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Barriers and enablers to prescribed opioids optimisation in patients with chronic non-malignant pain.

By

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Abstract

The aim of this research was to investigate stakeholders' perspectives on facilitators and barriers of opioid optimisation for patients with chronic non-malignant pain (CNMP) and use the insights gained to inform a proposed intervention. A systematic review of previous interventions was complemented by three linked qualitative studies with different stakeholder populations. Study 1 involved semi-structured interviews informed by the Theoretical Domains Framework (TDF) with 22 community pharmacists. Study 2 collected data on patients' perspectives from their posts' online discussion forums. In study 3, semi-structured interviews were conducted with three clinical pharmacists and eight pain consultants in pain clinics. Data in all three studies were analysed thematically using TDF domains as coding categories.

The systematic review revealed heterogeneity in previous interventions' terminology, methods, target populations and outcomes. They showed a focus on patient behaviour but insufficient consideration of influential psycho-social factors. Study 1 showed pharmacists perceived themselves as guardians of patient welfare but felt hindered in optimisation efforts by a lack of authority, training, and time. Study 2 revealed the life-alerting physical, emotional and social impacts of pain on patients. It highlighted the importance of a supportive relationship with healthcare providers but showed that patients felt unsupported and stigmatized. Study 3 highlighted the importance of individualized, patient-centred, but there were suggestions that some healthcare providers lack the training and knowledge needed to support patients through opioid therapy and tapering.

Based on the synthesised results and using the Behaviour Change Wheel (BCW) as a guide, the proposed intervention was designed with the aim of facilitating optimisation intended to improve providers' communication skills, reduce stigmatization of CNMP patients, encourage shared decision making and facilitate patient education on opioids via provider education and training, persuasion and modelling, in a blended learning programme. This should lead to more appropriate, individualized prescribing and tapering decisions and patients feeling understood and supported, leading to better compliance with treatment.

Dedication

To my parents & all chronic pain patients.

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Note: Copy of all published papers see (Appendix 1)

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Alenezi, A., Yahyouche, A. & Paudyal, V. Current status of opioid epidemic in the United Kingdom and strategies for treatment optimisation in chronic pain. *Int J Clin Pharm* **43,** 318–322 (2021). https://doi.org/10.1007/s11096-020-01205-y.	2021
Alenezi, A., Yahyouche, A. & Paudyal, V. Roles, barriers and behavioral determinants related to community pharmacists' involvement in optimising opioid therapy for chronic pain: a qualitative study. *Int J Clin Pharm* **44,** 180–191 (2022). https://doi.org/10.1007/s11096-021-01331-1.	2021
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Abbreviations

Abbreviation	Definition	Abbreviation	Definition
BCTTv1	The Behaviour Change Techniques Taxonomy (version 1)	MUR	Medicine Use Review
BCW	Behavioural change wheel	MRC	The Medical Research Council
BL	Blended learning	NHS	the National Health Services
BTC	Birmingham Treatment Centre	NICE	The National Institute of Clinical Excellence
BZD	Benzodiazepines	NSAIDs	Non-Steroidal Anti-inflammatory Drugs
CASP	The critical appraisal skills programme	PIS	Participant Information Sheet
CBT	Cognitive Behavioural Therapy	OTC	Over the Counter
CF	Consent Form	OUD	Opioid Use Disorder
CIC	Expert Citizens Charity	QoL	Quality of Life
COT	Chronic Opioid Therapy	RCT	Randomized Controlled Trial
COREQ	Consolidated Criteria for Reporting Qualitative Research	SBI	Screening, Brief Intervention
COVID-19	Coronavirus disease 2019	SBIRT	the Screening, Brief Intervention with Referral to Treatment
CNMP	Chronic Non-Malignant Pain	SR	Systematic Review
GPs	General Practitioners	SRQR	Standards for Reporting Qualitative Research
GDPR	General Data Protection Regulations	TDF	The Theoretical Domains Framework
HCRW	Health and Care Research Wales	UoB	University of Birmingham
HCPs	Healthcare Professionals	UoH	University of Hull
IASP	The International Association for the Study of Pain	UK	United Kingdom
MDT	Multidisciplinary Team	USA	United States of America
MeSH	Medical Subject Headings	WHO	The World Health Organization
MEDD	Morphine Equivalent Daily Dose		
MHRA	Medicines and Healthcare Regulatory Agency		

Chapter 1: Introduction

1.1 Background

The opioids dilemma has been around for the last three or so decades, yet up to this day, the number of people dying from overdosing on opioids is still on the increase, and there is no radical solution to it, despite the extensive research and investment that have been undertaken.

This thesis reports three linked qualitative studies investigating various stakeholders' (pain consultants, clinical pharmacists, community pharmacists and patients) views of the facilitators and barriers to opioid optimisation in the treatment of patients with chronic non-malignant pain (CNMP). The ultimate aim is to synthesise the insights derived from these sources to inform a proposal for an intervention to improve appropriate prescribing and patient usage of opioid medications in CNMP cases in response to the "opioid dilemma" caused by the conflicting concerns to alleviate pain while also safeguarding patients against the harms associated with prescribed opioids use and misuse. This chapter provides a rationale for the studies and sets them in context by outlining the background to current concerns around opioid use in CNMP and defining key terms and concepts, including CNMP, medication optimisation, and problem medication-taking behaviours. It also introduces the role of pain healthcare providers and community pharmacists in optimisation to justify the focus on these two professional groups in this thesis.

1.2. Pain and chronic pain

Pain is a complex experience that affects various biological, psychological, and social factors (1, 2). The International Association for the Study of Pain (IASP) describes pain

as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage”(2,3). This definition emphasises its multi-factorial nature. Most literature agrees that pain is a subjective experience with no objective measurements (4). Pain may be categorized according to its cause into nociceptive or neuropathic pain. Nociceptive pain results from nociceptor stimulation by chemical, thermal or other noxious stimuli. Neuropathic pain is due to an alteration in the nervous system (5). Furthermore, pain is classified into visceral and ischemic pain. The first is usually initiated in the body’s internal organs and is reflected in the somatic tissue, such as renal calculi, cholestasis, and pancreatitis. These conditions feature mainly nociceptive pain and are managed by non-steroidal anti-inflammatory drugs (NSAIDs)(6). Ischaemic pain is primarily due to obstruction, insufficient blood flow, trauma or injury, such as peripheral arterial disease (7).

Pain is commonly temporary and called acute pain. However, when pain persists for more than three months, it is considered chronic pain, which usually has a substantial negative impact on health and quality of life (3, 6). Pain is a stressor that leads to fear, anxiety, depression, uncertainty, and many other negative consequences that can affect patients’ emotions and how they interact with their surroundings (8). Chronic pain serves no protective function and usually disturbs sleep and other human needs and destroys vital human capability. The substantial effect of chronic pain on patients is not always due to biological factors but can also stem from psychological or social factors(9).

In the discussion of pain, it is common to distinguish non-malignant pain from that associated with malignancy. Chronic non-malignant pain (CNMP) is defined by the International Association for the Study of Pain IASP as pain that persists regardless of

normal tissue healing and persists for three months or more (3). The World Health Organization (WHO) categorizes CNMP as a chronic disease because it has most chronic disease features; for example, it may last a lifetime, can lead to functional impairment, is irreversible, requires patient rehabilitation and regular medical care and supervision (10). CNMP can persist and remain even after the physical cause has been resolved. It also can present due to pathological alteration in the central nervous system in the absence of another disorder (3, 7). Chronic pain may worsen with time (2, 11) and is usually associated with a substantial effect on the quality of life (12). In some cases, only a partial pain reduction is achieved with treatment, and there is often a significant impact on patients, their families, and carers. Fifty percent of CNMP pain patients have a diagnosis of depression, and 66% of them are unable to work as it affects their mood, sleep, and mobility (13). Half have considered suicide, regardless of the coping strategies used(14,15). The current evidence suggests a significant gap between an increasingly sophisticated understanding of the pathophysiology of pain and the common insufficiency of its treatment (16). In a study that compared the quality of life between CNMP patients admitted to multidisciplinary pain centres and cancer patients, the former reported their health-related quality of life (HRQoL) as miserable as that of dying cancer patients (17). Poorly managed CNMP leads to a deterioration in the emotional and physical states of the patient.

1.2.1 Chronic pain prevalence

CNMP is a widespread universal public health problem. Prevalence estimates of CNMP vary extensively due to different chronic pain definitions, assessment methods, and population characteristics presented in epidemiological studies (18). Typical CNMP estimates range from 10-30 % (2). According to another estimate over 35% of

the worldwide population lives with CNMP (19). Twenty percent of the European population suffers from CNMP (20,21). In the UK, the rate reaches 46.5%, which is considered the highest among Western countries, and 15% of these cases are in severe pain (22). Approximately 29% of England's population is estimated to live with musculoskeletal conditions such as osteoarthritis and rheumatoid arthritis(23). One-third of the UK population are suffering from CNMP and 10-14% of these patients are severely disabled (24). Two of the most extensive Pan-European surveys have both stated that the most common chronic pain conditions are chronic back pain and arthritis, particularly osteoarthritis (21). Nearly 60% of adults in Europe had experienced pain lasting from 2-15 years, and 21 % had suffered from pain for 20 years or more(21,25).

1.2.1.1 Future predictions of chronic pain prevalence

The prevalence of CNMP has increased in the 21st century and will continue to do so for several reasons. First, the population's rate of ageing is surging, as are poor states of health associated with CNMP, such as arthritis, heart disease, and diabetes. Obesity is the second reason for increasing CNMP, associated with diabetic neuropathy, orthopaedics issues, and cartilage degradation. The third reason is the progress in healthcare technology, which saves lives from catastrophic injuries from such events as crashes, sports, work, and wars, creating a group of young adults who suffer from lifetime chronic pain. The fourth reason is that surgical patients whose surgery is performed in an ambulatory care setting tend to have a higher rate of chronic pain due to inadequate management of acute pain following the surgery (26).

1.2.2 Cost of chronic pain

The cost of chronic pain is immense; it is one of the most common, expensive, and disabling conditions for the healthcare system and the workplace (21, 22). It has a substantial economic impact on society and healthcare systems because of the associated morbidities, high consumption of healthcare resources, lost income, and productivity loss (24,27,28). In a study in Ireland aiming to measure the direct and indirect economic cost of chronic pain among patients attending a pain management clinic, the data showed that each patient costs the health system around £9,514for the in-patient and the out-patient systems. The total cost, including the indirect cost, was £ 21,196 annually, and over half of this cost was attributed to wage replacement and lost productivity(24). Furthermore, CNMP patients cost the Irish economy around £1.66 billion annually as a direct cost of healthcare only (29). The UK's direct cost of prescribed analgesics reached £537 million in 2016, with at least an additional 50% from co-analgesics such as antidepressants and antiepileptics, which are usually used with other analgesics to manage CNMP. The indirect cost in loss of productivity was estimated to be up to £10.7 billion. The treatment of musculoskeletal conditions accounted for the third-largest area of NHS programme spending at £4.7 billion between 2013-2014(23, 30).

1.2.3 Treating chronic pain

Usually, the treatment of chronic pain calls for a bio-psycho-social multidisciplinary approach that may include psychological support and physical rehabilitation (31). An essential aspect of treating chronic pain is that all health care professionals must have knowledge of the tools used to help treat pain, optimise the medication use and reduce the negative consequences of long-term use. Their role should involve appropriate prescribing and regular assessment of the long-term use of opioids and other

controlled substances, as well as the education of their patients. Optimal management of chronic pain necessitates that healthcare providers understand the magnitude of chronic pain and treatment barriers that must be surmounted to ensure adequate care. Patients with CNMP vary widely in their needs due to the subjectivity and complexity of pain; therefore, healthcare providers need to be knowledgeable about different guidelines and risk assessment tools. Different tools can optimise CNMP management to support monitoring and analgesic regimens that can control pain while minimising the negative consequences and interactions with any concurrent medication(32,33).

1.3 The opioid dilemma

1.3.1 Opioid prescribing

For thousands of years, opioids have been used as an analgesic for medicinal purposes. In the first half of the 20th century, restrictive regulations were imposed on the use of opioids due to their powerful addictive properties. Nevertheless, the use of opioids for pain management is still considered fundamental in most of the world. In the 1990s, the USA recognised the mandatory early recognition and management of pain as a standard of care (34). An educational programme for pain management was designed by Purdue Pharma, the pharmaceutical company that had developed OxyContin. OxyContin was marketed as less addictive than morphine, leading to an increase of its sales by 146% due to the overprescribing of it by primary care physicians rather than pain specialists (35). Another factor is that the WHO's analgesic ladder, which is the most popular guideline for the treatment of chronic pain, states that the dose of strong analgesics can be increased as the pain intensity increases until the pain is controlled. There is, however, evidence that pain may or may not be controlled with increasing opioid doses. However, harm is dose related. This evidence shows that the WHO ladder and other guidelines fail to take into account the complexity of chronic

pain, which also leads to an increase in inappropriate opioid use and harm (36). CNMP patients initially respond well to opioids, but their pain scores do not respond in a linear way to opioids. Attempts to decrease chronic pain scores using higher doses or more prolonged use cause adverse effects (37).

1.3.2 Problem medication-taking behaviours

Medication-taking behaviours among CNMP patients are enormously complex including underuse, overuse, misuse, abuse and addiction (38). Literature on the use of opioids in CNMP emphasises adverse events on the patient, including overdose, physiological dependence and subsequent withdrawal, addiction, and negative impacts on functioning. Prescribed opioid abuse and diversion are the second most common form of illicit drug abuse following marijuana in the USA (39). It is striking that as many as 40% of long-term opioid users develop problem behaviour, including obtaining opioids from multiple prescribers, forging prescriptions, buying opioids from the black market, and intranasal or intravenous use of oral opioids. The predictors for opioid misuse and other risk assessment tools that clearly define risk factors for opioids still remain debatable, since few epidemiologic data are available on abuse by CNMP patients (40). However, commonly accepted risk factors for opioid abuse and misuse are personal or family history of drug or alcohol abuse, use of cannabis, psychosocial comorbidity, psychiatric morbidity, young age, back pain, multiple pain complaints, a higher degree of subjective pain and more significant pain influence on functional capacity (41,42). The North American opioid crisis highlights the importance of documenting potential opioid-related adverse events and problematic medication-taking behaviours. The volume of literature on problematic behaviour may indicate both

the high interest in and salience of problems due to the illicit and inappropriate medical use of opioids.

Accurate identification, enumeration, and categorisation of problematic opioid use, including dependence, misuse, abuse, and addiction are essential for proper CNMP management. However, they are poorly defined, so clinicians are faced with uncertainty regarding the long-term effects and the process of effectively assessing, predicting and preventing the occurrence of problematic medication-taking behaviours and optimising medication usage amongst these patients (43). There is a need to differentiate and identify the types of problematic opioid taking behaviour (e.g., misuse, abuse, addiction) and discern their frequency in treated CNMP patients. Attempts to calculate rates of these behaviours have suffered from imprecise and poorly defined terminology. There are two recent sets of consensus statements, one proposing a framework for measuring abuse liability for use in trials of analgesics for those with CNMP and the other a set of definitions for opioid-related adverse events, which identified eight loose and overlapping categories of problematic use, including misuse, abuse, addiction, aberrant use, dependence, nonmedical or nontherapeutic use, physical dependence, and psychological dependence. The vagueness inherent in these definitions, areas of overlap among them, and their sometimes-interchangeable use have made it difficult to determine exact rates and types of problematic opioid use (44). For example, a narrative review, documenting the findings of 25 studies involving CNMP using opioids, concluded that the prevalence of problematic opioid use behaviour fluctuated between 0% to 50% (45). This wide variation in the reported rate of these behaviours has a negative impact on clinical and policy decisions regarding the precision of using screening and treatment resources.

1.3.3. Opioid-related harms

The use of opioids in treating CNMP continues to raise concern globally, particularly regarding opioid analgesics such as oxycodone, morphine, fentanyl, and hydromorphone. Large-scale opioid prescribing is prevalent in several countries. However, in some, it has been accompanied by an increase in reported opioid abuse and deaths(46). There is a dearth of evidence regarding long-term opioid therapy effectiveness for CNMP as it is mainly based on short-period studies. For more valid evidence, a long-term randomized controlled trial (RCT) design is required to explore the real effect of long-term opioid use for CNMP. However, this seems impossible, due to the difficulty and ethical concerns in conducting such an RCT due to opioid side-effects and an expected large number of dropouts (47). Therefore, no firm evidence exists that confirms the long-term use of opioids in CNMP management sufficiently relieves pain and improves the quality of life. On the contrary, it is known that high opioid use can have severe effects on the respiratory, cardiovascular, gastrointestinal, musculoskeletal, immune, endocrine and central nervous systems (47 ,48).

1.3.4. Other challenges

Long-term opioid use is associated with several potential harms. However, there is a gap in understanding pain management strategies because many complementary and alternative medicines are often not considered or available as viable options to traditional opioid treatments(49). Patients perceive that treating their pain is more important than the potential risks of opioids(49). They express scepticism about the effectiveness of non-opioid analgesics and fear of withdrawal(49,50). During tapering, well-established communication and positive patient-provider relationships are pivotal in helping patients understand why they are being tapered and assuring them that they will not be abandoned (50). Furthermore, the limited time of clinical visits is a typical

issue of most health care systems, which is usually associated with diminished satisfaction among patients (51). Another major clinical dilemma is that no clear scientific evidence exists regarding the optimum speed of opioid tapering or individualised tapering strategies due to the dearth of published clinical trials and comparative effectiveness studies of long-term opioid tapering for CNMP, a challenge that may pose threats to the provider/patient relationship (51,52).

1.4. Professional involvement

1.4.1 Healthcare providers

For both the healthcare provider and the patient, controlling chronic pain can be challenging. In most cases, it is not possible to eliminate pain using pain medication, including strong analgesics like opioids, alone(53). Hence, the principal objective in CNMP involves reducing an individual's pain and attempting to improve the patient's general quality of life. Before prescribing opioids, healthcare providers must cautiously consider whether opioids are appropriate and whether alternative medication with fewer side effects can be used. If other alternatives have been exhausted and opioids are the only analgesic to use for a particular patient, extensive and regular assessment of the opioid's suitability should be implemented to reduce the patients' risk of problematic medication-taking behaviours (54). Communication about CNMP and its treatment is challenging, especially when opioids are involved. An effective provider-patient is essential for building successful communication and trust. It may increase patients' satisfaction, adherence and involvement in their condition management, and reduce healthcare utilisation. Unsupportive and broken-down patient-provider relationships and poor communication about pain management and tapering can exacerbate these challenges(55). Opioid tapering may require regular clinic visits, risk assessment, close monitoring of withdrawal symptoms, psychological and behavioural

counselling and referral for non-medication modalities for pain (50). A provider-patient relationship is the cornerstone of health care: how information is gathered, diagnoses made, treatment decisions, and progress or outcomes assessed. Denying patients the medications they expect or have been prescribed long-term may have a detrimental effect on this relationship and lead to doctors' frustration and burnout (50,55).

1.4.2 Pharmacists

Literature suggests that a well-structured CNMP management programme to promote medicines optimisation and to improve patients' quality of life should include multicomponent interventions delivered by a multidisciplinary team (38). Community pharmacists can play an important role in this. There are approximately 12,000 community pharmacies in England, distributed across rural, urban, affluent, and deprived areas. It is estimated that 90% of the English population live within a 20-minute walk of a community pharmacy and make at least one visit to a community pharmacy per year for an over the counter (OTC) purchase, prescription collection, or general healthcare advice (56). Community pharmacists have professional training related to medications' therapeutic use. They are well-positioned to continually evaluate medications' use appropriateness, monitor their potential risk, and check any medication interactions. They are often considered the most accessible health professionals yet are underutilised. The community pharmacists' role is changing from medication dispensing to more clinical-oriented services that focus on patients obtaining the optimal benefit from prescribed medication by working directly with them and advising other clinicians involved in the patient's care(57). This shift in the role has been supported by national and international policy. For instance, NHS England agreed to a five-year deal from 2019 until 2024, which guarantees community

pharmacies' funding levels. Through a structured framework, the deal sets out a clear vision for the expansion of clinical service delivery. This framework has three distinct service levels: essential, advanced, and locally commissioned, where all community pharmacies must demonstrate that they actively promote public health and well-being (58).

The community pharmacies under this framework provide traditional services, including medication dispensing and medicine use reviews. In contrast, the locally commissioned services are intended to improve access to healthcare services in disadvantaged areas where many people suffer from conditions such as smoking cessation, alcohol misuse and obesity, issues highlighted by The Strategic Review of Health Inequalities in England (59). There is growing interest in developing the capacity of the profession to provide interventions or direct treatment referrals for patients who may need special help. For example, the screening, brief intervention (SBI), with or without Referral to Treatment (SBIRT) evidence-based questionnaire has been used to identify and reduce risks associated with problematic use of drugs and alcohol (60). This can be done by screening all prescriptions and being vigilant for aberrant opioid use behaviours such as unapproved dose escalations, concurrent use of alcohol, requesting early refills or signs that indicate a patient is suffering from Opioid Use Disorder (OUD). This model has been deployed effectively in a range of community and clinical settings. Studies in the USA suggest that community pharmacists have constructive attitudes toward pharmacy-based screening and intervention to help chronic opioid therapy (COT) patients and patients with OUD (61). Also, numerous studies in the UK have proven the acceptability and feasibility of delivering brief alcohol interventions in community pharmacies (62,63). However, little is known about

community pharmacists' experiences, with a scarcity of literature focusing on the UK's pharmacists' perspective. Most of the undertaken studies, mainly surveys in the US, have shown pharmacists are facing enormous challenges within community pharmacy settings. In the current context of a growing long-term use of opioids for CNMP within the UK, gaining the pharmacists' perspective may underscore a need for interventions to mitigate the issue. One aim of the thesis, therefore, was to identify challenges faced by community pharmacists in the UK in the dispensing of prescribed opioids for CNMP.

1.5. Research Gap

Overall, literature is scarce about the challenge that healthcare providers are facing in opioid optimisation and tapering for CNMP patients. Despite the importance of factors associated with physicians' opioid prescribing practices, the conclusion from these sparse studies has been inconclusive. One study concluded that pain consultants are more likely to prescribe an extended-release opioid for at least 60 days, while another found that rheumatologists and general practitioners (GPs) were more likely to prescribe long-term opioids (64,65,66). However, the role of pain consultants in opioid prescribing practices remains largely unknown. Most North American studies concluded that opioid prescription practices for CNMP varied based on providers' personal, idiosyncratic beliefs regarding their appropriateness. More comprehensive understanding of the context and environment in which each specialist practises are crucial as different specialisms encounter various types of pain patients with different pain intensity and pain progression (67).

Few studies have explored healthcare providers' perspectives on opioid optimisation for CNMP in the era of opioid tapering process its challenges and there are calls for evidence-based strategies that may help in improving the care of CNMP patients who

have been prescribed opioids for a long time and now are facing mandatory tapering of their medications. Very little information is available on facilitator and barrier factors in the reduction or tapering of prescribed opioids (66).

This thesis responds to these identified needs by exploring pain healthcare providers, community pharmacists and patients' perspectives of prescribed opioids, and the facilitators and barriers to optimisation.

1.6 Research aim and objectives

Aim: The aim of this research is to explore barriers and enablers to long-term prescribing and use of opioids for chronic non-malignant pain (CNMP) and design an intervention that assists prescribed opioid optimisation.

Objectives: To attain the above-stated aim, the following objectives are pursued:

- To identify the quality, nature, process, and outcomes of interventions for medicine optimisation in CNMP patients. (Systematic review; see Chapter 4).
- To explore barriers and enablers to appropriate long-term prescribing and use of opioids for CNMP from the perspectives of community pharmacists(Chapter 5).
- To explore barriers and enablers to appropriate long-term use of opioids from the perspectives of patients using chronic pain patients' forums (Chapter 6).
- To explore barriers and enablers to appropriate long-term prescribing and use of opioids for CNMP from the perspectives of pain specialist healthcare professionals (pain consultants, clinical pharmacists) (Chapter 7).
- To design an intervention that assists prescribed opioid optimisation. (Chapter 8).

1.7 Structure of the thesis

This remainder of the thesis is organised into eight chapters, as follows:

Chapter 2 sets the thesis in context by highlighting the current status of the opioid epidemic in the UK (which differs from that in the USA). Chapter 3 provides an explanation and justification of the methods used to address the research objectives, including a systemic review of literature reporting interventions for medicine optimisation for CNMP, identifying the quality, nature, process and outcomes of such interventions. The first of the linked empirical components of the present research is reported in Chapter 5, which explores the perspective of community pharmacists. The second component, an investigation of patients' perspectives on opioid use and optimisation is reported in Chapter 6. Chapter 7 reports the third empirical study, which presents the views of clinical pharmacists and pain consultants. In chapter 8, the synthesized results from Chapters 4-7 are used to inform a proposal for an intervention intended to facilitate optimisation by improving communication and relationships between CNMP and their healthcare providers within an individualized, patient-centred approach to treatment. Chapter 9 concludes the thesis by highlighting the research contributions and implications, acknowledging its limitations, offering reflections on the research experience, and suggesting directions for future research.

Chapter 2: Opioid Epidemic in the United Kingdom

This chapter has been published in entirety. Current status of opioid epidemic in the United Kingdom and strategies for treatment optimisation in chronic pain

2.1 Publication

This chapter has been published in entirety as Alenezi A, Yahyouche A, Paudyal V. Current status of the opioid epidemic in the United Kingdom and strategies for treatment optimisation in chronic pain. International journal of clinical pharmacy. 2021 Apr;43(2):318-22. (Appendix 1).

2.2 Chapter description

It was decided to highlight the current status of the opioid epidemic in the UK as the extent of the epidemic in this country is different from North America. The UK healthcare context has played an extensive role in its extent, whether in the degree of prescribed opioid use for the CNMP or the data available of the effect of the inappropriate opioid prescribing. The chapter begins with a brief introduction, defines chronic opioid therapy, and then discuss the trends in prescribed opioid use in the UK and some other facts that need to be highlighted to understand the current opioid use in this country.

2.3 Introduction

The term ‘opioid epidemic’ specifically refers to increased deaths and hospitalisations due to prescribed and illicit opioids and their analogues. The opioid epidemic in the United States (US) has led to calls internationally regarding rational prescribing and use of prescribed opioids as well as the need to address the misuse of illicit opioids (for instance, heroin and opium) and diverted pharmaceutical opioids (such as buprenorphine, methadone, and morphine)(34,35). The aim of this chapter is to critically discuss current practice and research regarding the extent of prescribed opioid use, particularly in the context of chronic non-malignant pain (CNMP) management and identify how rising opioids (both prescribed and illicit use) related morbidity and mortality can be addressed.

2.3.1 Chronic opioid therapy (COT) in the management of CNMP

COT, defined as the use of opioids on most days for more than three months, remains the mainstay of CNMP (68). CNMP is a condition where patients persistently or recurrently experience pain for at least three months (3). CNMP affects 20% of adults worldwide. In the United Kingdom (UK), studies suggest that up to half of the population (about 28 million adults) may be living with CNMP (22). There is, however, a lack of evidence of improved patient outcomes in relation to the use of COT in CNMP. A recent randomised clinical trial has shown adverse effects and notably worse pain intensity in opioid users compared to non-opioid users, with modest difference in pain interference (69). Evidence also suggests that discontinuing COT in CNMP does not substantially reduce pain intensity (68). COT is associated with various adverse effects including suicide attempts and polydrug use (opioids with alcohol or benzodiazepines), serious

fractures, immunosuppression and increased risk for cardiovascular disease and early mortality. Adverse consequences of COT on the healthcare system and the wider society due to opioids dependence, misuse, abuse and addiction have also been reported (68). The term Opioid Use Disorder (OUD) is often used to define the clinical implications of COT. OUD is compulsive behaviour characterised by consumption of more opioids or for longer than originally intended that leads to serious impairment or distress (70).

In addition to CNMP, prescribing of opioids for acute indications such as surgical pain in opioid-naïve patients can also lead to a transition to COT. Data show that patients prescribed opioids within seven days of surgery are 44% more likely to become COT users within a year than those not prescribed an opioid (71).

2.3.2 Trends in prescribed opioid use in the UK

Many UK based studies show an upward trend in opioid prescribing and use in the National Health Services (NHS) parallel to that in the US. In 2017–2018, 12.8% of England's population had an opioid prescription dispensed, with approximately 50% taking them for at least one year(72). A 400% rise in prescription opioids has been reported in the past decade in the UK (73). Dispensing of opioids by community pharmacies increased in England from 33.1 million to 40.5 million between 2008 and 2018 (74).

Currently, in England, over half of drug deaths are known to involve an opiate (75). Direct links between prescribing practices (including any potentially inappropriate prescribing) and opioid-related harm and deaths need to be further investigated. However, the observed increase in prescription opioids corresponds to increased

opioid-related death trends. Overall, prescribed opioid associated deaths in England and Wales had a four-fold increase between 1993 and 2017 (75).

There is also an increasing trend in deaths associated with more potent opioids such as fentanyl products. For example, in England fentanyl-related deaths increased from eight in 2008 to 135 in 2017 (76). Guidelines recommend that such strong opioids be prescribed for unremitting cases, specifically for short-term use only, stepping patients down to weaker opioids as appropriate, or withdrawing if ineffective (77). However, prescribed doses are known to be too high and prescribed for too long. The rise in tramadol-related mortality combined with a rise in tramadol prescription supply illustrates the link between prescribing and opioid-related morbidity and mortality(78).

2.4 Geographical variations and link with deprivation

There appear to be regional variations within the UK in the prevalence of opioid use and deaths. Drug use in Scotland is disproportionately higher than in other parts of the UK. Between 2017 and 2018, Scotland had 1187 -related deaths per million populations, three times that in England and Wales (79). Regional variations in higher opioid-related deaths have been linked to higher deprivation, social issues, and the availability of street fentanyl. Inequality-associated social risk factors (childhood drug exposure, prison drug exposure, adverse childhood events, homelessness, unemployment, social marginalisation, mental illness, psychological trauma) are other linked risk factors (79, 80).

Links between deprivation and higher rates of both prescribed and illicit opioid use have been further demonstrated in the published literature. Opioid prescriptions are nearly two times higher in areas with greater deprivation in England (55). Approximately 90% of the highest opioid prescribing areas are located in the north of

England, demonstrating a strong link with deprivation(80). The greater prevalence of chronic pain and lack of adequate addiction treatment services in socio-economically deprived areas may lead to suboptimal prescribing practices. In addition, populations in deprived areas are more likely to take these medicines chronically, usually alongside antidepressants, benzodiazepines, or gabapentinoids (72,81, 82).

2.5 The need for better diagnosis and linked datasets

Better use and linkage of healthcare databases are needed in the UK to obtain a clearer picture of the extent of both prescribed and illicit opioid use. There is a need to establish linked datasets to identify the magnitude of inappropriate use of prescribed opioids including overprescribing, opioid abuse, diversion, adverse events including mortality, and underutilisation of substitution treatments for pain including CNMP and to develop further evidence-based approaches to addressing the problem(83). For instance, prescribed opioids can be obtained from various sources (the independent health sector and the internet), but data from these sources are not integrated. In addition, there is a lack of data on the sales of over-the-counter (OTC) opioid-containing preparations. The lack of integrated healthcare data between primary (general practice/ family physician clinics) and secondary (hospital) is also a barrier to treatment optimisation. For example, National Health Services primary care prescribers face challenges due to delayed or incomplete patient discharge medical records from hospitals(84,85). There is also a need to improve toxicological assessments to identify causative factors for overdose incidents, information-sharing on drug overdose and deaths and establishment of useful links between national datasets, including death registrations and national treatment monitoring systems(86).

2.6 Role of healthcare professionals and the need for person-centred guidelines

Person-centred care enhances the patient's involvement in their own care to meet their unique expectations in treatment, planning, and delivery elements. Non-consideration of patient needs can lead to suboptimal outcomes. For example, in the US, the misapplication or misinterpretation of the Centre for Disease Control guideline on opioid prescribing for chronic pain led to forced opioid tapering and abandonment for patients who were on COT(87). Many CNMP patients faced a significant challenge in obtaining proper care, reportedly resulting in profound physical, emotional, and societal costs. Such incidents reinforce the need for patient-centred guidelines(88). Best practices in CNMP management should include developing an effective pain treatment plan after accurate evaluation to establish a diagnosis, with measurable outcomes that focus on improving patients' quality of life (QoL), functionality, and daily living activities (38). Also, establishing a therapeutic alliance between patient and clinician based on compassionate, empathetic care is necessary to counter the suffering of CNMP patients(89).

One way to reduce the increase in opioid use is by re-evaluating and leveraging the existing healthcare professionals' (HCPs) roles. Health professionals' ability to balance CNMP treatment while minimising risks for OUD is vital to reduce opioid-associated morbidity and prevent overdose. Appropriate initiation, reduction, or discontinuation of COT is essential to minimise patients' risk of psychological distress and opioid-related hospitalisation(61). Due to the paucity of essential data surrounding the best approach to support COT patients or to treat OUD, a single clinician is unlikely to have the skills to manage these patients' needs. A multidisciplinary team (MDT) is needed, combining the skills of diverse healthcare professionals, including general practitioners, nurses,

psychiatrists, pharmacists and pain consultants, moulding various interventions including medications and non-pharmacological interventions. MDTs can successfully reduce prescribed opioids, and in turn, associated disorders and have been identified to have greater long-term effectiveness than usual care in reducing pain and disability and improving QoL and ability to return to work (38).

The National Institute of Clinical Excellence (NICE) in England is aiming to publish an updated guideline on the management of CNMP, which aims to include rational prescribing of opioids(90). However, the problem has not been addressed optimally, as these guidelines do not clearly state care and support for practical daily decisions in management(91). Individualised patient-centred care in the diagnosis and treatment of OUD related to CNMP is fundamental to improve the outcomes of treatment in these populations. Safe opioid stewardship, with regular re-evaluation of patient risk, is essential, which involves identifying risk factors from patient history, family history, current biopsychosocial factors, screening and diagnostic tools, and integrated behavioural, complementary interventions(92).

Improving access to services is vital in addressing opioid misuse. Access is often difficult for people with dual diagnoses of mental health problems and substance misuse and vulnerable groups such as the homeless populations (93). Therefore, primary care providers, particularly community pharmacists, play a vital role in facilitating accessibility. Patients presenting with a significant level of psychological, physical and/or socio-professional problems should be referred promptly to the appropriate service. Patients who repeatedly struggle with opioid abuse often end up homeless/imprisoned, less capable or motivated to improve their health because of their other life priorities (94). Healthcare professionals, including community

pharmacists, must be supported in managing patients' clinical and social needs, using innovative service models such as social prescribing (95).

Many patients may find perceived stigma (disgrace, humiliation) and discrimination in healthcare settings as barriers to seeking treatment or optimising existing treatment for CNMP and may end up abusing opioids. As many patients who misuse prescribed medications often do not join the 'typical' subculture of illicit users (i.e., social elements associated with illicit drug consumption such as street consumption, socialising publicly with other illicit users) or/ and do not seek help from addiction treatment services, their problems often go unrecognised and untreated (96). In addition, numerous opioid-dependent individuals seek advice from the internet, rather than their HCP, often accessing unreliable sources of information.

2.7 Conclusion

Suboptimal management of CNMP remains one of the key issues linked to the rising in the UK. Evidence from research literature and UK national statistics suggests that such rising trends correspond to increasing opioid-related harms and deaths. Opioid-related deaths are more prevalent in deprived areas, with the North of England and Scotland in particular facing more significant problems. Better linkage of data across care sectors will enable enhanced epidemiological surveillance and monitoring to target the rising opioid-related morbidity and mortality and identify the extent of the contribution made by prescribed and illicit opioids use. There is an urge to enable healthcare professionals to manage CNMP better as well as to prevent, detect, and address OUD earlier. These could be achieved through better education and awareness of OUD, development of person-centred guidelines and a MDT approach combining pharmacological and evidence-based non-pharmacological interventions.

A comprehensive approach to manage the changing needs of CNMP patients will help them to achieve functional recovery, autonomy, and improved quality of life, preventing negative outcomes from their treatment. This thesis contributes toward the development of such an approach by a systematic review of previously reported interventions and investigation of stakeholder viewpoints on prescribed opioid optimisation, which are used to inform an interventions proposal. The methods used to achieve the research objectives are discussed in the following chapter.

Chapter 3: Methodology

3.1 Chapter description

This chapter describes and provides justification for the methods used to carry out the research reported in this thesis, exploring the enablers and barriers to prescribed opioid optimisation for CNMP. It begins by showing, how a systematic review of literature was used to identify gaps in extant research on opioid optimisation and, in turn, refine the research objectives, scope and approach. The philosophy underpinning the empirical investigations and selected strategy and approach are explained. The sampling strategy, data collection methods and data analysis procedure for the three linked empirical studies are discussed. The chapter then explains how the synthesized data was used to design a proposed intervention with aim of improving opioid optimisation by enhancing the relationship between healthcare providers and patients. Lastly, research quality and ethical considerations are addressed.

It is widely acknowledged that “every piece of research, every researcher and every context is, in some way, different and a host of factors contribute to the interpretation of phenomena as knowledge constructed” (97). Therefore, it is critical that each researcher justify the choice of a conceptual framework, assumptions, sampling strategy, and data collection analysis procedures behind their work. This chapter is intended to meet the need.

In particular, the chapter offers a discussion and reflection upon the reasons for selecting a qualitative methodology for data collection and analysis. This research

contributes to the growing body of healthcare research that uses qualitative methods to into take account social and personal factors that contribute to influence health conditions and behaviours.

A key aim of the chapter, therefore, is to offer the reader a sense of the richness and unique contribution that can be made by adopting qualitative methods, underpinned by critical realism.

