly statistically significant.

Table 8.11 Comparison of self-reported pain, by report of any pain medication prescribed

	All participants (n=247)	Self-reported pain medication prescribed over the past year?		Mann-Whitney U test
		Yes (n=155)	No (n=92)	
Pain on day of recruitment (EQ-5D-5L) n (%)				
Median EQ-5D pain score (IQR)	3 (2 – 4)	3 (2 – 4)	2 (1 – 3)	U = 3255.5 z = -7.36 **p = 0.000** *r* = -.47[a] *n* = 247
1 – No pain or discomfort	55 (22.3)	12 (7.7)	43 (46.7)	
2 – Slight pain or discomfort	52 (21.1)	29 (18.7)	23 (25.0)	
3 – Moderate pain or discomfort	76 (30.8)	60 (38.7)	16 (17.4)	
4 – Severe pain or discomfort	52 (21.1)	43 (27.7)	9 (9.8)	
5 – Extreme pain or discomfort	12 (4.9)	11 (7.1)	1 (1.1)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Pain over the past seven days (IPOS) n (%)				
Median IPOS pain score (IQR)	2 (1 – 3)	2 (2 – 3)	1 (0 – 2)	U = 3437.0 z = -6.95 **p = 0.000** *r* = -.44[a] *n* = 246
0 – Not at all	54 (21.9)	13 (8.4)	41 (44.6)	
1 – Slightly	35 (14.2)	17 (11.0)	18 (19.6)	
2 – Moderately	74 (30.0)	57 (36.8)	17 (18.5)	
3 – Severely	74 (30.0)	60 (38.7)	14 (15.2)	
4 – Overwhelming	9 (3.6)	8 (5.2)	1 (1.1)	
Missing	1 (0.4)	0 (0.0)	1 (1.1)	

Abbreviations: EQ-5D-5L EuroQoL 5 Dimensions – 5 Levels, *IPOS* Integrated Palliative care Outcome Scale, *IQR* Interquartile range. [a]A significant difference with an effect size ≥ Cohen's definition of "medium"



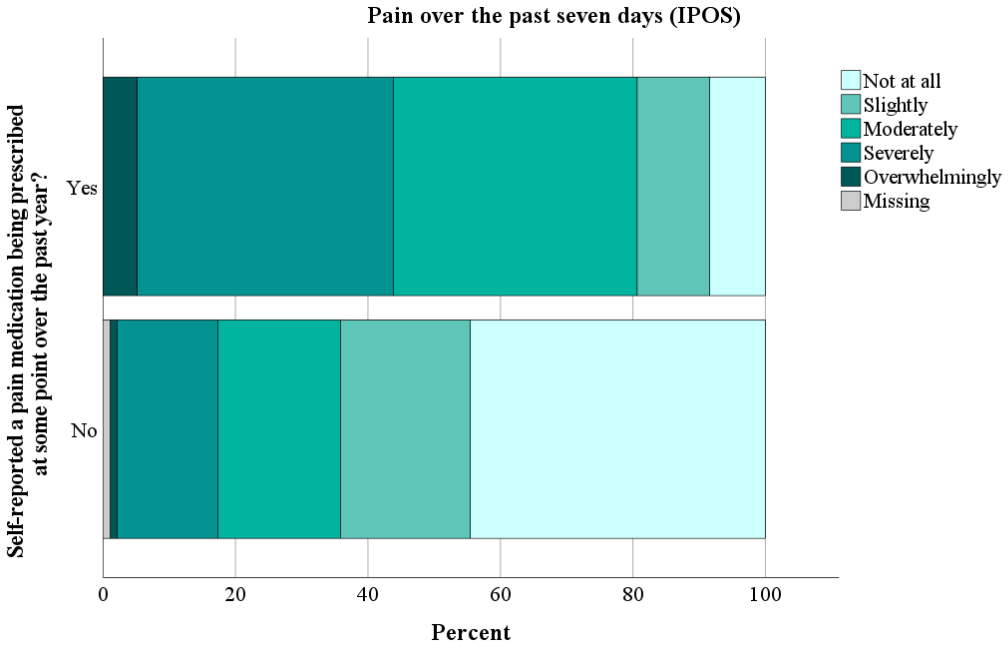


Figure 8-3 Prevalence of pain on day of recruitment and over the past seven days, as identified by the EQ-5D and IPOS

Participants who self-reported being prescribed a pain medication at some point over the past year were also asked to report on their experience of pain over the past year (see Table 8.12). Of the 155 participants, 142 (91.6%) reported experiencing moderate to severe pain over the past year. Additionally, 147 participants (94.8%) reported having pain for three months or more, with only four (2.6%) experiencing pain for less than months. Data on duration of pain was missing for four participants (2.6%).

Table 8.12 Pain over the past year for participants who self-reported being prescribed a pain medication at some point over the past year

Pain over the last year n (%)	Self-reported being prescribed a pain medication at some point over the past year (n=155)
A little pain	13 (8.4)
Moderate pain	74 (47.7)
Severe pain	57 (36.8)
Overwhelming pain	11 (7.1)
Missing	0 (0.0)

8.2.2.3 Pain experienced by participants

The following tables and figure (Table 8.13, Table 8.14 and Figure 8-4) provide a summary of pain participants experienced, as documented during their ICC clinical assessment. Table 8.13 groups the types of pain experienced by participants using the free-text answers from the clinical assessment; first, by all participants, and second, by those who self-reported a pain medication at some point over the past year and those who have not. Pain was categorised by location, diagnosis, related to a procedure (i.e. post-surgical) or as generalised pain. The most common pain experienced for all participants were osteoarthritic (26.7%), back (23.9%), hip (11.3%) and knee (10.5%). These were predominantly described as chronic issues. Pain was more common in those that self-reported being prescribed a pain medication at some point over the past year than those that did not.

Table 8.13 Pain experienced by participants, as assessed by the ICC team

Types of pain n (%)	All participants (N=247)	Self-reported a pain medication being prescribed over the past year?	
		Yes (n=155)	No (n=92)
Pain noted at assessment by location			
Back and/or sciatic pain	61 (24.7)	51 (32.9)	10 (10.9)
Hip pain	28 (11.3)	20 (12.9)	8 (8.7)
Knee pain	26 (10.5)	19 (12.3)	7 (7.6)
Shoulder pain	18 (7.3)	14 (9.0)	4 (4.3)
Leg pain	15 (6.1)	14 (9.0)	1 (1.1)
Facial/neck pain and/or headaches	15 (6.1)	8 (5.2)	7 (7.6)
Blister or ulcer pain	6 (2.4)	6 (3.9)	0 (0.0)
Ankle/foot pain	7 (2.8)	4 (2.6)	3 (3.3)
Wrist/hand pain	4 (1.6)	3 (1.9)	1 (1.1)
Arm pain	2 (0.8)	2 (1.3)	0 (0.0)
Chest pain	2 (0.8)	2 (1.3)	0 (0.0)
Groin pain	2 (0.8)	2 (1.3)	0 (0.0)
Pain noted at assessment from diagnosis or procedure			
Osteoarthritic pain	66 (26.7)	54 (34.8)	12 (13.0)
Neuropathic pain	10 (4.0)	10 (6.5)	0 (0.0)
Rheumatoid arthritis pain	8 (3.2)	7 (4.5)	1 (1.1)
Phantom pain	3 (1.2)	3 (1.9)	0 (0.0)
Amputation site pain	2 (0.8)	2 (1.3)	0 (0.0)
Claudication	2 (0.8)	1 (0.6)	1 (1.1)
Gout	2 (0.8)	2 (1.3)	0 (0.0)

Fibromyalgia	1 (0.4)	1 (0.6)	0 (0.0)
Hernia	1 (0.4)	0 (0.0)	1 (1.1)
Necrosis	1 (0.4)	0 (0.0)	1 (1.1)
Post-surgical pain	1 (0.4)	1 (0.6)	0 (0.0)
Generalised pain noted at assessment			
Aches and pains	6 (2.4)	2 (1.3)	4 (4.3)
Multiple joint pain	5 (2.0)	5 (3.2)	0 (0.0)
Cramps	4 (1.6)	1 (0.6)	3 (3.3)
No sources of pain noted at assessment			
No sources of pain	57 (23.1)	14 (9.0)	43 (46.7)
No sources of pain recorded at assessment			
Missing	1 (0.4)	0 (0.0)	1 (1.1)

Second, the clinical summary was used to quantify the types of pain participants experienced (e.g. one type of pain documented or more). The median (IQR) types of pain experienced for all participants was 1 (1-2), see Table 8.14 and a graphical representation Figure 8-4 by those who were prescribed a pain medication at some point over the past year and those who were not. This figure illustrates that the majority (77.4%) of those who self-reported being prescribed a pain medication had one or two different types of pain; with a smaller number of participants experiencing three or four types of pain. Some (9%) had no pain. The majority (47.3%) of those who self-reported no pain medication being prescribed had no pain, followed by one source of pain (37.4%). Fewer participants (15.4%) in this group experienced two or more different sources of pain.

Table 8.14 Median number of the types of pain experienced

	N	Median	IQR	Range	Missing data
Sources of pain	247	1	1 – 2	0 – 4	1

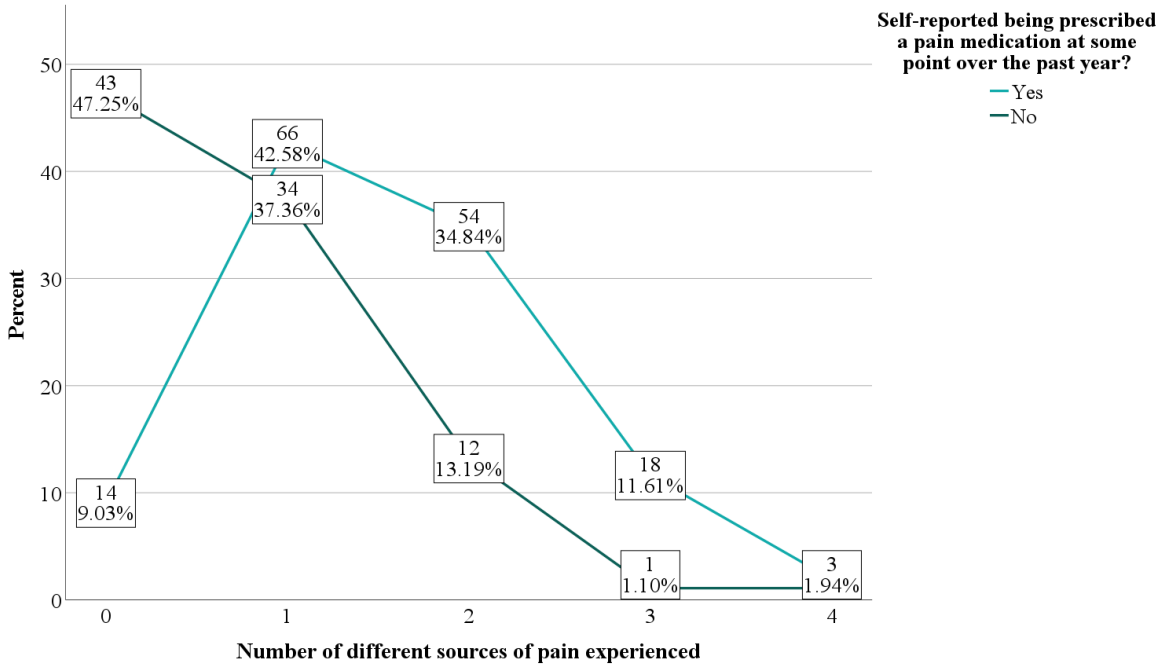


Figure 8-4 Number of different sources of pain experienced, by report of any pain medication prescribed

8.2.3 Proportion of participants with an opioid prescription documented on their medical record at some point over the past year (Research question 3)

The proportion of participants that were found to have an opioid prescription on their medical record at some point over the past year are presented in **Error! Reference s ource not found.**. There was no access to prescription data for 24 (9.7%) of the 247 participants. Of 223 participants with prescription data, over half (57.4%; 95% CI [45.8%, 58.2%]) were found to have an opioid prescription on their medical record over the past year.

Table 8.15 Proportion of participants who had an opioid prescription documented on their medical record at some point over the past year (n=223)

Opioid prescription documented on medical record at some point over the past year	N (%)
Opioid prescription present	128 (57.4)
Opioid prescription not present	95 (42.6)

8.2.4 Description of changes made to participants' pain medications following a medication review at the ICC (Research question 4)

Recommended changes to pain medications following clinical assessment and a medication review at the ICC (conducted at the time of recruitment) were extracted from medical records (including opioid and non-opioid analgesics) as it was considered important to understand the appropriateness of pain medications prescribed to older adults to improve their care. Some of the non-opioid adjuvant analgesics discussed in this section are not primarily recognised as analgesic in nature; however, recommendations in these instances were documented in relation to managing pain.

Of 247 participants, 260 recommended changes to pain medications were noted for 130 (52.6%) participants. The median [IQR] number of recommended changes regarding pain medication was 1 [1–3]. 85 (32.7%) of the 260 recommended changes were related to opioid analgesics, with the remaining 175 relating to non-opioid analgesics. 46 participants had recommended changes to both an opioid analgesic and a non-opioid analgesic.

In terms of the types of changes that were recommended; 86 participants were started on a new pain medication, 34 participants had a pain medication dose increased, 20 participants had a pain medication dose decreased, 59 participants had a pain medication stopped and 18 participants' repeat prescriptions for pain medication were amended.

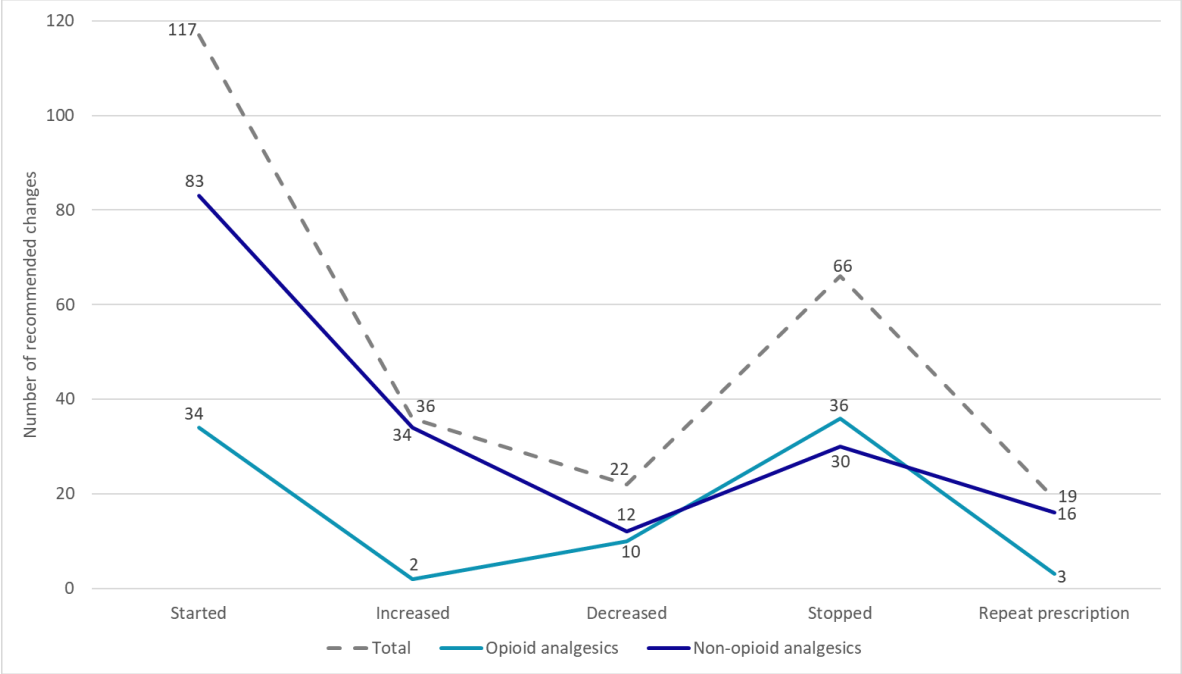


Figure 8-5 Number of recommendations to pain medications

Recommendations regarding starting a pain medication

Of the 260 recommended changes to pain medication, 117 (45.0%) related to starting a new pain medication. Most of the pain medications started were non-opioid analgesics, with under a third of recommendations involving an opioid. The main pain medication recommended was paracetamol (n=63; 73.3%), including water-soluble paracetamol. Of these, 22 participants were recommended a combination of paracetamol and an opioid (i.e. predominantly buprenorphine and codeine). While, 6 participants were recommended a combination of paracetamol and another non-opioid analgesic (i.e. predominantly NSAID gel). Other recommendations were made in relation to only starting the following non-opioid analgesics; capsaicin cream (n=2), duloxetine (n=1), gabapentin (n=1), NSAID gel (n=6) and pregabalin (n=1). Sole recommendations for starting opioids often steered towards transdermal patches buprenorphine (n=8) compared to those administered orally.

Recommendations regarding increasing a pain medication

36 (13.8%) recommendations were made in relation to increasing pain medication dose . As with recommendations for starting, most recommendations for increasing pain medication dose were for non-opioid analgesics, with 5% relating to an increasing an opioid. Increases to pain medication were most frequently made for paracetamol (n=27).

Recommendations regarding decreasing a pain medication

22 (8.5%) recommendations were made to decrease dose for pain medications. The recommended changes for decreasing pain medications were more evenly spread between non-opioid analgesics (54.5%) and opioids (45.5%) compared to changes made in relation to starting and increasing pain medications. Decreases were predominantly made to codeine, duloxetine and immediate release tramadol.

Recommendations regarding stopping a pain medication

66 (25.4%) recommended changes were made to stop pain medications. Marginally more recommended changes were made to opioids than non-opioid analgesics in relation to stopping. For opioid analgesics, it was predominantly recommended that co-codamol (n=21) was stopped. Non-opioid analgesics recommended for stopping were mostly related to amitriptyline, ibuprofen and naproxen (n=5).

Recommendations to amend a repeat template regarding a pain medication

Recommendations were also made in regards to participants repeat prescriptions, where 19 (17.3%) recommended changes were suggested. The recommended changes were mostly in relation to non-opioid analgesics, with just over 15% relating to opioids. Predominantly, changes to the repeat template were suggested in relation to paracetamol (n=10).

Reasons for recommendations

The reasons for these recommendations were also extracted to provide the context for why changes were recommended, and are summarised in Table 8.16. Multiple reasons were often provided in relation to each recommended change. The most common reasons, spanning the different types of changes (i.e. starting, increasing, decreasing,stopping and repeat template), were optimising and rationalising pain relief, as well as, minimising potential risks and managing adverse effects participants reported during their assessment/medication review. In relation to these reasons, the route of administration (i.e. uniform delivery and bypassing the digestive system), reducing the use of or separating combined pain medications (e.g. co-codamol), increasing the use of paracetamol, and reducing the use of ibuprofen were often

considerations behind optimising and rationalising pain medication, and minimising potential risks of harm.

Modified-release opioid analgesics and water-soluble paracetamol were considered useful in aiding compliance, with fewer tablets to take and that they were easier to swallow, respectively. Non-opioid adjuvant analgesics, such as duloxetine, were considered for the dual purposes of improving pain and mood.

Table 8.16 Reasons for recommended changes, by the type of change

Type of change	Reasons for recommended change (ordered by commonness)
Started	- Optimise and rationalise pain relief (n=79) - Improving compliance, mood or mobility (n=7) - Reduce possible risks and adverse effects (n=6) - In response to declining cognition (n=1) - Providing more uniform delivery (n=1)
Increased	- Optimise and rationalise pain relief (n=32) - Fitting in with other medication administration schedules (n=1) - Improving mobility (n=1) - Improving utilisation of pain medication (n=1) - Reducing possible risks and adverse effects (n=1)
Decreased	- Reducing possible risks and adverse effects (n=14) - Optimise and rationalise pain relief (n=10)
Stopped	- Reducing possible risks and adverse effects (n=39) - Optimising and rationalising pain medication (n=17) - No benefit noted (n=6) - Reducing medication burden (n=6) - Aid compliance (i.e. changing route of administration) (n=3) - Pain medication was not being utilised (n=3) - Avoid unnecessary medication (n=2) - Patient not keen on taking pain medications (n=2) 2 - In response to declining cognition (n=1) - Issued for acute management and no longer needed (n=1) -
Repeat template	- Ensure that repeat templates were kept up-to-date 3 - Amending re-order quantities 5 - Adding pain medications to the repeat template 4 - Adding pain medications to a dose-based medication box or system 3 - Removing pain medications that are no longer taken 2, 2, 1, 1, 1 - Avoiding pain medication waste 1

Note. Multiple reasons were listed in some instances.

Reviewing pain medications

Participants who self-reported being prescribed a pain medication over the past year were asked "How often are your pain and pain medications reviewed?" Of the 155 participants, pain medication was reviewed more than once a year for 34 (21.9%), annually for 30 (19.4%) or as and when needed/requested for 8 (5.2%). Whilst, pain medication had never been reviewed for 49 (31.6%) participants or over a year ago for nine (5.8%) participants. Nine (5.8%) participants expressed that their medications were reviewed infrequently (without inclusion of a time marker), 12 (7.7%) were unsure when their pain medication was last reviewed, two (1.3%) did not perceive a pain medication review as necessary and one (0.6%) was unable to comment as they were only issued pain medication within the past three months. Data was missing for one (0.6%) participant.

8.2.5 Proportion of participants who self-reported an opioid analgesic amongst those who reported being prescribed a pain medication (Research question 5)

Table 8.17 reports the proportion of participants who self-reported being prescribed an opioid analgesic amongst those who were prescribed a pain medication at some point over the past year. Of the 155 participants, the majority (65.8%; 95% CI [58.5%, 73.5%]) self-reported being prescribed an opioid analgesic. 70 participants who reported being prescribed an opioid analgesic also reported being prescribed a non-opioid analgesic. 53 participants reported being prescribed only non-opioid analgesics at some point over the past year.

Table 8.17 Proportion of participants who self-reported being prescribed an opioid analgesic at some point over the past year (n=155)

	N (%)
Opioid prescribed over the past year?	
Yes	102 (65.8%)
No	53 (34.2%)

When asked what pain medications they had been prescribed over the past year, they reported a median (IQR) of 2 (1–2) different pain medications (including opioid and non-opioid analgesics). The medications listed by patients were perceived to be adjuvant analgesics. A summary of the types of analgesia participants reported are presented in Table 8.18. Codeine, morphine and tramadol were commonly reported opioid analgesics. Paracetamol was a commonly reported non-opioid analgesic. Participants also reported using medications not commonly used as analgesic adjuvants (e.g. duloxetine) or disease-modifying medications (e.g. methotrexate).

Table 8.18 Summary of pain medications self-reported by 155 participants who reported a pain medication at some point over the past year

Pain medication n (%)	Prescribed a pain medication at some point over the past year (n=155)
Opioid analgesics	
Codeine	59 (57.8)
Tramadol	21 (20.6)
Morphine	18 (17.6)
Dihydrocodeine	7 (6.9)
Buprenorphine (Patch)	6 (5.9)
Oxycodone	5 (4.9)
Fentanyl (Patch)	2 (2.0)
Meptazinol	2 (2.0)
Adjuvants/non-opioid analgesics	
Paracetamol	94 (50.0)
Gabapentin	12 (7.8)
Amitriptyline	11 (5.9)
Pregabalin	9 (6.9)
Ibuprofen	7 (3.9)
NSAID topical gel	7 (3.9)
Naproxen	6 (2.9)
Capsaicin	4 (2.9)
Corticosteroids	3 (2.9)
Diclofenac	2 (2.0)
Duloxetine	2 (1.0)
Nitroglycerin spray	2 (0.0)
Nortriptyline	2 (1.0)
Abatacept	1 (0.0)
Allopurinol	1 (0.0)
Celebrex	1 (0.0)
Etoricoxib	1 (1.0)
Methotrexate	1 (0.0)
Rizatriptan	1 (1.0)

8.2.6 Adverse effects self-reported by participants who reported being prescribed a pain medication over the past year (Research question 6)

8.2.6.1 Freely recalled adverse effects from pain medication over the past year

In relation to the pain medications listed in Table 8.18, participants were asked as part of the survey "Have your pain medications caused you any problems (i.e. side effects)? If so, what problems have they caused?" Data for this question was missing for 19 of the 155 participants. Of the 136 participants with available data, 27 participants freely recalled 37 specific adverse effects that they attributed to pain medication (including opioids, non-opioid analgesics or both). A further 18 participants, had indicated that their pain medication had caused them adverse effects, but did not specify these in the survey. Table 8.19 focuses on the participants who self-reported using an opioid at some point over the past year (n=23). Of which, 11 participants reported a cognitive adverse effect. One other participant declared one adverse effect of unknown origin (i.e. headache), that may or may not have been caused by pain medication. Four of the 27 participants who freely recalled an adverse effect reported only being prescribed a non-opioid analgesic at some point over the past year. These four participants reported issues with drowsiness (n=2), headache (n=1) and gum problems (n =1) that they attributed to pain medications, which are not reported in the table below. Overall, the median number of adverse effects attributed to pain medication(s) was zero (range 0–3).

Table 8.19 Summary of freely recalled adverse effects attributed to pain medication in 23 participants self-reported using an opioid at some point over the past year

	Pain medication *n*	Unknown cause *n*	Cumulative *n*
Constipation	9	0	9
Drowsiness	6	0	6
Hallucinations	3	0	3
Nausea	3	0	3
Headache	1	1	3
Dizziness	1	0	1
Dry mouth	1	0	1
Electrical impulses	1	0	1
Falls	1	0	1
Floating	1	0	1
Gastrointestinal issues	1	0	1
Internal bleeding	1	0	1
Low mood	1	0	1

Sleepiness	1	0	1
Slurred speech	1	0	1
Sweating	1	0	1
Twitching	1	0	1
Total	**32**	**1**	**33**

Note. 17/23 participants self-reported both an opioid analgesic and non-opioid analgesics at some point over the past year.

Overall, the most commonly reported adverse effects attributed to pain medication were constipation (n=9) and drowsiness (n=6), followed by hallucinations (n=3) and nausea (n=3). Other adverse effects were listed but were not as frequently reported. More adverse effects were declared in participants who reported being prescribed an opioid analgesic at some point over the past year (including the 17 participants who also reported a non-opioid analgesic) than those who self-reported non-opioid analgesics only.

For those prescribed an opioid analgesic at some point over the past year (n=23), adverse effects may have been attributed to the following; codeine (including combined preparations) (n=15), tramadol (n=6), morphine (n=5), buprenorphine (n=1), co-dydramol (n=1) and oxycodone (n=1). Five were prescribed more than one opioid over the past year. Of the 17 participants also prescribed a non-opioid analgesic freely recalled adverse effects could have also been attributed to paracetamol (n=12), gabapentin (n=2), cortisone injections, naproxen (n=2), pregabalin (n=2), amitriptyline (n=2), capsaicin cream (n=1) and ibuprofen (n=1). Seven were prescribed more than one non-opioid analgesic.

For the four participants who reported being prescribed non-opioid analgesics only at some point over the last year, adverse effects may have been attributed to amitriptyline (n=2), naproxen (n=2), paracetamol (n=2), abatacept (n=1) and celebrex (n=1). Three participants reported being prescribed more than one non-opioid analgesic.

8.2.6.2 Adverse effects from pain medications over the past year when prompted

Participants were then asked about a list of common adverse effects that can arise from pain medication (see Figure 8-6).

11) Have your painkillers caused you any problems with the following? *Please tick all that apply.*

	Yes	No		Yes	No
Nausea (feeling sick)	☐	☐	Drowsiness/sleepiness	☐	☐
Vomiting (being sick)	☐	☐	Constipation	☐	☐
Memory	☐	☐	Fitting	☐	☐
Confusion	☐	☐	Falls	☐	☐
Attention/concentration	☐	☐	Headaches	☐	☐
Seeing or hearing things that are not present	☐	☐	Other	☐	☐

If other, please state: _____

Figure 8-6 List of common adverse effects that can arise from pain medication presented in the survey

In answer to this prompt, participants were able to identify more adverse effects that they directly attributed to their pain medication, as well as, more adverse effects that were potentially caused by their pain medications. Participants were also asked to consider any other adverse effects attributed to pain medication that had not been captured in the list. This led some to repeat the adverse effects freely recalled in response to the previous free-text question but also the identification of other adverse effects that had not been covered previously (either in the free-text or list of common adverse effects). Some data was missing for some of the common adverse effects listed, as either the 'Yes' or 'No' box were not checked, especially when participants were asked about any other adverse effects that had not been listed. Table 8.20 presents a summary of the adverse effects that were either attributed to or possibly caused by pain medications when prompted using the list of common adverse effects.

Table 8.20 Summary adverse effects directly attributed or potentially caused by pain medication when prompted using a list of common adverse effects, by pain medication type

Adverse effects	Self-reported an opioid analgesic at some point over the past year (n=57)[a]		Self-reported non-opioid analgesic only at some point over the past year (n=15)[b]		Cumulative *n*
	Pain medication *n*	Unknown cause *n*	Pain medication *n*	Unknown cause *n*	
Constipation	36	2	4	2	44
Drowsiness	33	1	8	0	42
Attention and concentration	17	0	3	1	21
Confusion	14	2	2	1	19
Memory	11	4	2	1	18
Headaches	12	0	2	0	14
Nausea	8	1	3	0	12
Falls	8	1	1	1	11
Hallucinations	5	1	3	0	9
Vomiting	4	1	0	0	5
Fitting	1	0	1	0	2
Total	**149**	**13**	**29**	**6**	**197**

[a] 42/57 of those who reported using an opioid also reported being prescribed a non-opioid analgesic at some point over the past year. 3/57 participants only reported adverse effects that they were unsure were caused by their pain medications. [b] 2/15 only reported adverse effects that they were unsure were caused by non-opioid analgesics.

The median number of adverse effects attributed to pain medications was zero (range 0–8). Overall, 67/72 participants reported 178 specific adverse effects that they attributed directly to their pain medications. Of which, 9 participants also reported that their pain medications may have caused other adverse effects identified in the list. Overall, there were five participants that did not attribute any of the adverse effects listed directly to their pain medication.

The most common adverse effects attributed to pain medication remained constipation (n=40) and drowsiness (n=41), but this time, were followed by issues with attention and concentration (n=20), confusion (n=16), memory (n=13), headaches (n=14), nausea (n=11), falls (n=9), hallucinations (n=8) and vomiting (n=4). Other adverse effects were acknowledged but not reported as often. Memory (n=5), constipation (n =4, and confusion (n=3) were the most commonly reported adverse effects of unknown origin. Overall, 46 participants directly attributed a listed cognitive adverse effect to their pain medications. Of which, four also expressed that they experienced another type of cognitive adverse effect potentially caused by their pain medications. Three additional

participants were unsure whether their pain medications caused any of the cognitive adverse effects listed.

Again, more adverse effects were declared in those who had been prescribed an opioid analgesic at some point over the past year. In those who reported an opioid analgesic, the 57 participants that attributed adverse effects to directly to the pain medication listed the following opioids: codeine (n=32), morphine (n=15), tramadol (n=13), dihydrocodeine (n=4), oxycodone (n=4), buprenorphine (n=2) and fentanyl (n=1). Fifteen reported being prescribed more than one opioid over the past year. 42 of the 57 participants were also prescribed a non-opioid analgesic. Adverse effects could have also been attributed to paracetamol (n=32), gabapentin (n=7), amitriptyline (n=4), ibuprofen (n=3), naproxen (n=3), cortisone injections (n=2), pregabalin (n=2), topical NSAID gel (n=2), capsaicin cream (n=1), duloxetine (n=1) and diclofenac (n=1). Of these, 13 participants were prescribed more than one non-opioid analgesic over the past year. For the 13 participants who reported being prescribed non-opioid analgesics, adverse effects could have also been directly attributed to paracetamol (n=9), amitriptyline (n=5), naproxen (n=2), pregabalin (n=2), abatacept (n=1), celebrex (n=1), nortriptyline (n=1) and topical NSAID gel (n=1). Seven of these participants were on more than one non-opioid analgesic.

Eleven participants provided an answer for ‘other’ adverse effects experience that they attributed to their pain medications when prompted . Of which, ten participants had been prescribed an opioid at some point over the past year;nine of which had also been prescribed a non-opioid (predominantly paracetamol or amitriptyline). One participant reported being prescribed non-opioids only (i.e. paracetamol, amitriptyline and pregabalin). Adverse effects included diarrhoea (n=2), fuzziness (n=2), delirium (n=1), dizziness (n=1), electrical impulses (n=1), grogginess (n=1), low mood (n=1), migraine with aura (n=1), muscle weakness and heaviness (n=1), and sleepiness (n=1). One participant repeated their free-text answer of electrical impulses. All other adverse effects had not been reported previously. A number of terms were used to describe cognitive adverse effects. Notably, one participant expressed that the grogginess they experienced was not perceived negatively.

8.2.7 Does HRQoL differ between those who self-reported cognitive adverse effects from pain medications and those that did not, and what factors are associated with cognitive adverse effects (Research question 7)

8.2.7.1 Does HRQoL differ between those who self-reported cognitive adverse effects from pain medications and those that did not

For those that attributed a cognitive adverse effect to pain medication and those that did not, a more detailed statistical comparison of HRQoL is presented (see Table 8.21, Table 8.22 and Table 8.23). The list of common adverse effects was predominantly used to determine the number of participants with cognitive adverse effects and supplemented by answers from the free-text questions. To allow for multiple (seven) comparisons, the Bonferroni correction is used, so that a p-value threshold of 0.007 (0.05/7), rather than 0.05 is sought.

Prevalence of reported problems

All participants, except two, reported problems on at least one of the EQ-5D-5L dimensions. One participant from each group, as shown in Table 8.21, reported a health profile of '11111' across the domains (i.e. no problems reported). Among the 155 participants, there were 101 unique health profiles. One participant was missing data from the 'mobility' domain, meaning that a full health profile or global HRQoL score could not be determined. Problems at the most severe (level 5) and next to worst (level 4) severity level for one or more dimensions were reported by 34 participants and 79 participants, respectively.

Table 8.21 Distribution of EQ-5D-5L dimension responses, by presence of a cognitive adverse effects attributed to pain medications prescribed at some point over the past year

Dimensions	All participants (n=155)	Cognitive adverse effect attributed to pain medication over the past year?		Statistics comparing (a) and (b)
		(a) Yes (n=48) n (%)	(b) No (n=107) n (%)	
Mobility				
1 - No problems	16 (10.3)	6 (12.5)	10 (9.3)	χ^2 (4) = 5.69 p = 0.22 Φ = 0.19 n = 154
2 - Slight problems	28 (18.1)	7 (14.6)	21 (19.6)	
3 - Moderate problems	50 (32.3)	11 (22.9)	39 (36.4)	
4 - Severe problems	51 (32.9)	18 (37.5)	33 (30.8)	
5 - Unable to walk	9 (5.8)	5 (10.4)	4 (3.7)	
Missing	1 (0.6)	1 (2.1)	0 (0.0)	
Self-care				
1 - No problems	89 (57.4)	21 (43.8)	68 (63.6)	χ^2 (4) = 12.22 p = 0.02 Φ = 0.28 n = 155
2 - Slight problems	30 (19.4)	9 (18.8)	21 (19.6)	
3 - Moderate problems	25 (16.1)	10 (20.8)	15 (14.0)	
4 - Severe problems	7 (4.5)	5 (10.4)	2 (1.9)	
5 - Unable to wash/dress	4 (2.6)	3 (6.3)	1 (0.9)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Usual activities				
1 - No problems	33 (21.3)	7 (14.6)	26 (24.3)	χ^2 (4) = 5.85 p = 0.21 Φ = 0.19 n = 155
2 - Slight problems	32 (20.6)	10 (20.8)	22 (20.6)	
3 - Moderate problems	43 (27.7)	12 (25.0)	31 (29.0)	
4 - Severe problems	28 (18.1)	9 (18.8)	19 (17.8)	
5 - Unable to do usual activities	19 (12.3)	10 (20.8)	9 (8.4)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Pain or discomfort				
1 - No pain or discomfort	12 (7.7)	2 (4.2)	10 (9.2)	χ^2 (4) = 3.52 p = 0.48 Φ = 0.15 n = 155
2 - Slight pain or discomfort	29 (18.7)	12 (25.0)	17 (15.9)	
3 - Moderate pain or discomfort	60 (38.7)	16 (33.3)	44 (41.1)	
4 - Severe pain or discomfort	43 (27.7)	15 (31.3)	28 (26.2)	
5 - Extreme pain or discomfort	11 (7.1)	3 (6.3)	8 (7.5)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Anxiety or depression				
1 - Not anxious or depressed	79 (51.0)	20 (41.7)	59 (55.1)	χ^2 (4) = 5.70 p = 0.22

2 - Slightly anxious or depressed	35 (22.6)	12 (25.0)	23 (21.3)	Φ = 0.19 *n* = 155
3 - Moderately anxious or depressed	24 (15.5)	11 (22.9)	13 (12.1)	
4 - Severely anxious or depressed	11 (7.1)	2 (4.2)	9 (8.4)	
5 - Extremely anxious or depressed	6 (3.9)	3 (6.3)	3 (2.8)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	

Abbreviations: EQ-5D-5L EuroQoL, *IQR* Interquartile range. *Degrees of freedom* presented in brackets. Φ = effect size (Phi coefficient or Cramer's V).

In total, most problems were reported in the 'pain or discomfort' dimension, where 73.5% of participants reported level 3 problems or worse. This was followed by problems in the 'mobility' (71%) and 'usual activities' (58.1%) dimensions. Less problems were reported in regards to 'anxiety or depression' (26.5%) and 'self- care' (23.2%) for level three problems or worse. Those who attributed cognitive adverse effects to pain medications had a higher prevalence of problems (considering severity levels 2 to 5) for all dimensions, except for 'mobility'. The association between whether participants attributed cognitive adverse effects to pain medications and the 'self-care' dimension reached statistical significance at the 5% level, but were not deemed to have a statistically significant relationship after the Bonferroni correction was applied. There was no significant relationship between attributing a cognitive adverse effect to pain medications and the other dimensions.

Self-rated health on day of recruitment

There was a small difference in self-rated health on the day of recruitment, with those who attributed a cognitive adverse effect to pain medication reporting a lower median score (i.e. 50) than those who did not (i.e. 60). This reaches significance at the 5% level but not after the Bonferroni correction.

Table 8.22 Self-rated health on day of recruitment, by presence of a cognitive adverse effects attributed to pain medications prescribed at some point over the past year

Self-rated health using EQ-5D-5L VAS	All participants (N=155)	Cognitive adverse effect attributed to pain medication over the past year?		Mann Whitney U test
		Yes (n=48) n (%)	No (n=107) n (%)	
Median [IQR]; (Range)	60 [50 – 80]; (15 – 100)	50 [45 – 70]; (20 – 100)	60 [50 – 80]; (15 – 100)	U = 2013.5 z = -2.17 p = 0.03 *r* = 0.17 *n* = 155
Missing	0 (0.0)	0 (0.0)	0 (0.0)	

Abbreviations: VAS Visual analogue scale, *IQR* Interquartile range. *Degrees of freedom* presented in brackets. Scored from 0 (i.e. worst health they can imagine) to 100 (i.e. best health they can imagine).

Health utility scores

In Table 8.23, the utility score for HRQoL is compared. The utility score shows a slightly lower median score of 0.56 for those who attributed cognitive adverse effects to pain medication compared those that did not (i.e. 0.62). The difference did not reach statistical significance.

Table 8.23 Health utility of participants, by presence of a cognitive adverse effects attributed to pain medications prescribed at some point over the past year

Health utility score	All participants (n=155)	Cognitive adverse effect attributed to pain medication over the past year?		Mann Whitney U test
		Yes (n=48) n (%)	No (n=107) n (%)	
Median [IQR]; (Range)	0.60 [0.36 – 0.78] (-0.18 – 1.00)	0.56 [0.27 – 0.71]; (-0.18 – 1.00)	0.62 [0.43 – 0.81]; (0.01 – 1.00)	U = 2104.0 z = -1.61 p = 0.11 *r* = 0.13 *n* = 154
Missing	1 (0.6)	1 (2.2)	0 (0.0)	

Abbreviations: IQR Interquartile range. *Degrees of freedom* presented in brackets. *Scoring*: Full health has a value of 1 and dead has a value of 0.

8.2.7.2 Factors associated with participants self-reporting cognitive adverse effects

To understand who is at higher risk of experiencing cognitive adverse effects from pain medication use, a logistic regression analysis was run. The dependent outcome was a

binary measure of the self-reported cognitive adverse effects attributed to pain medications prescribed at some point over the past year (i.e. presence or absence of a cognitive adverse effect). Table 8.24 shows the descriptive statistics for the candidate predictors for all participants, and how they vary by the outcome variable. Original continuous data for average daily dose of opioid analgesics over the past year followed a lognormal distribution (i.e. right-skewed); where a number of participants were found either to have not been prescribed opioid analgesics or received few prescriptions over the past year, but some had been prescribed multiple prescriptions/high daily doses. Therefore, a log transformation was used to reduce the skewness of the original data for this variable. Further details of how candidate predictors were selected and model diagnostics can be found in Appendix 9.

Table 8.24 Descriptives statistics for candidate predictors

Predictors	All participants (n=155)	Presence or absence of a self-reported cognitive adverse effect	
		Present (n=48)	Absent (n=107)
Age			
Median (IQR)	81 (74 – 85)	80 (72 – 84.8)	81 (76 – 86)
Missing n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Gender n (%)			
Male	56 (36.1)	11 (22.9)	45 (42.1)
Female	99 (63.9)	37 (77.1)	62 (57.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Average daily dose over the past year (in OME)			
Median (IQR)	1.8 (0.0 – 16.4)	2.1 (0.3 – 18.3)	1.8 (0.0 – 16.2)
Missing n (%)	12 (7.7)	1 (2.1)	11 (10.3)
Anticholinergic burden score n (%)			
Two or less	99 (63.9)	30 (62.5)	69 (64.5)
Three or more	50 (32.3)	18 (37.5)	32 (29.9)
Missing	6 (3.9)	0 (0.0)	6 (5.6)

The logit odds estimate and standardised odds ratio estimates with 95% confidence intervals for the final model are presented in Table 8.25. Due to missing data, 143 participants were included. The prevalence of the outcome was 32.9%. Being female was significantly associated with increased odds of reporting a cognitive adverse effect from pain medication (OR: 2.91, 95% CI [1.30, 6.52]; p =.009). Increasing average daily dose (in OME) and an anticholinergic burden score of three or more were not found to be significantly associated with increased odds of the outcome being observed.

Although not significantly associated with reporting cognitive adverse effects, a protective relationship of lowering the odds for the outcome was observed with younger age. The model had a Nagelkerke's R^2 of 11.2%.

Table 8.25 Results of a logistic regression for the outcome 'self-reported cognitive adverse effect' for 143 participants

				Unadjusted			Adjusted		
Variable	**logit**	***SE***	**Wald *z***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Intercept	1.721	2.17	.630	-	-	-	-	-	.427
Age	-.043	.03	2.556	0.96	0.91, 1.01	.083	0.96	0.91, 1.01	.110
Gender	1.068	.41	6.734	2.44	1.13, 5.30	**.024**	2.91	1.30, 6.52	**.009**
Average daily dose (OME)[a]	.113	.12	.938	1.17	0.95, 1.44	.147	1.12	0.89, 1.41	.333
ACB score	.223	.42	.287	1.29	0.63, 2.66	.483	1.25	0.55, 2.83	.592

Abbreviations: SE Standard error, *OR* Odds ratio, *CI* Confidence interval, *P* p-value, *OME* oral morphine equivalent, *ACB* anticholinergic burden. *Note:* Figures in bold represent significant findings. Nagelkerke $R^2 = 0.112$. [a] Logarithm transformation.

The sensitivity and specificity of the model was also considered (see Table 8.26). The model demonstrated poor prediction of the outcome; only 17% of those predicted to have cognitive adverse effects actually had them observed. In terms of specificity, the model was better at predicting the proportion of people without cognitive adverse effects. 92.7% of those who were predicted to be free from cognitive adverse effects were found not to have self-reported cognitive adverse effects from pain medications. The positive predictive value (PPV) of the model was 53.3% and the negative predictive value (NPV) was 69.5%.

Table 8.26 Observed and predicted frequencies for self-reported cognitive adverse effects

	Predicted		
Observed	Yes	No	% Correct
Yes	8	39	92.7
No	7	89	17.0
Overall % correct			67.8

Note: Cut-off value = 0.50, Sensitivity = 8/(8+39)% =17.0%, Specificity = 89/(7+89)% = 92.7%, PPV = 8/(8+7)% = 53.3%, NPV is 89/(89+39)% = 69.5%.

8.2.8 Does HRQoL differ between those with an opioid prescription over the past year and to those that do not, and what factors are associated with having an opioid prescription (Research 9)

8.2.8.1 Does HRQoL differ between those with an opioid prescription over the past year and those that do not

In this section, a detailed comparison of HRQoL is presented for those who had an opioid prescription documented on their medical record at some point over the past year and those that did not (see Table 8.27, Table 8.28 and Table 8.29). To allow for multiple (seven) comparisons to be made on the data in this section, the Bonferroni correction is used, so that a p-value threshold of 0.007 (0.05/7), rather than 0.05 is sought. A comparison of demographical and clinical characteristics between those with an opioid prescription at some point over the past year and those that have not can be found in Appendix 14.

Prevalence of reported problems

Overall, 212 participants reported problems on at least one of the EQ-5D-5L health dimensions. 10 participants reported a health profile of '11111' (i.e. no problems reported), nine of which did not have an opioid prescribed on their medical record. Among the 223 participants, there were 122 unique health profiles. One participant was missing data from the 'mobility' domain, meaning that a full health profile or global HRQoL score could not be determined. Problems at the most severe (level 5) severity level for one of more dimensions were reported by 34 participants. Of which, 29 had an opioid documented on their medical record. Problems at the next to worst (level 4) severity level for one or more dimensions were reported for 98 participants. Again, these were predominantly reported amongst those who had an opioid prescription documented on their medical record (n=64; 65.3%).

Table 8.27 presents the distribution of EQ-5D-5L dimension responses. In total, most problems were reported in the 'mobility' dimension, where 62.3% of participants

reported level 3 problems of worse. This was followed by 'pain' (57.8%) and 'usual activities (49.3%). Less problems were reported in regards to 'anxiety or depression' (20.6%) and 'self-care' (21.5%). Those who had an opioid prescription documented on their medical record had a higher prevalence of problems (considering severity levels 2 to 5). The association for having an opioid documented and 'pain' reached statistical significance. Whilst, the association with 'mobility' and 'usual activities' dimensions reach statistical significance at the 5% level but not after the Bonferroni correction was applied. There were no significant relationships in terms 'self-care' or 'anxiety and depression'.

Table 8.27 Distribution of EQ-5D-5L dimension responses, by presence of an opioid prescription documented on their medical record at some point over the past year

Dimensions	All participants (n=223)	Opioid prescription prescribed at some point over the past year?		Statistics comparing (a) and (b)
		(a) Yes (n=128) n (%)	(b) No (n=95) n (%)	
Mobility				
1 - No problems	33 (14.8)	15 (11.7)	18 (18.9)	χ^2 (4) = 11.64 p = 0.020 Φ = 0.23 *n* = 222
2 - Slight problems	50 (22.4)	23 (18.0)	27 (28.4)	
3 - Moderate problems	66 (29.6)	37 (28.9)	29 (30.5)	
4 - Severe problems	64 (28.7)	44 (34.4)	20 (21.1)	
5 - Unable to walk	9 (4.0)	8 (6.3)	1 (1.1)	
Missing	1 (0.4)	1 (0.8)	0 (0.0)	
Self-care				
1 - No problems	137 (61.4)	74 (57.8)	63 (66.3)	χ^2 (4) = 2.43 p = 0.658 Φ = 0.10 *n* = 223
2 - Slight problems	38 (17.0)	24 (18.8)	14 (14.7)	
3 - Moderate problems	32 (14.3)	19 (14.8)	13 (13.7)	
4 - Severe problems	11 (4.9)	7 (5.5)	4 (4.2)	
5 - Unable to wash/dress	5 (2.2)	4 (3.1)	1 (1.1)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Usual activities				
1 - No problems	68 (30.5)	30 (23.4)	38 (40.0)	χ^2 (4) = 10.33 p = 0.035
2 - Slight problems	45 (20.2)	25 (19.5)	20 (21.1)	

3 - Moderate problems	51 (22.9)	31 (24.2)	20 (21.1)	$\Phi = 0.22^a$ *n* = 223
4 - Severe problems	37 (16.6)	25 (19.5)	12 (12.6)	
5 - Unable to do usual activities	22 (9.9)	17 (13.3)	5 (5.3)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Pain or discomfort				
1 - No pain or discomfort	49 (22.0)	14 (10.9)	35 (36.8)	χ^2 (4) = 27.10 **p = 0.000** $\Phi = 0.35^a$ *n* = 223
2 - Slight pain or discomfort	45 (20.2)	25 (19.5)	20 (21.1)	
3 - Moderate pain or discomfort	71 (31.8)	45 (35.2)	26 (27.4)	
4 - Severe pain or discomfort	47 (21.1)	34 (26.6)	13 (13.7)	
5 - Extreme pain or discomfort	11 (4.9)	10 (7.8)	1 (1.1)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Anxiety or depression				
1 - Not anxious/depressed	126 (56.5)	69 (53.9)	57 (60.0)	χ^2 (4) = 3.11 p = 0.539 $\Phi = 0.12$ *n* = 223
2 - Slightly anxious/depressed	51 (22.9)	28 (21.9)	23 (24.2)	
3 - Moderately anxious/depressed	25 (11.2)	16 (12.5)	9 (9.5)	
4 - Severely anxious/depressed	15 (6.7)	10 (7.8)	5 (5.3)	
5 - Extremely anxious/depressed	6 (2.7)	5 (3.9)	1 (1.1)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	

Abbreviations: EQ-5D-5L EuroQoL, *IQR* Interquartile range. *Degrees of freedom* presented in brackets. Φ = effect size (Phi coefficient or Cramer's V). [a]A significant difference with an effect size ≥ Cohen's definition of "medium".

Self-rated health on day of recruitment

Participants self-rated health on the day of recruitment is presented in Table 8.28, by group. Those who had an opioid prescription documented on their medical record reported a slightly lower median score (i.e. 60) than those who did not (i.e. 65). However, this did not reach statistical significance.

Table 8.28 Self-rated health on day of recruitment, by presence of an opioid prescription documented on their medical record at some point over the past year

Self-rated health using EQ-5D-5L VAS	All participants (n=223)	Opioid prescription prescribed over the past year?		Mann Whitney U test
		Yes (n=128) n (%)	No (n=95) n (%)	
Median [IQR]; (Range)	60 [50 – 80]; (15 – 100)	60 [50 – 75]; (15 – 100)	65 [50 – 80]; (25 – 100)	U = 5512.0 z = -1.20 p = 0.23 *r* = 0.08 *n* = 223
Missing	0 (0.0)	0 (0.0)	0 (0.0)	

Abbreviations: EQ-5D-5L EuroQoL, *VAS* Visual analogue scale, *IQR* Interquartile range. Scored from 0 (i.e. worst health they can imagine) to 100 (i.e. best health they can imagine).

Health utility scores

Comparison is made, in Table 8.29, of the utility scores for HRQoL. This utility score shows a lower median score of 0.60 for those with an opioid prescription documented on their medical record compared to those that did not (i.e. 0.73). The difference is statistically significant.

Table 8.29 Health utility of participants, by presence of an opioid prescription documented on their medical record at some point over the past year

Health utility score	All participants (n=223)	Opioid prescription prescribed over the past year?		Mann Whitney U test
		Yes (n=128) n (%)	No (n=95) n (%)	
Median [IQR]; (Range)	0.67 [0.43 – 0.84]; (-0.18 – 1.00)	0.60 [0.35 – 0.81]; (-0.18 – 1.00)	0.73 [0.54 – 0.87]; (0.13 – 1.00)	U = 4142.0 z = -3.99 **p = 0.000** *r* = 0.27 *n* = 222
Missing	1 (0.4)	1 (0.8)	0 (0.0)	

Abbreviations: IQR Interquartile range. φ = effect size (Phi coefficient or Cramer's V). *Scoring*: Full health has a value of 1 and dead has a value of 0. [a] A significant difference with an effect size ≥ Cohen's definition of "small".

8.2.8.2 Factors associated with participants having an opioid prescription

Another objective of this study was to explore the relationship, if any, between the presence of an opioid prescription on participant's medical records at some point over

the past year and demographic or clinical characteristics (such as patient age). If individual participants are prescribed an opioid at some point over the past year, then understanding how certain variables may be associated with increased or decreased odds being prescribed an opioid may be useful. Therefore, a logistic regression analysis was conducted. Table 8.30 shows the descriptive statistics for the final candidate predictors for all participants, and how they vary by the outcome variable.

Table 8.30 Descriptive statistics for candidate predictors

Predictors	All participants (n=223)	Presence or absence of an opioid prescription	
		Present (n=128)	Absent (n=95)
Age			
Median (IQR)	81 (74 – 85)	81 (73 – 85)	82 (77 – 86)
Missing n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Gender n (%)			
Male	86 (38.6)	48 (37.5)	38 (40.0)
Female	137 (61.4)	80 (62.5)	57 (60.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Pain over the past week (IPOS)			
Median (IQR)	2 (1 – 3)	2 (2 – 3)	1 (0 – 2)
Missing n (%)	1 (0.4)	0 (0.0)	1 (1.1)
Depression over the past week (IPOS)			
Median (IQR)	1 (0 – 2)	1 (0 – 2)	0 (0 – 2)
Missing n (%)	1 (0.4)	0 (0.0)	1 (1.1)
Loneliness n (%)			
Disagree	162 (72.6)	87 (68.0)	75 (78.9)
Agree	59 (26.5)	40 (31.3)	19 (20.0)
Missing	2 (0.9)	1 (0.8)	1 (1.1)
Number of prescribed medications			
Median (IQR)	9 (6 – 12)	10 (7 – 13)	8 (6 – 10)
Missing n (%)	1 (0.4)	1 (0.0)	0 (0.0)
Self-rated health			
Median (IQR)	60 (50 – 80)	60 (50 – 75)	65 (50 – 80)
Missing n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Number of hospital admissions over the past year			
Median (IQR)	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)
Missing n (%)	3 (1.3)	1 (0.8)	2 (2.1)
Functional status (AKPS)			
Median (IQR)	70 (60 – 80)	70 (60 – 80)	70 (60 – 80)
Missing n (%)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: IQR Interquartile range, *IPOS* Integrated Palliative care Outcome Scale, *AKPS* Australian Karnofsky Performance Scale.

Model diagnostics were conducted (see Appendix 9 for graphs of residual distribution, heteroscedasticity and leverage discussed in this section). The distribution of residuals

was checked graphically and appeared normally distributed. The heteroscedasticity of residuals was also checked and heteroscedasticity was not present. Influential observations were considered using leverage to determine possible outliers. Two outliers were identified. However, removal of the outliers did not impact the model, so these cases were not excluded from the analysis.

The logit odds estimate and standardised odds ratio estimates with 95% confidence intervals for the final model are presented in Table 8.31. Due to missing data, 217 participants were included. The prevalence of the outcome was 58.1%. Higher pain scores and number of medications currently prescribed were significantly associated with increased odds of having an opioid prescription documented on their medical record (OR: 1.74, 95% CI [1.32, 2.29], p =.000 and OR: 1.13, 95% CI [1.03, 1.123], p =.006, respectively). Being female, feeling lonely, self-rated health, times admitted to hospital over the past year and functional status were not significantly associated with increased odds of an opioid prescription being observed. Younger age and lower scores for depression (as measured by IPOS) were not found to be significantly associated with lowering the odds for the outcome observed. The model had a Nagelkerke's R^2 of 21.4%.

Table 8.31 Results of a logistic regression for the outcome 'presence of an opioid prescription in medical records at some point over the past year' for 217 participants

				Unadjusted			Adjusted		
Variable	**logit**	***SE***	**Wald *z***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Intercept	-1.066	2.16	.243	-	-	-	-	-	.622
Age	-.019	.02	.775	0.96	0.92, 0.99	**.019**	0.98	0.94, 1.02	.379
Gender	.116	.32	.135	1.11	0.65, 1.92	.705	1.12	0.61, 2.08	.714
Pain	.555	.14	15.618	1.82	1.42, 2.34	**.000**	1.74	1.32, 2.29	**.000**
Depression	-.153	.14	1.21	1.12	0.90, 1.41	.314	0.86	0.65, 1.13	.272
Loneliness	.392	.36	1.179	1.82	0.97, 3.40	.063	1.48	0.73, 3.01	.277
Number of medications	.120	.04	7.42	1.15	1.07, 1.23	**.000**	1.13	1.03, 1.23	**.006**
Self-rated health	.004	.01	.205	0.99	0.98, 1.00	.185	1.00	0.99, 1.02	.651
Times admitted to hospital	.080	.11	.505	1.13	0.92, 1.39	.234	1.08	0.87, 1.35	.477
Functional status	.008	.01	.405	0.99	0.97, 1.01	.373	1.01	0.98, 1.03	.524

Abbreviations: SE Standard error, *OR* Odds ratio, *CI* Confidence interval, *P* p-value, *OME* oral morphine equivalent, *ACB* anticholinergic burden. *Note:* Figures in bold represent significant findings. Nagelkerke R^2 = 0.214. [a] Logarithm transformation.