Another major objective is to explain the role played by theory, particularly the Theoretical Domains Framework (TDF) in structuring the inquiring. It is shown how the TDF was used to guide the development of data collection instruments, as a templet for analysis and (along with the Capabilities, Opportunity, Motivation, and Behavioural-COM-B model and the Behavioural Change Wheel- BCW) to help with the transition from diagnosing behaviour to designing an intervention.

3.2 Systematic review

A systematic review of prior studies was conducted, to establish the evidence base on opioid prescribing and use, and to investigate previous approaches to health intervention. This review informed the decision on what area to research and what approach to take.

Systematic reviews involve several steps, starting with formulating the research question and then producing a protocol that describes definitions, search strategy, inclusion and exclusion criteria, and approach to synthesis, which need to be often peer-reviewed and piloted. Studies retrieved from databases should be screened on the relevance of the title, abstract, and full text, following the inclusion and exclusion criteria. Screening needs to be done by more than one researcher. The studies

included into the analysis are usually characterized by study quality, intervention, research design, type of analysis, and outcomes. The last stage includes the extraction of relevant quantitative or qualitative data to synthesize the evidence(101). Full details about the method used to conduct a systematic review for this thesis, see, section4.4.

3.2.1. Evidence synthesis through a systematic review of literature

Identifying the existing evidence within a subject area through a literature review has been suggested to offer several benefits to the researcher (99,100) as basic knowledge must be built on prior or existing work. Conducting a literature review helped the researcher to understand the extent and complexity of the current body of work and identify gaps. By identifying, summarising, analysing, and synthesizing a group of related literature, the researcher was able to form specific objectives and avoid repeating previous work (100). The validity and quality of existing work was evaluated against a set of criteria to reveal weaknesses, inconsistencies, and contradictions. The synthesis of evidence through systematic review and metanalysis should be valid, reliable, and repeatable and requires critical appraisal skills to judge the quality of scientific evidence of the included studies(89). Such reviews are increasingly valuable in healthcare for clinicians and clinical practice decision-making.

3.2.2. Limitations of Systematic Review

The quality of a systematic review (SR) depends on the quality of the work and findings, the clarity of the written report, and the ability to assess the strengths and weaknesses of the review(101).

The inherent flaws include varied locations and samples, lack of information on outcomes, inappropriate analysis, conflict with new experimental data, and duplication of publications.

Substantial heterogeneity was present, in the studies reviewed. Some sources of variability came from clinical heterogeneity, such as differences in patients, interventions, and outcomes in each study. Clinical heterogeneity assessment entails critical appraisal and there was, also methodologic bias (102).

Due to such limitations, the review provided an insufficient basis for the design of a new intervention. However, it provided valuable insight into the issues around opioid prescribing and use and into various mechanisms by which interventions may change behaviour. In particular, it revealed the dearth of literature addressing patients' and healthcare providers' perspectives on the issues around pain management, opioid prescribing and use, and the enablers and barriers to optimisation. In this way, it helped in the identification of gaps in knowledge to be addressed in the empirical studies. The design of these studies was further informed by the use of the Theoretical Domains Framework (TDF). Discussed later.

3.3 Research philosophy

Research is described as a logical investigation or question using data that has been collected, analysed, and interpreted to identify, define, predict or monitor a phenomenon(103). It is important to start by establishing assumptions about knowledge to suggest a road map to plan and perform research. The assumptions could be ontological (beliefs held about what the world is, what is reality, and what we can know about it) or epistemological (beliefs held about what we know about the

social world and how we know it). The interaction between ontology and epistemology will constitute the research philosophy.

3.3.1 Ontology

There are different ontologies, but the most common ones are objectivism/realism and subjectivism/ relativism(99,103,104,105). Objectivism believes the world is one, a total external reality that is independent of peoples' thoughts, beliefs, and understanding. Subjectivism believes that the world is not separable from cognition, and there are multiple realities, since it believes external reality is known through human perception and socially constructed meanings(105). This thesis is based on the belief that there is an objective 'reality', since it is well established that opioids cause various harms, including deaths, but also that behaviours around opioid prescription and use are influenced by social and institutional factors.

3.3.2 Epistemology

The choice of ontology has implications for epistemology, which is a viewpoint about what constitutes applicable knowledge and how it can be achieved. Those who agree with the concept of a single, objective reality will be inclined to assume that knowledge of it can be acquired by scientific observation and measurement. On the other hand, others who see the social world in terms of subjective experiences and sense-making consider that the meanings people attribute to their experiences are valid sources of knowledge, which can be obtained by shedding light on participants' world and examining it through their eyes(99,105). Consistent with the ontological position stated above, the decision was made to engage with the individual voices of people who suffer from CNMP and use opioids to manage their condition, as well as the healthcare providers who are involved in their treatment journey, in the belief that people's

experiences and attitudes can be best understood by interacting and engaging with the people concerned and seeing the world through their eyes.

3.3.3 Research paradigms

Understanding knowledge development and its precise nature provides the foundation for research and helps determine its direction. Views about the world and how researchers "see" the data vary according to their background knowledge and training; these views are referred to as paradigms (99,106). There are several research philosophies, such as positivism, interpretivism, realism, and pragmatism. Positivism and interpretivism were for many years, the dominant philosophies. Realism and pragmatism developed as responses to the complexity of reality and knowledge, as well as the difficulty of drawing definite understanding between distinct ontologies and epistemologies.

Positivism relies on an empiricist, rationalistic philosophy and this paradigm assumes that the world is independent of the researcher (107). It describes relationships of cause and effect using scientific methods in a completely deterministic manner (99, 105). This paradigm helps the researcher in the analysis of data collected on different variables. It is usually used to test a theory using direct data collection rather than derived through logic(97,99).

Interpretivism assumes that there are multiple realities, and knowledge is obtained and determined through understanding the perspectives of participants(97, 107). Therefore, interpretive researchers depend on participants' views of the situation being studied (104, 107). This approach deeply relies on the skills of the researcher, who acts as a research instrument, rather than on the research method(99,108).

Pragmatism claims that the research question should be considered first, then the researcher can derive both ontology and epistemology(104). Researchers can use any method, techniques, and procedures to answer their research questions, rather than adhering particularly to anyone approach. This paradigm is adopted when addressing a research question that needs different perspectives in order to be fulfilled(97-99).

Realism is like positivism in assuming a scientific method to the development of knowledge. It includes two types: direct realism and critical realism. Direct realism assumes that what individuals experience accurately represents their reality, while critical realism assumes that what individuals experience are images of things in the world, not exactly the things themselves (97-99,109). Critical realism utilises an interpretive epistemology that emphasises and accepts that people have different, imperfect understandings of reality(97-99).

The phenomenon this thesis is investigating is the use of opioids in CNMP. Some aspects of opioid use have an objective nature and can be observed and measured, e.g. the number of prescriptions issued or the number of deaths. However, the research essentially concerns a social phenomenon that involves subjective attitudes and perceptions. Different stakeholders (CNMP patients, community pharmacists, clinical pharmacists, and pain consultants) have different experiences and perceptions, and differences are likely, even within the same stakeholder group, e.g., different perceptions of pain, different levels of knowledge, different views on the efficacy and morality of particular behaviours. This thesis is exploratory in nature, with an emphasis on understanding more about healthcare providers and CNMP patients'

perspectives on enablers and barriers to long-term opioid use in managing CNMP. Accordingly, a critical realist philosophy is adopted.

In critical realism, social action is assumed to be influenced by economic and social structures. Critical realist researchers aim not only to identify behaviour patterns or describe experiences but also to understand why these patterns or experiences occur, drawing attention to multiple factors that influence people's thinking and behaviours(110,111). In this study, for example, the aim is not simply to describe opioid prescribing, deprescribing, or use behaviours, but to gain insight into the social factors (such as deprivation) and institutional factors (in this study, for example, the structure and mode of operation of the healthcare system) that facilitate or constrain particular behaviours. Critical realism proposes three" dimensions" of reality: empirical, actual, and real. The empirical dimension consists of objects and events as perceived by individuals(112). Critical realism acknowledges that there is a real world (the actual dimension) that exists independently of our perceptions, theories, and constructions. At the same time, it accepts that our understanding of this world and the meanings individuals attach to their experiences are inevitably based on our own constructions of reality. The empirical dimension describes human experiences of those events(113). The "real" dimension refers to the mechanisms, powers, structures, and tendencies that influence the events taking place in the actual dimension. While those domains can be observed, their impact or presence is not necessarily synchronized. The falling leaf analogy is often used to explain this although falling leaves are subject to gravity, they are often influenced by other mechanisms, such as wind or thermal currents(99,113). Critical realism is becoming more influential as it fits well with how people view and see the world around them,

and importantly, people can identify with its approach. Those who adopt a critical realist view maintain that the knowledge that can be obtained at any specific point is valid only in terms of the experience available at that time. This experience could shift and change depending upon structure and agency(100,112,113). Critical realism allows theory formation to be based on what is happening at a particular time, while accepting that the same outcome may not be achieved in different circumstances. In other words, critical realist researchers claim that knowledge is fallible and can be gained, but then it can change. It is objective in that it acknowledges a world that exists independently of people's perspectives and understanding, but it also accepts a degree of subjectivity and variability that should be taken into account (114).

3.4 Research approach

After deciding on a research philosophy, the selection of the proper research approach is important. The research approach and the research philosophy will affect the choice of the study design and the sampling, data collection, and analysis methods. There are two main research approaches, deductive and inductive (115). The deductive approach aims at theory testing, based on accurate scientific research. It is characterized by establishing causal relationships and using quantitative data, controls other factors which could reduce the effect of variables under investigation, and is statistically generalizable (97,99,115). The inductive approach focuses on creating theory and it is common in social science. It works in a natural setting and appreciates the role of the context of the research to allow explanations of reality and knowledge (104,105). In this study, the approach taken was a combination of deductive and inductive elements, known as abductive. Like the deductive approach, it started from a basis of theory; a theoretical framework, the Theoretical Domains

Framework was used to help structure the inquiry (see section 3.7 for the way in which the TDF guided the data collection). Insights derived inductively from participants' accounts of their beliefs and experiences were linked back to the TDF, which was used to aid interpretation and explanation (see section 3.10).

3.5 Research strategy

Researchers often classify research design into three broad types: descriptive, explanatory, and exploratory. The classification of these categories changes according to the purpose of the study (97,99,116). The purpose of exploratory research is to understand "what is happening," "seek new insights," and "evaluate phenomena in a new light"(97).The exploratory approach is helpful to analyse events, find new concepts, and develop ideas in a new context, as well as when the research problem is unclear or new. Exploratory study provides a deeper understanding and investigates the feasibility of a more detailed study for further developments(117). This approach has a crucial feature of flexibility to help the researcher understand the problem area.

The aim of descriptive research, in contrast, is to deliver an exact description of an individual, event, or situation, while explanatory research is concerned to determine the relationships among various variables, considering that a theory should explain how and why particular factors relate together, as well as the connections, relationships, and timings between phenomena and events, not a list these factors, concepts, or characteristics. However, these research types are not essentially mutually exclusive. Descriptive research, for instance, could incorporate elements of exploratory or explanatory research(104). At the same time, the descriptive approach creates a comprehensive snapshot of various aspects of observations from events. However, it needs a well-structured question about the research problem. Descriptive

study aims to provide an extensive profile of people, situations, and events. This type of research design can create new knowledge in a specific research field where the problem area might be unfamiliar and challenging to understand(118).

This study has elements of all three strategies. It is descriptive because it describes the current situation of opioid prescribing and use and what people are doing; it is explanatory because it tries to shed light on the reasons for people's behaviour (although it does not investigate formally the relationship between variables), and it is exploratory because it is looking at a complex phenomenon from new perspectives. Accordingly, the researchers initially created the study protocol, identified specific objectives and purposes, and then decided on methodological approaches to understand, describe and explain the factors contributing to suboptimal opioid prescribing and use.

3.6 Methodological choices

Paradigms help structure and clarify the reason for making particular decisions regarding research, which will help determine the choice among mono method (quantitative or qualitative), mixed methods or multi-method approaches. The advances in medicine that lead to improved health outcomes and longevity are mainly attributed to empirical quantitative studies. Previously, healthcare research has been dominated by quantitative methods established on positivist and post-positivist research paradigms (97,99,116,119). However, recently, many have criticized the biomedical model, which views health and illness in purely physical terms. This model, with its separation of body and mind, neglects the human dimension of suffering, and overlooks the importance of the patient's subjective experience (104,120). Recognition of the limitation approach led to a surge in the use of qualitative approaches, which are

concerned with reaching a comprehensive understanding of individuals' experiences of chronic illness and their medication use. Generally, this approach aims to contribute and enrich understanding of the particular phenomenon and generate new insights (104,107 ,121). Qualitative approaches were considered appropriate to the descriptive and exploratory purposes of this study. Accordingly, a qualitative multi-method approach was adopted(104,109).

The term multi-method research is used to describe the use of multiple forms of the same type of data: either qualitative data such as interviews and observations or quantitative data such as survey data and experimental data (97). This differs from mixed methods research, which combines qualitative and quantitative approaches. Both have been used and welcomed by scholars and critiqued. Whether combining quantitative with qualitative methods or combining different qualitative methods in one project, the objective is to benefit from the strengths of the multiple approaches. These combinations can provide a clearer understanding of a research problem (97, 99,110,122). For this thesis, the primary data were collected using interviews and textual analysis of data from patients' discussion forums.

3.6.1. Justification for choosing a qualitative methodology

The qualitative methodology describes a phenomenon's features, characteristics, or complexities to allow the understanding of a research problem or social phenomenon via participants' narratives(97,111). Qualitative research is defined as a kind of "systematic inquiry into meaning"(112,123). The term systematic implies that this kind of inquiry is orderly and planned. It also shows that the research is conducted according to a set of rules that have been agreed among the community of qualitative researchers(123). Generally, qualitative research is a process of interpretation that

seeks to describe and explain people's experiences to understand a phenomenon using words rather than numbers (97, 99). The qualitative report in a written form typically includes quotations from participants. Various methods are used to collect qualitative data, such as one-to-one interviews, observation, focus group, and case study. The word empirical denotes the inquiry is founded in the world of experience, with interpretation and explanation of problems from the researcher's perspective(97,99). The phrase," inquiry into meaning" speaks to how scholars involved in research attempt to comprehend how others try to make sense of the experiences they go through(124). This approach in the gathering of data and its subsequent analysis has seen an increase in popularity in healthcare research and pharmacy practice research, based on the view that not all research problems can be explained by the hard fact, numbers and graphs. This is different from the quantitative paradigm, which uses numbers to represent reality. Also, while the quantitative approach is used to measure outcomes of interventions, qualitative research can be used to understand the process by which any intervention may produce an outcome(125).

The goal of this study was to explore, analyse and interpret barriers and enablers of prescribed opioid optimisation. Based on the discussion above, it can be argued that the qualitative research methodology fits this purpose. Another reason why a qualitative method was more suitable has to do with the fact that there is very little research done on this topic and there is a requirement for a deeper understanding of not just quantitative data, such as numbers of prescriptions, or opioid-related death but also the qualitative elements, such as how individuals perceive and experiences opioid prescribing and use, or personal and environmental factors that influence their

behaviour. A qualitative approach is usually suited to elicit a range of experiences, and the meanings behind a phenomenon in-depth, which would address gaps in academic knowledge (104). An in-depth qualitative methodology was considered the most appropriate design to meet the aims of the study, in view of the paucity of evidence regarding the perceptions of UK patients and their healthcare providers around the use of prescribed opioids for CNMP. Most previous UK qualitative work concerned codeine-containing OTC medications. Qualitative work was also a natural methodological approach for the epistemological and theoretical perspective of this study(99,104). It allowed the researcher to investigate the healthcare providers and patients ' different perceptions of prescribed opioid optimisation in CNMP management and the factors which contributed to those perspectives. Furthermore, qualitative approaches in health research have been increasingly recognized as a means to provide substance and meaning to quantitative studies (125). An in-depth study of the significance of enablers and barriers to optimising the use of prescribed opioids for CNMP was likely to shed light on factors that can inform future interventions development. For this thesis, three studies were carried out to obtain healthcare providers' and patients' perspectives on opioid optimisation. Two of these, involving community pharmacists and clinicians' employed interviews. The third involved textual analysis of data from patients' discussion forums. The use of these methods is justified and explained in the following sections.

3.7 Use of Theory in the Research

Use of theory in pharmacy-based research has traditionally been lacking (126), and a lack of a theory-based approach was evident in the studies and interventions reported in the Systematic Literature Review conducted for this thesis. However, the UK's

Medical Research Council emphasizes the important role of theory in developing health interventions (127,128). Use of theory can strength research robustness and rigour and can increase the relevance and impact of the finding (126). In this study, therefore, a particular concern was to base the research on theoretical grounding. Theory was used in developing data generating instruments. Thereby ensuring that the research findings are data-driven(129,130). It was also used to form a coding framework for thematic analyses of the collected data (130).

The choice of a theoretical lens for research depends on consideration of various factors, including the research field and nature, and how others have used the themes. In this research, the theoretical strategy point was a behaviour change theory, the Theoretical Domains Framework.

3.7.1The Theoretical Domains Framework (TDF)

The Theoretical Domains Framework (TDF) is an integrative framework that combines fundamental theoretical components in behaviour modification theories(131). The TDF was introduced as an elaboration of the COM-B (capability, opportunity, motivation, behaviours) model on which the Behavioural change wheel (BCW) is based, to enable in-depth examination of the barriers to and facilitators of change, as well as to guarantee that change processes are successfully targeted. The framework is made up of 14 domains that are more intricate subdivisions of the capacity, opportunity and motivation dimensions.

According to the TDF, people's capabilities are defined by their knowledge, memory, behavioural regulation, skills, attention, and decision-making processes with respect to a behaviour; their opportunities are determined by social influences and environmental context and resources; and their motivations are determined by their

social/professional role and identity, beliefs about capabilities, optimism, intentions, goals, beliefs about consequences, reinforcement, and emotion. The COM-B and TDF can both be used to determine what has to change in order to achieve the desired behaviour, so both assist us in determining which behavioural factors to target in an intervention(132).

An advantage of the TDF as a guide to behaviour change is that its broad, multi-disciplinary basis allows and encourages consideration of a wider and more varied range of potential influences on behaviour than might be achieved by relying on a single theory or perspectives, aims to efficiently study and group the full range of behaviour change theories belonging to different traditions and disciplines such as sociology, psychology, nursing, anthropology, communications, economics, and marketing. The TDF is designed to uncover the way social and environmental factors shape behaviour and can be used to guide interaction with individuals, to find out how they perceive and experience these factors. In this way, it is consistent with the ontological and epistemological position outlined earlier. Examples of how this framework has been used include an investigation into the factors that influence doctors' prescribing behaviour, assessment of implementation difficulties in tobacco use prevention and cessation counselling among dental care providers and to explore behaviour of individuals involved in behaviour change interventions (133-135). After consideration of the philosophical background, assumptions and previous uses of the TDF, three empirical studies, reported in this thesis, were designed and conducted using similar approaches to those that have been used in other studies.

3.8. Primary data collection 1: The pharmacists' and clinicians' studies

3.8.1 Choice of method

There are many types of qualitative designs recognized in the literature, including narrative inquiry, grounded theory, ethnography, phenomenological analysis and action research(136). Phenomenological analysis is based on the belief that reality is a product of individual consciousness and the conventional borders between object and subject are an artefact of the "empirical turn"(137). Phenomenological data try not only to find common themes and identify the "essence" of the participants' experiences but also to understand the situations and conditions surrounding their experiences. This study made use of phenomenological analysis, to explore experiences related to prescription and use of opioids to manage CNMP during the opioid crisis era and the factors that can facilitate or hinder optimisation. Narrative inquiry via interview met the needs of this research because it gave pharmacists and clinicians the opportunity to present their experiences during this particular time.

There are different types of interviews, which are structured, semi-structured, and unstructured (97,99). The types differ from each other in terms of the extent to which the interview is guided and in the way that they are conducted. The main difference between the three types is "*the degree to which participants have control over the process and content of the interview*"(138).

Structured interview

The structured interview is an extremely rigid instrument, which is described as a "verbally administered questionnaire"(139). Questions are presented in a systematic format with no prompts and there is no scope for follow-up questions to further investigate responses if detail and deeper understanding is required. It enables interviews to be conducted more quickly. However, it does not allow participants to

express their interpretations of their experiences in their own words, as required by this study.

Unstructured Interview (In-depth or Narrative interview)

The greatest narrative flexibility is offered by the unstructured interview, also referred as the In-depth interview. It is described as a “conversation with a purpose”, that enables researchers to collect in-depth information on a phenomenon of interest(140). Also, it is described as a shared experience “in which interviewers and interviewees come together to establish a context of conversational intimacy in which contributors feel relaxed in sharing their story”(141). Such interviews offer the advantage of great flexibility. However, the volume of information collected makes analysis difficult(142).

Semi-structured interview

The semi-structured interview, is set up around a number of main questions which are necessary to define the areas that need to be studied, but it allows the researcher to ask more questions that are related to the same idea and to look for a response in more detail(141,142). It is a middle way between unstructured and structured interviews. This was the type of interview selected for this study.

A semi-structured approach to the interviews was considered the most appropriate for several reasons. Semi-structured interview is a common data collection method in healthcare research as it permits a flexible discussion (143). Firstly, as an early career researcher, the research student wanted a guide to support the interview process and the development of interview skills. Secondly, the use of an interview guides combined direction with flexibility; there was no fixed order to the interview questions, nor requirements for participants to answer every question. This approach was beneficial as changing the order of questioning allowed both the research student and

participants freedom to explore meanings in a way that had not been previously conceptualized or described in the guide (144). Thirdly, an interview topic guide seemed to suit the needs of several participants. Three participants asked to view a topic guide before the interview, stating that it would help them to prepare for the interview. This may have biased the focus of participants, but it also helped them to feel comfortable during the interview, which enhanced the relationship and trust between participant and interviewer.

3.8.2 Development of Interview schedules

Interview schedules were developed as a means to engage interview participants in conversation and ensure that issues of particular importance to the inquiry were addressed.

The TDF was used to develop the interview schedules, based on the gap found from conducting the systematic review. The TDF is proven to be helpful in developing interview schedules for qualitative healthcare research (144,145).Its use helped to ensure that the interview schedule was rooted in the theoretical determinants of opioid optimisation and the questions reflected the domains of the framework. Each domain was reflected by at least one question in the interview schedules. These questions allowed the researcher to obtain an understanding of the participants' experiences and facilitated interaction, which enabled the researcher to explore the meaning the participants attached to their experiences.

A potential drawback of using interview schedules is that they can restrictive and prevent the researcher from engaging in a responsive and flexible conversation(141,143). However, the researcher was not rigid when using the schedules and instead was open to any interesting points raised by the interviewee,

even if they did not appear on the schedule (141). The questions on the schedule were supplemented by a mix of open and closed prompts, used as bullet points rather than additional questions, which acted as a more general reminder for the researcher to direct the interview in the area of interest. Copies of interview schedules can be seen in Appendix 2.

3.8.3. Sample selection

A sampling method should be adopted to ensure that the sample is appropriate, and the data relevant (146). Sampling is defined as “the selection of specific data sources from which data are collected to address the research objectives”(141). Data are considered as the core of research, so the ways that the data are acquired must be based on sound judgement, particularly since inappropriately collected data cannot be repaired by analysis, even if done many times(139,141).

For a credible application of the methodology, data should be collected from the range of individuals interacting with the phenomenon of study, to provide a comprehensive view into reality and contribute to a rigorous application. The study needed to generate data that represented the fullness of experience in and around opioids optimisation. Thus, a sampling strategy was essential to ensure that the appropriate people were recruited to the study (146).

For this qualitative research, probability sampling was not necessary or appropriate, as creating generalizations to a wider population was not required. The concern was to recruit individuals with specific knowledge and experience relevant to the study objective. The populations sampled were healthcare providers who were involved in decisions and practices around the use of prescribed opioids for CNMP, including community pharmacists and pain specialists.

Sampling strategies

Two sampling strategies, convenience and snowball sampling, were employed for this study. The first sampling strategy, convenience sampling, was dictated by how the study population was accessed. Convenience sampling is described as selecting the most ready, willing, and able to participate in the study (139,141,147). For the study with community pharmacists, participants were recruited through the dissemination of invitation using the professional networks of the research team, including community pharmacy forums. In addition, a large chain of community pharmacies in England encouraged those interested in contacting the research student. For the pain clinicians' study, an invitation was disseminated during a virtual conference. All individuals who contacted the researcher and were deemed eligible to participate were invited to interview. Other participants were recruited by approaching the research team acquaintance and giving them the study package, referred to below. The other sampling strategy used in this study was snowball sampling, which in both studies, was employed alongside convenience sampling. Snowball sampling involved asking participants to refer the study, either to potential participants or to other gatekeepers who could share the study further. The main advantage of this technique was its ability to locate individuals who were not directly accessible to the researcher(148).

In both the studies conducted with pharmacists and clinicians, once invitations were sent to participants, individuals who were interested in participation contacted the research student for further information. Potential participants emailed or telephoned the researcher when making this initial contact. The research student requested those who made contact by email to telephone.

For each of these studies, study package (information sheet and consent form) was developed to fully inform all participants about the study, including the aims, the researcher, and an overview of the nature of the conversation and topics that would be discussed during the interviews. This information sheet also informed individuals that a sampling strategy was being used in the research. An example of this information sheet can be found in Appendix [3]. Similarly, the consent form was created to ensure that the participants understood and consented to all aspects of the study, including audio recording and withdrawing data from the research study. An example of this consent form for the study of the pharmacists has been provided in Appendix [4]. The potential participants were given a minimum of 48 hours to read through the information sheet and consider participation. After this period, if the potential participants had not already contacted the researcher, they were contacted again to ask if they would still like to take part. Willing participants were asked to return the completed consent form to the researcher by email with an electronic signature. Once the consent form had been returned, the researcher contacted participants according to the sampling strategy and arranged a time and place for the interview.

Sample size

Guidance has differed on the number of participants needed for an in-depth qualitative Ph.D. study. Morse (1995) advised interviewing 30-50 participants for a study, while Cresswell (2012) argued that research requires 20-30 participants (99,104). However, some guidance has argued that a prescriptive number of participants would not necessarily elicit enough information to develop a theoretical understanding of phenomena (149). Instead, sampling and interview methods should focus on collecting data until the theoretical significance of this experience was discovered, and

no new experience emerges from the interviews (150). This is referred to as achieving data saturation.

3.8.4 Piloting of interviews

Piloting of interviews is very important before starting the official interviews with the participants, to avoid future problems. According to Stewart (2016) a few interviews should be conducted before starting actual interviews, to test the instruments used for the data collection. Also, the pilot interview assists researchers to familiarise themselves with the procedures(151).

The interview schedules were piloted for both studies with two participants for each study, and minor changes were adopted as necessary. Reflective pieces were written to help the researcher understand how the interviews could be improved and analysed.

3.8.5 Interview procedure

The original intention was to collect the data using face-to-face interviews. However, due to the lockdown restrictions that were enforced in England during the data collection period (between December 2019 and May 2021) telephone interviews were used as an alternative. The use of phone interviews has been criticized for lacking the depth that can be achieved using face-to-face interviews, with speculation that contributors may be withholding information, as well as the concern that absence of body language and interaction between the interviewer and participants could endanger smooth conversation (152,153). However, it is more convenient than face-to-face interviews for both interviewer and interviewees and may be safer for researchers to undertake as they do not involve travel to unsafe environments(154). For this thesis, telephone interviews enabled the researcher to interview a variety of

participants from all over England, which may help to provide a bigger picture of healthcare providers' perceptions of opioid optimisation for CNMP. Also, telephone interviews provide the participants with a better degree of anonymity than face-to-face interviews, encouraging them to discuss sensitive topics (such as problematic opioid use among patients) more freely (152, 154). In addition to this, telephone interviews do not appear to harm the quality or quantity of data being collected(154). Also, the telephone interview was deemed by the interviewees as more acceptable, as they were busy healthcare providers and a telephone interview could more easily be fitted into their schedule, without disrupting their work.

Demographic data about the participants was collected at the beginning of each interview using a simple tick box demographic sheet. These demographic questions proved valuable in 'breaking the ice' with participants and establishing a rapport with which to open the main semi-structured interview. Interviews varied in duration, with most lasting around 30 minutes.

3.8.6 Transcription

Transcription is the transfer of the interview into textual form. The researcher immersed herself in listening to the recorded interviews multiple times to make sure that the interviews included all the required data to enable the researcher to identify themes, and to ensure that the quality of the recordings was appropriate for transcription.

The researcher assigned participants codes to protect their anonymity and confidentiality, using a sequence number. Two interviews in each of the community pharmacists' study and clinicians' study were transcribed by the researcher (AA). The other interviews were transcribed by a transcription company that the supervisory

team had the experience of using. The transcription company abided by General Data Protection Regulations (GDPR), subscribed to the Data Protection Act, and ensured their staff signed confidentiality agreements. The audio recordings were uploaded to a secure site, accessible by only the researcher and the transcription company. After transcription of all the interviews, the transcripts were uploaded to the same secure site, and the audio recording was deleted. All transcript documents were checked against the recording twice by the author, reviewing the content as well as deleting any potentially identifying information (e.g., people's names or places) to anonymize the transcripts.

3.9 Primary data collection 2: The qualitative study with patients diagnosed with CNMP

Due to the difficulty of gaining access to patients for interview, as a result of the delay in obtaining a letter permitting access to the pain clinic (see section 3.13) and restriction on face-to-face meetings imposed because of the COVID-19 pandemic, information on patients' perspective toward their pain, opioid use and tapering were obtained by analysing posts on patients' online forums.

Online discussion forums

The internet has become pervasive in everyday life, and its spread led to an ease of access to online support groups/discussion forums that offer support to patients, who may have difficulty communicating with healthcare providers and seek support from other who have shared similar experiences. This support has been linked to improvements in general wellbeing, as well as better utilization of healthcare services. Research has benefited from access to such forums as a source of naturalistic observations and means of the analysis of interactions (155). Online discussion

forums offer significant benefits in health research as the naturally occurring and unsolicited talk is seen as a useful source of data(156). They offer the opportunity to explore how unsolicited talk occurs in specific social settings. The increasing use of the internet by individuals for purposes of seeking support from peers and lay networks provides both opportunities for individuals to seek support for their distress in a positive way and for researchers to develop insights into how patients talk about their health condition, medication use and distress in a naturalistic setting (157).

In an online discussion, patients might express their needs, frustrations, and challenges in their journey with CNMP and use of opioids more freely with their peers than they do with their healthcare providers. We can gain important insights into how they talk about and seek help for pain, opioid use, and tapering by investigating these discussions. Due to their anonymity and accessibility, patients' discussion forums are recommended as valuable ways for otherwise difficult to engage users of traditional health services to access support. Online forums additionally allow researchers to gather data from sources independently of researcher involvement to investigate people's understanding of their health conditions and beyond. Previous research has explored how peer-to-peer interactions in several discussion forums unfold (158).

Despite the above advantages, however, Internet- Mediated research (IMR) raises particular challenges in adhering to the usual ethical principles of respect for autonomy and privacy, scientific integrity, social responsibility and avoidance of harm (BPS guideline)(159). For example, in IMR, the public-private distinction is often blurred, making it difficult to know whether individuals expected and were willing for their contributions to be accessed and observed outside a specific circle, or whether informed consent for inclusion in the research is needed. In using discussion forums

as source of data in this study, careful thought was given to the risk of disclosing identification data (related to individual participants or to the forum itself). In line with PBS guidelines (159,160), advice was sought in the legal and ethical implication of selecting forums, analysis textual data posted on them, quoting data in the thesis.

Online forums selection procedure:

The search for the online forums, inclusion and exclusion criteria, and analysis are fully described in Chapter 5, section 5.5.

3.10 Data analysis

Data analysis is a complex process that requires an appropriate approach in which the data is filtered through many phases(97,99).The approach used in this study, to analyse both the interview data and the posts from patients' discussion forums was the framework approach. This involved, first, familiarisation with data by listening to interview recording and carefully reading textual data-both interview transcripts and online posts. Segments of the data were then coded into one or more of the TDF domains, with each domain constituting a coding category. The appropriateness and occurring of the coding were verified by discussion with the supervisory tea. Data excerpts were organized into a Microsoft Word® table to facilitate comparison. When several codes were considered to form a meaningful unit, this was deemed a theme. The relevance of each TDF as a determinant of opioid prescribing and use behaviours was assessed based on the frequency with which related codes in the data, or the level of emphasis participants placed on the domain as a factor impacting on opioid optimisation. A content analysis of the framework table was then undertaken to identify sub-themes: factors which constituted a distinct and important concentration of data within the main theme. Summary account, illustrated with representatives quotations,

were completed for each domain and its subthemes, to build an overall picture of how each of the TDF domains may influences the optimisation of prescribed opioid use for CNMP.

Framework analysis is a common tool for data interpretive analysis that is applied to primary qualitative research. It was developed in the 1980s as a matrix-based approach that allows researchers to categorise and code data into pre-specified themes. It allows a greater level of depth, transparency and rigour in the analysis. This method is considered one of the most suitable in providing a holistic, descriptive overview of phenomena, taking a variety of subject-related data into account (161). However, one of its limitations is the issue of subjectivity in the early stages and the lack of ability to capture heterogeneity in highly synthesised data (162). Yet, building the primary framework or a “best fit” framework provided an efficient method to generate a context-specific conceptual model to define and rationalise the decision making and health behaviours of patients and healthcare providers(163). It enabled the researcher to explore the issues around opioid prescribing, use and tapering from a variety of perspectives. In this study, during analysis, both deductive and inductive data analysis was used. This means considering both what participants said and the meanings of what was said, as inferred by the lead researcher (AA), who spent considerable time in understanding, analysing, and coding to provide insight into the research problem. Clear explanations depending on participants' own descriptions of their intentions, beliefs, and circumstances clarify why they carry out actions. In the data coding process, segments of the text were mapped to the TDF. They were then organised thematically to reflect enablers of opioid optimisation, barriers to optimisation and behaviour change strategies.

Thematic analysis is a flexible approach that can be conducted within the critical realist paradigm and is considered to be a suitable approach aligning with the TDF and content analysis(164).

3.11 Intervention design

Health behaviour change interventions must be acceptable, realistic, person-centred, and address long-term health behaviour change. A framework for intervention creation is advised to help guide the development of behaviour change interventions and increase the likelihood that they will be effective and sustainable(165). There are, however, a plethora of frameworks for constructing behaviour change interventions. No research has proven that one of these ways is better than the others, and while intervention developers may carefully follow a published approach, it is recommended that they adopt these approaches flexibly to match their individual situation(165).

In this PhD project, the United Kingdom Medical Research Councils (MRC) framework and the Behaviour Change Wheel (BCW), were used to synthesize the data collected using the Theoretical Domains Framework (TDF) and to design the intervention(128, 166). Following is an overview of the MRC and BCW frameworks, as well as an explanation of why they were chosen.

3.11.1 The Medical Research Council (MRC) framework for developing and evaluating complex interventions

The MRC framework outlines four major steps in the designing and evaluation of health behaviour change interventions(128,166). Figure 1**:** Key elements of the development and evaluation as presented in Figure 1 illustrates the framework, which provides a non-linear four-phase process to constructing and evaluating an intervention. In order to develop an intervention, the MRC recommends conducting a systematic review to

identify the evidence base. This is typically done to investigate the effectiveness of already existing interventions and to investigate components and modes of delivery that are better associated with effectiveness (128).

The MRC steps are:

1. Designing an intervention in a systematic way. This includes utilizing the most up-to-date evidence and the relevant theory.

2. Testing the intervention. The MRC suggest taking a step-by-step approach, beginning with a series of pilot studies with the aim of overcoming the limitations of previous interventions.

3. Conducting a preliminary and final evaluation of the intervention

4. Integrating the findings of the research into clinical practice.

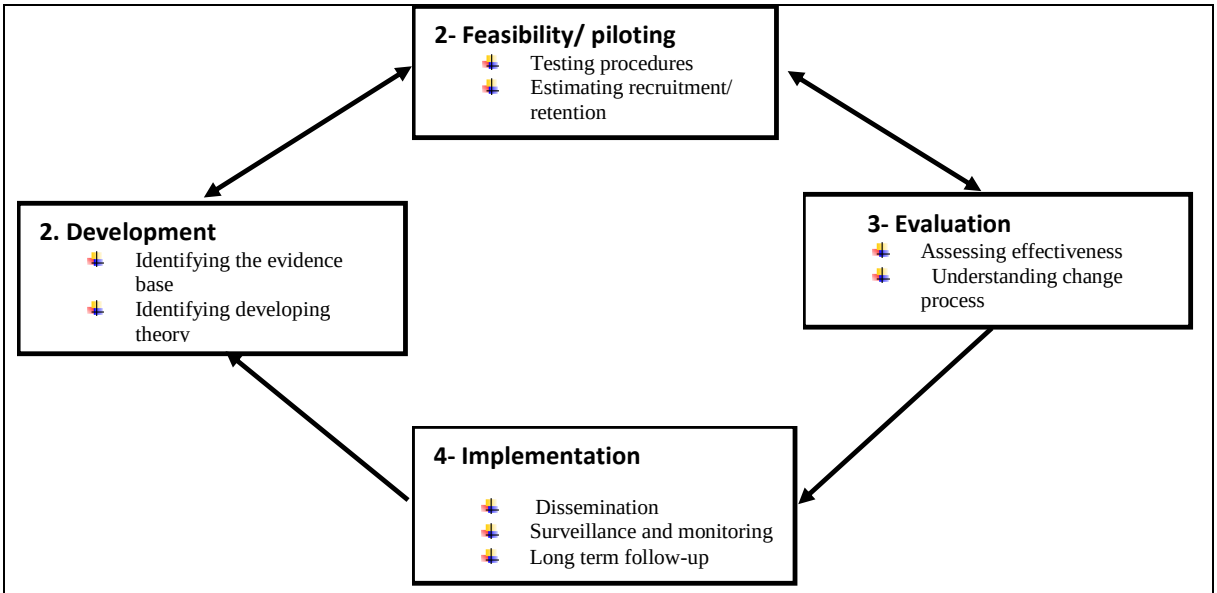


Figure 1: Key elements of the development and evaluation as presented in (128).

3.11.2 The Behaviour Change Wheel

The Behaviour Change Wheel (Michie et al., 2011) is a framework that was created to help with the transition from behavioural diagnostic to intervention design(167). Michie et al. (2011) identified 19 behavioural change intervention frameworks. The BCW was created as a synthesis of the theoretical ideas depicted in the 19 frameworks(167).

The BCW framework is based on a theoretical model that proposes people's capabilities (C), opportunities (O), and motivations (M) are the major drivers of their behaviour (B forming the "COM-B" model, (see Figure 2). Modifying one or more of the behavioural determinants, such as capability, motivation, or opportunity for the behaviour, according to the COM-B model, can lead to a change in behaviour, and modifying the capability or opportunity for the behaviour has an impact on motivation. Figure 2 depicts the Behaviour Change Wheel as described by Michie et al. (2011). The origins of behaviour are highlighted in green; the intervention functions are

highlighted in red, and the policy categories are highlighted in grey. The COM-B model's capability, opportunity, and motivation are at the centre of the wheel. In the COM-B paradigm, capability includes both psychological and physical capabilities. Physical capability refers to the physical abilities required to engage in a specific behaviour, whereas psychological capability relates to the essential knowledge and mental capacity. The term "opportunity" encompasses both the social and physical environments. The physical environment refers to an individual's surrounding circumstances, whereas the social environment refers to the people and conventions in the external world that impact behaviour. Motivation includes reflective (purposeful planning and intents) and automatic (more habitual and emotional reactions and reflexes). The BCW does not prioritise any of the individual components; rather, it enables insight into how modifying one or more of them might lead to the desired behaviour change.

The second and outer layers of the BCW show how behaviour modification occurs as a result of an interacting system with intervention functions and policy categories. Intervention functions are broad categories of methods for changing behaviour that can be used in an intervention. Education, persuasion, incentivisation, coercion, training, restriction, environmental restructuring, modelling, and enablement are the nine intervention functions listed by the BCW. It is conceivable for an intervention to serve many purposes. Communication/marketing, guidelines, finance, regulatory, law, environmental/social planning, and service provision are the seven policy categories listed by the BCW to help with the consideration of how the intervention can be delivered.

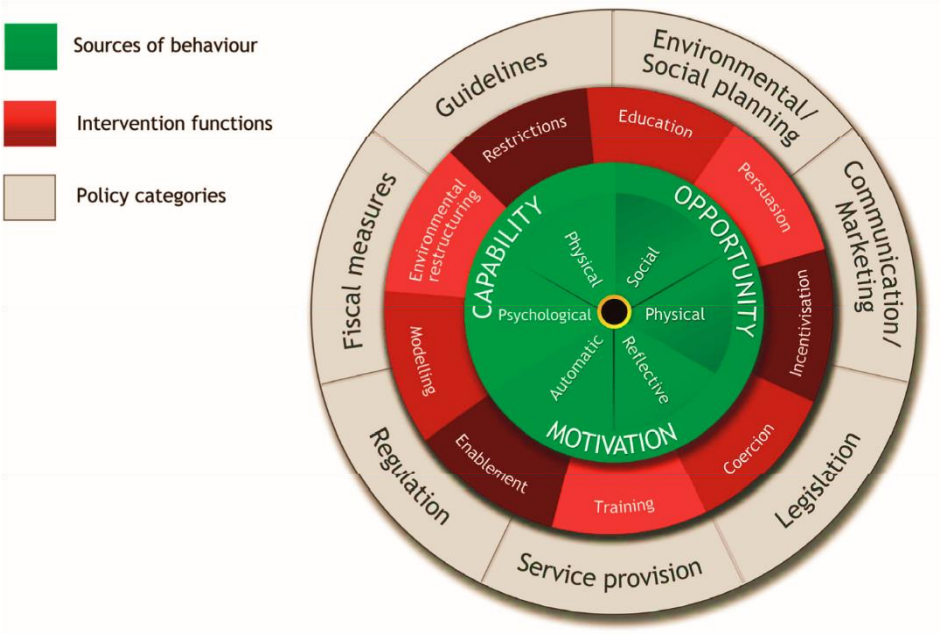


Figure 2: *The Behaviour Wheel, as shown in (167).*

The BCW informs three major stages of intervention design that can be completed in any order: Understanding the behaviour, identifying intervention choices, and determining content and execution alternatives. These stages can be broken down into eight major steps (See Figure 3).

The first stage of establishing the behaviour emphasises the need to describe the behaviour in terms of who must do it, what the person must do differently to make the desired change, when they will do it, where they will do it, how often they will do it, and with whom they will do it. This stage also emphasises the need to determine what needs to change within the individual or in their surroundings in order to change their behaviour. Identifying intervention functions and policies is related to identifying intervention choices. Identification of content and implementation choices is the final stage of the Behaviour Change Wheel. The behaviour change techniques constitute the intervention's content, and the implementation options indicate how each of the intervention's behaviour change techniques should be provided.

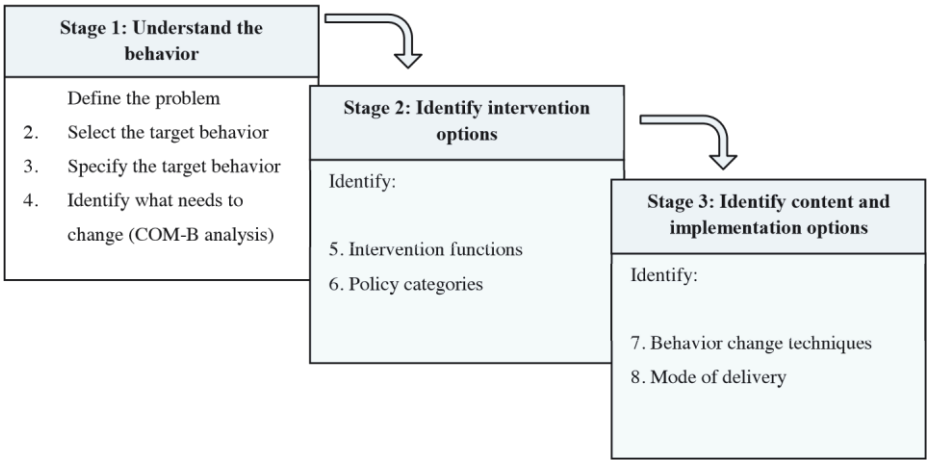


Figure 3: Stages of intervention design in the Behaviour Change Wheel as shown in (166)

The way these fireworks were applied in designing an intervention in this study is explained in detail in Chapter 8.

3.12 Research quality

The criteria for rigour needed to be applied throughout the research process. For instance, to achieve originality, this study needed to focus on prescribed opioids rather than OTC, as these had been under-explored in the UK existing literature. Also, the use of qualitative approaches added to this thesis originality, as most of the UK and international studies applied a quantitative approach. The research quality should be assessed using paradigm-appropriate criteria(168). Because this study uses a subjective ontology and critical realist epistemology, applying typical positivist quality criteria like validity and reliability would be inappropriate. Internal validity, which implies that the findings should correlate to a single "truth," is problematic for a study that allows the existence of numerous "realities"(169).Rather, the goal of this research is to provide meaningful interpretations of the experiences of the participants(170).

External validity is also a concern because the study is context-bound, with conclusions based on certain people's perceptions and values at a specific time. In terms of reliability, Stenbacka (2001) doubts the relevance of a notion with measurement connotations to qualitative research(171). The concept of consistency and stability that it conveys is meaningless in interpretive research, which sees the meanings people attach to their experiences as dynamic, shifting with new experiences and the continual process of making sense of them. Given these issues, this study instead uses Guba and Lincoln's (1989) proposed alternative quality criterion of trustworthiness, which is divided into credibility, dependability, transferability, and confirmability (169). These criteria are now commonly acknowledged as benchmarks for qualitative research evaluation (172).In this research, credibility was pursued by two approaches, each of which is supported in scholarly literature. The first is a process of close engagement with the research participants with the aim of building trust and rapport (169). This process began from sending invitations, through rich explanations of the research objectives, and explaining what the participants needed to do if they considered taking part in the study, including signing the consent form and sharing their contact details, which can be seen as demonstrating a degree of trust in the research process. The second approach to credibility is triangulation, the convergence among multiple sources of information. This thesis, as noted earlier, involved three qualitative studies, offering multiple perspectives on the same phenomenon(173).

Also, the researcher pursued dependability and confirmability, meaning that the research process was transparent, trackable, and carried out with integrity. This was achieved by an inquiry audit of the research processes and outcomes(164). All

material used in the research, such as written transcripts and consent forms, has been retained as evidence of the data collected and the process by which conclusions were reached. Also, the researcher has attended various training courses in different UK universities that focused on qualitative analysis. These included one weeklong qualitative analysis course at the University of Birmingham (UoB), and a two-week course on Data collection and analysis at the University of Hull (UoH). Also, three intensive training courses were taken, each one two weeks long (See Appendix 5 for all the researcher's training courses), that focused on the use of In vivo (Getting started with NVivo part1 and 2), and using NVivo to produce credible data analysis, The researcher ensured she retained familiarity with the use of TDF throughout the study and that all stages of the data analysis were strong and logical, the research methods chosen were suitable to collect data from the range of people who were experiencing the effect of the long-term of prescribed opioids. Finally, to establish the value of this study, thorough research of relevant literature and policy was necessary during data collection, analysis, and writing up to ensure that these original perspectives were real. Consequently, these standards were repeatedly discussed during this study to ensure a consistent application of this methodology from the study design to the presentation and discussion of findings.

Transferability can be enabled through providing sufficient detail about the qualitative study's context to allow a reader to assess whether the study's conclusions may be applied to similar situations. The researcher provided a thick description to enable the reader to judge the possibility of transferability, based on consideration of the level of similarity between the description of this research context and the one where the a transfer will be considered(169,175).

Based on the previously mentioned criteria, therefore, it can be claimed that this research has been carried out with demonstrable integrity and is able to provide a convincing interpretation of the experiences and perceptions of healthcare providers and CNMP patients.

3.13 Ethical considerations

Ethics is acting in goodwill and avoiding harm. The application of good ethical principles can diminish and prevent the occurrence of harm. It is imperative to safeguard all participants contributing to research (176). Qualitative studies differ from quantitative studies, in being performed in natural settings and involving interactions between the researcher and participants. Hence, it is vital that any researcher using the qualitative method be aware of any ethical issues that may arise from these interactions. Orb et al. (2001:94) identify ethical issues as including “informed consent, confidentiality, data generation and analysis, researcher/participant relationships, and reporting of final outcomes.” Ethical principles in the qualitative approach may involve autonomy, beneficence, and justice(176).The following are among the key ethical issues raised in this research.

Ethical and research governance approval

Ethical approval was required for this thesis, and two ethical approvals were obtained. For the community pharmacists' study, ethical approval was gained from the Science, Technology, Engineering, and Mathematics Ethical Review Committee (**ERN_19-1922**), see Appendix 6 for the ethical approval letter. Also. the research team applied for ethical review to the University of Birmingham (UoB) for the patients' discussion forums study; according to the UoB review team self-assessment, no ethical review

was required as there were no human participants and no other risks flagged. See Appendix 7 for the patients' forum ethical approval letter.

The research team had applied earlier for ethical approval from NHS ethics (Health and Care Research Wales (HCRW)) as the study was planned to be conducted in the Birmingham City Hospital and obtained the approval **20/WA/0232 on 5th Oct 2020**. See Appendix 8 for the ethical approval letter. However, due to the COVID-19 pandemic, the Research and Development (Medical) Department at Sandwell and West Birmingham Hospitals informed us that they were prioritizing COVID-19 research studies over any others and would notify us if our study was given access. The researcher emailed them periodically, but access to the pain clinic was not received till the date this chapter was written (a month before the thesis submission date). However, the researcher will explain some of the ethical issues that were considered by the ethics committee during the ethical approval process.

CNMP patients who are using their opioids to manage their condition were categorized as vulnerable. The interview questions for this study were not considered likely to cause any stress or distress to participants. However, there were elements of the study design that may have been unsuitable for vulnerable people . This raised issues around safeguarding processes which needed to be developed in case any participant raised safeguarding concerns that required escalating. The HCRW asked about the public and patients' involvement in the study.

Summary of main ethical issues

The initial documents that were submitted to the ethics committee considered the safeguarding issue, yet they were considered insufficient, and a complete protocol

was requested. The public and patients' involvement had not been considered initially, as the research team is deemed it unnecessary, as the study does not benefit from any public funds (see Appendix 9for the HRA study protocol).

Patient & Public Involvement:

The study followed the National Institute of Health Research guideline on patient and public involvement in research. The research team showed the proposal and recruitment materials, including study protocol, participant information sheets, and consent forms, to Expert Citizens Charity (CIC). Expert Citizens Charity is an independent group of people who have experienced multiple needs, including combinations of mental ill-health. The CIC team considered that the research would be beneficial in supporting healthcare professionals and patients on chronic opioid therapy. Also, the documents were shared with a national charity (Homeless Link.) to discuss how the research team could deal with distressed participants. The manager provided us with a link to the organization's webinar about safeguarding and other training courses for employees who deal with multiple needs individuals.

Moreover, the research team met with the Healthcare team at Birmingham Treatment Centre (BTC), sought their opinion about the study protocol and potential participants, and learned how the chronic pain clinic is operated. Finally, a patient with chronic lower back pain who used chronic opioid therapy read all the study documents (protocol, participant information sheet, consent form, interview questions). The patient confirmed that the participant information sheet and consent form were informative and easy to understand and suggested some questions for patients and healthcare providers.

If a participant raised a safeguarding concern, the interviewer would have discussed this with the participant and then consulted with the supervisory team. Participants were informed of this process in writing, on the participant information sheet and consent form, and verbally before the interview.

Emotional support and safeguarding

A protocol was created to be used if patients showed signs of any distress during the interviews when talking about opioid use, tapering, or discussing their health conditions. If this happened, the interview would have been stopped, and the researcher would have assessed the participants' level of distress and taken action according to the protocol (for the interview distress protocol, see appendix 10). However, this protocol was never used, as interviews with CNMP patients did not take place access was not granted in time due to COVID-19 pandemic research prioritization. See Appendix 10 for the full safeguarding protocol.

Participant privacy and data protection

To ensure that the interviewees' involvement in the study remained confidential, no messages were left by telephone, either by voicemail or with a person who was not the participant. Emails were exchanged between the researcher and participant only. All contact details, such as email addresses, phone numbers, and postal addresses, were deleted at the end of the study period after receiving the signed consent form. To ensure that the research maintained a professional appearance and for personal safety, all communication was via professional channels. The emails were sent from the University's affiliated address, and potential participants were instructed to contact the researcher privately, via email or telephone. Data confidentiality and storage of data were adhered to according to the University of Birmingham requirements. All

documentation related to the project was kept locked away in a secure filing cabinet within a locked postgraduate base room. For full details about participant privacy and data protection, see the study protocol, appendix 8.

3.14 Summary

The aim of this research was to understand the enablers and barriers to opioid optimisation for CNMP patients, with a view to developing an intervention to improve the current situation. A qualitative investigation was undertaken, underpinned by critical realism and informed by a systematic review of prior studies. Three studies were conducted, using the TDF as a guiding framework: two using telephone interviews with community pharmacists and pain-clinic based healthcare providers, and one involving textual analysis of posts on patients' online discussion forums. The data were mapped to the BCW model for intervention development. The next chapter presents the systematic review of interventions reported in previous literature.

Chapter 4: Interventions to Optimise Prescribed Opioids

Interventions to optimise prescribed medicines and reduce their misuse in chronic non-malignant pain: a systematic review

4.1 Publication

This chapter has been published in entirety as Alenezi, A., Yahyouche, A. & Paudyal, V. Interventions to optimise prescribed medicines and reduce their misuse in chronic non-malignant pain: a systematic review. *Eur J Clin Pharmacol* (2020). https://doi.org/10.1007/s00228-020-03026-4 (Appendix 1).

4.2 Chapter description

It was decided to synthesise the current literature on interventions employed to optimise medicine in CNMP patients. This was done with the aim of systematically reviewing the nature, process and outcomes of interventions used to optimise prescribed medicine use and reduce inappropriate use. This review helped informed the research questions for the next research chapters. The literature search was conducted by screening the retrieved literature for eligibility and summarising the study findings in a narrative synthesis.

4.3 Introduction

Chronic non-malignant pain (CNMP) which involves a complex and variable interplay between biological, psychological and social factors (2,3), is categorized by the World Health Organization (WHO) as a chronic disease, because it may last a lifetime, can lead to functional impairment, is irreversible and requires patient rehabilitation, frequent medical care and supervision (3). CNMP prevalence estimates greatly vary, ranging from 8% to 60% in the general population (19, 22). Adverse clinical, humanistic and economic consequences for patients, families and society have been reported (27).

Medication optimisation is defined as “the safe and effective use of medicines to enable the best possible outcomes”(90,177). Analgesics including opioids are a cornerstone in CNMP treatment. Optimising medicines use in CNMP includes preventing and mitigating ‘problematic behaviour’ in relation to the use of opioids and gabapentinoids, in addition to promoting adherence to the prescribed regimen (177). ‘Problematic behaviour’ is aberrant behaviour suggestive of addiction, misuse or abuse of prescribed opioids for use or administration other than intended by the prescriber and is commonly reported among CNMP patients. A previous literature review demonstrates that up to 50% of CNMP patients are known to demonstrate problematic behaviours (45).

Healthcare professionals face the problem of effectively treating CNMP while preventing inappropriate medications use, as well as promoting appropriate prescribing and deprescribing. Therefore, clinicians need strategies and assessment tools to help them weigh the risks and benefits of CNMP treatment. Previous systematic reviews have looked at interventions to prevent or reduce opioids misuse

(178, 179). The concept of medicines optimisation as a whole has not been investigated. The aim of this study was to systematically review the nature, process and outcomes of interventions used to optimise prescribed medicine use and reduce their misuse in CNMP patients.

4.4 Methods

This study was conducted based on the Cochrane Guideline and reported as per Preferred Reporting Items for Systematic Review and Meta-analysis (Electronic supplement 1 See Appendix 10) (180). Systematic reviews are protocol driven reviews based on a priori objectives and plans for literature search, data collection and analysis. A structured approach to identifying, appraising, and synthesizing all relevant studies on a given topic enables researchers to avoid bias in the review process (84). The protocol was developed as per the PRISMA-P (PRISMA-Protocol) guideline (registered PROSPERO ID = CRD42018111569).

4.4.1 Literature search

Electronic searches were conducted in Medline, EMBASE and CINAHL databases using medical subject headings (MeSH) and free text keywords, including medication adherence, patient compliance, adherent, adherence, non-compliant, noncompliance, non-adherent, non-adherence, chronic pain, chronic non-malignant pain and chronic non-cancer pain. The search was limited to the years 2000 onwards.

4.4.2 Inclusion and exclusion criteria

Studies in the English language using an intervention aimed at optimising the appropriate usage of prescribed pain medication among adults with CNMP using pain medication for three months or more were included. The following concepts were included in medicines optimisation: medication adherence, drug misuse, patient

compliance to prescribed treatment, including deviation and misuse, adherence/ non-adherence, compliance/non-compliance or safe and effective use of medicines. Studies eligible for inclusion included randomized controlled trials (RCTs), nonrandomized and quasi-experimental studies, case-control, cohort, and cross-sectional studies published in the English language. Eligible participants were 18+ years with CNMP. Studies involving participants from care homes, residential homes or hospices were excluded as these patients were assumed not to be self-administering their medicines. Both medicines optimisation outcomes such as misuse of opioids and clinical outcomes such as pain score, depression and anxiety scale and functional interference were considered.

4.4.3 Screening and selection

Two independent investigators (AA and VP) screened the study abstracts according to the inclusion and exclusion criteria. Any conflicts arising regarding the selection were resolved by a third investigator (AY), by discussion or by obtaining the study's full text.

4.4.4 Data extraction and quality assessment

A data extraction form was developed. Data on study characteristics, intervention types and outcome measures were extracted. The two authors independently extracted the data, and any disagreement was resolved through discussion or by a third reviewer. For studies utilizing RCT designs, the risk of bias was assessed using the outline criteria of the Cochrane Handbook for Systematic Reviews of Interventions (180). The critical appraisal skills programme (CASP) was used for the quality assessment for the rest of the studies. Two authors (AA and VP) independently performed the assessment, any disagreements were resolved through discussion with a third author (AY). Narrative synthesis of the data was conducted because the studies

were heterogenous in definitions, types of interventions, measurements and reporting methods. Meta-analysis should be conducted when included studies are sufficiently homogeneous in participants involved, interventions, terminology and outcomes to provide a precise summary (181).

4.5. Results

From 952 records initially identified, 21 studies met the inclusion criteria (Figure 4). The reasons for study exclusion are detailed Appendix 11. Of the 21 included studies, three were RCTs and 18 used observational designs.

4.5.1 Methodological quality: *RCTs*

The three RCTs were assessed for risk of bias using the Cochrane tool (180). All three studies (182,183,184) were judged to be at high risk of selection bias, due to the lack of clarity provided regarding the sequence generation process and allocation of participants (Table 1)

Other study designs

The quality of the quasi-experimental studies (n = 18) was measured using the CASP quality assessment tool (Table 2). All 18 studies addressed a clear study aim. The majority (n = 14) did not provide adequate information on the recruitment procedure. Five studies mentioned how the outcomes were measured, four studies did not and the others (n = 9) were unclear (Table 2).

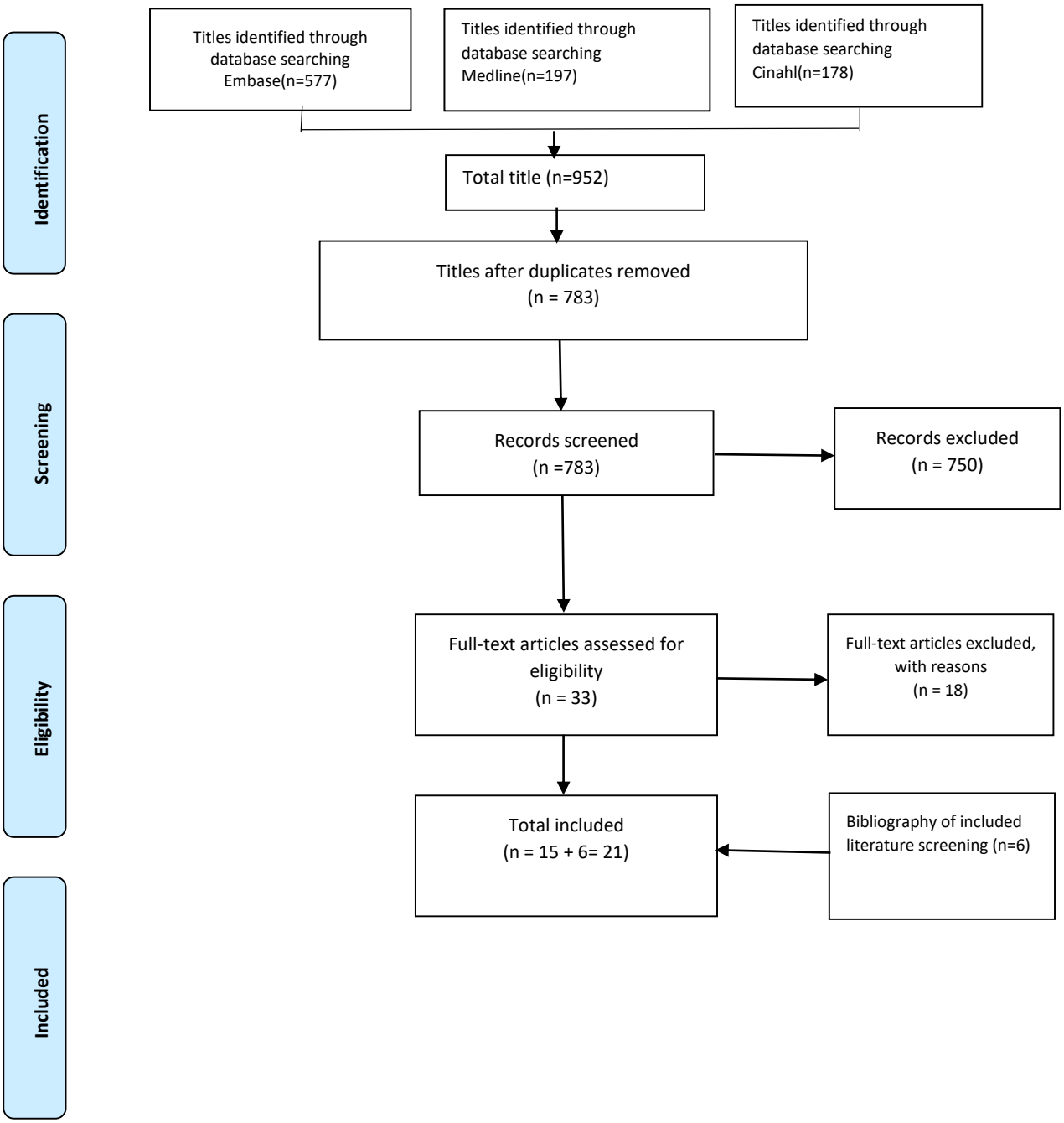


Figure 4: *PRISMA diagram of literature search and inclusion process*

Table 1**:** Risk of bias within included randomised controlled trials (RCTs).

QUESTION	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?
Jamison, et al. (USA) [173]	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Timmerman et al. (Netherlands) [174]	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Wilson et al. (USA)[175]	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk

Table 2**:** Quality assessment of included observational studies.

	Did the study address a clearly focused issue?	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have they take account of the confounding factors in the design and/or analysis?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?
Study ID (Country)								
Katz et al. (USA) [176]	Yes	No	Unclear	Unclear	No	No	Unclear	Unclear
Chelminski et al. (USA) [177]	Yes	Unclear	Unclear	Yes	No	Unclear	Unclear	Unclear
Manchikanti et al. (USA) [178]	Yes	No	No	Yes	No	No	Unclear	Unclear
Manchikanti et al. (USA) [179]	Yes	No	Unclear	Yes	No	No	Unclear	Unclear
Hariharan et al. (USA) [180]	Yes	No	Yes	No	No	No	Yes	Yes
Wiedemer, et al. (USA) [181]	Yes	No	No	No	No	No	Yes	Yes
Bethea, et al. (USA) [182]	Yes	Unclear	Unclear	Unclear	No	No	Unclear	No
Brown et al. (USA) [183]	Yes	Unclear	Unclear	Unclear	No	Yes	Unclear	Yes
Wasan et al. (USA)[184]	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes
Andersen et al. (Denmark) [185]	Yes	Unclear risk	Yes	Unclear	Yes	Unclear	Yes	Unclear
Kipping et al. (Germany)[186]	Yes	Unclear	No	Unclear	Unclear	No	Unclear	Unclear
Chang et al. (USA) [187]	Yes	Yes	Yes	Yes	Unclear	Unclear	No	No
Jamison et al. (USA) [173]	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes
Jacobs et al. (USA) [188]	Yes	Yes	Unclear	No	No	No	Unclear	No
Talusan,2016. (USA) [189]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
Knezevic et al. (USA)[190]	Yes	Yes	Yes	Yes	No	No	Unclear	Unclear
Schell et al. (USA)[191]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
McCann et al. (USA) [192]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

4.5.2 Characteristics of included studies

The studies were published between 2003 and 2018. Eighteen were conducted in the United States (182, 184-200), and the remainder in Denmark (201), Germany (202) and the Netherlands (183). Three studies were RCT (Table 3) (182-184). Nine studies used a prospective cohort design (188,191,194,195,199,201). Seven were retrospective cohort studies (189,190,192,193,196-198), one was a cross-sectional design (202) and one was a pre-post interventional design without a control group

(187). Six studies were conducted in primary care settings 188-190,196,198,200), four in pain centres (194,195,199,202), seven in outpatients' pain clinics 185,193,197,198,200,202), two recruited patients from primary care and pain clinics (187, 191) and one recruited patients from primary care and an internet site (184)(Table 3).

Medicines optimisation goals

Most of the included studies aimed to reduce the use or misuse/abuse of drugs or aberrant drug behaviour or to enhance appropriate use of prescribed opioids in CNMP patients. Four of the included studies aimed to reduce the use or reliance on opioids (184,190,196,201), nine aimed to identify and reduce misuse, abuse of drugs or aberrant drug behaviour (182,185,188,191,192,194,195,199,200). Two studies aimed to improve adherence (n = 2) (183,187), and four focused on patients' compliance with prescribed opioids (182,186,191,194,195,198,199,201). Considering pain type and locations, eight studies included both nociceptive and neuropathic pain patients (183,184,188,189,192,193,196,202). Eight studies focused on populations suffering from nociceptive pain, including low back pain, arthritis and other musculoskeletal disorders (182,186,191,194,195,198,199,201). Five studies did not specify the type of pain or provided insufficient patient information 185,187,190,197,200). None of the studies focused on other types of analgesics, especially co-analgesic medication (such as antidepressants or anticonvulsants) (Table 3).

Medication taking behaviour

The scope of medication taking behaviour was defined differently among the included studies. These included misuse (173, 177, 184), abuse(178) , aberrant drug-taking

behaviour (176, 182, 188), non-adherence (n = 3) (174, 183, 187), compliance (n = 3) (180, 186, 190) and illicit drug use (n = 1)(179) . Seven studies did not define any medication taking behaviour (175, 181, 185, 189, 191-193).

4.5.3 Type of interventions

Opioid treatment contract (OTC) with or without urine drug screening (UDS)

A total of 11 studies used single component interventions (Table 4) based on an OTC, is a bilateral contract between the patient and physician that defines each party's responsibilities. These included OTC alone or combined with urine drug screening to measure patients' adherence to the contract terms (Table 4). Only three studies published a copy or details of the OTC (186,188,189).

Behavioural interventions

Five studies used different behavioural approaches alone, either to reduce misuse and abuse or to reduce patient reliance on opioids, while one aimed to improve patient opioid adherence (Table 4). The interventions included a working alliance, which refers to the mutual relationship that grows between the therapist and patient during the treatment period (185), cognitive and behavioural treatments based on attachment orientations, which are defined as moderately stable schemas that regulate emotions and our responses to health behaviour and stressors (201); in clinic electronic diaries to answer 25 questions to monitor patients' craving progress (199); brief office-based introductory motivational interviews on the adherence to opioid medication (187); and internet-based pain management programme for targeting behavioural, cognitive, emotional and social factors (184).

Educational interventions

Only one study evaluated the effect of specific medication education on patients' adherence to their medication using a brief video and written information about the medication name, dosage, and frequency (183).

Multi-component interventions

Multi-component interventions were used by ten studies (Table 4). Each intervention included at least three components along with UDS and OTC. Most of these programmes followed the relevant local or national clinical practice guidelines for managing opioid therapy for chronic pain. The components of complex interventions included the following:

1. Urine drug screening and opioid treatment contract within a multi-component intervention. All the included studies categorized as multi-component interventions incorporated OTC. The studies generally included UDS alongside OTC (Table 4).
2. **Monthly clinical/pain assessment**

   Seven complex intervention studies involved a monthly physical or pain assessment (Table 4).

3. ***Risk assessment***

   Risk assessment was used to help determine risk potential for 'Aberrant Drug-Related Behaviour' (ADRB) (Table 3). Three studies used the Screener and Opioid Assessment for Pain Patients-Revised (SOAPP-R) questionnaire, a standardized score tool that can be answered by patients or their providers 190,197,198) (Table

4.One study used an opioids/ benzodiazepines combination risk assessment tool created by the study team as YES/NO questions (197). Other studies stated that ADRB was identified by self-reporting or evaluated by the healthcare providers using other tools but did not mention using a standardized questionnaire (190).

4. Prescription monitoring programme (PMP)

PMP are state-based electronic databases that are used to track prescriptions, mainly for controlled substances, including benzodiazepines, opioids and amphetamines. Five studies used PMP to optimise pain medication use and reduce inappropriate use (Table 4).

5. Opioid dose adjustments

Six studies used average daily Morphine Equivalent Daily Dose (MEDD) adjustment as an intervention to optimise medications use (Table 4).

6. Prescribing/dispensing small quantities/pill count

Three studies included pill counts or small quantities of opioids (186,194,197). Pill count was described as done in a random selection method; however, it was not clear who performed the count (194) (Table 4).

7. Team-based approach

Six studies used a team-based approach led by one or multiple providers 188,190,196,197,198,200). These included the combined skills of clinical pharmacist, internist and psychiatric (188), use of a structured package containing documents to be filled by patients regarding pain history medication use, psychiatric evaluation and educational information (196), a primary care provider-

run outpatient clinic aided by dedicated nursing, pharmacy and mental health care providers (197), pharmacist run opioid use clinics and informal consultative services in primary care including the use of telephone (190), and a multidisciplinary pain management team who met bi-weekly to review cases and recommend treatment plans (200). (Table 3)

8. Patient education within a multi-component intervention

Only two studies involved patient education as a component of their interventions (182, 197). These included group sessions (182)and printed educational material (197).

9. Provider education within a multi-component intervention

Three studies educated or trained providers before they participated in the studies (186,191,197). These included education on pain management and monitoring techniques.

10. Behavioural interventions within a multi-component intervention

Only one study offered behavioural intervention as a part of a complex intervention where patients participated in a structured motivational and cognitive behavioural training programme to prevent substance misuse (182).

11. Psychiatric consultation

Four studies included a psychiatric consultation plan or a psychiatrist as part of the treatment programme (182,188,197, 200). The studies differed in the role and goal of including this component which included psychiatric consultation as support for patients at high risk of misuse, abuse and addiction (182,188,200), assessment of

patient risk, stability and the presence of contraindications of using an opioid/BZD combination to treat CNMP(197).

12. Electronic diaries

Only one study used electronic diaries to monitor cravings among patients and the effect is reported briefly in the study (182).

4.6 Study outcomes

There was substantial heterogeneity in the nature of the outcomes (Table 5). These were systematically categorized as follows:

Medicine optimisation

(a) Appropriate use of pain medication:

Twelve studies aimed to enhance appropriate use, three measured patients' adherence (183,185,187), seven studies measured the reduction of patients ' opioids dose or reliance on opioids (184,190,196,197,198,200,201), four measured patients ' compliance (182,193,199,202).

(b) Inappropriate use of pain medication: Twenty studies aimed to reduce the problematic medication-takin behaviour including misuse, abuse, illicit drug use. Seven of these measured aberrant drug behaviours (186,189,190,191,193,195,198,200), seven measured abuse 182,185,187,189,194,198,200) and six measured misuse 182,184,187,188,191,198). (Table 4).

(c) Self-discharge from chronic opioid treatment

Some patients voluntarily discontinued chronic opioid therapy after implementing a structured opioid programme observed in three studies (189,196,198).

Clinical outcomes

Only nine studies assessed clinical outcomes such as pain intensity or functional improvement, depression and anxiety (182-185,187,188,191,196,201). One study measured patients' quality of life using the quality-of-life scale (196). (Table 5)

Other outcomes utilized included patient satisfaction (182,183,187,191), reduction in utilization of health care services (184,200), healthcare costs (187,191), provider confidence in managing CNMP patients, compliance with universal precautions (191), adherence to clinical guidelines (186,190,191,197,198,200,201) and provider satisfaction(196,198).

Table 3. Characteristics of included studies.