The sensitivity and specificity of the model was also considered (see Table 8.32). The model demonstrated good prediction of the outcome; with 80.2% of those predicted to have an opioid prescription on their medical record actually had a prescription observed. In terms of specificity, the model was not as good at predicting the proportion of people without an opioid prescription on their medical record. 56.0% of those who were predicted not to have an opioid prescription on their medical record were found not to have a prescription present. The PPV of the model was 71.6% and the NPV was 67.1%.

Table 8.32 Observed and predicted frequencies for self-reported cognitive adverse effects

	Predicted		
Observed	Yes	No	% Correct
Yes	101	25	80.2
No	40	51	56.0
Overall % correct			70.0

Note: Cut-off value = 0.50, Sensitivity = 101/(101+25)% = 80.2%, Specificity = 51/(51+40)% = 56.0%, PPV = 101/(101+40)% = 71.6%, NPV is 51/(51+25)% = 67.1%.

8.2.9 Patterns of opioid prescriptions in participants over the past year from medical record data (Research question 9)

For participants who were found to have an opioid prescription documented on their medical record at some point over the past year, a subgroup analysis was conducted. This analysis summarises the opioid analgesics prescribed to 128 participants over the past year (including the prescription type (i.e. regularly scheduled or pro re nata), opioid preparation (i.e. immediate-release or modified-release), route of administration, number prescribed, dose and duration (by day's supply)).

Prescription type and opioid preparation

Participants were mainly prescribed opioid analgesics on a pro re nata basis only (n=55; 43.0%), followed by regularly scheduled only (n=46; 35.9%). Fewer participants were prescribed both regularly scheduled and pro re nata opioid analgesics (n=27; 21.1%). Participants were predominantly prescribed immediate-release opioid analgesics only (n=94; 73.4%), with few being prescribed modified-release only (n=11; 8.6%).

Although, 23 (18%) participants were prescribed a combination of both preparation types.

Route of administration

The routes of administration for opioid analgesics are presented in Table 8.33. Most participants were administered opioid analgesics orally (97.7%), followed by transdermal patch (12.5%). This included 13 participants who had been prescribed opioid analgesics to be taken both orally and via transdermal patches. Opioid analgesics were to be administered subcutaneously for one participant.

Table 8.33 Routes of administration for opioid analgesics prescribed at some point over the past year

Route of administration	N (%)
Oral only	111 (86.7)
Oral and transdermal patch	13 (10.2)
Transdermal patch only	3 (2.3)
Oral and subcutaneous	1 (0.8)

Number of opioid analgesics prescribed over the past year

Table 8.34 presents a summary of the number of opioid analgesics prescribed at some point over the past year. The median (IQR) number of opioid analgesics prescribed was 1 (1–2). In considering the prescription type, the median (IQR) number of regularly scheduled opioid analgesics was 1 (0–1) and 1 (0–1) for pro re nata prescriptions.

Table 8.34 Number of opioid analgesics prescribed over the past year, including by prescription type

Number of opioids	N	Mean	SD	Median	IQR	Range
Total number of opioid analgesics	128	1.4	0.8	1	1 – 2	1 – 5
Number of regularly scheduled opioid analgesics	73	1.2	0.6	1	1 - 1	1 – 4
Number of pro re nata opioid analgesics	82	1.1	0.4	1	1 – 1	1 – 3

Abbreviations: IQR Interquartile Range, *SD* Standard Deviation.

Daily dose in oral morphine equivalents

The following four tables (Table 8.35, Table 8.36, Table 8.37 and Table 8.38) give details of daily dose in OME. The daily dose in OME is presented in two ways; average daily dose over the past year (i.e. total sum divided by 365 days) and daily dose by the total day's supplied (i.e. total sum divided by the day's supplied for prescriptions).

Table 8.35 reports the average daily dose for all opioids, followed by a breakdown by prescription type. The median (IQR) average daily dose over the past year for all opioid analgesics was 5.5mg (1.1–19.0mg). The median (IQR) average daily dose over the past year for participants with regularly scheduled prescriptions was 9.9mg (1.3–30.8mg). The median (IQR) average daily dose over the past year for participants with pro re nata prescriptions was 2.1mg (0.6–9.8mg).

Table 8.35 Average daily dose (mg/d) in oral morphine equivalents for all opioid analgesics, including by prescription type

Prescription type	N	Mean	SD	Median	IQR	Range
All opioid analgesics	128	18.6	36.8	5.5	1.1 – 19.0	0.1 – 270.7
Regularly scheduled	73	25.4	43.8	9.9	1.3 – 30.8	0.1 – 260.9
Pro re nata	82	6.4	8.5	2.1	0.6 – 9.8	0.1 – 38.5

Abbreviations: mg/d Milligrams per day, *IQR* Interquartile Range

Table 8.36 presents the daily dose by total days' supply (i.e. intended daily dose, based on the prescription issued). Due to a range in dose for some participants, the lowest and highest possible daily doses are given. The lowest possible median daily dose for all opioid analgesics by day's supply was 12mg and the highest possible median daily dose was 19.5mg. For regularly scheduled prescriptions, the lowest possible median daily dose was 17.9mg and the highest possible median dose was 20.0mg. The lowest possible median dose for pro re nata prescriptions was 12.0mg; lower than the regularly prescribed. Whilst, the median highest possible daily dose was 21.1mg, which was slightly higher than opioid analgesics regularly prescribed.

Table 8.36 Daily dose in oral morphine equivalents by day's supply for all opioid analgesics, including by prescription type

Prescription type	N	Daily dose in oral morphine equivalent by days' supply (mg/d) Median [IQR]; (range)	
		Lowest possible dose	**Highest possible dose**
All opioid analgesics	128	12.0 [6.4 – 20.0] (2.0 – 175.1)	19.5 [12.0 – 26.3] (2 – 175.1)
Regularly scheduled	73	17.9 [11.0 – 25.3] (2.0 – 175.1)	20.0 [12.0 – 38.0] (2.0 – 175.1)
Pro re nata	82	12.0 [6.0 – 17.4] (3.2 – 43.7)	21.1 [11.8 – 24.3] (6.0 – 60.0)

Abbreviations: mg/d Milligrams per day, *IQR* Interquartile range

A summary of average dose over the past year is presented in Table 8.37 by opioid type. Overall, the highest median average dose (in oral morphine equivalents) was given in relation to fentanyl, followed by buprenorphine and meptazinol. Codeine was prescribed to the majority of participants at the lowest median average daily dose of 1.5mg. Average median doses were generally higher for regularly scheduled opioid analgesics for all opioids, except tramadol. Lower average median daily doses were generally indicative of lower day's supply for that opioid type over the past year (refer to Table 8.40 for day's supply).

When considering the daily dose by the days supplied (i.e. intended daily dose, based on the prescription issued), the order of opioid analgesics by increasing dose changed (see Table 8.38). The highest median dose prescribed was still fentanyl, but was followed by morphine and oxycodone. Also, dihydrocodeine had the lowest possible median daily dose at 7.5mg. Median daily doses were, again, higher for regularly scheduled prescriptions for most opioid types, except for tramadol. Median daily doses were also similar between regularly scheduled and pro re nata prescriptions for codeine and oxycodone.

Table 8.37 Average daily dose in OME by opioid analgesic, including by prescription type

Opioid analgesic	Average daily dose in OME (mg/d) Median [IQR]; (range)					
	N	**All opioid analgesics (n=128)**	**N**	**Regularly scheduled (n=73)**	**N**	**Pro re nata (n=82)**
Codeine	81	1.5 [0.5 – 5.7]; (0.1 – 23.9)	29[b]	1.7 [0.9 – 9.6]; (0.1 – 23.9)	55[c]	1.1 [0.4 – 3.3]; (0.1 – 19.7)
Tramadol	32	11.7 [1.7 – 20.3]; (0.4 – 39.8)	15	2.5 [0.8 – 20.1]; (0.4 – 39.8)	18	16.5 [3.0 – 21.4]; (0.8 – 38.5)
Morphine	16	9.9 [1.5 – 49.2]; (0.4 – 137.2)	12	15.7 [3.0 – 58.3]; (1.5 – 132.8)	8	3.9 [0.6 – 5.4]; (0.4 – 9.8)
Buprenorphine	11	20.4 [4.7 – 33.8]; (0.9 – 74.8)	11	20.4 [4.7 – 33.8]; (0.9 – 74.8)	NA	-
Dihydrocodeine	10	4.1 [0.7 – 12.2]; (0.4 – 20.7)	6[b]	4.2 [0.7 – 12.6]; (0.4 – 20.7)	4[c]	3.6 [0.6 – 15.8]; (0.5 – 19.0)
Oxycodone	8	8.2 [1.6 – 52.8]; (1.2 – 66.7)	7	9.4 [1.2 – 41.4]; (0.6 – 49.6)	5	1.6 [0.6 – 23.0]; (0.6 – 25.3)
Fentanyl	6	65.7 [20.7 – 200.6]; (4.9 – 226.8)	6	65.7 [20.7 – 200.6]; (4.9 – 226.8)	NA	-
Meptazinol[a]	3	18.8 (7.7 – 19.5)	3	18.8 (7.7 – 19.5)	NA	-

Abbreviations: mg/d Milligrams per day, *IQR* Interquartile range, *NA* Not applicable, *OME* Oral morphine equivalents

36 participants were prescribed more than one opioid. Additionally, participants were prescribed both regularly scheduled and pro re nata prescriptions for codeine (n=3), morphine (n=4), oxycodone (n=4) and tramadol (n=1). This is reflected in the table above.

[a] The IQR is not presented, in addition to the range, where 3 participants had an opioid prescription for the opioid type.

[b] Preparations of codeine and dihydrocodeine for regularly scheduled prescriptions were present in 22 and 2 participants, respectively.

[c] Preparations of codeine and dihydrocodeine for pro re nata prescriptions were present in 34 and 3 participants, respectively.

Table 8.38 Daily dose in OME for opioid analgesic by day's supply

Opioid analgesic	Daily dose in OME (mg/d) by day's supply Median [IQR]; (range)								
	All opioid analgesics (n=128)			Regularly scheduled (n=73)			Pro re nata (n=82)		
	N	Lowest possible dose	Highest possible dose	N	Lowest possible dose	Highest possible dose	N	Lowest possible dose	Highest possible dose
Codeine	81	9.3 [4.7 – 12.0] (2.0 – 24.0)	12.0 [6.4 – 24.0] (2.0 – 24.0)	29[b]	9.7 [4.7 – 12.0] (2.0 – 24.0)	12.0 [6.4 – 24.0] (2.0 – 24.0)	55[c]	9.6 [6.0 – 12.0] (3.2 – 24.0)	12.0 [6.4 – 24.0] (6.0 – 24.0)
Tramadol	32	20.0 [15.6 – 20.0] (14.5 – 40.0)	40.0 [15.6 – 40.0] (14.5 – 40.0)	15	20.0 [15.0 – 20.0] (10.0 – 40.0)	20.0 [15.0 – 40.0] (10.0 – 40.0)	18	20.0 [19.9 – 20.0] (15.0 – 40.0)	40.0 [26.8 – 40.0] (15.0 – 40.0)
Morphine	16	30.9 [20.0 – 60.0] (10.0 – 120.0)	40.0 [20.0 – 60.0] (20.0 – 120.0)	12	45.8 [20.0 – 60.0] (20.0 – 120.0)	45.8 [20.0 – 60.0] (20.0 – 120.0)	8	30.0 [15.0 – 42.8] (10.0 – 45.7)	41.9 [25.0 – 56.4] (15.0 – 60.0)
Buprenorphine	11	24.0 [12.0 – 36.0] (12.0 – 72.0)	24.0 [12.0 – 36.0] (12.0 – 72.0)	11	24.0 [12.0 – 36.0] (12.0 – 72.0)	24.0 [12.0 – 36.0] (12.0 – 72.0)	NA	-	-
Dihydrocodeine	10	7.6 [4.0 – 12.0] (4.0 – 12.0)	12.1 [8.0 – 19.5] (8.0 – 24.0)	6[b]	9.0 [4.0 – 12.0] (4.0 – 12.0)	15.0 [8.0 – 19.5] (8.0 – 24.0)	4[c]	5.1 [4.0 – 10.5] (4.0 – 12.0)	10.1 [8.0 – 21.1] (8.0 – 24.0)
Oxycodone	8	30.0 [15.0 – 36.6] (11.3 – 52.9)	30.0 [16.9 – 36.6] (11.3 – 52.9)	7	30.0 [15.0 – 45.0] (15.0 – 52.9)	30.0 [15.0 – 45.0] (15.0 – 52.9)	5	30.0 [9.4 – 30.0] (7.5 – 30.0)	30.0 [13.2 – 30.0] (11.3 – 30.0)
Fentanyl	6	89.3 [30.0 – 191.3] (30.0 – 240.0)	89.3 [30.0 – 191.3] (30.0 – 240.0)	6	89.3 [30.0 – 191.3] (30.0 – 240.0)	89.3 [30.0 – 191.3] (30.0 – 240.0)	NA	-	-
Meptazinol[a]	3	20.0 (20.0 – 20.0)	20.0 (20.0 – 20.0)	3	20.0 (20.0 – 20.0)	20.0 (20.0 – 20.0)	NA	-	-

Abbreviations: mg/d Milligrams per day, *IQR* Interquartile range, *NA* Not applicable, *OME* Oral morphine equivalents

36 participants were prescribed more than one opioid. Additionally, participants were prescribed both regularly scheduled and pro re nata prescriptions for codeine (n=3), morphine (n=4), oxycodone (n=4) and tramadol (n=1). This is reflected in the table above.

[a] The IQR is not presented, in addition to the range, where 3 participants had an opioid prescription for the opioid type.

[b] Preparations of codeine and dihydrocodeine for regularly scheduled prescriptions were present in 22 and 2 participants, respectively.

[c] Preparations of codeine and dihydrocodeine for pro re nata prescriptions were present in 34 and 3 participants, respectively.

Day's supply of opioid analgesics

The following two tables (Table 8.39 and Table 8.40) give detail on the day's supply for the opioid analgesics prescribed; first, for all opioids (including a breakdown by prescription type), and second, by opioid type. Overall, the median (IQR) day's supply for all opioid analgesics for the lowest possible dose prescribed was 202 (41.8–373.5) days. The median (IQR) day's supply for the highest possible dose prescribed was 124 (28–339.8) days. The median day's supply was higher for regularly scheduled opioid analgesics compared to pro re nata.

Table 8.39 Day's supply for all opioids, including by prescription type

Prescription type	N	Day's supply Median [IQR]; (range)	
		Day's supply for lowest possible dose	**Day's supply for highest possible dose**
All opioid analgesics	128	202.0 [41.8 – 373.5] (7.0 – 954.0)	124.0 [28.0 – 339.8] (7.0 – 954.0)
Regularly scheduled	73	315.0 [46.5 – 371.5] (7.0 – 954.0)	240.0 [39.5 – 356.0] (7.0 – 954.0)
Pro re nata	82	77.0 [27.3 – 281.3] (7.0 – 660.0)	43.0 [14.0 – 168.0] (4.0 – 603.0)

Abbreviations: IQR Interquartile range. 36 participants were prescribed more than one opioid.

When considering opioid type (see Table 8.40), buprenorphine had the highest median day's supply, with 343 days. This was followed by meptazinol, fentanyl, tramadol, dihydrocodeine, oxycodone, morphine and codeine. The median day's supply was greater for all regularly scheduled opioid types, except for dihydrocodeine and tramadol. Notably, the pro re nata prescriptions for dihydrocodeine and tramadol were prescribed for over two thirds of the year, and more comparable to regularly scheduled prescriptions.

Table 8.40 Day's supply by opioid analgesics, including by prescription type

Opioid analgesic	Number of days Median [IQR]; (range)								
	All opioid analgesics prescribed (n=128)			Regularly scheduled (n=73)			Pro re nata (n=82)		
	N	Day's supply for lowest possible dose	Day's supply for highest possible dose	N	Day's supply for lowest possible dose	Day's supply for highest possible dose	N	Day's supply for lowest possible dose	Day's supply for highest possible dose
Codeine	81	75.0 [25.0 – 238.5.0] (7.0 – 660.0)	40.0 [13.0 – 149.5] (6.0 – 455.0)	29	164.0 [34.0 – 347.5] (7.0 – 652.0)	94.0 [33.5 – 281.5] (7.0 – 455.0)	55	50.0 [25.0 – 125.0] (7.0 – 660.0)	26.0 [13.0 – 65.0] (6.0 – 350.0)
Tramadol	32	245.0 [31.0 – 348.8] (10.0 – 726.0)	162.0 [22.0 – 266.3] (8.0 – 603.0)	15	60.0 [15.0 – 353.0] (10.0 – 726.0)	45.0 [10.0 – 322.0] (8.0 – 367.0)	18	285.5 [55.0 – 343.3] (15.0 – 603.0)	168.5 [31.0 – 243.8] (8.0 – 603.0)
Morphine	16	130.5 [19.0 – 354.8] (7.0 – 460.0)	130.5 [13.8 – 354.8] (4.0 – 439.0)	12	283.0 [35.8 – 354.8] (9.0 – 404.0)	283.0 [35.8 – 354.8] (9.0 – 404.0)	8	40.0 [11.5 – 81.5] (7.0 – 134.0)	34.5 [6.3 – 71.3] (4.0 – 82.0)
Buprenorphine	11	343.0 [143.0 – 371.0] (28.0 – 379.0)	343.0 [143.0 – 371.0] (28.0 – 379.0)	11	343.0 [143.0 – 371.0] (28.0 – 379.0)	343.0 [143.0 – 371.0] (28.0 – 379.0)	NA	-	-
Dihydrocodeine	10	184.0 [47.3 – 577.0] (33.0 – 631.0)	94.0 [24.5 – 301.5] (17.0 – 631.0)	6	184.0 [37.5 – 454.8] (33.0 – 631.0)	94.0 [19.3 – 310.8] (17.0 – 631.0)	4	315.0 [50.8 – 577.0] (50.0 – 577.0)	163.5 [26.3 – 304.5] (26.0 – 306.0)
Oxycodone	8	156.0 [36.0 – 534.0] (22.0 – 644.0)	156.0 [29.5 – 534.0] (22.0 – 644.0)	7	228.0 [14.0 – 342.0] (14.0 – 346.0)	228.0 [14.0 – 342.0] (14.0 – 346.0)	5	28.0 [21.0 – 280.0] (20.0 – 308.0)	22.0 [17.0 – 280.0] (14.0 – 308.0)
Fentanyl	6	307.5 [204.8 – 358.8] (60.0 – 400.0)	307.5 [204.8 – 358.8] (60.0 – 400.0)	6	307.5 [204.8 – 358.8] (60.0 – 400.0)	307.5 [204.8 – 358.8] (60.0 – 400.0)	NA	-	-
Meptazinol[a]	3	344.0 (140.0 – 356.0)	344.0 (140.0 – 356.0)	3	344.0 (140.0 – 356.0)	344.0 (140.0 – 356.0)	NA	-	-

Abbreviations: IQR Interquartile range.

36 participants were prescribed more than one opioid. Additionally, participants were prescribed both regularly scheduled and pro re nata prescriptions for codeine (n=3), morphine (n=4), oxycodone (n=4) and tramadol (n=1). This is reflected in the table above.

[a] The IQR is not presented, in addition to the range, where 3 participants had an opioid prescription for the opioid type.

Opioids currently prescribed

Opioid analgesics currently prescribed to participants (i.e. prescription issued 30 days prior to recruitment) were also considered. Of the 128 participants with an opioid prescription documented on their medical record over the past year, 80 (62.5%; 95% CI [54.6%, 71.2%]) were currently prescribed an opioid analgesic. Similar to the data presented above, the prescription type, opioid preparation, route of administration, number prescribed and dose are considered and can be found in Appendix 15.

8.2.10 Differences between self-report and documented opioid prescription data (Research question 10)

This section presents the differences between self-report and documented prescription data for opioid analgesics from medical records regarding being prescribed opioid analgesics over the past year.

Table 8.41 Determining the differences between self-report of an opioid prescription and having an opioid prescription documented within the medical record

		Documented		Total	
		Yes	**No**	**N**	%
Self-reported	**Yes**	**92**	**3**	**95**	66.4
	No	**11**	**37**	**48**	33.6
Total	**N**	**103**	**40**	**143**	100.0
	%	72.0	28.0		

A McNemar chi-square test demonstrated a difference between self-report and documented opioid prescriptions over the past year, with a small effect size (see Table 8.41 and Figure 8-7). Those who self-reported 'No' were more likely to have an opioid prescription documented on their medical record, compared to those who self-reported 'Yes' who did not have a documented opioid prescription, $\chi^2(1) = 4.6$, $p = 0.03$, $\Phi = 0.18$.

Discordant entries: 3 (f_{yn}) and 11 (f_{ny})
McNemar test statistic calculation (Uncorrected): $\chi^{2=}(f_{yn} - f_{ny})^2 / (f_{yn} + f_{ny}) = (3 - 11)^2/(3+11) = 4.6$ $\chi^2 = 4.6$, with a p-value of 0.03.

Figure 8-7 McNemar chi-square test statistic calculation

Agreement between self-report and documented data

Indicators of agreement between self-report and documented opioid analgesic data were also considered; using total agreement, the kappa statistic, and positive and negative agreement (see Table 8.41 and Figure 8-8). The overall percent agreement was 90.2%. Although, this does not account for agreement expected by chance alone. Therefore, the kappa statistic is considered, with values between 0.61 to 0.80 equalling substantial agreement. The positive and negative agreements also demonstrate good concordance between self-report and medical records.

Indicators of agreement
Total agreement (defined as the number of concordant 'Yes' and the concordant 'No' divided by the total sample size and expressed as a percentage): (92 + 37)/143=129/143=0.902 (90.2%) Kappa statistic: Po=[(92 + 37)/143]=129/143=0.90 Pe=[(95/143 x 103/143) + (48/143 x 40/143)=0.48 + 0.09=0.57 κ=Po – Pe/1-Pe=0.90 – 0.57/1 – 057=0.77 (Substantial agreement) To help interpret the κ values, both positive and negative agreement have been calculated: Positive agreement: (2 x 92)/(2 x 92 + 3 + 11)=184/198=0.93 (92.9%) Negative agreement: (2 x 37)/(2 x 37 + 3 + 11)=74/88=0.84 (84.1%)

Figure 8-8 Calculations for indicators of agreement between self-report and documented opioid prescriptions

8.3 Summary

The main findings from the quantitative components are:

- Moderate to severe pain is highly prevalent in community-dwelling older adults with frailty despite the presence of treatment. Pain was a main problem or concern by a third of participants.
- There were a number of recommended changes with focus to rationalising pain medication and reducing risk of adverse effects following assessment at the ICC.
- The recall of adverse effects associated with pain medication reported increased when aided by a list of common adverse effects.
- The case note review showed that there was a high prevalence of opioid prescribing in this population, with low doses of codeine and tramadol being the most commonly prescribed. Opioids were commonly administered orally and were predominantly immediate release.
- Pain severity and number of pain medications were associated with increased odds of opioids being prescribed.
- The presence of an opioid prescription at some point over the past year was also associated with poor health-related quality of life compared to those that did not.

The next chapter will explore the experiences, perspectives and concerns of those using opioid analgesics to manage chronic pain and have experienced a cognitive adverse effect, and their informal caregivers. The impact of these will be considered, as well as information and support needs.

Chapter 9: Qualitative component – Results

9.1 Introduction

This chapter presents the results of the qualitative interviews, which addresses Objective 3: 'To explore the experiences, perspectives and concerns of older adults and those that care for them regarding chronic pain, opioid analgesic use and cognitive adverse effects (including the challenges with managing pain, impact of chronic pain and opioid analgesics, and information and support needs)', and answers the following research questions:

(1) What are the experiences, perspectives and concerns of older adults and those that care for them, regarding chronic pain, opioid analgesics and cognitive adverse effects?
(2) What impact do chronic pain, opioid analgesics and cognitive adverse effects have on older adults and those that care for them?
(3) What information and support needs do older adults and those that care for them have regarding chronic pain, opioid analgesics and cognitive adverse effects?

The findings are presented in two parts; first, the participant characteristics and impact of dyadic interviews, and second, the themes that were identified from the interviews.

9.2 Participant characteristics

Interviews were conducted between the 30th May 2019 to 11th November 2019, and lasted an average of 64 minutes (ranging from 27 minutes and 103 minutes). Twenty-two patient participants who reported cognitive adverse effects and pain lasting longer than three months in the cross-sectional survey were approached to participate. Four declined and in-depth qualitative interviews were completed with 18 participants. The patient participants had a median age of 78 (ranging from 67 to 90) and 10 (55.6%) were female. Participants all reported their ethnicity as white, except for one participant who specified that their ethnicity was mixed. Table 9.1 presents patient participant characteristics.

Fourteen people who were identified as providing informal care for these patient participants contributed to the in-depth interviews. Twelve were interviewed alongside the patient participant (with two informal carers present in one patient participant interview) and two informal caregivers of one patient participant were interviewed together but separately to the patient participant. Informal caregivers had a median age of 70.5 (ranging from 22 to 86), all were white and 12 (85.7%) were female. Relationships to patient participants varied; most were either their spouse/partner (n=9) or their daughter/daughter-in-law (n=3). Other informal caregivers were the patient participants granddaughter (n=1) and family friend (n=1).

Where informal caregivers were present, participants narratives and experiences of pain, opioids analgesic use and cognitive adverse effects were either supported, built upon or there was dissonance. These different relationship dynamics may have shaped the findings in different ways. In supportive dyads, the story was mostly left to the patient participant to tell with minimal and agreeable input from the informal carer. In some instances, informal carers built upon the patient narrative by adding more detail and clarity (e.g the sequence of or details of what happened along the chronic pain journey). This was particularly helpful in the occurrence of cognitive adverse effects, where the patient participant was less aware of what had occurred. In some instances, there was a lack agreement between the patient and their informal caregiver which meant that different views or opinions of concepts were presented that needed to be managed within analysis. Overall, the joint interviews were useful in building the full picture and in understanding the different relationships and support networks that exist. Although, it may have limited or shaped what both the patient or family carer said. For example, an informal carer shared a perspective on the patient participant's more argumentative mood due to pain when they had left the room. Although, this was circled back to by the participants when both present.

Table 9.1 Participant characteristics: Patients

ID	Age	Gender	Marital status	Living…	eFI[a]	RCFS[b]	Pain experienced	Pain severity[c]	Pain duration	Analgesics used over the past year	Cognitive adverse effects[d]	Other adverse effects[d]
003	67	F	Missing	alone	Severe	Missing	Amputation site, arm, phantom limb	Moderate	6 years	Zomorph, Gabapentin	Attention, drowsiness memory	Falls
025	72	M	Married	with spouse	Severe	4	Hip	Severe	3 years	Longtec, Duloxetine	Attention, confusion, drowsiness, memory	N/A
027	74	M	Married	with spouse	Fit	2	Groin, postsurgical (hip), shoulder	Moderate	4 years	Codeine, paracetamol	Attention, confusion, hallucinations	Constipation
041	74	M	Divorced	alone	Moderate	5	Back	Slight	25–30 years	Co-codamol	Drowsiness	N/A
094	88	F	Divorced	alone	Severe	5	Knee, osteoarthritis	Moderate	1 year	Co-codamol	Attention, drowsiness, memory	Constipation, dry mouth
113	82	F	Married	with spouse	Severe	5	Back, headaches	Severe	20 years	Tramadol, amitriptyline, pregabalin	Auditory hallucinations, drowsiness	N/A
115	81	F	Widowed	alone	Severe	5	Arthritis, knee	Severe	1 year	Co-codamol	Drowsiness	Constipation, nausea, vomiting
125	67	M	Married	with spouse	Moderate	6	Amputation site, leg, phantom limb	Moderate	1 year	Codeine, morphine, tramadol, paracetamol	Attention, confusion, drowsiness memory, hallucinations	Constipation, low mood, slurred speech, twitching

Participant characteristics: Patients (Continued)

ID	Age	Gender	Marital status	Living…	eFI[a]	RCFS[b]	Pain experienced	Pain severity[c]	Pain duration	Analgesics used over the past year	Cognitive adverse effects[d]	Other adverse effects[d]
126	90	F	Widowed	alone	Moderate	4	Hip, knee	Moderate	1 year	Co-codamol, paracetamol	Drowsiness	Constipation, falls, gastrointestinal issues
137	71	M	Divorced	with partner	Severe	4	Knee	Moderate	1 year	Co-codamol, tramadol	Attention, confusion, memory	Constipation*
158	81	M	Married	with spouse	Severe	5	Osteoarthritis	Severe	5 years	Codeine, morphine, naproxen, paracetamol, pregabalin	Attention, drowsiness	Nausea
169	89	F	Single	alone	Moderate	4	Foot, osteoarthritis, sciatica, shoulder	Severe	7 months	Tramadol, gabapentin, paracetamol	Drowsiness	Constipation
171	72	F	Married	with spouse	Severe	6	Back, hip, sciatica	Over-whelming	20 – 30 years	Dihydro-codeine, morphine	Attention, confusion, drowsiness, memory	Constipation, nausea, headaches
177	85	F	Missing	alone	Mild	5	Back, hip, thigh	Severe	2 years	Co-codamol, ibuprofen	Attention, confusion, drowsiness	Constipation, headaches, risk of internal bleed

Participant characteristics: Patients (Continued)

ID	Age	Gender	Marital status	Living…	eFI[a]	RCFS[b]	Pain experienced	Pain severity[c]	Overall pain duration	Analgesics used over the past year	Cognitive adverse effects[d]	Other adverse effects[d]
197	70	M	Married	with spouse	Severe	5	Jaw, neck	Moderate	10 - 15 years	Co-dydramol	Drowsiness	Constipation
228	81	M	Married	with spouse	Severe	5	Arthritis, back, diverticulitis, postsurgical (knee)	Moderate	10 – 12 years	Morphine, paracetamol, ibuprofen gel	Drowsiness	Constipation
232	79	F	Widowed	alone	Moderate	5	Back, multiple joint	Severe	9 years	Longtec, paracetamol	Drowsiness	Falls, muscle weakness, nausea, vomiting
234	77	F	Divorced	alone	Severe	6	Back, neuropathic, shoulder	Severe	20 years	Co-codamol, paracetamol	Drowsiness	Constipation

Abbreviations: F Female, *M* Male, *eFI* Electronic Frailty Index, *CFS* Rockwood Clinical Frailty Score.
a Risk of frailty as assessed by routinely collected data on general practice records using the eFI, ranges from fit to risk of severe frailty.
b Frailty was also assessed by a clinician using the CFS, which ranges from very fit to severely frail.
c Pain severity over the week before attending the ICC, using the IPOS.
d Adverse effects reported in relation to the analgesia listed in the table.
* Unsure if adverse effect was caused by pain medication

9.3 Summary of themes

As outlined in Section 7.5.8.2, the findings resonated with two theoretical frameworks. These were the 'three lines of work' proposed by Corbin and Strauss[338] and Horne and colleagues model of adherence[344,345] (see Section 6.3.2 for a detailed description of these theories). These helped in summarising older adults and informal caregivers' experiences, perspectives and concerns in relation to chronic pain, opioid analgesic use and cognitive adverse effects, as well as the challenges, impact and support need regarding these.

Overall, four themes were identified, which included *insurmountable work* (relating to the 'lines of work' that patients and their informal caregivers carry out), *emotional and psychological wellbeing*, *searching for a sense of safety and security*, and *influencing factors*. These themes and their subthemes are described in Table 9.2.

Table 9.2 Themes, subthemes and their characteristics

Themes and subthemes	Characteristics
(1) Insurmountable work	**Tasks, activities and exertions that are undertaken and integrated into experiences of chronic pain and adverse effects**
Practicalities of managing chronic pain	The tasks, activities and exertions that are undertaken to diagnose and manage pain, as well as to avoid exacerbations of pain and cognitive adverse effects from pain medication.
Chronic pain and the social and environmental context	The integration of chronic pain and cognitive adverse effects in daily life, including the environmental (e.g. at home) and social (e.g. relationships and socialising) contexts
(2) Emotional and psychological wellbeing	**The emotional and psychological aspects of chronic pain and cognitive adverse effects, as well as maintaining or adapting identities and self-concepts.**
Overwhelming sense of loss	Coping and managing variable emotions in response to pain, as well as maintaining psychological wellbeing. This included a sense of loss, as well as feelings of isolation.
Coming to terms	Coming to terms with chronic pain and/or loss of function, as well as changes caused by pain management and adverse effects. This involves integrating their experience of pain into the everyday context, including consequences for everyday life (e.g. organising the day-to-day around pain, its management and adverse effects) and how they move forward with their lives.
(3) Searching for a sense of safety and security	**The search for a sense of safety and security in clinical encounters to minise feelings for despair and abandonment, and the role of caring in the experience of pain management.**
The importance of caring	The importance of caring in clinical encounters and the role of communication in their experiences of chronic pain and cognitive adverse effects.
Continuity and timeliness of care	The way in which their story of pain management and is understood in a clinical setting, and how timely access to care and support is.
(4) Influencing Factors	Internal (i.e. specific to the person) and external (i.e. healthcare professionals and settings of care, and family) factors influencing pain management, analgesic use and

Internal influencing factors	The factors that are person-specific that can influence decisions regarding pain management and analgesics use. These included factors around the impact of addiction, misuse and tolerance, adverse effects, attitudes, beliefs, concerns, choices and preferences, pain severity and knowledge.
External influencing factors	The factors that are external to the person that can influence pain management and analgesic use, otherwise known as third party influence (e.g. family, friends, healthcare professionals or settings of care)

9.3.1 Theme 1: Insurmountable Work

In the interviews, there was a strong narrative around the amount of 'work' that patients and their informal caregivers carry out to manage their chronic pain and adverse effects. This included the practicalities of managing pain, and integrating chronic pain into the environmental and social context.

9.3.1.1 Practicalities of managing chronic pain and cognitive adverse effects

Participants carried out a number of tasks that were necessary to manage chronic pain. This included finding the cause of the problem (i.e. diagnostic-related work), and managing regimens (such as medication) and symptoms. These tasks would be undertaken to prevent and manage crises, such as exacerbations of pain or experiences of cognitive adverse effects. These tasks can be cumbersome and are cumulative in nature (i.e. with each additional element comes more impact to their day-to-day lives).

Participants recognised challenges with finding the cause of chronic pain. Clinical assessments and/or diagnostic testing were often a part of their experience, which involved scheduling and attending visits to healthcare providers and undergoing scans (e.g., x-rays). Timelines to receiving a diagnosis of what was causing their pain varied. Some patient participants described how testing or physical examinations were not forthcoming, but would have helped in determining how to proceed more effectively and circumvent their experience of pain escalating to the level that it did. This forced some to seek diagnostic tests via private healthcare. Patient participants described the value of a diagnosis of pain, when it was provided, as they appreciated minimising uncertainty and knowing what was wrong.

> P: …the original doctor who we had, years ago, um, he said "When you was younger, you played so much sport, you've abused it." And as far as I know, and this is from when I had three injections in it, one of the surgeons said "We believe you've got two vertebrae touching, and there will be a follow up." And there hasn't been. So, I've no idea where we're going from there.
>
> 228 (Patient)

Uncertainty was common for participants when trying to determine the cause of their pain, despite undergoing clinical assessments and other diagnostic testing. This often made their experience of chronic pain feel unsolvable and something that they may have to live with. Problem-solving and theorising about the cause of pain was a central focus for some (such as other health conditions, one pain leading to another or not recovering from other incidents (e.g. falls)).

> P: But unfortunately, they haven't helped. It's just that they… you know, it just seems one of these unsolvable situations. And I don't want to think like that, 'cos once I've started thinking that this pain is never going to go, it's not going to go, is it? You know… I sort of do think one day they'll… something will come and, and they'll just [Makes noise: Pew], zap.
>
> 113 (Patient)

Access and adherence to prescribed therapies and recommendations meant engaging in numerous tasks related to pain management and associated physical challenges. This included non-pharmacological approaches, surgical and other non-surgical procedures, obtaining necessary medications and equipment, learning their pain medication regimen and prescribed exercises, travelling to clinical assessments and treatment, as well as waiting on healthcare professionals. Opioid analgesics were only one aspect of a broader experience of regimen work. Access to non-pharmacological approaches varied, with a majority of participants acknowledging that they would have liked to try more alternative methods to pain management. Complementary and alternative therapies included acupuncture and massage. Again, some paid privately to receive the care needed but maintaining in the long-term this was not feasible. There also appeared to be a conflict between mainstream medicine and alternative therapies, which potentially limited how pain was managed.

> P: Some of that […] holistic stuff. There was that, and, er, with some other people, then they, the doctors have said "No, that's no good. She doesn't want them, she wants this." I thought 'Oh, well, you know your job', so, I just let them get on with it, you know, but it would have been nice to have tried anything like that but… And sometimes you wonder 'Well, would it have actually [helped]…', you know.
>
> 003 (Patient)

Travelling to medical appointments, treatments or therapy contributed to the concept of 'insurmountable work', and came with multiple challenges.

> P: You see, […] I couldn't walk at all, and I had the doctor come here, I said "Could he come?" because I couldn't… and no one could take me to the doctors.
>
> 126 (Patient)

> P: …if you're getting physio, er, and telephone and you ring 'em, and of course, they can't come to you, yeah, so… and I couldn't get out, so, that killed it stone dead.
>
> 158 (Patient)

Experiences of obtaining pain medications and equipment to manage chronic pain and mobility issues were discussed. Pain medications were mostly introduced or changed by GPs when attending general practice. A reluctance to prescribe pain medications, which created additional work and/or frustration.

> P: And I said I've come here for some pain… […] Painkillers. "Oh, I don't know", la-la-la, "You can't have Ibuprofen." "I don't want Ibuprofen." They're no good either. He couldn't get it through his head. In the end, he gave me co-codamol, which he wasn't very happy about.
>
> 137 (Patient)

Challenges faced by patients included issues and delays with prescriptions being sent over to the chemist and obtaining all pain medications at the same time, when needed. For some, this occasionally meant purchasing over the counter pain medications to top them up in between. Support in ordering and collecting pain medication was provided by some informal caregivers (including family and friends). Some acknowledged these issues were temporary (such as a change in dose). Interactions with healthcare professionals about pain medications could also be combative.

> **I: And how have you found that change going from one tablet to three tablets [in relation to morphine]?**
>
> P: Bit of a nuisance, having to make sure I've got the three together, instead of just having the one, you see.
>
> **I: Does that cause any issues with the pharmacy to have them altogether?**
>
> P: At the moment it is, yeah. Well, not my pharmacy, the doctor's pharmacy, because I mean they're not sending 'em. 'Cos they sent one lot, and then they didn't send the other lot.
>
> 003 (Patient)

> **I: Fentanyl patch, is it?**
>
> P: Yeah, they're on 72 hours, so, it's like Monday, Wednesday and Friday, I change 'em. But, um, looks like Monday's going to come and go, and I'm not going to get any until Wednesday or Thursday next week. So… well, what can I do? […] You can't demand 'em, they just say "No, you're not due while the [Date]". Well, I don't know where they get, I don't know where they get that from.
>
> 115 (Patient)

Another aspect of insurmountable work was around the management of unused medications; this varied from returning unused medication to the pharmacy to disposing of them down the toilet. They also had to manage other medications that were prescribed to address the adverse effects of opioid analgesics.

> P: So, the month after that, they sent me another box of thirty, so, I've got two full boxes in the cupboard and then this last medication come, the bloke brought 'em, and I said "You haven't brought me anymore?" and he had, they had. So, […] I made him take 'em back to the chemist. They said the prescriptions had not been altered, but I mean, you never go through all them. […] I've never used any of 'em, because as I say, I put it down from having the patch on my arm.
>
> 094 (Patient)

Learning pain medication regimen was an important part of the chronic pain experience and predominantly discussed within the context of all the other medications they took. Where possible, streamlining medications was appreciated and made the management of medication regimen easier.

> P: I used to be on about seven tablets in a morning and seven at tea time. But now I'm on two. And then with them two, and then me paracetamol four times a day, so. Must be better not taking all that medication.
>
> 094 (Patient)

The use of multiple medications (including pain medications) meant that patient participants had to consider and manage potential interactions.

> P: …I think there are medications that you know that just don't work for you. And I think tramadol's probably a wonderful drug for other people but not with my mix. […] I mean what the doctor's say is, because I always ask this question, "Will it affect my other medications?" "Oh no, no, it would come up on the screen." That's what they tell you, "It will come up on the screen if it didn't go"
>
> 113 (Patient)

Patient participants developed routines and patterns with pain regimen. The majority found their pain medication easy to manage. Prescriptions were carved up over periods

of the day, in line with the advised dose and frequency. Sometimes it was the pain that reminded them of their next dose.

> P: Once in a morning when I take maybe… go in the afternoon, tea time, and then late on a night, I take 'em. If I take them late on a night, I get a better night's sleep. So, that's how I do it.
>
> 125 (Patient)

Routines were considered reassuring and minimised issues/work (e.g., the chance of missing doses or taking pain medications incorrectly). Most expressed that they knew which medications they had to take and when, and/or used systems to help them to remember whether they had taken them. Techniques for managing pain medication included using a compliance aid (otherwise referred to as a medication tray or NOMAD).

> Because I'm getting a bit older now as well, […] and I said "Can I have them in a NOMAD now?" So, she said "Well, yeah, we can sort that out for ya". And I thought if I do that, then I know what day it is and what times I've got to take them. Because I think myself, I wasn't taking 'em right.
>
> 003 (Patient)

> P: …I put 'em out and, you know, sort 'em.
>
> **I: Yeah, and do they fit in to your daily routine alright, taking them throughout the day?**
>
> P: Yeah, 'cos I don't really go anywhere. And if I do […] then I'll take the dose that I'm going to have at lunch time with me, so.
>
> 234 (Patient)

Learning and managing medication regimen was an important activity to patients and their sense of independence. Familiarity with medications (including pain medications)

was part of learning their regimen. Informal caregivers supported these systems and routines in various forms (e.g. collecting, organising and reminding).

> P: …I know [Carer participant's name] thinks 'You're a lazy bugger' and I probably am, but, you know, I'm the first one to admit it but I want to at least try and carry on, you know. I don't want to give up, if I can help it.
>
> 025 (Patient)

> P: I don't take any more than, no more than eight a day, if I'm on paracetamol all the time. And I obviously cut out those, if I'm taking co-codamol. I've got enough about me to be able to realise that you don't take all of them together.
>
> 234 (Patient)

The approach and consistency in how people approached taking their pain medication varied, although it was noted that they were more effective when taken regularly.

> P: I don't want to take it regularly, really. I suppose you should do, so you can keep it in your system, but there again, then you're constipated and that can cause problems with the other, so, you don't really like taking them all the time.
>
> 169 (Patient)

> P: But you've got to make sure that you do take them regularly. You know, it's no good forgetting.
>
> 234 (Patient)

Spacing pain medications throughout the day was challenging when their pain was not controlled, and regimens and routines were sometimes abandoned.

C: Yeah, you couldn't take any more than eight [Referring to co-codamol].

P: So, I was taking eight of them, instead of eight [paracetamol], and I think it did mix 'em actually.

C: Wouldn't surprise me.

P: Well, if you've got pain and then you could take 'em, don't ya?

C: He takes them like sweeties, and I'm saying "They're not sweeties, you know."

P: Sometimes I'm naughty.

137 (Patient and partner)

P: You don't know what to do with yourself, that's the thing. So, in other… you try anything. I mean I have thought to meself 'Shall I take another two?' You know, and take four altogether […] of the strong ones, er, but then I think 'No, I can't. You mustn't'. Because you've got to space them out. But you just cannot put up with how long it's gonna take before it gives you a little bit of relief.

234 (Patient)

Sometimes the 'work' that was carried out to manage pain medication regimen was disrupted. Doses were missed now and again for various reasons, which caused a break in their routine and could lead to ineffective management of their pain. Cognitive adverse effects or being admitted to hospital were described as potential causes for missing doses. Ownership over the management of medications was particularly challenged within a hospital setting, and was perceived to be a paternalistic approach.

P: …I think that's what's […] that's why I went wrong, because I wasn't having my tablets properly when I was in hospital because they just give you 'em when they decide to do the drug round. And you're getting them later than what they should be, do you know what I mean?

003 (Patient)

> P: I'm perhaps losing out on one lot, because I've either slept through in me chair or some other reason.
>
> 234 (Patient)

A number of patient participants described how certain pain medications were easier to manage than others, as they were more streamlined or worked well together.

> Paracetamol in the morning ones, and that's done with, until lunch time, when I take… need to take two more. It's working quite well with this patch, that's all I have to think of.
>
> 177 (Patient)

The management of symptoms (such as pain or adverse effects from pain medication) and loss of functionality were a large component of managing chronic pain. This included learning about the pain and adverse effects they were experiencing and how best to manage them, as well as monitoring and reporting these symptoms. Firstly, learning about pain and how best to manage pain will be discussed, followed by discussion regarding adverse effects.

In learning about their pain, patient participants provided accounts of their experiences of pain (such as location and severity) and loss of mobility, as well as the trajectories of the chronic pain and instances of acute pain. Where informal caregivers were present, they added to the narrative, either from their perspective or helping to clarify the narrative. Patient participants often described multiple sources of pain that they had to manage. Pain was overwhelmingly described by participants as severe. Additionally, pain was labelled as grating, shooting, throbbing or a deep ache. Most explained that their pain had been ongoing for years, whilst others chronic pain had developed more recently. For some types of chronic pain experienced, pain would flare up on and off from its onset to the current day. A few said their chronic pain had been the result of a fall, accidents or surgical intervention. Patient participants also highlighted the relationship between pain and mobility.

P: …I used to get the hip pain more when I used to do any walking, obviously, I don't do any walking, so, that's… but me, me hip still hurts me and all that. But it's not like, um, as bad as what it was before. Because obviously I'm not doing […] any walking.

125 (Patient)

P: Right, well, the chronic pain I've got, the […] most prominent one, at the moment, is in my shoulders. The left-hand shoulder is the worst one. There's no cartilage, apparently, between… in the shoulder, [Deep breath] so every movement, it grates, um, and it is just so painful […] Um, also back pain; I've got dreadful back pain, er, right at the base of my spine, and I can't stand for any length of time.

234 (Patient)

The management of chronic pain was viewed in multiple ways. For some, it was normal or considered a part of ageing, whilst others could not accept being in pain.

C: [Patient participant's name] doesn't do pain, he doesn't like any pain and this is the biggest problem. He thinks…

P: I'm a wuss.

C: … if you take pain relief, you shouldn't have any pain but I said "You do". It only sort of numbs it a little bit.

P: I can't accept that.

025 (Patient and wife)

P: …I don't know how to express it really, it's just normal now, to me, [being] in pain, you know.

094 (Patient)

Pharmacological approaches were a common thread in experiences of managing pain. Various pain medications were prescribed to manage patients' chronic pain. The opioid-

analgesics that were reported included buprenorphine transdermal patches, codeine, dihydrocodeine, fentanyl transdermal patch, morphine, oxycodone and tramadol. Disease-modifying medications or non-opioid analgesics were also prescribed alongside opioids in some instances. This included allopurinol or colchicine, duloxetine, gabapentin or pregabalin, ibuprofen and paracetamol. Occasionally, additional pain medication was introduced for the onset of acute pain (e.g. post-surgical pain). Analgesic efficacy varied; most pain medications offered no or slight pain relief.

> P: Yeah, but they [Referring to morphine and gabapentin] just take the edge off. That's all. They don't sort of take it down completely, they just take the edge off.
>
> 003 (Patient)

> P: …please accept that it's never gone, it's always there at the back, you know, niggling away, […] I can't get it out me mind this one, […] I take painkillers, loads of the bloody stuff, that's probably one of me problems you see, you see I take that bloody much that I think I should be free of pain altogether, and I… you aren't.
>
> 025 (Patient)

Understanding how best to manage their pain was often trial and error, especially with pain medications. Sometimes all possible options had been exhausted and managing pain seemed futile.

> P: I think it's a case of hit and miss, the doctor tries something, and you say "Oh, it doesn't work", they give you something stronger, and if it doesn't work, they give you something stronger, er, and that's how it went. […] To a degree, I understand that they're not going to give the strongest thing straight away, when it's not necessary, you know, that… um, but I just feel that there's been periods when we've had extreme pain, when it could have been eased.
>
> 158 (Patient)

C1: But you go to see the GP, and I must admit he just looked through the records and said "Yeah, well, we tried that, so, that doesn't work. We've tried this, so, that doesn't work."

P: Well, he said to me one day "What do you want me to do?" […] And, I said "Well, I want you to help me [Laughs] with the pain" and he just said "I don't know what to give you."

171 (Patient and husband)

A couple of patient participants highlighted that healthcare professionals should make sure that pain medications are actually needed and not prescribed liberally.

P: …make sure that people don't take 'em, if they don't need 'em. I think, possibly, there would be people taking them, er, [3 second pause] I suppose if I took a lot, if I was on a lot, I'd be a bit spaced out sometimes. And I think some people would want to feel like that, I wouldn't.

041 (Patient)

Although pain medication appeared to be the most common approach to managing pain, participants explained that a variety of methods were used in conjunction. These included complementary and alternative therapies, physiotherapy, equipment, non-surgical interventions (e.g. cortisone injections) and surgical intervention. Pain relief was often temporary and treatments needed to be maintained.

P: So, I'd seen specialist after specialist, and they kept saying it was muscular. I went to chiropractors, I went to bone setters, I did everything under the sun; nothing worked.

171 (Patient)

P: About every three month he sends for me and I go and have, um…

C: And she has steroid injections […] in her back, neck, shoulders, hips, and for a little while, you were a bit looser, aren't ya? […] And then, as they're wearing

off, I can see, because my mum turns into the tin man [All laugh] and it's almost like she needs oiling. Everything tightens up again.

P: Yes, it does really, yes.

C: […] And I think that probably needs reviewing as well now, because I'm… appears to have reached the end of its usefulness a bit, don't it?

232 (Patient and daughter)

Physiotherapy and prescribed exercises were relatively common in managing chronic pain. Although, its benefit for some patient participants was questioned by healthcare professionals. Repetition of 'old' exercises were a source of support for some, which was accompanied by a hesitancy to reengage with services in regards to the cost-benefit and frustration with current practice.

P: I don't want them to shove letters through me door, saying "Do this! Do that!" I want them to see me.

171 (Patient)

Equipment was either provided by professionals or sought to manage pain but did not always have the intended effect. This included, but was not limited to, electronic equipment, insoles, specialised chairs, perching stools, walking frames and wheelchairs.

P: Yeah, I mean the frame I found smashing.

C: You do walk well with the frame, don't ya?

P: Yeah, yeah, and, and it, it doesn't bother me, I mean it doesn't bother me what people think, […] if people are telling you it will do you good, you do it.

C: It's got a seat on, so, if he's walking and he starts to hurt, he can have a sit down for 5 minutes and then carry on.

025 (Patient and wife)

> C: You see, he'd probably never use the damn thing [referring to a heavy-duty walking frame], if he got out, you know.
>
> P: It's down the shed. And we had to move things out to get it in, 'cos the… it's full up down there. There's a lawnmower. We found a little spot for it at the end of the lawnmower and that's where it's gone back.
>
> 137 (Patient and partner)

Surgical interventions were perceived as a solution to address chronic pain and loss of mobility by a few participants, which required preparation and management. Again, this was not a possibility for some due to potential complications.

> P: …I think that they only really, what they can do, is just operate. Otherwise, I'll have to live with it, won't I?
>
> **I: How do you feel about the idea of living with it?**
>
> P: Not very nice, is it? No, that's why I said I'd definitely… he said "Would you go have it done?" I says "Yes, certainly would."
>
> 094 (Patient)

> P: ...I can't have an operation […] I need a hip replacement, but I can't have that either, because they can't put me out because I'm not strong enough, because I've had the heart thing done. I wouldn't be able to take the anaesthetic.
>
> 115 (Patient)

Other non-surgical procedures or treatments were also part of the work carried out to manage chronic pain. This included corticosteroid injections, traction, x-ray and other diagnostic tests, epidural, intravenous infusions and vertebroplasty.

Overall, there were various approaches to managing pain but patient participants often felt limited with choices and their pain was largely unresolved. Many continued with minimally effective or ineffective approaches, as it was all they could do and it was

better than nothing. Whilst, a few acknowledged that they felt the healthcare professionals had tried all they can.

> P: Er, there's other nights I think 'Oh, I'll get them down me, see if they'll help me a bit', you know. Yeah, well, as I say I've got a high threshold, er, you've got to have, I think, as you get older because you get a lot more aches and pains, so, then you haven't got to be frightened of pain.
>
> 041 (Patient)

Pain is a day-by-day experience for the patient participants, and it can be alarming if new pain or exacerbations of pain occur. Updating and disclosing issues with symptoms of pain varied, especially if they felt that they had exhausted pain management options.

> P: So, I thought there's no point in going to the doctor's [in relation to shoulder pain], because what's he gonna do? Refer me?
>
> C: Yeah, he'd probably refer you to physio and things like that, and then…
>
> P: Physio. I've been doing exercises for about 12 weeks and it ain't done any good.
>
> 027 (Patient)

> P: I'm in pain with me shoulder and me fingers, […] I don't know how to explain the feeling in me fingers, it's like a buzzer going off, down me fingers. I don't what that is, I've not told anybody else but like […] I don't think anybody else could feel it.
>
> 094 (Patient)

Another aspect of pain management that all participants had to learn and contend with were adverse effects of pain medications. They recounted the various adverse reactions with opioid analgesics, as well as non-opioid analgesics. The adverse effects from pain medication had often stretched further back than the past year and mirrored the trial-and-error process with pain management (see 9.3.3). Cognitive adverse effects were a

prominent part of a number of adverse effects experienced. When asked to prioritise the adverse effects that bothered them the most, the majority of participants said cognitive adverse effects, as well as constipation, nausea, sickness and mood.

> P: I mean when you feel drowsy, you can try and shut your eyes and go to sleep, but when you're feeling real sick, eurgh, as if you'd eaten summat that was no good for ya. Er, oh, you're wanting to wretch all the times, you know, they're really, eurgh. That's why I don't, I don't like taking 'em.
>
> 041 (Patient)

> C: I think the one that's worried me the most is the dizziness, for fear of my mum falling when there's no one here […] um, the lethargy, the helplessness, the heaviness, because that's seeing me mum sat there, just not wanting to be here. So, that one has really torn at the heart.
>
> 232 (Daughter)

Cognitive adverse effects were extremely distressing for both patient participants and their informal caregivers, and challenging to manage and it can be difficult to decipher what is happening. The anxiety that the adverse effects cause can also physically impact the informal caregiver.

> C2: It's not nice to see her like that because she ain't like that as a rule. It's upsetting to see her like it, because you feel helpless, and you don't know what to do for her.
>
> 171 (Family friend)

I: Um, and how did it affect you when he was quite dizzy and constipated during that time?

C: Well, I don't have time to feel anything. I just go to him. It's afterwards, then my stomach's going, doesn't it?

P: It does.

C: And I'm running to the toilet all the time, it upsets my stomach.

228 (Patient and wife)

Solutions to manage cognitive adverse effects, as well as other adverse effects, included but were not limited to amending the dose strength, stopping the pain medication and/or trialling a different pain medication. Although, as highlighted in the quotes below and above, in the moment that they occur, participants felt that there was very little that they could do and it was more of a waiting game for cognitive adverse effects to subside.

P: … I started cutting down on the painkillers [i.e., codeine and naproxen] […] to see if the pain got any worse [...] without it, and it didn't. So, I ended up cutting back and cutting back, till I was taking virtually nothing. Um, and my head cleared. But I still had the pain, unfortunately [Laughs].

158 (Patient)

Patient participants also highlighted that other medication could be prescribed alongside to manage some adverse effects caused by opioid analgesics but not for cognitive adverse effects.

P: … I mean I took things for the constipation, didn't I? That I couldn't take to alleviate the symptoms of feeling dizzy and disorientated, and all that. I couldn't take anything to counteract that, whereas, when I was constipated, I took […] Laxalose [Lactulose].

027 (Patient)

A few debated whether they could persevere with the cognitive adverse effects to see if they dissipated.

> P: I've tried them [i.e., tramadol] twice, I think. I think the first time it was more or less immediate. And the second time, it was, but I carried on thinking once it got in my system, it might get better but I just got worse and me husband said "You're stopping 'em."
>
> 171 (Patient)

> C: …so, me mum's prepared to carry on, so, then after about three days, me mum started to buck up and, yeah, started to…
>
> P: [Talks over daughter] Oh, yeah, I started… say, I started to look better.
>
> C: You know, her old self again, more, you know, more alert…
>
> 177 (Patient and daughter)

Adverse effects exacerbated and added to the complexity of other health conditions A few explained how adverse effects also added to the issues with other health conditions.

> I'm a diabetic as well, so, you've got your diabetes, but your diabetes makes you tired, you know, your tablets there, so, you just… [Sighs] I give up half the time, so.
>
> 003 (Patient)

Cognitive adverse effects were sometimes a common experience for patient participants no matter which pain medication they tried.