Study ID (country)	Aim	Study design & methodology	*Description of study population*			Study duration and setting	Medicines taking behaviour as defined in the study
			Sample size	Participant characteristics	Pain type(s)		
Katz et al. (USA)	To describe the results of urine toxicology screens and behavioural monitoring in patients with chronic non-cancer pain prescr bed opioids for daily use.	Retrospective cohort study using medical records to review patients' drug-taking behaviours, and urine toxicology reports.	**Baseline:**122 **Follow-up:**122	**Age mean:**45 **SD:** 11 **Female %:**49	**Condition(s):** low back pain, neuropathic pain. **Pain type:** nociceptive & neuropathic. **Medication(s):** Opioids, non-opioids.	**Study Duration:** 45 months **Study Setting:** two pain centres.	**Behavioural "issues"-** lost or stolen prescriptions, consumption in excess of prescr bed dosage, visits without appointments, multiple drug intolerances and allergies, and frequent telephone calls.
Chelminski et al. (USA)	To examine the effects of multi-disciplinary pain management on the outcomes of pain, disability, depression, and substance misuse.	Prospective cohort study using medical records and urine samples of the recruited patient.	**Baseline:** 85 **Follow-up**:63	**Age mean**:50 **SD:**NA **Female %**:40	**Condition(s):** Back pain, mixed aetiologies, chronic headache. **Pain type**: nociceptive &neuropathic. **Medication(s):** Opioids.	**Study Duration:** 3 months. **Study Setting:** primary care.	**Substance misuse-** detection of cocaine or amphetamines; Procurement of opioids from more than one provider; Diversion of opioids; UTS negative on at least two occasions for prescr bed opioids; UTS positive on at least two occasions for opioids not prescribed by our practice.
Manch kanti et al. (USA)	To evaluate the effect of implementing of a controlled substance agreement, including periodic review of medications, urine testing, pill counts, and verification of medication information on controlled substance.	Prospective cohort study with historical controls using medical records and urine samples of the recruited patient.	**Baseline:** 566 **Follow-up:**500	**Age mean:**48.5 **SD:** NA **Female %:**59	**Condition(s):** chronic pain. **Pain type:** Nociceptive. **Medication(s):** Opioids.	**Study Duration:** Not clear **Study Setting:** Multidisciplinary pain management centre.	**Abuse-**patient receiving controlled substances from any other place or source other than the prescribing physician at our centre, with the exception of controlled substances for acute injuries unrelated to the problem being treated, or for emergencies
Manch kanti et al. (USA)	To study the prevalence of illicit drug use in patients receiving opioids with adherence monitoring combined with random urine drug testing.	Prospective cohort study with historical controls using medical record and urine samples of patients.'	**Baseline:** 566 **Follow-up**:500	**Age mean**:48.5 **SD:** NA **Female %:**59	**Condition(s):** chronic pain. **Pain type:** Nociceptive. **Medication(s):** Opioids.	**Study Duration:** Not clear **Study Setting**: Multidisciplinary pain centre	**Illicit drug use**- use of an illicit drug during the month prior to the survey interview.
Hariharan et al. (USA)	To describe the long-term outcomes of a medication contract agreement for patients receiving opioid medications in a primary care setting.	Retrospective cohort study using medical records.	**Baseline:** 332 **Follow-up:**330	**Age mean**:49 **SD:**NA **Female %:**48	**Condition(s):** Back pain, Fibromyalgia Joint Diseases. **Pain type**: Nociceptive. **Medication(s):** Opioids.	**Study Duration:** 5 years **Study Setting**: Primary care	**Compliance-** patients receiving stable doses of contracted medications at prescribed intervals and adhering to the conditions of the contract agreement.
Wiedemer, et al. (USA)	To measure the impact of a structured opioid renewal programme for chronic pain	Naturalistic prospective outcome study using medical records and questionnaire.	**Baseline: 335** **Follow-up:** 171	**Age mean:**NA **SD:** NA **Female %:** NA	**Condition(s):** chronic pain. **Pain type:** not specified. **Medication(s):** Opioids.	**Study Duration:** 24-month.	None.

	run by a nurse practitioner and clinical pharmacist.					**Study Setting:** a primary care clinic.	
Bethea, et al. (USA)	To investigate alliance development for patients targeting chronic pain and opioid analgesic abuse. The study hypothesis growth in alliance would be lower for patients with greater substance abuse severity.	A prospective cohort study using Questionnaires.	**Baseline:** 36 **Follow-up:**25	**Age mean:**41.40 **SD:**9.81 **Female %:**44	**Condition(s):** chronic pain. **Pain type:** not specified. **Medication(s):** Opioids.	**Study Duration:** 12 weeks **Study Setting:** Veterans Administration-based pain clinic.	**Abuse** or **"aberrant medication-taking behaviours"** (AMTBs)- include not taking pain medication as prescribed, reporting lost/stolen prescriptions, and using supplemental opioids obtained from unauthorized or illegal sources.
Jamison, et al. (USA)	To see if close monitoring and cognitive behavioural substance misuse counselling could increase overall compliance with opioids.	A randomized trial using questionnaires and structured interview.	**Baseline:** 66 **Follow-up**:62	**Age mean:**47.7 **SD:**7.14 **Female %:**43.5	**Condition(s):** back pain. **Pain type:** Nociceptive. **Medication(s):** Opioids.	**Study Duration:** 6 months **Study Setting:** Veterans Administration-based pain clinic	**Substance misuse**- the use of any drug in a manner other than how it is indicated or prescribed. **Substance abuse**: is defined as the use of any substance when such use is unlawful, or detrimental to the user or others.
Brown et al. (USA)	To evaluate potential for aberrant- drug related behaviours among patients with chronic, moderate- to-severe pain and to determine investigator compliance with universal precautions approach to pain management.	Prospective open-label, nonrandomized, non-comparative, multi-centre observational study using questionnaires	**Baseline:**1487 **Follow-up**:561	**Age mean**:53 **SD:** Non **Female %:**57	**Condition(s):** Arthritis, skeletal muscle disease. **Pain type:** Nociceptive. **Medication(s):** Opioids.	**Study Duration:** 12 weeks **study Setting:** pain clinic in a hospital.	N**on-adherence- S**edation, frequent request of early refill, increase dose without authorization, repeated lost or stolen prescription or unexpected positive or negative urine drug screen.
Wasan et al. (USA)	To examine the relationships between self-reports of craving, and opioid misuse and to characterize self-reports of craving in patients prescribed opioids for chronic pain.	A prospective, longitudinal, descriptive, cohort study using Questionnaires.	**Baseline:** 66 **Follow-up**:62	**Age mean:**47 **SD:** NA **Female %:**43.5	**Condition(s):** Back or neck pain. **Pain type:** Nociceptive. **Medication(s):** Opioids.	**Study Duration:** 6 months **Study Setting:** pain clinic in a hospital.	**Substance misuse**- the use of any drug in a manner other than how it is indicated or prescribed. Substance abuse is defined as the use of any substance when such use is unlawful, or when such use is detrimental to the user or others**.**
Andersen et al. (Denmark)[185]	To investigate the association between attachment insecurity, pain, disability, distress, and the use of opioids.	A prospective study using questionnaires and patients' journals.	**Baseline:** 72 **Follow-up:**72	**Age mean:** 43 **SD:** 7.1 **Female %:**86.	**Condition(s):** Lower back and legs Upper back and arms **Pain type:** Nociceptive **Medication(s):** opioids	**Study Duration:** 13-week **Study Setting:** pain clinic in a hospital.	None
Kipping et al. (Germany	To investigated patients' reliability regarding their report of any current pain medication use.	A cross-sectional study using urine sample from recruited patients.	**Baseline:**343 **Follow-up**:343	**Age mean**:55.2 **SD:** 14.8 **Female %:**45%	**Condition(s):** low back, neuropathic, or viscera **Pain type:** nociceptive/ neuropathic **Medication(s):** opioids, non-opioids, co-analgesics.	**Study Duration:** at the first visit **Study Setting:** pain clinic.	**Compliance-** patients' drug intake behaviour in accordance with prescr bed instructions.

Chang et al. (USA)	To test the effect of office-based motivational interviewing (MI) on prescription opioid adherence in older adults with chronic pain.	Pre- and post-design using interviews and questionnaires.	**Baseline:** 33 **Follow-up:**30	**Age mean**:59.1 **SD**: 6.1 **Female %:**50	**Condition(s):** Chronic pain. **Pain type**: Not specified. **Medication(s):** Opioids.	**Study Duration:** 4-week **Study Setting**: primary care office and a pain management clinic.	N**on-adherent-** not taking medication at the proper dosage indicated, or take more than prescr bed.
Wilson et al. (USA)	To measure the effects of an Internet-based self-management program among patients who receive opioids from a primary care provider.	A randomized controlled trial.	**Baseline: 114** **Follow-up:92**	**Age mean:51** **SD: NA** **Female %:78**	**Condition(s):** back pain, fibromyalgia, arthritis, **Pain type:** Nociceptive, neuropathic **Medication(s):** Opioids	**Study Duration:** 4-week. **study Setting:** primary care and a pain management clinic.	None.
Jamison et al. (USA)	To investigate the benefits of interventions designed to track potential opioid misuse and to improve practitioner confidence in managing CNMP patients.	A Prospective Longitudinal Controlled Trial using questionnaires.	**Baseline:** 253 **Follow-up:**253	**Age mean**:53.7 **SD:**10.6 **Female**: %:59.7	**Condition(s):** Low back pain. **Pain type:** Nociceptive. **Medication(s):** Opioids.	**Study Duration:** 6 months. **study Setting:** primary care and Specialist clinics.	None.
Jacobs et al. (USA)	To assess the effect of two clinical pharmacists using a telephone risk assessment clinic to promote safe opioid prescribing.	A retrospective study using pharmacy and medical records.	**Baseline:** 608 **Follow-up:** 148	**Age mean**:64 **SD**: NA **Female** %:	**Condition(s):** Chronic pain **Pain type:** Not specified **Medication(s):** Opioids	**Study Duration:** 3 months. **study Setting:** Primary Care Clinic.	**Aberrant behaviour-** taking an opioid medication in any manner other than as prescribed.
Talusan,et al (USA)	To develop, implement, and evaluate an Opioid Monitoring Clinic as a clinical referral system within the primary care	A retrospective chart review of participants.	**Baseline: 61** **Follow-up: 39**	**Age mean: 53** **SD: NA** **Female %:7**	**Condition(s):** Back pain Pain type: Nociceptive**.** **Medication(s):** Opioids.	**Study Duration:** 6 months. **study Setting:** Primary Care Clinic.	**None.**
Timmerman et al. (Netherlands)	To investigate the effect of medication-specific education on pain medication adherence.	A randomized controlled trial.	**Baseline:**112 **Follow-up:**96	**Age mean**:52.5 **SD:**15.1 **Female** %:68.4	**Condition(s):** Chronic pain **Pain type:** Nociceptive, neuropathic **Medication(s):**): opioids, non-opioids, co-analgesics.	**Study Duration:** 12 weeks **study Setting:** Centre for Pain Medicine.	**Underuse-** missing a dose from once a week up to every day, **overuse** was defined as admitting to taking more medication than prescr bed**. Non-adherence** was defined as presence of underuse and/or overuse of prescribed medication.
Knezevic et al. (USA)	To assess the compliance of chronic opioid consuming patients in an outpatient setting and evaluate if utilizing repeated urine drug testing could improve compliance.	Retrospective analysis of prospectively collected data using urine samples and patient medical charts.	**Baseline:**500 **Follow-up:**500	**Age mean**:53.93 **SD:**14.76 **Female** %:54	**Condition(s):** Neck, back, Shoulder and knee pain, , peripheral neuropathy **Pain type:** nociceptive /neuropathic **Medication(s):** opioids.	**Study Duration:** not clear **study Setting:** Outpatient pain management clinic.	**Compliance**- urine sample was only positive for opioid medications that were prescribed by our pain clinic without the identified presence of any illicit drug.

Schell et al. (USA)	To evaluate the effect of interventions on the appropriate monitoring of chronic opioid therapy as well as the appropriate management of high-risk chronic opioid therapy > 200 mg MEDD.	A retrospective data analysis of clinical impact of these interventions.	**Baseline:222** **Follow-up: 58**	**Age mean:NA** **SD:NA** **Female %:NA**	**Condition(s): Chronic pain** **Pain type:** Not specified **Medication(s):** Opioids and Benzodiazepine.	**Study Duration: 7 months study** **Setting: 6** community-based outpatient clinics**.**	**None**
McCann et al. (USA)	To study the impact of a systematic approach that adhered to evidence-based guidelines for managing patients with non-malignant cancer pain.	A retrospective study using medical records.	**Baseline:**32 **Follow-up:**29	**Age mean:**66.86 **SD:** NON **Female %**:31	**Condition(s):** Neck, back, Shoulder pain, neuropathy **Pain type**: nociceptive &neuropathic **Medication(s):** opioids.	**Study Duration:** 18 months. **study Setting**: rural primary care practice.	**None**

NA: Not available

Table 4. Nature of intervention used by the included studies.

Intervention types and components			Single-component intervention (with or without urine drug screening)											Multi-components intervention									
			Katz, et al.)	Manhikanti et al.	Harian, et al.	Bethea, et al	Kipping,et al.	Wasn, et al.	Andersen, et al.	Chang, et al.	Wilson, et al.	Timerman, et al.	Knezevic, et al.	Chelinski, et al.	Manhikanti, et al.	Wiedemer, et al.	Jamison, et al.	Brown, et al.)	Jamison, et al.	Jacobs, et al.	Talusan, et al.	Schell, et al)	McCann, etal.
Structured CNMP programme		Urine Drug Screening (UDS)	×	×	×		×						×	×	×	×	×	×	×	×	×	×	×
		Opioids Treatment Agreement or contract (OTA/ OTC)			×									×	×	×	×	×	×	×	×	×	×
	Follow up	Monthly clinical/ physical /pain Assessment												×			×	×	×	×		×	×
		Risk Assessment/	×																	×	×	×	
	Educational	Prescription monitoring program														×				×	×	×	×
		Opioid Dose Adjustments												×		×				×	×	×	×
		Prescr bing small quantity/ Pill count													×	×		×					
		Healthcare provider-led intervention												×		×				×	×	×	×
		Patient education										×					×					×	
		Provider education/ Informatics Tool																×	×			×	
	Behavioural	Cognitive, emotional,				×		×	×	×							×						
		Psychiatric consultation												×		×	×					×	
	Technological	Electronic diaries						×									×						
		Internet based self-management programme									×												

OTA=opioid treatment agreements; OTC: opioid treatment contract; UDS= urine drug screen

Table 5. Description of intervention.

Study ID(country)	Description of intervention	Primary outcome	Primary outcomes-key findings (pre and post interventions)	Secondary outcome	Secondary outcomes-key findings	Author Conclusions
Single-component interventions						
Katz et al. (USA)	Patients monitored for 3yrs with urine Drug screen (UDS) and any behaviour suggestive of inappropriate medication use were documented.	Detection of "problem" (either r positive urine toxicology (UDT) or one or more aberrant drug-taking behaviours).	**Medicine optimisation outcome:** Of patients with no behavioural issues, Positive UDS alone was 21%, behavioural issues alone were 14%. patients with both positive UDS and behavioural issues were 8% of the patients. No aberrant drug behaviours were 57% of patients.	-	-	Requiring a report of behavioural issues and urine toxicology screens creates a more comprehensive monitoring system than either alone.
Manchikanti et al. (USA)	Random urine drug testing for chronic pain patients on chronic opioid therapy	The prevalence of illicit drug use in patients receiving opioids for chronic pain management	**Medicine optimisation outcome:** Illicit drug use was evident in 16% of patients including marijuana in 11%, cocaine in 5%, and amphetamines in 2%. There were decreases in obtaining opioids from multiple providers or sources from 17.8% to 9.2% (ARR, 8.6% [CI, 4.4% to 12.8%]).	-	-	The study showed significant reductions in overall illicit drug use with adherence monitoring combined with random urine drug testing. This study also showed absence of illicit drug use in the elderly
Hariharan et al. (USA)	Opioid Contract: specified the conditions under which opioids would or would not be prescr bed and patient respons bilities which included random urine drug testing.	Describe outcome of a medication contract agreement.	**Medicine optimisation outcome:** Contracts discontinued in 37% of patients. Contract cancelled for substance abuse in 17% of patients. 20% discontinued contract voluntarily 38% UDS positive for illicit substances	-	-	A more structured drug testing strategy is needed to identify nonadherent patients.
Bethea, et al. (USA)	An 8-session cognitive behavioural intervention. Sessions 1 and 2 focused on emotional bonds ,3, and 4 sessions focused on patient difficulties with pain control, managing opioid. Session 5, the focus on treatment goals and tasks. Sessions 6 and 7, therapist provided ongoing feedback on treatment progress. Session 8, the therapist and physician met with the patient to review the treatment and inform the patient of teams' decision of methadone tapering.	Relationship of the working alliance to treatment success (opioid adherence, and urine toxicology and decreasing pain, functional interference, and substance abuse	**Medicine optimisation outcome:** Correlations of the working alliance to opioid adherence failed to reveal statistically significant relationships until the end of treatment (r =.51). p= < .05 **Clinical outcome:** Correlations of the working alliance with treatment" outcomes failed to reveal statistically significant relationships between either patient or therapist alliance scores and average pain (r =−.53). p= < .05 Functional interference mood, and relationships with others (r =−.43)	-	-	Patient alliance was unrelated to opioid adherence and unauthorized drug use; in contrast, lower therapist alliance was related to poorer adherence and higher levels of unauthorized drug use. Examining "during treatment" outcomes including repeated assessments of pain, functional interference, opioid adherence and urine screening, Correlations failed to reveal statistically significant relationships between either patient or therapist alliance scores and pain ratings until the end of treatment.
Wasan et al. (USA)	Electronic diaries for ratings opioid craving at monthly clinic visits and daily during a 14-day take-home period. The device contained questions from the Brief Pain Inventory (severity, activity, function and mood), medication questions, and location of pain).	The relationship between craving and medication compliance, treatment outcome	**Medicine optimisation outcome:** Craving Index (CI mean values): at base line high risk control HRC =26.7, high risk experimental HCE =11.0, at the end of study mean CI values (HRC=24.5, HRE=9.6 the differences were statistically significant. P=<.05.	-	-	Craving is a potentially important psychological construct in pain patients prescribed opioids, regardless of their level of risk to misuse opioids. Targeting craving may be an important intervention to decrease misuse and improve compliance.

Andersen et al. (Denmark)	Cognitive behaviour therapy that included education in pain theory and management, meditation, relaxation training, visualisation, activity-rest scheduling, problem solving, change of maladaptive thoughts, assertive communication, value-based exposure, acceptance strategies supported by handouts.	Attachment anxiety association with pain intensity, association between attachment avoidance and the use of opioids	**Medicine optimisation outcome** Use of opioids (pre=40.41, post=31.89) p=0.033 **Clinical outcome:** **Pain intensity** (pre= 5.67, post= 5.45) p=0.820 **Depression** (pre= 10.08, post= 9.0) P=0.000 **Physical disability** (pre= 52.64, post= 50.4) p=0.394	-	-	Attachment insecurity plays an important role in the chronic pain management. Insecure groups did not differ significantly with respect to pain intensity and physical disability. The insecurely attached group was significantly more anxious and depressed at both pre- and post-treatment. Moreover, the insecurely attached group used significantly more morphine (mg/day) at pre- and post-treatment
Kipping et al. (Germany)	Blood and urine samples collected and analysed immediately after asking two chronic pain patients' groups (pain group, surgical group) about other pain medications that they used beside their prescribed pain medication.	The rate of noncompliance, under-reported and over-reported among pain clinic (PG) and presurgical control (SG).	**Medicine optimisation outcome** The noncompliance in PG (43.3%) and in SG (24%). P= < 0.05 Under-reporting (31% PG; 23% SG) P= < 0.05 Over-reporting (11% PG. 2% SG). P= < 0.05, frequently under-reported non-opioid analgesics.	-	-	Two types of noncompliance were defined: under-reporting and overreporting. Under-reporting of non-opioid analgesics is the main type of noncompliance.
Chang et al. (USA)	Motivational interviewing face-to-face session focused on increasing participants' awareness about their use of prescription opioids, followed by weekly phone -delivered follow-up sessions.	The effect of Motivational Interviewing on Prescription Opioid Adherence	**Medicine optimisation outcome:** Risk for opioid abuse (pre= 16.40, post 12.60) p =< 0.01 Self-efficacy on medication use (pre= 31.19, post= 34. 690. p=0 .009 **Clinical outcome score means:** Depression (pre=20.24, post= 14.59) p= .006 Pain severity worst pain (pre= 8.62, post= 8.62). p =0.862	Treatment satisfaction	Participants reported a good level of satisfaction (mean = 10.1)	Motivational interviewing can be effectively delivered in outpatient settings for older adults who are at risk for opioid misuse. Clinicians could incorporate MI techniques to enhance prescription opioid adherence
Wilson et al. (USA)	Internet-based self-management programme targeting cognitive, emotional, behavioural, and social pain determinants. The programme generates an individualised custom plan based on result of chronic pain assessment.	Improvements in pain intensity, pain interference and opioid misuse behaviours using The Current Opioid Misuse Measure (COMM).	**Medicine optimisation outcome:** Of treatment group COMM score pre= 12.4, post=9.1)**.** p =0.48 Decreased or stopped opioid =20.9% p= 0.04 **Clinical outcome score means:** Pain Intensity (pre=5.6, post 5.3) p=0.22 Pain Interference (pre= 5.5, post=5.3). p =0.39 Depression (pre= 12.5, post= 10.3.) p = .49	Health Care Utilization	Treatment group participants reported 2.8 total visits to health care providers during the 8-week study period compare to 2.2 in control group=0.36	Patients on opioids were able to engage and demonstrate positive outcomes using an Internet-based self-management programme.
Timmerman et al. (Netherlands)	A 5-minute educational video contained standardized information about the medication name, frequently used dosing schedules and written medication-specific information.	Medication adherence, education in pain.	**Medicine optimisation outcome** The non-adherence rates were 43% at 4 weeks and 49% at 10 weeks in the intervention group. p = 0.38 **Clinical outcome score means: In the intervention group** Pain intensity changed from 6.3 to 5.4 Perceived improvement changed from 3.6 to 3.7. p = NS	Patient satisfaction	Patient satisfaction changed from 4 to 4.3 in the intervention group. P = 0.136	Medication-specific education did increase knowledge of the prescribed therapy but did not improve adherence or treatment outcome parameters.
Knezevic et al. (USA)	Patients were asked to provide supervised urine toxicology specimens during their regular clinic visits, and were asked to do so without prior notification	The compliance with chronic opioid	**Medicine optimisation outcome** Repeated UDSs showed that patients' compliance of patients on opioid medications (63.6%) had improved. p = 0.383	-	-	Repeated UDS can improve compliance of patients on opioid medications and can improve overall pain management.
Multi-component Interventions						

Chelminski et al. (USA)	Structured clinical programme that combined the skills of internists, clinical pharmacists, and a psychiatrist, monthly follow-up by a nurse, pain contracts, medication titration, and psychiatric consultation.	Reducing substance misuse and improve Pain, depression, function scores.	**Medicine optimisation outcome:** Substance misuse was identified in 32%. **Clinical outcomes** **Average pain score:** (pre= 6.5, post= 5.5. p = 0.003 **Depression score** changed from 24 to18. P = 0.003 **Disability index** changed from 47 to 39. P=< 0.001	-	**-**	Substance misuse and depression were common, and many patients left the programme when they were no longer prescribed opioids. Effective care of patients should include rigorous assessment and treatment of these comorbid disorders and intensive efforts to ensure follow up.
Manchikanti et al. (USA)	Pain patients on chronic opioid therapy signed controlled substance agreements. Adherence monitoring was carried out by appropriate history, periodic evaluation of appropriate intake of drugs, random drug testing, and pill counts	Reduction in opioid abuse	**Medicine optimisation outcome** Opioid abuse reduced by 50% post intervention=NA	-	-	Adherence monitoring, including controlled substance agreements and various periodic measures of compliance, was associated with a 50% reduction in opioid abuse.
Wiedemer,et al. (USA)	A structured opioid renewal programme for chronic pain run by a nurse practitioner (NP) and clinical pharmacist.	Adherence to opioid treatment agreements (OTA) and use of UDS	**Medicine optimisation outcome:** The number of OTAs increased by 70% The number of UDS increased by 93%.45% patients adhered to the OTA and resolved their aberrant behaviours, (38%) self-discharged, (13%) were referred for addiction treatment, and (4%) with consistently negative UDS were weaned from opioids.	Reduction in ER and unscheduled PCP visit and cost.	ER visits reduced by 72.7% p=NA unscheduled PCP visits reduced by 59.6% Pharmacy cost reduced from $129,793 to $5,236. Provider Satisfaction was 84%.	An NP/clinical pharmacist-run clinic, supported by a multi-specialty team, can successfully support a primary care practice in managing opioids in complex chronic pain patients, both in changing abnormal illness behaviour (wa k-ins, medication complaints) and in freeing up more time to deal with important medical problems.
Jamison, et al. (USA)	Patients at High-Risk of misusing opioids were under close monitoring by implementing the terms of a controlled substance agreement and were asked to participate in a structured cognitive behavioural training program for prevention of substance misuse.	Increase opioids compliance using the Drug Misuse Index (DMI) and urine drug screening.	**Medicine optimisation outcome** **Positive (DMI) %** among subjects, High-Risk Control (HRC)=73.7, High-Risk Experimental (HRE) 26.3. p=<0.05 **Urine Screens:** Normal (%) in (HRC)64.7, (HRE) 88.2. p=<0.05 **Clinical outcomes:** **Average pain** (HRC =65.32, HRE= 57). p=<0.001 **Depression** (HRC = 9.06, HRE = 6.06.) p=<0.01 **Activity interference** (HRC=67, HRE=63.73. p=<0.05	Patients satisfaction with treatment	The High-Risk Experimental group rated the compliance interventions as generally helpful. The subjects rated the individual counselling sessions on 10 scale (mean = 8.61) and compliance checklists (mean = 8.13).	The results of this study demonstrate support for the benefits of a brief behavioural intervention in the management of opioid compliance. among chronic back pain patient at high-risk for prescription opioid misuse.
Brown et al. (USA)	Morphine sulphate extended release capsules, a treatment agreement, card for obtaining/ tracking prescriptions, screener and opioid assessment for patients with pain revised, pill count, pain-patients follow-up tool, urine drug testing.	Evaluate and monitor aberrant behaviour Using The screener and opioid assessment for patient with pain Revised (SOAPP-R) UDS.	**Medicine optimisation outcome:** At the baseline 47 %were considered low risk for opioid misuse/abuse, 52 % moderate, and 1 percent high risk. 90% of the patients remine at the same level of risk at the end of the study. **positive Urine drug screen**% changed from 14 to 10%. P=NA	Investigator compliance with the use of universal precaution (UP) to pain management.	A total of 64% of investigators were compliant with UP, and there was tendency to assign patient to lower level than the protocol specified.	Most patients at primary care were categorized as at least a moderate risk of opioid misuse/abuse at baseline. The plan for patients at moderate risk included counselling, monitoring for aberrant drug related behaviour. Patients at high risk for aberrant drug related behaviours were withdrawn from study.
Jamison et al. (USA)	A structured opioid therapy protocol of monthly monitoring and compliance checklists. Patients were contacted by telephone once a month and were asked to complete the assessments.	Opioid compliance.	**Medicine optimisation outcome:** **Medication compliance** (pre= 51.5, post= 60.8%). **Opioid use for pain** (pre= 87.0%, post= 79%) **Clinical outcome score means:** **Pain scores** (pre=7.0, post=6.7). **Activity interference (**Daily routine pre=6.862, post=6.7).	Practitioner confidence in identifying patients at risk for misuse and Patients satisfaction	**Patients satisfaction** was (74.2%). **Confidence in opioid prescribing** (pre= 53.5%, post= 36.2%) P<0.01 **Confidence in identifying patients at risk for misuse of pain**	The patients reported greater compliance with their opioid medication. Many PCPs still lacked confidence in managing pain patients and reported reluctance to prescribe opioids for chronic noncancer pain. This study demonstrates the benefits of careful monitoring of chronic pain

					medication (pre=42.9%, post=63.9%) P<0.05	patients and need for pain management support within primary care.
Jacobs et al. (USA)	Clinical pain pharmacists reviewed patients' chart to assess recent opioid use, side effects, laboratories values, and aberrant behaviours and then contacted patients by phone two weeks prior to the prescription renewal date. Based on an assessment, pharmacists documented recommendations on the appropriateness of a patient's opioid regimen, adjunctive nonopioid medications, side effect management, the frequency of UDS, provider follow-up, and laboratory monitoring.	Pharmacist-led telephone risk assessment clinic effect on opioid using in primary care clinic.	**Medicine optimisation outcome:** Recommendations to change opioid regimens= (32.4%). Decrease the MEDD of opioids (33.3%). Discontinuation of opioid therapy (15; 22.7%), **OTC** use (pre=4.7%, post= 64.8%) p < .0001 **UDS** (pre= 62.8%, post 79.7%) p=0 .002 **PDMP** report (pre= 30.4%, post= 100%) p=< .0001	-	-	A clinical pharmacist-run telephone risk assessment promotes safe use of chronic opioid therapy through improved monitoring and identification of aberrant behaviours in more than one third of assessed patients
Talusan, et al. (USA)	An advanced practice registered nurse led opioid monitoring clinic (OMC)which included protocol for urine drug screening, PMP database access, reports of opioid dispensing from Pharmacy Care line, clinic referral template allowing communication between primary care providers and OMC.	Reduction in the Morphine Equivalent Dose (MED) and identified abuse, the use of illicit drugs.	**Medicine optimisation outcome** Opioids discontinued in 36%. p value=NA Reduction of (MED)59%, p= <0.001. The mean MED/d (pre-54 mg/d, 22 mg/d).	Level of satisfaction among primary care providers (PCP).	**PCP satisfaction**= 100% with the Monitoring Clinic service. **PCP following the guidelines for opioid** =90%. **PCPPDMP access**= 54%. **UDS ordered**=.93% **And** significant pharmacy cost savings.	Opioid Monitoring Clinic can be an effective programme to help identify abuse and misuse of prescription opioids among high-risk patients and can improve patient safety and provider satisfaction.
Schell et al. (USA)	Multidisciplinary pain oversight committee to facilitate appropriate management of chronic opioid therapy (COT) using urine drug testing a prescription drug monitoring programme (PDMP), patient education and provider education.	Appropriate opioid use (reduction in opioid dose).	**Medicine optimisation outcome** Opioid dose per patient decreased 20% from baseline. Patients who received an opioid and benzodiazepines decreased 41.7% during the study period.	-	. -	Multidisciplinary pain oversight committee led to increase appropriate COT monitoring and appropriate management of high-risk patients.
McCann et al. (USA)	Structured management of opioid medication started by listing CNMMP patients on opioid from electronic health record of a single rural practitioners then notifying them 3 months before the change in practice. The notification letter explained options for the patients were to continue opioid, manage their pain without opioids, or be referred to another provider.	Patients weaning from opioids and reduction in opioid dose	**Medicine optimisation outcome** **Wean from opioids**=38% **Continued opioid =** 53%. Transferred care= 9%. **Mean morphine equivalent** mg/day decrease from (30.61 mg/day) to (17.01 mg/day) (p = .0397; CI, 0.68 to 26.51) **Clinical outcome score means:** **BPI Pain Scale (0 to 10) (mean)** = (pre 5.75 post 6.20) **BPI Quality of Life Scale** (0 to 10)(pre5.84 post 6.11)95% CI (1.44 to 0.55)	-	-	Intervention provided a high degree of compliance with controlled substance regulations and is associated with a reduced number of opioid prescriptions. Patients on lower doses of opioid medication are more likely to wean their use with this model.

Abbreviations: COMM=The Current Opioid Misuse Measure, HRC=High Risk Control, HRE=High Risk Experimental, MED=Morphine Equivalent Dose, OTA=opioid treatment agreements, PCP=primary care providers, p= significance level, PG=Pain Group, r= correlation values SG=Presurgical Group UDS= urine drug screen, NA=Not Available, NS=nonsignificant.

Impact of the interventions

UDS was used in simple intervention and complex interventions as the only objective tool to detect inappropriate drug-taking behaviours. The use of UDS was associated with a significant reduction in inappropriate medication use (182,188,192,195,202) (Table 5). For example, a study which aimed to identify controlled substance abuse in patients receiving prescription opioids showed a statistically significant decreases in obtaining opioids from multiple providers or sources from 17.8% to 9.2% (ARR, 8.6% [CI, 4.4% to 12.8%]) (194). One study concluded that UDS should not be used alone and should be used with a comprehensive monitoring system (192). Three studies that were conducted in a pain speciality setting and used UDS and OTC found these were associated with improvements in detecting inappropriate drug-taking behaviours but did not measure clinical outcomes such as pain intensity and depression score (192,194,195). Two studies that used the same sample of patients and used historical control participants concluded that UDT and OTC significantly reduced problematic behaviour by detecting patients who were obtaining opioids from multiple providers (194,195). Behavioural interventions showed that these interventions are beneficial in reducing the inappropriate use of medication, pain intensity and depression score and in improving patient compliance (185,187,201). Another study suggested that careful monitoring of patients' medication cravings can reduce the inappropriate use of medication and the level of pain experienced is weakly associated with craving opioids (199). Only one study used special medication educational intervention alone and found a non-significant effect on medication optimisation and no significant effect on pain intensity, depression and functionality interference (183).

Overall, treatment programmes incorporating multidisciplinary teams were associated with decreased risk of opioid misuse and improved functioning and pain condition (182,185,188,196,199). One study that used a pharmacist and nurse-led interdisciplinary approach in advising primary healthcare providers, prescription management and patient monitoring using UDS in the opioid renewal clinic showed that approximately half who were referred for complexity, including history of substance abuse or need for opioid rotation or titration, continued to adhere to the opioid treatment plan(200). Another study that aimed to support providers, change prescribing behaviours and improve their adherence to clinical guidelines, reported that opiate use was successfully discontinued in nearly one in ten patients (190). Generally, the structured programmes were associated with a reduction in the inappropriate use of medication but clinical outcomes such as depression, pain, and quality-of-life scores were stable during study time were rarely reported (196) (Table 5). A study which included daily patient visits to a primary care physician clinic and involved verification of the controlled substance contract, UDS, board of pharmacy monitoring, pain-targeted history and physical, and calculation of the average morphine equivalents used showed that 8% of patients elected to wean opioids, 53% continued opioid medication and 9% transferred care. Mean morphine equivalent mg/day was the prime determinant for ability to wean (17.01 mg/day) compared with maintaining (30.61 mg/day) ($p = .0397$; CI, 0.68 to 26.51) (196). Patients maintaining opioid treatment showed no statistically significant change in clinical outcomes such as quality of life and depression scale point compared with the baseline (196). Another study conducted in a multidisciplinary primary care programme, which monitored patients with psychiatric comorbidity showed an improvement in patients' mood and pain scores

but a high dropout rate among patients with misuse behaviour was observed (188). An RCT consisting of monthly electronic diaries, urine toxicology screens and medication adherence counselling for six months reported an improvement in adherence to the prescribed regimen among high-risk patients, and patients' satisfaction (Table 5) (182).

4.7. Discussion

This study aimed to systematically review the nature and outcomes of interventions to optimise the use of prescribed medication among CNMP patients. An array of different types of single component and multi-component complex interventions were being evaluated to optimise medication use. A variety of definitions were used for medication optimisation with a range of other outcomes evaluated which included clinical outcomes, costs, patients and healthcare satisfaction and quality of life.

The results demonstrate an inadequate number of high-quality studies focusing on medication optimisation among these patients. The majority of studies (n = 10) had a limited sample size and were often conducted in a single setting. Studies differed in recruitment methods and participant inclusion criteria. In addition, there was substantial heterogeneity in the types of populations being studied, their co-morbidities and medications. Studies were of low to moderate quality. It was often unclear which component targeted which behavioural issue. A lack of consistency in defining the appropriate use of pain medication was identified.

Most of the studies categorized as simple interventions aimed either to detect or reduce the problematic taking behaviours without taking into consideration their effects on patients' clinical outcomes such as pain intensity, depression, anxiety and relapse after stopping their medication (189,192,193,194,202). A previous qualitative study

suggested that healthcare providers commonly believed that OTAs were useful for provider self-protection, but they do not prevent opioid misuse (203).

The multi-component interventions included in this review were often based on the United States' own chronic pain management guidelines such as Department of Defence Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain (197,198). Such multi-component interventions were shown to be more comprehensive and targeted detection and reduction of problematic medication-taking behaviour, taking into consideration patients' physical and psychological states, as well as their satisfaction (197,198). However, the complexity of these interventions makes it unclear to conclude which components targeted which behaviour. Such understanding is needed in order to personalize the interventions for the CNMP population which may differ in various ways and from one demographic region to another. For example, patients with a history of addictions and other substance use disorder may need different monitoring than those without such issues (182,186,188). Safe and effective pain management requires knowledge of the principles of chronic opioid therapy as well as effective assessment of risks associated with opioid abuse, addiction and diversion using multi-component interventions. An earlier systematic review specifically focused on opioid misuse also addressed that multi-component interventions that targeted both patients and healthcare professionals are essential to minimize their misuse for CNMP patients(204).

The lack of literature regarding interventions for non-opioid medication and the heterogeneity of studies are major limitations of the published literature.

4.7.1 Implications for practice

The review suggests that the most promising approach to increase the appropriate use of prescribed pain medication among CNMP patients is a structured opioid clinic with a multidisciplinary approach. Clinicians' ability to appropriately prescribe opioids to CNMP patients with or without problematic medication taking behaviour can be achieved with an appropriate level of understanding and using the components of the complex interventions including UDS and OTC and personalizing pain management according to patient need. Random drug testing might be more suitable to detect misuse and abuse than regular testing and save more money. Well-structured chronic pain programmes structured opioid clinics designed to support and improve healthcare providers' communication skills and knowledge for all healthcare providers should be implemented. More attention should be paid to the costs and benefits of interventions and the impact on the burden on clinical staff as this is potentially important to inform policy and practice decisions (198).

Collaborative relationships and communication between different healthcare settings are important to facilitate medication optimisation. Providing high quality, patient-centred care and ensuring patient safety for CNMP patients who are on chronic opioid therapy requires collaboration among healthcare providers (205). Clinicians need to attend more to the negative impact of psychiatric and behavioural issues on the use of opioids. Additionally, they should initiate discussions with patients who are being prescribed opioids in order to evaluate their medication-taking behaviours and treatment effectiveness, as well as to screen for their risk of prescription opioid misuse and provide intervention as needed. Clinicians must be aware CNMP patients face

multiple physical, psychological and social challenges that may impede them from taking their medications as prescribed (206-208).

4.7.2 Strengths and limitations

This is the first systematic review to include a wide variety of studies on the nature and outcomes of interventions used to optimise medicines use in CNMP patients. The search was limited to three databases and the English language. The search criteria did not include specific chronic pain types or diagnoses, which might have led to the omission of studies.

4.7.3 Implications for research

There is a need for further studies on interventions to optimise the use of prescribed pain medication, applying high methodological standards and including randomized controlled designs. There is also a need for future studies to better define misuse and other problematic medication-taking behaviour and related complications of opioid therapy, to develop diagnostic procedures for these disorders. Moreover, behavioural issues should be categorized according to their seriousness and their effect on the patient's quality of life. The studies should also report changes in outcome measurements such as pain levels and psychosocial, physical and occupational functioning and patient's satisfaction at different time points, rather than only before and after the intervention implementation. The validity and reliability of measurement tools should be carefully tested and explicitly reported. Both interventions and tests should be tailored to specific CNMP populations such as patients with different types of pain, comorbid psychiatric conditions and different behavioural issues. Future efforts should be directed at RCT to examine structured pain management programmes that would determine whether reported effects are real, examine durability and promote

sustainability. There is also a need for the development of clear and consistent terminology and measurement criteria to facilitate comparisons of research evidence. Research should assess the drawbacks of applying these interventions. Future interventions should include collaborative and structured opioid clinic approaches using nurse, pharmacist or a primary care physician who must be trained in delivering a motivational interview or educational interventions.