> C: I think that was probably a recurring theme, them through all… throughout them all. Um, I can't say exactly but I think […] I think it was the opiate-based ones that caused a lot of the dizziness… the only thing that didn't cause you dizziness was the Co-codamol.
>
> 232 (Daughter)

Overall, there was a struggle between managing pain and cognitive adverse effects.

> C: You know, but if I think 'Oh, well, he's out of pain, but he's still seeing funny things', do you know what I mean? [Deep breath] There must be something in between, mustn't there? There must be…
>
> 027 (Wife)

> P: I was just out of it all the time, um, and they make you feel ill, so, then you're not just controlling your… you're not just dealing with your pain, you are dealing with another problem because you feel so ill, as well with it.
>
> 171 (Patient)

Disclosure of cognitive adverse effects, and adverse effects in general, to healthcare professionals varied. Some reported managing the reactions themselves.

> **I: Did you have a discussion with the GP around stopping taking them or just a personal decision?**
>
> P: No, I just stopped taking 'em. You can't… they're GP's, that's all they really do, is take… let's face it, they just give you medication, don't they?
>
> 126 (Patient)

Additionally, they would speak with family and friends. Family were also often witnesses to the cognitive adverse effects and had more recollection of the experience.

> P: And she said "You should… we'll have to get you to drop it." Because she said "You're not right, mother." [Laughs] So, we gradually… the doctors didn't but I did it myself, we just stopped taking them four times a day to two.
>
> 094 (Patient)

Barriers to being able to disclose issues with adverse effects included noticing them in the first place, which posed its own challenges. Sometimes cognitive adverse effects were noticed immediately or they were able to identify patterns and associations with the opioid analgesics and the onset of adverse effects.

> P: But I got used to being dozing off, 'cos I thought, you know, I didn't realise it… what it was that's causing it, until me granddaughter said, but, um, nothing really bothered me.
>
> 094 (Patient)

> P: But, um, what I've deduced for myself, is that, and this is to do with tramadol. And this is basically why I was reducing it myself, because, I don't think tramadol and gabapentin, in the system of the person, works very well… certainly not in my system. I don't think those two work very well together.
>
> 113 (Patient)

Participants highlighted challenges in knowing exactly what caused their adverse effects, especially cognitive adverse effects. Patient participants described how they underwent standardised tests for memory but they would come back within the normal range. Rarely, some patient participants might also be subjected to investigative tests because of other adverse effects.

> **I: And how did it affect you when you started noticing these side effects?**
>
> P: Well, I think I panicked a bit, you know, without… with all that, you know, thinking that, your, you know, your memory loss and everything like that went, you know, and with me brother dying of, um, having dementia and then dying, you know, and you think 'Oh my god', you know. You just think of all these things that you're going through, and have I got, you know
>
> 003 (Patient)

> C: And then they said, at first, it was irritable bowel […] They sent you to see someone who… he had all these tests done and then they said "No, it's your medication. Go back to your GP, that needs sorting." […] [Deep breath] you know, he's gone through like colonoscopy's and endoscopy's, for it not to be anything there. […] And it was just the case it was painkillers.
>
> 197 (Wife)

Cognitive adverse effects from pain medications were sometimes put down to other health conditions.

> C1: We, er… me and [Husband's name] got concerned when she started falling asleep. And then they just kept putting it down to her diabetes but she didn't have diabetes when we had concerns.
>
> 003 (Daughter-in-law)

For some, cognitive adverse effects felt like something that had to be engulfed into everyday life.

> P: But I've noticed that with the medications I'm like in a fog.
>
> 171 (Patient)

> P: I've told them that they affect me.
>
> **I: And how was their response?**
>
> P: Well, "What is there… what else can we give you? Because you're on so much medication. We… you have to be careful of…", you know, "We can try this or try that", er, but there's not a lot of response, because there's… I don't think there's anything else they can do.
>
> 234 (Patient)

There were times that cognitive adverse effects also impacted their ability to complete tasks related to personal care.

Interviewer: And what was that like for you both [in reference to increasing Longtec dose]?

C: It was horrendous.

P: I don't remember it.

C: Because I was going mad because he wouldn't get up. […] He didn't go in the shower, he didn't want to do nothing [Interviewer's name].

P: I didn't want to get shaved, I mean and I get shaved every day. It's one of me things I've always said, I have a shave. However, poorly I've felt and however poorly I've been […] I had to have a shave.

025 (Patient and wife)

Language across the interviews to describe cognitive adverse effects varied. Participants sometimes used non-descript language to explain the adverse effects they experienced, in that the pain medications caused 'all sorts' of problems or caused a 'bad reaction'. There was no common language for explaining cognitive adverse effects and many used their own terms to describe how it felt.

P: I was just saying "Them Co-prodamol's [Co-codamol] were making me feel really sick." And, er, were real woozy in the head and he said "Oh, we'll put you on a lower dose then."

041 (Patient)

P: Well, it's not like being drunk, it's not a nice feeling. It was, um, it's a bit slap happy feeling, but, do you know what I mean?

I: So, just feeling a bit euphoric?

P: Yeah, you have a pain but you can't feel it anymore because your heads messed up. I didn't, I didn't like it at all. Um, it's very hard to describe. I gather everybody has that… the same thing.

137 (Patient)

Another aspect to participants' management of chronic pain and pharmacological approaches was crisis and prevention management. Patient participants explained how severe episodes of pain (i.e. onset of new pain or an exacerbation of existing pain) and/or loss of function could lead to a crisis situation. Where a crisis does arise (such as a fall), there is 'work' they have to put in to addressing the event and try to minimise its impact. Crises would sometimes result in a hospital visit, especially when support in the community was not available.

> P: I never felt a thing, […] and I'm sat there with my leg under me knee, because I rang me daughter and said "I've fallen again", because I kept falling. And I said "But I've really hurt meself." And, so, she said "Oh, don't worry. We'll be there in a minute", […] 'cos I rang on me alarm thing, and she rang, rang them all, and they all come round [Laughs]. I had three of 'em 'ere. But she rang again, me daughter, and said to 'em "Don't touch her", you know, till they come. And I didn't feel a thing, and I didn't know that I'd broken it or done anything wrong…
>
> 094 (Patient)

> P: That was another episode, and that was another pain that [I] can't describe.
>
> C: It was the… it… his neck locked completely.
>
> P: And, anyway, we got the paramedics out, they whipped us into hospital…
>
> 158 (Patient and wife)

The intended solution (i.e. pain medication itself) may also lead to crises. Cognitive adverse effects can leave people feeling vulnerable when they started or were taking opioid analgesics.

> **I: Why is it that you don't really want them?**
>
> P: Yeah, I just don't like feeling. Er, my eyes will be like everything's distorted and, um, you feel dizzy and sick, as though, if you stand up you could possibly

fall over. Because that's how they, they make me. So, I have to be very careful with what I take.

234 (Patient)

9.3.1.2 Chronic pain, cognitive adverse effects and the environmental and social context

Chronic pain influences how lived space and everyday life are organised, as well as, relationships with others. Opioid analgesics and cognitive adverse effects can also have a profound impact on these. Both patients and informal caregivers described how chronic pain, loss of function and adverse effects from pain medication (such as opioid analgesics) have to be integrated into day-to-day activities and exertions. This ranges from instrumental activities of daily living (such as cleaning, cooking and shopping) to other activities specific to each individual (such as relationship work and socialising).

Participants described challenges and limitations with housekeeping and maintaining the home due to pain or loss of function. Activities included assistance with cleaning, washing, shopping, cooking and gardening. A number of patient participants described completing tasks as and when they felt able to, and often stopping when the pain begins to flare up. There was a sense of loss over their inability to do tasks that they used to do (such as cleaning) or enjoyed doing (such as gardening), and many tried to continue what tasks they could. Although pain was identified as the main factor that participants had to work around, one patient participant added that they also try to get housework done around cognitive adverse effects also:

I: And did you just decide to stop taking them [co-codamol] or did you make any alterations to the way you took them to manage the side effects?

P: Er, no, I didn't change really, I just, you know, I still took… when I needed them for the pain, I'd just take 'em and that's it. Regardless of whether I'm going to sit here and go to sleep. Um, I've tried to get things done as I wanna do it, like, you know, I try do little jobs and things, as I say, but I do it sitting down, so.

234 (Patient)

Patient participants explained the limitations with activities such as shopping (e.g., being able to view the shelves from a wheelchair), and how this relied on family to be available. For some, this support was not available and they would have to find a way to manage routine tasks around their issues with mobility and chronic pain.

> I have to go on a Friday to the shops, because I mean there's nobody to go for me. So, I go with somebody else who's in 'ere [residential home], in a taxi, and er, I have to go everywhere by taxi. You see, we only get a bus about every hour and a half. And it ain't long enough, you know.
>
> 169 (Patient)

A number of patient participants described challenges with preparing meals and carrying beverages due to pain or loss of mobility. Some had to use electronic openers and other tools to avoid causing pain or assist with the limited movement in their hands. In some instances, meal preparation was difficult or even dangerous.

> I did try last week to fry bacon and egg, but try'na do it with, [Sighs] with one hand and that, and I can't pick the bacon out, you know with the tweezer things, and it… well I did it eventually, but it was dangerous because of the fat was spluttering and, oh dear.
>
> 094 (Patient)

Where patient participants struggled with housekeeping or maintaining their home, support was sometimes provided informally by family and friends to varying degrees (depending on what was needed) or they employed a cleaner or formal caregivers, or had a mixture of support. Informal and formal caregivers supported with multiple activities, including but not limited to cleaning, washing, shopping, cooking and gardening. Family who provided care expressed that there can often be a lot to juggle.

What other bits do you do to provide support for [Patient participant's name]?

Carer: [Laughs] Everything! [All laugh] I do everything [Interviewer's name]. I do all the cooking, cleaning, the washing, the ironing, everything.

025 (Wife)

C: But it's very stressful when I'm having to work full time and… er, we get some[one] come in here in the mornings, someone… we have people staying with you overnight when you're bad and it's… there's a lot of plates spinning. A lot of plates spinning. And at the moment, we're keeping the plates up, aren't we?

232 (Daughter)

In some instances, where their informal caregiver provided care, they would sometimes need support from wider family if the informal caregiver had health issues or other commitments to manage.

I: And how have you found managing, because you said you've had a few health issues yourself?

C: My daughter comes and helps, she's our carer now, ain't she?

P: Does shopping for us and cleaning.

C: Cleaning and all like that.

125 (Patient and wife)

Patient participants explained how issues with their home setup contributes towards their experience of pain. Some struggled to mobilise from their chair or bed, and could benefit from new furniture to help reduce their levels of pain (such as a recliner). A couple of patient participants described how they were more cautious going up and down stairs, or that their pain meant that they were restricted to the ground floor of their homes.

> P: But it was so intense that I couldn't stand or sit… getting in this chair and sitting down, it was extremely painful to say the least. And, I couldn't bend my knee fully, so, er, it meant that I couldn't get up the stairs, even though I've got a chairlift. 'Cos I couldn't sit in the chair lift; I couldn't bend me knee enough to allow me to sit in it to get upstairs. So, I slept in this recliner for about a week.
>
> 158 (Patient)

> P: I'm in here all the time, but I walk backwards and forwards to the loo, because I have a caravan toilet in the hall way, which [Person's name] put in, because she knew I couldn't do the stairs, […] temporary arrangement, she got me a bed, got rid of me coffee table, well, it's upstairs I think. She got rid of me chair that matches me settee, and we got this one.
>
> 094 (Patient)

The home environment may need to be modified to accommodate their pain or loss of function. Some found that although modifications were put in place (such as support bars to help them go outside in the garden), they were not able to use them as there was nothing they could use after that point. Others felt that they would benefit from adjustments to their current setup:

> P: …'cos my arms are real bad […] it had a new, you know, ball and socket put in it, 'cos it was really bad, […] and me muscles get so tight, you know. And it really, really kills. And plus, my kitchen ain't what it should be because I've got to reach up like that to get over the sink or whatever and over the things, whereas it should… if it was down low, it would be alright but it ain't, so… but like I say, you can't complain.
>
> 003 (Patient)

Patient participants described activities they adopted to maintain and promote their overall health; either because of their chronic pain or to minimise it. This included self-care (including personal care) and managing other health issues or chronic conditions, which included repurposing household items.

> P: You see, when I'm watching television, I'll sit like this and put a cushion behind me, like that. So, that I'm resting me a- … that's it, rakes right across but that is, it's like a pain and an ache, you know what I mean?
>
> 232 (Patient)

Chronic pain and loss of mobility made managing personal aspects of care (including washing and dressing) problematic, and support was needed. This support was usually provided by family, friends or a care company. Sometimes formal support was lacking for people with chronic pain, unlike other conditions (i.e. diabetes).

> C: Well, I get him washed and everything. Well, he gets washed his self.
>
> P: I can… if I go on that chair there to the bathroom, I can…
>
> C: I take him there, don't I?
>
> P: I can sit on the toilet, which is opposite the sink and can wash, wash me top and thingy, and get shaved, and I have to obviously hold myself up in, in a… I've got a frame in there, what I hold meself… me wife helps me wash down below. Because I can't do that on me own.
>
> 125 (Patient and wife)

> P: I mean, like I can't bend down to cut me toe nails and things like that. Er, and I'll be paying £25 for a… to get them done, every so often, over so many weeks, and I was talking to other people, they said "Well, you can get that done through your doctor."
>
> 126 (Patient)

Chronic pain often impacted on relationships and social lives. Participants described the work around maintaining and negotiating relationships. Although this included relationships with friends, it also included relationships with partners, spouses and family (some of whom may act as informal caregivers). A number of patient participants explained that they had to manage unhelpful attitudes and expectations. Family and friends sometimes exhibited a lack of understanding and sympathy

regarding their experience of chronic pain for various reasons (such as needing to cancel plans):

> P: [In relation to an increase in pain] …oh, yesterday and the day before, it was terrible. Because I usually go to a club on Tuesday, but I didn't go and me friend was real mad, I think.
>
> 169 (Patient)

A number of patient and informal caregiver participants felt that it was hard for some family and friends to understand and appreciate the difficulties they face because they have not experienced it themselves. Patient participants often did not want to bore people with their issues with pain and mobility, this often hindered how they disclosed their experiences to others. Some explained that their family and friends have their own experiences of pain to manage without them adding to the load, and sources of support may be limited.

> P: People aren't interested in your ailments, they get bored [Both laugh]. They don't… they're not interested, people avoid you if you talk about ailments. Er, so, I think it's best not to complain a lot about it. They know that it upsets me, not being able to walk far and all that…
>
> 126 (Patient)

> P: But, er, try not to discuss too much… it's too boring and too miserable, er, to keep on, I mean they've got pain themselves…
>
> 234 (Patient)

Both patients and informal caregivers discussed how there was a negotiation of roles (e.g. role reversal between children and parents) due to chronic pain and its management. The changes in these roles can lead to 'work' being undertaken to manage this different dynamic:

> P: And it's awfully difficult when you've been independent, saying to the girls "Oh, this needs doing" and "I want that that", you know.
>
> 177 (Patient)

> C: It's awful to see somebody you love in pain, um, but it's put a lot of strain on, it's put a lot of strain on our relationship, because I'm a nurse, and as a nurse you want to make things better, don't you? And I can't make things better and that's put a lot of strain on our relationship. But it's also put a lot of strain on, um, my relationship with me husband, because I want to spend time here with me mum. You know, me mum looked after me when I was a kid, it's my turn to, to care for her.
>
> 232 (Daughter)

A few of the male patient participants explained that their frustrations with pain would be directed towards their partner and cause friction within their relationship:

> P: So, it's not only debil- … it's annoying. And yeah, I'll admit, I've taken it out on, er, my wife, a bit, haven't I?
>
> C: There's only me to get annoyed with.
>
> 228 (Patient and wife)

Chronic pain, the use of opioids and cognitive adverse effects were impactful to participants social lives and feelings of isolation. This added to an otherwise difficult experience. Patient participants described the 'work' involved in adjusting to changes in their social life (i.e. engaging in previous or new social activities) and being able to go out in light of their chronic pain, loss of function or adverse effects from pain management. Many expressed how the experience of getting out and socialising were invaluable to them and their mood. A number of patient participants described how their experiences of being able to go out and socialise were often affected by transport options. Public transport was discussed as an alternative option but patient participants explained that there were certain challenges with this mode of transport, including: suitability for people with mobility issues or there is limited bus service in the area. The

convenience and cost of transport often needed to be factored in because of their chronic pain, especially when mobility aids were needed.

> P: 9 times out of 10 you can't get out, you know, I mean that I've got a taxi driver that, you know, but I mean a lot of times he's off the road […] But that's a lot of money, because the taxi fare. You're talking £20 there and back, you know, £10 there, £10 back, and that's if you want to go out with ya mate… friend and have dinner as well, so, you know, it's a lot of money on top of that, what you ain't always got. I make sure I have got it because I mean we see each other every fortnight, you know, my friend. She's only… the only one that's stood by me since I've been like this, you know.
>
> 003 (Patient)

The ability to drive was acknowledged as something that impeded on tasks that needed to be carried out. Patient participants explained how they were unable to continue driving, either for periods of time or permanently, due to pain or adverse effects. However, for some, it was where they felt most 'normal' and allowed them to forget about their pain.

> P: If I still had the car, I wouldn't have been able to drive it, because you could have got dozy and falling asleep, couldn't ya? So, mind you, I think it says that, "Don't, don't drive, if you're taking them."
>
> 126 (Patient)

> P: It the most normal way I feel, is […] when I'm behind the wheel of me car. Ain't that odd? I get all me confidence back. You know, I'm meself. I forget about me leg and me back [Laughs]. But even… but I'm comfortable, it's a comfortable car.
>
> 232 (Patient)

Some participants described how they sought alternative modes of transportation or are considering them, which included the use of motorised scooters to help them gain some

independence and control. Family often supported with travel when they could but had other commitments of their own that they had to balance (such as working full-time), and may not always be able to help.

> P: No. Don't do anything. I've got meself an electric buggy to get meself about, that's how bad it is.
>
> 025 (Patient)

Some participants removed themselves from certain social situations because of all the medications they were taking (including opioid analgesics), and minimised the 'work' involved.

> P: That's why I […] don't drink a lot now. I don't hardly drink at all, with all the medication I'm on. I was… never was a drinker…
>
> 232 (Patient)

For a few participants, in addition to other factors (such as pain), the adverse effects from pain medications also impacted their desire and ability to go out and socialise. Informal caregivers also expressed concerns of how cognitive adverse effects could leave their family member vulnerable when they are out, and that they would feel happier if they could resolve the issues with the adverse effects.

> C1: [In relation to Zomorph and Gabapentin] And I think this is why [Husband's name] wants it sorting out because if she goes out on her own, and she's in a shop or she went for a cup of coffee with… on her own, and she's like that [in reference to falling asleep], someone could easily rob her, she ain't got a chance.
>
> 003 (Daughter-in-law)

P: Well, we didn't use to go out or go anywhere but now we go…

C: Yeah, now I take him… we go out now. We go out twice a week.

P: …twice a week.

C: Or, you know, we try and get out twice a week and, er… because obviously he… not that he used to have a load to drink but he liked to drink a pint or two but obviously when he was on the morphine and all that he couldn't, so, you know we didn't go out, literally, did we?

P: No.

C: But it was mainly how he was reacting to 'em, the kicking out, the flailing out.

125 (Patient and wife)

As pain improved and adverse effects subsided, patient participants felt more comfortable going out again. This improvement was often felt by the informal caregivers, as some sort of normality was achieved and they could enjoy participating in activities together.

C: When he's able to come out, it's just such a, a joy, really, you know, to be able to share things again.

158 (Wife)

9.3.2 Theme 2: Emotional and psychological wellbeing

The management of chronic pain and cognitive adverse effects strongly impacted emotional and psychological wellbeing for both patients and their informal caregivers. This included an overwhelming sense of loss, and managing frustrations and coming to terms with their situation. Participants also described how they coped and managed the variable ups and downs, and how they tried to maintain emotional and psychological wellbeing.

9.3.2.1 Overwhelming sense of loss

Participants often framed their narratives around ‘loss’. Most explained that their lives had changed dramatically because of chronic pain, pain management or managing adverse effects. Pain was characterised as more than a physical symptom, and one that is accompanied by great emotional pain. This impacted both patient participants and their informal caregivers.

> P: Your mood goes down and your pain levels go up. I mean that’s, that’s not just me, it’s everybody, isn’t it?
>
> 113 (Patient)

> C1: Yeah, it’s surprising how it just, how it just…
>
> P: It just affects ya.
>
> C1: …affects you, ruins your world altogether.
>
> P: I mean, my mood must impact on him. He’s marvellous and he does everything, but I must get him down. I know I do, but he don’t show it…
>
> 171 (Patient and husband)

Loss was also related to time (e.g. the days that can be lost to chronic pain or managing adverse effects or time that activities can be completed). This could be related to the severity of pain that day or organising their day around pain management or adverse effects. Although, pain management can be beneficial in reducing the impact of chronic pain, when treatment was found effective enough.

> C: But if we’ve got to do anything, we have to do it first thing in the morning, you know.
>
> P: That’s me for the day.
>
> 228 (Patient and wife)

Frustrations were expressed in relation to boredom and the physical limitations of pain or cognitive adverse effects. Boredom and finding the motivation to do things were often at odds with one another.

> P: That's me big one problem is boredom, ain't it? I'm bored.
>
> C: On his other hand, you don't want to do anything.
>
> P: I don't want to do anything, yeah.
>
> 025 (Patient and wife)

> P: Er, 'cos I can gerr' a bit… like everybody as they're getting older, get a bit downhearted with things, you get bit fed up, especially when you're having real bad achey days.
>
> 041 (Patient)

In a few instances, both patients and informal caregivers described how they were still hopeful that something might resolve the chronic pain. One patient participant highlighted that her husband has stayed optimistic but she does not believe anything will change.

> P: …You just hope that the next thing they do is going to be you[r] 'Eureka!' moment. And I haven't had one yet, and I'm 80 odd, but…
>
> 113 (Patient)

> P: Hopeful, that this time it might be just something that would work.
>
> C1: Well, you, you haven't finished yet, so, we will just have to, sort of, carry on but I mean…
>
> P: Sounds like my husband's optimistic, and he's stayed optimistic. I'm afraid that after all these years, I'm pessimistic, I don't think anything is going to change.
>
> 171 (Patient and husband)

Grieving losses because of pain and loss of mobility was common, in particular, the consequences for everyday life. Patients and informal caregivers often discussed the impact of chronic pain and how it changes everything. Especially, that is tends to limit their lifestyle choices. Frustration and disappointment were often felt when they struggled with everyday tasks. Patient participants explained that they had to adjust to being unable to do the things that they used to be able to do.

> P: Yeah, it's not, not much of a life, is it, if you're in pain all the time.
>
> 126 (Patient)

> P: I'm a person that doesn't really like being indoors, but I've just had to get used to it.
>
> 234 (Patient)

Some participants highlighted that depression had become part and parcel of their experience.

> P: Oh, well, you get… er, that… I'm a …not a depressive person.
>
> C: No, you're not.
>
> P: Er, but, that got me depressed, not being able to do things, er, you know, because then you think, well, what use is it, I can't do anything.
>
> 158 (Patient and wife)

> P: I just think that the depression is one of the worst things that comes from it, as well [Deep breath].
>
> C2: She hates it.
>
> P: Because I've always been a strong person, [Deep breath] and now, I just seem to be crying all the time.
>
> 171 (Patient and family friend)

Most patients felt that being housebound negatively affected their mood as they could be alone all day, and relied on family or friends in helping them to go out. Some explained how this would also be impacted by poor or winter weather, as it could cause them to fall or not be able to use their walking aids.

> P: But I was, I suppose taking more because I was in a lot of pain with me knee, and it was deadening a little bit but I was… I spent a lot of time just sat watching telly for three months, er, it was one of the worst periods of my life. Er, it was November, er, I got a bit of Black Dog, depression, with just being house bound all the time. The weather was quite bad, there was a bit of snow and ice about, so, I couldn't even go out.
>
> 041 (Patient)

> P: But you don't go anywhere, you know, and if you wanted to go to the beach or an outing anywhere, they don't realise how much you'd appreciate being able to go out, away from your house, you know what I mean?
>
> 126 (Patient)

Chronic pain management was impactful on the informal carers, as they were often heavily involved in the process but often on the periphery of clinical encounters. They often reported feeling distressed or upset, especially when the pain was severe.

> C: It does upset me and I do tend to get a little bit cross because he won't always go and see the GP if it's really bad. I'm saying to him "Let me make you an appointment?" "No, I don't want to go to GP. I'll just take a couple of tablets; I'll go and have a lay down and that." But it takes a lot to get you to go, doesn't it, to the, um, GP…
>
> 197 (Wife)

Integrating aspects of care (such as appointments) into their daily life suddenly became the focus, in that, some are otherwise housebound. Chronic pain also seemed to be

entangled with other health issues, and when one aspect improves another worsens. All these experiences add up and add to the 'stew' of their 'medical life'.

> P: …apart from going for consultations, um, for the doctors or to the, the [Healthcare centre name], I haven't been able to get out.
>
> 177 (Patient)

Altering or adjusting to loss of hobbies and/or interests was commonplace for patient participants as a result of their chronic pain or loss of function. One patient highlighted the role of humour and how their struggle to mobilise with their leg pain had become a bit of a joke within their walking group when they started to get moving. Some patient participants explained how they had changed their involvement in hobbies or use mobility aids to accommodate their pain and physical ability.

> P: I played golf for a long, long… for many years and that had to go, I'm afraid. That was the worst part of it [Laughs] […] I go down now and, er, pass the time away, I suppose. I run the old men's section like, […] we have a meeting on a Wednesday, don't we? Er, we play on a Wednesday, but I can't, I just go and organise it, you see, so. But I enjoy it, it keeps me occupied, you see.
>
> 025 (Patient)

Some hobbies and interests could not be adapted around pain and loss of mobility and meant that they had to stop it altogether. This ranged from activities that require concentration (such as reading), or activities they used to do with their hands (e.g. matchstick modelling and sewing) to more full body activities (e.g. walking and dancing). A few felt that they had given up everything because of chronic pain.

> P: I was an avid reader, I can't pick up a book now, can't read, can't concentrate [Sighs], I just… I can't do any of the things that I used to do. […] I just used to love reading, I could lose myself in a book, [Deep breath] but I can't now.
>
> 171 (Patient)

P: …I mean I can't grip anything really hard, um, I can't do, er, the hobby I used to do, can I, now?

C: No.

P: Which was, um, matchstick modelling, because I can't hold the small pieces.

228 (Patient and wife)

Although, some patient participants described engaging in activities to help distract them from and cope with their chronic pain:

P: …sometimes if it's really bad, I'll take a couple of pills and just stay in bed, and start reading and then somehow […] Er, and reading that is soothing for me and it sends me off to sleep.

041 (Patient)

The implication of these changes is often significant to not only those that experience the chronic pain, but also those around them. They often discussed how they had to relinquish expectations and focus on each day as it comes, as they do not know how their pain will be. This often meant missing out on things like family events (such as attending their grandchildren's graduation). One patient participant and their spouse (who also suffers from chronic pain) highlighted the difficulty with planning ahead when asked how chronic pain impacts their quality of life:

P: […] but we can't plan things, because…

C: We can't.

P: …from day-to-day, we don't know how we're gonna be. You know, er, there's been times when we plan to do something and then I woke up in the morning, and felt absolutely terrible.

C: You just can't do anything.

P: And just can't do it.

158 (Patient and wife)

9.3.2.2 Coming to terms

Maintaining or reconstructing their identity and self-concept was one element of coping. This involved coming to terms and contextualising their experience of chronic pain, loss of function and experiences of adverse effects into everyday life, as well as giving a new direction to their identity in light of these experiences. This had implications for implications on their expectations of what would be meaningful to them in terms of pain management but also their approach (e.g. engaging with healthcare or what types of support were perceived to be helpful).

Coming to terms with the implications of chronic pain and pain management took time, and this was easier some days than others. Some mentioned that their experience was either a part of ageing or that they just had to accept the cards they were dealt in the best way that they can (i.e. stoicism). This often involved having a game face on where they had to grin and bear it.

> P: It's part of life, ain't it? You know, that's… this… my, my philosophy on life is that you, you get your cards they dealt ya and you gotta live by it.
>
> 041 (Patient)

> P: …so, I'm not free of pain [Laughs] but I try not to be miserable, if you know what I mean, try to keep going.
>
> 094 (Patient)

There was discussion around protecting and/or adapting self-concepts as a result of their chronic pain and pain management, as well as the degree to which they are able to integrate the consequences of chronic pain in how they move forward with their lives. Adaptations to self-concepts reflected physical, social, emotional and psychological changes. These adaptations were often made in comparison to who they felt that they used to be (e.g. independent, energetic, active).

> I was a very, very energetic person, I used to go keep fit and swimming, and, er, I used to like walking and driving, and, so, all that stopped now. And, so, I find life very boring to be honest, and painful, not being able to do things I've wanted to do.
>
> 126 (Patient)

> C: Not being able to do anything, and me mum's gone from being really dynamic to being frightened and in pain a lot of the time, and…
>
> P: Oh, I could do anything.
>
> C: Oh, and yeah, you would do anything!
>
> 232 (Patient and daughter)

Protecting elements of their self-concept was important for some, such as continuing to complete the tasks they could manage to maintain their sense of independence or mediating the impact of cognitive adverse effects from pain medication to everyday life.

> P: Yeah, because I do have arthritis in me feet as well, believe it or not. And, er, he said to take them during the day though – "It will help with the pain in your feet and your wrists" but I… if I did, I wouldn't… I'd be sat in this chair all day long. And that's not me, you know, er, when the times comes for that, then they can put me in a box, you know.
>
> 041 (Patient)

Some felt they could move forward with their chronic pain as it stands. A few highlighted that it is hard not to adopt a fatalistic view, especially when pain management is ineffective. Uncertainty around how pain could be resolved or hope that there would be a treatment that would effectively manage their pain factored into this. Informal caregivers would sometimes be the provider of a positive approach, to keep their spirits up.

> P: Er, and then, at the [Healthcare centre name], so, I thought 'Oh, well they'll sort it out. I'll be, I'll be back to normal. I'll be driving and, you know, doing my classes and everything', and the, the consultation turned out not to be quite what I wanted. Er, because he talked about the degenerative position about me back, just base of me spine, you see […] So, that's really brought it up-to-date, as it's as much as I, I know, and I've been for this scan, so I'm waiting the results of that, but it does look as if it's something I've got to live with.
>
> 177 (Patient)

9.3.3 Theme 3: Searching for a sense of safety and security

Patient participants and their informal caregivers expressed wanting what would be deemed as usual care, but their experiences were often far from this. This deviation from an expected standard level of care led to feelings of despair and abandonment, which were also impacted by anxiety and uncertainty.

9.3.3.1 The importance of caring

Patients and their informal caregivers (where present) felt that provision of clear communication from healthcare professionals was important to the patient-doctor relationship.

> C: That's half the trouble with the medical […] you know, medical profession. What they talk about goes over there, it doesn't go in here and stay. You know, and if you're ordinary people, you don't understand it. But some people will not explain things. They think you should know.
>
> 228 (Wife)

Experiences of chronic pain and adverse effects vary greatly, therefore it was considered important to tailor approaches to the individual. However, the need for clear, open and honest communication was important to all participants to enable a good patient-provider relationship. The approach of caring needed to allow for the patient voice too.

> C: Er, try and listen to what the doctor says, and if it's in your capabilities of doing what they're telling you to do, [then] do it. If you can't do it, tell 'em. And then, they've got to think of something else to do. You know, […] there must be an alternative to what there is. And, and I think that they ought to do that.
>
> 137 (Partner)

Issues relating to how the healthcare system is structured (as discussed in Section 9.3.4.2 External influencing factors) were often acknowledged as a limitation to the care provided by healthcare professionals. Additionally, the neglect of an ageing population.

> P: I mean… you see it's all changed, but years ago, when you got to a certain age, a doctor would come and visit you every few months. Check on the elderly patients… they've got that many, they don't bother. So, you feel as if you're not wanted. Yeah, so, they just don't bother with ya.
>
> 094 (Patient)

In line with this, time given in appointments was often too short and undermined the importance placed on their care and pain management needs.

> P: That's the modern world today, ain't it? It's what they can afford to give ya and that's all there is to it. You go to doctor's, you get 5 or 10 minutes and that's it, finished, you know. […] They're under the cuff as well as everybody else, and that's… it's not the doctors' fault.
>
> 025 (Patient)

> P: No, the days of talking to GP's have gone I think, actually. Recently, you think 'Well, it's a waste of time'. […] They're all, they're all so overworked, I think, er, there's not enough of 'em. I mean it's crazy, this ten-minute appointment business is…
>
> 137 (Patient)

Patient participants often felt that they were not valued by healthcare professionals, which contributed to a negative experience of care.

> I mean, they're not bothered whether you're in pain or not, they're not bothered about ya, you know, you just gotta get on with life, […] you're not getting the help, and that's it…
>
> 115 (Patient)

Some patient participants highlighted the importance of relaying the information provided to more than just the patient; it is important to assess whether there is this need.

> **I: Is there any advice you'd like to give to health professionals about using pain medications, like prescribing pain medications to people?**
>
> P: Well, just be a bit more open about it. But then… [Laughs] you see, there's no point in telling me, tell her for me please. That's what I should be doing. I should be asking people to tell [Carer participant's name]. Because I will forget, I won't remember.
>
> 025 (Patient)

Informal caregivers also acknowledged that they felt dismissed and excluded from clinical consultations, and that healthcare professionals could be more compassionate about their involvement.

> C: I think carers need to take the sort of, stand, because sometimes we're not listened to, and I think [that] they think we're just […] over caring. […] I mean they could give you anything and you'd take it, wouldn't ya? It's only because now he says […] to me, "Am I alright taking this?" You know, sort of thing. […] I think carers in general should say "Look, we're the person here, we're

> looking… we look after this person, we see 'em 24/7, we know what's right and what's wrong."
>
> 197 (Wife)

> I think probably one of the things is don't be bowled over, because the doctors sat there in front of you with a lot of letters after his name. You're the one that knows your family member the best. And stick with it, and if something doesn't work, say it doesn't work, be their advocate, be their voice, because that's what I am for you, aren't I? I'm your voice.
>
> 232 (Daughter)

Healthcare professionals were considered a source of knowledge and information to participants regarding pain medication and other forms of pain management. However, the level of information provided about opioid analgesics sometimes fell short.

> P: I want to know what this is doing to me and what it isn't doing to me. I don't take these tablets because… you know, it not my prerogative, it's [Doctor's name], you know, that he's given me these tablets.
>
> 003 (Patient)

> P: She opened a couple of windows […] for me because I couldn't believe it and I said "Look", I said "I've always been given to understand that you can't… that I couldn't take Paracetamol with the medication I'm on." […] With the Longtec.
>
> 025 (Patient)

Participants wanted to feel listened to and hoped that healthcare professionals would consider the all options for pain management that are available, and that when these options may be limited (e.g. deemed as unsuitable) that this could be better communicated.

> P: …you'll get the odd doctor that'll listen, you know, the other doctors are just want you in and out, so, I just tell them that "The tablets was affecting me and is there anything else?" And they say "No, you've been through 'em all."
>
> 171 (Patient)

> C: Yeah, that's it, yeah. I mean some people may be fine on them […] but then they've got to realise that some people maybe aren't fine on 'em. And there's got to be a happy medium and that, you know, they maybe can tweak that, so, that… like for you, you could get the pain relief without all the [adverse effects]
>
> 197 (Wife)

Patient participants were unclear regarding how long they were expected to continue pain medications. Many described how they remained on them for a long time, and some highlighted that they were either not aware of the implications of long-term use or wondered about the impact of long-term use on their health and wellbeing.

> P: And I've been on them [Referring to co-codamol] 10 years at least, and this is why, as I say, the [Healthcare centre name] said it wo-, you know, they'd put in the report that it wasn't… I'd a been on them too long, and they said it was damaging me kidneys, so, they suggested the patch, and paracetamol, which I take four times a day.
>
> 094 (Patient)

> P: I used them for a month, and, I thought 'Oh, what happens now?', you know, will the pain…? And, I sensed, when I, I took the last one off, after a couple of days, I sensed a pain coming back. So, that worried me, […] you know, so, I ordered some more, got some more and started the second, so, […] that's good. Now, how long I continue with them, I don't really know. Um, but I shall follow this month's lot, and then, I'll think about it then.
>
> 158 (Patient)

Patient participants and informal carers both stated that healthcare professionals should provide patients with a clear explanation and rationale of why they are being prescribed the pain medication, how they work, possible interactions with other medication, what adverse effects may occur and why, and when they might expect to experience a positive effect from it.

> P: Yeah, […] why you're taking 'em, but explain what they're actually going to do for you. Not just say "Here you are. That'll help." That's it.
>
> C: 'Cos that's how we were […] and we didn't know no better.
>
> 228 (Patient and wife)

> P: I know they've got thousands of patients to deal with but there are times when you have, er, some form of medicine and you think to yourself 'Well, I don't know, this is not right. It's not helping, it's not doing this.' Um, but they don't explain that reason as to why.
>
> 234 (Patient)

Participants suggested that the quality of communication was often linked to the amount of time they were given in consultations.

> C: Give an extra few minutes, because to be quite honest, a lot of them when you go in, they are doing the prescription as you walk in, they don't read anything. It's a quick in and out. And it never used to be like that, but you see, people are living longer, so there's more patients, so, we have less time.
>
> 025 (Wife)

> C: Well, I think they ought, I think they ought to spend more time with the patient, […] because they're not getting the right, […] if it's not your doctor, they're not getting the right idea, are they? Ten minutes is nothing, is it?
>
> 137 (Partner)

Participants advised that it was important to ensure that healthcare professionals listen to full story and that their attention is not divided. Being present and engaged, listening carefully to the problem, and eye gaze were mentioned as components to meaningful communication.

> C2: …they just look down… half the time they're looking at the screen, instead of the patient.
>
> C1: It's simple, it's simply the fact [Carer 2's name] that they haven't got the time.
>
> 171 (Husband (C1) and family friend (C2))

> C: Listen to your patient, listen to what their telling you. Don't just think 'I've only got ten minutes', because someone like me mum goes off on a tangent but gets to the point, where she wants to be.
>
> 232 (Daughter)

A number of patient participants did report that they talked to their general practitioner about the cognitive adverse effects to determine how they could be managed (as discussed in Section 9.3.1.1). Communication around cognitive adverse effects mirrored the approach desired with chronic pain (i.e., taking the time to listen and support them).

> P: But it was just bringing that… ringing somebody up and talking to 'em, you know, and sort of, just calming me down really, 'cos it was just… it was horrendous, it was, you know.
>
> 003 (Patient)

> P: …if I say to the doctor "Look, I can't take that tablet. It's made me feel off." He might say "In what way?" And I'll tell him but he'll just say "Right, stop taking them." Well, or…
>
> C1: Persevere and see if it goes off.
>
> P: They've got to the point with me that they don't know what to do.
>
> 171 (Patient and husband)

9.3.3.2 Continuity and timeliness of care

Continuity of care was identified as challenging to obtain as they were often unable to see the same GP twice.

> P: …at our practice, maybe all practices now, you never see the same doctor twice. So, you feel as if you're always at the beginning of a book, you know. "Well, I've said that before, but I told him about that", so, this is why nothing ever gets pushed further. […] You need a build-up; you need a history.
>
> 113 (Patient)

However, one participant acknowledged that sometimes having a different doctor has its advantages and can help to progress pain management.

> P: It's not all bad. […] I've said to [Carer participant's name] on more than one, one occasion, that "Oh, I've, I've rang up and I've [2 second pause] had to see this doctor I don't know." I say "Well, sometimes, just sometimes, that could be a good thing, a fresh set of eyes looking at your problem." Which proved the case when we got this with the [Healthcare centre name], it's a doctor we'd never seen before. Didn't know her, but she recognised something that the others didn't, and followed it through, where the others didn't.
>
> 158 (Patient)

There needs to be an awareness of medical history, such as what people have already been prescribed and not presuming certain pain medications will work (e.g. pain

medications from the same ‘family’). This would provide a sense of security for patients and their informal caregivers, and avoid vulnerability to a possible crisis (e.g. adverse effect)

> C: I think that they should actually look at the side effects, look at the medications that you’re on and then […] start on a smaller one, and then that way, if you go on to a higher one, and you are having a few problems, they can say “Well, actually, he weren’t too bad on that one. We can put it back down to that one.” But I think, now you go in, and they just say “Right, oh, you’re in pain, oh, yeah, you’re in severe pain. Let’s put you on this.” And, and I think they should go into it more.
>
> 197 (Carer)

> C: …I do think it’s a time thing […] but sometimes take a little bit of time in the first instance, saves masses of time and heartache in the long-term.
>
> **I: Yeah. And if you hadn’t been there that time, do you think they would have just put her back on the same drug?**
>
> C: They would, and because my mum’s been on so many things she probably wouldn’t remember.
>
> 232 (Daughter)

Another key aspect was ensuring that healthcare professionals should ensure that pain medications are reviewed regularly. It was considered important to monitor and rationalise pain medication use.

> C1: I think they should have reviews. And just because someone says their pains not… why up it and then keep ‘em on it. So, just say “Right, we’re only going to up it for a month, get back in touch if it’s still no better.” Then they can do it longer, not continuously.
>
> 003 (Daughter-in-law)

P: …if they give you a load, you've got to take 'em, and then these […] get taken. I think it gets to be just…

C: Habit.

P: …habitual.

027 (Patient and wife)

It was thought that healthcare professionals should enable quicker access to support. A sense of safety appeared to be related to open and ongoing care due to having clear touchpoints of care or knowing they could speak with a healthcare professional.

C: Yeah. Oh, it's difficult. I think it… really at the point of need, to access that more quickly.

158 (Wife)

I mean I have told people to try and go down the pain clinic route. […] I felt safe because I was going every month, and […] if anything come out, he would try it.

171 (Patient)

The more common story was around the aspect of waiting on healthcare professionals. This included waiting on medication, treatments, follow-ups and referrals. Pain management was often considered a waiting game and one that required persistence, obtaining what they needed themselves (where possible) or accepting their situation.

P: …the pain with arthritis and the arm, as I say, I'd rather… either me legs or me arm, I was in that much pain, it was eight months before I got the doctor to do something about me arm.

094 (Patient)

> P: Um, and, so, that went back to [Healthcare professional's name] I think it is, er, he told me what was wrong, and then nothing else was mentioned ever, about pain management. So, I don't know. They've never ever got back to me. But I don't… as I say, I don't think there's anything they can do.
>
> 234 (Patient)

9.3.4 Theme 4: Influencing factors

Experiences and impact of chronic pain, opioid use and cognitive adverse effects appeared to be influenced by internal factors (i.e. specific to the person) and external factors (such as healthcare professionals and settings of care, and family and friends).

9.3.4.1 Internal influencing factors

There were various factors that participants reported that influenced the way in which they approached pain management. Firstly, addiction, misuse and tolerance were considered to be factors that could negatively influence pain management. In that, opioid analgesics and other pain medications may be relied upon or misused. Both patient participants and informal caregivers expressed concerns and debated whether continuation with pain medication was out of habit or necessity.

> C1: …I'm no doctor but she should have been weaned off 'em by now. […] Has an addiction occurred? So [Patient participant's name] is thinking she's in pain, thinking she might get them tablets took off her. […] Psychologically, [Patient participant's name]'s thinks 'Oh, what if they take… I'm going to get pain again.' Is this a psychological side effect of the medication she's been on? […] I don't know, is that why they are keeping her on 'em?
>
> 003 (Daughter-in-law)

> I've got to get out of bed and get me tablets. I'm addicted to 'em in, in effect, there's no two ways about it, yeah. Until I… you know, the pain ebbs once the tablets have been taken, you see.
>
> 025 (Patient)

Building up a tolerance to pain medication was an issue for a few participants, especially informal caregivers. Additionally, these concerns reflected the length of time that patient participants had been receiving certain treatments.

> P: Co-codamol I was, I was lovely on that.
>
> C: …but you built up a, you built up a massive resistance to it. I was worried.
>
> 232 (Patient and daughter)

Adverse effects were not just something that were experienced but also shaped the way in which patient participants adhered to pain medication, although not always.

> P: Er, you know, as I say, I'm not being dramatic but unless the pain is really, really bad, then I'd rather do without […] and just try and mitigate it by taking, you know, Para's [Paracetamol] or something of that vein, that I know is not going to send me loopy.
>
> 027 (Patient)

> P: That's what really put me off, was all this, you know, this hallucination lark and all this. Well, I'm not taking them, I can't be doing with them.
>
> 125 (Patient)

The way in which participants viewed pain and how it was managed were shaped by *attitudes and beliefs*. Pain was viewed as an individualised experience but a communal one in the sense that it appeared to become more common with ageing.

> P: I'm now a 70-year-old person, who's suffering, like everybody else does, trying to get things out of a GP and the system. The NHS is free. So, I just think it's not good enough, personally. Um, when I look back, I didn't have that problem getting pain sorted out then, why should I have a problem now?
>
> 137 (Patient)

Attitudes and beliefs also related to how they understood pain medication itself. They often attributed the type and strength of pain medication in relation to managing certain levels of pain. Although, there were differing opinions about what was considered to be strong pain medication.

> C: Er, Co-codamol.
>
> P: They're OK, they're like… to me they're all, I don't know how you describe it, they're all like headache pills, they're not strong medication.
>
> 137 (Patient and partner)

> P: And I'd said to him "But I really don't want it [i.e. co-codamol]", I said "I refused it from [Doctor's name]", I said "Because, um, I knew from working among Codis [co-codaprin], that Codis was very strong."
>
> 177 (Patient)

Yet, being indifferent and holding no particular attitudes or beliefs about pain medication prior to using it still influenced the way in which pain medication was used

> C: [Patient participant's name] would take anything the doctor give him.
>
> 025 (Wife)

> P: …if you had a pain, like a headache or a general backache or something like that, take a couple of tablets and then if it eases it, that's fine. […] I was neither for and against, but from what I've told you earlier, […] my opinions were, if I need to take a tablet, I'll take it. But by the same ruins, if I feel like I don't need to take it, I won't.
>
> 158 (Patient)

Concerns were also a possible influence on how pain was managed, which were often orientated around pain medication itself and adverse effects. Concerns tended to be informed by attitudes and beliefs.

> **I: Is that a concern for you, becoming addicted to a pain medication?**
>
> P: Oh, yeah. Well, I don't like the fact you can be addicted to anything. […] I did drink too much, but I wasn't an alcoholic, but I was very close to it, so, that worries me. So, it's the same with something like that. It's, um, you're losing some sort of self-control when you're addicted to something.
>
> 137 (Patient)

> P: Well, the co-codamol, I wasn't happy about at all, because I knew that that was a strong [one].
>
> 177 (Patient)

Concerns were also expressed around the long-term use of pain medication or how newly prescribed pain medications would interact with other medications for specific health conditions (such as diabetes) when information leaflets warned against combining them.

P: I mean a lot of tablets say "Do not take if you're a diabetic." […] And I think 'Look, I'm a diabetic'…

C2: Well, the doctors prescribed it. I think that's wrong.

P: But you just have to trust in what they've done. […] It does concern me but what do you do about it?

171 (Patient and family friend)

P: If I live like this another 10 year's […] they'll have to keep upping the dosage and what does that do? You know, if you find that, well, after so long it doesn't work, so, they put a bit more in and a bit more in. […] Er, if you know that it was only two years, you'd think 'Well, it don't matter'

177 (Patient)

Choices and preferences were also considered to be person-specific. Choices with pain medications were potentially limited by certain factors, which included allergies and other health conditions. Additionally, route of administration was sometimes a limiting factor.

P: Because I can't take paracetamol and aspirin because I'm allergic to it all. So, I can't take nothing like that you see. […] I'm allergic to them. Like, certain painkillers that everybody else can take.

003 (Patient)

P: Yes, well, he tried to put me on Tramadol but it didn't….

C: Oh, no, that had bad effect on you. […] Heart, his heart was really racing. […] He was having a real bad, like palpitations.

P: So, that weren't good for me […] with having a heart problem.

197 (Patient and wife)

Preferences were limited and there was an overwhelming sense that participants would prefer not to be on medication in general, let alone pain medication.

> P: I mean I'd be happy not to take any medication. But, um, that is not an option with what I've got going on.
>
> 234 (Patient)

Pain affected patient participants in different ways (as well as impacted family caregivers). Pain severity and the efficacy of pain management strategies were often influencing factors in their course of treatment.

> P: It's pain versus every other effect. At what any particular time, what's the greatest? If the pain levels there, then I would, you know, probably to take something strong. You know, and accept the consequences, but on a normal balanced thing, I won't take 'em.
>
> 027 (Patient)

Pain severity also influenced how patient participants were able to manage other health conditions, and vice versa.

> P: I think it upsets your stomach and causes constipation, because I also have the diverticulitis. And, so, you have to be very careful what you eat, er, you must not get constipated, 'cos you… then you have a flash, and I've had two, you see.
>
> 126 (Patient)

> P: I've never been right since. I've always had COPD, but I learnt to live with that. It was, sort of, part of me life, you know what I mean, but I… and I did cope. But since I broke me back, I've not even coping very well with that. It's made that worse.
>
> 232 (Patient)

Participants knowledge and understanding of pain management varied, especially around opioid analgesics. What participants understood about pain medications sometimes influenced how they managed their pain. Many explained that they did not know much, if anything, about pain medication before they were prescribed them.

> **I: And what did you know about painkillers before you had them?**
>
> P: Well, nothing, other than the descriptive name, you know, painkillers, that they were there to kill pain, relieve pain, to a varying degree.
>
> 027 (Patient)

> P: …reading and hearing about these opioids, you know, and I think 'Well, I don't really know what opioids were', you know. I've never talked about that kind of thing. 'Cos mine have only been like, what I thought as being as light medication, that, you know, your doctor gives you and you can take it, and it either cures you or it doesn't, you know.
>
> 177 (Patient)

Some participants felt that they learnt more about pain medication once they had been prescribed, but this was not always the case.

> P: I know that they're, they can be addictive. I know they've got side effects, which with me, causing me to feel sick and drowsy. Er, and long-term use can possibly cause other problems.
>
> 041 (Patient)

> **I: Did you come to learn a bit more about them when taking them?**
>
> P: …no, not really. I just took 'em as they said, and stopped when the, you know… I take everything in me stride, really. It's up to… I believe in what they're doing, if you know what I mean.
>
> 094 (Patient)

Sometimes participants held misconceptions about pain medication, which might falsely influence their decisions. They would sometimes seek information to help them dispel misunderstandings and misconceptions they had to help them understand more about pain medication.

> P: Because after all that's said and done, what's Co-prodamol's [Co-codamol] and painkillers like Tramadol and all them, they're only cocaine-based and morphine-based, aren't they? Opiates.
>
> 041 (Patient)

> I couldn't make out why co-codamol and paracetamol was any different, I thought they can't be any different, because their 500 milligrams. But then when you look, there's more… other things in co-codamol than there is paracetamol, so […] it's not that it's a stronger, it's anything stronger in it, it's just other things are in it. […] But you gotta work it out yourself, you know.
>
> 115 (Patient)

Participants described how the knowledge they had gained had been predominantly from the information leaflets given with the medication. However, some patient participants highlighted that the information leaflet is not always easy to understand or that they did not see the value in reading them.

P: …I think with all these things though, er, to be honest, is if you look at the papers on the tablets, they will say a variety of things, you know, you could get…

C: Side effects.

P: …well, yeah, the side effects, you could get, you know, diarrhoea or constipation, or bizarre things, that one person maybe suffered, that they put on to, to cover their selves.

027 (Patient)

P: You get more information from the packet that you read. I don't read the leaflets anymore, because whatever's on the leaflets on most of 'em and I think 'Don't read it, and then you won't get it'

171 (Patient)

9.3.4.2 External influencing factors

Participants identified external factors that were influential to their experiences, which included family, friends, healthcare professionals and different settings of care (including primary care, specialised care, care homes and care in hospital).

Family and friends can provide a large amount of support. Family were concerned about ineffective management of pain or adverse effects experienced by the patient participants, and they can act as a third party influence. Patient participants described how their informal caregivers and wider family members were influential to treatment decisions regarding pain management.

> C: Yeah. Everything that she gets… "Ah right, let's have a look, let's see what it is, and I'll look it up, and speak to the doctors […] so, nothing goes in your body that we don't know anything about."
>
> 232 (Daughter)

This included shaping medication regimen and attending appointments to ensure that they could be part of the decision-making process, ask questions on the patient's behalf and retain the information provided.

> P: [Son's name] turned around to me and said "Mam, are you taking these tablets right or what?" I said "Yeah". So, he went "I don't think you are Mam, because you're taking a few" And then he said "You should be taking them at the right times". So, then we asked for, you know… well they, they put the spokes in, [Laughs] as usual, and then I got a Nomad. So, it's in one of them now.
>
> 003 (Patient)

Patient participants also developed their understanding and/or perceptions of pain medication and adverse effects through interactions with family and friends, as well as other people with chronic pain.

> P: …our mother never encouraged us to take anything, you know what I mean? Her answer was a good early night and a cup of hot milk, and we grew up healthy, we didn't need anything, you know, but when we have, we trusted the doctors. […] We've never really needed medication, you know.
>
> 177 (Patient)

Generally, family provided reassurance and eased patient anxieties – either dispelling reservations patients had around pain medication or helping them to find a more suitable approach. Although, sometimes their experiences of opioid analgesics were very different to what family and friends had experienced. There were also factors that

impacted on their family and friends' ability to help and support. This included working full-time, child care responsibilities, living further afield, going away on holiday and having pets.

All participants discussed how interactions with healthcare professionals influenced their experiences with pain, pain management, and how adverse effects were managed. Many shared their personal experiences with healthcare professionals, with mixed experiences. Familiarity with healthcare professionals was important to participants.

> P: Well, you just explain to 'em, what it's like, I mean, you don't know what there is that they can give you, do ya? Really. It's up to them to check and see what else they could give you, ain't it?
>
> 126 (Patient)

> P: Because I'd only ever had this one doctor and his father, all through the health service, been very fortunate and he was always there, you know, no problems. Well, this one, it's different routine, and so, I've seen the one doctor, um, and he'd put me on the Co-codamol.
>
> 177 (Patient)

Trust and respect were often described in relation to healthcare professionals, in that their clinical knowledge and expertise were valued. Especially when it comes to taking pain medication that has been prescribed. However, for some, this trust and respect had faded, especially when they did not feel heard (see Section 9.3.3).

> P: I just think 'Well, the doctors given me 'em, they must be alright', you just take them.
>
> 094 (Patient)

> P: They say that because of my heart bypass and things, I mustn't have things, because they'll… I'll bleed internally. And, I say "Well, I don't care, really,

because I'm in pain", but they don't listen, because they're doctors. So, they give you paracetamol, which is a joke.

137 (Patient)

Some participants questioned who the 'right' healthcare professional was to decide on how their pain was managed. Additionally, there was concern that healthcare professionals do not know enough about the potential interactions between medications.

P: …but now it's all these, um, nursing practitioners now, ain't it? It's not your doctors anymore anyway, it's your nursing practitioner, now what – how the hell, and this is what gets me, do they know as much as a doctor? Because they haven't done as many years as a doctor.

003 (Patient)

P: I don't think the doctors really know enough about the mixes, and should I have given them that versus that, but that's not my problem, because I'm not a GP.

137 (Patient)

Access to settings of care was considered to be highly influential to pain management, which includes primary care, specialised care, care in hospital and care homes. Patient participants highlight how they struggled to get the appropriate support from their general practice.

P: Er, it's an unfortunate business, because, if I was a lot younger, I would change. Nobody's gonna take…

C: There's that much wrong with him.

P: Nobody's gonna take me on now.

C: They'd have such a big bill for his medication. You know, nobody's gonna take him on, especially at his age.

228 (Patient and wife)

Participants identified factors that made it challenging to effectively engage with primary care to manage their pain. This included structural and process issues in the way general practices are setup and the possibility of home visits.

> P: There, you know, if there weren't nowt up, I wouldn't be there. And that's something, I don't go there anyway, 'cos I can't get in the bloody rooms [in reference to their bariatric wheelchair].
>
> 003 (Patient)

The way in which the general practices are setup can make it challenging to book an appointment. This included being able to book an appointment and needing to use a computer to access online services (e.g. to order medications).

> P: …if I want to see my doctor's, I've got to drive all the way down at half past seven in the morning, to the doctor's, 'cos you can try ringing and, and you just won't get an appointment. Er, the only way you can get an appointment is by being there at 8 o'clock when they open the doors, and going in and asking for an appointment.
>
> 041 (Patient)

> P: And then everything's on the internet, ain't it?
>
> C: Yeah, that's it, and we don't have the internet, no.
>
> P: And we don't have a computer. […] So, so, it's really bad at the moment. […] Generally, my wife rings them up and she [will] get it all sorted […] and I just go down and pick the, um, medications up.
>
> 195 (Patient and wife)

Primary care and community services often acted as a barrier to going into hospital, when they could be accessed.

P: Well, I was in agony. […] So, in the end I went to A&E. Because I tried to get an appointment at the GP, but they weren't taking appointments that week.

C: No, they weren't.

P: Somehow, it's all this two-week business, it's got worse now. If you want an, an appointment, you can't get one.

137 (Patient and partner)

A number of participants described how primary care has changed and the level of care that they used to receive is just not available anymore due to larger patient lists and challenges with staffing.

P: And the latest conversation we've had, is that they can't recruit doctors in [City name]; people don't want to come to unfashionable places, like [City name]. So, they're having great difficulty. So, at the moment, I can only see it getting worse.

158 (Patient)

One particular issue was around the frequency at which pain medication was reviewed.

I: And you didn't notice any side effects from that one?

P: Well, no, not really, I mean they were capsules [co-codamol], they were easy to swallow. They ease the pain but I never thought they was causing trouble. I mean if […] I'd had proper checks up, they would have realised before that they were leaving me all that time on them.

094 (Patient)

C: Um, you don't get called in for a pain management review. […] You only go when we ask for it. […] And I think, probably… I don't know, twice a year reviews with the nurse practitioner or something on a regular basis might manage it a little bit better. […] But it's only when we sit and talk about it, and I say "Right, it's time, we need to go and get that sorted now." Um, but they

> don't ever call me mum in for… they call you in for reviews for everything else.
>
> 232 (Daughter)

A number of participants described how their pharmacy often reviewed their medication and helped them to understand more about what they have been prescribed.

> C: Yeah, the chemist; every 6 months, calls you in and they go through your medications and see if you've got any problems.
>
> P: Yeah.
>
> C: […] If we go on to a new medication, they've started now, that they ring ya and say "[…] We've noticed [Patient participant's name]'s gone on this new medication. Has he had any side effects?" And they do that, but that's only been recent.
>
> 197 (Patient and wife)

A small number of participants reported receiving specialist care. Some of the patient participants who had been able to access specialised support reported that they had found the pain clinics to be helpful in managing their pain, including psychological as well as physical benefits.

> P: Well, I was at the pain clinic for quite a long time, the pain clinic at [Hospital name], and when I first started, there was a chap there who was extremely good.
>
> 113 (Patient)

> P: It [i.e. pain] just seemed to go to from the one level to another level, and that's when I started going back to see the specialists. They told me they couldn't do anything for me, [Deep breath] so, they sent me to pain clinic. […].
>
> 171 (Patient)

However, they described how access to the pain clinic was sometimes withdrawn or stopped.

> P: …this gent came round and he said to me "How do you think the acupuncture doing? I said "Well, I can't honestly say I've gleaned any benefit from it. I haven't." […] And I told him I'd been to the acupuncturist in [Road name] but had to pay for it, and I said they obviously have a long way to go before they catch up with these people. And then, the next thing I knew, I got a letter saying [Laughs] that they'd struck me off the pain clinic register.
>
> 113 (Patient)

> P: …we got letters to say it was finishing, and we would be referred [2 second pause] on. […] But anyway, he actually referred me to this other pain lady. She just gave me a load of tablets that sent me whacky.
>
> 171 (Patient)

For others, specialised support felt non-existent or challenging to access through primary care.

> C: …the specialist at the [Healthcare centre name], I mean she hasn't been sent anywhere else to see what, you know, whether acupuncture or anything else might help, so, I don't know, it feels as if they're non-existent, really, apart from seeing the doctor.
>
> 177 (Daughter)

> C: …my daughter actually works for the pain, the pain management. And I didn't know there was this there, 'cos she keeps saying to me "If me dad don't get any better, why don't you ask the GP if he'll refer you to there, and see that whether that would help." […] Um, but it's really awkward, because as I say, we need to see a GP, but we can't really see […] a GP, because he's not sick… he's not an emergent.
>
> 197 (Wife)

Participants also described the financial costs associated with specialised care. Additionally, some patient participants were told that there was nothing that the specialist services could do for them.

> P: And another one, [Specialist's name], he's a back specialist, I paid £110 to see him private, [Carer 2's name] came with us. […] He called our name, we went in, she picked a magazine up, she opened the first page, and we was walking out.
>
> C2: I said "Why? Why? Have you got to go somewhere?" She said "No, that's it." I couldn't believe it, […] and that was it.
>
> 171 (Patient and family friend)

Overall, awareness of and access to support for chronic pain was limited.

> **I: And what is your opinion about the support available for chronic pain?**
>
> P: Well, we are only just beginning to learn. I mean that was the first experience really, of people helping us, helping me with me pain, was the [Healthcare centre name]. [...] We were hardly supported at all.
>
> 25 (Patient)

In hospital, patients often felt a lack of control over their pain management – either in terms of their medication regimen (as highlighted in Section 9.3.1.1) or feeling fully informed about what pain medications they are being given.

> I know they ain't got time and that, I don't want to be critical of them, but they say would you like some strong pain relief, and, so, they give you these little things, and, well, there's some Para's [Paracetamol] in there, there's maybe little white tablets, so, there's three or four little white tablets in there, and say

> "Oh, um, we'll give you some opioids", you don't actually know what you're taking.
>
> 027 (Patient)

> C: Yeah, but to be fair he was over prescribed at the beginning and that was the hospitals fault. When he came out of hospital they told me what to give him, and he was actually doubling up but that's what they told me to do, on this list, you know what they wrote by hand. But then it gor'out of hand. He couldn't, oh, it was absolutely horrendous. He was fighting, he was delirious, shouting and balling.
>
> 125 (Patient)

Adverse effects also impacted the amount of time they stayed in hospital.

> P: And then I was supposed to come out and they said "Oh, no, you… are you alright?" And I sat up and I was like [Demonstrated disorientation], then "Oh, no", you know, I'd have to stay another day, and then I had to stay another day, didn't I? Till it all came out my system.
>
> 027 (Patient)

One participant discussed how a care home played a role in their pain management whilst recovering from surgical intervention following a fall:

> P: I was in the home, they was, the home was good me, […] to get used to me leg, walking, trying to get me walking, but I can't walk without some support. […] As I say, she [daughter] turned me… this room into a bedsit sort of thing, got me the bed and everything, and that. She spent weeks getting it, because she said she could see me in the home, losing meself.
>
> 94 (Patient)

9.4 Summary

The main findings from the qualitative component are:

- Pain is a subjective experience and treatment needs to be tailored to the individual.
    - Careful consideration needs to be given to pain management (e.g. potential burden) and multi-modal approaches may be useful.
- Chronic pain creates *'insurmountable work*' not only in terms of pain management but for everyday life. This includes managing the trial and error process to pain relief and cognitive adverse effects, as well as searching for sense of safety and security from clinical care.
- Pain is not just a physical symptom, it has emotional, social and financial consequences for both patients and their families.
    - Emotional and psychological wellbeing was greatly impacted by participants experiences of pain management, especially when support from healthcare was lacking. A limited sense of safety and security appeared to be related to feeling of despair and isolation.
- There are internal and external influencing factors that shape the way in which older adults and their informal caregivers manage pain.
    - Cognitive adverse effects are bothersome and difficult to manage, as well as impactful to adherence.
    - Timely access to support is challenging due to issues with access to primary care, which also limited reporting of adverse effects.
- Causation was often determined by observing patterns in relation to opioid use.
- Informal caregivers play an important role in pain management but need to be more empowered to do so.
- Clear communication is needed regarding pharmacological approaches (including why it is being prescribed, they worked, what to expect, possible adverse effects and interactions, as well as any contraindications with existing conditions).

The next chapter integrates findings from the study components and discusses them in the context of existing research.

Chapter 10: Integration and discussion

The overall aim of this thesis was to understand opioid use in the pain management of older adults, how opioids impact older adults' cognition, and explore their experiences, perspectives, concerns, and information and support needs regarding these, with a systematic review synthesising evidence on the impact of opioids on cognition (and how cognition is assessed) and the mixed methods study investigating opioid use, pain management, and the impact on cognition.

This chapter intends to demonstrate how the aims and objectives of this thesis have been addressed, and helps to offer new and overall insights. First, it will discuss the quantitative and qualitative findings (as presented Chapter 8 and Chapter 9, respectively), which is followed by a summary of novel findings from each study component and a modified critical interpretative synthesis integrating the thesis findings using an integrative grid.[460] The integrative grid presents both a synthesis of the findings from the mixed methods study (including the quantitative cross-sectional survey and case note review, and qualitative interviews), followed by an integration of the findings from the systematic review. Using the integrative table to draw together findings from all aspects of this thesis, grouping results by the main phenomena (i.e. pain in older adults, pain management, the role of opioid analgesics and opioid-induced cognitive adverse effects). This is followed by a discussion of intersecting contributions to existing evidence. Then, a reflection on the strengths and limitations, and implications for clinical practice and policy, and future research.

10.1 Integration of findings

A discussion of systematic review findings can be found in Chapter 5. Before integrating, the quantitative (see Section 10.1.1) and qualitative (see Section 10.1.2) findings are discussed separately also. They are then brought together with the systematic review findings in Section 10.1.3, alongside novel contributions.

10.1.1 Discussion of quantitative findings

Pain is highly prevalent in community-dwelling older adults with frailty, with over 60% experiencing moderate to severe pain in the week prior to recruitment. Other studies considering the prevalence of current pain in older adults living in the community range from 20% to 46%.[24] Pain was also identified as a main problem or concern for just over a third of the study population. The most common types of pain expressed by participants include back, hip and knee pain. This mirrors trends observed in the literature.[24,137] Those reporting using pain medication over the past year were more likely to report moderate to severe pain despite treatment, as well as more sources of pain.

Part of the overall aim of this thesis was to better understand opioid analgesic use in older adults. This study provides a comprehensive and rich description of opioid prescribing via a case note review. 51.8% of participants were prescribed an opioid at some point over the past year. Similarly, high opioid prescribing rates in older adults are observed in other studies examining prescribing trends.[47,49,87,218] The findings of this study demonstrated that low doses of codeine, tramadol and morphine are commonly prescribed to older adults. When exploring patterns and duration of opioid prescribing in primary care for this population, an observational study found a decrease in the use of tramadol in the oldest-old.[49] Although, age-related differences were not explored within this study, the high prevalence of tramadol and codeine does warrant some concern as literature has highlighted that these are not the most appropriate opioid analgesics to use within vulnerable older adults and clinicians should be cautious with prescribing these.[60,72,236,463] The recommended changes to pain medications following the clinical assessment and medication review at the ICC (conducted at the time of recruitment) support this concept of rationalising pain medication to optimise pain management and reduce the risk of adverse effects. There were a number of recommended changes (for 52.6% of the study population). However, there were few recommendations to reduce or stop opioid analgesics in this study. This may be explained by reported barriers in prescribing opioids in the first instance by healthcare professionals, which include fear of causing harm and stigma.[42] Where recommended changes were made in relation to opioids in this study, there was a move towards transdermal patches as the route of

administration and separate preparations rather than combined preparations (e.g. co-codamol).Additionally, health-related quality of life was significantly worse for those who were prescribed an opioid at some point over the past year, compared to those that were not.

This study identified factors that may be associated with increased odds of having an opioid prescribed, which include higher pain severity and number of medications. A scoping review identified a large number of context-dependent factors that influence opioid analgesic prescribing trends in older adults but the findings are inconsistent.[235] Other studies identify risk factors associated with an opioid prescription more widely among adults that included (but were not limited to) being aged ≥65, experiencing pain within the past 30 days, being widowed, being depressed and reporting fair or poor physical health.[50,464] Inappropriate prescribing of medication is associated with frailty and polypharmacy.[198] Factors such as depression, functional status and self-rated health were also explored in this study but were not significantly associated with increased odds of having a prescription. This may be due to the different measures used in this study (such as self-reported depression and not using a formal screening instrument) and its smaller sample size. Patient characteristics have often been explored in more depth, whilst there is less understanding of prescriber-driven and system-driven characteristics. A retrospective database study found that larger general practice lists and ruralness are associated with high-dose opioid prescribing.[238] Further understanding of the *when, why* and *how* factors influence opioid prescribing is needed, as well as *which* factors (with consideration to patient-, prescriber- and system- driven factors).[235]

In this study, recall was enhanced by using a list of common adverse effects associated with opioid analgesics. In support of the findings from this study, Lampela and colleagues (2007) found a large disparity between physician-identified adverse effects and the adverse effects reported by older patients, with elderly participants tending to neglect drug effects as they may have been perceived as unavoidable and a part of ageing.[260] Additionally, a cross-sectional prevalence study exploring adverse effects of analgesia in patients with multiple myeloma also demonstrated improved recall when using a prompt and difficulties in being certain of their origin.[261] The recall of adverse

effects in older adults with chronic conditions is significantly lowered for each additional medication prescribed.[465] Therefore, healthcare professionals should enquire about adverse effects (regardless of whether they have complained of adverse effects) and a list of common adverse effects may be useful in aiding recall and reporting of adverse effects. Adverse effects of analgesia have been demonstrated to significantly reduce quality of life in multiple myeloma patients.[261] In this study, health-related quality of life scores were lower in those who attributed cognitive adverse effects to pain medication but this did not reach statistical significance. This may be due to the smaller sample size and being part of the wider programme of research.

There were some limitations to the quantitative components. Summarising and quantifying the types of pain experienced by participants was particularly challenging. It was not possible to include a pain assessment (e.g. body map) within the cross-sectional survey as it needed to remain brief in length and to avoid duplication of data as pain was assessed by ICC staff during the patient's clinical assessment. This led to issues with summarising the types of pain experienced and how to quantify issues with multiple types of pain. Another limitation was that the complete sample was used in determining the predictive ability of the logistic regression models, which can lead to bias and optimism in the predictive ability.[466] However, models were exploratory in nature and the limited predictive ability (particularly with cognitive adverse effects regression) suggests that using the whole sample to determine sensitivity and specificity is not likely to create much bias. Ideally, for internal validation (i.e. using the same dataset on which the model was built), other approaches could have been used but it was not possible to use a split-sample approach (i.e. splitting the dataset into a development and validation sample) or cross validation and bootstrapping as the sample was small.[466]

There were also several strengths to the quantitative components. One main strength was the level of detail of the data collected about opioid prescribing in this population via a case note review. In particular, systematically converting all prescription data into OME to allow for comparison between different opioids, which enables meaningful comparison to other literature summarising opioid use in other populations. However, the limitations to this approach are also recognised. Specifically, the challenges of using

secondary data and potential differences between what was prescribed and how it was used.[359] Although, the case note review supplemented the cross-sectional survey data and potential challenges with patients recalling opioid prescriptions. Cross-sectional studies are a useful tool for estimating prevalence[467] and allowed this study to collect self-reported data on pain medication and opioid use, enabling a cross-comparison with the case note review data. There was also a good level of corroboration between self-report and medical record data. Another strength is its exploration of self-reported cognitive adverse effects attributed to pain medications, as there is limited data regarding this method of assessing opioid-induced cognitive impairment.[261] However, it was not possible to develop an all-encompassing list of adverse effects and this study focused on commonly experienced adverse effects, with particular attention to cognition. Participants were able to recognise the adverse effects on the list and were equally capable of identifying ones they did not experience or ones that were not listed.

10.1.2 Discussion of qualitative findings

Participants' narratives encompassed the insurmountable amount of *'work'* that they have to do to manage chronic pain and opioid use, as well as the additional impact of cognitive adverse effects. This was accompanied by emotional and psychological factors, which included an overwhelming sense of loss. Searching for a sense of safety and security was emphasised as important but was often missing in participants experiences. This led to feelings of abandonment, anxiety, despair and frustration were present when this did not occur. Internal (person-specific) and external (i.e. family, friends, health and care professionals and settings of care) factors identified as influential to adhering to pain management.

These themes are dynamic and reflect the concept of '*management process*' outlined by Corbin and Strauss.[338] This refers to the fluctuating and changing nature of the structure under which pain management takes place (i.e. within the home) and the reciprocal impact of a change in pain (e.g. worsening) and the necessary changes to a person's self-concept in light of pain and the reconstruction of their life. The themes provide a framework for considering chronic pain in this population and what might constitute meaningful pain relief (see Figure 10-1). Specifically, what matters to the person when

managing their pain (e.g. the importance of caring in clinical encounters), and how treatment and cognitive adverse effects may impact their day-to-day lives. It may not be possible to completely resolve pain but it may be possible to support patients to achieve a desired outcome (e.g. health and care support for home modifications or thinking beyond the home setting). Given increasing calls for a more targeted and integrated approach to pain management in older adults,[87,215,468] understanding the way pain can impact various aspects of older adults' lives may help to navigate discussions around pain and planning how best to optimise care in this population. The aspects depicted in Figure 10-1 are likely to be variable in the degree to which they may be influenced, but it provides an insight into the aspects at play in chronic pain management. Some of the main findings are summarised in the paragraphs below within the context of existing evidence.

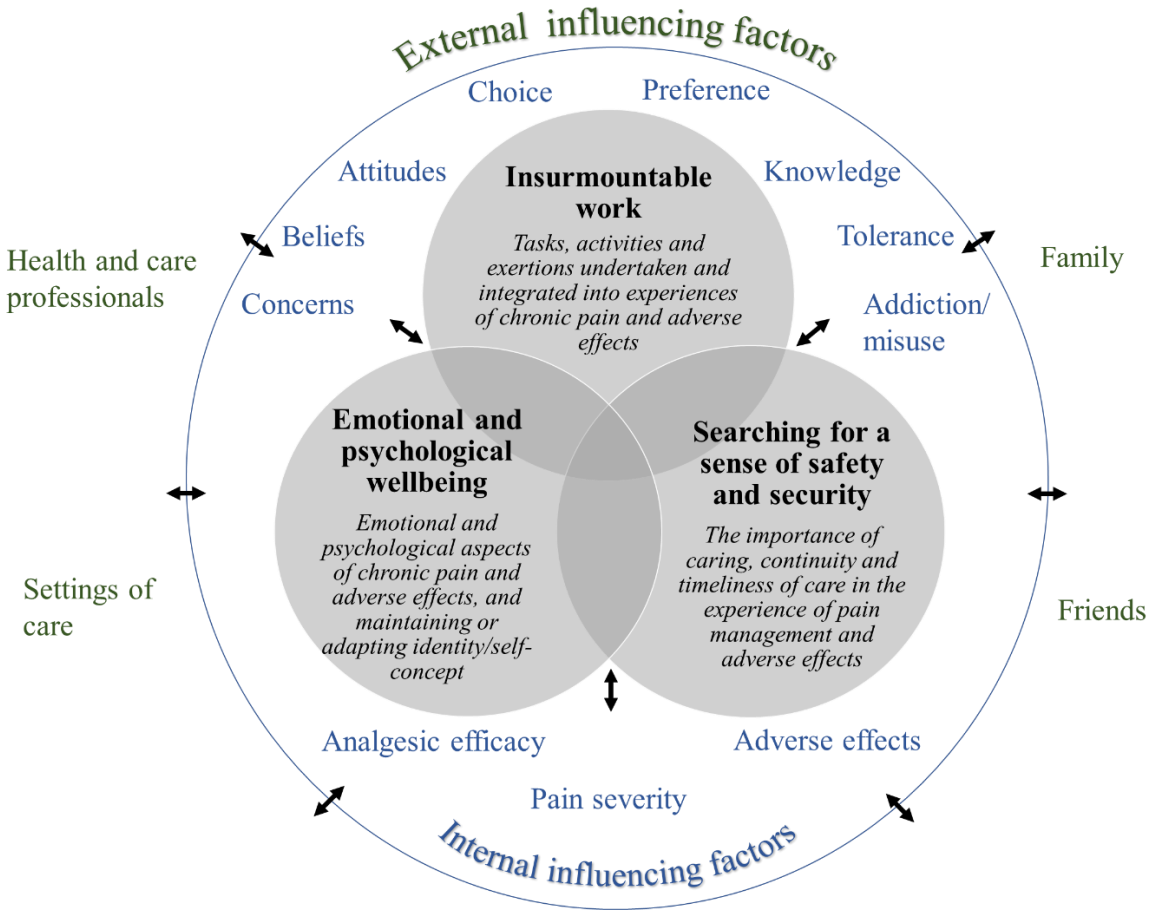


Figure 10-1 Framework for pain management in older adults

Classification of pain influences how pain is managed, as well as patients and family carers sense of safety and security.[469] Interviewees highlighted the lengthy and inconclusive journey towards understanding what was causing their pain and potential resolutions. In particular, testing and physical examinations were not always forthcoming. Classifying pain was viewed as helpful in managing pain more effectively and avoiding situations where pain escalates, and may potentially lead to crises (e.g. use of accident and emergency services). Multiple strategies were used to minimise pain, which included opioids and other analgesia, physiotherapy, steroid injections, mobility aids and self-care routines. Pain management strategies can adopt many approaches, including pharmacological, psychological, physical rehabilitation and interventional procedures.[121] How these strategies are used and combined in older adults requires careful consideration, such as their potential burden or appropriateness. Loss was a common thread across the interviews, in terms of changes to their ability to complete basic daily tasks or activities, as well as to their concept of self. In light of these losses, what constitutes effective pain relief might look different to this population.

Healthcare professionals have often been encouraged to find an *'acceptable'* balance between pain relief and adverse effects,[70,215,470] but in practice, this can be challenging and requires an open, honest and ongoing patient-provider relationship. Greater support is needed for both patients and informal caregivers when navigating pain medication and adverse effects – including accurate recording of adverse effects associated with opioid analgesics. Some participants commented on limited options and how healthcare professionals did not know what other strategies they could try. Pain management could be a considerable process of trial and error, and despair was often felt when options appeared to be exhausted. Participants recognised their limited understanding of opioid analgesics and other pharmacological approaches. The knowledge that they had formed came from personal experience, medication information leaflets, as well as family and friends. Healthcare professionals need to consider how information is presented, especially where health literacy may be limited.[167] Clear communication can support older adults and their informal caregivers in decision-making when uncertainty is present. The importance of caring in clinical encounters was seen as essential, and related to participants sense of safety and security.

Adherence to pain management regimen is a multifactorial problem; including internal and external factors (as discussed in detail in Sections 9.3.4.1 and 9.3.4.2). Attitudes, beliefs, concerns and knowledge are recognised as influential in decision-making regarding prescribed medication.[162,164,471] Despite attitude, beliefs, concerns and poor knowledge, the majority of participants in this study acknowledge the necessity of pain medications, which reflects the Necessity-Concerns Framework adopted within Horne and colleagues' adherence model.[345] Participants related practical acceptance of using opioid analgesics to several reasons, including trust in professionals and the benefits outweighing the negatives. Other studies have found similar complex paradoxical relationships and balancing acts between attitudes, beliefs, concerns, knowledge and the necessity of medication.[164,245,471] There was the view that pharmacological approaches would not have been suggested if the doctor did not perceive some benefit. Another qualitative study of older adults lived experience of medication-related problems around hospital discharge demonstrated similar participant beliefs.[165] All participants emphasise the importance of avoiding an over-reliance on pharmacological approaches and approaches that have lacked efficacy in the past.

Opioid analgesics were generally perceived as something that would help, but in practice, they only minimally reduced pain severity. There was a similar story with other pain management strategies, although some were found more effective than others. A descriptive study of pain management strategies in older adults with chronic pain demonstrated similar results; where multiple strategies were adopted and most were viewed as only moderately helpful on average.[145] Frustration was reported when pain management strategies had a limited effect on pain, where participants often resigned themselves to a life with pain. There was a general disdain towards taking medication. One aspect of this, that is pertinent to opioid use, is the route of administration. Where used, transdermal patches were thought to be more convenient to use and minimised the risk of adverse effects. Methods of drug administration are important to consider, especially in providing appropriate care to older adults and managing age-related changes in the barriers to drug delivery (such as physiological changes).[472]

Cognitive adverse effects were particularly bothersome and difficult to manage and influential to adherence to opioid analgesics. Occasionally, these cognitive adverse effects were used to the patient's advantage and incorporated into daily life (such as taking opioid analgesics before bed). Participants recognised challenges to identifying and recalling adverse effects due to complex pain trajectories, the number of medications tried and attributing to ageing or other health conditions. Patterns and relationships were often used to make assumptions about causality. The more severe adverse effects appeared to be more salient to older adults and their informal caregivers, with vivid descriptions of some of their most impactful experiences of adverse effects. In terms of recognising critical cognitive adverse effects, the interviews indicated that participants occasionally reported adverse effects. Evidence suggests that older adults remember more severe adverse effects compared to mild effects from medication but are less likely to recognise critical adverse effects (defined as ones that should prompt contacting their doctor) when there is a delay to recall.[473] Barriers to reporting such issues included challenges with accessing primary care and a lack of alternatives to pharmacological approaches.

In this study, informal caregivers described their experiences of being *'observers'* of the cognitive adverse effects and the distress it could cause (such as feelings of helplessness). A multi-centre survey among informal caregivers who managed medication for older adults showed that those reporting a greater number of medication-related problems were likely to experience poor mental health status and higher levels of carer strain.[95] Patient participants sometimes lacked awareness of the spells of cognitive adverse effects, meaning the responsibility of monitoring and recording such events sometimes fell to their informal caregiver. These more complex tasks have been recognised as more demanding than more practical activities (such as obtaining and handling medication).[96] Informal caregivers in this study could recollect various aspects of adverse effects but described how it could be challenging to remember what happened, when and why. This could be because of all the additional *'work'* they do day-to-day to help manage chronic pain. All participants emphasised that there was a fine balance between pain management and adverse effects.

Qualitative studies exploring opioid use and medication-related problems in older adults have often either focused on factors that influence adherence (including the impact of adverse effects) or how adverse effects are inextricable from the broader socioemotional context of their everyday lives.[63,474] The results of this study brings these narratives together via its use of multiple theories to help understand the data and also considers the impact on informal family caregivers, which has seldom been explored in this context. Informal caregivers play an important role in the complex and dynamic experience of managing chronic pain at home, predominantly as a source of support and as an advocate. They often feel overwhelmed and experience feelings of helplessness as pain is left unresolved. Additionally, there is an increased workload that caregivers take on when pain is exacerbated or maintained in some instances, such as supporting activities of daily living. Studies have explored the impact of chronic pain on the family, albeit regarding perspectives on health and medication generally,[246] in younger or mixed-aged populations[103,157] or with specific types of pain.[102,157] The role of informal caregivers in mediating the chronic pain experience in older adults living at home is poorly understood,[121] and these findings shed light on their experiences.

Exploring experiences can help improve caregiving dyads,[157] as well as provide a better understanding of information and support needs. This study captured different types of caregiving relationships (i.e. the relationship with the participant), which included spouses, children and family friends. The nature of the relationship affects the experience of care and what informal caregivers can help with.[475] This study found that informal caregivers have their own experiences of pain that they have to contend with. Different narratives were also observed, ranging from quietly supportive (i.e. where carers let patient participants tell the narrative and supported when needed), a building on narrative (where family carers added to and clarified the patient's story) and combative (where there was open disagreement on events or other aspects), These differences in themselves may impact on the patient and family caregiver experiences. There were mixed accounts regarding the toll caregiving took and management of their own health issues – these included references to having a higher pain threshold than the person they cared for or acknowledging the challenges of their caregiving role within the limits of their own health concerns (including chronic pain). Evidence suggests that older caregivers (such as spouses) have an increased risk of experiencing pain of their

own.[476] Chronic pain can negatively impact psychological and physical wellbeing of older caregivers.[477] Some participants had to manage on their own and did not have access to such support. In these instances, there appeared to be a greater sense of loneliness and difficulties with managing chronic pain.

Informal caregivers also play an important role in the appropriate use of medication by older adults.[96] It was clear from patient accounts that informal caregivers shaped attitudes, beliefs, decision-making and adherence to pain medication, as well as provided practical support with medications generally. Maladaptive beliefs and attitudes may come from informal caregivers if they are ill-informed. Informal caregivers acknowledged that more support is needed to build confidence in managing medication, as well as greater recognition of their role in providing care for the patient. Other evidence has supported the notion of providing informal caregivers with educational resources and support when accepting increased responsibility for medicines and other aspects of care.[90,96,246] Commonly, routines with medications routines were developed to aid adherence to medication or dose-based medication boxes.

Age-related parameters present unique challenges to managing pain in this population, which include the underreporting of pain, complex manifestations of pain and age-related changes in pharmacokinetics (as discussed in Chapter 2). However, these challenges often place the onus at a person-level as orientated towards attitudes, beliefs and characteristics of older adults. This study also emphasises how current infrastructure restricts older adults' ability to access pain management, and even when accessed, information and support provided are limited. Participants explained, in-depth, the structural barriers to accessing support, such as obtaining an appointment with their general practitioner or specialised services, knowing what support is available or time limitations with discussing pain amongst other health concerns. Delays in receiving timely support led to feelings of isolation and despair, and raised safety concerns, with many expressing that being under a service with open line of communication, even if not used regularly, provided peace of mind. With changes to the way health and care are provided,[20,87,468] as well as the desire to 'age in place' (i.e. the desire to remain at home as long as possible),[161] older adults increasingly require

support from primary and community services.[478] These structural barriers need to be addressed to enable better approaches to pain management.

Participants explained that it was important to acknowledge the subjectivity of pain and tailor approaches. There was an onus placed on the importance of caring in clinical encounters; communication needed to be open and honest from all parties, especially around pain medication. This included the patient being clear about what they could manage and the informal caregiver being part of the conversation. In terms of information needs, they wanted to be informed about why they were being prescribed, how they worked, what to expect, possible adverse effects and interactions, as well as any contraindications with existing conditions. The quality of the information and the time given to discuss their pain were considered vital components of effective pain management. They highlighted that this was particularly important when options for managing treatment were limited. They recommended being vigilant for adverse effects and reporting these to determine whether pain medication was actually needed. Empowering informal caregivers was essential, as were local sources of support. Overall, quicker access to support with chronic pain was needed and an open channel of communication to mirror the exacerbations of pain they often experienced.

In summary, participant accounts provided an enhanced understanding of the role of opioid analgesics in pain management and the challenges of managing chronic pain. Chronic pain is burdensome to community-dwelling frail older adults and their informal caregivers. This population describe the onerous effect that chronic pain, opioid use and adverse effects have on their daily lives and the changes that have occurred to their sense of self and roles with informal caregivers. There was a conflict between their struggles with managing pain and moderating their experiences as they did not wish to bother others. Informal caregivers shared feelings of distress and frustration as they often felt helpless and sometimes left out of the care loop.

In reflecting on the strengths and weaknesses of this study component, one main strength was the use of interviews with frail older adults and their informal caregivers to collect rich and in-depth data. Thematic analysis and writing an analytic coding journal

allowed me to reflect on the process of developing the themes, and how the theories outlined in Section 6.3.2 could guide this interpretation (i.e. moving from the descriptive to the analytical). This could have been strengthened further by conducting linked interviews with patient participants' GPs but this was beyond the scope of this study as it was not possible to access the patients GPs from the primary care setting. It is recognised that some participants were not referred to the ICC based on their frailty scores, but were referred on the basis that visiting the centre would be beneficial based on their health issues. These patients were included as they had a recognised need for the frailty service, and their narrative was anticipated to be similar to the older adults recruited that were thought to be at risk of severe frailty. Another limitation of this study was that participants were recruited from one organisation in Hull, Yorkshire, which is a deprived area where opioid prescribing is high compared to other areas.[48] Therefore, the results may have limited transferability.

10.1.3 Novel contributions and integration of findings

The complex interplay between and impact of pain, opioid use and cognition are poorly understood in older adults, which leads to challenges in pain management. The body of work presented in this thesis has generated new knowledge to help fill this gap. The novel contributions of this thesis are summarised below, which includes contributions concerning each research objective.

Objective 1: In synthesising the evidence on the impact of opioids on cognition in older adults with chronic pain, the systematic review brought together different approaches for assessing the effect of various opioid analgesics on cognitive function and examined their usefulness. By bringing the evidence together, the review offers insights into improving approaches to pain management. The researcher also identified challenges that might be important in assessing the impact of opioid analgesics in this population, including the variation in cognitive domains assessed and the impracticality of assessments in clinical practice. Comparing the cognitive domains assessed across each screening tool and neuropsychological assessment led to the identification of cognitive domains that may be the most pertinent to older adults. This component also highlighted a need for further exploration of the cognitive domains that are most affected in this

population (ensuring that cognitive function is the primary objective) and more explicit reporting of opioid analgesics and assessments under study.

Objective 2: By investigating opioid analgesic use in frail older adults to manage pain and the impact on cognition, this study generated a novel description of opioid prescribing (such as opioid type and daily dose) and cognitive adverse effects in this population. The findings suggest that pain medications in this older adult population have not been regularly reviewed, and pain medication could be better optimised and rationalised as illustrated by the review of pain medication on attending the ICC. This should include pain management reviews as a part of regular and formal follow-ups. To improve the identification and reporting of cognitive adverse effects in older adults, discussions adopting the use of prompts may aid self-report/disclosure of adverse effects noted by patients in relation to their pain medication. The researcher also found an association between opioid analgesic prescribing on older adults' health-related quality of life, as well as factors associated with increased odds of opioid prescribing.

Objective 3: The qualitative interviews explored the experiences, perspectives and concerns of older adults living with chronic pain and their informal caregivers. This provided a novel and rich understanding of pain, opioid use and the impact on cognition. This is the first study to explore how opioids are used to manage chronic pain at home and the associated cognitive adverse effects impact on informal caregivers. Participants' accounts highlight the multidimensional loss that people with chronic pain and their informal caregivers are adapting to, as well as the paradox of managing pain and cognitive adverse effects. Importantly, it shows that older adults with chronic pain see pain management as a futile process and the caring in clinical encounters was frequently felt to be missing from their experiences. The findings emphasise the need for adaptation to infrastructure and processes of accessing support with managing pain, with services needing to be responsive and flexible to changes in pain severity and episodes of pain. New recommendations that openly acknowledge that the current system is not responsive (i.e. a largely biomedical model and limited drug treatments) are needed in practice. The qualitative study also demonstrated the complexities of identifying and disclosing issues with pain and cognitive adverse effects, how people

use opioid analgesics in practice, as well as the challenges with fine-tuning approaches (e.g. changes to dose) and options with pain management. Knowledge and understanding of opioid analgesics have an important part of this, as well as how professionals communicate.

This thesis highlights the prevalence and severity of pain, a symptom that is commonly neglected in frail older adults but potentially remediable if healthcare professionals identify and assess it comprehensively and systematically, and use a multimodal approach to managing it. Opioid analgesic use is also highly prevalent and can lead to opioid-induced cognitive impairment that can be challenging to detect in clinical practice. There are no clear approaches to how this can be best assessed. Screening tools and neuropsychological assessments are commonly used in research but are harder to adopt in practice. Self-report is usually the method that patients adopt to express issues with opioid-induced cognitive impairment, although recall can be limited but improved with a common list of adverse effects. Importantly, pain is not an isolated experience and informal caregivers have a prominent role. Overall, improved identification, assessment and management of pain and opioid-induced cognitive impairment may improve quality of life and promote wellbeing.

A modified critical interpretative synthesis[460] was completed to synthesise the results from the quantitative and qualitative components to expand the understanding and validate the data, and integrate findings from the systematic review. The data are compared side-by-side in Table 10.1, and consideration is given to where the data confirm, diverge or expand the insights into the phenomenon presented (see Section 7.6 for more detail on the approach). This is followed by a discussion of intersecting findings in the context of existing literature and a reflection on the overall strengths and weaknesses of this research, as well as its implications for clinical practice, policy and future research.

Table 10.1 Modified critical interpretative synthesis of results from mixed-methods study and the systematic review

	Mixed Methods Study			Systematic review	
Phenomenon	**Quantitative results**	**Qualitative results**	**Integration and synthesis of results**	**Results**	**Additional insights**
Pain in older adults	- Pain was an explicit problem or concern for just over a third of frail older adults in a primary care setting. - Pain was highly prevalent. Although pain ratings varied between the week prior to and on the day of recruitment, reports of moderate to extreme or overwhelming pain were present for over 55% of the sample regardless of the timeframe considered. - Problems, concerns and ratings related to pain were significantly more prominent/worse for those who self-reported a pain medication over the past year compared to those that did not (with	- Concerns about pain were prominent and what it meant for the future. Concerns were often downplayed as a part of ageing, and managing pain felt futile and came one day at a time. - Sources of pain had different times of onset and trajectory but were experienced for years; forming one story of pain. Timelines to receiving a diagnosis of pain varied and sometimes not received. - There was a process of work to manage chronic pain that was further limited by functional issues, including changes to	Pain remains a prominent issue despite treatment. Moderate-to-severe pain is particularly common. Experiences of pain differ from day-to-day, which makes it challenging to plan ahead. Mobility and physical function were often a priority and felt to be reduced by experiences of pain. Older adults have complex experiences of pain (with multiple sources that are usually experienced for long periods of time). Different sources and episodes of pain were often amalgamated together into the 'story of pain'. Pain was considered more than just a physical symptom that impacts the patient, informal caregiver and day-to-day life. Yet, it is frequently downplayed. There was a connection between unresolved and unmanageable	- Studies have primarily explored opioid-induced cognitive impairment in older adults with chronic non-cancer pain. ▪ Chronic non-cancer conditions included back pain, osteoarthritis and postherpetic neuralgia.	Older adults with chronic non-cancer pain have been the predominant focus of opioid-related research. In particular, research has lacked focus on frailty.

	chronic pain being present in 94.8%) - Multiple sources of pain were present, with the most common being arthritic (26.7%), back (23.9%), hip (11.3%) and knee (10.5%).	everyday life and concepts of self. - Emotional pain accompanies the physical and impacts informal caregivers as well as the older adult.	pain with being accepted as a 'normal' part of ageing. Informal caregivers play an important role as an advocate and source of support but feel helpless when pain is unresolved.		
Pain management in older adults	- Recommended changes to pain medication were made for 130/247 participants, with just under a third relating to opioid analgesics. - Changes to opioids were usually focused on decreasing or stopping, with a focus on rationalising pain medication, and managing potential risks and adverse effects. - There was a steer towards transdermal patches rather than oral administration, as well as separating combined preparations (e.g. co-codamol).	- Financial costs of pain were identified, such as obtaining tests privately as they were not forthcoming generally. Solutions were often pharmacological. - Concerns were predominantly around medication strength, adverse effects, becoming addicted and long-term use. These were influential to pain management decision-making. - Understanding of pain medication is limited; differing ideas of what was considered a strong opioid analgesic.	Classifications of pain were helpful or would have been helpful in managing pain more effectively, avoiding pain escalating, and reducing uncertainty that led to a reduced sense of safety and security. Careful consideration to pain management is needed in this population, with attention given to alternative approaches other than focusing pharmacological treatments and what meaningful pain relief would look like in relation to the *lines of work*. If pharmacological options are prescribed, thought needs to be given to its appropriateness. More formal of pain medications reviews are needed as patients trust in HCP decision-making and may not initiate	As above.	This thesis provides an in-depth exploration into the pain management of frail older adults. A predominance of chronic non-cancer pain was also noted in the mixed-method study.

	- 31.6% (n=49/155) of those with experiences of pain medication reported that they had never been reviewed.	- Informal caregivers were influential to shaping decision-making regarding pain management. - Changes to opioids were made in relation to adverse effects and inefficacy. Normally, in relation to self-reported issues as formal reviews of pain medication were infrequent. - Trust in HCPs to prescribe appropriate medications and occasionally led to long-term use of opioids. Rationalising pain medication was seen as important. - Information and support were stunted by limitations in care settings (e.g. appointment length) and timely access to the correct channels. Communication and continuity of care were	discussion/query the medications prescribed. Pain should be afforded the attention that other chronic conditions receive. Streamlining medications was not only important clinically, but also to patients, to ensure they are only taking medication that was necessary. The management of pain is influenced by internal factors (e.g. attitudes and beliefs) and external factors (i.e. access to support from HCPs or influence from informal caregivers). A limited understanding of opioid analgesics and pain medication generally can result in ineffective use. Current infrastructure limits the information and support provided, as well as engagement with older adults regarding pain management. Patients need a clear rationale for prescribing, outlining possible interactions and adverse effects (and why they might be		

		essential components to managing pain. Being 'on the books' gave a sense of safety.	experienced), and a plan to review. Feelings of despair and isolation were experienced when access to support was limited, with open-ended access perceived as a safety net to reduce risks and providing an open line of communication that could be accessed when needed.		
Opioid analgesic use in older adults	- Over half of the participants with prescription data had an opioid prescription documented on their medical record at some point over the last year. - There was a high level of concordance between self-report and documented opioid prescriptions. - Those who self-reported 'No' were more likely to have an opioid prescription documented, compared to those who reported 'Yes' but did not	- Limited knowledge of opioids; struggled to remember opioid names or misnaming them. Knowledge came from medication information leaflets, personal experience or family/friends. - Recall of opioids prescribed over the past year were aided by memorable events (e.g. adverse effects). - Perceived as something that would help with managing pain, whether taken regularly or on a PRN basis. In practice, they only took the 'edge'	There was a high prevalence of opioid prescribing in frail older adults in primary care within the year prior to recruitment. Patients themselves may struggle to remember what has previously been prescribed, which may be due to limited knowledge. Commonly prescribed opioids included codeine, tramadol and morphine. Of which, were generally prescribed at low doses. Oral opioid analgesics were often prescribed, but where they had been used, accounts supported use of transdermal patches that were thought to be	- Opioid analgesics assessed in the literature included buprenorphine, codeine, dextromethorphan, dextropropoxyphene, ethylmorphine, fentanyl, methadone, morphine and oxycodone. - Largely oral administration and duration of use varied. - Comparison between the efficacy and impact of different types of opioid analgesics was limited, as few studies in older adults were	Existing evidence has studied some of the opioid commonly used in frail older adults but not tramadol. Of which, sometimes led to impactful negative experiences. Further attention is needed around the efficacy of specific opioid types. In particular, alternatives to oral administration. The quality of reporting around opioid analgesics needs to be improved in research studies.

	have an opioid prescription documented. - Low doses of codeine, tramadol and morphine were commonly prescribed. Opioids were mostly prescribed on a PRN basis and were for oral administration. - HRQoL was significantly lower for those with a documented opioid prescription compared to those that did not. - Higher pain scores and number of medications prescribed were significantly associated with increased odds of having an opioid prescription documented on their medical record. - 80/128 (62.5%) had an opioid prescribed within the 30 days prior to recruitment.	off. Although, this was similar for non-opioid analgesics mentioned. - Opioids may be prescribed but they may not be used or might be disposed of. Efficacy and adverse effects often determined continued use. Allergies and other health conditions were also limiters to pharmaceutical choices. - Other non-pharmacological approaches were adopted alongside opioid analgesics. - Patterns and routines were used to aid pain medication regimen, although they were sometimes taken incorrectly. Certain routes of administration were preferable to others. - Delays with receipt of opioid analgesics, disagreements	more convenient to use and had less risk of adverse effects. There may be a disparity between what people are prescribed and how they approach taking pain medication. Opioid analgesics were frequently prescribed on a PRN basis, although data indicated they may be used more regularly. Routines were developed and used to help with adherence to opioids. The presence of opioid prescriptions was significantly associated with lower HRQoL, which was corroborated by patient and informal caregiver accounts. Higher pain severity and number of medications may be associated with having an opioid prescribed. Opioid analgesics were generally perceived as something that would help, although in practice, they were minimally effective. Continuation of ineffective	identified and only four considered efficacies. ▪ Generally, pain relief may be achieved with low daily doses. ▪ Opioid switching may be useful in improving quality of life. - Significant variation in the quality of reporting details of opioid analgesics being assessed.	Medical record data could be used more effectively to minimise the chance of being prescribed opioids that have previously been used. Especially, as it can be challenging for patients and their informal caregivers to remember opioids that have been used historically. This mixed methods study was able to provide a detailed account of opioid prescribing, although a less causal evaluation of cognitive function.

		regarding when repeat medication could be requested or changes in dose interrupted use when needed.	treatment may be due to limited options with pain management or the minor level of pain relief was perceived to be better than nothing. Misunderstandings were common but could easily be reduced by clear and honest discussions around pain medication with HCPs (e.g. how they work). Medication leaflets are not always easy to read or understand, and may raise more questions than they answer (e.g. not to be used with certain health conditions).		
Opioid-induced cognitive adverse effects	- More adverse effects were identified when prompted with a list of common adverse effects compared to free recall. - Adverse effects reported were mostly related to pain medication but some were of unknown origin. - Adverse effects were more commonly reported in relation to	- Experiences of adverse effects fuelled a trial-and-error approach to pain management and impacted adherence. - Screening tools were occasionally used to assess impact on memory following self-reported concerns. - Cognitive adverse effects were considered one of the most	The way cognitive adverse effects are expressed vary in terms of language used and how they are recalled. Prompting patients with a list of adverse effects may aid identification of more adverse effects than free recall. There were challenges in remembering and identifying their history of cognitive adverse effects, especially with the	- Recruitment setting varied without specific focus to primary care or frail older adults. - Screening tools and neuropsychological assessments used varied. ▪ More consideration needs to be given to the their usefulness (e.g. sensitivity and	Primary care is an under researched setting when considering chronic pain, opioid use and cognition. There are a number of challenges identified with older adults managing chronic pain at home. There was no scope to include self-report within the systematic

	opioid analgesics than other pain medication. - The most common freely recalled adverse effects were constipation, drowsiness, hallucinations and nausea. Whilst, the most common adverse effects when prompted were constipation, drowsiness, and attention and concentration. - Diverse language was used when freely recalling cognitive adverse effects. - Being female was significantly associated with increased odds of reporting a cognitive adverse effect from pain medication. - Although not statistically significant, a protective relationship of	bothersome consequences of opioids. - Noted in relation to time since taking the opioid, change in dose or thought to interact with other medication. Recognition that it can be challenging to identify cause (e.g. ageing or on multiple medications) - Disclosure of adverse effects to HCPs varied due to challenges engaging with primary care or prescribed more pain medication (including pain medication that previously caused adverse effects). - Distressing for patients and informal caregivers (who witnessed and were more aware of cognitive impact).	complex pain trajectories and series of pain medications tried. Cognitive adverse effects were commonly reported, alongside issues with constipation and nausea. Patients and informal caregivers prioritised adverse effects, with cognitive adverse effects perceived as one of the worst (alongside constipation, nausea, sickness and mood). Timing and consistency between opioid use and cognitive adverse effects led to conclusions about their relationship (i.e. cause and effect), often in relation to starting an opioid or a change in dose. Additionally, interactions with opioid analgesics and other medication were considered by patients. The strength of association between opioid use and cognitive adverse effects was clearer for some compared to others. Cognitive adverse effects were often distressing to patients but more so family caregivers, as patients lacked awareness of the	specificity to detect cognitive changes). ▪ Neuropsychological assessments are impractical for use in clinical settings. - Mixed effects on cognition; changes were observed in studies where higher doses were present. ▪ Cognitive domains that may be negatively impacted were identified, including: attention, language, orientation, psychomotor function, and verbal working/short-term and delayed episodic memory). - Pain relief may be achieved with low daily doses without cognitive detriment. - Concurrent medications were often present (with	review; focus was given to screening tools and neuropsychological assessments to allow for comparison with other reviews in other populations. However, self-report was more common than screening tools in deducing impact to cognition in the mixed methods study. The use of screening tools followed self-reported complaints of changes to cognitive function, with opioid analgesics being one consideration rather than directly associated. Some were concerned that issues with cognition could be degenerative (e.g. Alzheimer's or dementia).

	lowering the odds for cognitive adverse effects was observed with younger age. - HRQoL was slightly lower for those reporting a cognitive adverse effect compared to those that did not, but this was not statistically significant.	- Strategies to balancing pain and cognitive adverse effects included: dose change, stopping the opioid, persevering or incorporating within daily routine.	event and caregivers were often witnesses. Cognitive adverse effects were recognised by patients and informal caregivers as impactful to quality of life. Balancing pain and cognitive adverse effects were challenging, and the process was often based on trial-and-error.	cognition susceptible to polypharmacy and anticholinergic burden) but not always controlled for.	Older adults and informal caregivers do not characterise cognitive adverse effects in terms of domains, and may describe adverse effects in different ways. Timing, consistency and plausibility led to conclusions of cause and effect. Cognitive adverse effects are impactful to patients and their informal caregivers. Therefore, how they can be meaningfully identified in practice matters. It may be that a structured discussion through adverse effects between patients and HCPs is more practical within a clinical setting, and could form part of a pain management review.

					Although, there are recognised limitations to self-report (such as recall), where using a common list of adverse effects in clinical practice may improve the number of adverse effects recalled. Further understanding is needed to understand which approach might best support identifying issues and for what purpose (clinically or in research). Recording of adverse effects within medical records could be better.

Abbreviations: HCPs Healthcare professionals, *HRQoL* Health-related quality of life, *PRN* Pro re nata

10.2 Discussion of intersecting contributions

The process of understanding opioid use in older people to manage pain and the impact on cognition led to several intersecting findings. This section will discuss the synthesis of the mixed method study findings and integrated findings from the systematic review (presented in Table 10.1) to address the overall aim of this thesis by presenting results by common phenomena in the context of existing literature. These include understanding pain in older adults, pain management in older adults, the role of opioid analgesics, and identification and reporting of opioid-induced cognitive impairment.

10.2.1 Pain in older adults

Pain ratings varied when patients were asked to reflect on pain at different times. Despite this, prevalence of current moderate to severe pain remained high, in particular for those who self-reported using a pain medication at some point over the past year. Pain prevalence estimates vary greatly worldwide (and are determined by how pain is defined) but generally increase with age.[4,122,138] Estimates considering the prevalence of current pain of older adults living in the community ranged from 20% to 46%.[24] A prospective study found that 21.5% of community-dwelling older adults reported moderate to severe pain at baseline.[139] Current pain prevalence in this sample, even when focusing on moderate to severe pain, exceeded these estimates with 56.7% on the day of recruitment and 63.6% in the week prior to recruitment. Qualitative accounts supported the varied nature of pain and suggest that it is not well managed in this population. This higher percentage may have been due to the population sampled. The setting participants were recruited from aimed to primarily treat frail older adults with long-term conditions who were assessed as being at risk of hospital admission by their GP and classed as at risk of being severely frail. Few studies have focused on older adults at risk of or with frailty.[85] The predominance of chronic non-cancer pain noted within the synthesis (i.e. the focus of included studies or experienced by participants in this study) emphasises and supports the need for more optimal approaches.

The experience of pain has long been characterised by its inter-individual variability; influenced by numerous factors (such as demographic characteristics and genetic

factors).[479] In particular, several age-related parameters bring unique challenges when managing pain in older adults (such as multiple chronic conditions and physiological responses to medication).[31] In this study, older adults' experiences of pain were complex and usually experienced for long periods of time. For patients and informal caregivers, understanding and learning about pain is a complicated process – especially, when multiple sources of pain and other health concerns are experienced. As summarised in Table 10.1, the most common sources of pain included arthritic, back, hip and knee, with many participants experiencing multiple sources of pain. This mirrors trends observed in the literature.[24,137] A higher number of pain sites has been associated with an increased risk of all-cause mortality compared to having no pain. Although, at least half of this association may be accounted for by four mediators (including opioid use).[144] Multiple sites of pain in this study, when explored in-depth, were often amalgamated together into the 'story of pain' and were challenging to untangle. It is important to recognise and understand the person-specific experiences of pain to provide optimal pain management and consider the impact of analgesia.

Impairments to physical function and everyday life because of pain are not uncommon in older adults.[100,215,480] In this study, functional status was only examined in relation to the overall sample or presence of opioid use over the past year (where it did not significantly differ between those who had an opioid prescribed over the past year and those that did not). Therefore, it is not possible to draw concrete conclusions about physical impact on the study population. However, the association between pain and mobility was well-recognised throughout the interviews with older adults and function was highly valued. Additionally, the interviews extended understanding and provided detailed accounts of how pain impacts various everyday activities (see Section 9.3.1.2). Limitations to mobility and function generally worsen with age and are more prominent in female and lower socioeconomic groups.[481] Although, persons with pain and who use analgesia are more likely to report limitations with mobility.[481,482] Additionally, older adults experience considerable issues with activities of daily living, especially when pain is present. Careful consideration is needed when deliberating pharmacological and non-pharmacological management of pain to promote mobility in older adults. Further attention is also needed regarding the impact of pain intensity on activities of daily living, as exemplified in this study.

Expanding on the quantitative components, findings from the qualitative interviews indicated that pain was considered more than just a physical symptom. Chronic pain had emotional and psychological consequences (for both patients and informal caregivers) and was discussed alongside other chronic conditions. Chronic pain has been viewed holistically within the biopsychosocial model, which considers the biological, psychological, and social factors that can moderate a person's experience of pain.[336] Although, it concentrates on pain as more of an individual experience and how biopsychosocial factors impact person-specific outcomes. In this study, chronic pain is also viewed with a holistic lens but considers the implications for both older adults and their informal caregivers with chronic pain work, everyday work and biographical work, as well as the internal and external factors that influence these. It has also been argued that there may be a benefit to considering chronic pain as a disease model, as it is consistent with other diseases (e.g. unique and sometimes disease-specific changes with an impact on quality of life).[469,483] Although there are certain advantages to mechanism-based, symptom-based and/or diseased-based approaches to pain, the goals of understanding and managing pain should focus on improving quality of life and considering the challenges that patients and informal caregivers manage day-to-day.

Pain severity was often moderated by patient participants in this study. Pain was identified as a main problem or concern by around a third of participants, whilst the prevalence of pain was much higher. Although the pain might not have been a main problem or concern for some who expressed moderate to severe pain, the view that pain is expected and irremediable may mean that these problems are easily disregarded. Underreporting of pain is recognised as an issue in older adults and is impacted by attitudes and beliefs.[121,124] Unmanaged or untreated pain can have a negative impact on quality of life and health outcomes.[153] Stoicism has been implicated as one reason for underreporting in this population, although this is largely based on empirical investigation.[124,125] This study echoed the attitudes and beliefs identified in the literature, including stoicism, pain as a 'normal' part of ageing, inefficacy of treatment and limited options, perceived lack of support from healthcare, as well as other external barriers (such as infrastructure of healthcare settings).

10.2.2 Pain management in older adults

Older adults do not always have access to adequate pain care.[145,484] Several components of this thesis highlight how pain is a prevalent issue in older adults, especially chronic non-cancer pain, but is poorly managed. Compared to people that had not self-reported using a pain medication at some point over the past year, data from the cross-sectional survey showed that pain was more of a main problem or concern for older adults that had used pain medication. Pain in the week prior to and on the day of recruitment was significantly worse for this group. Qualitative accounts echoed the subjective and complex nature of pain, as well as the impact on wellbeing. In particular, the moderation of pain by older adults to healthcare professionals regarding their experiences of pain (e.g. stoicism). There was also a clear conflict between implicit trust in healthcare professionals and their negative experiences of opioid-related problems in this study. This aligns with the understanding that chronic pain and use of pharmacological approaches to manage pain in this population may accelerate or increase risks of negative health outcomes.[19,107,215,226] Frustrations and dissatisfaction in the effective management of pain in older adults have also been expressed by primary care clinicians, in particular, concerns around the use of opioid analgesics and insufficient training.[485]

The use of inappropriate medication in older adults poses a significant challenge but can be managed via regular reviews and interventions promoting appropriate use.[486,487] In particular, frailty and polypharmacy have been identified as factors highly associated with inappropriate prescribing.[198] The changes to pain medications observed in this study sample (as described in Section 8.2.3) and accounts from participants highlight that pain medication could be optimised and reviews of medication are infrequent. In line with this, participants reflected on how chronic pain was often not afforded the same attention as other chronic conditions that received more regular reviews throughout the year. Rationalising pain medication is not only important from a clinical point of view (e.g. medication waste, cost) but was also important to patient participants to ensure they were only taking necessary medications. Participants identified issues with inefficacy and/or adverse effects as the main reasons for making changes to pain

medication, although this was not always communicated with healthcare professionals. A survey found that successful desprescribing in older adults requires effective communication centred around a rationale for deprescribing (such as adverse effects or improving wellbeing).[488]

Pain management possibilities will always be influenced by their specific contexts,[489-491] including the structure of the environment (e.g. access to resources and appointments, continuity of care), and the skillset and expertise of healthcare professionals, as highlighted in this study. These *'external influences'* do not always allow for optimal pain management to occur in this population, especially in the reorganisation of primary care due to the pandemic.[492] Good communication is fundamental to pain management strategies.[61] Recent developments like the 'Evidence-based clinical practice guidelines on the management of pain in older people'[61] and 'Assessment of pain in older people',[121] both of which focus on routine assessment and individualised, holistic, multi-disciplinary care, may be able to help address some of these proposed issues in older adults. Wider strategy, such as the 'Core standards for pain management services in the UK',[53] may also provide the opportunity for integrated systems and services to improve how pain is managed.