4.8. Conclusion

A well-structured CNMP management programme to promote medicines optimisation should include multi-component interventions delivered by a multidisciplinary team of healthcare professionals and target both healthcare professionals and patients. There was heterogeneity in definitions applied and interventions evaluated. There is a need for the development of clear and consistent terminology and measurement criteria to facilitate better comparisons of research evidence.

In the light of the conclusions and limitations identified from the systematic review of extant research, a need was identified for further investigation of the factors that might contribute to the success or failure of an intervention to consider the viewpoint of different personal who might form part of MDT, and to explore the perspectives of pateints who the target of various prescribing are policies and practices. Three empirical studies were conducted for this purpose. Chapter five reports the first of these, investigating the perspectives of community pharmacists.

Chapter 5: Qualitative study with community pharmacists

Roles, barriers and behavioural determinants related to community pharmacists' involvement in optimising opioid therapy for chronic pain: a qualitative study.

5.1 Publication

This chapter has been published in entirety as Alenezi, A., Yahyouche, A. & Paudyal, V. Interventions to optimise prescribed medicines and reduce their misuse in chronic non-malignant pain: a systematic review. Eur J Clin Pharmacol (2020). https://doi.org/10.1007/s00228-020-03026-4 (Appendix 1).

5.2 Chapter description

Concerns about prescribed opioid use for CNMP treatment and safety have grown over the last 20 years, especially after the North America opioids crisis. Community pharmacists are well-positioned to play a key role in prescribed opioid optimisation and educating patients about opioid-related, risks, and there is growing interest in developing the capacity of the profession to provide interventions or direct treatment referrals for patients who may need special help. However, little is still known about the community pharmacists' perceptions of enablers and facilitators of prescribed opioid optimisation. This chapter highlights these enablers and facilitators based on semi-structured interviews conducted with community pharmacists from different regions of England.

5.2 Introduction

Chronic pain is defined as pain that persists for more than three months (3). The World Health Organization (WHO) data suggest that the prevalence of chronic pain is 22% of the world population (25) and in the UK 46% of the population suffer from chronic non-malignant pain (CNMP) (22). The concerns about prescribed opioid and chronic opioid therapy (COT) effectiveness, safety, and abuse in CNMP have grown, especially with the alarming death rate related to medical and illicit use of opioids in North America (209). The extent of the increased opioid use, including misuse, remains less debated in the UK. Yet, UK based studies indicate an upward trend in the use of prescribed opioid in the National Health Services (NHS) parallel to that in the US(72,210).

Medicine optimisation, which means ensuring safe, effective, and efficient medicine use, is becoming a key priority in the UK's NHS to manage long-term conditions (90). Community pharmacists have a role in optimising prescribed opioid use in CNMP patients and ensuring safe, effective opioid use as well as making sure that these patients are benefiting from using these medications.

Findings from literature suggest that a well-structured CNMP management programme led by a multidisciplinary team is critical to optimise COT use and improve CNMP patients' quality of life (38). One of the most important services that patients with chronic diseases receive at community pharmacies in the UK is Medicine Use Review (MUR) which has been performed since 2005. MUR is a 'concordance/compliance review' and annual face-to-face patient–pharmacist consultation for patients using two or more prescribed medicines, who are regular customers of the pharmacy (211).

Through such reviews and other patient contact, community pharmacists are well-positioned to deliver many services that can lead to optimisation of opioid use in CNMP (61).

A systematic review (2020) found that community pharmacists faced various challenges when trying to play the role of opioid therapy optimiser (212). The first set of challenges is related to patients, including demand for early refill, unrealistic expectations of pain relief and inadequate access to non-pharmacological treatment. There are also difficulties dealing with patients on high doses of opioid. The second set of challenges is pharmacist-related challenges such as lack of training, lack of confidence, lack of access to medical records and lack of guidelines and policy that integrate pharmacists with other healthcare providers in managing CNMP (212). Other studies from the USA and the UK suggest that community pharmacists have constructive attitudes toward expanding their role in optimising opioid use and pharmacy-based screening and intervention to reduce substance use disorder in patients with CNMP (61).

There are, however, gaps in the literature on community pharmacists' contribution to opioid optimisation in the UK. Most existing UK studies focus on pharmacists' role regarding over-the-counter medication. This may be because the extent of the opioid crisis in the UK is different from those in USA, Canada and Europe, where other studies have been done (213-115). To the authors' 'knowledge, this is the first qualitative study of UK pharmacists regarding their roles, associated barriers and behavioural determinants regarding their roles in opioid therapy optimisation.

5.2.1 Aim of the study

The aim of this study was to explore community pharmacists' perceptions regarding their roles, barriers and determinants related to their involvement in optimising prescribed opioids for CNMP.

5.3 Ethical approval

Ethical approval was granted by the Science, Technology, Engineering and Mathematics Ethical Review Committee of the University of Birmingham (ERN_19-1922). Written informed consent was obtained from all participants.

5.4 Method

5.4.1 Study design

This study was reported based on the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist for comprehensive reporting of qualitative studies (216) (see Appendix 12). Data were collected between January and May 2020 via semi-structured interviews informed by the Theoretical Domains Framework (TDF). The TDF was developed from a synthesis of psychological theories to help apply theoretical approaches to behaviour change interventions. TDF domains represent environmental, cognitive, and social factors that may affect behaviour (166,167,217,218). The TDF has been widely used to understand behaviours and implementation challenges in various settings and content areas in health care, including community pharmacies (219,220) and hence is suitable in the context of this research.

5.4.2 Sample

Community pharmacists working in various regions (cities and rural areas) in England were recruited through the dissemination of invitation using the professional networks of the research team, including community pharmacy forums, a large chain of

community pharmacies in England and acquaintance of the research team. The inclusion criterion was currently working in community practice, and there were no exclusion criteria. The primary researcher (AA) introduced the study to the pharmacists and asked if they would consider taking part in the study. A 'snowballing' sampling method was used to recruit more participants, whereby interviewed pharmacists identified others who might be interested in taking part. (See Figure 5).

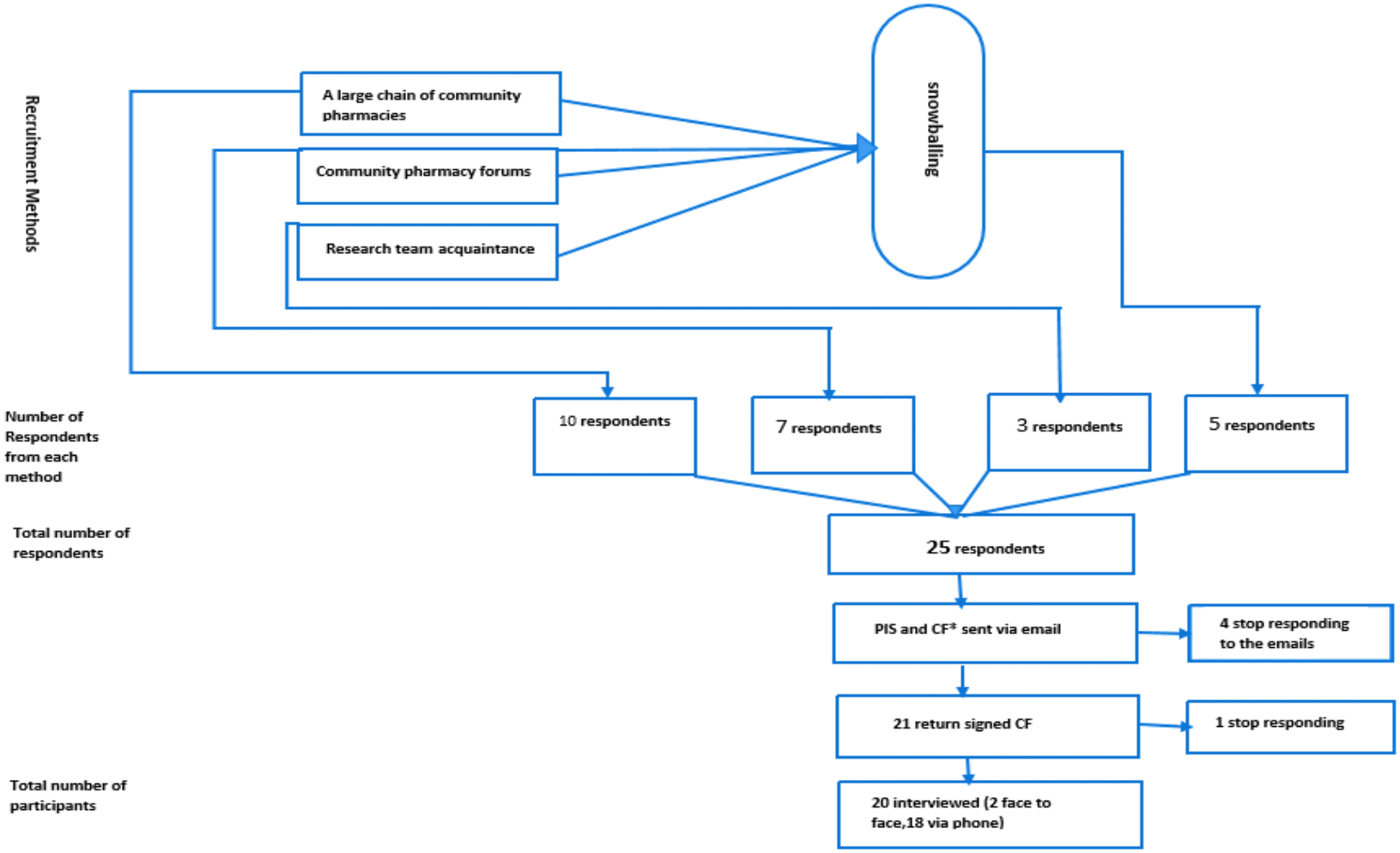


Figure 5: Study sample recruitment flowchart

PIS: *Participant Information Sheet*

CF: Consent Form

5.4.3 Interview topic guide and procedure

The TDF informed the development of an interview guide containing open-ended questions and standardized prompts available for use if needed. It was reviewed within the research team and pilot tested with two community pharmacists. However, some questions under specific domains such as intention were considered repetitive or irrelevant by the participants and were deleted in the following interviews. However, each domain was represented by at least one question (See Table 6). Written information about the study was offered (by email) before the interview. An agreed interview date, time, and location (for face-to-face interviews) were then arranged. All interviews were conducted by AA. Face-to-face interviews were at the pharmacist's place of work. Telephone interviews (when lockdown in response to COVID-19 prevented face-to-face interview) were conducted in the researcher's home in a quiet room, at a time convenient to the participant. No follow up interviews were conducted. Interviews ranged in duration from 25 to 65 minutes, mostly taking around 35 minutes. All interviews were audio-recorded and anonymously transcribed verbatim. Recruitment and interviewing ceased after reaching thematic saturation based on initial analysis and coding (no new themes or codes could be identified from the last two interviews) (221).

Table 6. Mapping of interview schedule to TDF domains.

Domain	Content	Sample questions as applied to this study
Knowledge	An awareness of the existence of something	What does chronic opioid therapy optimisation mean to you? What are the knowledge barriers to optimising opioid therapy for chronic pain?
Skills	An ability or proficiency acquired through practice	When considering filling a prescription for an opioid, how do you evaluate patient risk for misuse? What training have you had in how to appropriately review opioid prescription and identify opioid-related abuse and misuse?
Social/professional role and identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting	What are your general thoughts about dispensing opioid prescriptions?
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use	How can pharmacists contr bute in recognizing the various forms of opioid abuse and misuse and in preventing inappropriate prescribing and diversion of opioids?
Optimism	The confidence that things will happen for the best or that desired goals will be attained	How optimistic are you that the use of e-prescription or prescription monitoring programmes will reduce inappropriate use of opioids?
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation	What are the advantages and disadvantages of opioid prescription review for each patient/ education about opioid to identify problematic medication use?
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus	How does your experience (good or bad) of reviewing opioid prescriptions/ education about the opioids in the past influence whether or not you would do it again?
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way	Do you intend to review each opioid prescription and assess misuse and abuse? Why do you feel this way?
Goals	Mental representations of outcomes or end state that an individual wants to achieve	Do you think optimising chronic opioid therapy is a personal goal or an institutional goal? What factors may interfere with the goal?
Memory, attention, and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between 2 or more alternatives	What reasons might prompt you to decide to carefully assess opioid-related abuse and misuse and review an opioid prescription?
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviours	To what degree do resources and physical context influence your careful review of opioid prescription /education about the opioids?
Emotion	A complex reaction pattern involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event	How confident are you when dispensing high dose opioid prescription? How does this feeling influence what you do?
Social influences	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour	Tell me about your communication with prescribers regarding opioid prescriptions. When you need to contact the prescr ber, are they accessible? What do you do if you cannot reach the prescriber?
Behavioural regulation	Anything aimed at managing or changing objectively observed or measured actions	What additional strategies do you think might mitigate inappropriate opioid use among CNMP patients?

5.4.4 Qualitative data analysis

Data were analysed using the Framework method. Through listening to recordings and reading transcripts, a familiarisation process took place, from which AA attained an overview of specific beliefs within the data (222). Following this step, excerpts from the interview transcripts were coded into one or more of the 14 TDF domains. Data were coded systematically using a deductive approach, whereby each TDF-14 domain served as a coding category (223). Initially, a second researcher (VP) coded two randomly selected transcripts to ensure the credibility and dependability of the data analysis. Disagreement in coding between the two researchers was resolved through discussion with another research team member (AY) until consensus was reached. The team agreed on the coding framework and subsequent interview codings were regularly discussed in the team to ensure that they were consistent. Coded interview excerpts were compared and organized into a framework table generated in Microsoft Word®. When several codes could form a meaningful unit, this was deemed a theme (145,224). A domain was deemed relevant if excerpts were coded frequently or if the participants emphasised the significant impact of behavioural determinants within a domain on their involvement in COT optimisation. A content analysis of the framework table was then undertaken to identify subthemes. Themes that shared the same central concept as the theme but were particularly important for the research question were considered a sub-theme. For example, 'e-prescription' was considered as subtheme under the umbrella of 'Environmental Context'. Subthemes within each domain were summarised to give an overall impression of how each domain may influence the optimisation of prescribed opioid use for CNMP in the community pharmacy setting and illustrated using supporting quotations.

5.4.5 Research trustworthiness

This study is part of AA's PhD studies after being trained in conducting research at the University of Birmingham. The research trustworthiness was sought by applying Lincoln and Guba's principles (169,224,225). Credibility was enhanced through the adoption of appropriate, well-recognized research methods informed by previous comparable studies. Data analysis and coding were conducted by two researchers (AA, VP) (226). To facilitate transferability, the author described the findings and supported the descriptions with quotes from the interviews. To enhance dependability and confirmability, the Theoretical Domains Framework was followed in conducting this study (227,228).

5.5 Result

Participants' distribution and characteristics are presented in Tables 7 and 8.

Table 7. Distribution of participants (N= 20)

Location	N
London	2
Birmingham	2
Bradford	2
Leicester	2
Hull	2
Stourbridge	1
Solihull	1
Normanton	1
Coventry	1
Wakefield	1
Hemel Hempstead	1
Sunbury-on-Thames	1
Missing information	3

Table 8. Sample characteristics (N=20)

Characteristics	N
Speciality and role	
Community Pharmacist	16
Community pharmacist and Manager	1
Community and Hospital Pharmacist	3
Sex	
Male	17
Female	3
Age in years	
25-35	16
36-45	3
46-60	1
Years of experience	
1-5	11
6-10	3
11-15	4
20+	2

Key themes are presented below with illustrative quotations.

For summary of the results, see Table 9.

Table 9: Theoretical Domains Relevant to Community pharmacists' Role om Prescribed Opioid Optimisation with Illustrative Quotations

Theme	TDF domains & non-TDF subtheme	Codes/ constructs	Illustrative quotations
Pharmacists' self-perception	Social and prof role and identity	Primary guardian of patient welfare	"Obviously, I am a pharmacist, and so my interest is always in patient health and patient's outcome" (Participant 2).
		Secondary role	"We're not involved in it directly… It would be totally the medicine management team at the surgery …As a pharmacist, you would intervene by highlighting it to the doctor because the doctor is going to take the decision at the end of the day" (Participant 17).
		Safeguarding action	" I would say it is part of my job to check whether they are… the amount that he was taking, Oramorph, isn't going to cause him on overdose or a serious reaction with alcohol misuse" (Participant 14).
Capabilities	Knowledge	Knowledge of condition/ scientific rationale	"Opioids are not for chronic use ……they're only when needed….in a flare-up or acute pain" (Participant 8).
	Skills	Skills development through training	"We did cover the guidelines, but it was quite some time ago" (Participant 17).
		Experience	"Tell if someone's misusing but, that's just from experience... or like, you know, intuition kind of thing. You would usually know anyway" (Participant 14).
	Beliefs about capabilities	Empowerment (lack of)	"It's currently, it's impossible to monitor and optimise opioid, opioid treatments". (Participant 18)
Infrastructure and systemic constructs	Environmental Context and Resources	Barriers: Information	"Without access to medical records …. that'd probably be a barrier". (Participant 19)
		Funding and resources	"The, erm, funding, I think that it's one of the things that they probably might need to kind of fund to sort of, as a service…." (Participant 3).
		Systems	"There's nothing stopping that patient taking their prescription to another pharmacy "(Participant 10)
	E-prescriptions		"They might not have the time to …do proper checks to make sure… and they might just print it" (Participant 5).
Personal Factors	Social Influences	Inter-group conflict with GP	"That, I think, [causes]frustrations with all community pharmacists because we don't have, erm, I think professional to professional communication between prescribers and pharmacist, so …..patients have to come back the next day or a few days after ……if there is a single piece of information that we need to clarify or double-check . Sometimes……you have to call back two, three times, and you still can't get an answer. The patients might have to take their prescription somewhere else…. I think there's a huge barrier between pharmacists and prescribers" (Participant 13).
		With patients	"Obviously, if you have a bad experience with a patient, then sometimes you think twice about something, you know, doing something" (Participant 11).
	Emotion	Empathy	"If [I] find out that the patient is misusing other substances with the opioid …. I'd be worried about them" (Participant 4).
		Stress	"Monitoring and ta king to every patient and keeping tabs is going to be a very strenuous task, that would be very stressful" (Participant 6).

Theme 1: The pharmacists' self-perception of their identity and social and professional role

A dominant theme throughout the interviews, arising from the TDF domain, ‘Social and Professional Role and Identity, was pharmacists' perception of themselves as guardians of patient welfare. Some expressed this in general terms, as an intrinsic part of their professional role. This is illustrated in the quote below.

*"Obviously, I am a pharmacist and so my interest is always in patient health and patients' outcome" (*Participant 2*).*

Others elaborated on particular safety concerns, including appropriate dosage, ensuring that patients achieve optimum benefit from their medication and do not suffer undesirable physical or mental consequences, and looking out for signs of risk. As one respondent commented,

"I would say it's part of my job to check whether [patients] are, erm, abusing alcohol, or their Oromoph. The amount he is using isn't going to cause him overdose or a serious reaction" (Participant 14).

When such concerns arose, they felt a responsibility to take action. Some viewed prescribed opioid optimisation as a specific responsibility, but others viewed their role as secondary, with the clinician having the main role, compared to over-the-counter opioid-containing products, where pharmacists have a bigger role to play. One interviewee explained,

"About over the counter selling of co-codamol [we have a role] but, for prescriptions, then we're not involved in it directly… It would be totally the medicine management team at the surgery … As a pharmacist, you would intervene by highlighting it to the

doctor, because the doctor is going to take the decision at the end of the day" (Participant 9).

Pharmacists highlighted specific activities they performed pursuant to their safeguarding role, particularly medicine use review (MUR) in which they asked about patients' use of the medication and any problems they encountered. At these interviews, they might also ask patients about their alcohol consumption and over-the-counter medications, but admitted that they did not routinely raise these issues, as expressed in the example below.

*"We used to have the medicine use review, so that was an excellent opportunity to sit down with the patient and ask if their pain is controlled, they are taking any medication" (*Participant 11).

Another safeguarding activity was the provision of education and advice, including warning of possible side effects. In the event of serious concerns, pharmacists reported deferring supply of medicine and referring to the prescriber, for example, to query the dose, highlight interactions with other medications, or report suspicions of a patient's misuse or abuse of prescribed medication or other substances. Some participants gave examples of situations where they might check to prevent any negative consequences.

" I would say it is part of my job to check whether they are… the amount that he was taking, Oramorph, isn't going to cause him on overdose or a serious reaction with alcohol misuse". (Participant 14).

Theme 2: Capability

The theme ‘Capability’ is related to the competencies pharmacists possess that facilitate their role in prescribed opioid optimisation, arising from the TDF domains, ‘Knowledge’, ‘Skills’ and ‘Beliefs about Capabilities’.

In performing their role, pharmacists relied on their professional judgement around supply of prescribed opioids, drawing on knowledge and skills derived from training and experience. They displayed an understanding of the meaning of COT optimisation as ensuring the balance between effective control of patients' condition and avoiding harmful side effects. They revealed knowledge of opioid-related problems, most of them mentioning dependence, tolerance and addiction, as well as physical and psychological side-effects such as depression. They also showed awareness of other treatment options, including non-opioid medication and complementary, non-pharmacological therapies that might reduce the need for opioids:

"Opioids are not for chronic use they're only when needed...in flare-up or acute pain" (Participant 8).

However, the majority reported having little or no formal training on how to review opioid prescriptions and identify misuse; only *"one lecture or something"* (Participant 17) but *"no sort of course"* (Participant 15). Some, moreover, admitted that their knowledge might not be up-to-date, since they qualified *"a very long time ago"* (Participant 20). Nevertheless, they generally felt confident in dispensing opioids and also suggested that, over time, they acquired an *"intuition kind of thing"* (Participant 14) that helped them to identify warning signs of misuse, such as over-ordering, early re-ordering and taking multiple medications. Despite their knowledge, skills and

experience, however, several interviewees were pessimistic about their capability to contribute effectively to COT optimisation, due to their lack of authority.

"Since we're sort of almost the end point before the patient gets their medication, so apart from the medication check, there's very little I can do" (Participant 15).

Theme 3: Infrastructure and systemic constraints

Pharmacists also highlighted specific constraints preventing them from playing a more direct and effective role in COT optimisation. The TDF domain 'Environmental Context and Resources' constituted one of the largest bodies of responses in the data set and revealed the importance of lack of resources and systemic constraints in explaining the limited involvement of community pharmacists in COT optimisation. For example, pharmacists spoke of lack of information, whether guidelines, detailed patient records, or statements of policy issued by the employing pharmacy or chain, to guide them in assessing prescription appropriateness or the possible need for an intervention. With regard to patient information, it was pointed out that, although pharmacists could access summary care records, in practice, they would not do it without a specific reason, and in any case, the information contained might be too brief to be really helpful. For example, one participant said,

"It doesn't show the full history; it's only a brief summary" (Participant 5).

Where guidelines existed, their effectiveness, it was suggested, was undermined by ambiguity or inconsistency:

"Each area, each prescriber, you know, they will have different guidelines, different rules" (Participant 1).

Pharmacists also pointed to a lack of funding and resources, especially lack of time, as a barrier to more effective prescribed opioid optimisation. They discussed the

difficulty of finding time to review, monitor and educate the huge number of patients they encountered and perceived involvement in opioid optimisation as an additional burden on an already heavy workload. As interviewees pointed out, devoting the necessary time to review each opioid prescription and having a detailed conversation with every patient would not be feasible without additional staff.

"Pressure is building up and I "wouldn't be interested in something that increase my workload" **(**Participant 15).

Additionally, lack of funding was discussed as a particular issue for many. Several participants suggested that opioid prescription review needed to be a funded service, to persuade pharmacies to undertake it, and for pharmacists to devote their time to it. Currently, they reported, the number of MURs performed annually was being reduced for financial reasons, and each pharmacy received payment for 250 reviews instead of 400 as previously, with further reductions forthcoming. Moreover, the reviews were limited to specific categories of medication, which did not include pain management:

"We used to focus on blood pressure medication, diabetics and the like, so pain wasn't among those" (Participant 16).

Ideally, it was suggested, MURs should be conducted for a wider range of conditions and medications than at present and more frequently. One experienced pharmacist suggested the need for a facilitative tool such as a short questionnaire to assess alcohol intake, break-through pain, and the like, to guide pharmacists in collecting the information needed to inform optimisation interventions.

A large volume of comments focused on factors related to the system of prescription ordering and processing, particularly the difficulty created by repeat prescribing and prescription delivery services, which reduced contact between patient and pharmacist

and, hence, opportunities for education and monitoring. An added difficulty, especially with over-the-counter medications, was patients' freedom with regard to the choice of pharmacy and number of pharmacies visited, potentially enabling them to engage in what one pharmacist likened to a *"pub crawl"* for medications, making it difficult to monitor their behaviour. Moreover, the development of e-prescriptions, a widely used component of prescribing systems, was seen as of limited value in monitoring and controlling opioid prescriptions and opioid use. Whilst it was acknowledged that e-prescriptions ensure legality, reduce the possibility of error and create a better audit trail, overall, it was suggested, they would make little difference, and they might make it too easy for patients to obtain repeat prescriptions without review, especially since it was feared that other healthcare providers might not do the proper check, as stated by one participant:

"They might not have time to do proper checks of the prescriptions and just print it" (Participant 17).

Some participants indicated that an electronic prescription drug monitoring program such as the Prescription Drug Monitoring Programs (PDMPs) would be useful in the detection of opioid abuse/misuse. They were aware of the limitation of other electronic programs and suggested that although these may be necessary, they are not adequate to solve the problem of patients going from one pharmacy to another.

"I get there would be an electronic program, it would be good if it's regular patients, but what if someone goes from another pharmacy or place?" (Participant 10).

This might highlight community pharmacists' perception of their relative powerlessness to monitor and control opioid prescribing or even, sometimes, knowledge of how that role is carried out.

Theme 4: Personal Factors

Other perceived constraints, captured by the TDF domain, Social Influences, were said to stem from relationships with other healthcare providers and patients, whose roles, expectations and perceptions affected pharmacists' performance of their role. A key issue in this regard was the difficulty for some pharmacists of communication with prescribers in the event of any query. While some respondents indicated that doctors were usually accessible and that queries were usually answered within a reasonable time, others expressed frustration at the delays they experienced when they could not get through to the prescriber and were forced to hold a prescription until the required check could be made.

"Sometimes you have to call back two or three times and you can't get on answer. There's a huge barrier between pharmacists and prescribers" (Participant 11).

Pharmacists also reported difficulties in COT optimisation arising from patients' attitude and understanding. They pointed out that patients are understandably concerned primarily with their symptoms and simply want relief from pain, so tend to be resistant to the idea of reduction and put pressure on pharmacists who, in turn, are wary of upsetting a patient. They also felt unable to intervene in a patient's right to make their own lifestyle choices. Nevertheless, they suggested that patients' complex individual needs require a gradual, personalized approach and frequent follow-ups, in which pharmacists might contribute. By helping to manage potential expectations and providing education on the advantage of deprescribing and limitation of medication, its correct use, potential risk and the role of medication as one component in an overall plan for pain management, they aspired to an ultimate aim of enabling patients to take more responsibility for their own pain management.

Among personal factors, Emotions, such as stress or empathy for patients, emerged as of limited relevance, being mentioned by only two interviewees. Instead, pharmacists were more concerned about the need to address the aforementioned infrastructural and systemic challenges in order to play an enhanced role as part of an integrated approach to the safety of patients using opioids.

5.5 Discussion

Four themes were identified in relation to the community pharmacists' perceptions of their current and future roles, barriers and behavioural determinants around optimisation of opioid therapy for CNMP. The majority of sub-themes fell under the TDF domains. The few exceptions reflected issues raised by pharmacists beyond the discussion of their own role, or those spanning more than one domain. Pharmacists expressed a belief that they had a limited role, if any, in relation to prescribed opioid optimisation. They appeared to act as medication dispensers or patient educators rather than medicine optimisers. However, participants perceived themselves as gatekeepers capable of minimizing the misuse of opioid-containing products, consistent with the existing literature(229-230).

Nevertheless, their perception of doctors as the ultimate authority over patient care deterred pharmacists from contributing more to opioid optimisation, as noted in previous studies (231-233).

Moreover, pharmacists of varying experience reported that opioid prescriptions, misuse and addiction were barely addressed in their training or continuing education. The findings align with previous studies arguing that there is inadequate education on pain management provided to medical students (234-236). This suggests that training

curricula need review in order to fit the NHS aim of giving the pharmacist an enhanced role in patient-centred care.

This study's findings suggested some pharmacists may be reluctant to be involved more in prescribed opioid optimisation and screening for opioid misuse or abuse. This finding supports previous anecdotal reports of pharmacists' stress and discomfort when faced with a new responsibility, particularly in clinically complex, ambiguous and ethically sensitive situations(234,237). Indeed, many participants viewed prescribed opioid optimisation as not community pharmacists' responsibility and perceived they lacked the required authority, reimbursement, infrastructure and time for greater involvement in this area. Thus, for pharmacists to realize their potential in this area, improved resources and structures are needed to enhance clinical practice in the community setting (238).

Another perceived determinant of pharmacists' limited involvement with prescribed opioid optimisation was the lack of regular communication with patients. This may be attributed to the growing use of online and mail-order pharmacies, as well as disability or limited mobility preventing CNMP patients from visiting the pharmacy (239). Also, some participants mentioned that they did not discuss opioid risk, as they expected the prescriber to do so. This resulted in a situation where patients received no information about opioids ' possible risks. Pharmacists could provide such information but may be deterred by the sensitivity of risk and problematic use issues (240). More training and professional development regarding communication about sensitive issues could overcome this reluctance (241).

MUR services are designed to help pharmacists to discover medication-related problems. However, participants stated that even during MURs, prescribed opioids

were not their priority. This may be attributable, in part, to a reported deficiency of patient information . It would be reasonable for them to have access to diagnosis and information on co-morbidities to increase the clinical relevance of pharmacist recommendations and improve communications with other healthcare providers(211, 242).

This study is not without limitations. Given the convenience sample involved in this study, findings may not be transferable. Also, topic sensitivity may have resulted in some response bias. The gender composition of the sample was skewed in favour of males and so may not reflect the actual gender balance in the profession. In addition, more than half of the sample had between 1-5 years' experience. Further research is needed to explore possible impacts of gender and experience on pharmacists' knowledge and capabilities toward opioid therapy optimisation.

5.5.1 Implications for practice

There is a need for a clearer definition and guidelines on the use of opioid for chronic pain and the optimisation role that pharmacists can perform. Further education and training on pain and opioid use disorder are needed, consistent with the NHS vision of the expanded role of pharmacists in clinical aspects of patient care. There is also a need for direction and support from pharmacy organizations. For example, reimbursement would facilitate the expansion of pharmacists' role in patient care and encourage their involvement as opioid risk educators and gatekeepers.

5.5.2 Further Research

Further studies should explore the experiences and perceptions of pharmacists working in general practices and hospitals. In addition, the perspectives of wider stakeholders are imperative. This study is one of three interlinked complementary

studies, the others exploring the perceptions of other CNMP healthcare providers and patients separately. The findings of the studies may be used to guide the development of future interventions and/or to inform policymakers of how to integrate the community pharmacists into opioid therapy optimisation.

5.6 Conclusion

The role of community pharmacists in optimising opioid therapy for chronic pain was perceived by the study participants to be currently unclear. There is a potential to use community pharmacists' skills and knowledge to facilitate their involvement in treatment optimisation, monitoring and educating patients. However, pharmacists perceived the need for appropriate training and tackling of systemic and resource constraints. There is a need to involve wider stakeholders in developing innovative clinical pharmacy services allowing enhanced roles of pharmacists by addressing the barriers and behavioural determinants of further involvement identified in this study.

The next chapter addresses some of the issues raised by pharmacists in this study, and contributes to the need for investigation of opioid-related issues from various stakeholder perspectives, by reporting on a study of CNMP patients' perspectives and experiences of using opioids.

Chapter 6: Qualitative study of chronic pain patients' forums

Patient Perspectives on the Appropriate Use of Prescribed Opioids in Chronic Non-Malignant Pain: Analysis of Online Forums Using the Theoretical Domains Framework

6.1 Publication

This chapter has been accepted for publishing entirety in the Journal of Pain Research as Alenezi, A., Yahyouche, A. & Paudyal, V. Patient Perspectives on the Appropriate Use of Prescribed Opioids in Chronic Non-Malignant Pain: Analysis of Online Forums Using the Theoretical Domains Framework**.** *J Pain Res.* (Appendix 1).

6.2 Chapter description

In view of concerns about the harmful effects of long-term use and patient misuse of opioids in chronic non-malignant pain, this study provides insight into patients' perspectives on their experience of living with chronic non-malignant pain (CNMP), prescribed opioid use, and optimisation via analysing chronic pain patients' forums.

6.3 Introduction

Medicine optimisation is crucial for the management of chronic non-malignant pain (CNMP). It is defined as “the safe and effective use of medicines to enable the best possible outcomes”(117).‘ Patient-centred principles allow greater contributions by patients to their treatment and promote greater satisfaction with healthcare, as well as maintaining productive patient-provider relationships(243).

Guidelines discourage long-term opioid therapy as its effects on CNMP is uncertain, and usually associated with harm including diversion, addiction, overdoses, and death(244). Moreover, Busse et al. evaluated the evidence on opioid efficacy by reviewing 96 randomized control trials (RCTs) of opioids’ effects for CNMP and found that opioids provide similar benefit compared to nonopioid alternatives in pain improvements, other physical and social functioning. Also, opioids were connected to high risk of toxicity and dependence(245).

The North American opioid crisis of overdose death has been soaring over the past years. Even though the majority of overdose deaths were caused by illegally made fentanyl, prescribed opioids were responsible for 28 percent of deaths in the United States in 2019(246,247). With the increased use of prescribed opioids in England, attributed deaths have risen, particularly in areas with higher deprivation(,80, 247).

In the UK, over five million people each year are diagnosed with CNMP, i.e., pain lasting over three months (3, 22). It affects patients' emotional and social wellbeing and the overall quality of life (248). There are significant impacts on patients, families, and carers, as 50% of CNMP patients experience depression, and 66% are unable to work. Patients with CNMP are sometimes considered "intractable" because they fail to

respond to repeated surgery or medications, or their pain may even worsen. CNMP management is challenging and dissatisfaction among patients reaches up to 60% (249). Patients have reported frustration and ineffective communication with healthcare professionals about opioids and pain management(250). Healthcare providers may be constrained in meeting patients' expectations due to inaccessibility of alternatives and limited knowledge of CNMP(251). In the UK, not all CNMP patients have access to specialist pain services. A national audit in 2012 indicated that only 40% of pain clinics had a physiotherapist, psychologist and physician, resulting in poor patient outcomes due to unrelieved pain and high healthcare system utilization(252). CNMP patients are driven by the need for pain relief and quality of life improvement. However, their interaction with healthcare providers can be complicated and stressful. Lack of a definitive diagnosis and precise treatment plan lead to unsatisfactory outcomes and poor pain control, with patients often resorting to self-medication and diversion as coping strategies(250,251). These patients' suffering is multidimensional as they struggle from their conditions and the misunderstanding in their surroundings. Because pain is such a personal experience, the patient's perspective should be highlighted (250). There is a need for an investigation of their struggles related to managing their conditions in an era of pressure on the medical society for prescribed opioid optimisation (reduction or tapering), as evidence indicates that opioids' harms outweigh the benefit in managing CNMP.

Despite the importance of patient-centred care, little is known about barriers and enablers to optimising prescribed opioids for CNMP from patients' perspectives. This study was conducted to gain insight from patients' forums into patients' experiences of CNMP management and to address this gap in the literature.

6.3.1 Rationale for the study

Several studies have analysed online forums to explore the nature of forum interaction and patients' perspectives in relation to their condition experience and online support. (253-255) They offer distinctive insight into the experiences of contributors as they chat about topics without researcher influence. Therefore, material from online forums can be deemed as practically authentic natural data(156,157,256).

6.3.2 Aim

The study aims to identify the barriers and enablers to the use of chronic opioid therapy from CNMP patients' perspectives.

6.4 Ethical considerations

The study was granted ethical approval from the University of Birmingham and adhered to British Psychological Society (2007) guidelines(159). Consent was not considered essential as all the material was in the public domain and freely available to be viewed without registration with the website, an approach widely used in other studies(253-255). No direct permission was obtained from the forums' owners, yet the term and conditions statements of the included forums were reviewed by the authors. Any forum that prohibited the accessing, printing, use or storage of the forum content for research or non-commercial professional use was excluded. Also, the anonymity of the data has been protected as forums have not been identified and data excerpts have been paraphrased, with any identifying information removed.

6.5 Method

This research utilized a qualitative study design based on analysing the views of CNMP patients who are prescribed opioids, using posts on online forums. The research is innovative in its focus on patients via online discussion forums.

Online forums are websites where users post messages about different issues, looking for health, emotional and informational support. They are a valuable source of data as they are places of free expression without pressure from the medical profession(156, -158). Search, data extraction and catagorization were undertaken by the primary researcher, AA. Using several keywords, chronic pain health forums and general health forums were systematically identified through the Google and Bing search engines (see Appendix 13). Websites were then screened following the criteria listed in table 1. Four online support groups were identified: two specifically dedicated to chronic pain and two with forums for various conditions, including chronic pain. One of these forums was excluded as it prohibited any reproduction of posts, even for research use. Relevant sections and threads were defined using the forums' internal search, using keywords based on previous reviews (see Appendix 13). To enable systematic representation of the forum discussions, a few pages of search results per forum were reviewed, excluding any post before 2016, surveys, advertisements, or links (See fig 6). Only posts posted by CNMP patients who were either current or former prescribed opioid users were included. Threads posted between January 2016 and December 2020 were downloaded and copied into Microsoft Word, organized according to the keywords and sub keywords. For example, pain medication was sub-categorized into Tramadol, codeine, oxycodone (see Appendix 13). Due to the extensive volume of data retrieved, the record of 360 threads was divided into two corpora to make the data more manageable (See Data Analysis, below): 237 threads in corpus 1 and 123 threads in corpus 2. Both corpus 1 and corpus 2 were analysed in the same way, applying the same definitions of the TDF dimensions, and in reporting sub-themes, relevant items from both were considered. Data were analysed until

saturation, defined as a point where no new perspectives could be detected with enough quotes that represented the same perspective.