10.2.3 The role of opioid analgesics in older adults

This thesis has provided an increased understanding of opioid use in managing pain in older adults (and those at risk of severe frailty), both in terms of patterns of prescribing via a case note review, and experiences of how opioids are used in practice and their impact. The approach of considering prescription data alongside experiences of using opioids has provided a novel perspective and allowed for the interrogation of one against the other. Other studies have often only adopted one of these approaches[49,63,225] or have not included the aspect of frailty.[85] Notably, there are differences in the way medication is prescribed and how it is taken in practice.[493] Nonadherence to analgesia is a common problem in this population, often due to attitudes and concerns regarding addiction,[493] and was also noted in this study. Prescription data indicated that older adults may not necessarily take opioid analgesics as intended, with some using opioids prescribed on an 'as and when' basis being used more regularly. Whilst, findings from

the qualitative interviews demonstrated a more complex story. Most patients explained that they took their pain medications as prescribed, although, in some interviews, narratives changed throughout – where participants acknowledged taking them in excess or at the wrong times. Although, most felt they were following the regimen correctly. The use of mixed method research has been deemed as important to the success of interventions improving medication-taking ability,[494] albeit to qualitatively understand experiences with interventions. Understanding the differences between what people are prescribed and actual medication adherence before developing interventions may lead to improvements in prescribing practices and adherence. Route of administration may also play a part in adherence.[472] As with other studies,[472] qualitative accounts in this thesis indicated that transdermal patches might be more appropriate for older adults who struggle with swallowing and gastrointestinal issues. Although, they were infrequently prescribed. Pharmacological management pain has often centred around several key principles, including by mouth (i.e. oral routes where possible).[21] However, other routes may be better for this population.

One issue with understanding opioid prescribing in older adults is that the accuracy of recall regarding medications and medical conditions may be poor.[366] However, the qualitative findings identified challenges with recalling the specific details, which included the number of pain medications that have been prescribed, remembering the names of medications, which 'family' of medications they belong to and the different sources of pain they were prescribed opioids in relation to, as well as the period of time they have to recall medications over. The lines between these factors often blurred and sometimes made it challenging to unpick experiences of specific opioid analgesics (e.g. switching from codeine to buprenorphine). One way to circumvent such issues, and reduce recall burden, was to use primary care data, although this has its own weaknesses.[495,496] Overall, there was a good level of corroboration between self-report and medical record data when reflecting on any opioid use over the past year. Although, prescription data may underestimate use due to absent prescriptions (such as out-of-hours or community prescribing)[495] or may overestimate use as older adults may not take medication as prescribed.[493] However, other studies have demonstrated similar issues with recalling analgesia used and supported the use of other sources to capture use (such as prescribing data or pharmacy data).[261] One main challenge with this study

related to obtaining access to primary care record data on the electronic medical record system used by the ICC (i.e. SystmOne), as general practices had not always granted permission for read access. . This could mean that opioid prescribing was underestimated, as prescription data was not accessible for all study participants and those with missing data may have been prescribed opioids.

Opioid analgesics have often been regarded as effective drugs in the treatment of pain.[228] Namely, in managing severe acute pain and cancer pain. While opioids have a place in pain management, there has been a long-standing debate about their usefulness in chronic non-cancer pain.[228,229] Despite this, their use is escalating[49] and leading to concerns around inappropriate prescribing.[497] The prevalence of opioid analgesics used in this study population and the number of recommended changes to pain medication mirrors these issues. Pharmacological treatment of chronic pain in older adults has been demonstrated as partially effective and is limited by adverse effects (such as cognitive impairment).[215] This finding concurs with the results of this mixed methods study, which highlights that only minimal pain relief is often the case against the stark impact of adverse effects. Qualitative accounts provided descriptions of being left on opioid analgesics for a long time.

This study found that those with an opioid prescription on their medical record had a significantly lower median score for health-related quality of life compared to those that did not. This was also supported by the accounts of how opioid analgesics impacted everyday life (see 9.3.1.2). The impact of opioid prescriptions on quality of life and the *'work'* caused by ineffective management of pain identified by interviewees have important implications for opioid prescribing in this population. Other studies have found similar impacts on health-related quality of life with central nervous system depressant medications (such as prolonged use of opioids).[498,499] Supporting more careful consideration to monitoring prescribing in this population, a retrospective cohort study demonstrated that older age was associated with long-term opioid use, alongside observing high-risk prescribing in predominantly northern areas of the UK compared to the population average (including Yorkshire and the Humber).[48] The prescription data raised questions about the types of opioids commonly prescribed in this population (i.e.

codeine, tramadol and morphine), as they often have deleterious effects and are not best suited for older adults.[60,72,463]

The findings from the interviews highlight how pharmacological approaches were common and alternatives to medication were under-used, which could be, in part, due to limitations in access to support (such as pain clinics). The minimal consideration of non-pharmacological approaches has also been observed in other studies.[491] This study highlights how a tailored approach to pain management is needed, with an exploration of different types of treatment. The variation in the experience of pain severity and benefits from treatment means that a 'one size fits all' approach is not possible. There is potential to use non-pharmacological approaches alone or in conjunction with medication.[21,26,500] It is also important to be cognisant that complete pain relief may be an unrealistic aim or is associated with increased adverse effect burden in this population.[21,29] Therefore, the *'insurmountable work'* and the *internal* and *external* barriers outlined in this thesis may be useful to understanding what successful pain relief might look like for the individual may be useful (such as being clear-headed, reducing unnecessary burden or socialising with family and friends).

The original WHO analgesic step ladder has been modified over the years to improve how it is applied towards other types of pain beyond cancer pain.[55-57] Clinicians have been encouraged to use the guidance to tailor pain management to individual patients and reflect advances in practice.[55-57] Although, there has been a fine balance between maintaining simplicity and encompassing the most recent interventional innovations.[501] This study, as highlighted earlier in this section, noted several recommended changes to opioid analgesics that were currently prescribed to older adults (including ensuring repeat prescriptions were up-to-date). The evolving framework, lack of clarity and various strategies for how to manage pain[56,57] might explain these suggested changes to opioid prescribing in the study population. In addition, occurrences of adverse effects and the changes in pain severity as noted in the cross-sectional survey and qualitative interviews may also have contributed to these recommended changes.

10.2.4 Identification and reporting of opioid-induced cognitive impairment

This thesis has contributed to the knowledge of how cognitive adverse effects from opioid analgesics are recognised, recalled, expressed, disclosed and assessed in the older adult population. The systematic review considered cognitive domains impacted by opioid use, and identified screening tools and neuropsychological assessments that have been investigated in older adults, as well as considered their usefulness. Whilst qualitative accounts provided an understanding of how cognitive adverse effects are identified and reported in practice. Given the unique parameters that pose specific challenges to pain management in older adults (such as physiological changes and increased risks of drug-related harm),[32,435] suitable methods are needed to identify deleterious effects (such as opioid-induced cognitive impairment) in this population.[104] Especially, as this thesis highlighted that older adults may not always recognise or attribute cognitive adverse effects to pain medication.

The systematic review identified potential cognitive domains that may be impacted negatively by opioid analgesics in this population and indicated that low-dose opioids may provide effective relief with less impact on cognition. Attention, language, orientation, psychomotor function, and verbal working/short-term and delayed episodic memory were found to be worsened by opioid use. These findings were not completely dissimilar to cognitive domains associated with poor cognitive performance in other populations (e.g. attention and memory).[79,80,82,83] However, the diversity in how cognitive domains are understood poses issues with direct comparison. This review also recognised similar limitations to other studies in other populations when interpreting the findings (such as methodological issues and sample sizes of included studies).[79-81,83] Therefore, a conservative approach needs to be taken when considering these findings. Despite often being used in research to assess cognitive impairment, screening tools and neuropsychological assessments demonstrated a lack of suitability – either in sensitivity in detecting changes or practically in terms of the duration of assessment.

The mixed methods study findings further raised the question of: ‘How can we best identify adverse effects in older adults?’ Much like the other aspects of pain and pain management, understanding the impact of opioids on cognition was also complex. Self-

report was not a focus of literature where formal screening tools and neuropsychological assessments had been adopted,[79-83] but was commonly adopted in clinical practice. In patient accounts, the use of screening tools only followed self-reported complaints of changes to cognitive function, with opioid analgesics being one consideration rather than the main cause (such as dementia). Self-report of adverse effects relied on recognising a relationship between the opioid analgesic and noticing impaired cognition, and often led to conclusions about their relationship (i.e. cause and effect). There is potential value in applying Bradford Hill's criteria for causation to opioid use and its associated effects, as they are widely accepted and applied.[257,258,502] They also provide a structure for considering the aspects of association, such as detecting a temporal sequence and consistency of the association. This not only aids research practice but perhaps how patients themselves think of and identify adverse effects. Additionally, the use of a list might help older adults to identify common adverse effects. Drawing definite conclusions about opioid use and cognitive adverse effects was beyond the scope of this study. However, it does highlight the value of self-report and exploring aspects of association identified by participants experiences.

Freely recalled adverse effects and interview data highlighted the breadth of language used to describe cognitive adverse effects (such as 'woozy' or 'heads messed up'), as well as non-specific language that could relate to any and all adverse effects (such as 'all sorts' or 'bad reaction'). These were a far stretch from specific cognitive domains identified in the literature. Participants acknowledged the challenges with describing and explaining cognitive adverse effects, which may limit older adults' ability and willingness to disclose their experiences with healthcare professionals. No studies exploring the language that people use to describe cognitive adverse effects were found. Although, language has often been explored in terms of native spoken language, comprehension and adherence.[503] Consideration to what patients mean when describing adverse effects, especially when non-specific terms are adopted, should be given attention when they disclose such experiences. The use of a patient-centred checklist of possible common adverse effects, as recommended in this thesis, could be beneficial in clinical practice to support patients in describing the adverse effects they experience.

No previous studies exploring the impact of cognitive adverse effects (attributed to pain medication) on health-related quality of life in older adults were found, only the impact of prolonged opioid use.[498] In this study, the median EQ-5D health-related quality of life scores were lower for those who reported cognitive adverse effects attributed to pain medication compared to those that did not. This may have been due to the small number of participants attributing cognitive adverse effects to pain medication. Although not statistically significant, interviewees recognised cognitive adverse effects (as well as other adverse effects) as impactful to their quality of life. Similarly, an online cross-sectional survey found that health-related quality of life scores were lower in those currently constipated due to opioid analgesics compared to those that were not – although, this was also not a statistically significant difference.[504] However, a cross-sectional study exploring the '*global'* impact of all adverse effects attributed to analgesia demonstrated a clinically significant impact to health-related quality of life in patients with multiple myeloma.[261] Patients and informal caregivers accounts in this study do emphasise the impact of singular adverse effects (such as cognitive adverse effects). However, they also highlight a narrative where a variety of adverse effects are experienced alongside each other. Cognitive adverse effects were commonly reported alongside constipation, sickness and nausea. Additionally, when asked to prioritise the adverse effect that they found most impactful – a number were unable to choose between effects experienced. Usually, cognitive adverse effects drew with opioid-induced constipation and nausea.

10.3 Reflections on strengths and weaknesses

The strengths and weaknesses of the individual thesis components have been discussed in Chapter 5 (i.e. systematic review), Section 10.1.1 (i.e. quantitative components) and Section 10.1.2 (i.e. qualitative component). However, the contributions and implications of the findings presented can only be understood if the overall quality of this research has been evaluated. Therefore, it is important to reflect on the strengths and limitations of the mixed methods approach as a whole.

The use of mixed methodology is increasingly recognised as a powerful approach to answering multifaceted research questions, with the potential to provide a more

complete answer and added depth in understanding phenomena.[328,398] Therefore, using a combination of quantitative and qualitative components in this research study potentially enabled a description of pain, opioid analgesic prescribing and cognitive adverse effects, as well as an exploration of experiences, perspectives and concerns regarding these. To understand whether this was achieved in practice, it is essential to evaluate the quality of this mixed methods research.

Mixed methods research can be more complicated to design and undertake compared to single-method research. Therefore, the question of how the quality of mixed methods research should be assessed is not straightforward, with specific criteria potentially limiting the flexibility to adopt diverse research designs that are attributed to mixed method approaches. Despite this, bespoke evaluation criteria can provide a useful framework for assessing the quality and setting out expectations for mixed methods studies rather than evaluating individual quantitative and qualitative components separately.[326] A number of frameworks for evaluating mixed methods research have been proposed, focusing on researchers' perspectives,[369] the larger process of research[505] or supporting a core set of minimum criteria that represent a ‘good’ mixed methods study.[326]

The comprehensive framework proposed by O’Cathain incorporates domains and items that have been considered important by several authors (overlapping with other frameworks),[505] which are summarised in Table 10.2. Therefore, it was deemed suitable to use this to evaluate this study; the domains of quality are considered and discussed in turn in the sections below.

Table 10.2 Quality framework for mixed methods research proposed by O'Cathain[505]

Stage of study	Domains of quality	Items within domain	Definition of item
Planning	Planning quality	Foundational element	Logical and critical review of the literature to situate the study.
		Rationale transparency	Justification for the use of mixed methods.
		Planning transparency	Details of the paradigm, design, data collection, analysis and reporting are provided.
		Feasibility	The design and components can be completed with the resources available (such as time, money and manpower).
Undertaking	Design quality	Transparency	Description of design from known typology.
		Suitability	Design is appropriate for addressing overall research question, and matches reasons for combining methods.
		Strength	Strengths and weaknesses of the methods used are considered to minimise shared bias.
		Rigour	Methods are implemented in a way that remains true to the design.
	Data quality	Transparency	Each method is described in sufficient detail.
		Rigour/design fidelity	The extent to which methods are implemented with rigour.
		Sampling adequacy	Sampling technique and sample size for each method are adequate in the context of design.
		Analytic adequacy	Data analysis techniques are appropriate for the research question and are undertaken properly.
		Analytic integration rigour	Any integration taking place at the analysis stage of a study is robust.
Interpreting	Interpretive rigour	Interpretive transparency	It is clear which findings have emerged from which methods.
		Interpretive consistency	Inferences are consistent with the findings on which they are based.
		Theoretical consistency	Meta-inferences are consistent with current knowledge or theory.

		Interpretive agreement	Others are likely to reach the same conclusions based on the findings presented.
		Interpretive efficacy	Inferences from the whole study adequately incorporate inferences from quantitative and qualitative components.
		Interpretive bias reduction	Explanations are given for inconsistencies between findings and inferences.
		Interpretive correspondence	Inferences correspond to the purpose of the study, overall research question and research questions within this.
	Inference transferability	Ecological transferability	Transferability to other contexts and settings.
		Population transferability	Transferability to other groups and individuals.
		Temporal transferability	Transferability to the future.
		Theoretical transferability	Transferability to other methods of measuring behaviour.
Disseminating	Reporting quality	Report availability	Study is successfully completed within allocated resources of time, money and manpower.
		Reporting transparency	Key aspects of the study reported, according to 'Good reporting of a mixed methods study (GRAMMS)'.[506]
		Yield	Whole is more than the sum of the parts.
Application in the real world	Synthesisability	Quality criteria	Example: Justification of the mixed methods design.
	Utility	Utility quality	The findings are used by consumers and policy makers.

10.3.1 Planning quality

This section considers the foundation on which this research was based, as well as the transparency of the reasoning behind the use of mixed methods and planning. In addition, the feasibility of the design and its components.

Foundational element

This research was based on preliminary work and guided by a critical review of the literature. This included scoping the literature to better understand the key concepts under study (i.e. pain, opioid use and cognitive adverse effects in older adults), as well as to identify evidence gaps. This enabled the development of appropriate and novel research questions, as well as being able to position the findings within the literature. Due to the time available, the systematic review was not treated as a primary step to informing the design of the mixed method study, although, it aided understanding. In addition, it increased familiarity with existing literature and challenges to researching the phenomena under study.

Planning and rationale transparency

Transparency around the main aspects of the study is essential and these need to be clearly detailed (such as the paradigm adopted and design). Additionally, transparency at the planning stage supports evaluation and understanding of the other domains of quality. Explicit details relating to these main concepts are presented in Chapter 6 and Chapter 7. In addition, the decision to adopt a mixed methods approach was justified in Chapter 6 on the basis that a single methodology would not be able to fully answer the research question. The results of this thesis demonstrate the added value of using mixed methods to address this question. Collecting both quantitative and qualitative data alongside each other allowed for comparison and interrogation across the data, as well as explanations and expansion of quantitative data, which can be considered a strength. This meant that pain, patterns of opioid use and cognitive adverse effects from the cross-sectional survey and case note review could be explored within the interview transcripts. Adopting a single methodology or collecting quantitative and qualitative data from different participants would have led to drawing less firm conclusions and could have limited capturing the complex nature of the paradigms explored. Describing the phenomenon under study helps to identify and summarise patterns and trends. Yet, pain, opioid use and cognitive adverse effects are subjective and can vary from person to person, and they benefit from exploration at an individual level.

Feasibility

Several factors may impact the feasibility of conducting a mixed methods study, which includes time, funding and resources. This study adopted a convergent design, where quantitative and qualitative data were collected in parallel. This was appropriate within the timeframe available and the methods adopted (see Section 10.3.2 for further discussion regarding study design). Additionally, the study protocol received input from the study team (including other PhD students and clinical collaborators from the recruitment site), patient and public involvement representatives, and the research ethics committee. This helped to ensure that the study was feasible to conduct with the resources and time available.

The pragmatic approach to data collection by embedding this work within a non-randomised controlled study was seen as a strength of this research, as it allowed for streamlined collection of data and access to the population of interest. Although, this could also be perceived as a potential limitation. For example, this research study could have been redirected from its primary aim, as the main focus of the wider study was evaluating the frailty service. However, contributing to the design and development of the PACE protocol helped to mitigate this, although it did add complexity at the stage of planning. In particular, it did limit the number of questions that could be included in the survey. As the designated section in the survey for this study intended to collect self-report data and identify potential participants for in-depth interviews, the space allocated within the survey allowed for the inclusion of pertinent questions to address these aims.

In terms of overall length, the cross-sectional survey included measures of wellbeing and quality of life, and questions from two other PhD students, in addition to the section on pain medication. This meant that the survey was relatively lengthy and there was potential for survey burden and fatigue, especially when being conducted in a clinical setting. The questionnaire was reviewed by patient and public involvement representatives and was felt to be of appropriate length, as PhD sections were optional based on relevance. However, there were some issues with questionnaire fatigue. Although there were limitations, there were a number of recognised benefits to being

embedded within the wider programme of research. This included access to a suitable study population and medical record data, as well as increased resources (i.e. the project lead and other PhD students) in collecting survey data. This also supported the completion of in-depth interviews alongside the cross-sectional survey and case note review.

10.3.2 Design quality

This section considers the transparency, suitability, strength and rigour of the design and methods implemented. This mixed methods study adopted one of the core designs outlined by Creswell and Plano Clark,[326] which was a convergent design. A clear description and visual diagram of the convergent design are presented in Chapter 6. As discussed earlier, the quantitative and qualitative components were conducted alongside each other and allowed for a 'describe AND explore' approach to address the overall research question and pragmatic approach. It enabled data to be collected and analysed both separately and independently, using techniques that are associated with each method, and then bringing the data from these approaches together to compare and validate responses.[326] The survey and case note review enabled the identification of interview participants, collection of self-reported data and a description of pain, opioid use and cognitive adverse effects in the study population. Whilst, the interviews allow for a deeper exploration of these in a subgroup of the study sample (e.g. interrogation of the quantitative data). Therefore, a direct comparison of the researcher's standpoint (i.e. the survey and data extracted from medical records) can be made with the participant's perspectives (i.e. in-depth interviews).[326,507]

Although this study adopted a convergent design, there are other ways in which the methods could have been conducted (e.g an explanatory sequential design). An explanatory sequential design allows for the research to be conducted in two phases, meaning the second qualitative phase can be fully informed by the initial quantitative phase.[326] Although the convergent design occurs as one phase, the interview topic guide was framed around the cross-sectional survey structure and questions, as well as extracted opioid prescription data at an individual level from interview participants' medical records before conducting the interview. This meant that there was some level

of integration at the stage of data collection that helped with understanding the topics in-depth and where data may confirm or diverge. This was also considered important as prescribing can differ from actual use.[494,508] Pain is also a complex phenomenon that is challenging to understand in a snapshot as it varies from day to day.[154]

Time is an important factor to consider when selecting a design. Sequential designs require an extended time to complete, as implemented in two phases.[326] Also, the qualitative phase may not be possible to specify in advance, such as participants to be selected for interview and criteria to use for participant selection.[326] This may lead to a delay to timelines, as likely to require an addendum to be submitted to the ethical review board.[326] The benefits of collecting multiple types of data within a shorter timeframe would have been lost and limited the multiple perspective view on a complex phenomenon that was possible with the chosen design. It may have also reduced the strength of inferences. The extended time required for completing phases sequentially would also not have been feasible within the timeframe available for this thesis.

Mixed methods research acknowledges that all methods have inherent biases but the use of more than one method to collect and analyse data about the same phenomenon minimises the biases associated with using one method.[509] Surveys and semi-structured interviews are commonly used in mixed methods research to generate confirmatory data despite different approaches to data collection, analysis and interpretation.[510] Each method in this study provided detailed information about pain, opioid analgesics and cognitive adverse effects but are not impervious to bias. The convergence and divergence of data have been explored in this chapter, with consideration given to the benefits and pitfalls of combining these methods. The biases of specific methods have been addressed in Section 6.4.1.4, but methods were combined to minimise these issues with self-report bias (such as recall) and issues with measurements (such as use of secondary data from medical records to understand opioid prescribing). Considered as a whole, and even by components, a selection bias may exist as participation was voluntary and convenience sampling was used. Those who did not wish to participate may or may not have similar characteristics and perceptions that were not captured. The non-participant rates were assessed and reported for the characteristics that were

available, and were not dissimilar. The number of participants not assessed for eligibility or were deemed ineligible are also presented.

10.3.3 Data quality

This section considers data transparency and rigour, sampling adequacy, and analytic adequacy and integration rigour. The consideration given to the adopted methods is provided in Chapter 6 and a detailed description of the methods used can be found in Chapter 7.

In terms of sampling adequacy, the considerations to sampling techniques and sample sizes of the quantitative and qualitative components are explained in Chapter 7. This study intended to recruit older adults who were potentially frail on the basis that it is important to understand their issues with opioid use, cognitive adverse effects and challenges with pain management in line with anticipated growth of this populations needs.[29,68,85,215] The choice to explore these topics of interest in a group that had been identified as at risk of severe frailty by GPs using the eFI aimed to result in a population that were living with frailty, as well as being part of the referral criteria of the service and therefore, in PACE. In practice, only a small percentage of the older adults recruited were characterised as severely frail when using the CFS. Evidence supports this overestimation of frailty status in community-dwelling older adults when using the eFI.[511] There were challenges with referral criteria as participants with moderate risk of frailty were beginning to be referred and it was not possible to access any frailty scores from medical records until consent was obtained. However, 75.3% of participants were found to have some form of frailty (i.e. mild to very severe) and participants that were not recognised to be frail were all aged 65 and over (i.e. still in line with how this thesis defined older adults).

This study achieved a diverse sample in relation to a number of characteristics (including age, gender and deprivation) but it lacked ethnic diversity. This is not entirely unexpected with the 2011 Census showing that approximately 94.1% of Hull's population is white,[412] but may bias the findings. Opioid prescribing in Hull and

surrounding areas are at the higher end of the scale.[48,238] Therefore, the data presented in this thesis may reflect patterns of use and experiences of older adults who are more likely to be prescribed opioids than some other geographical areas. Additionally, as participation in the study was voluntary, a selection bias may exist, and since the data collected is limited to one setting of care, the results may not be transferable.

In terms of analytic adequacy and rigour, statistical tests were chosen based on the research questions outlined to address the objective. Where multiple tests were run on the data, the significance value was adjusted accordingly. Additionally, the logistic regression analyses were bound by routine data collection and it was not possible to obtain a larger sample. In line with this, the independent variables were limited and model diagnostics were conducted. The use of thematic analysis was deemed appropriate, it allowed for theoretical flexibility with the analysis and how it was shaped, which was essential to the inductive-interpretative approach[326] adopted in this thesis.

This thesis made an attempt to integrate quantitative and qualitative findings, where 'the whole can be greater than the sum of the parts'.[381] This study used a modified critical-interpretative synthesis at the stage of analysing integrated data, as described in Section 10.1.3. In its adaptation to synthesise reviews of quantitative research with qualitative research,[460] it also has application to mixed methods research and the way in which it recognises the benefits of combining these methods. There are certain limitations to considering the data in isolation or only from one method. For example, prescription data does not allow for the consideration of over-the-counter medication, which may underestimate the use of weaker opioid analgesics. Additionally, understanding exposure to opioid analgesics is not straightforward as patients may not fill their prescriptions or follow medication regimen – which is not captured in primary care data. Therefore, the qualitative data helped to unpick these issues and consider the difference between *'theoretical'* and *'actual'* use.

10.3.4 Interpretative rigour

This section discusses interpretation and theoretical consistency. Inferences have been situated in the literature and linked to theoretical grounding. In line with the O'Cathain evaluation matrix (see Table 10.2),[506] the overall contributions of this study came from the integration of findings across the quantitative and qualitative components and objectives. The use of modified critical interpretative synthesis allowed for transparency in where the results have come from and how they have been brought together. Inferences have also been sense-checked with my supervisors and the wider research team. Explanations have been given where there are inconsistencies in the data, with current literature being used to critically explore the reasons for these divergences.

In summary, the findings of this thesis are based on data from Hull (England), in a predominantly white population (with higher rates of opioid analgesics prescribed in the area)[48] and in one setting of care. The application of these findings may therefore be limited culturally and geographically, and should be considered with an awareness of the study setting and sample.

10.3.5 Reporting quality and real-world application

This research was completed within the proposed timeframe, and has been reported with reference to the guidelines on good reporting of a mixed methods study.[506] Dissemination and real-world application of this research can only be fully evaluated at a later timepoint following the completion of sharing the study findings, as they take time to occur. To date, aspects of the individual study components have been shared with a range of audiences (including academic, clinical and public members). Dissemination has included presentations at various stages (such as local, national and international research and clinical events/groups), sharing study findings in peer-reviewed journals, and via social media posts. Those who participated in the qualitative study will receive a plain language summary of the findings. Altogether it is hoped that these routes of dissemination will raise the profile and importance of recognising and addressing pain, opioid use and cognitive adverse effects in older adults. In addition,

how approaches to pain management might be empathetic, tailored and flexible to the person.

10.4 Implications

The findings of this thesis have several implications for clinical practice, policy and future research, these are presented below.

10.4.1 Clinical practice and policy

The findings suggest that pain is a main problem or concern for a number of older adults even when treatment is present, and that older adults may water-down their accounts of pain. Chronic pain impacts on older adults' function and quality of life, and the way in which pain is assessed and treated is largely variable in clinical practice.[512] Fundamental aspects of chronic pain are often neglected, which includes psychological, social, and contextual factors.[512] In this thesis, participants described the importance of caring, continuity with care, and ensuring that issues are followed-up. When executed well, these aspects led to a sense of safety and security in an uncertain journey with chronic pain. These aspects could be better integrated and promoted as best practice across different settings of care with this population, particularly within primary care.

More routine reviews of chronic pain may provide an opportunity to flag and address particular issues (such as the appropriateness of opioid analgesics (e.g. efficacy and adverse effects, or the psychological and emotional impact)), and avoid exacerbations of pain and unnecessary *'work'* for older adults and their informal caregivers. This would provide a platform for professionals to proactively discuss how older adults can be supported if exacerbations of pain or issues with pain medications do occur. This study found that the use of a simple list of common adverse effects may assist older adults to identify more adverse effects attributed to opioid analgesics (and other pain medication), which would be easy to implement and aid discussions around pain medication. Clinical judgement may also have a role in identifying adverse effects.

Specific information and support needs were reported by study participants. Clinicians may need to be cognisant of educating patients and their informal caregivers about what help is available (such a pain clinics), as awareness was limited and access to help was often reactive rather than proactive. Clear and honest communication may also improve pain management and the patients' relationship with pain medication, such as adherence to medication regimen. Patients and informal caregivers emphasised the need to be clear about the purpose of opioid analgesics or other pain medication prescribed (i.e. how it works and what taking it should achieve), how to take it properly, the potential adverse effects and a plan to review. In particular, prescribing an opioid analgesic should not be viewed as an outcome in its own right. More so, it is important to assess whether prescribing the opioid analgesic has contributed to their care goals and daily lives (such as improving mobility). This will mean focusing on understanding the positive and negative implications on everyday life, and treating the patient-provider relationship as a partnership working towards common goals. Generally, greater acknowledgement of pain as more than just a physical symptom by healthcare professionals is required in pain management. Additionally, consideration to the type of opioid analgesic prescribed and the route in which it is administered is needed.

Current policy and practice pose challenges to improving pain management in older adults. Access to primary care and the time given to consultations are not sufficient for older adults living with multiple conditions and complex needs. The increasing demand on primary care coupled with service constraints has necessitated changes to service delivery, with less home visits, more telephone consultations, triaging of calls and modifying appointment systems.[242,513] The limited resources and lack of control have made it challenging to manage the evolving demography and epidemiology.[514] Additionally, guidance for long-term conditions may lead to large numbers of medication being prescribed, with risk of adverse drug reactions.[36,204,515] Notwithstanding, primary care has undergone an unprecedented reorganisation during the COVID-19 pandemic.[492] Progress requires several changes at all levels. For example, on a system-level, ensuring that opioid prescription information is shared between settings, and that current medication lists are up-to-date and adverse effects are better recorded. Whilst, on a service level, addressing the recognised barriers with accessing support and adopting an 'open door' policy for older adults may increase their

sense of safety. However, it is important to recognise the pressures that primary care providers currently face (such as workforce issues and workload)[516-518] that may constrain addressing such recommendations.

10.4.2 Future research

The findings of this thesis have implications for how opioid-induced cognitive impairment should be assessed in older adults. Clinically, guided discussion through common adverse effects and self-report may be best placed to understand adverse effects in this population. Further exploration of methods suitable for research purposes are needed and should compare self-report, screening tools and neuropsychological assessments. Future studies should ensure that opioid-induced cognitive impairment is the primary outcome, and focus on clear reporting of opioid analgesics and screening tools/neuropsychological assessments. In particular, for opioid use, it would be useful for studies to adopt OME or provide sufficient detail that this could be calculated. The Bradford Hill criteria[257,258] may also have application for how causation could be assessed and captured. Though confounding factors will always be present, this research has identified factors specific to research in older adults that future research may want to consider. Research exploring opioid analgesics in older adults, especially in those who are considered to be frail, is still in its infancy. Greater understanding is still needed regarding different opioid types and their impact. Further exploration of the cognitive domains that are most affected in this population is also needed.

Although existing literature does explore healthcare professionals' views on opioid use in chronic pain management, few studies triangulate experiences and perspectives between patients, family carers and healthcare professionals. This was also beyond the scope of this study, as we accessed patients and their families in an integrated care setting and did not have access to patient's primary care teams. Future research should explore the relationship between patients, family carers and primary care professionals. Much of the discussion with patients and family carers was oriented around the interactions with their general practice. It was not deemed beneficial to recruit the ICC staff for qualitative interviews, as they have a limited interaction with patients and provide recommendations to general practitioners. The attitudes, perspectives and

experiences of ICC staff may differ due to their focus on delivering integrated care to older frail populations.

This thesis also has implications for wider research practice in relation to opioid use and opioid-induced cognitive impairment in older adults, in terms of overarching approaches. The embedding of this work within a non-randomised, controlled study and the mixed methods design are considered a strength of this research. Yet, it was found that this type of approach is often missing in prior work in the field. As research continues to explore potential strategies to address opioid-induced cognitive impairment in older adults, maximising the benefits of mixing quantitative and qualitative methods will be important to build the evidence-base in a way that is efficient. The findings of this thesis also suggest that the inclusion of informal carers alongside patients in this work was invaluable, as they often support the person in adapting to the limitations of pain, are observers of adverse effects and support chronic pain and everyday *'work'*. This perspective is underexplored in terms of managing chronic pain at home and needs further consideration. Additionally, the systematic review highlighted the methodological pitfalls when conducting research within this older population. This thesis has made a methodological contribution to the study of chronic pain and how it is experienced. These findings may also have potential transferability to other population groups (e.g., younger populations), which could be considered in future research.

Chapter 11: Conclusions

This thesis examined the use of opioids in older adults and their impact on cognition using a systematic review and a mixed methods study. Overall, the findings illustrate that pain often remains a persistent issue in older adults despite treatment. Opioid analgesics are often prescribed; with less suitable opioids forming the basis of treatment (i.e. codeine and tramadol) and can lead to opioid-induced cognitive impairment for some. Chronic pain, opioid use and opioid-induced cognitive impairment are impactful to both patients and their informal caregivers and create insurmountable *'work'*. They were limited further by structural barriers to accessing care. Simple changes to patient-provider communication could improve pain management (including appropriate access to and compliance with opioid analgesics). Clinician-led discussion and more formal pain management reviews that can be individualised to address the multi-dimensional impact of pain may be suitable for this population. It is important to recognise that pain management may not mean pain relief, but managing it in a way that improves quality of life. A list of common adverse effects associated with pain medication may aid this discussion. Although, further comparison between self-report and more formal assessments is needed to consolidate what approach may be most beneficial in identifying opioid-induced cognitive impairment in clinical practice and research.

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Appendix 1: Training and academic activities during PhD

Table 1 Training log during the PhD

Training	Duration	Date	Vitae Researcher Development Framework (see Figure 1)
Regular training			
ICAHR Postgraduate Workshop	1 hour	Once a month	A1, A2, A3, B2, B3, D1 and D2
ICAHR Seminar Series	1 hour	Once a month	A1, A2 and A3
ICAHR Journal club	1 hour	Once a month	A1, A2 and A3
2017			
Formatting your thesis	2 hours	04/11/2017	A1 and B3
Creating and delivering conference presentations	2 hours	29/11/2017	B1, D2 and D3
Finding quality journal articles for postgraduates	1.5 hours	08/12/2017	A1, A2 and A3
Quantitative Methods	17 hours per week	25/09/2017 – 11/12/2017 (12 weeks)	A1, A2 and A3
2018			
Systematic Review	12 hours per week	17/01/2018 – 14/03/2019 (9 weeks)	A1, A2 and A3
Research Misconduct	3 hours	13/02/2018	C1 and C2
Research Governance	3 hours	27/02/2018	C1 and C2
Public engagement of research	2.5 hours	06/03/2018	D1, D2 and D3
Microsoft Word 1: Essentials for academic writing	2 hours	22/03/2018	A1, A2, A3 and B2
Microsoft Word 2: Features for structuring your dissertation/thesis	2 hours	29/03/2018	A1, A2, A3 and B2
Microsoft Word 3: Consolidating thesis chapters with a master document	2 hours	05/04/2018	A1, A2, A3 and B2
Searching the literature	2 hours	03/05/2018	A1, A2 and A3
Introduction to NVivo 12	1 hour	02/08/2018	A1, A2 and A3
Good Clinical Practice eLearning (Primary Care)	Online (in own time)	28/08/2018	C1 and C2

2019			
Introduction to Regression Analysis	12 hours per week	15/01/2019 – 12/03/2019 (9 weeks)	A1, A2 and A3
Understanding clinical statistics	12 hours per week	17/01/2019 – 14/03/2019 (9 weeks)	A1, A2 and A3
Speed reading techniques	2 hours	07/11/2019	A1, A2 and A3
Writing critically	2.5 hours	29/11/2019	A1, A3
2020			
Cochrane Library: Advanced search	1 hour	11/06/2020	A1, A3
EMIS Health Live: The New Normal	1 hour	20/07/2020	A1
2021			
Assessing rigour – Qualitative Research Masterclass	1.5 hours	29/04/2021	A1, A2 and A3
The Digital Researcher	1 week	28/06/2021 – 02/07/2021	D2
2022			
Reading camp	2 hours	12/08/2022	B1, B2 and A1

ICAHR: Institute for Clinical and Applied Health Research

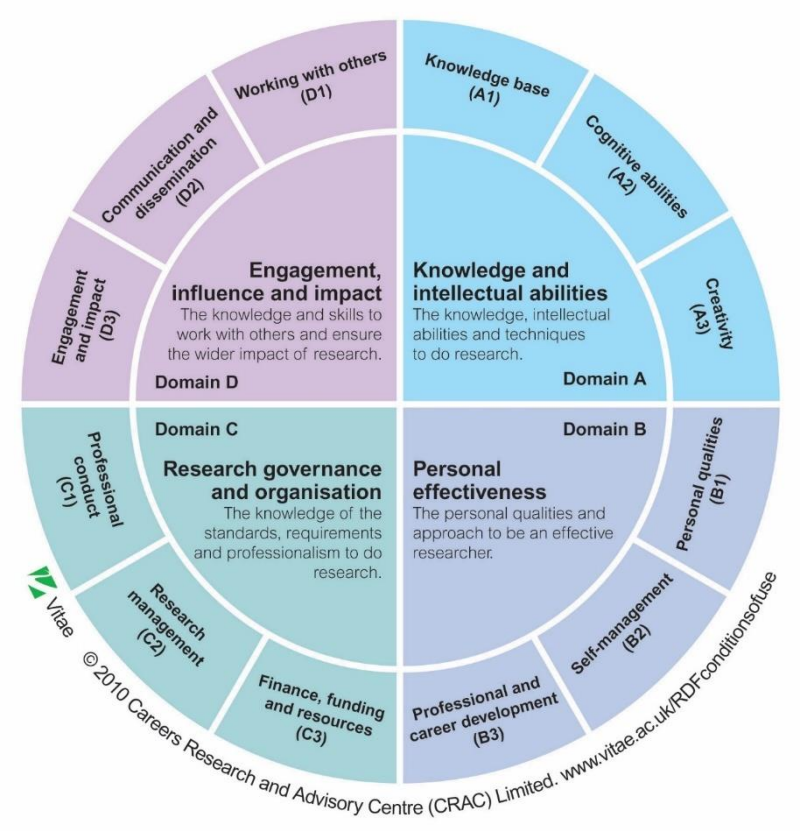

Figure 1 'Vitae Researcher Development Framework', www.vitae.ac.uk/rdf

Table 2 Teaching and additional presentations log during the PhD

Teaching, presentations and marking activity	Duration	Date
2018		
Royal Society of Medicine: Evidence and Impact Presentation title: "Complexity in palliative care"	40 minutes	17/12/2018
2019		
European Association for Palliative Care 2019. Invited Parallel session: Understanding patients' needs: a national qualitative study with patients, family carers and professionals	30 minutes	23/05/2019
Widening Participation Tutor on the Academic Assignment Programme. Supporting three students in their academic assignments.	14 hours per student across 6 weeks	06/06/2019 – 17/07/2019
End of Life Partnership Annual Conference: Exploring complexity in end-of-life care Presentation title: "A framework for complexity on palliative care"	40 minutes	24/10/2019
Widening Participation Tutor on the Realising Opportunities Programme. Supporting two students in their academic assignments.	14 hours per student across	06/06/2019 – 06/11/2019
2020		
Your journey to university Academic Seminar Leader	2 hours	01/07/2020
Realising Opportunities Lecture Presenter and Seminar Lead	2 hours	16/07/2020
Your journey to university Academic Assignment Tutor. Supporting three students with their academic assignments.	14 hours per student across 4 weeks	03/07/2020 – 04/08/2020

Appendix 2: Systematic Review – Journal of Pain and Symptom Management Publication

Review Article

The Effects of Opioids on Cognition in Older Adults With Cancer and Chronic Noncancer Pain: A Systematic Review

Sophie Pask, BSc, MSc, Myriam Dell'Olio, BSc, MSc, Fliss E.M. Murtagh, MD, PhD, and Jason W. Boland, MD, PhD, SFHEA

Wolfson Palliative Care Research Centre (S.P., F.E.M.M., J.W.B.), Hull York Medical School, University of Hull; and Academy of Primary Care (M.D.), Hull York Medical School, University of Hull, Hull, United Kingdom

Abstract

Context. Opioids are prescribed to manage moderate-to-severe pain and can be used with older adults; however, they may lead to several adverse effects, including cognitive impairment.

Objectives. To identify, appraise, and synthesize evidence on the impact of opioids on cognition in older adults with cancer/chronic noncancer pain, and screening tools/neuropsychological assessments used to detect opioid-induced cognitive impairment.

Methods. A systematic literature review following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (international prospective register of systematic reviews registration: CRD42018092943). MEDLINE, EMBASE, PsycINFO, CINAHL, Cochrane Library, and Web of Science were searched up to December 2018. Randomized controlled trials, quasi-experimental studies, and observational studies of adults aged 65 years and older with cancer/chronic noncancer pain taking opioids were included. A narrative synthesis was conducted.

Results. From 4036 records, 10 met inclusion criteria. Five studies used one screening tool, and five studies used a range of neuropsychological assessments; assessing 14 cognitive domains. Most studies demonstrated no effect of opioid use on cognitive domains, whereas four studies showed mixed effects. In particular, attention, language, orientation, psychomotor function, and verbal working/delayed episodic memory were worsened. Changes to cognitive function were predominantly observed in studies with higher mean doses of opioids (120−190.7mg oral morphine equivalent daily dose).

Conclusion. Both improvements and impairments to cognition were observed in studies with higher mean opioid doses. In clinical practice, a brief screening tool assessing attention, language, orientation, psychomotor function, and verbal working/delayed episodic memory may be beneficial to detect worsening cognition in older adults with chronic pain using opioids. J Pain Symptom Manage 2020;59:871−893. *Crown Copyright © 2019 Published by Elsevier Inc. on behalf of American Academy of Hospice and Palliative Medicine. All rights reserved.*

Key Words

Opioids, cognition, cancer, chronic pain, pain, elderly, systematic review

Introduction

Chronic pain is a common problem for older adults (65 years and older), affecting at least 50% in the community and 80% in care homes.[1,2] Persistent pain, often moderate-to-severe intensity, in older adults is frequently attributed to cancer and chronic noncancer conditions.[2–6] Pain can have a pronounced impact on older adults' independence, social engagement, ability to self-care, and quality of life.[7–10] Yet, it is often underassessed and poorly managed in this group.[1]

Opioids are used to manage moderate-to-severe pain[11] and can be used with older adults when they have pain despite other treatments.[2,12] Short-term opioid use has some benefit in older adults with chronic noncancer pain.[13,14] On the other hand, studies on the safety and efficacy of the long-term use of opioids in

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older adults are limited.[13–16] Evidence suggests that it is unlikely to benefit and may be harmful to those with chronic noncancer pain.[15,17,18] Effective opioid therapy is dependent on the balance between analgesic effectiveness and adverse effects.[19] Opioid use can lead to a number of adverse effects that impact gastrointestinal, neurological, cardiovascular, pulmonary, urological, endocrinological, and immune systems; including cognitive impairment.[20–25] Although these adverse effects are common for all age groups, older adults are at greater risk because of comorbidities and polypharmacy.[20] In particular, older adults can experience high medication burden and risk of drug interactions.[9,26–28] Developing our understanding of opioid-related risks in older adults is necessary,[29–31] including how we can effectively screen for opioid-related issues.[2,30]

Opioid-induced cognitive impairment can lead to a reduced attention span, disorientation regarding time, restlessness, agitation, hallucinations, and delirium;[32] all of which can have a pronounced impact on older adults' and their carers' quality of life.[32] Concerns about these issues can also affect health care professionals' initiation of opioid therapy.[33] Opioid use and its impact on cognitive function in older adults is understudied. The evidence base largely focuses on adult cancer and chronic noncancer populations, without focus to older adults.[34–38] Previous systematic reviews of the evidence on older adults have focused on postoperative cognitive impairment[39] or opioids for the management of chronic noncancer pain.[40] Understanding the relationship between cognition, opioids and pain management in older adults' is important in enhancing knowledge of health care professionals to guide clinical practice, as well as improving patients and carers understanding of opioids.[41,42] In addition, systematic identification and assessment of cognitive impairment could be useful in guiding opioid therapy. However, there is little consensus on which tools and assessments are effective in identifying cognitive impairment and which cognitive domains are impacted by opioids.[34,43,44]

Therefore, the aim of this systematic review was to identify, appraise, and synthesize the following:

1. Evidence on the impact of opioids on cognition in older adults with cancer and chronic noncancer pain.
2. Screening and assessment tools that have been used to detect and assess opioid-induced cognitive impairment, and to discuss their usefulness for identifying cognitive issues in older adults.

Methods

The protocol for this systematic review was prepared according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols[45,46] and registered with the international prospective register of systematic reviews (registration: CRD42018092943) before screening and data extraction.[47] This systematic review was reported in accordance with the PRISMA guidance.[48]

Search Strategy

MEDLINE, EMBASE, and PsycINFO (via Ovid), CINAHL Plus (now CINAHL Complete, via EBSCO), Cochrane Central Register of Controlled Trials in the Cochrane Library (via Wiley), Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index, Emerging Sources Citation Index, Conference Proceedings Citation Index—Science and Conference Proceedings Citation Index—Social Science & Humanities), ProQuest, and OpenGrey databases were searched from inception to December 2018. Search terms were identified from existing reviews. Free-text terms for searching titles, abstracts, and key words were combined with database-specific MeSH terms that reflect the following aspects: [opioids] AND [cognition] AND [older adult population] (Appendix: Example of the full search strategy). No electronic limits were applied to database searches.

The reference lists of relevant systematic reviews and first author's EndNote library were screened to identify further studies that may not have been identified in the database searches. Where full texts were not available or lacked information to confirm eligibility, authors were contacted.

Study Selection

The studies returned from the search were imported into EndNote X8 (Clarivate Analytics, London, UK), and duplicates were removed. Titles and abstracts were screened for inclusion by two authors (S. P. and M. D.) independently in duplicate. For articles that potentially met inclusion criteria on title and abstract, S. P. and M. D. then assessed full texts for eligibility. Disagreements between the two authors at all stages were resolved through discussion with a third reviewer (J. W. B.).

Table 1 lists the criteria for including studies. For the purpose of this review, older adults in this systematic review were defined by the chronological age of 65 years and older, as commonly adopted by most developed countries to describe older adults.[49,50]

Data Extraction and Analysis

S. P. and M. D. extracted data to electronic data extraction forms, independently in duplicate. Data extraction forms were crosschecked for accuracy and missing data. Data collected included general information (author and year, type of publication, country

Table 1
Inclusion and Exclusion Criteria

Study Characteristic	Include	Exclude
Participants	Older adults aged 65 yrs and older with cancer and/or chronic noncancer pain (including an overall mean age of 65 yrs and older, a mixed population with at least 50% aged 65 yrs and older, or a clear subgroup analysis reporting on participants aged 65 yrs and older)	Populations where substance misuse, psychiatric illnesses, neurocognitive/neurodegenerative diseases (e.g., Alzheimer's), and brain injury are present or studies that only consider healthy older adults
Exposure and assessment	Studies exploring opioid use where screening tools and/or neuropsychological assessments have been used to detect opioid-induced cognitive impairment	Studies that consider recreational use and perioperative use of opioids, that aim to block the effects of opioids, or that use opioids for antitussive relief, diarrhea, or use opioids not used within clinical practice
	Studies exploring multiple medication effects on cognition, as long as opioids were included and a clear subgroup analysis was available	Studies that use self-report assessment or a health care professional opinion of cognitive function
Study design and publication type	RCTs, quasi-experimental studies, and observational studies, which had been published in peer review or gray literature	Case reports, reviews, or systematic literature reviews, qualitative studies, opinion pieces, editorials, comments, news, and letters
Publication date, setting (including country or care setting), or language	Any	

RCTs = randomized controlled trials.

of origin, source of funding, and conflicts of interest), study characteristics (aim, study design, inclusion and exclusion criteria, recruitment procedures, and study duration), participant characteristics (number of participants, source and setting of population, age, gender, disease characteristics, comorbidities, and concurrent medications), how cognitive impairment was assessed (screening tools and/or neuropsychological assessments), and other outcomes collected, details of opioid treatment (type, dose, route of administration, and length of use), statistical analyses used, and the effect of opioids on cognition, limitations, and conclusions.

Quality was independently assessed by two authors (S. P. and M. D.) using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields (QualSyst) 14-item checklist for quantitative studies.[51] A summary score is calculated for each article by dividing the total sum by total possible sum.[51] In this systematic review, the reviewers used the calculated score to define the quality of articles as strong (score of >0.80), good (0.71–0.79), adequate (0.50–0.70), or poor (<0.50) and did not exclude on account of poor quality, in line with other systematic reviews.[52,53]

A narrative synthesis was used, guided by Popay et al.[54] A theory of how, why, and for whom the intervention worked was not developed for this systematic review as previous reviews of a similar nature found variable effects on cognition after opioid use. An exploratory approach was used, with study design/methods, sample size, diagnosis, tools/assessments used, and opioid dose and length of use identified as factors to consider in the synthesis. Second, tabulation was used to develop a preliminary synthesis of included studies to aid interpretation of patterns across studies. Data regarding dose were transformed into oral morphine equivalent daily dose (MEDD) to enable dose comparison between studies. Third, outcomes of tools and assessments were mapped against cognitive domains assessed to analyze similarities and differences across studies. In addition, the cognitive outcomes were mapped against previously identified cognitive domains affected by chronic opioid use (namely cognitive flexibility, cognitive impulsivity, and verbal working memory),[43] as well as additional domains captured by the screening tool and neuropsychological assessments of included studies. Finally, a critical reflection of the strengths and limitations on the robustness of the synthesis is included in the discussion.

Results

Study Selection

A total of 4036 unique records were identified. Of these, 57 full texts were screened, and 10 full texts were found eligible for inclusion (Fig. 1: PRISMA flowchart). For a summary of included studies, see Table 2.

Study Characteristics

Included studies were conducted in the U.K. ($N = 3$), Italy ($N = 3$), U.S. ($N = 3$), and Finland ($N = 1$). All studies were published in English. The studies comprise three randomized controlled trials (RCTs),[55–57] six observational,[58–63] and one quasi-experimental design.[64] Four studies adopted the use of comparison groups to determine the efficacy of opioid use vs. conventional therapy;[55] assess the difference between central nervous system (CNS)

medication users and controls (with opioid subgroup analyses);[60] determine the difference between opioid users and nonopioid users;[61] and investigate whether opioids or the disease itself had an impact on cognition.[64]

Population and Settings

A total of 1087 participants were included in the 10 studies. Changes to cognition from opioid use were explored by two studies in older adults with cancer pain,[63,64] six studies in older adults with chronic noncancer pain,[55,57–59,61,62] and two studies that included both.[56,60] Across nine of the 10 included studies,[55–59,61–64] 44 participants had cancer pain, 462 participants had chronic noncancer pain (predominantly osteoarthritis and postherpetic neuralgia), and 16 participants were healthy controls. In the study by Puustinen et al.,[60] diagnoses were only available for 156 CNS medication users and 243 CNS medication nonusers of the 565 recruited. This included both cancer and noncancer diagnoses. However, participants who were taking opioids only had diagnoses of painful arthritic diseases.

Study settings varied; two were conducted at a hospice (with one including both inpatients and outpatients).[63,64] The other studies were conducted within

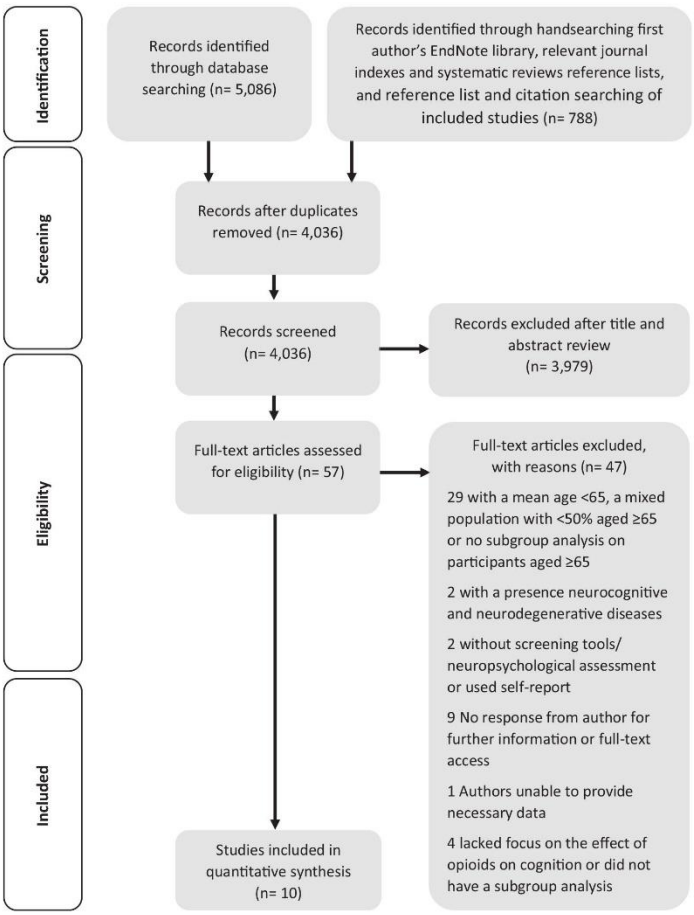

Fig. 1. Prisma flowchart.[48]

Table 2
Summary of Studies

Study/Country of Origin	Design	Participants Recruited (Sample); Including Diagnosis and Age (Mean Age, Range, and/or Percent of 65 yrs and Older)	Setting	Opioid Type and Oral MEDD (Range)	Tools and Assessments	Quality Score
1. Clemons et al.[64] U.K.	Quasi-experimental	29 participants (64.5, 51.7%, aged 65 yrs and older) Group 1: 16 healthy participants (65.4); Group 2: six advanced cancer patients not taking opioids (62.8); and Group 3: seven advanced cancer patients taking opioids (61)	Hospice (inpatient/outpatient)	Controlled-release morphine sulfate or morphine sulfate solution (104.3 mg; 50–200 mg)	GRT, LMT, NART, RT, and SCWT	Adequate (0.55)
2. Corsinovi et al.[55] Italy	Randomized, single blind, and controlled	154 participants with persistent osteoarthritis-related pain; Group 1: 52 participants taking oxycodone (79.2), Group 2: 52 participants taking codeine (77.1), and Group 3: 50 participants on conventional therapy (77.1)	Nursing home	Immediate-release oxycodone 32 mg[a] Immediate-release codeine 11.5 mg[a]	MMSE	Strong (0.93)
3. Gianni et al.[58] Italy	Observational (prospective cohort)	93 participants with osteoarthritis-related pain (79.1)	Multicenter (ambulatory)	Buprenorphine 60–95 mg	MMSE	Good (0.77)
4. Guerriero et al.[59] Italy	Observational (longitudinal prospective cohort)	60 participants with moderate-to-severe chronic noncancer pain (81.7)	Rehabilitation center	Prolonged-release oxycodone 34.8 mg[a]	MMSE	Strong (0.91)
5. Kamboj et al.[56] U.K.	Double-blind, placebo-controlled, and crossover study	14 participants; 12 (85.7%) with cancer pain and 2 (14.3%) with chronic back pain (65.2)	Palliative care unit (inpatient/outpatient)	Sustained-release opioid 190.7 mg (30–800 mg) Immediate-release morphine 21.4 mg (5–100 mg)	PR, VFT, TMT, FT, DS, MST, TST, EC, ECD	Strong (0.82)
6. Karp et al.[61]	Observational (cross-sectional survey)	57 participants with noncancer diagnoses (76.1) Opioid use present in 27 participants	Older adult pain management program	Not reported	MMSE, D-KEFS TMT, DSST, ILT	Adequate (0.55)
7. McNamara[63] U.K.	Observational (single-center, noncomparative, and open label)	19 participants with cancer pain (65.7)	Hospice	Fentanyl 120 mg (60–1080 mg)	CDR	Good (0.73)
8. Pappagallo et al.[62] U.S.	Observational (longitudinal survey)	20 participants with postherpetic neuralgia (72.2)	Pain treatment center	Slow-release morphine 47.1 mg (15–90 mg) Compounded slow-release oxycodone 55 mg (15–90 mg) Hydromorphone 64 mg Methadone 100 mg Overall MEDD dose 54.4 mg	MMSE	Adequate (0.68)
9. Puustinen et al.[60] Finland	Observational (longitudinal and population-based)	565 participants, including cancer and noncancer diagnoses (70.5) Opioid use present at baseline	Municipality of Lieto	Codeine, dextropropoxyphene, ethylmorphine, and dextromethorphan Dose not taken into account	MMSE	Strong (0.86)

(*Continued*)

Table 2
Continued

Study/Country of Origin	Design	Participants Recruited (Sample); Including Diagnosis and Age (Mean Age, Range, and/or Percent of 65 yrs and Older)	Setting	Opioid Type and Oral MEDD (Range)	Tools and Assessments	Quality Score
		($N = 9$), follow-up ($N = 43$), and at both time points ($N = 3$). Opioid users had arthritic diseases				
10. Raja et al.[57] U.S.	Double-blind, placebo-controlled, and crossover study	76 participants with postherpetic neuralgia (71)	Referrals and advertisements (center not clearly acknowledged)	Controlled-release morphine 91 mg (15–225 mg) Methadone (alternative to morphine) 150 mg	MMSE, GPT, HVLT, SST	Strong (0.93)

MEDD = morphine equivalent daily dose; GRT = grammatical reading test; LMT = logical memory test; NART = national adult reading test; RT = reaction time; SCWT = Stroop color and word test; MMSE = Mini-Mental State Examination; PR = prose recall; VFT = verbal fluency test; TMT = trail making task; FT = finger tapping test; DS = digit span test; MST = map search test; TST = telephone search test; EC = elevator counting; ECD = elevator counting with distraction; D-KEFS TMT = Delis-Kaplan executive function system trail making test; DSST = digit symbol subtest; ILT = incidental learning test; CDR = cognitive drug research computerized assessment; GPT = grooved pegboard task; HVLT = Hopkins verbal learning test; SST = symbol substitution task (Wechsler adult intelligence test—revised).
[a]Opioid combined with acetaminophen (Corsinovi et al.[58]) and naloxone (Guerriero et al.[60]).

a municipality (i.e., single urban area)[60] as well as multicenter ambulatory services,[58] nursing home,[55] palliative care unit (inpatient and outpatient),[56] pain treatment center,[62] an older pain management program,[61] and rehabilitation center.[59] One study did not clearly specify a study setting but recruited participants through general practitioner referral/advertisements.[57]

Tools and Assessments Used to Identify Changes to Cognition

Table 3 summarizes the screening tool and neuropsychological tests used to identify and assess changes to cognition from opioid use, including a description, cognitive domains assessed, and outcomes of the tests.

Type and Combination

One screening tool and 21 neuropsychological assessments were used to identify changes to cognition from opioid use. Five studies[55,58–60,62] adopted the use of a screening tool (i.e., the Mini-Mental State Examination [MMSE]) in isolation, and five studies[56,57,61,63,64] used a combination of neuropsychological tests. The MMSE was the most used instrument across all studies. Studies using neuropsychological assessments to assess cognition adopted different combinations of assessments. Clemons et al.[64] stated that the national adult reading test was resistant to the effects of drugs, whereas the Stroop color and word test was likely to give an indication of changes to cognition from opioid use. Kamboj et al.[56] also acknowledged that the prose recall test would be sensitive to opioid-induced recall impairments. The Cognitive Drug Research (CDR) computerized assessment used by McNamara[63] was developed to assess effects from novel compounds on cognitive function, in both volunteers and patients in clinical drug development.[65] Other studies did not discuss the tools/assessments relevant to detect opioid-induced cognitive impairment.

Administration

The timing of screening tool and neuropsychological assessment administration varied across studies. Most studies provided limited description around when tests were administered (80%; $n = 8$).[55,57–63] Those that provided more detailed information about administration generally provided timings in terms of hours or minutes after taking opioids to ensure that opioid plasma levels were at their peak and/or that the timing of tests remained consistent at each visit.[56,64] Nine of the 10 studies measured cognition at baseline, but follow-up periods ranged from two weeks to 52 weeks. Karp et al.[61] conducted neuropsychological assessments within two weeks of

recruitment to minimize effects of newly prescribed treatments on the assessment outcomes.

Cognitive Domains

Fourteen cognitive domains were covered by the tool and assessments (Table 3). Cognitive domains captured include attention, cognitive flexibility (including verbal and nonverbal fluency), concentration, language, memory (both short-term and long-term, as well as speed of memory retrieval), orientation, premorbid intelligence quotient, psychomotor function, psychomotor sedation, psychomotor speed, reaction speed, and reasoning.

Changes to Cognition

There were mixed effects of opioids on cognition in older adults with cancer and chronic noncancer pain (Table 3). Four studies (112 participants taking opioids)[56,60,61,63] demonstrated a change in cognition from opioid use when comparing the effects of morphine with a matched placebo,[56] switching opioids,[63] or between those who received opioid treatment and a control group comparison.[60,61] Control group comparisons consisted of nonopioid users ($N = 27$),[61] and those using no CNS medication ($N = 384$) and nonusers of corresponding medications ($N = 556$).[60] In six studies (233 participants taking opioids), no changes to cognition were observed from baseline to follow-up between groups[55,64] or in a cohort of participants.[57–59,62] Sixteen healthy controls and six advanced cancer patients not taking opioids[64] and 33 participants receiving conventional therapy (i.e., acetaminophen, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors) not taking opioids[55] were used as control group comparisons. In four of the 10 included studies, exploring changes to cognition from opioid use was the primary outcome;[56,57,60,64] however, in six studies, it was a secondary outcome.[55,58,59,61–63]

Mapping Cognitive Domains and Outcomes to Opioid Use in Older Adults

As discussed previously, studies assessed cognitive function using either a screening tool in isolation or a combination of neuropsychological assessments covering 14 cognitive domains. The screening tools and neuropsychological assessments used have been mapped against these different cognitive domains (Fig. 2). Of the three cognitive domains identified by Baldacchino et al.,[43] the screening tool and neuropsychological tests of included studies captured verbal working memory, whereas none captured cognitive impulsivity. Cognitive flexibility was captured by three studies.[56,61,64] Delayed recall/long-term memory was the most common additional domain covered by included studies, followed by attention, language, orientation, concentration, psychomotor function, psychomotor speed, memory retrieval speed, premorbid intelligence quotient, psychomotor sedation, reaction speed, and reasoning.

Opioid Treatment and Concurrent Medications

Opioids used varied across studies (Table 4). Six studies[56–59,63,64] examined the use of one opioid only (including buprenorphine, fentanyl, morphine, and oxycodone). Three studies[55,60,62] used more than one opioid (including codeine, dextromethorphan, dextropropoxyphene, ethylmorphine, hydromorphone, morphine, methadone, and oxycodone). Of which, two studies compared differences between drugs, including opioids in comparison to antidepressants[57] and between different opioids (oxycodone and codeine).[55] Whereas, one study included participants taking one of four opioids without comparison.[62] Oral administration of opioids was most common, followed by transdermal patch and syringe driver. Two studies did not report route of administration.[57,60] Karp et al.[61] did not provide detail around the type(s) of opioids used or route of administration.

MEDD across all studies ranged from 11.5 to 190.7 mg, with two studies not accounting for dose.[60,61] The length of use also varied from approximately seven days to 72 weeks, with one study not accounting for length of use.[61] In studies that demonstrated no difference to cognition, mean MEDD daily dose ranged from 11.5 to 104.29 mg,[55,57–59,62,64] excluding the 13 participants who were provided with 15 mg of methadone (150 mg of MEDD) because of adverse effects from morphine.[57] In studies that demonstrated a change to cognition, mean MEDD was 190.7 mg during an 11.7-day study period,[56] 120–240 mg during a 14-day study period,[63] and dose not taken into account when comparing baseline with a 7.6-year follow-up[60] or between opioid users vs. nonopioid users, without consideration to dose or length of use.[61] Pain relief was achieved with low daily doses of opioids in a number of studies without detriment to cognition.[55,57–59] Opioid switching also demonstrated improvements to patients' global assessment of well-being that were deemed clinically significant.[63] One study found that pain worsened along with general well-being, mood, and concentration.[64]

Most studies provided some description around the use of multiple concurrent medications. Three studies reported that pain medications previously taken by patients were discontinued before study commencement.[55,57,58] However, Gianni et al.[58] specified that medications were only stopped if they lacked efficacy. Corsinovi et al.[55] acknowledged that

Table 3
Summary of Cognitive Tests Used in Each Study, Cognitive Domains Assessed, and Outcomes of Tests

Study	Timing of Test	Assessments and Tools Used	Description Provided by Authors	Cognitive Domain	Outcomes and Comparison Between Groups
Clemons et al.[64]	Tests completed 1.5 hours after oral morphine administration and four hours after controlled-release opioid between midmorning and midafternoon. Tests were completed at a similar time across all visits from baseline to a maximum of 23 days. Visits varied per participant	GRT	The test consists of 64 sentences with varying levels of complexity. The test has been proven to be sensitive to drug effects. The participant is provided with a demonstration card, which had a written statement with the answer. Multiple practice cards (without the same answer) were then shown, and the participant was asked to determine whether the statement was true or false. The series of cards were presented within three minutes. Scores were calculated using the mean time to answer each item and the percentage of errors. A different sequence of cards was used at each test	Concentration and reasoning	No difference in the percentage of errors between cancer groups[a]
		LMT (Subtest of Wechsler Memory Scale)	A fictitious news event (58–64 words in length) was presented to participants. Participants are asked to recall the news event. Each story is divided into 21 details; with one point awarded for each detail recalled word perfect or an exact synonym. Half points are awarded for a close approximation. Different passages were used at each test session	Everyday memory (including short-term and long-term memory)	No difference in memory score and mean time per item between cancer groups[a] *Authors did acknowledge that morphine group took slightly more time per item*
		NART	A word-reading test to test participants' capability of pronouncing 50 phonetically irregular words. The total number of errors is then tabulated. The authors acknowledge that the test is resistant to drug effects	Premorbid IQ	No difference in mean IQ scores between cancer groups[a]
		RT	This test determines the effect of opioids on the mean RT by reducing concentration. Reduced concentration would result in varied response times and would increase the SD of scores. This would contrast with participants who have full concentration because their response times should be narrower in range and have a reduced SD. After each session, the SD of all response times during that session was calculated	Reaction speed and concentration	No difference in reaction speed between cancer groups[a]

		SCWT	This test measures the time taken for participants to read a color word when printed with incongruent ink (e.g., the word *green* printed in red). The correct response is to say the color of the word instead of reading the word. A practice session of 20 items was conducted, followed by the test. The total time taken and number of errors were recorded	Selective attention and cognitive flexibility	No difference in performance on word, color, or color-word cards between cancer groups[a] *Authors acknowledge that morphine group had slightly diminished performance on color card*
Corsinovi et al.[55]	Baseline and at six months. No other details provided	MMSE	Cognitive status was assessed using the MMSE: lower scores were an indication of cognitive impairment	Cognitive function, including attention, language, memory, and orientation	No difference in cognitive function; GLM between groups ($F = 0.1$; $P < 0.877$). GLM within groups ($F = 1.3$; $P < 0.28$)
Gianni et al.[58]	Baseline and at follow-ups (7, 14, 30, 60, and 90 days)	MMSE	MMSE was used to evaluate cognitive impairment, while adjusted for age and education	Cognitive function, including attention, language, memory, and orientation	No difference in cognitive function[a]
Guerriero et al.[59]	Baseline and Week 52	MMSE	Cognitive state was assessed with normal cognition being scored as >25	Cognitive function, including attention, language, memory, and orientation	No difference in cognitive function[a]
Kamboj et al.[56]	Pretreatment and post-treatment (45 minutes after treatment)	DS	Participants forward and backward DS was assessed in a standard format	Attention and working memory	No difference between forward DS (placebo: 6.2 ± 1.2 and morphine 6.0 ± 0.8) in forward DS or backward DS (placebo: 3.6 ± 1.1 and morphine: 4.0 ± 1.0)
		FT	Participants were asked to press a computer keyboard space bar with their dominant hand using their index finger as quickly as possible for one minute. The score was the number of taps recorded	Psychomotor sedation	No difference in tapping rate between placebo (267.1 ± 44.6) and after morphine administration (260 ± 38.5)
		PR (Rivermead behavioral memory test)	Four versions of the PR were used. Participants listened to a news story (prose passage) and were asked to recall the passage immediately, pretreatment and post-treatment. Later in the post-treatment session, participants were asked for delayed recall of the news stories from pretreatment and post-treatment. The delay between immediate and delayed recall was 65 minutes for the pretreatment story and 20 minutes for the post-treatment story. Standard scoring was used, with one point for every correctly recalled idea unit or exact synonym. Half points were awarded for partial recall or synonym. Previous research demonstrated sensitivity to opioid-induced recall impairments[100]	Immediate and delayed episodic memory	Decline in immediate recall after morphine but no main effect of treatment ($F(1,13) = 4.366$, $P = 0.057$) Decline in delayed recall for prose passages before and after morphine, significant main effect of treatment ($F(1,13) = 13.18$, $P = 0.003$) Individual comparisons showed morphine impaired recall post-treatment; 6.6 ± 2.9 idea units recalled after placebo and 4.2 ± 2.8 after morphine ($F(1,13) = 13.01$, $P = 0.003$) Recall of pretreatment story was reduced after morphine administration (4.7 ± 2.0 idea units) compared with placebo 6.1 ± 2.5 idea units ($F(1,13) = 6.53$, $P = 0.024$)

(*Continued*)

Table 3
Continued

Study	Timing of Test	Assessments and Tools Used	Description Provided by Authors	Cognitive Domain	Outcomes and Comparison Between Groups
		TMT	A timed tracking task that consists of two parts. Part A comprises joining numbered circles (i.e., 1–25), and Part B requires participants to join alternating numbers (i.e., 1–13) and alphabetized circles (A–L). Mistakes would be highlighted to participants, but the timing would be continuous. Sample sheets were provided for both parts to ensure that the participant understood the task. A difference score is produced by subtracting A from B, which produces a score that highly correlates with mental ability tests	Attention, psychomotor speed, and cognitive flexibility (Part A & B: psychomotor performance; Part B: attention and B − A: cognitive flexibility)	Improved performance on Part A after morphine administration compared with placebo ($Z = 2.13$; $P = 0.033$). On Part B, those on morphine were slower ($Z = 2.12$; $P = 0.034$) Set shifting and conceptual flexibility (time to complete Trail B − Trail A) was increased after morphine administration ($Z = 2.28$; $P = 0.023$)
		VFT	Participants were asked to generate as many words as possible in one minute with a particular letter (e.g., B or M) to assess phonemic fluency, avoiding proper nouns and inflections of the same word. Semantic fluency was assessed using categories of fruit and vegetables	Phonemic fluency and semantic fluency (cognitive flexibility)	No significant effects of treatment for phonemic fluency (10.1 ± 5.0 words after placebo; 9.5 ± 3.3 after morphine) or semantic fluency (10.6 ± 4.7 words after placebo; 9.5 after morphine)
		Tests of everyday attention			
		EC	Participants are asked to imagine themselves in an elevator where they do not have a visual floor indicator. They were asked to count tones (played on a tape recorder) to determine which floor they would be on. Seven sets of tone sequences were to be counted, varying from three to 14 tones within one series. A score of 7 (one point per series correctly counted) indicated a normal performance, whereas 6 indicated possible abnormality and 5 indicates abnormality	Sustained auditory attention	No difference in performance between placebo (6.5 ± 0.5) and morphine (6.2 ± 1.0)
		ECD	This task requires participants to count low-frequency tones while ignoring high-frequency tones. A series of low- and high-frequency tones containing between two and 14 target low tones is played. Participants are awarded a point for each series when the correct number of low tones was counted	Selective auditory attention	No difference in performance between placebo (7.2 ± 2.5) and morphine (9.3 ± 8.2) groups

		MST	A time-limited task that requires participants to search for and mark symbols on a map of Philadelphia within two minutes	Selective visual attention	No difference between placebo (37.6 ± 16.9) and morphine (36.9 ± 14.8) in number of symbols correctly identified
		TST	This is a timed visual task. Participants are asked to imagine that they are in Philadelphia and need to find a plumber or a restaurant. They are asked to scan the yellow pages directory for plumbers or restaurants and place a mark on entries that had the same symbols (e.g., two stars or two circles). Participants are asked to work as quickly and accurately as possible and to not check their responses. The time taken to complete the search and number of correctly marked targets are recorded (false positives were ignored). The number of targets divided by the time taken to complete the task to create the dependent variable (time per target)	Selective attention	No difference between placebo (4.8 ± 1.0) and morphine (5.1 ± 1.4) in time per target
Karp et al.[61]	Not reported	MMSE	Cognitive function was assessed to determine participant eligibility. All subjects were required to have a MMSE score of ≥24 to participate	N/A	N/A
		D-KEFS TMT	Mental flexibility was assessed with the TMT of the D-KEFS. This test is similar to the traditional TMT but comprises five subtests that may be used to correct for processes other than mental flexibility that may be contributing to a slow response time or to set-shifting errors. These tests are also age adjusted. The D-KEFS Trail Making subtests administered to patients include the number-letter switching condition (similar to the traditional Trails B) that is a measure of mental flexibility. The other is a test of motor speed (similar to the traditional Trails A)	Mental flexibility (cognitive flexibility) and psychomotor speed	No difference between opioid users (7.7 ± 3.9) and nonopioid users (9.3 ± 4.4) in mental flexibility (number-letter switching), t = 1.38, df = 50, $P = 0.17$ No difference between opioid users (9.9 ± 3.5) and nonopioid users (10.7 ± 3.4) in psychomotor speed, t = 0.81, df = 50, $P = 0.42$ Reduced number (26 opioid users/26 nonopioid users)
		DSST (Wechsler Adult Intelligence Scales—Revised)	Highly sensitive to neuropsychological dysfunction[31] and is another probe of mental flexibility. This visuoperceptual decoding task requires the subject to associate single-digit numbers with unfamiliar symbols. A stimulus set of nine printed digit-symbol pairs is presented above rows of numbers without the appropriate symbols. The	Cognitive flexibility (referred to as mental flexibility)	No difference between opioid users (10.9 ± 3.0) and nonopioid users (11.7 ± 2.8), t = 0.91, df = 49, $P = 0.37$ Reduced number (25 opioid users/26 nonopioid users)

(*Continued*)

Table 3
Continued

Study	Timing of Test	Assessments and Tools Used	Description Provided by Authors	Cognitive Domain	Outcomes and Comparison Between Groups
			subject is instructed to draw the correct symbol below each of the numbers using the digit-symbol code presented above. The score is based on the number of substitutions completed within 90 seconds		
		ILT	Memory was assessed with the ILTs administered immediately after the DSST. Paired recall involves completing a number of DS items without access to the code key; free recall, simply reproducing the symbols from memory. These tests of memory were only administered if patients completed four rows of the DSST test within 120 seconds. The reason for this was to standardize the time each patient was exposed to the digit/symbol stimuli	Memory (including free recall and paired recall	Unprompted memory was worse in opioid users (6.3 ± 1.1) compared with nonopioid users (7.0 ± 1.1) in the free recall test, t = 2.17, df = 39, $P = 0.04$ No difference in paired recall between the opioid users (6.9 ± 4.2) and nonopioid users (7.7 ± 5.1), t = 0.56, df = 39, $P = 0.58$ Reduced number (20 opioid users/21 nonopioid users)
McNamara[63]	Baseline and Day 14 (last recorded assessment—used as the last value when data were missing—last value carried forward	CDR computerized assessment	A series of tests were used, including simple RT, choice RT, digit vigilance, memory scanning, immediate and delayed word recall, word recognition, picture recognition, and critical flicker fusion threshold. Tasks are presented on a microcomputer, and participants responded using one of two buttons within a single box. For a further breakdown on tests, see Hanks et al.[101]	Power of concentration (*ability to attend to change or concentrate for sustained periods*)	No significant difference between baseline (1654 [1484, 1825]) and last recorded visit in ability to concentrate (1623 [1469, 1776], $P = 0.6771$)
				Quality of concentration (*accuracy and speed of concentration, combined*)	No significant difference between baseline (89.3 [86.8, 91.7]) and last recorded visit in accuracy and speed of concentration (89.2 [85.6, 92.9], $P = 0.8341$)
				Quality of working memory (*ability to retain and retrieve information in short-term memory*)	Significant improvement in quality of working memory between baseline (1.5 [1.3, 1.8]) and last recorded visit (1.7 [1.6, 1.8], $P = 0.0345$)
				Quality of secondary memory (*ability to retain and retrieve information in long-term memory*)	No significant difference between baseline (207 [188, 226]) and last recorded visit in ability to retrieve information from long-term memory (192 [167, 217], $P = 0.3218$)
				Speed of memory (*speed of information retrieval*)	Significant improvement in speed of memory from baseline (5551 [4583, 6519]) and last recorded visit (4878 [4246, 5511], $P = 0.0212$)
Pappagallo et al.[92]	Baseline and two months	MMSE	Cognition was assessed using the MMSE	Cognitive function, including attention, language, memory, and orientation	No difference in cognition at two-month follow-up (29.9 ± 0.1, $N = 20$, $P = 0.6$)
Puustinen et al.[60]	Measured at both Phase 1 and Phase 2	MMSE	The test comprises 23 items, and the sum of scores ranges from 0 to 30. Higher scores indicate better cognitive performance. The mean	Cognitive function, including attention, language, memory, and orientation	MMSE scores of opioid users were significantly worse than the group (no medications with effects to CNS) ($P = 0.032$)

			change in MMSE sum scores during follow-up was used as an outcome variable		MMSE scores of opioid users were significantly worse than the control group (nonusers of corresponding medications) ($P = 0.021$) The combination of opioids and other CNS medications was also associated with cognitive decline ($P = 0.007$)
Raja et al.[57]	Baseline and maintenance. Each treatment period lasted eight weeks (with titration, maintenance, and taper phase), with three treatment periods (opioid, tricyclic antidepressants, and placebo). Treatment periods were separated by a week without drugs	MMSE	Cognitive function was assessed to determine participant eligibility	N/A	N/A
		GPT	No description provided	Concentration and psychomotor function	No difference in performance[a] *Practice effects observed*
		HVLT	The test comprises a 12-item word list, which is composed of four words from three semantic categories. Participants read the word list and aim to memorize the words. The word list is then read to the participant at a rate of two seconds per word. The participant's free recall of the list is recorded. This is repeated for two more trials. At the end of the third trial, the participant is read 24 words and is asked comment *yes* for words that appeared on the recall list (12 targets) and *no* for words that did not (12 distractors). Half of the distractors are from the same semantic category as the targets (related distractors), whereas half are drawn from other categories (unrelated distractors). There are six forms of the test and requires no more than 10 minutes to administer	Verbal learning and memory	No difference in performance[a]
		SST (Wechsler Adult Intelligence Test—Revised)	No description provided	Manual dexterity and psychomotor speed	No difference in performance[a]

GRT = grammatical reading test; LMT = logical memory test; NART = national adult reading test; IQ = intelligence quotient; RT = reaction time; SCWT = Stroop color and word test; MMSE = Mini-Mental State Examination; GLM = general linear model; DS = digit span test; FT = finger tapping test; PR = prose recall; TMT = trail making task; VFT = verbal fluency test; EC = elevator counting; ECD = elevator counting with distraction; MST = map search test; TST = telephone search test; N/A = not available; D-KEFS TMT = Delis-Kaplan executive function system trail making test; df = degrees of freedom; DSST = digit symbol subtest; ILT = incidental learning test; CNS = central nervous system; GPT = grooved pegboard task; SST = symbol substitution task.

[a]Clemons et al.:[64] Statistical significance between advanced cancer groups was not reported, and inferences were based on author description and mean trends. Gianni et al.:[58] *P*-value not provided, but authors note that the outcome is not statistically significant. Guerriero et al.:[59] Statistical significance is not reported, but mean MMSE score from baseline to end point was provided in graph, and authors acknowledge that MMSE score remained stable across time points. Raja et al.:[57] *P*-values were not provided, but authors noted that treatment did not influence performance on any measure. Authors presented means and SDs.

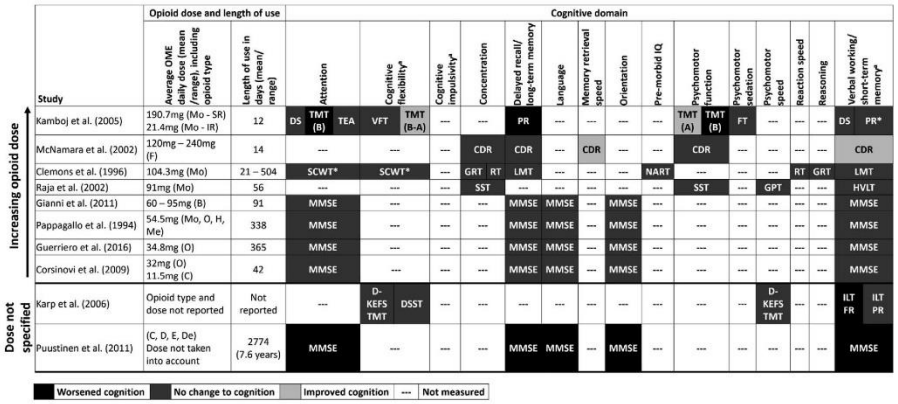

Fig. 2. Impact of opioids on cognition, mapped by cognitive domain. *Opioids*: (B) = buprenorphine; (C) = codeine; (D) = dextropropoxyphene; (De) = dextromethorphan; (E) = ethylmorphine; (F) = fentanyl; (H) = hydromorphone; (O) = oxycodone; (Me) = methadone; (Mo) = morphine; IR = immediate release; SR = sustained release. *Screening tools and neuropsychological tests*: CDR = cognitive drug research computerized assessment; D-KEFS TMT = Delis-Kaplan executive function system trail making test; DS = digit span test; DSST = digit symbol subtest; FT = finger tapping test; GPT = grooved pegboard task; GRT = grammatical reading test; HVLT = Hopkins verbal learning test; ILT = incidental learning test (including free recall and paired recall); LMT = logical memory test; MMSE = Mini-Mental State Examination; NART = national adult reading test; PR = prose recall; RT = reaction time; SCWT = Stroop color and word test; SST = symbol substitution task; TEA = tests of everyday attention; TMT(A) = trail making test (Part A); TMT(B) = trail making test (Part B); TMT(B – A) = trail making test (Part B – Part A); VFT = verbal fluency test. [a]Cognitive domain from Baldacchino et al.[43] *No significant change to cognition, but authors acknowledged a trend toward a decline in performance.

concurrent medications were taken at stable doses three weeks before the study and continued at stable doses. Other studies detailed that rescue medication was provided for breakthrough pain, but the authors did not clearly specify if any other medications were taken.[58,63] Three reported the use of concurrent medications taken by participants at the time of testing,[56,62,64] including opioids.[64] Puustinen et al.[60] aimed to capture the use of any CNS medication but provided different subgroup analyses. Two studies did not clearly report whether concurrent medications were taken.[59,61]

Risk of Bias and Reporting Quality

The mean quality score for included articles was 0.77. There were three adequate-quality articles,[61,62,64] two good-quality articles,[58,63] and five strong-quality articles.[55–57,59,60] The RCTs demonstrated consistently high quality (strong: 0.82–0.93). Observational studies varied in quality, ranging from adequate to strong (0.55–0.91). The quasi-experimental study was adequate in quality (0.55). Two RCTs reduced chances of selection, performance, and detection bias by using double-blind, placebo-controlled, and randomized approaches.[56,57] Although, one did not provide detailed information around randomization to treatment order and allocation concealment.[56] A single-blind approach lacked detail around random sequence generation and allocation concealment. However, chances of performance and detection bias were reduced by blinding the researchers to the intervention participants received.[55] Other included studies may be susceptible to selection, performance, and detection bias because of the absence of randomization and blinding. All studies, where relevant, described attrition and exclusion from the analysis. Subject selection and sampling frames were not well reported across most studies, along with power calculations to ensure whether the sample size was appropriate. Nonrandomized studies often failed to control for confounding.[58–64]

Discussion

This systematic review builds on previous reviews[34–37,40] by focusing attention to the cognitive effects of opioids in older adults with cancer and chronic noncancer pain. The current review also aimed to ascertain the screening and assessment tools used to identify changes to cognition from opioid use in this population. This complements recent systematic reviews and meta-analyses exploring the neuropsychological consequences of opioid use in adults with a chronicity of and/or dependent on opioid use[43] and

Table 4
A Summary of Opioids Used Across Included Studies and Oral Morphine Equivalent Conversion

Study	Opioid Type, Route of Administration, and Length of Use	Reported Opioid Dose (Mean Dose and/or Range)	Oral MEDD (Mean and/or Range)	Average MEDD (Mean and/or Range)
Clemons et al.[64]	**Type:** Controlled-release morphine sulfate or morphine sulfate solution **Route:** Oral **Length of use:** No exact date of commencement for five of seven participants. Earliest known date was used; approximately three to 72 weeks	104.3 mg/day (50–200 mg)	104.3 mg (50–200 mg)	104.3 mg (50–200 mg)
Corsinovi et al.[55]	**Type:** Immediate-release oral oxycodone **Route:** Oral **Length of use:** Six weeks	Baseline: 5 mg/12 hours Average daily dose: 10–20 mg/day Average dose at end of study: 16 mg/day	Baseline: 20 mg Average daily dose: 20–40 mg Average dose at end of study: 32 mg	32 mg
	Type: Immediate-release codeine **Route:** Oral **Length of use:** Six weeks	Baseline: 30 mg/eight hours Average daily dose: 90–120 mg/day Average dose at end of study: 115 mg/day	Baseline: 9 mg Average daily dose: 9–12 mg Average dose at end of the study: 11.5 mg	11.5 mg
Gianni et al.[58]	**Type:** Buprenorphine **Route:** Transdermal **Length of use:** Three months	End of three-month observation 11.7 μg/hour in 3.5%; 17.5 μg/hour in 11.6%; 35 μg/hour in 74.4%; 52.5 μg/hour in 9.3%; 70 μg/hour in 1.2%	End of three-month observation 20–31.7 mg/day in 3.5% 30–47.5 mg/day in 11.6% 60–95 mg/day in 74.4% 95–145 mg/day in 9.3% 125–190 mg/day in 1.2%	60–95 mg
Guerriero et al.[59]	**Type:** Oxycodone prolonged release **Route:** Oral **Length of use:** 52 weeks	Baseline: 10 mg/day Week 4: 14.4 ± 4.9 mg/day Week 52: 17.4 ± 7.7 mg/day During follow-up, the daily dose increased to 20 mg/day in 42% of patients at four weeks and to 40 mg/day at 52 weeks in only 6% of patients	Baseline: 20 mg Week 4: 28.8 ± 9.8 mg Week 52: 34.8 ± 15.4 mg During follow-up, the daily dose increased to 40 mg/day in 42% of patients at four weeks and to 80 mg/day at 52 weeks in only 6% of patients	34.8 ± 15.4 mg
Kamboj et al.[56]	**Type:** Sustained-release morphine **Route:** Oral (50%), transdermal patch (42.9%), and syringe driver (7.1%) **Length of use:** 11.7 days (SD 4.7 days)	190.7 ± 266.6 mg/day (30–800 mg/day)	190.7 ± 266.6 mg (30–800 mg)	190.7 ± 266.6 mg (30–800 mg)
	Type: Immediate-release morphine **Route:** Oral **Length of use: Mean:** 11.7 days (SD 4.7 days)	21.4 ± 25.6 mg/day (5–100 mg/day)	21.4 ± 25.6 mg (5–100 mg)	21.4 ± 25.6 mg (5–100 mg)
Karp et al.[61]	Not reported	Not reported	Not reported	Not reported
McNamara[63]	**Type:** Fentanyl **Route:** Transdermal **Length of use:** 14 days	Baseline: 25 μg/hour or 50 μg/hour Maintenance dose of 50–100 μg/hour (25–450 μg/hour)	Baseline 60–90 mg or 120–190 mg Maintenance dose of 120–240 mg (60–1080 mg)	120–240 mg (60–1080 mg)
Pappagallo et al.[62]	**Type:** Slow-release morphine **Route:** Oral **Length of use: Mean:** 11.86 months (3–20 months)	47.1 mg/day (15–90 mg/day)	47.1 mg (15–90 mg)	54.5 mg
	Type: Compounded slow-release oxycodone **Route:** Oral **Length of use:** Mean: seven months	27.5 mg/day (7.5–45 mg/day)	55 mg (15–90 mg)	
	Type: Hydromorphone **Route:** Oral **Length of use:** Mean: 21 months	16 mg/day	64 mg	

(*Continued*)

Table 4
Continued

Study	Opioid Type, Route of Administration, and Length of Use	Reported Opioid Dose (Mean Dose and/or Range)	Oral MEDD (Mean and/or Range)	Average MEDD (Mean and/or Range)
	Type: Methadone **Route:** Oral **Length of use:** Mean: seven months (range 2–12)	10 mg/day	100 mg	
Puustinen et al.[60]	**Type:** Codeine, dextropropoxyphene, ethylmorphine, and dextromethorphan **Route:** Not reported **Length of use:** Not clearly reported (dichotomized into regular and irregular use)	Dose was not taken into account	N/A	N/A
Raja et al.[57]	**Type:** Controlled-release morphine **Route:** Not reported **Length of use:** Eight weeks	91 mg/day (15–225 mg/day)	91 mg (15–225 mg)	91 mg (15–225 mg)
	Type: Methadone (alternative to morphine) **Route:** Not reported **Length of use:** Eight weeks	15 mg/day	150 mg	150 mg

MEDD = morphine equivalent daily dose; N/A = not available.

long-term opioid use in adults with chronic noncancer pain.[44]

Opioid-Induced Cognitive Impairment in Older Adults With Cancer and Chronic Noncancer Pain

Mirroring previous systematic reviews on the cognitive effects of opioid use in adults with malignant and nonmalignant pain,[34–36] the current review found varied effects on cognition from opioid use, with six studies demonstrating no change to cognition from opioid use. Drawing together the findings from adult cancer populations[36] and chronic noncancer populations,[35] an updated review indicated that there was either no difference or worsening cognition in adult cancer patients and no difference or an improvement in cognition in chronic noncancer populations.[34] In the current review, a noncomparative study exploring domains of cognitive function in an older adult population with cancer found that domains did not change (i.e., concentration, quality of secondary memory, and psychomotor function) or improved (speed of memory retrieval and verbal working memory), although numbers were small.[63] In another study with a predominant cancer population, changes to cognitive domains were either not present (i.e., psychomotor sedation or verbal working memory), improved (i.e., cognitive flexibility), worsened (i.e., attention), or improved then worsened (i.e., psychomotor function) across the different neuropsychological assessments used,[56] although again, the sample was small. Whereas in a study that explored cognitive changes from long-term opioid use in chronic noncancer patients (i.e., patients with painful arthritic diseases) via a subgroup analysis, there was a decline in cognitive function.[60] However, there were also very few participants. Karp et al.[61] found that opioid users experienced more difficulty with unprompted memory compared with opioid users, in those with nonmalignant pain. Nevertheless, the sample size and reporting around opioid use were limited. These findings contrast with previous reviews, with improvements to cognition detected in cancer populations and the decline of cognition in a chronic noncancer population. However, methodological limitations, small sample sizes, and variation in study design pose challenges to drawing definite conclusions from the included studies.

Dose increase was associated with impaired cognition in a previous systematic review.[34] There is no definitive definition of 'high dose' in the scientific literature;[66] U.K. guidance states that the risk of harm increases at doses above 120 mg/day without increased benefit.[67] Changes to cognition in the current review were mostly observed in studies that adopted the use of higher mean opioid doses (i.e., 120–190.7 mg MEDD).[56,63] However, Puustinen

et al.[60] demonstrated changes to cognition from long-term use of opioids, although dose was not taken into account. Karp et al.[61] also found that unprompted memory was impaired in those who used opioids compared with those who did not, without taking dose into consideration. A number of studies found that low doses of opioids were a valid treatment for moderate-to-severe chronic pain without any associated cognitive impairment.[55,57–59,62] Although, some studies considered to have a low mean dose demonstrated some wide ranges in dose, including higher doses.[57,58,62] Transient improvements to short-term memory and memory retrieval speed were also observed after switching from morphine to fentanyl.[63] Potential benefits of opioid rotation and opioid switching[68] and the usefulness of fentanyl in comparison to morphine[69] were also recognized in excluded studies. However, a multinational study on the prevalence and predictors of cognitive dysfunction in adult cancer patients demonstrated no difference in cognitive effects between three commonly used opioids (fentanyl, morphine, and oxycodone).[70] Although, this study used the MMSE, which may not have been sensitive enough to capture subtle differences to cognition. Overall, the type of opioids assessed and the doses used across studies varied greatly.

The previous reviews commented on the methodological weaknesses of studies assessing cognitive function in cancer and chronic noncancer populations.[34–36] The weaknesses identified were the use of nonrandomized and noncontrolled study designs, lack of suitable control groups as well as issues around the cognitive effects of pain itself, polypharmacy, and other confounders impacting on cognitive outcomes. These issues were also recognized within the current review. Studies that adopt a controlled design are thought to be of the highest quality.[34] This review did not restrict by controlled design or study quality as there is limited evidence in this population, and we aimed to be inclusive of all possible studies. Kendall et al.[35] highlighted that changes to cognition varied between study designs. They found no difference to cognition or an improvement in RCTs and noncontrolled comparative designs and no difference or worsened cognition in observational studies. Because of the limited number of included studies in this review and the small number of studies that detected a change in cognition, as well as the variety of study designs adopted, it was not possible to determine the role of study design in patterns of changes to cognition from opioid use. There are also challenges around the appropriateness of study design in this older adult population, such as long-term exposure to harmful effects of medications.[60,71,72]

Impaired cognition is frequently associated with the pain or disease experience.[73] The use of an appropriate control group is considered important as the use of healthy volunteers does not account for the effects of pain or the disease itself.[34] An ideal control group would include older adults eligible for opioid therapy but not receiving the treatment.[34] The prolonged use of a placebo or not providing suitable treatment could pose ethical issues, but such methods can be beneficial if they adopt sound methodological considerations.[56,71,72] One included study used older adults with advanced cancer not taking opioids and healthy volunteers as control groups to determine the impact of opioids and the disease itself on cognition.[64] However, the reporting of group differences in study outcomes was vague and differed between the results and discussion sections of the article; making it challenging to interpret the impact of the disease itself and from the use of opioids. The control groups in the other studies consisted of conventional therapies without use of opioids,[55] those not taking CNS medications or nonusers of corresponding medications,[60] and older adults not taking opioids (and unclear if they are eligible for opioid therapy).[61] Therefore, the control groups adopted in other studies did not best reflect controlling for appropriate risk factors in the context of opioid-induced cognition. Other included studies did not adopt a control group, although, two studies used participants as their own controls in crossover designs.[56,57]

Older adults commonly take several concurrent medications.[27] Older adults' cognition is susceptible to polypharmacy and anticholinergic burden from the use of multiple medications.[74,75] A longitudinal cohort study evaluating the combined use of multiple CNS medications (including opioids) in healthy older adults, excluded from this review, indicated that the combined use of CNS medications, particularly at high doses, was associated with cognitive decline in healthy older adults.[76] We acknowledge that medications for a number of medical conditions may also impact on cognition. The cognitive effects of opioids from included studies are difficult to determine because of differences in or lack of controlling for the use of multiple medications in a number of studies,[55–57,60,61,63,64] as well as unclear/poor reporting.[58,59,61] This may explain some of the variability in the cognitive outcomes of included studies. By controlling for medications before study commencement or during, a better understanding of baseline cognition and opioid impact can be gained. Other confounding factors, such as degenerative cognitive impairment associated with age, should also be considered. Most included studies had signs of severe

cognitive impairment or dementia (usually assessed by MMSE score) as an exclusion criterion.[55–62]

More understanding around the effect of opioids on cognition in older adults with cancer and chronic noncancer pain is still needed. Currently, there is a small number of studies available. The limitations of current evidence, because of the heterogeneity of results and methodological approach, suggest that we need a more standardized approach, with clearer reporting.

Screening Tools, Neuropsychological Assessments, and Cognitive Domains

There are a wide variety of screening tools and neuropsychological assessments available, but there is little consensus around a standardized approach to identifying and assessing changes to cognition from opioid use.[34–36] In particular, there is limited understanding of which tools and assessments may distinguish clinically meaningful changes to cognition in older adults with cancer and chronic noncancer pain. Determining which tool(s) and/or assessment(s) are appropriate in this population could provide an accurate way to detect changes to cognition over time and inform adjustments to treatment.[35,64]

The MMSE was the only screening tool identified and predominantly used across included studies. The MMSE was designed for use with patients with dementia and is commonly used to assess cognitive function.[77,78] Despite wide acknowledgment in the literature that the MMSE lacks sensitivity to detect minor changes to cognition, it is still predominantly used as reasonably quick to administer and engrained in clinical practice.[79–82] A significant association between cognitive decline (including attention, language, orientation, and both short-term and long-term memory) and opioid used was demonstrated in an observational longitudinal study included in the current review using the MMSE.[60] However, the small number of participants using opioids and issues with adjusting for some risk factors (e.g., alcohol use) limits the interpretation and generalizability of these findings to other elderly populations. A large longitudinal study, using self-reports of cognition, explored the relationship between opioids on clinical outcomes for patients receiving palliative care. The study found that opioid use was not related to worsened cognition in an adjusted analysis.[83] Although, the authors acknowledged that the low cognitive symptom scores could have been because of the exclusion of low MMSE scores (i.e., ≤24) and that the included sample represented a group with lower risk of cognitive deterioration.[83] Other included studies in this review that adopted the MMSE did not detect a difference. Evidence supports the use of other, more nuanced, and brief screening tools subsequently developed to detect mild changes to cognition in older adults compared with the MMSE.[78,84,85] The use of alternative screening tools has been recognized in substance misuse research, including opioid misuse.[86–88]

Neuropsychological effects from opioid use are well documented.[34–36,42–44] Neuropsychological assessments can detect subtle changes to cognition from opioid use.[89] However, we do not know if performance on neuropsychological tests relate to clinically relevant effects or recommendations.[42,43,89] The single measure focus of neuropsychological tests (e.g., attention) is problematic in drawing conclusions around cognitive impairment from opioid use,[42] as multiple domains appear to be affected. The included studies that adopted neuropsychological tests used multiple assessments to assess different cognitive domains. The incidental learning tests (i.e., free recall), prose recall test, trail making task, and subtests of the CDR computerized assessment detected changes to cognition.[56,61,63] The use of multiple assessments may be challenging in clinical practice, as this would take significantly more time to perform.[90] Tools to detect opioid-induced cognitive impairment in a primary care setting need to be comprehensive, easy to administer within a short time frame, valid, and reliable.[89]

A better understanding of the cognitive domains that are affected by opioid use in this older adult population could lead to the use of or development of a more suitable assessment tool and a clearer definition of what constitutes opioid-induced cognitive impairment. Baldacchino et al.[43] identified cognitive flexibility, cognitive impulsivity, and verbal working memory as important cognitive domains in adults using opioids chronically. A more recent systematic review and meta-analysis found that long-term opioid use in adults reduced attention compared with other treatments that targeted the CNS.[44] All studies in the current review assessed verbal working memory; with one detecting an improvement using the CDR computerized assessment[63] and one finding a decline to cognitive performance using the MMSE in this domain.[60] Cognitive flexibility was only measured in three studies and assessed with five different neuropsychological assessments;[56,61,64] with only the trail making task (Task B − A) detecting an improvement in this domain.[56] Attention was also found to be affected in a longitudinal population-based study that screened cognition using the MMSE.[60] There are concerns regarding the ecological validity of neuropsychological assessments, in that, there is a lack of agreement around the constructs that some tests aim to measure, leading to difficulties in interpreting the outcome.[91] This may contribute to the varied findings across studies. Practice effects are also a recognized characteristic from completing multiple assessments, where

test performance may be attributed to increased familiarity.[92] Of the included studies that conducted multiple assessments,[55–60,62–64] two discussed practice effects, whereas only one study controlled them.[57] Therefore, practice effects may have had influence over the cognitive outcomes.

None of the existing screening tools and neuropsychological assessments of included studies are suitable to evaluate all cognitive domains.[93] Other domains that demonstrated cognitive change in the current systematic review included delayed episodic memory, language, orientation, and psychomotor function. How we define opioid-induced cognition in older adults may need to consider additional cognitive domains (i.e., delayed recall/long-term memory and psychomotor function). However, because of the methodological designs of the studies, small sample sizes, and populations included, there could be some noise around cognitive effects from opioids, such as issues of pain, the disease itself, and the use of appropriate control groups. There may also be other cognitive domains to consider that have not been captured in the included studies. Limited reporting of the timing of administration may have also hindered understanding of whether the tools and assessments would detect a change in cognition because of opioids (e.g., ensuring opioid plasma levels were at their peak).[64]

Driving is a complex task that requires a range of cognitive skills (such as attention and executive functions), visuospatial skills, motor ability, and multisensory perception.[94,95] Previous reviews explored the impact of opioids on driving ability in adults with cancer and/or chronic noncancer conditions as part of their assessment of opioid-induced cognitive impairment.[35–38] The findings from these systematic reviews are limited because of the scarce number of studies available, as well as the absence of clinically relevant information and appropriateness of tests to assess cognition and driving ability among chronic pain populations in terms of clinical practice and everyday tasks.[36,37] Studies assessing driving ability were considered within the current review; however, studies were not eligible for inclusion as study populations were younger than 65 years.

Clinically, opioid neurotoxicity in older adults often presents itself as sedation, confusion, as well as hallucinations, mood disorders, and cognitive impairment.[40,42] The screening tool and neuropsychological assessments of included studies in this systematic review do not capture issues with some cognitive adverse effects, like hallucinations, and may not detect sedation and confusion in a clinically meaningful way. Yet, these are considered clinically important side effects[42,96,97] as well as impactful on patient well-being.[98]

Strengths and Limitations

This systematic review was guided by the PRISMA Protocols checklist[45,46] to ensure that the protocol development and reporting were robust. Multiple search engines were searched (inclusive of language, publication status, and publication date) to enable the identification of all possible literature. Another strength was our exclusion of studies where cognitive function may already be compromised either by existing health conditions (e.g., patients with dementia) or where patterns of opioid use were likely to differ (e.g., perioperative use or substance misuse).

There were several potential limitations. Studies that relied on self-report or clinical opinion, which may be of interest in clinical practice, were not included. However, the focus on formal screening tools and neuropsychological assessments allowed for ease of comparison with previous reviews. Another limitation was defining an older adult population. We used a chronological age of 65 and older; as commonly adopted by most developed countries and for providing a suitable cut-off value for inclusion.[49,50] We recognize that some included participants could be younger than 65 years and that chronological age does not account for individual patient characteristics/responses to prescribed medications.[99] Most included studies consisted of chronic noncancer pain populations, which may limit the generalizability of findings to cancer pain populations. In addition, some studies may have been underpowered, as they explored changes to cognition from opioid use as a secondary outcome. This review adopted the QualSyst tool to assess study quality, as it allowed for the standardized and empirically grounded assessment of a variety of study designs.[51] However, it lacked the ability to identify specific biases, which may have led to inflated quality grades of included studies.

Overall, the methodological issues, small sample sizes, and poor reporting in the included studies limit how we can interpret the effects from the opioids on older adults' cognition and the interpretation of the review findings. Therefore, this review does not make recommendations or implications for practice that go beyond the scope of the included evidence.

Implications for Practice

This review highlights the absence of a standardized approach to assessing opioid-induced cognitive impairment in older adults with cancer and chronic noncancer pain, and how current approaches adopted in research studies lack suitability. Therefore, the use of formal screening tools and neuropsychological assessments of opioid-induced cognitive impairment cannot replace clinical judgment and identifying clinically meaningful adverse effects, such as

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Appendix. Example of the Full Search Strategy

Example of Ovid MEDLINE® Epub Ahead of Print, In-Process, and Other Nonindexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946 to Present Search Strategy:

1. exp Analgesic, Opioid/
   [Drug Terms (Non-MeSH)]
   Alfentanil
   Alphaprodine
   Buprenorphine
   Buprenorphine, Naloxone Drug Combination
   Butorphanol
   Codeine
   Dextromoramide
   Dextropropoxyphene
   Dihydromorphine
   Diphenoxylate
   Enkephalin, Ala(2)-MePhe(4)-Gly(5)-Enkephalin, D-Penicillamine (2,5)-
   Ethylketocyclazocine
   Ethylmorphine
   Etorphine
   Fentanyl
   Heroin
   Hydrocodone
   Hydromorphone
   Levorphanol
   Meperidine
   Meptazinol
   Methadone
   Methadyl Acetate
   Morphine
   Nalbuphine
   Opiate Alkaloids
   Opium
   Oxycodone
   Oxymorphone
   Pentazocine
   Phenazocine
   Phenoperidine
   Pirinitramide
   Promedol
   Sufentanil
   Tapentadol
   Tilidine
   Tramadol
2. Dezocine.mp
3. Dihydrocodeine.mp
4. Opiate*.mp
5. Opioid*.mp
6. Propoxyphene.mp
7. Tapentadol.mp
8. Trimeperidine.mp
9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10. exp Cognitive Dysfunction/
11. cognit*.mp
12. 10 OR 11
13. exp Aged
    Aged, 80 and over
    Frail elderly
14. Elder*.mp
15. Geriatr*.mp
16. Old* adult*.mp
17. Old* age*.mp
18. Old* Generation*.mp
19. Old* people*.mp
20. Senior*.mp
21. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22. 9 AND 12 AND 21

Appendix 3: Data extraction form

General Information					
Date of extraction					
Person extracting data					
Study ID (author and year)					
Study title					
Citation					
Type of publication					
Country of origin					
Source of funding					
Possible conflicts of interest					
Notes					
Systematic review eligibility criteria					
	Inclusion			**Exclusion**	
Population					
Exposure					
Comparison					
Outcome					
Type of study					
Decision (provide reason)					
Notes					
DO NOT CONTINUE IF STUDY IS EXCLUDED FROM REVIEW					
Study characteristics					
Aim/objectives					
Study design					
	Inclusion			**Exclusion**	
Inclusion and exclusion criteria					
Sampling technique					
Recruitment procedures					
Study start date					
Study end date					
Notes					
Participant characteristics					
Source/setting of population					
Age (including mean or percentage over 65)					
Gender					
Primary disease characteristics					
Comorbidities					
Concurrent/multiple medications					
	Total	**Group 1**	**Group 2**	**Group 3**	**Exclusions/ Withdrawals**
Number of participants					
Notes					
Screening tools, neuropsychological assessments and outcomes collected					

	Name of tool	Sensitivity (if available)	Specificity (if available)
Screening tool used			
	Timing or schedule		
Details provided around screening tool			
	Assessment name	**Cognitive domain assessed**	**Timing or schedule**
Neuropsychological assessment			
Details provided around neuropsychological assessments			
Other outcomes/data collected			
Notes			
Opioids			
Type of opioid			
Dose			
Route of administration			
Length of use			
Other details			
Statistical analyses used (if applicable)			
Statistical techniques used			
Results			
Results for statistical analyses on cognition			
Any change in cognition?			
Notes			
Limitations and mitigation			
Strengths (acknowledged by authors)			
Limitations (acknowledged by authors)			
Strategies used to overcome limitation			
Notes			
Conclusions			
Key conclusions, and supporting statements			
Notes			
Risk of bias (Quality assessment)			
	Yes (2)	**Partial (1)**	**No (0)**	**N/A**
(1) Question/ objective sufficiently described?				
(2) Study design evident and appropriate?				
(3) Method of subject/ comparison group				

selection *or* source of information/ input variables described and appropriate?				
(4) Subject (and comparison group, if applicable) characteristics sufficiently described?				
(5) If interventional and random allocation was possible, was it described?				
(6) If interventional and blinding of investigators was possible, was it reported?				
(7) If interventional and blinding of subjects was possible, was it reported?				
(8) Outcome and (if applicable) exposure measure(s) well defined and robust to measurement /misclassification bias? Means of assessment reported?				
(9) Sample size appropriate?				
(10) Analytic methods described/ justified and appropriate?				
(11) Some estimate of variance is reported for the main results?				
(12) Controlled for confounding?				
(13) Results reported in sufficient detail?				
(14) Conclusions supported by the results?				
Notes	**Total sum** (number of "yes" * 2) + (number of "partials" *1) **Total possible sum** 28- (number of N/A * 2) **Summary score** total sum / total possible sum			

Appendix 4: Quality assessment of included studies

Criteria	Clemons et al. (1996)	Corsinovi et al. (2009)	Gianni et al. (2011)	Guerriero et al. (2016)	Kamboj et al. (2005)	Karp et al. (2006)	McNemara et al. (2002)	Pappagallo et al. (1994)	Puustinen et al. (2011)	Raja et al. (2002)
1. Question/ objective sufficiently described?	1	2	2	2	2	2	2	1	2	2
2. Study design evident and appropriate?	1	2	2	2	2	0	2	2	2	2
3. Method of subject/ comparison group selection or source of information/ input variables described and appropriate	1	1	1	1	1	1	1	1	2	1
4. Subject (and comparison group) characteristics sufficiently described?	2	2	2	2	2	0	1	2	2	2
5. If interventional and random allocation was possible, was it described?	NA	1	NA	NA	1	NA	NA	NA	NA	2
6. If interventional and blinding of investigators was possible, was it reported?	NA	2	NA	NA	2	NA	NA	NA	NA	2
7. If it was interventional and blinding subjects was possible, was it reported?	NA	2	NA	NA	2	NA	NA	NA	NA	2
8. Outcome and exposure measure(s) are well defined and robust to measurement/ misclasification bias? Means of assessment reported?	1	2	1	2	2	2	1	1	2	1
9. Sample size appropriate?	1	2	1	2	1	1	1	1	1	2
10. Analytic methods described/justified and appropriate?	1	2	2	2	2	2	2	1	2	2
11. Some estimate variance is reported for the main results?	0	2	1	2	1	1	2	2	0	2
12. Controlled for confounding?	2	2	1	1	2	1	1	1	2	2
13. Results reported in sufficient detail?	1	2	2	2	2	1	2	1	2	2

14. Conclusions supported by the results?	1	2	2	2	1	1	1	2	2	2
Summary score	0.55	0.93	0.77	0.91	0.82	0.55	0.73	0.68	0.86	0.93

Notes. Scoring: 2 (Yes), 1 (Partial), 0 (No) and NA (Not applicable).

Summary score = Total sum ((Number of 'Yes'*2) + (Number of 'Partial'*1))/**Total possible sum** (Number of 'NA'*2).
Grouping: Strong (score of ≥0.80), good, (0.71–0.79), adequate (0.50–0.70) and poor (<0.50).

Appendix 5: PACE participant information leaflets

Patient Information Sheet

A large-print version of this sheet is available on request.

Invitation to take part in a research study

We would like you to take part in a research study. To help you to decide if you would like to take part, we have written this information sheet. It should explain why the research is being done, what you will be asked to do, and why we would like you to take part. Please take your time to read the information. You can talk with your friends or family about it if you like.

What is this study about?

We are trying to find out how the new service you have been invited to or just visited has helped improve your overall health and wellbeing; compared to how you have been cared for until now. Your answers will help in the improvement of this service.

Why have I been invited to take part?

We would like you to take part in this study because you have recently been invited to attend an appointment at the new service at the Jean Bishop integrated care centre or at you care home by your GP. Your GP has identified you as being eligible for this study.

What will happen if I take part?

If you take part in the study, you will be asked to sign a consent form. You will be asked to complete a short questionnaire at the first meeting either at the Jean Bean Integrated Centre or at the care home you live in. Someone from the research team will help you fill in the questionnaire. If you are unable to complete the questionnaire at the first meeting, another date and time convenient for you will be set. It will take you about 45minutes to complete the questionnaire. Someone from the research team will contact you to ask if you are happy to complete a shorter version of the questionnaire in 2-4 weeks and in 10-14weeks time.

We would like you to answer the questions as honestly as you can and there are no right or wrong answers. You will be asked if you would like to nominate a family member or carer to help fill in the questionnaire for you. There is a separate consent form (consultee form) to be completed by the nominated person, please ask for a copy of this.

What else will happen if I take part?

Some people taking part will be asked if they would like to take part in an interview with a researcher if they are affected by any of the following; chronic breathlessness, unintentional weight loss or use of medicine for pain and possible side effects. The interview can be held on the same day you complete the questionnaire or at a different time and place if it is easier for you.

If you take part, a member of the research team will do the interview and it will last around 45 minutes. Each topic will have a slightly different focus but will involve questions around your experience of one of topics listed above. It will also involve your opinion on caring experience, management of care, communication with health professionals, information and support needs, and the impact or potential concerns around these issues.

Do I have to take part?

No. It is up to you to decide if you would like to take part. If you decide not to take part, this will be noted and you will not be asked again. You will also continue to receive care and support from your GP practice or any health professional as usual. If you were to take part, you can still change your mind and stop taking part at any time without giving any reason.

What are the possible benefits of taking part in the study?

It is unlikely that there will be any direct personal benefit for you taking part. However, the information that you will give us will help decide if your overall health and wellbeing has improved by using this new service and give us ways to improve this service in the future.

Are there potential risks of taking part?

There is no significant risk in taking part, other than the time the study will take. However if you have any worries, you can talk about them with the research team or your GP. We would like to stress that taking part is up to you and you can stop taking part at any time without reason.

Will my involvement be confidential?

Yes. All the information we collect will be kept confidential, to fit with the General Data Protection Regulation (GDPR) 2018. The University of Hull is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Hull will keep identifiable information about you for 10 years after the study has finished.

Your rights to access change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your information at https://www.hyms.ac.uk/research/research-centres-and-groups/wolfson/pace or by contacting PACE@hyms.ac.uk.

The GP Practice will collect information from you and your medical records for this research study in accordance with our instructions.

The GP practice will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Hull and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Your GP Practice will pass these details to University of Hull along with the information collected from you and your medical records. The only people in the University of Hull who will have access to information that identifies you will be people who need to contact you to collect data/information or audit the data collection process. The people who analyse the

information will not be able to identify you and will not be able to find out your name, NHS number or contact details.
The research team from the University of Hull will keep identifiable information about you from this study for 10 years after the study has finished.

Expenses

You will be provided with prepaid envelopes, if needed, to return any documents to the research team. There will be no other costs to you.

What will happen to the results of the research study?

The results from this study will be written as a report for the NHS Hull clinical commissioning group (NHS Hull CCG). The results will be written up into journals, presented at conferences and public engagement events. If you would like to receive a summary of the study result, please inform someone from the research team. All personal details will be anonymised in all publications and public documents.

If I find it necessary to make a complaint, who should I contact?

If you have any concerns, questions or complaints about this research, you can contact Dr Maureen Twiddy (01482 463279, 8am to 5pm weekdays) or email Maureen.Twiddy@hyms.ac.uk Dr Twiddy is based at University of Hull but is independent of the research team.

How can I get involved in the study?