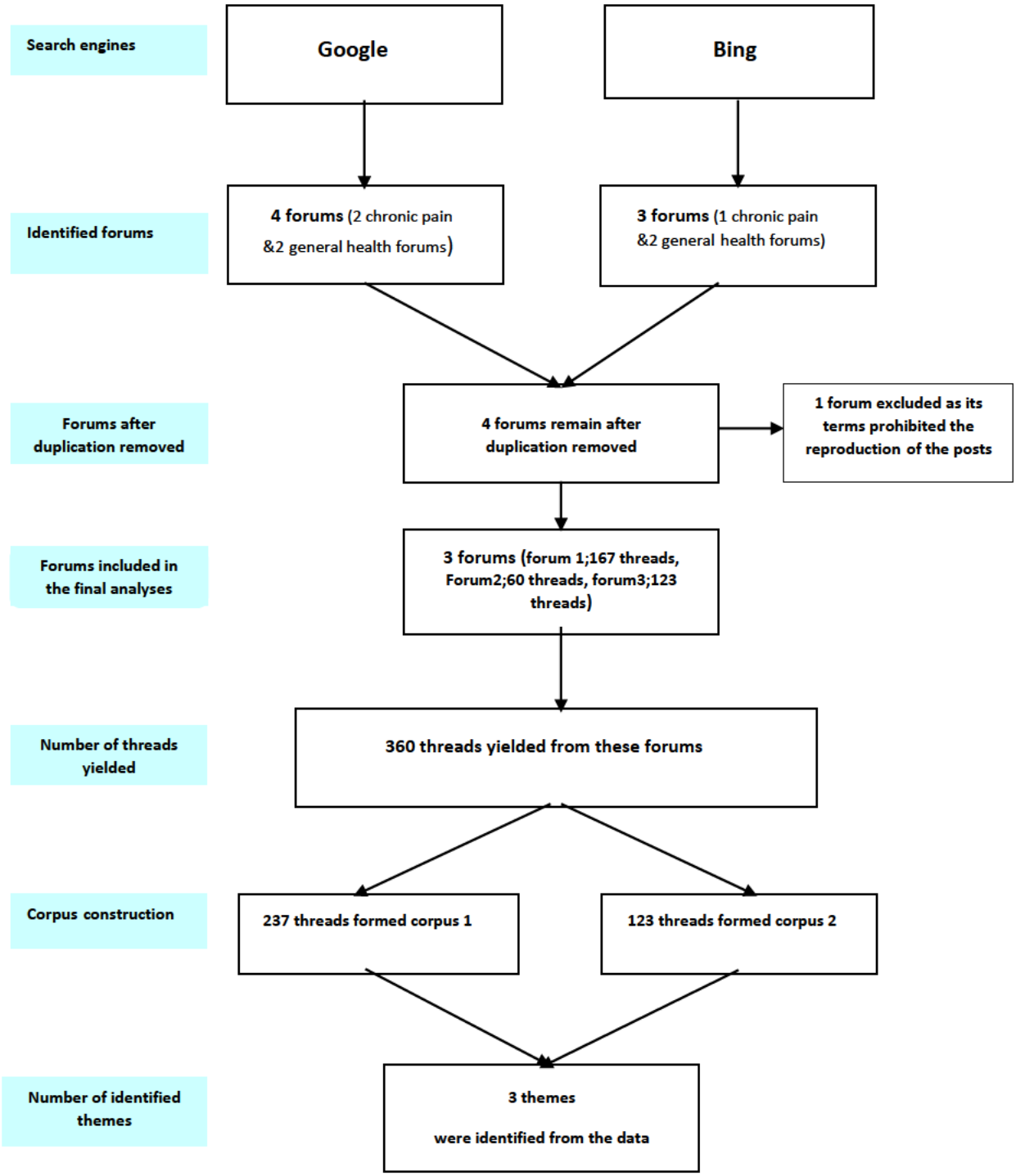


Figure 6: Flowchart of online forums and threads search process

6.5.1 Data analysis

The development of the Theoretical Domains Framework (TDF) from a synthesis of psychological theories has helped apply theoretical approaches to behaviour change interventions. TDF domains represent environmental, cognitive, and social factors that may affect behaviour (217-219). The TDF has been widely used to understand behaviours and implementation challenges in various settings and content areas in health care 218). It was used in this study as an analytical tool to assist in identifying and classifying relevant posts from the patient forums. Table 11 shows the 14 domains of the TDF with their definitions and indicates their application to the forum data.

Data were analysed using the Framework method to allow an in-depth reflection of the meaning and patterns of the data to be identified. Extracts from each corpus were coded systematically, using a deductive approach, with each TDF-14 domain used as a coding category (223-227).The data analysis was regularly discussed in research team meetings and any disagreement in coding between the researchers was resolved through discussion until consensus was reached. Multiple posts by the same forum member expressing the same topic were compressed into a single post to prevent the over-counting of an idea or biasing of the data by individual contributors. Threads duplicated between corpora 1 and 2 were reviewed. Coded quotations were organized into a framework table generated in Microsoft Word®. Excerpts were grouped together into topics and then reviewed and refined until meaningful and distinct main themes and subthemes were developed (222). A domain was judged relevant if excerpts were coded frequently or if the researchers believed the posts showed that domain to have a significant impact on the appropriate use of prescribed opioids. A content analysis of the framework table was then undertaken to identify subthemes that shared the same

central concept as the main theme and were particularly important for the research question. For example, within the theme, facilitators of COT optimisation, a frequently occurring feature was the need for an individualized approach to opioid prescribing and tapering support. This latter was considered as a subtheme. Subthemes within each domain were summarised to give an overall impression of the potential impact on how each domain may influence the optimisation of opioids in CNMP and illustrated using supporting quotations. Coding stopped once data saturation of the main themes was achieved.

Table 10: Mapping study question to TDF domains.

Domain	Content	Sample questions that the study aims to answer by analysing online forums
Knowledge	An awareness of the existence of something.	What knowledge do CNMP patients have about their condition and medication?
Skills	An ability or proficiency acquired through practice.	What skills do CNMP patients have that may help them to optimise the use/withdrawal from chronic opioid therapy?
Social/professional role and identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting.	What is the CNMP patient's role in optimising chronic opioid therapy?
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use.	Do patients believe they are capable of optimising use/withdrawal?
Optimism	The confidence that things will happen for the best or that desired goals will be attained.	To what extent do patients have confidence that they will achieve a desirable outcome (e.g., pain reduction, quality of life, withdrawal from opioids)?
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of behaviour in a given situation.	What are CNMP patients' beliefs about the consequences of use or withdrawal from opioid therapy?
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus.	What reinforcement can the healthcare system and healthcare providers offer that may help patients in optimising opioid therapy for CNMP?
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way.	Do CNMP patients using opioids for pain intend to optimise or withdraw from opioid use?
Goals	Mental representations of outcomes or end-state that an individual wants to achieve.	What are patients' goals of using/withdrawing from chronic opioid therapy?
Memory, attention, and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between 2 or more alternatives.	What resources are available to support patients' memory, attention and decision processes in relation to opioid optimisation/withdrawal?
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviors.	What are the circumstances of the situation or environment of CNMP patients that discourage or encourage the development of appropriate use of chronic therapy/withdrawal from chronic opioid therapy?
Emotion	A complex reaction pattern involving experiential, behavioral, and physiological elements, by which the individual attempts to deal with a personally significant matter or event.	How are patients affected emotionally by their experiences with opioid withdrawal and pain?
Social influences	The interpersonal processes can cause individuals to change their thought, feeling and behaviours.	How do patients' relationships with others influence their thoughts and behaviour with regard to opioid use and withdrawal?
Behavioural regulation	Anything aimed at managing or changing objectively observed or measured actions.	What strategies are applied to optimise the appropriate use of chronic therapy/withdrawal from chronic opioid therapy?

6.5.2 Research trustworthiness

The research trustworthiness was sought by applying Lincoln and Guba's principles (225). Credibility was enhanced through the adoption of appropriate, well-recognized research methods informed by previous comparable studies. Rigour was supported by the purposeful inclusion of online forums and following practical guidelines for qualitative research using online forums (156-158,256). The spontaneous nature of the conversations without the researcher's presence prevents researcher bias. Systematically keeping a logbook of the data collection and analysis process, along with regular research team meetings during the analysis phase to discuss emergent themes, boosted the dependability and confirmability of this study. Public accessibility and the systematic approach of this study to collecting the data enable other researchers to repeat it for other research or/and to reappraise the original researchers' conclusions (159,227,228,).

6.6 Results

360 threads were identified and a total of 1978 posts were randomly analysed. This study focuses on UK opioid optimisation and following the British Psychological Society (2007) guideline, only UK patients' forums that met the inclusion and exclusion criteria have been included. See Table 10.

Three major themes, each with their respective subthemes, were identified from the dataset and mapped against the TDF (See Table 11). Key themes are described below with summary narratives and illustrative quotations.

Theme 1: The experience of living with CNMP

A dominant theme throughout the data was patients' experience of pain. Contributors frequently contextualized their posts by providing information on the location, cause (for example, accident, surgery or health conditions) and duration of their pain. Patients also attempted to describe the intensity of their pain and report improvement or deterioration, either using verbal descriptors such as "*excruciating*" (Thread 55, forum 3) or in terms of scores on the pain scale:

"*I had occasions when my pain score was zero and at its worst,4/10*" (Thread 16, forum1).

Posts also revealed how CNMP impacted every aspect of patients' lives: physical, social, mental and emotional. With regards to the physical impact, for example, they reported impaired function such as being bedridden, unable to walk.

"*Most of the time I'm curled up in bed and only walk a short distance"* (Thread102, forum 2),

Physical limitation, in turn, produced social constraints affecting study, work, leisure and relationships: cancelled outings, inability to spend time with family, financial dependence on others and confinement to home, causing severe psychological impact. For example, a young woman who had to give up university and was confined to her parents' house, which she said had become her "*prison"* described her feeling that "*the pain is driving me crazy, quite literally*" (Thread 233, forum 1).

Patients also experienced a sense of loss resulting from the inability to continue activities that had previously provided satisfaction and meaning in their lives, as in the case of a young man whose inability to continue in his job resulted in losing "*the feeling of satisfaction, that my day had meant something"* (Thread 128, forum1). Faced with such losses, patients reported depression extending sometimes to suicidal ideation:

"*If I have to live a life with chronic pain and no way of easing it, I truly don't think I would bother"* (Thread 133, forum3).

A prominent subtheme was the idea that pain becomes part of the sufferer's identity, in their own and others' eyes. Several patients described that they had been assigned, adopted, or even embraced, a social identity /role as "*disabled*", with implications, for instance, for support through the welfare system. In contrast, others strenuously rejected the connotations of disability. One participant spoke scathingly of those who "*basically give up, quit their jobs, claim disability benefit and sit around their homes all day in pain*", asserting her refusal to become one of them.

A key issue for those who rejected the “disabled” label was the condition of dependence. While there were constraints on their functioning and activities they could not perform without help, some found this difficult to acknowledge. As one contributor posted,

"*I don't want to be seen as a needy, non-functional human*" (Thread 304, forum 1).

Thus, data revealed pain to be a dominant, life-altering experience for constant sufferers. They monitored changes, positive and negative, in pain intensity, shared experience of the social limitations imposed by pain and restricted mobility and sought comfort and reassurance in the face of psychological impacts of often considerable

severity. Some accepted a social role as “*disabled*” and” dependent”, but this was rejected by others, who sought to preserve their former sense of self.

Theme 2: Facilitators of COT optimisation

The second theme concerned factors that appeared to help and support patients in optimising or reducing their usage of opioids. Some were internal factors, reflecting the TDF domains, Knowledge and Skills. Others were external, reflecting the domains, Social Influences and Environmental Context and Resources. A subtheme was identified here, which is the need for an individual approach to opioid prescribing, tapering and support, in recognition of patients' different needs and responses.

Patients' knowledge emerged as a major factor influencing individuals' perceptions of opioids and alternative treatment options. Posts showed patients to be active seekers of knowledge, who asked questions, exchanged ideas and conducted research in order to better understand their conditions and the benefits and risks of the treatment options available, for example:*"I did some research on pethidine and found out how bad it really was"* (Thread 98, forum 2).

Informal sources, particularly print and broadcast media, played a key role in patients' knowledge search:

"*I watched a really interesting programme on BBC4 about them [opioids]*" (Thread 61, forum 3).

Members used the forum to fill gaps in their knowledge and understanding, or to seek a "second opinion" about a proposed new treatment or strategy, appreciating the opportunity to communicate with others who had experienced some of the same challenges:

"*Maybe you can offer advice on my predicament, especially considering you have been where I currently am and have come off opioids?"* (Thread 56, forum1).

Although the forum protocol did not allow members to offer specific medical advice, contributors freely shared information they had read or heard, and recounted their personal experiences of treatments and their effects, good and bad, for example:

"There is a longer-acting tablet that should last for 12 hours, then you can occasionally add the liquid as a top-up" (Thread 11, forum 2).

"The Tens machine is very good for muscular pain. I have one myself. I also found a Tens belt which was much easier to use, requiring no sticky pads" (Thread 163, forum1).

However, patients acknowledged the limitations of their expertise and frequently advised inquirers to consult their GP or other professionals. Patient-provided information and ideas could, however, help to inform such discussion and give patients confidence to ask questions and discuss alternatives.

A prominent sub-theme in the information exchanged, reflecting the Skills dimension of the TDF, related to coping strategies that patients used to manage pain and substitute for or offset the side effects of medication. These fell into two broad categories, physical and psychological. Patients shared their experiences of several physical approaches: diet, exercise, relaxation and heat. For example, one described how she had eliminated carbohydrates to account for her reduced mobility and increased her fruit and vegetable intake to alleviate constipation associated with her medication. Another described the benefit of having "*my trusty special cushion to sit on and a hot water bottle to hand"* (Thread 132, forum 3).

The most commonly reported approach was exercise, including exercises prescribed by a physiotherapist (sometimes in private practice), yoga, swimming, Pilates, or simple stretching and walking. Generally, such activities were reported as coping strategies that the patient found useful.

Patients also mentioned psychological approaches such as practising mindfulness, distracting themselves with recreational activities and investing in their sense of personal well-being:

"*Buy yourself a new book, go out for coffee, plan a holiday… doing something for you will make you feel a whole lot better*" (Thread 285, forum 1).

For a very small number, however, the solution was simply to accept the pain, rather than having false hopes and unrealistic expectations. As one asserted," *Pain is something you can get used to and learn to cope with*" (Thread 289, forum 2) while another reported on the breakthrough she experienced through coming to terms with her pain:

"Since my mindset changed to accept the pain, I've been so much more positive and coped much better" (Thread 133, forum 3).

In coping with their condition, patients made use of a variety of resources available in the surrounding environment, which facilitated their understanding and motivation towards opioid optimisation. Whilst several contributors drew attention to useful material on the internet, such as a website suggesting *"gentle physio exercise to try"* (Thread 125, forum 3), the majority of resource-related posts highlighted support and advice received from various healthcare professionals, such as nurses at a pain clinic or hospital:

"*My pain nurse keeps in contact via telephone to make sure I'm coping ok*" (Thread 49, forum 2).

Supportive relationships with these professionals, reflecting the Social Influence dimension of the TDF, emerged as a crucial facilitator of opioid optimisation. A good doctor was characterized as one who was knowledgeable – though not necessarily a pain specialist, and who showed empathy and understanding. Patients valued having someone who "*seemed to get what I was saying*"(Thread 58 forum 1) and not only provided information but planned care jointly with the patient.

Health professionals were not, however, the only source of support. A common subtheme was patients' need for support from a wide range of others including family, friends, an advocate, employers and teachers. The support available from such individuals, however, depended on their knowledge and understanding: "*My friends mean well, but really I need support from someone who knows what's going on*" Thread 19, forum 1). This is why the patient forum was so important to many members:

"*Knowing there is someone out there who 'gets it' is really motivating and encouraging and makes you feel like you're not alone*" (Thread 251, forum 2).

Such sources of knowledge, practical advice and emotional support seemed to be far more important and relevant to patients (as judged by the number of posts and patients' emphasis on their importance) than aids to memory, attention and the decision process, such as a tapering chart or pain diary (each mentioned only once) or even behavioural intervention, which rarely appeared in the data. Although a number of patients discussed experiences of opioid tapering or doctors' prescribing decisions, it was often not clear who initiated the changes, or for what reason. Only one contributor

explicitly acknowledged a past addiction and behavioural intervention taken to address it:

"*I was addicted to co-codamol and I had to be weaned off them and my doctor referred me for pain management*" (Thread 154, forum 3).

None of the contributors ascribed treatment changes to current addiction. From the variety of resources and strategies mentioned by patients as facilitating their opioid optimisation, one concern emerged clearly: the need for an individual approach to treating CNMP and managing patients' use of opioids. Posts revealed that patients differ widely in their needs and in their responses to particular medications but perceived this as insufficiently recognized by health practitioners. Rigid imposition of a standardized treatment, or tapering regime, reportedly led to side effects, increased pain, or withdrawal problems, sometimes causing non-compliance with treatment. Patients wanted doctors to recognize them as individuals, *"discuss the pros and cons for your own personal circumstances and to enable and support them in finding their own solutions"* (Thread 198, forum 1).

Theme3: Barriers to COT optimisation

Patients described difficulties they faced in effectively managing their condition and their medication, which reflected the TDF domains: Environmental Context and Resources, and Social Influences, as well as two sub-themes outside the TDF: the challenges of tapering or withdrawal and the balancing of risks.

A major issue affecting medicine use behaviours was the perceived lack of effective alternatives to the medicines patients were currently using. Many patients had tried and discontinued numerous medications that did not sufficiently control the pain, or

produced side effects, allergies or intolerance. Consequently, several felt that opioids were the only option remaining:

"I have tried everything available and this was the only option for me" (Thread 317, forum 1)

"The only ones that have ever worked have been the opioids" (Thread 145, forum 3).

Regarding non-pharmacological alternatives, some had found physiotherapy helpful, but others

found the exercises difficult, and thought they compounded the problem:

"The physio keeps giving me exercises that worsen the pain!" (Thread 277, forum1).

Patients also highlighted difficulty accessing formal health services for the support and care they needed. It might be necessary to travel a considerable distance for an appointment with a specialist at a hospital or pain clinic, and there were reports of long waiting lists for a referral.

Moreover, there was a lack of continuity of care, as different professionals were seen on each visit. There were reports of prescribing decisions made by a doctor who did not actually know the patient or rarely saw him or her. As one contributor reported,

"I see a different GP every time. My assigned GP is ok, but she's hardly ever there" (Thread 344, forum 3).

There were also reports of a lack of reliable access to the GP, preventing patients from mentioning ideas and questions they wanted to raise. Even when patients gained access to healthcare professionals, many described what they perceived as unhelpful encounters and unsupportive relationships with doctors, who, they claimed

had dismissed their worries. For example, one who expressed concerns about medication-related risk declared,

"I just get dismissed whenever I bring it up" (Thread 53, forum 1).

Another, who sought help with depression, was simply given the telephone number of the Samaritans. Faced with what they perceived as dismissiveness and impatience, some patients were deterred from seeking further help:

"I was too afraid to go to the doctor again because I was made to feel I was going too much" (Thread 251, forum 2).

Some patients clearly felt misjudged and subject to negative assumptions by health professionals, for example being seen as drug-seeking or uncooperative if they reported difficulties with tapering or having the reality of their pain called into question.

"They say I'm drug-seeking, need psych care and don't want to take part [in the programme offered], which is so untrue" (Thread 102, forum 2).

"Straight up, he told me, you're just addicted, there is no pain" (Thread 60, forum1).

"The system makes you feel like a junkie at times" (Thread 172, forum 1).

One reason for such attitudes on some doctors' part may be a lack of specialized knowledge in the area of CNMP and its treatment. A number of participants were critical of health professionals' shortcomings in this area:

"There remains a huge lack of knowledge and understanding of the medication needs of CNMP patients" (Thread 26, forum 2).

There were suggestions that it may be necessary to change GPs several times before someone suitably knowledgeable and sympathetic was found.

In the face of what was sometimes perceived as an absence of support from the health services, patients reported anger and frustration, as well as fear at the prospect of unremitting pain, which overshadowed thoughts of tapering or withdrawal. Nevertheless, a number of patients described attempts to taper medication or come off opioids by various means, and some were keen to do so, because of worries about harmful effects of long-term opioid use. In many instances, patients resorted to ways of using their medication, which were potentially dangerous. For example, one contributor recommended another to cut a fentanyl patch in two to reduce the side effects associated with it. Others divided slow-release tablets to maximize the benefit of the existing dose, or to achieve gradual reduction and showed no awareness of the risk involved. Others who followed doctors' directions still faced challenges. Several reported experiences of a sudden drastic reduction in the dose of medication without notice or a clear plan for managing the effects, which could be severe. One patient recalled,

"I was cut off; two days later, in so much pain, vomiting and had had no sleep, I was admitted to my doc's clinic for the weekend" (Thread 161, forum 1).

Patients frequently referred to the problems associated with withdrawal, which some described as “horrendous", and if undergone without adequate support, could thwart the best of intentions. The idea that the main concern was to alleviate the pain by any means possible was summed up by one patient, who argued,

"Chronic pain is hell… taking medications that help make your life better is the only way to go" (Thread 61, forum 3).

Patients saw themselves as struggling to balance competing risks: the harmful effects of long-term opioid use, the impact (experienced and anticipated) of withdrawal and the possibilities of renewed or increased pain and disability if they stopped a medication they found effective.

"I’m just so afraid being left in continuous, unbearable pain" (Thread 341, forum 3).

Overall, the picture emerging from the patient forums was that patients wanted to manage their medication appropriately and were willing to consider or attempt tapering. However, they were often confused, frightened, and overwhelmed by the severity of the challenges involved, particularly if they had difficulty accessing service or felt they were being unheard, pushed to withdrawal too quickly, or unsupported in balancing the opioid-related challenges with the physical, social and mental effects of constant pain. The themes emerging from the patients’ posts, and their relationship to the TDF domains, are summarized in Table 12.

Table 11*:* Theoretical Domains Relevant to Patients' Perspectives of Barriers and Enablers to Appropriate Use of Prescribed Opioid with Illustrative Quotations.

Theme	TDF domains & non-TDF subthemes	Codes/ constructs	Illustrative quotations
The experience of living with CNMP	Pain	Pain intensity	"much more tolerable levels" (Thread 318 forum1)
		Pain physical impact	"Most of the time I'm curled up in bed and only walk a short distance" (Thread102, forum2)
	Emotion	frustration and anger	"Because I can't get up or downstairs, may not be able to spend Christmas downstairs with my family. It's devastating!" (Thread110, forum3)
		suicidal ideation	"If I have to live a life with chronic pain and no way of easing it, I truly don't think I would bother" (Thread133, forum3).
		The sufferer's identity	"I have had daily migraines for 12 years, the worse as time passes". (Thread197, forum 3)
	Social and prof role and identity	Rejection of 'disability' and 'dependence' identity	"I don't want to be seen as a needy, non-functional human" (Thread 304, forum 1).
Facilitators of COT optimisation	Knowledge	patients' knowledge	"In order to successfully undertake this thorough investigation! must initially have completed much knowledgeable research" (Thread36, Forum2).
	Skills	coping strategies	"Since my mindset changed to accept the pain, I've been so much more positive and coped much better" (Thread133, forum3).
	Social Influences	Advice from healthcare professionals	"My pain nurse keeps in contact via telephone to make sure I'm coping ok" (Thread49, forum2).
		Supportive healthcare providers	"Although he is not a pain management specialist, I have sufficiently high regard for him" (Thread45, forum1).
	Environmental Context and Resources	Empathy from professionals	"Knowing there is someone out there who 'gets it' is really motivating and encouraging and makes you feel like you're not alone" (Thread 259, forum3).
		Empathy from family	"He didn't understand and believe my pain, he is a difficult to partner any way" (Tread 83, forum1)
	Memory, attention, and decision processes	Opioid tapering decision	"I was addicted to co-codamol and I had to be weaned off them and my doctor referred me for pain management" (Thread 154, forum3).
	The need for an individual approach to opioid prescr bing and tapering support	Every patient different	"It can take ages to get the right [medications] combination, were all different" (Thread306, forum3)
Barriers to COT optimisation	Environmental Context and Resources	lack of effective alternatives	"The only ones that have ever worked have been the opioids" (Thraed145, forum3)
		Lack of access to specialist services (pain clinic)	"I had to wait 5 months for the first appointment at the pain clinic" (Thread58, forum1).
	Social Influences	Unsupportive relationships with professionals	"I just get dismissed whenever I bring it up" (Thread53, forum1).
		Labelled as a drug addict	"Straight up, he told me, you're just addicted, there is no pain" (Thread 60, forum1).
	the challenges of tapering or withdrawal and the balancing of risks.		"For a week and a half,I have been having a horrendous time. …Sleep disturbance is dreadful …My bladder has given up the ghost as have my bowels... Feel utterly desperate…"(Thread16,forum1)

6.6 Discussion

No previous study has explored the enablers and barriers to optimising the use of prescribed opioids for CNMP using patients' online forums. This study analysed a sample of posts on CNMP and general health forums and yielded three major themes which reflected patients' experiences of living with pain, facilitators of prescribed opioid optimisation and barriers to prescribed opioid optimisation.

The first theme highlighted the impact of CNMP patients' quality of life and a sense of control over their life. This study's finding is consistent with a large-scale survey of CNMP patients, which concluded that improvement in their energy, concentration, sleep, family, employment, social relationships, enjoyment of life and recreational activities should be appropriate targets of their treatment (249,). Pain was seen to be a multidimensional, dynamic interaction of biological, psychological and social factors, suggesting the potential value of individualized assessment and appropriate management of psycho-social factors in the early stage of pain conditions.

Furthermore, the early establishment of a balanced provider-patient relationship through awareness of social, physical, and physiological aspects in patients' conditions supports patients' ability to open up, know and accept their condition .The present study emphasizes the importance of the provider-patient relationship, as both an enabler (if positive) and a barrier (if negative) to prescribed opioid optimisation, consistent with previous studies (52-250). Moreover, the literature provides consistent evidence that patient-provider collaboration in the identification of treatment goals and shared decision-making results in improved outcomes (250). Patients place health care continuity with providers as a high priority to optimise their care and facilitate knowledge and trust. High care continuity is linked with lower hospitalization,

emergency department visits and medical errors and improved patient safety, as it is easier for the providers to manage medical problems in the office or over the phone and prevent extra redundant healthcare utilization (257).

The study findings revealed that some patients showed potentially dangerous ignorance of how to use opioids. For example, cutting fentanyl patches could lead to serious harm, including death, as the dose that is supposed to be delivered over 72 hours could be delivered immediately, leading to overdose (258). Whereas strict adherence to other pain analgesics is not necessary and deviation from them may be acceptable, following the instructions for using opioid medications is vital. Opioid-related overdose and other serious adverse effects have been periodically reported in UK clinical practice (259). Patients' misinformation results from attempts to fill the gaps in information from professional sources. A recent study exploring the role of UK community pharmacists in optimising prescribed opioids revealed time and systemic constraints on their ability to educate CNMP patients on opioids (260). Yet GPs may lack the required knowledge and specialists can be difficult to access (51). Patient education on CNMP and appropriate opioid use for pain relief, and patients' discussion of their concerns with healthcare providers are crucial. It is widely accepted that structured educational programmes that include information about CNMP and treatment options emphasise the importance of appropriate medication use and provide practical tools to prevent unintended side effects(261). These programmes might be more effective when offered in a patient-tailored approach and addressing individual needs. This could be achieved by tailored discussions with health care providers, particularly pharmacists (38,262).

Prominent barriers were poor access to pain services or non-pharmacological treatments as well as perceived ineffectiveness of alternatives tried. Uneven distribution of facilities for psychological and physiotherapeutic treatment may explain why pain treatment is frequently solely pharmacologic, although recommendations increasingly promote a multi-modal treatment strategy (263). Kroenke et al suggested that the early engagement with non-pharmacological treatment could be considered a prerequisite for ongoing opioid therapy as part of treatment agreements. They suggested that collaborative care models in which mid-level providers, particularly nurses, provide follow -up, could enhance patient motivation. Non-pharmacological treatment may be critical for improving the quality of care(263.264). This is also consistent with patient reports that continued encouragement from their care team would be a significant facilitator to their pain treatment engagement(252). This last point is also related to the factor of support, another recurring theme in our data. Besides care management and structured follow up, our findings suggested peer and family support interventions as other potentially effective strategies, models well-supported in the treatment of other chronic conditions(265).

This study is a one-sided view of chronic pain treatment. The patients' perspective alone is insufficient evidence that there are major gaps in chronic pain treatment. There are many national programmes that have been started as part of optimisation for treatment of chronic pain with a multimodal focus. For example, according to the 2013 The national pain audit for specialist pain services, there are 97 pain management programmes in the UK. Also, The Royal College of Anaesthetists' Faculty of Pain Medicine and the Royal College of General Practitioners have both emphasised the importance and advantages of a multidisciplinary approach (252). These programmes

are multimodal treatment packages based on cognitive behavioural therapy (CBT) and allied rehabilitation treatments that aim to restore function by supporting and maintaining changes in behaviours that perpetuate or increase pain. They are not mainly concerned with the pain itself, but rather with improving self-management and independence, allowing individuals to live as normally as possible despite the limitations imposed by their pain(266).

6.6.1 Strengths and limitations

Rigorous methods for data collection and thematic analysis were used, and we believe that thematic saturation was achieved. All the posts sampled were posted by CNMP patients who were either current or former prescribed opioid users. The collection of threads related to opioid use from three different forums provided a broad overview of all possible issues related to the study's objectives. The study may help advance the field by increasing the awareness of health care professionals. By assessing patients' beliefs and knowledge base about their condition and treatment options, healthcare professionals may be able to focus on perceived gaps in caring for patients with chronic pain, including a focus on dissemination of knowledge about treatment options for chronic pain, including non-opioids.

Nevertheless, some limitations should be addressed. The data collected reflected a range of perspectives from CNMP patients with different pain conditions. This means the findings do not provide information related to specific CNMP conditions. The subjectivity of the patients' statements is the primary limitation of this study. Another limitation of this study is a selection bias. It is not known whether patients who are motivated to feel better and reduce their usage of prescription opioids or use them more appropriately and taper them, may be more likely to engage in online forums and

discussions about alternatives to treat chronic pain, or conversely whether patients who are not improving or not motivated to try alternative options may be more prone to posting on online forums. Amongst patients who are forum contributors, there may also be a recall bias related to whether their pain has been better or more poorly controlled in the recent past.

Another flaw in this study that has to be addressed is that the categorization of posts, although guided by published definitions of the TDF domains, inevitably entailed some interpretation by the researchers, especially in identifying implicit meaning rather than simply counting instances of occurrence of specific words (although the latter, too, can risk distortion of qualitative context)(267).

Another limitation of this research is that it only looked at open access forums and excluded private community forums. Because a constant user ID allows other participants to track and know each other over time, forums that require registration have a greater percentage of repeat participation. This helps forum users to form relationships and develop bonds, while anonymity may hinder the team's capacity to form relationships that strengthen social harmony. Also, contributors feel safer and more open to collaborate, since their information is only accessible to authorised users who share a same interest or relationship , resulting in high user engagement(268,269).

Furthermore, current health models emphasize the importance of healthcare professionals' and patients' collaboration in medicine optimisation practices, yet healthcare providers were not included in this study. As such, it is important that their perspectives on opioid optimisation are investigated.

6.6.2 Practical implications and recommendations

Online forums may offer patients, especially distressed patients, a unique opportunity for support and sharing experiences. Healthcare providers could encourage their patients to open up about the information sources that they use to look up information about their condition, medication use or any alternative methods to manage their pain. Also, they could suggest useful resources for coping strategies, such as trustworthy websites, articles or books. Adverse outcomes of medications in CNMP have been well documented (270-271). It is imperative that patient perspectives are taken into account when designing pain services. A recent systematic review demonstrated that designing evidence-based and patient-centred intervention that overcomes the recent CNMP practice gaps and address patients' needs more appropriately is essential (38).

6.6.3 Future research

There was some concern about the applicability of strategies to all pain patients. As such, prospective research could develop and trial a complex intervention to account for identified challenges at the medication, patient, prescriber and health system levels, and also be flexible in nature to allow clinicians to tailor intervention strategies to individual patient needs. There are self-care interventions and alternative approaches that CNMP patients use daily to cope and manage their pain, which they are usually reluctant to share with their clinicians. Therefore, future research may investigative these self-care interventions and their associated outcomes using patients' online forums. Also, exploring the healthcare providers' perspective around the same topic is crucial for a deep understanding of patients' need to optimise their prescribed opioid therapy. Research can evaluate the accuracy of information shared via online forums, considering the amount exchanged and the large number of people who view it, as this

study revealed that some of the medication information exchanged between users is inaccurate. This study has highlighted the danger of glaring misinformation that could be spread via these forums (e.g. cutting fentanyl patches in half). Nevertheless, the data from patients' online forums could be used as a valuable tool for performance improvement for health care entities, subject to awareness of potential bias in the opinions of forum contributors. It would be worthwhile conducting more studies using these forums.

6.7 Conclusion

Analysis of CNMP patients' posts on online forums highlighted the devastating impact of pain on social functioning, relationships and mental health. The main facilitating factor was the support of knowledgeable and empathetic healthcare providers; too often, however, provider-patient relationships were perceived as unhelpful, the difficulties being compounded by the problems of access and continuity. Patients were left angry, depressed and fearful, leading to potentially dangerous medication use and additional demand on services. The findings highlighted the need for multi-dimensional, individualized treatment approaches to support and enable patients' appropriate opioid use.

Given the importance of patients' access to relationship with healthcare providers, it is important that patients' perspective is complemented by that if that of the providers with whom they interact, and who are responsible for many of the decisions (e.g., prescribing and tapering) that affect patients. The next chapter contributors to meet this need by reporting an investigation of the perspectives of clinical pharmacists and consultants working in pain clinics.

Chapter 7: Qualitative study with pain healthcare providers

Roles, barriers and behavioral determinants related to pain healthcare providers' involvement in optimising opioid therapy for chronic pain: a qualitative study

6.1 Publication

This chapter has been accepted for publishing British Journal of Pain as Alenezi, A., Yahyouche, A. & Paudyal, V. Roles, barriers and behavioral determinants related to pain healthcare providers' involvement in optimising opioid therapy for chronic pain: a qualitative study**.**

7.2 Chapter description

Around 20% of CNMP patients in the UK receive long-term prescribed opioid therapy, raising concern about harmful effects. Poor understanding and management of opioid reduction can lead to damaged patient-provider relationships and poor compliance with treatment. This chapter explores pain healthcare providers' perspectives of the enablers and barriers of prescribed opioids for CNMP patients.

7.3 Introduction

More than 5 million people in the UK suffer from chronic non-malignant pain (CNMP), A significant percentage (20%) of patients receive long-term prescribed opioid therapy(22, 72), despite the insufficient evidence of the efficacy of using opioids long-term in CNMP management. Long-term opioid use is associated with several potential harms, including overdose (OD), opioid use disorder (OUD), and possibly death. Opioid-related deaths reported a 40% increase from 2007 in England. Scotland has the highest drug-related death rate in Europe (272). In response to widespread concerns about opioid-related harms, tapering has become common practice; the clinical practice guideline recommends against initiating long-term opioid therapy for CNMP and discontinuation in most patients on prescribed opioids(273). Since 2012, multiple UK health agencies, including the UK Medicines and Healthcare Regulatory Agency (MHRA), have promoted policies to reduce opioid prescribing and have contributed to a decline in overall opioid prescribing, yet the amount of opioids prescribed continued to rise steadily between 2006-2017(272,274). The MHRA, in April 2019, agreed that opioid medicine packs must be labelled with a warning to inform patients about the risk of long-term use of these medications(264). Also, it announced, in September 2020, that other warnings were to be inserted into patient information leaflets about the risk of dependence and addiction(265). Yet, literature shows that traditional education approaches such as passive dissemination of educational materials alone are ineffective(276).

Pain medication management is not always straightforward; practising clinicians are faced with the twin dilemmas of managing chronic pain effectively while tapering long-term opioid therapy. Communication about CNMP and its treatment is challenging,

particularly when opioids are involved. A recent study showed that UK healthcare providers have no time to communicate with patients about their opioid use during the visit due to time pressure(247). Unsupportive, broken-down patient-provider relationships and poor communication about pain management and tapering can exacerbate these challenges(277).Opioid tapering may require regular clinic visits involving a multidisciplinary team to assess risk, close monitoring of withdrawal symptoms, psychological and behavioural counselling and referral for non-pharmacological modalities for pain(38, 278). The provider-patient relationship is the cornerstone of health care, the means by which information is gathered, diagnoses made, treatment given, and progress or outcomes are assessed (279). Denying patients the medications they expect or have been prescribed long-term may have a detrimental effect on this relationship and lead to doctors' frustration and burnout (279, 280). Clinical guidelines encourage opioid deprescribing and tapering for CNMP pain but give little advice about discussing opioid tapering with patients(276,281,282). Consequently, there is a gap in understanding pain management strategies because many complementary and alternative medicines are often not considered or available as viable options to traditional opioid treatments(276-278,283). Patients perceive that treating their pain is more important than the potential risks of opioids and have expressed skepticism about the effectiveness of non-opioid analgesics and fear of withdrawal(50,276,284). Well-established communication and positive patient-provider relationships during tapering are considered pivotal in helping patients understand why they are being tapered and assuring them that they will not be abandoned(49.50). Furthermore, the limited duration of clinical visits is a typical issue of most health care systems, that is usually associated with diminished satisfaction

among patients (48). Additionally, there is no clear scientific evidence regarding the optimum speed of opioid tapering or individualized tapering strategies due to the dearth of published clinical trials and comparative effectiveness studies of long-term opioid tapering for CNMP, which represents another major clinical dilemma. These challenges may threaten the provider-patient relationship.

Some international (mainly North American) studies have explored healthcare providers' perspectives on opioid use for CNMP in the era of opioid tapering and challenges(283-285). There are strong assertions of the need for evidence-based strategies that may help in improving the patient-centred care of CNMP sufferers who have been prescribed opioids long term and now are facing mandatory tapering of their medications, which some of them consider the only option that helps them to cope in the face of severe, persistent pain. Very little information is available on factors that may facilitate optimisation of prescribed opioids or barriers to reduction or tapering of prescribed opioids in NHS. Qualitative data collection approaches provide opportunities to obtain in-depth information needed to advance our understanding of providers' concerns and reactions to these challenging health encounters.

7.4 Aims and objectives

- To identify challenges faced by healthcare providers in UK in the optimising of prescribed opioids for patients with CNMP.
- To understand the perspective of healthcare providers about optimising prescribed opioids, as well as their experiences with patients and prescribers.
- To seek healthcare providers' suggested interventions for opioid optimisation and tapering.

7.5 Method

7.5.1 Ethical approval

Ethical approval for this study was issued by the Ethical committee (Wales REC 3) in October 2020, with REC reference: 20/WA/0232, Protocol number: RG_19-160 and IRAS project ID: 270017.Written informed consent was obtained from all participants included in the study. See appendix 8

7.5.2 Study design

The study design was informed by a checklist for comprehensive reporting of qualitative studies, the COREQ (Consolidated Criteria for Reporting Qualitative Research)(286) (see Appendix 12). Data were collected between February and June 2021 via semi-structured interviews informed by the Theoretical Domains Framework (TDF). TDF was developed through a collaboration between health service researchers and psychologists to identify and understand health professionals', patients' and policymakers' barriers and enablers to behavioural change. Development of the TDF involved the synthesis of 33 predominant theories of behaviour and behaviour change clustered into 14 domains, which are considered as the key factors for the barriers and enablers of behaviour changes. The TDF domains represent environmental, cognitive, and social factors that may affect behaviour(217-219) . The TDF has been widely employed to explore behaviours and implementation challenges in various settings and content areas in health care and hence is suitable in the context of this research (219).

7.5.3 Sample

Pain consultants and clinical pharmacists working from various pain clinics in England were recruited through the dissemination of invitation in a webinar for pain healthcare providers and via acquaintance of the research team. The inclusion criterion was pain

clinic healthcare providers including pain consultants, nurses, clinical pharmacists, psychologists and physiotherapists, and there were no exclusion criteria. The primary researcher (AA) introduced the study pack which contained the study information sheet and consent form to one of the webinar management team and asked if they would agree to consider disseminate it during the webinar. The invitation was disseminated and most of the study participants were from this webinar. Also, a 'snowballing' sampling method was used to recruit more participants, whereby interviewed pain healthcare providers identified others who might be interested in taking part.

7.5.4 Interview topic guide and procedure

While the questions were designed to allow the interviewees to freely express their thoughts, the TDF was used to develop an interview guide containing open-ended questions and standardized prompts available for use if needed. It was reviewed and pilot tested with two pain consultants. Each domain was represented by at least one question (See Table 13). Written information about the study was sent via email a week or more before the interview. An agreed interview date and time were then arranged. All interviews were conducted by AA via telephone interview conducted in the researcher's home in a quiet room, at a time convenient to the participant, as a response to the COVID-19 lockdown. No follow up interviews were conducted, and interviews lasted between 25 to 45 minutes, mainly taking around 30 minutes. All interviews were audio-recorded and anonymously transcribed verbatim. Recruitment and interviewing ceased after reaching thematic saturation based on initial analysis and coding (no new themes or codes could be identified from the last two interviews) (221).

Table 12: Mapping of Interview schedule of TDF domains.

Domain	Content	Sample questions that the study aims to answer by analysing online forums
Knowledge	An awareness of the existence of something	What does opioid therapy optimisation means to you?
Skills	An ability or proficiency acquired through practice	What approach do you take when working with your most challenging patients and you think may help them to optimise the use/withdrawal from chronic opioid therapy?
Social/professional role and identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting	could you briefly describe your experience, attitude, and belief about the use of long-term opioid for CNMP patients?
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use	Can you describe the daily challenges that you face as a chronic pain consultant with regards to long term opioid tapering?
Optimism	The confidence that things will happen for the best or that desired goals will be attained	How do you think the use of opioid to manage CNMP could be improved in the future?
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of behaviour in a given situation	What are healthcare providers beliefs about the consequences of use or withdrawal from opioid therapy?
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus	What reinforcement can the healthcare system and regulatory bodies can offer that may help healthcare providers in optimising opioid therapy for CNMP?
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way	Are there external incentives in place to encourage you to try to optimise long term opioid for CNMP? (NHS and other regulatory bodies deprescribing guidelines)
Goals	Mental representations of outcomes or end-state that an individual wants to achieve	Is optimum opioid use among CNMP patients one of your primary goals?
Memory, attention, and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between 2 or more alternatives	Is there anything that could help you and your colleagues to focus on appropriate opioid prescribing and appropriate assessment?
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviours	What are the circumstances of the situation or environment that could help you and your colleagues to focus on appropriate opioid prescribing, withdrawal and appropriate assessment?
Emotion	A complex reaction pattern involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event	What are healthcare providers emotions by their experiences dealing with CNMP patients who are demanding opioids prescriptions who the once who resistance opioid tapering?
Social influences	The interpersonal processes can cause individuals to change their thought, feeling and behaviours.	How does patient satisfaction in your relationship with patients affect the way that you prescribe, deprescr be opioids or assess patients?
Behavioural regulation	Anything aimed at managing or changing objectively observed or measured actions	What approach do you take when working with your most challenging patients?

7.5.5 Qualitative data analysis

Data were analysed using the Framework method. A familiarisation process took place through listening to recordings and reading transcripts, from which AA obtained an overview of the data (222). Then, excerpts from the transcripts were coded into one or more of the 14 TDF domains. Data were coded applying a deductive approach, with each TD domain used as a coding category (223). The data analysis was frequently debated within research team meetings and any disagreement in coding between researchers was resolved through discussion until consensus was reached. Coded excerpts were organized and compiled into a framework table created in Microsoft Word®. When multiple codes formed a meaningful unit, they were considered a theme. A domain was judged important if excerpts were coded repeatedly or if the interviewee highlighted the significant influence of behavioural determinants in a domain on their involvement in COT optimisation. A content analysis of the framework table was then undertaken to identify subthemes. Ideas that shared the same central concept as the theme but were specifically related to the study objectives were considered as sub-themes.

7.5.6 Research trustworthiness

This study is part of AA's PhD studies after being trained in conducting research at the University of Birmingham. It is one of three studies intended to inform design of an intervention to optimise the use of prescribed opioids for CNMP, some of which have already been published in peer reviewed journals using the same methodology. The research trustworthiness was sought by applying Lincoln and Guba's principles (225). Credibility was enhanced through the adoption of appropriate, well-recognized research methods informed by previous comparable studies. Data analysis and coding

were discussed regularly in research team meetings (226). Transferability was facilitated as the authors described the findings, supported with quotes from the interviews. Dependability and confirmability were enhanced through the utilization of the Theoretical Domains Framework for this study (227, 287).

7.6 Findings

A total of eleven participants took part nine consultants three clinical pain pharmacists. For the participants' geographical distribution see Table 14. For the sample characteristics see Table 15.

Both consultants and clinical pharmacists participating in this study had similar views with regard to their understanding of opioid optimisation, enabling and constraining factors, and strategies for achieving optimisation. Five of the TDF domains emerged as highly relevant in their responses, both in the number of mentions and the degree of emphasis placed on the factors indicated. The five domains were Knowledge, Social and Professional Role and Identity, Environmental Context and Resources, Social Influence and Behaviour Regulation. Responses gave rise to three themes: Enablers of optimisation, Barriers to optimisation and Strategies for optimisation. For the theoretical domains relevant to pain healthcare providers in prescribed opioid optimisation with illustrative quotations see Table 16.

Table 13: Distribution of Participants (N= 11)

Location	N
London	2
Birmingham	2
Bradford	2
Leicester	2
Hull	2
Stourbridge	1
Solihull	1
Normanton	1
Coventry	1
Wakefield	1
Hemel Hempstead	1
Sunbury-on-Thames	1
Missing information	3

Table 14: Sample characteristics (N= 11)

Characteristics	N
Speciality and role	
Community Pharmacist	16
Community pharmacist and Manager	1
Community and Hospital Pharmacist	3
Sex	
Male	17
Female	3
Age in years	
25-35	16
36-45	3
46-60	1
Years of experience	
1-5	11
6-10	3
11-15	4
20+	2

Table 15: Theoretical Domains Relevant to Pain Healthcare Providers in Prescribed Opioid Optimisation with Illustrative Quotations.

Theme	TDF domains & non-TDF subtheme	Codes/ constructs	Illustrative quotations
Enablers of optimisation	Knowledge	Knowledge and experience of HCPs	"We are suddenly an elite group of physicians…. We know a bit about chronic pain and others don't" (Rec4, pp2,7).
		Awareness of problematic use behaviours	"You know, selling on eBay and selling on Amazon, which occasionally sadly still happens; you know there is street value for those drugs" (Rec7, p4).
	Professional Role and Identity	Primary guardian of patient welfare	"It has a role, but it's like a knife, you have to use it responsibly" (Rec7, p6).
		Tapering and Cessation	"They get cross with you because you don't want to prescribe opioids" (Rec5, p4).
	Social Influence	Therapeutic alliance	"We will be with them, we will be supporting them, reassuring them that it's a journey and they're not going to go there on their own" (Rec8, p5).
		Doctor-patient relationship	"The clinician's manner… may even account for some sort of placebo effect… it's a big factor" (Rec4, p4).
		Social attitudes toward opioids	"There is a national direction now to optimise opioids for chronic pain patients or reduce them. The last couple of years… it's easier now to promote optimum opioid usage than five years ago" (Rec2, p4).
	Environmental Context and Resources	Guidelines	"You know, the Faculty of Pain Medicine has produced a beautiful resource on opioids" (Rec7, p4).
		Availability of multi-disciplinary team	"We work in an MDT … two physios, a psychologist and myself, all at the same time" (Rec3, p2).
Barriers to optimisation	Knowledge	Lack of knowledge among other HCPs	"a rheumatologist who has somebody with rheumatoid arthritis and they're now starting to get widespread pain. The rheumatologist doesn't have the skills or understanding to recognize that this problem is separate from the underlying condition" (Rec3, p3).
		Absence of sufficient knowledge about pain, or opioids	"You get a cohort of patients who are already on really high doses, so the GPs refer them to us and say, can you help sort this patient out because they're on really high doses of opioids and I don't know what to do now," (Rec10, p2)
	Environmental context and resources	Patient- related	"Social factors are very important… you know, education level, socio-economic level and there's the psychological aspect… depression … anxiety … people who are psychologically broken" (rec4, pp5-6).
		Culture-related	"We watch too much Netflix, we don't do enough exercise and we eat refined sugar, and we smoke, and we engage in unhelpful behaviours that damage us psychologically" (Rec5, p5).
		Systemic factors	"There is pressure on clinicians to reduce the duration of the consultation, reduce the number of consultations, or the number of meetings with the patient, and this makes it very difficult" (Rec2, p5).
Strategies	Behavioural Regulation	Education	"We need something to shake the beliefs of these people, these patients, statistics, information" (Rec8, p6).
		Consistent messaging	"We work in an MDT …we're essentially giving them the same advice, from four different angles.
		Managing expectations	"We always try to reduce expectations…14 million people suffer with chance pain and normalizing what they are feeling is very important" (Rec4, p4).
		Formal, practical strategies	"There are centres that go to more extreme measures, for example, measuring the opioid level in patients' blood and urine" (Rec2, p3).
		An individualized approach	"There's no one strategy, you know, it has to be tailored depending on the condition and the patient" (Rec7, p7).

Theme 1: Enablers of optimisation

This theme was dominated by the three TDF domains, Knowledge, Professional Role and Identity and Social Influence, with a lesser role played by two items under Environmental Context and Resources.

Knowledge

A major enabler of opioid optimisation is the extensive knowledge and experience of consultants and clinical pharmacists in the areas of CNMP and the use of opioids:

"We are suddenly an elite group of physicians…. We know a bit about chronic pain and others don't" (Rec4, pp2,7).

*"I started here six years ago. I inherited hundreds of patients from my predecessor …and there were all kinds of pain-taking behaviour". (*Rec2, p2).

Several respondents showed familiarity with research in the UK and USA and referred to the weakness of the scientific evidence for the efficacy of opioids:

"The indications for prescribing opioids for CNMP are very limited based on the scientific evidence" (Rec2, p1)

"*Long-term studies all point toward more harms than benefits; their side effects are very significant. So, I don't have faith or a big role for them in non-cancer pain*" (Rec2, p1).

With regard to the harmful effects of opioids, all but one of the interviewees mentioned a variety of impacts.

"People who are on opioids periodically end up in the emergency department with sickness and constipation. Many times, they end up with low thyroid [and] musculoskeletal problems" (Rec7, p5).

Other participants pointed out the risk of immune system impairment, sexual dysfunction, depression, and reduced life expectancy. They also indicated their awareness of problematic use behaviours (such as early or over-ordering) and diversion (giving prescribed opioid medication to others or selling it).

"You know, selling on eBay and selling on Amazon, which occasionally sadly still happens; you know there is street value for those drugs" (Rec7, p4).

Professional Role and Identity

Based on their knowledge of the potential risk of opioids, respondents saw themselves as guardians of patient safety, a perception reflected in their understanding of the concept of optimisation, and in their prescribing behaviour. Although two participants acknowledged a limited role for opioids in particular circumstances, in general, they perceived opioid optimisation as meaning withdrawal, whenever possible. They declared a reluctance to initiate opioids and indicated that, when opioid-taking patients were referred to them, their normal approach was to start tapering, with the aim of eventual cessation:

"Optimisation these days predominately means stopping opioids" (Rec5, p1).

"It has a role, but it's like a knife, you have to use it responsibly" (Rec7, p6).

"There has been a trend, especially among the young consultants like me, not to start patients on opioids" (Rec4, p2).

As some consultants acknowledged, their stance on opioids was often in tension with patients' wishes and expectations:

"They get cross with you because you don't want to prescribe opioids" (Rec5, p4).

Nevertheless, they held firm in their belief that in most cases, tapering and cessation was the appropriate approach for patient safety and carried out a variety of activities to facilitate the process, including assessment and review of patients, both on referral to the service and as part of an ongoing programme of monitoring:

"I do a psychometric analysis of patients on coming into the service; we assess depression, anxiety, low mood and so on" (Rec2, p1).

"I don't follow a questionnaire, but I have a flexible way of taking a history from the patient one to one, like [asking], do they[opioids] actually work?" (Rec4, p3).

Social Influence

Assessment and review formed the basis of a therapeutic alliance in which healthcare providers took time to develop an understanding of the patient, gain their trust, provide information and support them through the difficult process of adjustment to a new treatment regime. As, one consultant explained,

"We will be with them, we will be supporting them, reassuring them that it's a journey and they're not going to go there on their own" (Rec8, p5).

Participants showed awareness of the importance of the doctor-patient relationship for the success of treatment, noting the impact of their support on patients' sense of well-being and ultimate outcomes, in addition to and separate from any specific pharmacological or other intervention to the extent that, as one consultant claimed,

"The clinician's manner… may even account for some sort of placebo effect… it's a big factor" (Rec4, p4).

A further social factor contributing to enable optimisation, in clinicians' view, was a change in social attitudes toward opioids. They pointed to the opioid crisis in the USA and subsequent growing awareness of and concern about the dangers of opioids as creating pressure for reduction:

"Because of articles from the BBC and other media about what is happening across the pond in the US, there is some understanding …about opioids" (Rec7, p5).

"There is a national direction now to optimise opioids for chronic pain patients or reduce them. The last couple of years… it's easier now to promote optimum opioid usage than five years ago" (Rec2, p4).

Thus, participants saw hopeful signs of communication and liaison among professionals, tending in the direction of opioid reduction.

Environmental Context and Resources

Despite the existence of the professional and social factors mentioned above, clinicians cited only two factors in the Environmental Context and Resources domain, which they identified as specific enablers of opioid optimisation. One (mentioned by three participants) was the availability of guidance from The National Institute for Health and Care Excellence (NICE) and other sources, which helped to promote clinicians' knowledge and understanding of opioids and might, in turn, lead to more appropriate prescribing behaviour or tapering efforts:

"What helps is the opioid awareness guidance which came out about five years ago" (Rec2, p2).

"You know, the Faculty of Pain Medicine has produced a beautiful resource on opioids" (Rec7, p4).

A further important enabler of optimisation (though not universally available) was the availability of a multi-disciplinary team. Two consultants described themselves as working in such a team, for example:

"We work in an MDT … two physios, a psychologist and myself, all at the same time" (Rec3, p2).

Others spoke of their efforts to liaise with GPs:

"I write to the GP clearly to review the patient in one to two weeks, reduce [the opioid] and stop". (Rec2, p3).

Such communications and structural arrangements helped provide consistency of approach and messaging to the patient, as well as a holistic approach to care that provided patients with alternative therapies to supplement or replace pharmacological treatment, and psychological support in coping with pain and other challenges.

To summarize, enablers of opioid optimisation were of two kinds: those that helped clinicians to develop and carry out interventions aimed at opioid tapering and withdrawal, and those that supported patients' compliance with treatment. The former included clinicians' knowledge, experience and training, their sense of professional identity focused on patient safety, the growing national trend towards opioid reduction and the availability of certain sources of information and guidance. The main enabler for patients was the development of a supportive doctor-patient relationship. Where multi-disciplinary teams were available, these also provided valuable support for both clinicians and patients.

Theme 2: Barriers to optimisation

This theme was constituted mainly of codes under the TDF domain, Environmental Context and Resources, with a contributing role also played by factors under the Knowledge domain.

Knowledge

Consultants indicated that they frequently encountered problems arising from GPs' or other specialists' misconceptions and lack of knowledge, both about chronic pain and about opioids, which resulted in inappropriate prescribing behaviour. With regard to pain, for example, one interviewee cited the situation of

"a rheumatologist who has somebody with rheumatoid arthritis and they're now starting to get widespread pain. The rheumatologist doesn't have the skills or understanding to recognize that this problem is separate from the underlying condition" (Rec3, p3).

In the absence of sufficient knowledge about pain, or opioids and alternatives, a common strategy was to initiate opioids, and prescribe ever-increasing doses, so that by the time a patient is referred to the pain service or a consultant pharmacist, the cycle of opioid dependence, side effects and continued or increased pain are entrenched

"In no time they double, triple, quadruple [the dose] and then the patient is referred to the pain service to see is there any other medicine to prescribe... and there is no such medicine" (Rec7, p2)

"*You get a cohort of patients who are already on really high doses, so the GPs refer them to us and say, can you help sort this patient out because they're on really high doses of opioids and I don't know what to do now,*" (Rec 9, p2)

At the other end of the scale are GPs who, rather than escalating opioid dosage, decide, due to reports of opioid dangers or under pressure from Clinical Commissioning Groups (CCGs), to drastically and rapidly reduce the opioid prescription, rather than following a gradual tapering regime. As a result, patients face difficulty with withdrawal effects and are strengthened in their belief that they need more opioids, and become resistant to tapering:

"The GPs often do things quite abruptly. So, they'll just halve people's opioids, or they'll just stop things suddenly…the patient then comes to us and complains" (Rec 11, p4).

Patients, too, suffer from misconceptions and lack of knowledge about the nature and role of opioids, and the risks associated with them. In some cases, this may occur because of the primary prescriber's own lack of knowledge, but there were suggestions, too, that prescribers may have actually withheld information from patients:

"They are not very knowledgeable, or they haven't been informed or they have been denied the knowledge of what harm it can cause. He was escalated on medication…and he was never told by the GP what the side effects are" (Rec2, p5).

Thus, misconceptions and lack of knowledge on the part of both GPs and patients contribute to a situation where patients are inappropriately prescribed opioids, or tapering is poorly managed, yet despite unsatisfactory outcomes, patients continue to expect and demand opioids and resist efforts to reduce the medication.

Environmental context and resources

Codes in this domain fell into two main categories. The first reflected patient-related factors, including their social circumstances and psychological state, that were

acknowledged by consultants to influence the likelihood of a patient becoming dependent on opioids and make optimisation difficult. The second concerned broader, system-related factors that put pressure on health services, impeded patients' access to information and support, and constrained the effort towards optimisation that could be made by the consultants.

Patient- related

There was wide recognition among the consultants that patients' attitude and behaviour towards opioids, and the success of optimisation efforts, were negatively affected by a range of psycho- social factors:

"*Social factors are very important… you know, education level, socio-economic level and there's the psychological aspect… depression … anxiety … people who are psychologically broken*" (Rec4, pp5-6).

One participant estimated that around two thirds of patients referred to him suffered from anxiety or depression, while others noted that such conditions made patients more likely to cling to opioids and need more support with optimisation.

"*They would be having a history of these kinds of things and all these together make… the classical patient where you are going to need a special clinic to start withdrawal*" (Rec5, p3).

Additional difficulties were said to arise from pressures in society that encouraged unhealthy lifestyles and unhelpful behaviours that affected patients' physical and mental health, undermining the work of consultants and clinics:

"We watch too much Netflix, we don't do enough exercise and we eat refined sugar, and we smoke, and we engage in unhelpful behaviours that damage us psychologically" (Rec5, p5).

*"We are somewhat handicapped as a consequence of the society that we live in" (*Rec3, p5).

A common complaint concerned what consultants called a culture of passivity, whereby patients perceived health improvement as something that was provided to them or done to them, rather than something that needed their active engagement, such as lifestyle changes.

"There is an element of passive treatment, isn't it? You take a pill, and you will be better… a bigger pill, or stronger pill, or a big injection… something that's happening to them" (Rec3, p2).

"They do not really take charge of managing their condition, which they should, and are just … thinking, okay. I'll take the pill and it will make me feel better" (Rec2, p2).

Participants saw such attitudes as culture-related, although they differed in their perceptions of the source of such cultural pressures; one perceived the expectation of "passive" treatment to be characteristic of particular ethnic groups, while others saw it as a specifically Western problem. One consultant, for example, suggested that the Western welfare system medicalizes common problems and 'facilitates' disability.

"We're living in the UK, people have a facilitated disability, because they can go on benefits. Whereas in other societies, potentially, where there isn't that system, people will continue to function despite feeling the pain" (Rec5, p4).

A result of such a culture, in the view of three participants, was some patients' adoption of a "sick" role, which brought them care and attention from those around them, and which they feared losing.

"They've created a life around their opioid use and the pain…if you take that sickness role away... they may not get the attention and care they were getting before" (Rec3, p4).

Thus, participants recognized that patients' resistance to, and difficulty complying with, optimisation strategies, such as tapering, alternative therapies or lifestyle changes could be the result of a complex array of psychological, social and cultural factors. They asserted the importance of assessing and addressing such factors as an essential part of any intervention. Conversely, they insisted failure could be expected if healthcare providers did not take the necessary holistic approach:

"*Because the mistake that was originally made was to start the opioids without managing the whole person, and now you're taking the opioids away without managing the whole person, and that's where clinicians come into conflict with patients*" (Rec5, p3).

Systemic factors

Although, as indicated above, interviewees perceived that some of the responsibility for inappropriate opioid use lay with patients, due to their expectations and lifestyle choices, they also acknowledged that certain factors in the healthcare system itself were not conducive to opioid optimisation. They spoke of the pressure faced by healthcare providers and lack of a clear and consistent understanding and practice

across the health services, which made optimisation difficult for prescribers and confused patients.

Foremost among the systemic constraints mentioned were time pressures, which limited efforts in the assessment, monitoring and education of patients. Participants noted the time that was needed to build rapport with patients and carefully explain treatment options and decisions, but commented that often, the required time was not available. Indeed, there were pressures to reduce patient contact time still further.

"There is pressure on clinicians to reduce the duration of the consultation, reduce the number of consultations, or the number of meetings with the patient, and this makes it very difficult" (Rec2, p5).

Some participants reported having as little as 10 or 15 minutes to spend with a patient, which was totally inadequate to provide the necessary support and information, particularly when they needed to explain a new treatment approach or tapering decision.

"*I f I have an hour with a patient, I can start giving examples, giving stories, opening some literature, showing some graphics, statistics, leaflets etc. But if you are trying to deliver a message to a patient in 10 minutes, and that message is completely the opposite of what the patient wants to hear there's definitely going to be a conflict*" (Rec8, p3).

It was acknowledged also that GPs face similar time constraints, which hinder proper assessment of patients' pain.

A rare exception to the narrative of time pressure was, however, provided by a clinical pharmacist who reported a more favourable situation.

"In our clinic, we have the luxury of having longer appointments, you know, sometimes up to one hour, so we can obviously do a lot more with a patient" (Rec 10, p2).

In addition to time pressures, clinicians reported facing social and commercial pressure, as a result of the power of large drug companies and their aggressive marketing of their products. One of the older consultants, in particular, reported his past involvement with such companies and reported how GPs and other clinicians were misled by distorted presentation of evidence by drug companies, which had contributed to inappropriate prescribing of opioids, as had occurred in the USA in the OxyContin crisis.

"We are as badly affected as them, being brainwashed… with skewed results… on work by drug companies" (Rec8, p3).

In the UK such pressures are to some extent mitigated by the role of regulatory bodies, such as NICE. However, despite the existence of guidelines from such bodies, it was pointed out that there are no clear, standard criteria for opioid use and cessation, leaving individual prescribers to make their own decisions.

"The prescription…and weaning is happening based on the whims and fancies of individual clinicians, rather than an agreed standard structure" (Rec7, p2).

The problem was said to be compounded by lack of coordination among the multiple agencies involved in the care of CNMP patients or between different areas, leading to inconsistent messaging and practice.

"They're developing guidelines, but one area has already developed their own and they're different to what everybody else is thinking and it's causing confusion … the

chances of patients moving to a different area is quite… likely, and if you're giving them a different message, it's quite difficult" (Rec 8, P3).

Thus, clinicians perceived a number of factors in the health service that made opioid optimisation confusing and difficult for both doctors and patients, particularly as they interacted with barriers arising from lack of knowledge, and pressures in the social environment. Such factors were said to contribute to inappropriate initiation and prescribing of opioids, patient dependence on opioids and resistance to optimisation, and difficulty for those specialists who faced competing pressures when trying to educate patients and steer them towards alternative treatment approaches.

Theme 3: Strategies

This theme reflects strategies that clinicians claimed to use or suggested should be used to optimise (and, where possible, avoid) the use of opioids in patients with CNMP. The strategies mentioned were located within the TDF domain, Behavioural Regulation. They included education for patients and other clinicians, with the subthemes consistent messaging across the MDT, and managing patient expectations, the use of formal, practical protocols including contracts and testing regimes; and the provision of social and emotional support, all within an individualized patient-centered approach.

Education

The strategy most frequently mentioned and reportedly, widely applied, was providing both patients and other clinicians, such as GPs, with education about the limited role and potential risks of opioids.

"Spreading of knowledge to other clinicians…" (Rec4, p7)

"We need something to shake the beliefs of these people, these patients, statistics, information" (Rec8, p6).

Interviewees claimed already to be exerting efforts in this regard, as indicated in the previous sub-theme of Professional Role and Identity, although they asserted that more needed to be done in this respect. In relation to patients, the declared aim was to try to get them to recognize how opioids are affecting them and, in turn, to use them appropriately and be open to the possibility of reduction. For example, a clinical pharmacist remarked that

"If you give them the information, then they are very careful" (Rec9, p6)

It was suggested that often, patients have not been informed by the primary prescriber about the side effects of opioids and that provision of such information facilitates patients' engagement with, and motivation towards, tapering or suggestion of alternative treatments. Interviewees recognized, however, that there is also a need to educate other healthcare providers about opioids to enable them to prescribe appropriately and advise patients correctly. While several participants spoke of GPs in this regard, it was recognized that the problem is actually more widespread, given the number of disciplines potentially involved in patient care, with the power to prescribe:

"When you say clinician, it is not just about that; I'm talking about, you know, anyone who is involved with medication, including pharmacy, including new nurse prescribers, so many people hold prescribing [power] for practice" (Rec7, p4).

Education of these professionals is necessary, not only to improve prescribing practice but also to ensure a consistent message to patients, the next strategy mentioned.

Consistent messaging

Participants argued that patient education was more effective and optimisation more successful if patients received the same message multiple times, from all the people involved in their care, as part of a coordinated team effort.

"Whatever it is, it needs to be repeated by the whole team" (Rec8, p6).

"We work in an MDT …we're essentially giving them the same advice, from four different angles" (Rec3, p2).

"All the clinicians … will be giving that same message to the patient, about where medication fits into the whole aspect of management, and most [responsibility] is in the patient to actually self-manage things" (Rec 11, p5).

Whilst the clinicians interviewed claimed already to be working in MDTs and striving for such consistency, their recognition of shortcomings of collaboration in some areas (reported above under Theme 2, Barriers) suggests that this is a strategy that needs to be given more attention, with collaboration among professionals working in different areas of the healthcare system.

Managing expectations

A further sub-theme within the strategy of patient education is the need for clinicians to help patients to form and maintain realistic expectations related to their condition and its treatment. This might mean, for example, coming to an acceptance that some level of pain is normal, and that complete removal of all pain is not to be expected

"We always try to reduce expectations…14 million people suffer with chance pain and normalizing what they are feeling is very important" (Rec4, p4).

It also means making clear at the outset of a treatment that it is to be of limited duration and is not intended to be a permanent solution:

"Telling the patient that this is a temporary thing, you're not going to be on it forever" (Rec2, p3).

Formal, practical strategies

A few participants suggested that effective opioid optimisation would require the implementation of a variety of practical measures which either do not currently exist or, even if they exist, are not universally or widely practised. One practitioner, for example, advocated the establishment of a national register of people prescribed opioids (Rec2, p6). The same interviewee also noted that in some centres, it is the practice to carry out regular testing to monitor drug usage and check for non-compliant behaviour:

"There are centres that go to more extreme measures, for example, measuring the opioid level in patients' blood and urine" (Rec2, p3).

These strategies were not, however, recommended by the majority of interviewees. A more common suggestion was that opioid initiation should be accompanied by the agreement of a contract between patient and prescriber, setting out the conditions for opioid usage and a clear plan for tapering and eventual cessation:

"If you have to give a small dose of opioids, then you can say… you're worried about opioids, their side effects, potential risks and say, look, this is what we're using it for, we're going to excpect you make some sort of contract, basically" (Rec4, p4).

"I think the patients need to know that if they're going to go a trial for two weeks, for example, that if it doesn't work, we will reduce them down and then stop them, you

know… and then, if you do end up staying on them then we will continually monitor them, like, twice a year or something like that…" (Rec 10, p4).

It was acknowledged that some prescribers do use such contracts, but as indicated previously under 'Barriers', it was considered problematic that many practitioners initiate opioids without a contract or clear plan and interviewees believed that setting up such contracts and plans, guided by clear criteria, should be standard practice in the prescription of opioids.

Social and emotional support

As noted in Theme 2, Barriers, practitioners recognized that many patients are socially disadvantaged or experienced mental health issues, which contribute to their dependence on opioids and resistance to alternative treatment or optimisation plans. This being the case, interviewees emphasised the importance of providing patients with social and emotional support to allay their anxieties and help them to find more helpful ways of coping with their conditions; what one practitioner called*" managing the whole person*" (Rec5, p3). Sometimes, it was suggested, this would involve targeted support by a member of a multi-disciplinary team.

One practitioner, however, went beyond this to suggest directing patients to additional sources of support within the community. In his view, patients' difficulties are often due to a "*void*" in their social and emotional lives, which they attempted to fill with medication:

"I discovered that the void needs to be filled with something else, and I actually spent a lot of time exploring the voids in their lives and finding replacements" (Rec3, p4).

Possible "*replacements*", he suggested, might include counselling, the Samaritans, religious institutions, and social organizations, any of which might potentially supply something that was previously lacking in the patient's life and strengthen their ability to reduce their opioid use:

"If they fill that void, the opioid kind of comes out pretty easily" (Rec3, p5).

An individualized approach

Although practitioners called for consistent messaging and the availability of agreed principles and guidelines, they nevertheless recognized that patients are individuals with different needs and should be treated accordingly.

"Knowing a bit more [about the patient] always, you know. This is individualized medicine" (Rec4, p5).

"There's no one strategy, you know, it has to be tailored depending on the condition and the patient" (Rec7, p7).

"Guidelines can help but only to an extent because each patient's clinical situation has to be taken into account. So you can't always apply the guidelines directly to each patient" (Rec11, P3).

The implication was that, while a degree of standardization of messaging and recognized principles around opioid prescription are desirable, practitioners also need the flexibility to use their professional discretion in a patient-centred approach tailored to the individual's circumstances and in their best interests.

7.7 Discussion

As far as we know this is the first study that investigated UK pain healthcare providers' view about the enablers and barriers for optimisation of prescribed opioids for CNMP.

This study's findings show consistency among pain doctors and pharmacists, and between their knowledge and understanding of optimisation, professional role and identity, and thoughts about behaviour regulation. They know about the problem of opioids and the lack of evidence for their efficacy, so, in their professional role, they try to avoid initiating opioids, reduce/withdraw those already initiated, offer alternatives, educate patients, and advise other professionals accordingly. They have a sense of their safeguarding role and sequent prescribing behaviour. This 'social guardianship' idea is similar to reports in other studies (288-290). Overall, the UK and North American studies reveal a higher hostility to opioids than studies from different cultures. In a newly published Thai study that explored pain specialists' perspectives about long-term opioid use in CNMP management, Thai pain specialists reported that they would consider using potent, high-dose opioids for patients with complex and severe chronic pain who are not responsive to non-opioids (291). This difference might be explained by the different extent of the opioid crisis around the world, as well as the influence of sociocultural differences on the healthcare providers' behaviour (292-294).

The participants in this study reflected the UK national trend, and clinical guidelines that recommend against initiating long-term opioid therapy for these patients and cessation in most patients on prescribed opioids. Some respondents favoured regulations and guidelines. This contradicts a US study where participants did not favour guidelines, because they interfere with professional autonomy (288,295). Also, the findings suggested that participants intended to build a strong therapeutic alliance with their patients by changing their passivity mindset, offering an alternative, educating patients and motivating them to engage more and be responsible for their pain. Most studies recommend a multidisciplinary and patient- centred approach to

support patients with their pain, opioid use and tapering (188). Pain acceptance and openness by perceiving pain as a continuing reality, avoiding risky treatment, taking responsibility, and improving their quality of life are associated with positive physical and psychological experiences among these patients. Yet, a study showed that clinicians perceive that a patient-centered approach to opioid tapering, is burdensome, dreaded, and emotionally exhausting(89) . Furthermore, patients resist opioid tapering, individuals on high doses, those with severe pain, anxiety disorder, depression and OUD usually meet the opioid tapering discussion with anger, hostility and even threats of physical harm. Also forced tapering can easily destabilize some patients, which can lead to suicide or severe psychological issues(295-297).

Moreover, the study findings showed areas of tension and conflict between the idea that responsibility lies with the patient and awareness that patients' ability to take responsibility is undermined by social and cultural factors. For example, patients with chronic pain are eligible for social benefits which is seen by healthcare providers as a factor that might hinder opioid tapering. Also, there is a conflict between patients' demands for a pain-free life, and the healthcare providers' resistance to prescribing what they believe is harmful to patients.

Financial incentives, which may be either positive (reward people), or negative (penalize people), can provide economic encouragement to show desired behaviour. Financial incentives have been used in healthcare to affect participation rates and programme adherence(298). Building intrinsic motivation takes time and needs work, but financial incentives may help, for example, to increase adherence to an intervention that teaches needed skills and knowledge. Financial incentives can be provided by the government or insurance companies. It can be provided on many levels, for instance,

incentives for patients to participate in certain health programmes or for healthcare providers to incorporate certain interventions, treatment and rehabilitation for their patients. These incentives may vary, depending on the healthcare system in a country, but they are usually initiated if the benefits to society or the government budget exceed the expense of providing the incentive. The use of long-term opioids is usually associated with increased healthcare resource utilization (298,299). Therefore, CNMP sufferers may be encouraged to take more responsibility for their pain or encouraged to taper from long term opioids by changing their social benefit rate according to their treatment. For example, perhaps the patients who use self-care, non-pharmacological treatment, non-opioid to manage their CNMP could get higher social benefit than those on long-term opioids. There could also be incentives for healthcare providers who have a lower rate of opioid prescribing and a higher rate of involvement in opioids tapering.

Additionally, efforts to optimise opioid use for CNMP face additional challenges, such as fragmentation and inconsistency in the system (multiple agencies involved, but no set of agreed standards and criteria for initiating tapering or stopping opioids,) so decisions depend on individual whim. Also, poor coordination between general practice, specialist hospitals and other services has been identified as a problem that hinders CNMP patients' care. These problems documented in the UK healthcare literature, usually have the biggest impact on those with complex bio-psychosocial needs(300, 301), individuals considered as 'frail', and individuals with long-term conditions (301,302). These studies highlighted that the healthcare system in England has failed to ensure that vital clinical functions are delivered in a coordinated and person-centered manner. This would involve avoiding and acting in response to urgent care needs, appropriate management of multiple long-term conditions, and promoting

support of social health alongside with mental and physical wellbeing. However, the burden of these individuals' care is high in patient outcomes, emotional, practical and financial terms(300-304).