Thanks you for taking the time to read this information sheet. **If you would like to know more, please contact the research team using the details below:**

Dr Mabel Okoeki (Project Lead)

Telephone: (01482) 463728

Email: PACE@hyms.ac.uk

PACE
Proactive Anticipatory
Care Evaluation


Consultee information sheet

Proactive Anticipatory Care Evaluation
Information for Consultee

Introduction

We feel your relative/friend is unable to decide for himself/herself whether to participate in this research.

To help decide if he/she should join the study, we would like to ask your opinion whether or not they would want to be involved. We would ask you to consider what you know of their wishes and feelings, and to consider their interests. Please let us know of any advance decisions they may have made about participating in research. These should take precedence.

If you decide your relative/friend would have no objection to taking part, we will ask you to read and sign the consultee declaration that will be provided. We will then give you a copy to keep. We will keep you fully informed during the study, so you can let us know if you have any concerns or you think your relative/friend should discontinue the study.

If you decide that your relative/friend would not wish to take part, it will not affect the standard of care they receive in any way; just let us know.

If you are unsure about taking the role of consultee, you may seek independent advice.

We will understand if you do not want to take on this responsibility.

A participant information sheet, the same as would have been provided to your relative/friend, will be provided to you along with this information sheet.

Appendix 6: Consent forms

HULL YORK MEDICAL SCHOOL

PACE
Proactive Anticipatory Care Evaluation

NHS
Hull
Clinical Commissioning Group

Participant consent form

	Please initial each box
I confirm that I have read and understood the participant information sheet for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily.	☐
I understand that my participation is voluntary and I am free to withdraw at any time without giving reason, without my medical and legal rights being affected.	☐
I understand that responsible individuals may look at relevant sections of any data collected during this study from the research team, regulatory authorities or NHS Trust, were it is relevant to taking part in this research. I give permission for these individuals to have access to the data.	☐
I understand that by filling in and signing this form, I give permission for my GP records and hospital records to be accessed by the research team for the purpose of this study.	☐
I understand that my information may be subject to review by responsible individuals from the University for monitoring and audit purposes.	☐
I understand that my information may be subject to review by responsible individuals from the University for monitoring and audit purposes.	☐
I understand that the information collected about me may be published or will be used to support other research in the future, and may be shared anonymously with other researchers.	☐
I agree to take part in the above study.	☐

Name of participant (Print)	Date	Signature
Name of person taking consent (Print)	**Date**	**Signature**

PACE Informed consent Version 3 08/01/2019 IRAS ID: 250981

Study ID: _____

☐ Tick here if participant has given consent but is physically unable to sign and has requested a witness.

I witness that _____ has agreed to participate in this research study. I confirm that I have initialled the consent statement as per their wishes.

Name of witness (Print)	Date	Signature
Name of person taking consent (Print)	**Date**	**Signature**

Tick the appropriate box once completed

Participant's copy	☐
Research team/site file copy	☐
Medical record copy	☐

PACE
Proactive Anticipatory Care Evaluation

NHS Hull Clinical Commissioning Group

Consultee declaration form

	Please initial each box
I _____ have been consulted about _____ participation in this research project. I have had the opportunity to ask questions about the study and understand what is involved.	☐
In my opinion he/she would have no objection to taking part in the above study.	☐
I understand that I can request that he/she is withdrawn from the study at any time, without giving any reason and without his/her care or legal rights being affected.	☐
I understand that by filling in and signing this form, I give permission for his/her GP records and hospital records to be accessed by the research team for the purpose of this study.	☐
I understand that relevant sections of his/her care record and data collected during the study may be looked at by responsible individuals from the University of Hull or from regulatory authorities, where it is relevant to their taking part in this research.	☐
I agree to their GP or other care professional being informed of their participation in the study.	☐
I agree to take part and advise on behalf of the potential participant in the above study.	☐

Name of consultee (Print)	Date	Signature

Relationship with participant: _____

Name of person taking consent (Print)	Date	Signature

Tick the appropriate box once completed

Consultee's copy	☐
Research team/site file copy	☐
Medical record copy	☐

Appendix 7: PACE cross-sectional survey

HULL YORK MEDICAL SCHOOL

NHS Hull Clinical Commissioning Group

PACE
Proactive Anticipatory Care Evaluation

Name _____
Date _____
Site ID: _____
Researcher ID: _____

The Information sheet will be read to you again to ensure you understand everything about the study and answer any questions you might have.

Your answers will be kept confidential and seen only by the research team

If you have any queries, please contact the study researcher

Dr Mabel Okoeki (Project Lead)

Telephone: (01482) 463728

Email: PACE@hyms.ac.uk

SECTION ONE

ABOUT YOUR WELLBEING (IPOS)

Q1. What have been your main health problems or concerns over the past week?

.....

.....

.....

Q2. Below is a list of symptoms, which you may or may not have experienced. For each symptom, please tick one box that best describes how it has affected you over the past week.

	Not at all	Slightly	Moderately	Severely	Over-whelmingly
Pain	0☐	1☐	2☐	3☐	4☐
Shortness of breath	0☐	1☐	2☐	3☐	4☐
Weakness or lack of energy	0☐	1☐	2☐	3☐	4☐
Nausea (feeling like you are going to be sick)	0☐	1☐	2☐	3☐	4☐
Vomiting (being sick)	0☐	1☐	2☐	3☐	4☐
Poor appetite	0☐	1☐	2☐	3☐	4☐
Constipation	0☐	1☐	2☐	3☐	4☐
Sore or dry mouth	0☐	1☐	2☐	3☐	4☐
Drowsiness	0☐	1☐	2☐	3☐	4☐
Poor mobility	0☐	1☐	2☐	3☐	4☐
Please list any other symptoms not mentioned above, and tick one box to show how they have affected you over the past week.					
_____	0☐	1☐	2☐	3☐	4☐
_____	0☐	1☐	2☐	3☐	4☐
_____	0☐	1☐	2☐	3☐	4☐

Over the past week:

	Not at all	*Occasionally*	*Sometimes*	*Most of the time*	*Always*
Q3. Have you been feeling anxious or worried about your illness or treatment?	0☐	1☐	2☐	3☐	4☐
Q4. Have any of your family or friends been anxious or worried about you?	0☐	1☐	2☐	3☐	4☐
Q5. Have you been feeling depressed?	0☐	1☐	2☐	3☐	4☐
	Always	*Most of the time*	*Sometimes*	*Ocassionally*	*Not at all*
Q6. Have you felt settled or comfortable?	0☐	1☐	2☐	3☐	4☐
Q7. Have you been able to share how you are feeling with your family or friends as much as you wanted?	0☐	1☐	2☐	3☐	4☐
Q8. Have you been given as much information as you needed?	0☐	1☐	2☐	3☐	4☐
	Problems addressed/ No problems	*Problems mostly addressed*	*Problems partly addressed*	*Problems hardly addressed*	*Problems not addressed*
Q9. Have any practical problems resulting from your illness been addressed? (such as financial or personal)	0☐	1☐	2☐	3☐	4☐
	On my own	*With help from a friend or relative*			*With help from a member of staff/researcher*
Q10. How did you complete this questionnaire?	☐		☐		☐

SECTION TWO HEALTH QUESTIONNAIRE (EQ-5D-5L)	
Under each heading, please tick the ONE box that best describe your health TODAY	
MOBILITY	
I have no problems in walking about	☐
I have slight problems in walking about	☐
I have moderate problems in walking about	☐
I have severe problems in walking about	☐
I am unable to walk about	☐
SELF-CARE	
I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*	
I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐

PAIN / DISCOMFORT	
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐
ANXIETY / DEPRESSION	
I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

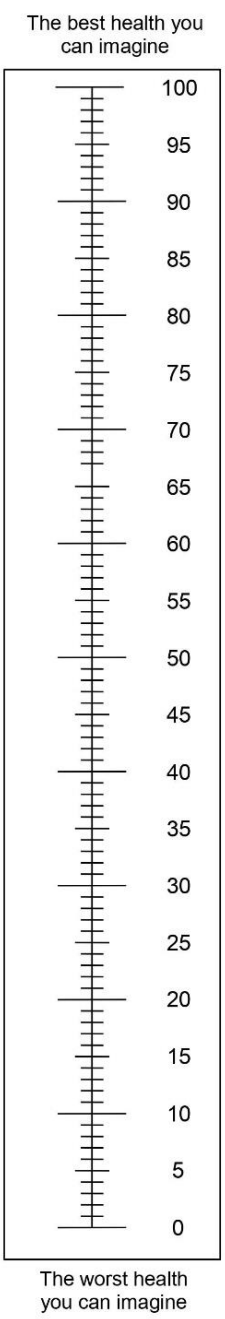
100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



SECTION THREE

SYMPTOMS SURVEY

We will like to ask you some health questions that will help us to better understand chronic breathlessness, unintentional weight loss or use of medicines for pain management, whichever is relevant.

Please tick the boxes and provide answers where appropriate to questions that are applicable to you.

Now some questions about your health:

Over the past 12 months, have you been prescribed any medications to manage pain?	Yes	☐	No	☐	Not sure	☐
Have you suffered with breathlessness for most days in the last month?	Yes	☐			No	☐
Have you lost some weight, without trying, in the last 12 months	Yes	☐	No	☐	Not sure	☐

If you have experience of using medicines to manage pain, please turn to page 9.

If you have experience of chronic breathlessness please turn to page 11

If you have experience of unintentional weight loss, please turn to page 13.

<u>If you answered No to all the answers above, please go to page 14.</u>

SECTION A

USING MEDICINES TO MANAGE PAIN

Please answer only if you have been prescribed medicines to manage pain in the last twelve months.

If you have not, please go to page 11 Section B

1) Over the last 12 months, how has your pain been?

No pain at all	A little pain	Moderate pain	Severe pain	Overwhelming pain
☐	☐	☐	☐	☐

2) How long have you been affected by pain?

_____

3) What medications are you currently taking to manage your pain?

_____

_____

_____

4) Have you talked to your GP or another health professional about your pain?

Yes	No
☐	☐

5) Please could you tell me a bit more about your answer above? (e.g., who did you talk to? What happened from this discussion? If you answered no, please go to question 6)

_____

_____

6) Do you feel that you had the opportunity to talk about using pain medications with your general practitioner or another health professional?

Yes	No
☐	☐

7) Did you have any initial concerns about taking the pain medications you were prescribed?

Yes	No
☐	☐

8) If yes, what concerns did you have?

_____

_____

_____

9) Have your pain medicines caused you any problems (i.e. side effects)?

Yes	No
☐	☐

10) If so, what problems have they caused?

_____

_____

_____

11) Have your painkillers caused you any problems with the following? *Please tick all that apply*

	Yes	No		Yes	No
Nausea (feeling sick)	☐	☐	Drowsiness/sleepiness	☐	☐
Vomiting (being sick)	☐	☐	Constipation	☐	☐
Memory	☐	☐	Fitting	☐	☐
Confusion	☐	☐	Falls	☐	☐
Attention/concentration	☐	☐	Headaches	☐	☐
Seeing or hearing things that are not	☐	☐	Other	☐	☐

If other, please state: _____

12) Do you take/use pain medicines in the way the health professional suggested? [If answered 'Yes' skip to question 14]

Yes	No
☐	☐

13) If no, please explain more.

_____

_____

_____

_____

14) If you have made changes to taking your pain medications, did you discuss this with your GP or health professional?

Yes	No
☐	☐

15) How often are your pain and pain medications reviewed?

_____

SECTION B

BREATHLESSNESS

Please answer only if you have suffered with breathlessness for most days in the last month

(if you have none, go to page 13 section C)

1) On average over the **past month**, how would you describe his/her breathlessness? (Please tick **one** that best describes your breathlessness).

I am not troubled by breathlessness except on strenuous exercise ☐

I am breathless when hurrying on the level, or walking up a slight hill ☐

I walk slower than most people on the level, or stop after a mile or so, or stop after 15 minutes at my own pace, ☐

I stop for breath after walking about 100 yards or after a few minutes on level ground ☐

I am too breathless to leave the house, or I am breathless undressing ☐

2) How long have you experienced breathlessness?

less than 6 months ☐ between 6 months and 1 year ☐ Over 1 year ☐

3) Does your breathlessness affect your normal day-to-day activities?

Never	Rarely	Sometimes	Often	Very Often	Always
☐	☐	☐	☐	☐	☐

4) Do you feel anxious or depressed **because of your breathlessness**?

Never	Rarely	Sometimes	Often	Very Often	Always
☐	☐	☐	☐	☐	☐

5) Have you had to give up or change any of the following **because of your breathlessness**?

Please specify where appropriate.

☐ Hobbies _____

☐ Exercise _____

☐ Family Roles e.g. looking after family members_____

☐ Social Roles e.g. meeting friends_____

☐ Work/Volunteer Roles _____

☐ Sexual Activity _____

☐ I have not had to give up or change anything

6) Who do you normally talk to **about your breathlessness**?

General practitioner (GP)	☐	Heart Failure nurse	☐
Practice Nurse	☐	Macmillan nurse	☐
Healthcare Assistant	☐	Long term conditions nurse	☐
Respiratory specialist doctor	☐	Family/friends	☐
Respiratory nurse	☐	No-one	☐
Heart Failure specialist doctor	☐	Other (please specify)	_____

7) Roughly, how often do you see a GP, nurse, or other health professional from your GP surgery **about your breathlessness?**

Every week	Every month	Every three months	Every six months	Yearly	Other (please specify)
☐	☐	☐	☐	☐	_____

8) Does your GP, nurse, or other health professional from your GP surgery ask you about how breathlessness **affects your daily life?**

Yes	☐	No	☐	Not sure	☐

9) What treatments **for your breathlessness** have been organized by your GP, nurse, or other health professional from your GP surgery **in addition to your usual treatment (e.g. inhalers or heart tablets)?** (tick all that apply)

Pulmonary Rehabilitation	☐	Psychological Treatments	☐
Breathing Exercise Techniques	☐	Morphine-like medicines	☐
Handheld Fan	☐	Oxygen	☐
Anxiety Treatment	☐	Other (please specify)	_____

10) **Do you have any of the following conditions?**

COPD (also called emphysema or chronic bronchitis)	☐	Other cancer	☐
Heart disease	☐	Asthma	☐
Lung Cancer	☐	Other (please specify)	_____

SECTION C

UNINTENTIONAL WEIGHT LOSS

Please answer if you have lost weight, without trying in the last 12 months

Appetite

1) Has how much you eat changed in the last 12 months?

Yes, I eat more ☐ No, it's the same ☐ Yes, I eat less ☐

2) My appetite is currently:

Very good ☐ Good ☐ Average ☐ Poor ☐ Very poor ☐

3) Currently, how does food taste to you?

Very good ☐ Good ☐ Average ☐ Bad ☐ Very bad ☐

Weight loss:

4) In the last 12 months, roughly how much weight do you think you have lost?

A few pounds ☐ Half a stone ☐ A stone ☐ Over a stone ☐ Not sure ☐

5) Are you worried about your weight loss?

Yes ☐ No ☐ Not sure ☐

6) Have you mentioned your weight loss to anyone?

A hospital Doctor	☐	Your spouse	☐
Your GP	☐	Family member or friend	☐
Practice nurse	☐	Other person	☐
Another nurse	☐	If other people, please specify	
Carer	☐	_____	

7) Did any of the above weigh you?

Yes ☐ No ☐ Can't remember ☐

8) Have any of the following offered you advice on how to gain weight?

A hospital Doctor	☐	Your spouse	☐
Your GP	☐	Family member or friend	☐
Practice nurse	☐	Other person?	☐

Another nurse	☐	Can't remember	☐
Carer	☐	If other person, please specify_____	

9) What advice/help were you given?

A change in your diet	☐	Can't remember	☐
A referral to your dietitian	☐	Other help?	☐
A new medicine prescribed for you	☐	If other help, please specify:_____	

Are you happy for us to contact you for a more detailed follow-up interview on your experience of any of the symptoms above?

Yes ☐ No ☐

Preferred Contact Detail

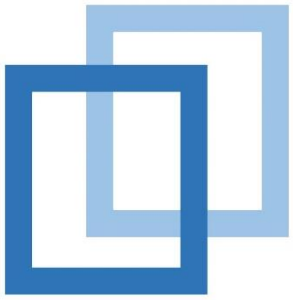
Telephone_____ **Mobile** _____

Date of Birth _____

Signature _____

Thank you for completing the questionnaire

Appendix 8: PACE data extraction form



PACE

Proactive Anticipatory Care Evaluation

Baseline data collection (Records)

(To be completed by the researcher team only)

Patient Name: _____

Date: _____

Site ID: _____

Researcher ID: _____

NB. Unless a value is needed, please tick the appropriate box				
Date of data collection	☐☐/☐☐/☐☐☐☐			
Has informed consent been taken?	Yes ☐		No ☐	
If yes, what type of consent:	Written ☐		Witnessed verbal observed ☐	
How was the patient invited to the study	**Intervention**		**Control**	
	ICC ☐	Care home ☐	GP ☐	Care home ☐
Has the patient nominated a carer to take part in the study (those lacking capacity)	Yes ☐	No ☐	N/A ☐	
Type of consultee	Personal ☐	Nominated ☐	N/A☐	

PATIENT DEMOGRAPHICS			
Date of birth	☐☐/☐☐/☐☐☐☐		
Gender	Female ☐	Male ☐	

ETHNICITY					
White	☐	Mixed/multiple ethnic groups	☐	Asian/Asian British	☐
Black African/Black Caribbean/ black British	☐	Other ethnic group	☐	Prefer not to say	☐
Not recorded	☐				

RELATIONSHIP/MARITAL STATUS

Single ☐ Married/civil partnership ☐ Separated ☐ Divorced ☐

Widowed ☐ Not recorded ☐

LIVING SITUATION

Spouse/partner ☐ Other family ☐ Alone ☐ Other_____

Post code	☐☐☐☐ ☐☐☐☐

Australia-Modified Karnofsky Performance Status (AKPS)	
AKPS Assessment Criteria (Scale 0 – 100%)	☐ %

MEDICAL DIAGNOSIS			
Co-morbidities		**Other**	
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			
CLINICAL INFORMATION			
Weight (last weight)	**KG**	**Date of collection**	
Height	**M**		
BMI	**KG/M^2**		
Smoking status	Yes ☐	No ☐	Ex-smoker ☐
ACTIVITY OF DAILY LIVING (BARTHEL 10)			
Total score:		**Date collected:**	

INTERVENTION DELIVERED COMPONENTS (Patient Summary)				
Patient concerns/Active diagnosis				
Problem	**Plan/action of intervention**	**Goal**	**Who is responsible**	**Additional comments**
Functional Assessment				
Problem	**Plan/action of intervention**	**Goal**	**Who is responsible**	**Additional comments**

MEDICATIONS				
Problem	**Plan/action of intervention**	**Goal**	**Who is responsible**	**Additional comments**
Medications to stop				
Medications to change				
Medications to add				

Named clinical care coordinator (Enter name of complex care manager)					
Named clinical care coordinator (If not complex case manager)					
GP	☐	**Social services**	☐	**Physiotherapist**	☐
Carer	☐	**Pharmacy technician**	☐	**Occupational therapist**	☐

RESPECT DISCUSSION (Preferred place of care)

Health Professional – Additional Information

Onward referrals (Please select the service you would like to be referred to)					
Anticoagulation	☐	Lymphedema	☐	Specialist nurse - Heart failure	☐
Bladder and bowel	☐	Memory clinic	☐	Specialist nurse – Home oxygen	☐
Community nurse	☐	Nutrition	☐	Specialist nurse – Pulmonary rehab	☐
Community rehab	☐	Pain management	☐	Specialist nurse - Respiratory	☐
Dental	☐	Palliative care	☐	Stop smoking	☐
DVT service	☐	Podiatry	☐	Stroke service	☐
Fall service	☐	Sexual health	☐	Trusted assessor	☐
Intermediate care	☐	Social services	☐	Other	
Let's talk	☐	Specialist nurse - Cardiac	☐		

ACUTE REFERRALS					
CT Scan	☐	Audiology	☐	Endoscopy	☐
Bone density	☐	ECG Monitoring	☐		

PATIENT HEALTH QUESTIONNAIRE (Pre-assessment questions) Would you say your physical health is						
Would you say your physical health is	Good	☐	Fair	☐	Poor	☐
Has your health got worse in the last 6 months	A lot worse	☐	A little worse	☐	A little better	☐
	A lot better	☐	Stay the same	☐		
If you have any change, can you describe?						
Did anything in particular happen to cause this change?						
Are you worried about your health at the moment	Yes	☐	No	☐		
Do you have a carer or someone who looks after you regularly?	Yes	☐	No	☐		
General:						
Approximately how many hours a day do you rely on a carer						
If you do not have a carer, do you feel like you need one?	Yes	☐	No	☐	N/A	☐
Have you had a fall in the last year?	Yes	☐	No	☐		
And did you need medical attention from the fall?	No	☐	A&E	☐		
	GP	☐	Hospital admission	☐		
Are you worried about falling?	Yes	☐	No	☐		
General						
Have you had a hospital stay in the last year?	Yes	☐	No	☐		
How many times were you admitted to hospital?						
Why were you admitted to hospital?						
Do you smoke?	Yes	☐	No	☐		
Do you drink alcohol?	Yes	☐	No	☐		

MEDICATION AND TREATMENT				
Do you take 5 different medications in a day?	Yes	☐	No	☐
How many medications do you take a day?				
COGNITION				
I have problems with memory, which affects my day to day life	Agree	☐	Disagree	☐
I find myself getting confused for no reason	Agree	☐	Disagree	☐
I sometimes worry and get upset over little thigs	Agree	☐	Disagree	☐
I have difficulties making decisions	Agree	☐	Disagree	☐
EMOTIONAL FUNCTION				
I often feel lonely	Agree	☐	Disagree	☐
I find myself tearful for no reason	Agree	☐	Disagree	☐
I feel fearful	Agree	☐	Disagree	☐
HOME LIFE				
My home is comfortable, warm and clean	Agree	☐	Disagree	☐
I am happy with where I live	Agree	☐	Disagree	☐
ADL and IADL				
My home is difficult for me to manage	Agree	☐	Disagree	☐
I need help to move about my home	Agree	☐	Disagree	☐
General				
I need help to get washed, dress and undress	Agree	☐	Disagree	☐
I can make and eat the meals I want, when I want	Agree	☐	Disagree	☐
I can do my own housework and laundry without any help	Agree	☐	Disagree	☐

I can use the toilet without anyone helping me	Agree	☐	Disagree	☐
I can go out and about and do the things I want to do	Agree	☐	Disagree	☐
I cannot use public transport without help	Agree	☐	Disagree	☐
I do not know if I am getting everything I am entitled to	Agree	☐	Disagree	☐
I need help sorting out money and benefits	Agree	☐	Disagree	☐
I worry about getting my affairs in order	Agree	☐	Disagree	☐
I know where to get help when I need it	Agree	☐	Disagree	☐
SOCIAL AND COMMUNITY				
I have family, friends and people around me	Agree	☐	Disagree	☐
I can look after those I need to care for	Agree	☐	Disagree	☐
I have people I can rely on for help	Agree	☐	Disagree	☐
I am content with the physical and sexual side of my life	Agree	☐	Disagree	☐
I have hobbies and interests that keep me busy	Agree	☐	Disagree	☐
I feel spiritually content	Agree	☐	Disagree	☐
I am happy with how I spend my days	Agree	☐	Disagree	☐
Do you have support from any voluntary organisations e.g. hospice, day centre or memory café	Yes	☐	No	☐
Are you currently receiving any social care input	Yes	☐	No	☐
What social care input are you receiving?				

STUDY COMPLETION						
Has the patient completed all the study questions?	Yes	☐		No	☐	
If no, please state reason (and complete study withdrawal form, if appropriate)	Study withdrawal	☐		Lost to follow up	☐	
	Alive or deceased	Alive	☐			
		Deceased	☐			
Date of withdrawal	☐☐/☐☐/☐☐☐☐					
If died, please state actual place of death:						
Hospital	☐	Care home	☐	Home/personal residence	☐	
Hospice	☐	Other				
Date of death	☐☐/☐☐/☐☐☐☐					
FEEDACK						
Would you like to receive a summary of the study results:	Yes	☐		No	☐	
Name:						
Preferred method of contact	Telephone	☐		Email	☐	
	Post	☐		Other		
Telephone						
Email						
Address						
Best time to contact you	Morning ☐		Afternoon ☐		Evening ☐	
Form completed by (name)						
Signature						
Date	☐☐/☐☐/☐☐☐☐					
END						

Appendix 7: Thesis data extraction form

HULL YORK MEDICAL SCHOOL | PACE Proactive Anticipatory Care Evaluation | NHS Hull Clinical Commissioning Group

ID No.		Site ID		Date recruited		Extraction date	

Opioid use over the last 12 months (To be completed for all study participants)				
PRE-ASSESSMENT/SELF-REPORT	Yes ☐	No ☐	Unsure ☐	Not recorded ☐
Name opioids				
SYSTEM ONE (Opioids prescribed in last 12 months)	Yes ☐	No ☐	Unsure ☐	Not recorded ☐
Name opioids				

PRE-ASESSMENT	Date collected:		
Medications and treatment			**Additional information**
Do you take more than five different medications a day?	Yes ☐	No ☐	If yes, how many?
Do you have problems getting your medication?	Yes ☐	No ☐	
Do you have problems with remembering to take your medications?	Yes ☐	No ☐	
Do you have problems with swallowing your medications?	Yes ☐	No ☐	
Do you have any problems with side effects from your medications?	Yes ☐	No ☐	
Do you have any concerns about your medications?	Yes ☐	No ☐	

Pain medication deprescribing recommendations (Interventions)		Date of review:
	Problem and plan	**Reasons for change**
START		
STOP		
CHANGE		
OTHER (Repeats/ Advice)		

Other concurrent medications (Template/recent repeat prescriptions)								
No.	**Name**	**Dose**	**No.**	**Name**	**Dose**	**No.**	**Name**	**Dose**
1			**5**			**9**		
2			**6**			**10**		
3			**7**			**11**		
4			**8**			**12**		

Cognitive Assessment (Tabbed journal)		Date assessed:		
No cognitive problems	☐	Other comments regarding cognition:		
Unclear if cognitive problems	☐			
Evidence of cognitive problems	☐			
6 Item Cognitive Impairment Test (if available)			Not present?	☐
0 – 7 = Normal, 8 – 9 = MCI, 10 – 28 = Significant cognitive impairment			Total Score	

Anticholinergic burden (Tabbed journal)	Date assessed:
Score:	

Opioid use over the last 12 months (Tabbed journal)					
Date of prescription	Name	Route	Dose (Units and frequency)	Quantity given	Reason for prescription (If available)

Date of prescription	Name	Route	Dose (Units and frequency)	Quantity given	Reason for prescription (If available)

Date of prescription	Name	Route	Dose (Units and frequency)	Quantity given	Reason for prescription (If available)
Chronic pain present? If so, note below					Not present? ☐
Rockwood CFS			eFI Score		
Other information					

Appendix 8: List of opioid search terms

Opioid reference list				
Route of administration	**Generic name**		**Common brand names**	**Other possible brand names**
Oral	Buprenorphine		Espranor, SL (Suboxone), Prefibin, Subutex, Temgesic, Tephine	
	Codeine		Co-codamol and Zapain	Kapake, Solpadol and Tylex
	Diamorphine		None listed	None listed
	Dihydrocodeine Tartrate	IR	DF1 18 Forte and Co-dydramol	
		MR	DHC Continus	
	Fentanyl		Abstral, Actiq and Effentora	Recivit
	Hydromorphone	IR	Palladone	
		MR	Palladone SR	
	Meptazinol		Meptazinol and Meptid	
	Methadone		None listed	None listed
	Morphine	IR	Morphine sulphate, Oramorph and Sevredol	
		MR	Morphgesic, MS Contin, MST Continus and Zomorph	Filnarine and MXL
	Oxycodone	IR	Oxynorm, Shortec	
		MR	Longtec, Oxycontin	Abtard, Carexil, Ixyldone, Leveraxo, Oxeltra, Onexila XL, Oxypro, Oxylan, Reltebon, Renocontin, Zomestine
	Tapentadol	IR	Palexia	
		MR	Palexia SR	
	Tramadol	IR	Tramal, Tramacet (with paracetamol)	
		MR	Maxitram, Tilodol, Tradorec, Tramquel, Tramulief, Zamadol, Zeridame and Zydol	Invodol, Mabron, Maneo, Marol and Oldaram
Transdermal patch	Buprenorphine		Butec, BuTrans, Prenotix, Reletrans, Sevodyne and Transtec	Bupeaze, Buplast, Bupramyl, Hapoctasin andRelevtec,
	Fentanyl		Durogesic DTrans, Matrifen, Fentalis Reservoir, Tilofyl	Fencino, Mezolar Matrix, Mylafent, Opiodur, Osmanil, Victanyl and Yemex.

Appendix 9: Considerations for logistic regression analyses

Two logistic regression analyses were undertaken:

1. Factors associated the presence of any cognitive adverse effects attributed to pain medications prescribed at some point over the past year.
2. Factors associated with the presence of an opioid prescription at some point over the past year.

There are a number of candidate predictors that could be selected from the data collected. However, the careful selection of predictor variables based on subject knowledge, without studying the predictor-outcome relationship in the data under study, is recommended.[466] Therefore, the literature was reviewed and the clinical relevance of variables was also considered. Candidate predictors that were similar in nature were compared and excluded as appropriate.[519] The variables considered for each logistic regression are discussed in the respective sections below.

Predictors of the presence of any cognitive adverse effects attributed to pain medications prescribed at some point over the past year

Selection of candidate predictors

As outlined in Section 7.4.4.5, the number of candidate predictors was limited to increase robustness and the validity of the model as the sample size was small and there was a low percentage of participants with the outcome. In reviewing the literature, studies used a variety of different predictors to construct their models, which fell into the following broad categories: patient demographics, neighbourhood deprivation, disease-related characteristics (such as cancer), pain characteristics, pharmacologic pain treatment, other medications, frailty and functional ability (see Table 1 Summary of models and candidate predictors presented in literature). These studies adopted varying measures of cognitive function (i.e. outcome variable); this was kept in mind when selecting candidate predictors for this logistic regression.

Table 1 Summary of models and candidate predictors presented in literature

Author (Year)	Study type	Outcome variable	Modelling method	Data		Study population	Candidate predictors
				Source	Years		
Campbell et al. (2016)	Retrospective cohort	Cognitive impairment	LogR	EH	2001 - 2004	- Older adults aged ≥65 - Minimum of one primary care provider visit in the year prior to enrolment - Minimum of one prescription in the year prior to enrolment - Minimum of one inpatient, outpatient or ED visit within 12 months post enrolment	Age, gender, ethnicity, number of chronic conditions and daily mean total daily ACB score
Khezrian et al. (2019)	Retrospective cohort	Triad of Impairment; cognitive, pshyical & emotional function	MRM	ABC1936	1999 - 2004	- Older adults free from dementia - Aged 63 - 68 years of age when recruited into wave one - Complete neuropsychological, physical examination and SF36 health survey data	Age, gender, BMI, comorbidity score, childhood IQ, education and polypharmacy

Kurita et al. (2011)	Prospective cross-sectional	Cognitive dysfunction using MMSE score; grouped by definite (<24), possible (24 – 26) and none (>26)	OLR with CL	EPOS	2005 - 2008	- Adults aged ≥18 - Verified malignant disease - Regularly scheduled opioids for moderate to severe cancer pain for at least 3 days	Age, gender, cancer diagnosis, localisation of metastases, time since diagnosis, KPS, RESS, BTP, BPI, total daily opioid equivalent dose, duration of opioid treatment, other medications relevant for cognitive function
Lang et al. (2008)	Retrospective cross-sectional	Cognitive function (assessed by neuropsychological tests)	OLQR	ELSA	2002 - 2004	- Older adults age ≥50 - Complete socioeconomic status data and cognitive function tests	Age, gender, smoking, alcohol consumption, diabetes diagnosis, vascular problems, visual problems, self-reported hearing loss, depressive symptoms, individual wealth, income, educational level and IMD quintile
Levine et al. (2021)	Pooled data from 5 prospective cohort studies	Changes in dependent variables: global cognition, executive function and memory	LMM	ARIC, CARDIA, CHS, FOS and NOMAS	1971 - 2017	- No history of dementia or stroke at each cohort's baseline - No incidence of dementia or stroke before first cognitive assessment - Participants who reported race other than Black or White were excluded, as	Age, gender, ethnicity, cohort, years of school, alcohol use, cigarette smoking, BMI, waist circumference, physical activity, time-varying cumulative mean systolic BP, hypertension treatment, fasting glucose,

						too few participants to assess. - One or more assessments of cognition and BP (at or before first measurement of cognition)	LDL, cholesterol, history of atrial fibrillation, age × follow-up time, gender × follow-up time, ethnicity × follow-uptime, time-varying cumulative mean systolic BP × follow-up time and hypertension treatment × follow-up time.
Neelamegam et a. (2021)	Prospective study	Change in cognitive function using a series of neuropsychological tests	GLMs (Unadjusted, partially adjusted and fully adjusted)	PATH Through Life Study and PBS	2005/2006 – 2009/2010	- Older adults aged ≥60 from Wave 2 and 3	Age, gender, years of education, smoking status, alcohol consumption, physical activity, stroke, diabetes, family history of dementia, depression, hypertension status, BMI and APOE-ε4.
Rouch et al. (2021)	Prospective study	Cognitive performance; general cognition (MMSE), verbal/visual memory (WPT+BT), attention/speed processing (WDSST+ZCT) & language skills/	LPMM	PAQUID	1991 - 2003	- Community-dwelling older adults aged ≥65 - Received a pain assessment	Age, gender, education, comorbidities, depression and analgesic drugs.

		executive function (IST)					
Siddiqui et al. (2020)	Prospective study	Cognitive function (assessed by Cognistat)	LR	MMDAE	2017 - 2018	- Inpatients from the somatic general university hospital departments - Older adults aged between 65 and 90 years of age with and without central nervous system depressants (including opioids)	Age (at baseline), gender, education, CIRS-G total score and HADS
Soysal et al. (2019)	Retrospective naturalistic cohort	Cognitive decline; using MMSE scores	PLM	SLaM CRIS	2007 - 2016	- First received a dementia diagnosis (according to ICD-10 criteria) between 2007 and 2016.	Age, gender, ethnicity, marital status, deprivation score, dementia subtype, HoNOS65+ symptoms scores, HoNOS65+ functional problem scores, hospitalisation prior to dementia diagnosis, and AChEI prescription.
van der Leeuw et al. (2018)	Prospective study	Cognitive impairment (measured by a repeatable battery for assessing neurological status	CR	CCMA	2011 - 2017	- Community-dwelling older adults aged ≥65 - Residents of lower Westchester Country (New York)	Age, gender, education and cognitive impairment.

		and trail making test)					

Abbreviations: ABC1936 Aberdeen 1936 Birth Cohort, *ACB* Anticholinergic Cognitive Burden, *AChEI* acetylcholinesterase inhibitor, *APOE- ε4* Apolipoprotein E epsilon 4, *ARIC* Atherosclerosis Risk in Communities Study, *BMI* Body Mass Index, *BP* Blood Pressure, *BPI* Brief Pain Inventory (i.e. Pain intensity right now), *BT* Benton Test, *BTP* Breakthrough Pain, *CARDIA* Coronary Artery Risk Development in Young Adults Study, *CCMA* Central Control of Mobility in Aging study, *CHS* Cardiovascular Health Study, *CIRS-G* Cumulative Illness Rating Score – Geriatrics, *CL* Cumulative Logits, *CR* Cox Regression, *CRIS* Clinical Record Interactive Search application, *ED* Emergency Department, *EPOS* European Pharmacogenetic Opioid Study, *EH* Eskenazi Health (Safety-net health care system in US), *ELSA* English Longitudinal Study of Ageing, *FOS* Framingham Offspring Study, *GLMs* General Linear Models, *HADS* Hospital Anxiety and Depression Scale, *HoNOS65+* Health of the Nation Outcome Scales, *ICD* International Classification of Diseases, *IMD* Index of Multiple Deprivation (Neighbourhood), *IQ* Intelligence Quotient, *IST* Isaacs Set Test, *KPS* Karnofsky Performance Status, LDL Low-density Lipoprotein, *LLM* Linear Mixed-effects Model, LPMM Latent Process Mixed Models, *LR* Linear Regression, *LogR* Logistic Regression, *MMDAE* Medication Misuse & Dependence Among Elderly, *MMSE* Mini-mental State Exam, *MRM* Multiple Regression Models, *NOMAS* Northern Manhattan Study, *OLR* Ordinal Logistic Regression (Proportional Odds Model), *OLSR* Ordinary Least Squares Regression, *PAQUID* Personne Agée QUID, *PLM* Piecewise Linear Mixed model, *RESS* Revised Edmonton Staging System (i.e Pain mechanisms), *SF36* Short-Form-36, *SLaM* South London and Maudsley NHS Foundation Trust, *WDSST* Wechsler Digit Symbol Substitution Test, *WPT* Word Paired-associate Test and *ZCT* Zazzo's Cancellation Task.

A number of factors were significantly associated with increased odds of cognitive dysfunction within the authors' respective studies. These included older age, gender, daily opioid doses of 400 milligrams or more, cumulative opioid exposure, low Australia-modified Karnofsky Performance Scale (AKPS) scores, increasing anticholinergic burden score, chronic pain, comorbidity, lung cancer diagnosis, time since cancer diagnosis (<15 months) and living in a neighbourhood with high levels of deprivation.[183,210,297,520,521] Additionally, a systemic review and meta-analysis demonstrated that baseline frailty was significantly associated with increased risk of geriatric cognitive disorders.[208] One study demonstrated that polypharmacy was associated with increased odds of impairment with cognition, and physical and emotional factors in older adults.[209] However, another study found that polypharmacy (as defined by the number of medicines) did not appear to predict a decline in cognitive function in a naturalistic cohort of patients with dementia.[522] The role of gender in cognitive function was also unclear.[297,523] Additionally, patients with breakthrough pain had significantly lower odds of cognitive dysfunction than those without breakthrough pain.[297]

From the approaches and predictors adopted by these studies, it was deemed important to adjust for demographic variables by including age and gender in the model. Additionally, in line with the aim and objectives of this thesis, daily dose in oral morphine equivalents was also included (using the average daily dose over the past year). In terms of medication and related burden, there were three variables that could have been adopted as candidate predictors (anticholinergic burden score, number of medications and polypharmacy). As these variables were similar in nature, it was decided that only one would be included to avoid potential issues around multicollinearity. When considering these variables and the literature, anticholinergic burden score was included in the model as indicative of risk of cognitive issues arising from medication. Polypharmacy and number of medications were not as indicative of risk, and are dependent on the types of medications prescribed. Pain, frailty and functional status, although important, were not included in the final model due to the small sample size. The focus, therefore, remained on opioid analgesics and medication related burden. Comorbidities and certain diagnoses were also considered, as highlighted by the literature. However, on reflection of the descriptive statistics (see

Table 2), it was decided that these predictors would not be included in the model. Given the small sample size, it was important to focus on the most important predictors. As using routine data, the sample size could not be increased, and therefore, there was a limit on the maximum number of predictors that could be included in the logistic regression equation. Additionally, these data were collected for descriptive purposes and were not based on more robust approaches (such as the International Classification of Diseases or the Charlson Index of comorbidities). Neighbourhood deprivation as measured by the Index of Multiple Deprivation quintiles was also not included, despite being measured, to circumvent potential issues with including an area-based measure in a model that largely incorporates individual-level variables. These quintiles are given to people based on their catchment area, rather than based on individual characteristics.

Table 2 Descriptives for all predictor variables considered

Independent variables	**Pain medication at some point over the past year (n=155)**	**Cognitive adverse effect**	
		Yes (n=48)	**No (n= 107)**
	Column %	*Column %*	*Column %*
Age			
Median (IQR)	81 (74 – 85)	80 (72 – 84.8)	81 (76 – 86)
Mean (SD)	79.8 (7.3)	78.3 (7.3)	80.5 (7.2)
Missing	0	0	0
Gender			
Female	99 (63.9)	37 (77.1)	62 (57.9)
Male	56 (36.1)	11 (22.9)	45 (42.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Average daily dose over the past year			
Median (IQR)	1.8 (0.0 – 16.4)	2.1 (0.3 – 18.3)	1.8 (0 – 16.2)
Mean (SD)	15.4 (35.2)	19.2 (45.2)	13.6 (29.2)
Missing	12	1	11
Anticholinergic burden			
Two or less	99 (63.9)	30 (62.5)	69 (64.5)
Three or more	50 (32.3)	18 (37.5)	32 (29.9)
Missing	6 (3.9)	0 (0.0)	6 (5.6)
Frailty (Rockwood CFS)			
Median (IQR)	5 (5 - 6)	5 (5 – 6)	5 (4 – 6)
Mean (SD)	5.1 (1.0)	5.1 (1.1)	5.1 (1.0)
Missing	5 (3.2)	3 (6.3)	2 (1.9)
Functional status (AKPS)			
Median (IQR)	60 (60 – 80)	60 (50 – 70)	70 (60 – 80)
Mean (SD)	66.1 (11.8)	64.8 (12.5)	66.7 (11.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Pain (IPOS)			

Median (IQR)	2 (2 – 3)	2 (2 – 3)	2 (2 – 3)
Mean (SD)	2.2 (1.0)	2.4 (0.9)	2.2 (1.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Number of comorbid groups			
Median (IQR)	4 (3 – 5)	4 (3 – 5)	4 (3 – 6)
Mean (SD)	4.4 (1.6)	4.2 (1.4)	4.5 (1.6)
Missing	0	0	0
Deprivation (IMD)			
IMD 1 (Most deprived)	67 (43.2)	14 (29.2)	53 (49.5)
IMD 2	35 (22.6)	12 (25.0)	23 (21.5)
IMD 3	19 (12.3)	7 (14.6)	12 (11.2)
IMD 4	15 (9.7)	7 (14.6)	8 (7.5)
IMD 5 (Least deprived)	14 (9.0)	6 (12.5)	8 (7.5)
Missing	5 (3.2)	2 (4.2)	3 (2.8)

Model diagnostics

A boxplot of the standardised residuals was used to test for normality and equal variance, as well as identification of outliers.[524] In boxplots, a normal distribution is demonstrated by a symmetrical box and whiskers, with the median sitting within the middle of the box. In Figure 1, the boxplot indicates that there is a slight asymmetric curve; as the 'Yes' group has a slightly larger upper whisker and the median is not in the exact centre of the box. This is similar for, but less pronounced in, the 'No' group; where the lower whisker is slightly larger. It is also important to consider potential outliers (i.e. values that are out of typical range), as they may have a large influence on the regression model.[466] Extreme outliers are defined as any observation that is at least three times the interquartile range above the third quartile or at least three times the interquartile range below the first quartile.[466] The whiskers of the boxplots do not exceed three or minus three, which means that there are no extreme outliers.

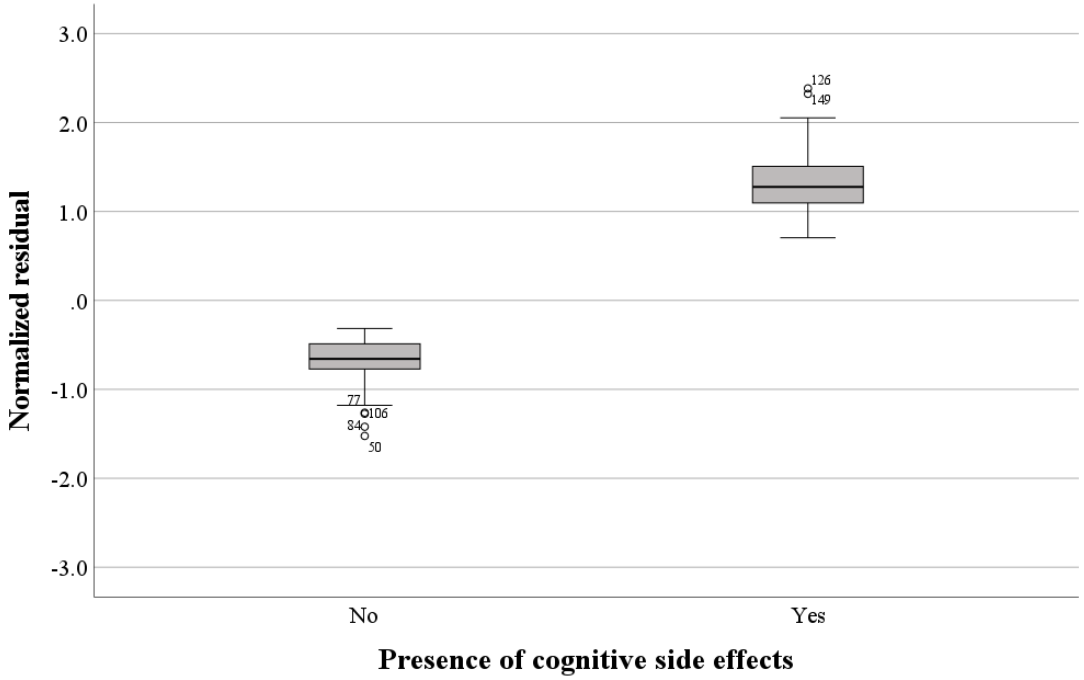


Figure 1 Boxplot of the standardised residuals by presence of cognitive adverse effects

In analysis of the residuals, heteroscedasticity was also considered. Deviance residuals were plotted against predicted probability (see Figure 2) to identify cases where the model fits poorly or cases that may exert an overtly large influence on the estimates for the model's parameters.[525] If the model fits well, it is expected that most of the values with fall within a horizontal band between -2 and +2, and form two parallel lines.[525,526] Any standardised residuals outside of ±2 may be considered as potential outliers and warrant some concern. One participant was identified as a potential outlier.

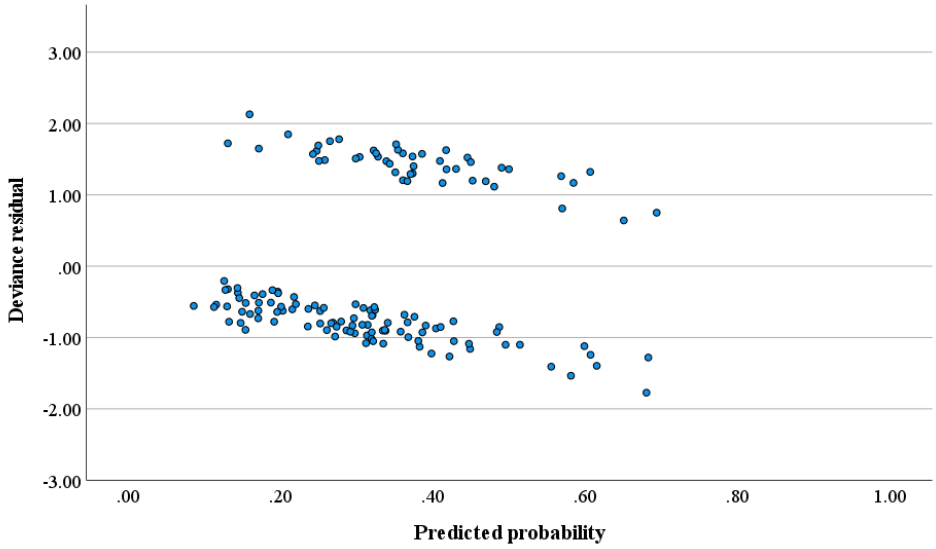


Figure 2 Raw and deviance residuals by predicted probabilities

As the model diagnostics (i.e. assessment of heteroscedasticity) indicated there is a potential outlier, a sensitivity analysis was conducted to determine its effect on the model by removing the outlier and re-running the regression. When comparing the final logistic regression model presented in Chapter 8 (see Table 8.25) with Table 3 below (excluding the outlier identified), there was little difference between the models. There was minimal change to the odds ratios and p-values. The odds ratios also maintain their direction and are a similar size. Therefore, the effect of the outlier is minimal and the final model (inclusive of all 143 participants) is robust.

Table 3 Results of the logistic regression for the outcome 'self-reported cognitive adverse effects for 142 participants (excluding the outlier)

				Unadjusted			Adjusted		
Variable	**logit**	***SE***	**Wald *z***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Intercept	2.004	2.20	.830	-	-	-	-	-	.427
Age	-.048	.03	3.073	0.96	0.91, 1.00	.068	0.95	0.90, 1.01	.080
Gender	1.180	.42	7.727	2.69	1.21, 5.96	**.015**	3.253	1.42, 7.47	**.005**
Average daily dose (OME)[a]	.139	.12	1.371	1.19	0.96, 1.46	.117	1.15	0.91, 1.45	.242
ACB score	.097	.43	.052	1.22	0.59, 2.53	.589	1.10	0.48, 2.55	.820

SE Standard Error, *OR* Odds Ratio, *CI* Confidence Interval, *P* P-value, *OME* Oral Morphine Equivalent, *ACB* Anticholinergic Burden. *Note:* Figures in bold represent significant findings. Nagelkerke $R^2 = 0.129$. [a] Logarithm transformation.

As the values were log transformed, further model diagnostics (such as Leverage or Cook's Distance) were not deemed appropriate to run.

Predictors of the presence of an opioid prescription at some point over the past year

Selection of candidate predictors

Understanding the factors that may relate to and possibly predict an opioid prescription is potentially very useful. As with the previous logistic regression, candidate predictors were limited due to the small sample size. The studies of interest focused on various outcome variables, which included: any opioid use (which was often defined as the participant having at least one opioid analgesic), use of strong opioids or opioid use trajectories (such as persistent use). Despite any use of opioids being the main outcome of interest for this regression, factors related to strong opioid use and the trajectories of use were also important to consider in understanding factors that might predict opioid use generally. Studies used a number of different predictors to form their models, which fell into the following broad categories: patient sociodemographics (such as age, gender), disease-related characteristics, pain characteristics, functional ability, other medications and health practices (such as smoking and alcohol use), see Table 4 Summary of models and candidate predictors presented in literature.

A number of factors were significantly associated with increased odds of having an opioid prescription within the authors' respective studies. These included older age, being female, race, ethnicity, being divorced or widowed, lower levels of education, frequent experience of pain, increasing severity of pain interference, pain location (e.g. back pain) or condition (e.g. rheumatoid arthritis), self-perceived poor health, increasing comorbidities, history of cancer, cardiovascular issues, a high BMI, limited function, number of medications, use of depressive agents, being a smoker, poor mental health, emotional wellbeing (increased feelings of loneliness or financial concerns), low wealth/high poverty rates, region and proximal death.[50,217,218,225,233,234,431,464,527-529] Aside from the models presented in the table below, a systematic review and meta-analysis also found that being male, using depressive agents, having depression and being unemployed were significantly associated with high dose opioids.[530] Another study found that larger practice size lists, ruralness and deprivation were associated with high dose prescribing rates of opioids.[238] The likelihood of heavy opioid use was also found to be increased by the number of chronic non-cancer pain diagnoses.[431] Additionally, an observational study and an evaluation study found that musculoskeletal issues were one of the most common reasons for prescribing strong

opioids.[49,531] In terms of persistent use, using transdermal formulations, receiving higher doses of opioids, history of mental health issues and previous dispensing of non-opioids (including paracetamol, pregabalin and benzodiazepines).[532] Unhealthy alcohol use (defined as 4 units of alcohol for women and 6 units for men per day as least once a week) had a protective effect with opioid prescription.[50] However, other studies showed that heavy opioid use was associated with substance abuse diagnoses or there was no association between alcohol and opioid use.[218,431] Another factor related to decreased odds of an opioid prescription included having dementia.[217]

There were different findings regarding some demographic characteristics. Increasing age was found to be associated with increased odds or higher prevalence of having an opioid prescribed.[50,233,464] In line with this, higher incidence of long-term opioid use and more regular opioid use was noted within older age groups.[217,527,532] An observational study using descriptive statistics also found that the oldest patients were likely to be prescribed an opioid analgesic, especially a strong opioid.[49] Contrary to these findings, another study found that the receipt of any opioid decreased with older age.[225] Variations in opioid strength were also noted by age, with a smaller percentage of older adults using opioids stronger than morphine.[464] In some models, age had no association with opioid use or opioid strength prescribed.[218,238,431,533] In terms of gender, a number of studies reported that being female was associated with increased odds of having an opioid prescription, higher incidence of long-term use of opioids generally or higher incidence of chronic use of strong opioids.[50,217,527,529] The trends in percentage change of opioid use observed in a cross-sectional longitudinal analysis supported the idea that more women than men received opioid prescriptions.[47] Although, Richards and colleagues noted that being male was associated with receipt of high dose opioids [530]. Some studies found no marked association with gender and their outcome within their main adjusted models.[218,233,234,431,528,532,533]. However, in a sensitivity analysis, Lalic and colleagues found that subgroups of older adults (aged 65 and over) that being female predicted persistence of opioid use.[532] Therefore, with these considerations in mind, age and gender (with ‘being male’ acting as the reference category) were important factors to adjust for in this model.

Table 4 Summary of models and candidate predictors presented in literature

Author (Year)	Study type	Outcome variable	Modelling method	Data		Study population	Candidate predictors
				Source	Years		
Axon et al. (2020)	Retrospective, cross-sectional	Opioid use (opioid user, non-user)	LogR	MEPS	2017	- Adults aged ≥50 with a diagnosis or hypertension or hypercholesterolemia - Alive for the full year - Experienced pain in the past four weeks - Pain has interfered with normal work outside the home and housework	Adopted Andersen's Behavioural Model of Health Services Use, which includes the following factors: predisposing (age, gender, ethnicity and race), enabling (education status, employment status, marital status, health insurance provider, poverty indicator and income), needs (chronic conditions, pain severity, perceived physical health status, perceived mental health status, ADL limitations, IADL limitations, functional limitations, and work, housework or school limitations), personal health practices (regular exercise and smoking status) and environmental (region).
Bedene et al. (2019)	Cohort	Dynamics of opioid prescriptions (using opioid	LogR	DHM	2012 – 2016	- Residents of the Netherlands aged ≥19	Age (by group), gender, education, immigration status, standardised household income, marital status, smoking status, comorbidity

		reimbursement data)					over the past year, depression, loneliness, ability to meet financial needs, physical health, BMI and other factors (heavy drinking, living alone and unemployment)
Campbell et al. (2011)	Longitudinal cohort study	Trends in long-term use of prescribed opioids	LR (PCA)	CONSORT	1997 – 2005	- Adults aged ≥18 from two USA health plans with CNCP	Age and gender
Carrington-Reid et al. (2010)	Retrospective cohort	LR: Duration of opioid use LogR: Short-term use, discontinued use	LR LogR (with binomial error)	Medical record data	2001 – 2007	- Practice patients aged ≥65 who had recently started an opioid treatment for cancer pain	Age, gender, pain type, cognitive impairment, depression diagnosis, BADL deficits, IADL deficits, comorbidity score (Charlson) and number of days observed
Curtis et al. (2018)	Retrospective	Model 1: High dose, long-acting opioid prescriptions Model 2: Total OME prescribing per 1000 patients	1: Mixed-effects LogR 2: Mixed-effect LR	Practice-level data, aggregated to CCGs	1998 – 2017	- General practices in England.	Models 1 and 2 included the following fixed-effect variables: patients aged >65, proportion of patients with a long-term health condition, IMD and QOF. Additionally, the models included the following random-effect variables: practice list size and extent of ruralness or urbanisation of practice post code.

Davidoff et al. (2019)	Retrospective	Model 1: Any pain medication Model 2: Any opioid	LogR	SEER/MHOS	2007 – 2012	- Respondents aged ≥66 who either have ≤5 years of a cancer diagnosis or without cancer	Age, gender, race/ethnicity, marital status, education, pain interference, cancer history (stratified by pain interference), coronary artery disease, stroke, pulmonary disease, diabetes, depression, arthritis, sciatica, poverty rates, region, low incpome subsidy, plan type and proximity of death.
Edlund et al. (2010)	Secondary data analysis of longitudinal administrative data from a commercially insured population and Arkansas Medicaid enrolee's	High opioid utilizers (i.e. top 5%)	Multiple LogR	HCIRD	2000 and 2005	- Adults aged ≥18 - One or more recorded CNCP diagnosis - Minimum of one opioid analgesic prescription given in the year, either 2000 or 2005 - Enrolled and eligible for benefits for at least nine months in the given year, either 2000 or 2005	Age, gender, chronic pain diagnoses, mental health and substance use diagnoses. * Association between heavy utilisation and number of CNCP and MH/SUD diagnoses also explored
Frenk et al. (2019)	Retrospective cohort	Opioid use (those that did versus those that did not)	LogR	NHNES	2011 – 2014	- Survey respondents aged ≥ 16 who completed the household interview and physical examination - Complete data on questions regarding	Age, gender, race/Hispanic origin, health insurance status, self-rated health, pain in the past 30 days, anxiety over the past 30 days, depression over the past 2 weeks, number of non-opioid prescription

						prescription medication use	medications used, used at least one benzodiazepine over the past 30 days, used an antidepressant over the past 30 days, current drinking status and illicit drug use over the past 6 months.
Grol-Prokopczyk et al. (2019)	Retrospective	Current use of a prescription opioid analgesic	Multiple LogR	HRS	2004 – 2005	- Respondents aged ≥65 - Sample weight higher than zero - Complete pain information	Independent variables included: education and wealth quartiles. Control variables included: age, gender, race/ethnicity and marital status. Pain level and health insurance type were evaluated as potential mediators.
Lalic et al. (2018)	Cohort study	Persistent opioid use (persistent, non-persistent)	LogR	PBS	2013 – 2015	- Adults aged ≥18 without a cancer diagnosis who were new opioid users between 2013 to 2015	Age, gender, concessional status, characteristics of the initial opioid dispensing (strong opioid, total OME dispensed and route of administration), depression, psychotic illness, alcohol dependence, migraine, total number of other comorbidities, and prior use of benzodiazepines, paracetamol, NSAIDs, pregabalin and stimulants.

Marttinen et al. (2021)	Population-based cohort study	Analgesic purchases (including opioids)	LogR	GOAL	2012	- Older adults from Finland aged between 62-66, 72-76, and 82-86 in 2012, with complete prescription data	Age, gender, education in years, smoking status, alcohol unit consumption per week, number of comorbidities, metabolic syndrome, pain levels and leisure-time physical activity.
Oh et al. (2019)	Retrospective cohort	Chronic use trajectory group membership (minimal, discontinuing, incident chronic and prevalent chronic)	Multiple LogR	NACC UDS	2005 – 2017	- Participants enrolled at national ADC throughout the USA - Older adults aged ≥65 at initial NACC UDS visit, with medication recorded at every visit - Three or more visits to facilitate trajectory trends with quadratic components - No history of cancer	Age (at enrolment), gender, race, years of education, type of residence, hypertension, diabetes, cardiovascular disease, urinary incontinence, dementia, current smoking, alcohol abuse, number of medications, antidepressant agent, NSAID, and anxiolytic, sedative or hypnotic agent.
Shiue et al. (2021)	Longitudinal cohort	Opioid use at follow-up (yes, no)	LogR	JoCoOA	2006 – 2010 and 2013 – 2015	- Adults aged ≥45 residing in Johnston County, North Carolina - Reported no opioid use at baseline - Complete medication and follow-up data	Age, gender, race, employment status, educational attainment, marital status, smoking status, BMI, household poverty rate, health insurance, history of depressive symptoms, perceived social support, pain catastrophising, polypharmacy (>5 medications)

Steinman et al. (2015)	Observational study	Percentage of visits an opioid was in use	LogR	NAMCS/ NHAMCS	1999 - 2010	- Older adults aged ≥65	Age, gender, race, ethnicity, national region, chronic conditions (including arthritis, depression, chronic renal failure and congestive heart failure), count of chronic conditions, reason for visit (musculoskeletal or other), chronicity of the main reason for visit (new/acute, chronic or other), specialty of the treating physician and clinical setting

Abbreviations: *ADC* Ageing-funded Alzheimer's Disease Centres, *ADL* Activities of Daily Living, *BADL* Basic Activity of Daily Living, *IADL* Instrumental Activities of Daily Living, *BMI* Body Mass Index, *CCGs* Clinical Commissioning Groups, CNCP Chronic Non-cancer Pain, *CONSORT* Consortium to Study Opioids Risks and Trends, *DHM* Dutch Health Monitor surveys, *GOAL* Good Ageing in Lahti Region survey, *JoCoOA* Johnston County Osteoarthritis Project, HCIRD HealthCore Integrated Research Database, HRS Health and Retirement Study, IMD Index of Multiple Deprivation, LogR Logistic Regression, LR Linear Regression, LogR Logistic Regression, MEPS Medical Expenditure Panel Survey, MH Mental Health, NACC UDS National Alzheimer's Coordinating Centre Uniform Data Set, NSAID Non-steroidal Anti-inflammatory Drugs, NHNES National Health and Nutrition Examination Survey, PBS Pharmaceutical Benefits Scheme, PCA Percent Change Annualised, QOF Quality and Outcomes Framework, SAIL Secure Anonymised Information Linkage databank (Primary Care Practice data), SEER-MHOS Surveillance Epidemiology and End Results – Medicare Health Outcomes Survey, SUD Substance Use Disorder, USA United States of America

As listed in Table 4, studies included pain within their models in a number of ways, which included: location, condition, severity frequency and duration. These characteristics of pain were captured within this data. In this study, pain was summarised in the clinical consultation in various ways (as discussed in 8.2.2); there was a lack of consistency in whether pain was summarised by location or condition. Frequency of pain was also captured inconsistently, such as whether pain was considered to be acute or chronic. Participants were asked about how long they had experienced pain for as part of the survey (see Appendix 5), however, it was challenging for participants to recall their pain accurately and they often had multiple sources of pain that they had experienced for different durations. As part of the survey, participants had also been asked to reflect on pain and discomfort on the day of recruitment (via the EQ-5D) and pain over the past week (via the IPOS). The pain item from the IPOS was adopted in the final model as a summary of pain overall rather than focusing on aspects like location or condition, as well as, to minimise measurement error and avoid multicollinearity of including more than one predictor focusing on pain. Additionally, the EQ-5D asks participants to focus on the day of recruitment only, as well as, consider discomfort within their answer.

Measures of deprivation, either at an individual- or an area- level, were considered. Individual-level included level of education, whilst area-level focused on regional differences and poverty rates. This dataset was limited by the measures of deprivation available to use and it was only possible to adopt an area level variable (i.e. the Index of Multiple Deprivation). As with the previous model, it was decided that it would be best not to include in the final model, as it largely included individual level factors.

Factors related to emotional wellbeing were present throughout the literature. Therefore, it was important to include relevant variables, such as depression and loneliness. There were two measures that captured depression; the IPOS and the EQ-5D. The IPOS focused solely on whether the person felt depressed and captured this for a longer time period. The EQ-5D asked the person whether they felt anxious or depressed on the day of recruitment. Therefore, the depression item from the IPOS was included. It was not possible to use a more formal and extensive measure of depression.

Poor health was also associated with opioid use. There were two possible measures that could have been adopted from this data set, which included a question regarding the person's self-perceived physical health and self-rated health on the day of recruitment as captured by the EQ-5D. As the EQ-5D is a validated measure, this was included with the aim of reducing measurement error.

Frailty was an important consideration. There were two measures of frailty in this dataset (the eFI and the CFS). The eFI data available varied and depended on the general practitioner referring (i.e. provision of an exact score (e.g. 0.46) or a grouping (>0.36). The CFS was considered but demonstrated large confidence intervals, which suggests measurement error. Although, the AKPS is not a measure of frailty, it provides an understanding of functional status. Therefore, it was decided that functional status would be adopted. The confidence intervals were smaller and it was easier to trust the null effect observed.

As with the previous model, it was important to consider the association of other medications of opioid use. Anticholinergic burden was less pertinent to this model, at it indicates risk of adverse effects from medication. Therefore, the number of medications and polypharmacy were considered. The number of medications appeared to be predominantly used in the literature, and it was decided to retain the continuous variable in the model.

Comorbidities and specific conditions were also found to be associated with opioid use. However, the data collected regarding these factors were for descriptive purposes and were not appropriate to include.

Model diagnostics

As with the previous regression, a boxplot of the standardised residuals was used to test for normality and equal variance, as well as identification of outliers. Normal distribution is demonstrated by a symmetrical box and whiskers, with the median sitting within the middle of the box. In Figure 3, the boxplot indicates that there is a slight

asymmetric curve, as the ‘Yes’ group has a slightly upper whisker. However, the median is at the centre of the box. This is similar for, but more pronounced, in the ‘No’ group; where the lower whiskey is larger. Additionally, the whiskers of the boxplots do not exceed three or minus three, which indicates that there are no extreme outliers (i.e. values outside of the typical range).

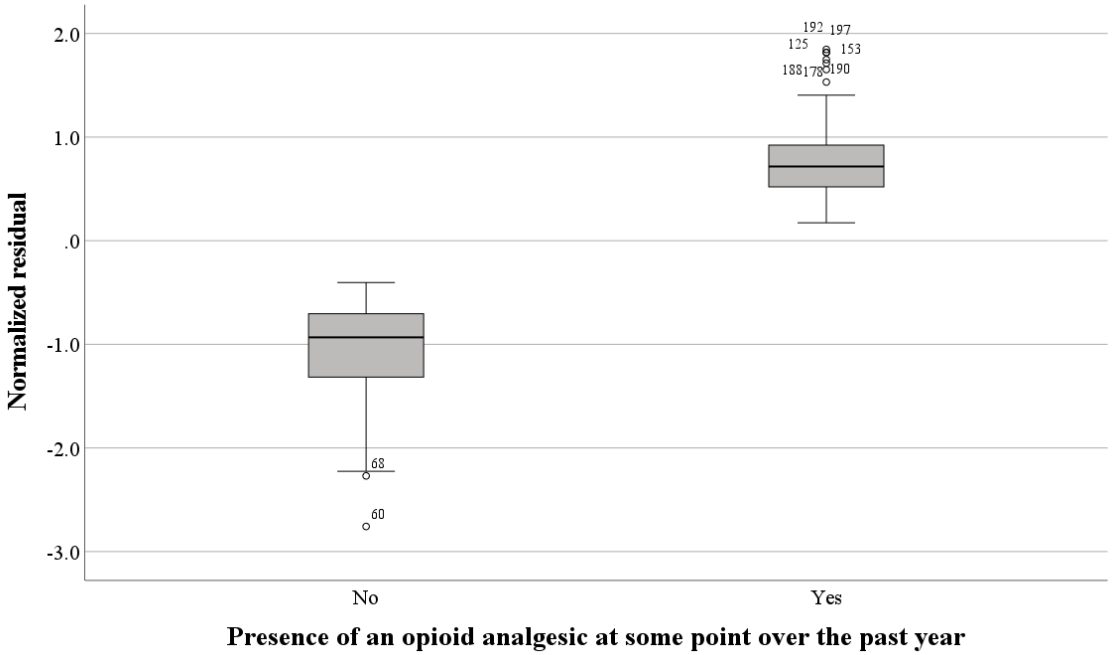


Figure 3 Boxplot of the standardised residuals by presence of an opioid analgesic at some point over the past year

Heteroscedasticity was also considered by analysing the residuals. Deviance residuals were plotted against predicted probability (see Figure 4) to identify cases where the model demonstrates a poor fit or cases that may exert an overtly large influence on the estimates for the model’s parameters.[525] If the model fits well, the values should fall within the horizontal band (between -2 and +2) and form two parallel lines.[525,526] Values outside of ±2 may be considered as potential outliers and warrant some concern. In figure 4, one participant was identified as a potential outlier.

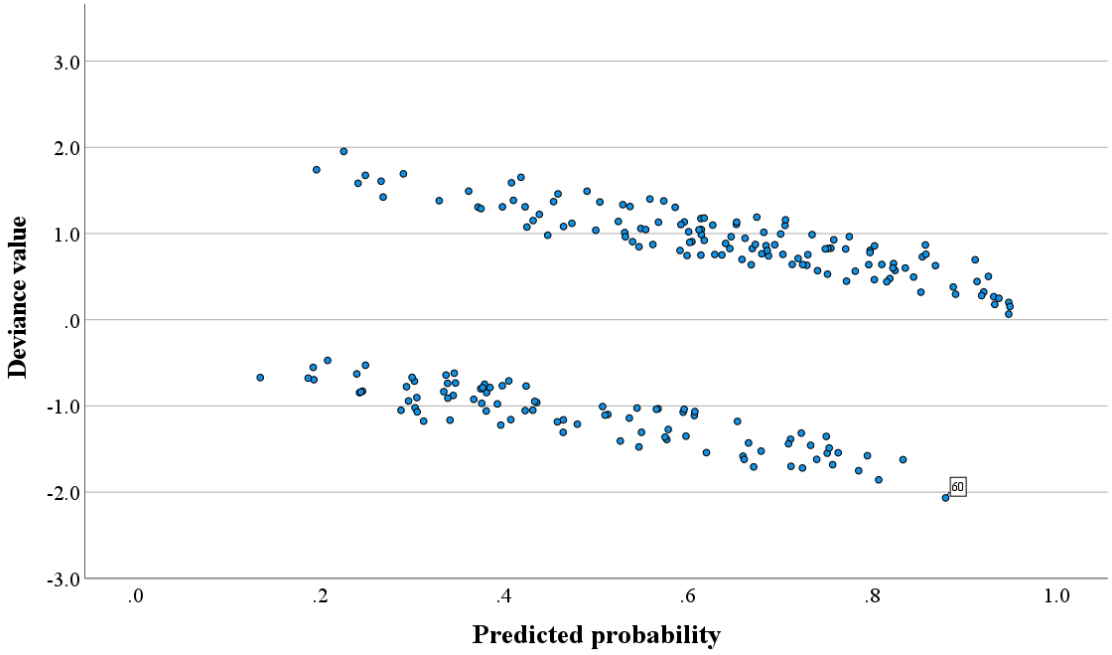


Figure 4 Raw and deviance residuals by predicted probabilities

As the assessment of heteroscedasticity indicated that there was a potential outlier, a sensitivity analysis was conducted to determine its effect on the model by removing the outlier and re-running the regression. When comparing the final logistic regression model presented in Chapter 8 (see Table 8.31) with Table 5 below (excluding the outlier identified), there was little difference between the models. There was minimal change to the odds ratios and p-values. The odds ratios also maintain their direction and are a similar size. Therefore, the effect of the outlier is minimal and the final model (inclusive of all 217 participants) is robust.

Table 5 Results of a logistic regression for the outcome 'presence of an opioid prescription in medical records at some point over the past year' for 216 participants

				Unadjusted			Adjusted		
Variable	**logit**	***SE***	**Wald *z***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Intercept	-1.159	2.19	.280	-	-	-	-	-	.597
Age	-.020	.02	.793	0.96	0.92, 0.99	**.017**	0.98	0.94, 1.02	.373
Gender	.158	.32	.247	1.13	0.66, 1.95	.658	1.17	0.63, 2.19	.619
Pain	.574	.14	16.348	1.85	1.44, 2.38	**.000**	1.78	1.34, 2.35	**.000**
Depression	-.187	.14	1.755	1.12	0.89, 1.40	.344	0.83	0.63, 1.09	.185
Loneliness	.489	.37	1.761	1.92	1.01, 3.62	.045	1.63	0.79, 3.36	.184
Number of medications	.130	.05	8.280	1.15	1.07, 1.24	**.000**	1.14	1.04, 1.24	**.004**
Self-rated health	.003	.01	.131	0.99	0.98, 1.00	.169	1.00	0.99, 1.02	.717
Times admitted to hospital	0.082	.11	.511	1.13	0.92, 1.39	.230	1.09	0.87, 1.36	.475
Functional status	.009	.01	.485	0.99	0.97, 1.01	.381	1.01	0.98, 1.04	.486

Abbreviations: SE Standard error, *OR* Odds ratio, *CI* Confidence interval, *P* p-value. *Note:* Figures in bold represent significant findings. Nagelkerke $R^2 = 0.230$. [a] Logarithm transformation.

Lastly, leverage was used to determine outliers, which quantifies the leverage of individual points on the line. Ideally, all observations should have leverage measures that are less than two time the expected value.[524] The expected value can be calculated by the following by adding one to the number of variables included in the model and dividing by the sample size. Leverage values that exceed the following calculation will warrant attention: (two multiplied by the number of variables plus two) divided by the sample size.[524] Figure 5 shows that there are two cases might warrant attention.

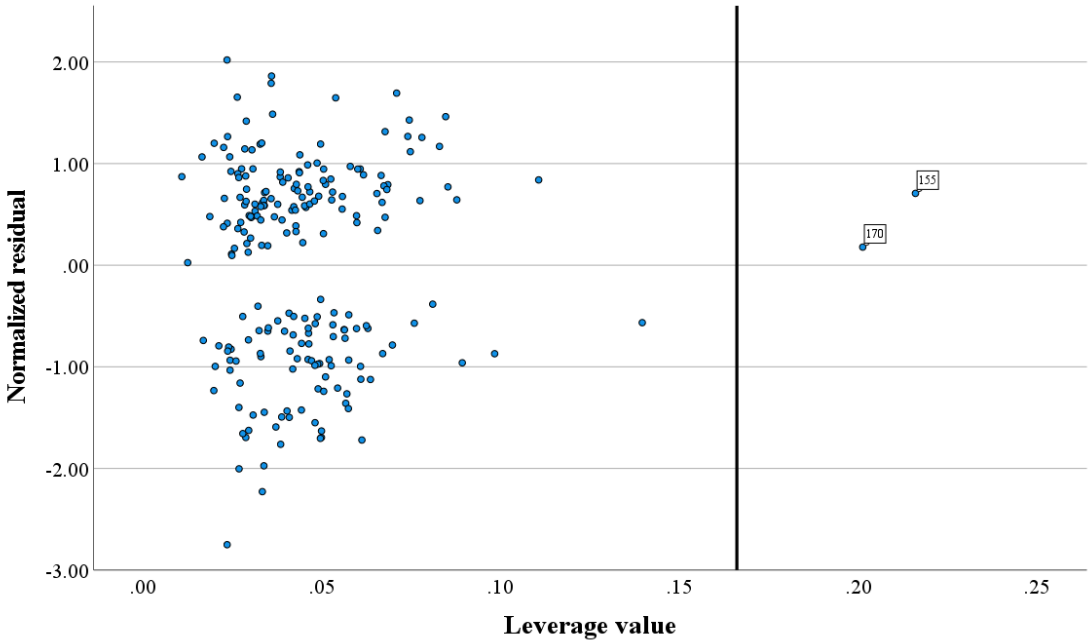


Figure 5 Residuals versus Leverage

Therefore, another sensitivity analysis was conducted to determine the influence of these two cases on the model. Despite excluding the two cases from the analysis, there was minimal change to the model in terms of odds ratios and p-values. Additionally, the odds ratios maintain their direction and are of similar size. The two outliers appear to have a minimal impact and the final model presented in Table 8.31 is robust.

Table 6 Results of a logistic regression for the outcome 'presence of an opioid prescription in medical records at some point over the past year' for 215 participants

				Unadjusted			Adjusted		
Variable	**logit**	***SE***	**Wald *z***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Intercept	-1.390	2.22	.550	-	-	-	-	-	
Age	-.016	.02	.178	0.96	0.92, 1.00	**.025**	0.98	0.94, 1.03	.458
Gender	.133	.32	15.376	1.12	0.65, 1.94	.683	1.14	0.62, 2.12	.673
Pain	.550	.14	1.158	1.81	1.41, 2.32	**.000**	1.73	1.32, 2.28	**.000**
Depression	-.150	.14	1.196	1.12	0.89, 1.41	.335	0.86	0.66, 1.13	.282
Loneliness	.397	.36	8.069	1.79	0.95, 3.36	.070	1.49	0.73, 3.03	.274
Number of medications	.128	.05	.185	1.15	1.07, 1.24	**.000**	1.14	1.04, 1.24	**.005**
Self-rated health	.004	.01	.003	0.99	0.98, 1.01	.210	1.00	0.99, 1.02	.667
Times admitted to hospital	.007	.14	.509	1.08	0.84, 1.37	.558	1.00	0.77, 1.32	.957
Functional status	.009	.01	.393	0.99	0.97, 1.01	.438	1.01	0.98, 1.04	.476

Abbreviations: SE Standard error, *OR* Odds ratio, *CI* Confidence interval, *P* p-value. *Note:* Figures in bold represent significant findings. Nagelkerke $R^2 = 0.212$. [a] Logarithm transformation.

Appendix 10: Participant information sheet

PATIENT AND FAMILY CARER INFORMATION SHEET

Qualitative Interviews

A large-print version of this sheet is available on request.

Introduction

We would like to invite you to take part in our study. Your participation will help us to understand your thoughts on and experiences of one of the following topics:

- Chronic breathlessness
- Unintentional weight loss
- Use of medicines for pain

To help you to decide if you would like to take part, we have created this information sheet. It explains why the research is being done, what you will be asked to do, and why we are asking you to take part. Please take time to read the following information carefully and talk about it with others if you wish. You can contact someone from the research team and ask them to explain anything that is not clear to you. The Wolfson Palliative Care Research Centre based at the University of Hull runs the study.

What is the study about?

The purpose of this study is to explore your experiences of chronic breathlessness, unintentional weight loss, and the use of medicines for pain and possible side effects. This will help us better understand these problems as well as how they can be managed better.

Why have I been invited to take part?

You have been invited to take part in an interview because you have indicated that you have experience of or care for someone who is affected by chronic breathlessness, unintentional weight loss, or use medicines for pain. You have indicated when you completed the survey questionnaires that you are willing to be contacted about taking part in an interview or have a family member who might also want to participate but was not present on your assessment visit.

Do I have to take part?

No. It is up to you to decide if you would like to take part. If you decide not to take part, this will be noted and you will not be asked again. You will also continue to receive care and support from your GP practice or any health professional as usual. If you to take part, you can change your mind and stop taking part at any time without giving any reason.

What will happen if I take part?

If you take part, you will be asked to sign a consent form and then take part in an interview with one of our researchers, which will take about 45 minutes. The interview can be at the Jean Bishop Integrated Care Centre, your resident care home or at a place and time convenient for you. Each topic will have a slightly different focus but will involve questions around your experience of one of topics listed above. After the interview, members of the research team will carry out the transcription. Information collected, which can identify you will be anonymised at the time of the transcription.

What are the possible benefits of taking part in the study?

Although there is no direct benefit, you may value the chance to talk through your experiences. However, the information that you give us will help us to better understand experiences of chronic breathlessness, unintentional weight loss and effects of use of pain medicines, so this will help others with these problems in the future.

Are there any potential risks of taking part?

There are no significant risks in taking part. . We would like to stress that taking part is up to you and you can stop taking part at any time without reason and without your medical care or legal rights being affected.

Will my involvement be confidential?

Yes. All the information we collect will be kept confidential, to fit with the General Data Protection Regulation (GDPR) 2018. The University of Hull is the sponsor for this study based in the United Kingdom. We will be using information either from you or him/her in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your or his/her information and using it properly. The University of Hull will keep identifiable information about you or him/her for 10 years after the study has finished.

Your or his/her rights to access change or move your or his/her information are limited, as we need to manage your or his/her information in specific ways in order for the research to be reliable and accurate. If you or he/she withdraw from the study, we will keep the information about you or him/her that we have already obtained. To safeguard your or his/her rights, we will use the minimum personally identifiable information possible.

You or him/her can find out more about how we use your or his/her information at https://www.hyms.ac.uk/research/research-centres-and-groups/wolfson/pace or by contacting PACE@hyms.ac.uk.

The research team from the University of Hull will collect information from you or him/her for this research study in accordance with our instructions.

The research team from the University of Hull will use your or his/her name and contact details to contact you or him/her about the research study, and make sure that relevant information about the study is recorded for you or his/her care, and to oversee the quality of the study. Individuals from the University of Hull and regulatory organisations may look at your or his/her research records to check the accuracy of the research study. Your or his/her details will be passed to University of Hull along with the information collected from you or him/her. The only people in the University of Hull who will have access to information that identifies you or him/her will be people who need to contact you or him/her to collect data/information or audit the data collection process. The people who analyse the information will not be able to identify you or him/her and will not be able to find out your or his/her name or contact details.

The research team from the University of Hull will keep identifiable information about you or him/her from this study for 10 years after the study has finished.

However, if you or he/she raise an issue of concern for your or his/her or others' health, we may ask your or his/her permission to contact your or his/her GP or other health professional to seek specific help or advice for you or him/her.

Expenses

You will be provided with prepaid envelopes, if needed, to return any documents to the research team. There will be no other costs to you.

What will happen to the results of the research study?

The results of this study will be presented at conferences and public engagement events, and will be written up for publication in academic journals. If you would like to receive a summary of the

study findings please inform the researcher. With your permission, publications may include anonymised quotations.

If I find it necessary to make a complaint, who should I contact?

If you have any concerns, questions or complaints about this research, you can contact Dr Maureen Twiddy (01482 463279, 8am to 5pm weekdays) or email Maureen.Twiddy@hyms.ac.uk Dr Twiddy is based at University of Hull but is independent of the research team.

How can I get involved in the study?

Thank you for taking the time to read this information sheet. **If you would like to know more or wish to take part, please contact the research team using the details below:**

Helene Elliott-Button, Ugochinyere Nwulu or Sophie Pask
Telephone: (01482) 463728
Email: PACE@hyms.ac.uk

Appendix 11: Qualitative study consent form

PACE
Proactive Anticipatory
Care Evaluation

Hull
Clinical Commissioning Group

Consent Form for Research Participants
(Qualitative Interviews)

	Please initial each box
I confirm that I have read and understood the participant information sheet for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily.	☐
I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical and legal rights being affected. Furthermore, I understand that I am able to withdraw my data up to the time of transcription and analysis	☐
I consent to be interviewed and agree to the interview being recorded and direct quotes used during data/result presentation anonymously.	☐
I understand that responsible individuals may look at relevant sections of any data collected during this study from the research team, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to this data.	☐
I understand that my information may be subject to review by responsible individuals from the University for monitoring and audit purposes.	☐
I understand that the information collected about me may be published or will be used to support other research in the future, and may be shared anonymously with other researchers.	☐
I agree to take part in the above study.	☐

Name of Participant	Date	Signature
Name of person taking consent	Date	Signature

☐ Tick here if participant has given consent but is physically unable to sign and has requested a witness

I witness that _____ has agreed to participate in this research study. I confirm that I have initialled the consent statements as per their wishes.

_____	_____	_____
Name of witness (Print)	Date	Signature
_____	_____	_____
Name of person taking consent (Print)	Date	Signature

Office Use Only

Tick the appropriate box once completed

Participant's copy	☐
Research team/site file copy	☐
Medical record's copy	☐

Appendix 12: Qualitative interview topic guides

Topic Guide
Understanding your experience of painkillers
An interview schedule for patients

Introduction

Thank you so much for agreeing to be interviewed today. My name is Sophie Pask and I am a postgraduate student from the Wolfson Palliative Care Research Centre at the Hull York Medical School. The purpose of today's interview is to capture your views on and experiences of using painkillers and side effects from taking these medications, especially on things like your memory and attention. We will also talk to friends and family. This will help us to understand the issues that patients and families have with prescribed painkillers, and how we could improve peoples' experiences or understanding of them. The interview should take about 45 minutes, depending on how much you would like to share. The information you do share in this interview will be anonymised, so please feel free to say what you would like to.

You can stop the interview at any point or skip any questions, should you wish to. Also, we can pause for breaks if you need to, and can restart the recording when you are ready. If you are happy to continue, please could you sign the consent form?

And are you happy for the interview to be audio recorded today? And is it OK for me to make a few notes during the interview? Do you have any questions before we start?

**** Start recording ****

Understanding your experience of prescribed painkillers

(1) Could you start by telling me about why you were prescribed painkillers (cause, duration, intensity/severity, impact on daily living)?
   - Did the health professional make the decision or did you?
     - Can you name the painkillers? What did you know about painkillers before you started taking them?

(2) Did you discuss any alternatives before being given painkillers? What alternatives did you discuss?
   - How did you feel about the alternative options, and why? Opinions on support available?

(3) Before you started taking your painkillers, what were your thoughts about taking them?
   - Did you have any concerns or attitudes towards taking them? If yes, what?

(4) What were your thoughts about painkillers after you had used then?
   - Did these opinions change once you started taking them? How?
     - [*If concerned once started taking them*] Why did these concerns develop?
     - [*If applicable*] What are your thoughts about using them in the long-term?

(5) Could you tell me about how taking painkillers fits into your daily routine?
     - How do you find managing your painkillers with other medications?

(6) How have painkillers affected your pain? Satisfactory relief?
   - How has taking painkillers affected your general wellbeing?
   - Issues with taking painkillers? Avoidance? Forget to take?

(7) On the questionnaire you completed on your visit to the clinic, you mentioned that you experienced problems with memory/general confusion/concentration or attention/ seeing or hearing things that are not present from taking painkillers:
- When did you first notice it was affecting your _____?
- How did this affect you day to day?
- Who did you speak to you when you noticed it was affecting your _____?
- Did your family members notice?
- What concerns did you have when you noticed?
- Did it affect the way you took your medication?

(8) *If applicable:* You mentioned that you also experienced other side effects (i.e. _____, _____):
- How did this/these side effects affect you day to day?

(9) Which side effect bothered you the most?

(10) Do your family provide care for you?
- What kind of support do they provide?

(11) Did the side affects you experienced have any impact on your family?
- Did you need support from your family during this time?

(12) *If applicable:* You mentioned that you had been prescribed painkillers but not taken them, could you tell me more about why you decided to stop taking them?
- *Or if altered doses/timing:* Could you tell me why you don't take painkillers the way the healthcare professional suggested?

Communication with health professionals, and information and support needs

(1) What were you told about painkillers when you were prescribed them?
- What would you have liked to be told?
- Was the information clear?
  - *If not clear:* What could have been improved?
- Was the information helpful/unhelpful? Why?

(2) Were you told about the possible side effects that you might experience?
(3) Did you discuss what to do if you experienced any problems with the medication?
(4) Was a review plan put in place?
- What are your thoughts about this?
  - *If no review in place:* Would you have liked one?

(5) What would be your advice to health professionals with prescribing painkillers to older adults?
(6) What would be your advice to other patients being prescribed stronger painkillers?

Is there anything else you would like to add that we have not covered?

I'd like to thank you again for taking the time to be interviewed today, your views will be a great help to the project.

**** End recording ****

Topic Guide

Understanding your experience of caring for someone taking painkillers

Interview schedule for carers

Introduction

Thank you so much for agreeing to be interviewed today. My name is Sophie Pask and I am a postgraduate student from the Wolfson Palliative Care Research Group at the Hull York Medical School. The purpose of today's interview is to capture your views on and experiences of caring for someone who is taking painkillers and side effects from these medications, especially on things like memory and attention. We will also talk to patients. This will help us to understand the issues that patients and carers (including friends and family) have with painkillers, and how we could improve peoples' experiences or understanding of them. The interview should take about 45 minutes, depending on how much you would like to share. The information you do share in this interview will be anonymised, so please feel free to say what you would like to.

You can stop the interview at any point or skip any questions, should you wish to. Also, we can pause for breaks if you need to, and can restart the recording when you are ready. If you are happy to continue, please could you sign the consent form?

And are you happy for the interview to be audio recorded today? And is it OK for me to make a few notes during the interview?

Do you have any questions before we start?

****** Start recording ******

Understanding your experience of caring for someone taking painkillers

(1) Can you start by telling me why your friend/family member was prescribed painkillers (cause, duration, intensity/severity, impact on daily living)?
   - Do you provide support to your friend/family member in managing their medications (including painkillers)? If yes, what do you do?
   - What other kinds of support do you provide?

(2) Were any alternatives tried before painkillers?
   - What alternatives were discussed?
   - What were your thoughts about the alternative options, and why?

(3) What were your thoughts about them being prescribed painkillers?
   - Did you have any concerns/thoughts about them taking painkillers? If yes, what were they? (e.g. stigma, length of use)
   - Could you tell me about how taking painkillers fits into their daily routine?
     - Is it challenging (for them) to manage with other medications?

(4) How did they affect their pain? Satisfactory relief?
   - How do painkillers affect their general wellbeing?

(5) Were you told about the possible side effects that they might experience?
- What did you think when you were told about the possible side effects?

(6) Did you discuss what to do if you experienced any problems with the medication?

(7) What side effects did your friend/family member experience? LIST SIDE EFFECTS
- How did these side effects affect them day to day?
- How did this affect you?

(8) What was the most concerning side effect?
- What affected them the most?
- Did you need to provide more support during this time?

(9) When did you first notice that the painkillers were affecting their [memory/general confusion/concentration or attention] or causing [them to see things that weren't there]:
- How did this affect them day to day?
- How did this affect you?
- Who did you speak to you when you noticed it was affecting their _____?
- What concerns did you have when you noticed?
    - Did it affect the way they took their medication?

Communication with health professionals, and information and support needs

(10) Could you tell me what you knew about painkillers before they started taking them?

(11)What were you told when they were prescribed to your friend/family member?
- Was the information clear? If not, what could have been improved?
- Do you feel you know enough about them now?
- What would you have liked to be told?

(12) Was a review plan put in place?
- If not, do you think one was needed?

(13) What would be your advice to health professionals with prescribing painkillers to older adults?

(14) What would be your advice to other carers of patients being prescribed painkillers?

Is there anything else you would like to add that we have not covered?

I'd like to thank you again for taking the time to be interviewed today, your views will be a great help to the project.

**** End recording ****

Topic Guide
Understanding your experience of painkillers
A joint interview schedule for patients and carers

Introduction

Thank you so much for agreeing to be interviewed today. My name is Sophie Pask and I am a postgraduate student from the Wolfson Palliative Care Research Centre at the Hull York Medical School. The purpose of today's interview is to capture your views on and experiences of painkillers and side effects from these medications, especially on things like memory and attention. This will help us to understand the issues that patients and families have with prescribed painkillers, and how we could improve peoples' experiences or understanding of them. The interview should take about 45 minutes, depending on how much you would like to share. The information you do share in this interview will be anonymised, so please feel free to say what you would like to.

You can stop the interview at any point or skip any questions, should you wish to. Also, we can pause for breaks if you need to, and can restart the recording when you are ready. If you are happy to continue, please could you sign the consent form?

And are you happy for the interview to be audio recorded today? And is it OK for me to make a few notes during the interview?

Do you have any questions before we start?

**** Start recording ****

Understanding your experience of prescribed painkillers

(1) Could you start by telling me about why painkillers were prescribed?
- Cause of pain, duration, intensity/severity, impact on daily living
- Did the health professional make the decision or did you?
- What did you know about painkillers before you started taking them?
- Can you name the painkillers prescribed?

(2) Were any alternatives discussed before being given painkillers?
- What alternatives did you discuss?
- How did you feel about the alternative options, and why?
- What is your opinion in support available for people with moderate to severe/chronic pain?

(3) Before your experience with painkillers, what were your thoughts about them?
- Did you have any concerns or attitudes towards them (e.g. stigma, addiction, length of use)? If yes, what?
- Concerned about using them?

(4) Did these opinions change once _____ started taking them? How?
  - [*If concerned once started taking them*] Why did these concerns develop?
  - [*If applicable*] What are your thoughts about using them in the long-term?

(5) Could you tell me about how taking painkillers fit into the daily routine?
  - How do you find managing your painkillers with other medications?

(6) How have painkillers affected the pain? Satisfactory relief?
   - How have the painkillers affected your general wellbeing?

(7) On the questionnaire you completed on your visit to the clinic, _____ mentioned that they caused problems with memory/confusion/concentration or attention/ seeing or hearing things/ drowsiness, that are present from taking painkillers:
   - When did you first notice it was affecting _____?
   - How did this affect the day to day?
   - Who did you speak to you when you noticed it was affecting _____?
   - Did your family members notice?
   - What concerns did you have when you noticed?
   - Did it affect the way you took your medication?

(8) *If applicable:* You mentioned that you also experienced other side effects (i.e. _____, _____):
   - How did this/these side effects affect you day to day?

(9) Which side effect bothered you the most?

(10) Do your family provide care for you?
   - What kind of support do they provide?

(11) Did the side affects you experienced have any impact on your family?
   - Did you need support from your family during this time?

(12) *If applicable:* You mentioned that you had been prescribed painkillers but not or stopped taking them, could you tell me more about why you decided to stop taking them?
   - *Or if altered doses/timing:* Could you tell me why you don't take painkillers the way the healthcare professional suggested? Avoidance? Remembering to take?

Communication with health professionals, and information and support needs

(1) What were you told about painkillers when they were prescribed them?
   - What would you have liked to be told?
   - Was the information clear? *If not clear:* What could have been improved?
   - Was the information helpful/unhelpful? Why?
   - Do you know enough now?
(2) Were you told about the possible side effects that you might experience?
(3) Did you discuss what to do if you experienced any problems with the medication?
(4) Was a review plan put in place?
   - What are your thoughts about this?
      - *If no review in place:* Would you have liked one?
(5) What would be your advice to health professionals with prescribing painkillers to older adults?
(6) What would be your advice to other patients being prescribed stronger painkillers?

Is there anything else you would like to add that we have not covered?

I'd like to thank you again for taking the time to be interviewed today, your views will be a great help to the project.

**** End recording ****

Appendix 13: Ethical approvals

Hull York Medical School

Hull
University of Hull
Hull, HU6 7RX, UK

York
University of York
York, YO10 5DD, UK

T 0870 1245500
info@hyms.ac.uk
www.hyms.ac.uk

3 October 2018

Dr Mabel Okoeki
Research Associate
Wolfson Palliative Care Research Centre
Hull York Medical School

Dear Mabel

18 25 – Proactive Anticipatory Care Evaluation (PACE) study

I have reviewed this study on behalf of HYMS Ethical Committee with respect to the documents received on 28 September 2018. I am pleased to inform you that I do not have any HYMS-specific or ethical concerns, or additional requirements. On receipt of HRA approval please forward a copy of this letter for our files.

On behalf of the Ethics Committee, we wish you success with this study.

Please let me know if I can be of further assistance.

Kind regards

Yours sincerely

Professor Thozhukat Sathyapalan
Chair
HYMS Ethics Committee

Cc: Prof F Murtagh

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Fliss Murtagh
Allam Medical Building
University of Hull
Cottingham Road
Hull
HU6 7RX
fliss.murtagh@hyms.ac.uk

Email: hra.approval@nhs.net

22 March 2019 **[Re-issued 04 April 2019]**

Dear Professor Murtagh

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Proactive Anticipatory Care Evaluation (PACE) study**
IRAS project ID:	**250981**
REC reference:	**18/YH/0470**
Sponsor	**University of Hull**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations in England and Wales should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter. You should then work with each organisation that has confirmed capacity and capability and provide clear instructions when research activities can commence.

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Professor Fliss Murtagh
Tel: 01482 463 164
Email: fliss.murtagh@hyms.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

IRAS project ID	250981

Your IRAS project ID is **250981**. Please quote this on all correspondence.

Yours sincerely

Gemma Oakes
Assessor

Email: hra.approval@nhs.net

Copy to: *Dr Andrew Taylor, University of Hull [Sponsor Contact]*
a.f.taylor@hull.ac.uk
Dr Marie Girdham, NHS East Riding of Yorkshire Clinical Commissioning Group [Lead NHS R&D Contact]
Marie.girdham@nhs.net

IRAS project ID	250981

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Introduction leaflet]	2	19 September 2018
Copies of advertisement materials for research participants [Introduction leaflet]	3	09 January 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance Certificate]		24 September 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [evidence of sponsorship insurance or indemnity]		18 October 2018
HRA Schedule of Events [Site Type 1 - ICC]	1	20 March 2019
HRA Schedule of Events [Site Type 2 - Care]	1	20 March 2019
HRA Schedule of Events [Site Type 3 - GP Practices]	1	04 April 2019
HRA Statement of Activities [Site Type 1 - ICC]	1	18 January 2019
HRA Statement of Activities [Site Type 2 - Care Homes]	1	18 January 2019
HRA Statement of Activities [Site Type 3 - GP Practices]	1	18 January 2019
Interview schedules or topic guides for participants [patient topic guide (breathlessness)]	2	19 September 2018
Interview schedules or topic guides for participants [health professional topic guide (Breathlessness)]	2	19 September 2018
Interview schedules or topic guides for participants [patient topic guide (pain medicine)]	2	19 September 2018
Interview schedules or topic guides for participants [Carers topic guide-pain medicine]	2	19 September 2018
Interview schedules or topic guides for participants [health professionals topic guide (pain medicine)]	2	19 September 2018
Interview schedules or topic guides for participants [patient/care topic guide (unintentional weight loss)]	2	19 September 2018
Interview schedules or topic guides for participants [health professional topic guide (unintentional weight loss)]	2	19 September 2018
IRAS Application Form [IRAS_Form_23112018]		23 November 2018
IRAS Application Form XML file [IRAS_Form_23112018]		23 November 2018
Letter from funder [confirmation of scholarship]		03 January 2017
Letter from sponsor [letter of sponsorship]		16 October 2018
Letter from sponsor [letter of sponsorship]		16 October 2018
Letters of invitation to participant [Letter of invitation]	3	09 January 2019
Letters of invitation to participant [Letter of invitation with track changes]	3	09 January 2019
Non-validated questionnaire [Questionnaire for patient's information (records)]	3	09 January 2019
Non-validated questionnaire [Questionnaires for patient information (records) with track changes]	3	09 January 2019
Non-validated questionnaire [Baseline questionnaire (those with capacity)]	2	19 September 2018
Non-validated questionnaire [baseline questionnaires (without capacity)]	2	19 September 2018
Non-validated questionnaire [Baseline questionnaire (control group)]	2	19 September 2018
Non-validated questionnaire [Follow up questionnaire (with capacity)]	2	19 September 2018
Non-validated questionnaire [follow up questionnaire (without	2	19 September 2018

capacity)]		
Other [Response to REC amendment]		14 January 2019
Other [University of Hull lone worker policy]		15 December 2016
Participant consent form [consultee declaration form]	3	08 January 2019
Participant consent form [consultee declaration form with track changes]	3	08 January 2019
Participant consent form [Patient consent form]	3	08 January 2019
Participant consent form [patient informed consent form (interview)]	3	08 January 2019
Participant consent form [informed consent form (interview) with track changes]	3	08 January 2019
Participant consent form [Informed consent form with track changes]	3	08 January 2019
Participant information sheet (PIS) [Consultee Information Sheet]	3	08 January 2019
Participant information sheet (PIS) [Control Participant Information Sheet]	3	08 January 2019
Participant information sheet (PIS) [Health Care Professional - Qualitative Interviews Information Sheet]	3	08 January 2019
Participant information sheet (PIS) [Patient & Family Carer Information Sheet]	3	19 September 2018
Participant information sheet (PIS) [Patient Information Sheet]	3	08 January 2019
Research protocol or project proposal [Project protocol]	10	09 January 2019
Summary CV for Chief Investigator (CI) [Fliss CV]	1	18 September 2018
Summary CV for student [Helene CV]	1	19 September 2018
Summary CV for student [Gochi CV]	1	19 September 2018
Summary CV for student [Sophie's CV]	1	19 September 2018
Summary CV for supervisor (student research) [Jason CV]	1	19 September 2018
Summary CV for supervisor (student research) [Joseph CV]	1	19 September 2018
Summary CV for supervisor (student research) [Miriam's CV]	2	19 September 2018
Summary, synopsis or diagram (flowchart) of protocol in non-technical language [Summary of project]	2	17 August 2018

IRAS project ID	250981

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	The applicant has confirmed The Jean Bishop Integrated Care Centre will act as a Research Site in the study. Submission of an amendment is required to include further Research Sites in the study.
2.1	Participant information/consent documents and consent process	Yes	Following REC review, very minor non-substantial changes were made to the participant information sheets to comply with HRA Standards. REC review was not required.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	There are 3 site types participating in the study. A statement of activities has been submitted for all 3 site types and the sponsor is not requesting and does not expect any other site agreement to be used.
4.2	Insurance/indemnity arrangements assessed	Yes	The sponsor has confirmed the design, management and conduct of the study will be covered under its insurance arrangements. A Certificate of Insurance has been provided.
4.3	Financial arrangements assessed	Yes	External funding has been secured from University of Hull. No funding will be provided to Site Types 1 and 2. Funding will be provided to Site Type 3, a detailed in Schedule 1 of the

Health Care Professionals: A member of the External Research Team will recruit eligible staff participants, undertake the consent process and remaining research activities.

- **Site Type 2 – Care Homes (Intervention Group):**

  Patient Participants: these organisations will screen, identify and approach potential patient participants for the study. A member of the External Research Team will undertake the consent process and remaining research activities.

  Health Care Professionals: A member of the External Research Team will recruit eligible staff participants, undertake the consent process and remaining research activities.

- **Site Type 3 – GP Practices (Control Group):** these organisations will carry out search of patient records to identify potential patient participants, and send mail out to them. External research staff will access/review medical records.

  All remaining research activities will take place off-site.

Please note that the remit of HRA Approval is limited to the NHS involvement in the study. Research activity undertaken at non-NHS sites is therefore not covered and the research team should make appropriate alternative arrangements with relevant management at these organisations to conduct the research there.

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).

The sponsor position and training requirements for the 3 types of participating NHS sites are appropriate for the study, as follows:

- **Site Type 1 - Jean Bishop Integrated Care Centre – ICC (Intervention Group):** A Local Principal Investigator is required and has been identified.

- **Site Type 2 – Care Homes (Intervention Group):** A Local Principal Investigator is required and has been identified.

- **Site Type 3 – GP Practices (Control Group):** A Local Collaborator is required at the participating NHS sites.

GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

In respect of HR Guidelines, the following arrangements are expected:

- **Site Type 1 - Jean Bishop Integrated Care Centre – ICC (Intervention Group):** Where arrangements are not already in place, network staff (or similar) undertaking any research activities that may impact on the quality of care of the participant, would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance.

- **Site Type 2 – Care Homes (Intervention Group):** Where arrangements are not already in place, network staff (or similar) undertaking any research activities that may impact on the quality of care of the participant, would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance.

- **Site Type 3 – GP Practices (Control Group):** As this study is taking place in GP practices you are advised to contact the primary care management function to follow local processes.

Use of identifiable information held by an NHS organisation to identify potential participants should be undertaken by a member of the direct care team for those participants. No additional arrangements (honorary research contracts or letters of access) should be necessary for identification and referral of potential participants at the PICs.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.

- The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.
- Please note the final list of documentation does not match with the final list of REC approved documentation. This is due to the submission of a non-substantial amendment (that does not require submission to REC) in order to bring the study in line with HRA Standards.

IRAS project ID	250981

Appendix 14: Demographic and clinical characteristics of those with an opioid prescription documented on their medical record versus those that do not

Some demographic and clinical characteristics that were presented for all study participants in Table 8.5, are now presented in the table below by participants who had an opioid prescription documented on their medical record and those that did not (see Table 1). Statistical comparisons of these groups are also presented. As multiple comparisons are made, a p-value threshold of 0.005 (0.05/11) was sought.

Table 1 Demographic and clinical characteristics for 223 participants, by presence of an opioid prescription at some point over the past year

Demographic and clinical characteristics	**Opioid prescription present on medical record at some point over the past year?**		**Statistics comparing (a) and (b)**
	(a) Yes (n=128) n (%)	**(b) No (n=95) n (%)**	
Age			
Median [IQR]; (range)	81 [73 – 85]; (65 – 99)	82 [77 – 86]; (65 – 98)	**Mann Whitney U test** U = 5117.0 z = -2.02 p = 0.04 *r* = 0.14 *n* = 223
Missing	0 (0.0)	0 (0.0)	
Gender			
Female	80 (62.5)	57 (60.0)	χ^2 (1) = 0.14 p = 0.70 Φ = 0.03 *n* = 223 *(Fisher's exact test p = 0.78)*
Male	48 (37.5)	38 (40.0)	
Missing	0 (0.0)	0 (0.0)	
Ethnicity			
White	113 (88.3)	82 (86.3)	χ^2 (2) = 1.76 p = 0.42 Φ = 0.09 *n* = 214
Mixed/Multiple Ethnic Groups	9 (7.0)	9 (9.5)	
Black African/Black Caribbean/Black British	0 (0.0)	1 (1.1)	
Missing	6 (4.7)	3 (3.2)	
Living Situation			
Spouse/Partner	59 (46.1)	43 (45.3)	χ^2 (3) = 1.36 p = 0.72 Φ = 0.08
Alone	58 (45.3)	43 (45.3)	

Other family	9 (7.0)	7 (7.4)	*n* = 220
Other	0 (0.0)	1 (1.1)	
Missing	2 (1.6)	1 (1.1)	
Smoking Status			
Former smoker	58 (45.3)	46 (48.4)	χ^2 (2) = 0.29 p = 0.86 Φ = 0.04 *n* = 222
Non-smoker	55 (43.0)	38 (40.0)	
Current smoker	15 (11.7)	10 (10.5)	
Missing	0 (0.0)	1 (1.1)	
Index of Multiple Deprivation			
1 (Most deprived)	51 (39.8)	43 (45.3)	χ^2 (4) = 5.36 p = 0.25 Φ = 0.36 *n* = 219
2	29 (22.7)	20 (21.1)	
3	17 (13.3)	16 (16.8)	
4	14 (10.9)	3 (3.1)	
5 (Least deprived)	14 (10.9)	12 (12.6)	
Missing	3 (2.3)	1 (1.1)	
Capacity			
Yes	125 (97.7)	91 (95.8)	χ^2 (1) = 0.63 p = 0.43 Φ = 0.05 *n* = 223 *(Fisher's exact test p = 0.46)*
No	3 (2.3)	4 (4.2)	
Missing	0 (0.0)	0 (0.0)	
Number of comorbid groups			
Median [IQR]; (range)	4 [3 – 5]; (2 – 9)	4 [3 – 5]; (1 – 8)	**Mann Whitney U test** U = 5991.5 z = -0.19 p = 0.85 *r* = 0.01 *n* = 223
Missing	0 (0.0)	0 (0.0)	
Functional status (AKPS)			
Median [IQR]; (range)	70 [60 – 80]; (50 – 90)	70 [60 – 80]; (50 – 90)	**Mann Whitney U test** U = 5670.0 z = -0.89 p = 0.38 *r* = 0.06 *n* = 223
Missing	0 (0.0)	0 (0.0)	
Electronic Frailty Index Score			
Fit	2 (1.6)	1 (1.1)	χ^2 (3) = 0.56

Mild frailty	4 (3.1)	3 (3.2)	p = 0.91 Φ = 0.05 *n* = 212
Moderate frailty	27 (21.1)	24 (25.3)	
Severe frailty	88 (68.8)	63 (66.3)	
Missing	7 (5.5)	4 (4.2)	
Rockwood Clinical Frailty Scale			
Median [IQR]; (range)	5 [5 – 6]; (2 – 7)	5 [5 – 6]; (1 – 8)	χ^2 (7) = 10.32 p = 0.17 Φ = 0.22 *n* = 217
Missing	3 (2.3)	3 (3.2)	

Those with an opioid prescription documented on their medical record at some point over the past year and those that do not have a similar distribution of demographic and clinical characteristics. No significant differences were found in these comparisons. Although, age reaches statistical significance at the 5% level prior to correction (U = 5117.0, p = 0.04). Participants who had an opioid prescription documented on their medical record were slightly younger, with a median (IQR) age of 81 (73–85) compared to those that did not (median (IQR) age of 82 (77–86)).

Appendix 15: Opioids analgesics currently prescribed

Prescription type and opioid preparation

43 (53.8%) were prescribed a regularly scheduled opioid analgesic, 30 (37.5%) were prescribed an opioid analgesic on a pro re nata schedule, and seven (8.8%) were prescribed both a regularly scheduled and pro re nata opioid analgesic. Participants were predominantly prescribed an immediate-release opioid analgesic (n=55; 68.8%). Fewer participants were found to have a modified-release preparation (n=18; 22.5%) or a combination of immediate-release and modified-release opioid preparations (n=7; 8.8%).

Route of administration

Table 1 presents the routes of administration. The most common route of administration was oral (90%), followed by transdermal patch (16.3%). Subcutaneous administration occurred in one participant only.

Table 1 Routes of administration for participants (n=80)

Route of administration	**N (%)**
Oral only	66 (82.5)
Transdermal patch only	8 (10.0)
Oral and transdermal patch	5 (6.3)
Oral and subcutaneous	1 (1.3)

Number of opioid analgesics currently prescribed

Table 2gives details of the number of opioid analgesics prescribed, as well as a breakdown of regularly scheduled and pro re nata. Overall, the median number of opioid analgesics prescribed was 1.

Table 2 Number of opioid analgesics currently prescribed, including by prescription type

Number of opioids	N	Mean	SD	Median	IQR	Range
Total number of opioid analgesics	80	1.2	0.4	1	1 – 1	1 – 3
Number of regularly scheduled opioid analgesics	50	1.1	0.2	1	1 – 1	1 – 2
Number of pro re nata opioid analgesics	37	1.1	0.2	1	1 – 1	0 – 2

Daily dose in oral morphine equivalent

The following table (Table 3) provides a summary of the daily dose in oral morphine equivalent for all opioid analgesics currently prescribed, followed by a breakdown of those that were regularly scheduled and scheduled pro re nata. Median daily doses for all opioid analgesic ranged between 12.0mg for the lowest possible dose and 24.0mg for the highest possible dose. Median daily doses were higher for regularly scheduled opioid analgesics.

Table 3 Daily dose in oral morphine equivalent for opioid analgesics currently prescribed, including by prescription type

Prescription type	N	Daily dose in oral morphine equivalent (mg/d)		Missing
		Lowest possible dose Median [IQR]; (range)	Highest possible dose Median [IQR]; (range)	
All opioid analgesics	80	12.0 [9.0 – 31.5]; (1.5 – 210.0)	24.0 [12.0 – 40.0]; (1.5 – 220.0)	0
Regularly scheduled	50[a]	20.0 [12.0 – 37.0]; (1.5 – 210.0)	24.0 [12.0 – 40.0]; (1.5 – 210.0)	0
Pro re nata	37[a]	12.0 [6.0 – 20.0]; (3.2 – 80.0)	24.0 [11.7 – 40.0]; (6.4 – 100.0)	0

[a]10 participants were prescribed more than one opioid; including more than one PRN (n=1), more than one regularly scheduled (n=2) and one or more of both prescription types (n=7).

Daily dose in oral morphine equivalents by opioid analgesic are provided in Table 4. The highest median daily dose was 120mg OME for fentanyl. This was followed by morphine. Median daily doses were lower for other opioid types. Daily doses were the lowest for codeine; with a median dose of 9.0mg OME for the lowest possible dose and 12.0mg OME for the highest possible dose. Daily doses for regularly scheduled opioid analgesics were higher for all opioid types, except for tramadol, where doses were similar across prescription types.

Table 4 Daily dose in oral morphine equivalents by opioid analgesics, including by prescription type

Opioid type	Daily dose in oral morphine equivalent (mg/d) Median [IQR]; (range)								
	All (n=80)[a]			Regularly scheduled (n=50)			Pro re nata (n=37)		
	N	Lowest possible dose	Highest possible dose	N	Lowest possible dose	Highest possible dose	N	Lowest possible dose	Highest possible dose
Codeine	40	9.0 [3.2 – 12.0] (1.5 – 24.0)	12.0 [6.4 - 24.0]; (1.5 - 24.0)	18	10.5 [3.2 – 13.5] (1.5 – 24.0)	12.0 [6.4 – 24.0] (1.5 – 24.0)	22	7.7 [3.2 – 12.0] (3.2 – 24.0)	15.0 [6.4 – 24.0] (6.4 – 24.0)
Tramadol	15	20.0 [20.0 – 40.0] (10.0 – 40.0)	40.0 [20.0 – 40.0] (15.0 – 40.0)	5	20.0 [17.5 – 30.0] (15.0 – 40.0)	40.0 [17.5 – 40.0] (15.0 – 40.0)	10	20.0 [18.8 – 40.0] (10.0 – 40.0)	40.0 [35.0 – 40.0] (15.0 – 40.0)
Buprenorphine	10	24.0 [12.0 – 45.0] (12.0 – 72.0)	24.0 [12.0 – 45.0]; (12.0 – 72.0)	10	24.0 [12.0 – 45.0] (12.0 – 72.0)	24.0 [12.0 – 45.0] (12.0 – 72.0)	NA	-	-
Morphine	10	40.0 [20.0 – 105.0] (10.0 – 180.0)	50.0 [20.0 – 105.0] (20.0 – 180.0)	8	60.0 [20.0 – 105.0] (20.0 – 120.0)	60.0 [20.0 – 105.0] (20.0 – 120.0)	4	30.0 [12.5 – 55.0] (10.0 – 60.0)	40.0 [25.0 – 55.0] (20.0 – 60.0)
Dihydrocodeine[b]	5	12.0 [6.5 – 12.0] (4.0 – 12.0)	18.0 [10.0 – 24.0]; (8.0 – 24.0)	3	12.0 (9.0 – 12.0)	18.0 (12.0 – 24.0)	2	8.0 (4.0 – 12.0)	16.0 (8.0 – 24.0)
Oxycodone[c]	4	28.2 [17.8 – 41.3] (15.0 – 45.0)	28.2 [17.8 – 41.3] (15.0 – 45.0)	4	22.5 [15.0 – 41.3] (15.0 – 45.0)	22.5 [15.0 – 41.3] (15.0 – 45.0)	1	11.3	11.3
Fentanyl[b]	3	120.0 (60.0 – 210.0)	120.0 (60.0 – 210.0)	3	120.0 (60.0 – 210.0)	120.0 (60.0 – 210.0)	NA	-	-
Meptazinol[b]	2	20.0 (20.0 – 20.0)	20.0 (20.0 – 20.0)	2	20.0 (20.0 – 20.0)	20.0 (20.0 – 20.0)	NA	-	-

Abbreviations: mg/d Milligrams per dium, *IQR* Interquartile range, *NA* Not applicable

[a] 10 participants were prescribed more than one opioid; including one participant who was prescribed a regularly scheduled and pro re nata prescription for oxycodone and two participants prescribed regularly scheduled and pro re nata prescriptions for morphine, which is reflected in the table above.

[b] The IQR is not presented, in addition to the range, where 2 - 3 participants had an opioid prescription for the opioid type.

[c] The IQR and range are not presented where one participant had an opioid prescription for the opioid type.