Implications for practice

The results of the present qualitative study have implications for clinical practice. It is essential to enhance the collaboration between health professionals (GPs, pain specialists, clinical pharmacists, etc.) to enable opioids optimisation. This may be achieved by drawing up specific guidelines to facilitate intercommunication among all professionals involved in the treatment and follow-up of these patients(305).

Clinicians may need to use a systematic approach to assess patients before starting tapering. They could use standardized questionnaires to assess physical, and psychological aspects of patients' opioid use, before starting tapering, rather than using their own clinical judgment(306,307). Evidence-based assessment tools are usually comprehensive and cover most of the CNMP patients' expectations during care visits, which a clinician may overlook if they only rely on their memory and arbitrary clinical judgments. Also, these tools are scientifically reliable and valid screening tools to help detect current and future aberrant drug-related and other important factors that clinicians need to consider before starting to taper long-term opioids.

These tools may help clinicians determine the appropriate tapering speed according to patients' pain intensity, anxiety and depression score, the duration of opioids use, and the type of medication to low, medium, and fast tapering. Also, written questionnaires that patients can fill prior to the clinic visit can help clinicians save time and customize the visit according to patients needs to create a closer relationship using good communication skills.

Future research

Designing an evidence-based intervention that considers the perspectives of CNMP patients who are on long term opioids and all healthcare providers those patients encounter during the opioids use or tapering journey is necessary to optimise the use of prescribed opioids.

It would be useful to explore policymakers' perspective of implementing finical incentives for patients to facilitate opioids tapering. Also, there is a need to explore why UK pain specialists are not utilizing available standardized self-reported assessment instruments to assess the patients' pain intensity, functional abilities, beliefs and expectations, and emotional distress, for in depth evaluation and treatment planning.

Limitation

The limitation to the present study was that the sample of professionals was relatively small as recruitment of participants was hindered by the COVID-19 pandemic, moreover, it consisted exclusively of men. Nevertheless, it provided a valuable complementary view of pain clinicians' perspectives on opioids optimisation for CNMP.

7. 8 Conclusion

The result suggest that main facilitating factor of opioids optimisation was the pain clinicians' knowledge about the CNMP and the limited use of opioid for the condition. Also, it recommends that patient-centred care and education for healthcare providers and patients about the prescribed opioids used for CNMP may lead to opioid optimization. Also, there is a need for better collaboration among healthcare professionals in assessing, supporting patients as well as developing interventions that are based on the perspectives of CNMP patients, and all healthcare providers involved in opioid optimization.

This study was the third of three complementary studies exploring different perspectives in the use of opioids for CNMP. The next chapter show how the findings from the three studies, as well as the systematic review reported in Chapter 4, were used to inform an intervention proposal aiming to improve patient-provider relationships and cooperation in opioid optimisation.

Chapter 8: Discussion and Intervention Design Proposal

The design of evidence- and theory-informed intervention on prescribed opioid optimisation for chronic non-malignant pain patients

8.1 Publication

This chapter in preparation for publication.

8.2 Chapter description

This chapter summaries the result of all the previous discussed studies and triangulates their finding to propose an intervention that aim to optimise the use of prescribed opioid for CNMP by applying the MRC framework, and BCW, to inform the synthesis of data, and the intervention design.

8.3 Introduction

More than 5 million people in the UK suffer from chronic non-malignant pain (CNMP), with increased prevalence in older adults, females, people living in deprived areas, and populations affected by social inequities, such as the homeless(22). CNMP is a complex biopsychosocial condition, and management should be guided by considering the relationship between pain, mental health, and physical state. Untreated CNMP could adversely affect an individual's life and society as a whole(301,308,309). CNMP management is costly to the healthcare system due to the number of people affected and the considerable resources and time necessary to provide the right comprehensive and integrated care. A multidisciplinary team (MDT)is offered in interprofessional chronic pain clinics, but variations in the availability of these clinics, and exceptionally long waiting lists in some area areas are common barriers that face patients and their care providers(310,311).

For many years, a common approach to the treatment of CNMP has been the prescription of opioids, and some patients take prescribed opioids for long periods, with doses increasing as they become tolerant to the opioid and pain worsen. However, concerns have arisen about the extent of opioid prescribing and use, the dubious efficacy in CNMP, opioid misuse, and harms even death resulting from opioids. Such concerns have been intensified by the North American opioid crisis, leading to guidance discouraging long-term opioid use for the management of CNMP, and calls for opioid tapering and eventually cessation among current users. Healthcare providers face challenges in balancing the risks and benefits of opioid use, however, optimisation efforts have proved difficult. The literature and the empirical

studies reported in this thesis reveal problems of inappropriate prescribing, poorly managed tapering and patient non-compliance with treatment regimens. Patients are suffering, both from their pain and from problems related to opioid use and withdrawal. There is evidence that those problems may be compounded by a poor clinician-patient relationship.

The quality of the patient-provider relationship correlates with patients' outcomes in many areas of medicine. Positive interactions that build good relationships between patients and providers can lead to better patient outcomes, understanding of their diagnostic and therapeutic options, instruction recall, and treatment satisfaction (312). The quality of the patient-provider relationship directly influences the quality of care received. Improved patient-provider relationships result in better management of chronic diseases (e.g. hypertension , diabetes,), improved pain control, and decreased hospital readmissions(303,312). However not all patients are on an equal footing to have a positive experience or relationship with their healthcare providers. The literature shows that minority and stigmatized groups consistently experience poorer communication quality in patient-provider interactions and are at risk of having negative interactions with their doctors (313,314). CNMP patients who are using a long-term opioid to manage their pain, those who are going through opioid tapering, or former prescribed opioid users usually have complex needs that require physical, psychological, and social support, and failure to meet these needs is likely to undermine the success of their pain management, including optimisation.

There have been many attempts to develop interventions to assist healthcare providers in effectively treating CNMP while preventing negative consequences of long-term opioid use or promoting deprescribing(38). Such interventions often viewed

sub-optimal opioid use as a patient-side problem and targeted patients' use behaviour using a variety of mechanisms, including education, and more restrictive and coercive measures such as opioid contract enforced with the aid of blood and for urine testing, with possibility of removal from the programme for non-compliant patients. However, these interventions were based on empirical exploration, not developed using any theoretical frameworks, or required complex facilities that are not accessible in all settings or contexts(252,315).

To improve opioid optimisation, there is an urgent demand for evidence-based interventions that use a systematic approach, taking into consideration the context and selected potential intervention components based on the synthesis of data and information. Multi component interventions that connect all the stakeholders and address all patients' needs during their journey through the healthcare system are essential. Ideally, these types of intervention should be theory-based interventions that are targeted, tested, developed and evaluated according to causal determinants of behaviours, and can be trialled across different contexts, populations, and behaviours. The Medical Research Council (MRC) in the UK has established guidelines for evaluating and developing complex interventions to improve health (128). The MRC framework specified four phases for intervention development: 'development'; 'feasibility/piloting'; 'evaluation'; and 'implementation'.

There are many intervention design frameworks available that share the same general approach, with different details and emphasis (131,165,166,315). The use of a combination of these frameworks can help researchers benefit from their strengths(316). The Behaviour Change Wheel (BCW) (Michie et al., 2011) which explores capabilities, opportunities and motivations for change has become one of the

highly cited health behaviour change intervention frameworks as it is a systematic approach to intervention design, can be applied to direct the synthesis of information and data from multiple sources, can help to fill in the gaps where there is a lack of research evidence, and assists signposting to potential intervention components (167). The BCW links with the Theoretical Domains Framework (TDF); an integrative framework combining basic theoretical constructs used in theories of behaviour change (317). The TDF comprises 14 domains that divide the main parts of the BCW into smaller sections. For example, capabilities encompass knowledge, memory, behavioural regulation, skills, attention and decision processes, whilst opportunities include social influence and environmental context and resources. Motivations include social/ professional role and identity, beliefs about capabilities, optimism, intentions, goals, beliefs about consequences, reinforcement, and emotion. The TDF promotes the use of the BCW because it can be applied to identify how the targeted behaviour can be achieved and develop an intervention with the appropriate components.

The aim of this chapter is to propose a novel behaviour change intervention to optimise the use of prescribed opioids for CNMP, describe the proposed intervention and model its processes and outcomes. The intervention aims to improve the way CNMP patients who are using or being tapered from long term prescribed opioids to manage their pain are handled by different stakeholders within the healthcare system during their treatment journey. The design of the intervention was informed by the UK MRC guidelines, the BCW and TDF(128,131,166).

8.4 Method

The intervention was developed through triangulation of four data sources: systematic review of prior studies and three qualitative studies to identify, from different

perspectives enablers and facilitators to long term use of prescribed opioids in CNMP patients. Each source is briefly described below (for full details, please see Chapter 4,Chapter 5,Chapter 6,Chapter 7 of this thesis).

8.4.1 Data sources

Systematic review (Alenezi, et al., published see Appendix 1)

The research started with conducting a systematic review of the nature, process, and outcomes of interventions used to optimise prescribed opioids, which included 21 studies (see Chapter 4 of this thesis). Only four studies were theory-based and were single interventions with very limited effects. The others were multicomponent but were not theory-based and had limited effect on optimising the use of long-term opioid therapy for CNMP. Thus, the review provided insufficient information to inform the development of an intervention.

A qualitative study with community pharmacists (Alenezi, et al., published see Appendix 1)

The researcher carried out semi-structured telephone interviews with 20 community pharmacists using the TDF as a topic, guide focusing on their perceived roles, barriers and behavioural determinants in relation to opioid therapy optimisation. Participants' responses were coded and analysed inductively using a framework approach and mapped to the 14 domains of the TDF. These domains, treated as sub-themes, were then grouped into three main themes: Optimisation facilitators, barriers and suggested behaviour change strategies.

A qualitative study of CNMP patients using patients' forums (Alenezi et al., Published see Appendix 1)

In this study, the researcher collected posts from two CNMP forums (two forums for chronic pain, the other a general forum with subsections for chronic pain). The collected posts included those concerned with experiences of CNMP, the use of opioids (including tapering and withdrawal) and interaction with healthcare services. The posts were analysed using the TDF as coding categories and giving consideration to both the manifest content (the words actually used) and the latent or implicit content (the underlying meaning of what was said).

A qualitative study with pain healthcare providers (Alenezi et al., submitted to European Journal of Pain)

Pain consultants and clinical pharmacists operating through pain clinics were interviewed about their experiences of dealing with patients with CNMP, their attitudes and practices towards prescribing and tapering, and the factors that influenced both their treatment approaches and patient responses. Again, the data were analysed using the TDF as a framework.

8.4.2 Intervention development process

The aim of the current paper is to describe how the data from the three qualitative studies and systematic literature reviews were synthesised. We used the MRC framework, and BCW, to inform the synthesis of data, and the intervention design. Below is a description of the process used to design this intervention.

MRC stage 1: identifying the evidence base

This step involved reviewing previous studies and exploring stakeholder perspectives to identify problem behaviours and select a behaviour to be targeted in the proposed intervention. It was addressed via steps 1-3 of the BCW.

BCW step 1: define the problem in behavioural terms

Evidence from the literature was supplemented with new evidence from the three empirical studies conducted. They were used to understand the complex array of medical, social, psychological and systemic factors that encourage opioid use and prescribing and pose challenges to tapering and withdrawal. See Table 17. For a summary of the data sources and analysis process used to inform the intervention design see Table 18.

BCW step 2: select the target behaviour

The TDF domains, as well as interventions suggested by the study participants, influenced this decision. The likelihood of behavioural change, the expected impact of changing the behaviour/s, the extended influence of change on other behaviours, and the ease with which each behaviour may be measured were among the selection criteria considered. Atkins and Michie suggest intervention designers focus on one or two target behaviours, on the basis that focused intervention and small improvements are more beneficial than attempting rapid and large-scale change(318).

BCW step 3: specify the target behaviour

The data from the qualitative investigations were utilised to determine who should perform the behaviour, what the person should do differently to create the intended change, when they should do it, where they should do it, how often they should do it, and with whom they should do it.

MRC stage 2: identifying/developing theory

This step included establishing a theoretical understanding of the potential change mechanism. The BCW'S COM-B model and the TDF were utilised to create a theoretical knowledge of the target behaviour(s) and to guide the intervention function selection(131,166).

BCW step 4: identify what needs to change to achieve the desired behaviour

To change behaviour, BCW suggests pinpointing what needs to change by mapping the target behaviour's barriers and enablers to the TDF (128,131,166). Therefore, TDF was utilised to investigate what intrapersonal and environmental components would need to change in order to affect the target behaviour/s.

BCW step 5: identify intervention functions to achieve the desired behaviour

The BCW framework contains nine intervention functions: persuasion, education, training, environmental restructuring, modelling, enablement, incentivisation, coercion and restriction, representing broad categories of means by which an intervention can change behaviour (166). In the BCW, intervention functions link to each theoretical domain in the TDF (131). Thus, the theoretical domains associated with the themes of the qualitative studies were mapped to relevant intervention functions within the BCW (166). In selecting intervention components, no policy categories were considered, as the scope of this research would not allow changes in policy.

BCW step 7: identify behavioural change techniques

The BCW, as well as the MRC guidelines, were used to identify behavioural modification approaches(128). All of the qualitative studies' findings, were used as data sources to contribute to the selection of behaviour change approaches. The theoretical domains found through the three empirical studies were mapped to their respective behaviour change approaches described in the BCW, following the MRC criteria. The BCW suggests behaviour modification approaches for each TDF domain(128,131,166, 217). The qualitative data was then used to evaluate each behaviour change technique's probable acceptability to the target demographic.

BCW step 8: identify mode of delivery

Options for the mode of delivery were informed by the results of the systematic review of previous interventions, the qualitative studies data an experiences and perceptions of providers-patient relationships and the suggestions of the study participants.

MRC stage 3: modelling process and outcomes

Modelling a multifaceted intervention can provide crucial information regarding the design of both the intervention and its evaluation, according to the MRC recommendations, which recommend that through be given to implementation of the intervention early in the design process(166). We created a model of the intervention to show how and in what context the behaviour change techniques would be applied, and how the outcomes could be evaluated

Table 16: TDF Analysis of the determinants from the three qualitative studies.

COM-B Construct	COM-B Micro-Construct	The TDF	The study	Who	Was the domain a Barrier or Facilitator?	Perceived Barriers and Facilitators to prescribed opioid optimisation
CAPABILITY	Psychological	Knowledge	Community pharmacists' study	Community pharmacists	Highly relevant as a barrier	Community pharmacists were often challenged by the lack of relevant knowledge, skills and training in the areas of CNMP and the use of opioids
			HCPs' study	Pain clinicians	Highly relevant as a facilitator	Pain consultants and clinical pharmacists have extensive knowledge and experience in the areas of CNMP and the use of opioids
				GPs	Highly relevant as a barrier	Consultants indicated that they frequently encountered problems arising from GPs' or other specialists' misconceptions and lack of knowledge, both about chronic pain and about opioids
			Patients' study	Patients	Highly relevant as a barrier	Patients sought knowledge but were getting it from informal sources such as the internet because it was not provided by prescribers.
				GPs	Highly relevant as a barrier	Patients were critical of GPs shortcomings in knowledge about chronic pain and about opioids
		Memory, Attention, and Decision Processes	Community pharmacists' study	Community pharmacists	Not occurring	
			HCPs' study	Pain clinicians	Not occurring	
			Patients' study	Patient	Low relevance as a facilitator	The use of a tapering chart or pain diary (each mentioned only once)
CAPABILITY		Behavioral Regulation	Community pharmacists' study	Community pharmacists	Not occurring	
			HCPs' study	Pain clinicians	Not occurring	
			Patients' study	Patient	Not occurring	
	Physical	Skills	Community pharmacists' study	Community pharmacists'	Moderately relevant as a barrier and facilitator	Lack of training CPs use professional judgment to hold opioid prescriptions until the required check is made. CPs can support opioid monitoring by carrying out Medicine Use Review.
			HCPs' study	Pain clinicians	Moderately relevant as a facilitator	Pain healthcare providers are skilful at managing chronic pain and opioid tapering, yet data showed that they are not using standardized questionnaires to assess physical and psychological aspects of patients' opioid use, before starting pain treatment or opioid tapering, rather than using their own clinical judgement.
			Patients' study	Patients	Moderately relevant as a facilitator	Patients adapt physical and psychological coping strategies to manage pain and opioid tapering or offset the side effects of medication.
OPPORTUNITY	Social	Social influences	Community pharmacists' study	Community pharmacists	Moderately relevant as a barrier	Community pharmacists believe that prescr bed opioids and chronic pain are prescr bers' responsibilities. Community pharmacists' relationships with other healthcare professionals, such as the difficulty of communication with prescribers in the event of any query, affected pharmacists' performance of their role Patients simply want relief from pain, so tend to be resistant to the idea of reduction or they prefer to discuss their medication use with the prescr ber rather than the community pharmacist. Pharmacists prefer not to intervene in a patient's rights and lifestyle choices.
			HCPs' study	Pain clinicians	Highly relevant as a facilitator	HCPs showed awareness of the importance of the doctor-patient relationship and its impact on patients' sense of well-being and ultimate outcomes,

						HCPs pointed to the importance of communication and liaison among professionals, tending in the direction of opioid reduction.
			Patients' study	GPs and other healthcare providers	Highly relevant as a barrier	Many patients described unhelpful encounters and unsupportive relationships with doctors whom they perceived as dismissive of their worries and suffering CNMP patients showed the need for support from a wide range of others including family, friends, an advocate, employers, and teachers.
	Physical	**Environmental context and Resources**	Community pharmacists' study	Systemic Factors for pharmacy managers and policymakers	Highly relevant as a barrier	The lack of information, whether guidelines, detailed patient records, or statements of policy issued by policymakers or the employing pharmacy or chain, to guide community pharmacists in assessing prescription appropriateness or the possible need for an intervention The lack of funding and resources, especially lack time for prescription review or patient education end monitoring. Repeat prescr bing and prescription delivery services, which reduced opportunities for education and monitoring Lack of authority.
				Patients	Highly relevant as a barrier	CNMP patients' complex individual needs
			HCPs' study	Pain clinicians	Highly relevant as a facilitator	The availability of guidance from The National Institute for Health and Care Excellence (NICE) and other sources, The availability of a multi-disciplinary team. Two consultants described themselves as working in such a team
				Patients	Highly relevant as a barrier	Patient-related factors, including their social circumstances and psychological state
				Systemic factors	Highly relevant as a barrier	Lack of a clear and consistent understanding and practice across the health services Time pressures, which limited efforts in the assessment, monitoring, and education of patients. The problem was said to be compounded by a lack of coordination among the multiple agencies involved in the care of CNMP patients
			Patients' study	Systemic factor	Highly relevant as a barrier	Difficulty of access to GPs and clinics.
				GPs and HCPs	Highly relevant as a barrier	Lack of an individual approach to opioid prescribing, tapering, and support Lack of recognition of patients' different needs and responses
				Others	Highly relevant as a barrier	Support from others including family, friends, an advocate, employers, and teachers
MOTIVATION	**Reflective**	**Beliefs about Capabilities**	Community pharmacists' study	Community pharmacists	Highly relevant as a barrier	Due to the lack of authority and training, community pharmacists were pessimistic about their capability to contr bute to prescribed opioid optimisation
			HCPs' study		Not occurring	
			Patients' study	Patients	Not occurring	
		Social/Professional Role & Identity	Community pharmacists' study	Community pharmacists	Highly relevant as a facilitator	Pharmacists perceived themselves as guardians of patient welfare.
			HCPs' study	Pain clinicians	Highly relevant as a facilitator	Pain clinicians saw themselves as guardians of patient safety,
			Patients' study	Patients	Moderately relevant as a barrier	Patients felt misjudged and subject to negative assumptions and seen as drug-seeking or uncooperative if they reported difficulties with tapering.
		Beliefs about Consequences	Community pharmacists' study		Moderately relevant as a facilitator	Pharmacists were motivated by beliefs about the harmful consequences of opioid use and benefits of education
			HCPs' study		Not occurring	
			Patients' study	Patients	Not occurring	
		Optimism	Community pharmacists' study		Low relevance as a barrier	Pharmacists were pessimistic about their capability to contr bute to prescribed opioid optimisation.
			HCPs' study		Not occurring	
			Patients' study	Patients	Low relevance as a facilitator	Optimism that they could achieve their opioid dose reduction target (few cases)

		Intentions	Community pharmacists' study		Low relevance as a facilitator	A few intended to review opioid prescriptions more thoroughly
			HCPs' study		Not occurring	
			Patients' study		Not occurring	
		Goals	Community pharmacists' study		Highly relevant as a barrier	Prioritizing other tasks and conditions over reviewing prescribed opioids even during MURs
			HCPs' study		Low relevance as a facilitator	
			Patients' study	Patients	Low relevance as a facilitator	Few were involved in joint goal setting with their provider
	Automatic	**Reinforcement**	Community pharmacists' study		Moderately relevant as a facilitator	They wanted encouragement (e.g., financial incentive to include prescr bed opioids in MURs)
			HCPs' study		Not occurring	
			Patients' study		Not occurring	
		Emotion	Community pharmacists' study	Community pharmacists'	Low relevance as a barrier	Community pharmacists mentioned the stress of involvement in opioid optimisation They barely mentioned empathy toward these patients
			HCPs' study	Pain clinicians	Low relevance as a barrier	Few demonstrated empathy.
			Patients' study	Patients	Highly relevant as a barrier	Patients reported anger, frustration, and fear of pain and opioids tapering or withdrawal Patients were often confused, frightened, and overwhelmed by the severity of the challenges and difficulty accessing service They felt they were unheard, pushed to withdrawal too quickly, or unsupported in balancing the opioid-related challenges with the physical, social and mental effects of pain, tapering or withdrawal

Table 17: Summary of data Sources and analysis process used to information the intervention design.

cesses for intervention design	Data sources	Analysis	Output
Understand opioid prescribing and use behaviour	Qual. studies	Thematic analysis to identify enablers and barriers of opioid optimisation Map analysis to TDF domains Describe problem behaviours Reflect on what the intervention should target	Understand opioid prescribing and use behaviour from perspectives of pharmacists, patients and clinicians and understand the relationship between prescriber behaviours and patient use behaviours
Identify how intervention could change prescriber' interaction with patients	Qual. studies	Theoretical domains identified in the qualitative studies mapped to intervention functions on BCW	Understand how intervention can change behaviour
Consider types of intervention and modes of delivery and their effectiveness	Qual. Studies Systematic review	Theoretical domains mapped to behavioural change techniques (BCTs) proposed by BCW BCTs proposed by participants in qual. studies or reported in the systematic review also considered.	Selected BCTs and modes of delivery
Model proposed intervention process and outcomes		Intervention functions identified in BCW guided operationalization of BCTs	

8.5 Result

8.5.1 MRC stage1: identifying the evidence base

BCW step 1: define the problem in behavioural terms

Data triangulation revealed many reasons behind difficulty in opioid use optimisation. Pharmacists highlighted lack of relevant knowledge and training, inadequate resources and time, and systemic constraints, as well as relationships with prescribers and patients (see Chapter 5 for details). Patients' posts revealed the dominant, life altering nature of CNMP and its physical, psychological and social impacts, which they tried to alleviate via opioids. They sought, via discussion forums, to obtain and share knowledge about opioids and coping strategies to deal with pain and medication-related problems, apparently to compensate for the lack of information from formal sources. Pain healthcare providers were reluctant to prescribe opioids and favoured tapering for patients referred to them. They attributed difficulties in this area to patients' social and psychological problems, which led to dependence on opioids, and lack of knowledge among GPs and other non-pain specialists, leading to inappropriate prescribing and continuation of opioids, or forced and hasty tapering without adequate recognition of patients' complex needs. Overall, a factor that stood out was challenging interaction due to discrepancies in perceptions, expectations and/or communication between the patient and healthcare providers, which could be caused by either one or both parties. Therefore, the reason for prescribing opioids should be considered when conceptualizing approaches or intervention(s) that best can help opioid tapering (38, 261). Patients highly valued healthcare providers' understanding towards their anxieties and worries, effective listening, empathy and appropriate support from them and their surroundings, including the healthcare system, but perceived that in practice, these needs were often not met(319). Emotion emerged as highly relevant for patients,

but not for pharmacists and doctors. There were some indications of their judgement, stereotyping, or even stigmatizing CNMP patients on long term opioids. They may also be affected by scientific data around the prescribed opioids overdose death rate, which may induce bias in decision-making(312,313). Another explanation may be due to institutional constraints that forced opioid tapering, which led to misapplication of opioid guidelines and a tapering pace that was not individualised to each patient's needs. The lack of a patient- centred approach, shared decision-making and empathy toward CNMP patients using long term opioids make healthcare providers seem highly dependent on mental short-cuts, leading to reliance on stereotypes when dealing with CNMP patients who have difficulties coping with their pain without using prescribed opioids(281,282). The problem was defined as the absence of a high-quality prescriber-patient relationship.

BCW step 2: select the target behaviour

The qualitative studies highlighted that there is a gap between how patients perceived their condition compared to their providers. The patient study highlighted that each patient is different, and they expected their healthcare providers to listen to their needs, yet healthcare providers held unified beliefs about CNMP patients who are on long-term opioids. Therefore, the behaviours to be targeted for change are:

- Healthcare providers not giving patients sufficient information about their condition and their medications, particularly prescribed opioids
- Not agreeing on a plan or contract with the patient
- Dismissing patients' concerns
- Stigmatizing patients.

These behaviours were selected because it is feasible to implement interventions to change them and doing would have a positive impact on prescriber-patient relationships (e.g., improved trust). Extended impacts could be: improved patient knowledge, better compliance, reduction in misuse and easier opioid tapering or cessations. Targeting these areas would meet patients' needs and would be consistent with healthcare providers' perceptions of their safeguarding role and desire to achieve better patient understanding and compliance.

BCW step 3: specify the target behaviour

Healthcare providers need to apply patient-centred care in their daily practice and discuss patients' concerns as well as educate the patients about their condition and medication using effective communication skills, show empathy and compassion and avoid stigmatizing and stereotyping. Table 19 specifies the target behaviours, in terms of who should perform them, what changes in behaviour will be required, and the context (when, where frequency and other parties involved) in which the target behaviours should occur.

Table 18. Specification of Behaviours.

	Target Behaviour: improve the patient-provider relationship and patient- centre approach through understanding their needs			
Behavioural specifications	**Improve Communication skill**	**Show empathy, avoid stigmatization and stereotyping, understand the patient stigma**	**Shared decision making and patient-centred care**	**Patient education**
Who needs to perform behaviour?	Healthcare providers who encounter CNMP patients using long-term opioids or, going through tapering	Healthcare providers who encounter CNMP patients using long-term opioids or going through tapering	Healthcare providers who encounter CNMP patients using long-term opioids or going through tapering	Healthcare providers who are encounter CNMP patients using long-term opioids or going through tapering
What does a person need to do differently to achieve desired change?	Practise active communication skill building with feedback, reflection, empathy and positive affirmation. Share chunks of information (rather than a monologue) and check-in with the patient. Make sure they are engaging in a dialogue rather than a monologue. implementing patient comprehension tools, such as teach-back and visual aids, to enhance communication and improve the provider-patient relationship.	Intentionally try to be empathetic, patient and compassionate Pay attention to nonverbal (body language) Validate the patient's experience, preferences, and concerns. Work to empower people or groups experiencing stigma, for example, by building skills and efficacy to address internalized stigma and cope with and challenge stigma and building partnerships. Increase knowledge about the science behind implicit bias, emphasising how biases influence behaviours and patient outcomes, increase self-awareness of existing implicit biases, make conscious efforts to overcome implicit bias, and enhance awareness of how implicit bias influences others. Watch verbal and non-verbal cues Be time-efficient and avoid stress	Consciously make an effort to see each patient as a unique individual Create an atmosphere of acceptance, promoting patient-centred care, trust and improved treatment engagement Invite the patient's perspective into the visit by asking explicitly about ideas, concerns and expectations regarding their agenda for the visit Partnership building by intentionally viewing the clinical inter-action as equally working toward the common goal of helping patients achieve good health Use clinical pathways, adhere to established standards of care, and practise evidence-based medicine.	Educate patients about their condition, pharmacological options and non-pharmacological treatment options. Explain that prescribed opioids are not for long term use Discuss tapering and plan the best tapering approach. Provide patient with tapering support services if available or provide him/her with written information on how to handle withdrawal Encourage patients to apply self-management
When will they do it?	Each time they encounter these patients.	Each time they encounter these patients.	Each time they need to change the CNMP treatment plan	Each time they encounter these patients
Where will they do it?	In clinic or through the phone.	In clinic or through the phone.	In clinic or through the phone.	In clinic or through the phone.
How often will they do it?	All the time	All the time	Each time they need to change the CNMP treatment plan	All the time
With whom will they do it?	With CNMP patients who are going through long term opioids therapy	With CNMP patients who are going through long term opioids therapy	With CNMP patients who are going through long term opioids therapy	With CNMP patients who are going through long term opioids therapy

MRC stage 2: identifying/developing theory

BCW step 4: identify what needs to change to achieve the desired behaviour

In understanding the behaviour and what needs to change to modify it, enablers and barriers of prescribed opioid optimisation behaviours identified in the qualitative studies were mapped onto domains of the theoretical domains framework. Facilitating factors were linked to the Knowledge and skill of healthcare providers. The professional role of healthcare providers was another primary driver of prescribed optimisation, as they prioritized scientific evidence and safety and were influenced by the national trend of opioid tapering. A barrier factor was patients' fear and mistrust, linked to the Emotion domain in the TDF, which was a big factor against prescribed optimisation. Other barriers to effective communications and relationships between healthcare providers and patients were perceived lack of time for patient education and monitoring, limited contact between providers and patients (both reflecting Environmental Context and Resources), some providers' limited knowledge about pain and opioids (Knowledge), providers' stress (Emotion) and tendency toward biased, stereotyped view of patients using opioids long-term. Table 20 relates these factors to the COM-B model.

Table 19: Enablers and barriers to provider-patient relationship.

COM-B	Influence factors	TDF domains	Role
Capability	Knowledge of opioid dangers and alternatives	Knowledge	Enabler
	Lack of knowledge of CNMP and opioids	Knowledge	Barrier
	Lack of awareness of the individual need	Knowledge	Barrier
	Lack of active listening skills	Skill	Barrier
	Providers' stress	Emotion	Barrier
Opportunity	Lack of time	Env. Context	Barrier
	Infrequent context between provider and patient	Env. Context	Barrier
	Patients fear and mistrust	Emotion	Barrier
Motivation	Guardianship pf patient welfare	Prof. role	Enabler
	Social pressure for tapering and cession	Soc. influence	Barrier
	Bias and stereotyping of long-term opioid users	Soc. influence	Barrier

BCW step 5: identify intervention functions

The research team identified five intervention functions that were relevant to bringing about the desired change., which would improve the provider-patient relationship, encourage healthcare providers to show empathy and understanding and so build a better bond. These were (1) Education (2) Persuasion (3) Training (4) Modelling and (5) Patient education. Relating these to the target behaviour specified in step 3 and the required changes identified in step 4, communication skills could be improved by training in active listening techniques, the use of patient comprehension tools and reflection, and by modelling examples of effective, empathic communication. Stigmatization and stereotyping could be reduced by education to raise awareness of bias and its effects, and by persuasion to convince providers of the importance of addressing this factor. Shared decision-making could be encouraged by persuasion and training in techniques for patient engagement. Patient education (information provision) could be improved by education to fill gaps in providers' own knowledge and by persuasion to highlight the need and value of such activity. All four target behaviours would benefit from training to help providers cope with time constraints and work-related stress that might deter them from working on these areas.

BCW step 6: identify behaviour change techniques

Ten behaviour change techniques (BCTs) proposed by the BCW can be used to address the five theoretical domains: environmental context and resources (e.g. time constraints), social influences, social and professional role and identity (healthcare providers' safeguarding role), and emotion (patient emotion and healthcare providers' stress due to time constraint and stressful task) identified in the qualitative studies .

As the qualitative studies explored barriers and facilitators of prescribed opioid optimisation from the perspectives of healthcare providers and CNMP patients, the findings from this study suggested behaviour change techniques that are likely to be acceptable to the population of interest to improve the provider-patient relationship. The findings suggested that these behaviours change techniques are likely to be effective in improving provider-patient communication. The techniques are Verbal persuasion/persuasive communication, instruction, behavioural information, demonstration of behaviour, imagery, stress management, time management, self-monitoring of behaviour, habit information and feedback. Table 21 shows how BCTs are linked to the targeted changes and selected intervention functions.

Table 20: Identifying BCTs.

COM-B	Domains and changes needed	Intervention function	BCTs
Capability	**Knowledge** Awareness of individual need Knowledge of pain and opioids	Education	Instruction Behavioural information
	Skills Communication skills	Modelling Training	Demonstration, imagery, self-monitoring Feedback Habit formation
	Emotion Provider' stress	Training	Stress management
Opportunity	**Environmental Context Resources** Lack of time Limited contact	Training Education	Time management Behavioural information
	Emotion Patient' fear and mistrust	Education Modelling Persuasion	Behavioural information Verbal communication, persuasive, imagery
Motivation	**Social influences** Social pressure of tapering without considering individual need	Education	Behavioural information
	Social influences Bias, stereotyping	Education Persuasion	Behavioural information Verbal communication, imagery

BCW step 8: Identify mode of delivery

In the systematic review, internet-based learning and face to face courses were some of the means that have been used to deliver educational interventions for both patients and healthcare providers (184,187). Distance learning is perceived as a more convenient and more flexible choice to complete the course ,320). Also, the use of internet-based learning to teach a wide range of topics to a variety of health care providers is becoming more common. According to the research literature, online learning can be equally as effective as more traditional types of education and training (e.g., as face to face lectures or courses). Video, slideshows, animation, emails, and additional means for communication (live chat rooms, bulletin boards, and audio) are examples of widely used internet-based learning. Some courses were coupled with face-to-face teaching modalities, such as lectures and small group learning, in addition to using the Internet. Blended learning (BL), usually referred to as hybrid learning, is a term that explains the combination of face-to-face education in the classroom with online learning experiences. While maintaining the benefits of face-to-face learning, BL offers the flexibility of collaborative learning alongside the practical self-directed learning provided on the online platform(321).

So, the best way to deliver the intervention decided to be blended learning through video, online courses with lectures and small group learning.

MRC stage 3: Modelling process and outcome

The intervention is hypothesized to improve healthcare providers' understanding of patients' emotional needs, increase the quantity and the quality of communication and promote shared decision-making. Such a change in healthcare providers'

communication behaviours will increase patient trust in providers and willingness to cooperate with optimisation plans. Drawing on the COM-B model, the intervention would work by increasing the capability, opportunity and motivation for effective, empathetic communication, specifically the behaviours specified in the BCW step3. It would do so via operationalization of the BCTs identified above, to fulfil the four identified intervention functions.

The BCTs, behavioural information, verbal communication and imagery will be used to increase motivation for improving communication with patients, by increasing understanding of the harmful effects of bias and stigmatization, and the beneficial effects of empathy on patient outcomes and persuading providers of the value of good communication.

The intervention will improve providers' capability for better communication and relationships with patients by providing instruction to ensure they have adequate information about CNMP and opioids and theoretical knowledge about bias and its influence on behaviour. The BCT, modelling (behaviour demonstration) and imagery will be used to improve providers' communication skills by demonstrating effective communication techniques, including the use of patient comprehension tools. The intervention will also provide training in stress management techniques. Participants will be encouraged to self-monitor their use of the target behaviours and practise them consistently so that clear empathic communication becomes a habit. The intervention will increase the opportunity for effective interaction by examining them on an online assessment tool asking some questions about the educational material. Before and after the intervention, patients' satisfaction questionnaires for the patients of providers who attend the intervention could be used to evaluate the impact of the interventions.

Table 22 shows how the identified intervention functions and BCTs would be operationalized to produce the intended behaviour changes.

Table 21: Operationalization of BCTs in intervention strategies.

Intervention functions (step 5)	**Definition**	**BCTs (step 7)**	**Intervention strategies/mode of delivery (step 8)**
Education	Increase knowledge or understanding	**Instruction**: teach new behaviour required for performance of target behaviour (not as part of a graded hierarchy or as part of modelling) e.g., give clear instructions	**Instruction**: Teach healthcare providers about stigma and stereotyping and who Internal Security IS usually more l kely to be suscept ble to these feelings teach how to how stigma or stereotyping can be avoided and how empathy and building supportive provider-patient can be achieved e.g., give step by step guidance on how to communicate with patients who are likely suffering from stigmatisation. Increase knowledge about the science behind implicit bias, emphasising how biases influence behaviours and patient outcomes
		Behavioural information: provide information about antecedents or consequences of the behaviour, or connections between them, or behaviour change technique	**Behavioural information**: Provide information about showing empathy and its positive consequences on patient outcomes.
		Feedback: of monitored (inc. self-monitored) behaviour	After finishing the education and the training courses, the participants can be assessed by examining them on an online assessment tool asking some questions about the material and the best behavioural for different situations. Also, a feedback survey could be given to the patients about their experiences with their providers and how they discuss their concerns about their pain and prescr bed opioid use and tapering.
Persuasion	Using communication to induce positive or negative feelings or stimulate action	**Verbal persuasion/persuasive communication:** cred ble source presents arguments in favour of the behaviour. Note, there must be evidence of presentation of arguments; general pro-behaviour communication does not count.	Provide information about bias and stigma consequences on patient outcome and the positive effect of empathy. Provide information on the effect of this behaviour on the patient outcome. Use imagery to motivate healthcare providers to show empathy to patients and increase communication with them.
Training	Imparting skills Providing an example for people to aspire to	**Habit formation:** perform the same behaviour in the same context	Training for healthcare providers about how to avoid stigma and stereotyping by improving the following: **Habit formation of better communication** skills with patients. Practise active communication skill building with feedback, reflection, empathy, and positive affirmation. Share chunks of information (rather than a monologue) and check-in with the patient. Make sure they are engaging in a dialogue rather than a monologue. Implementing patient comprehension tools, such as teach-back and visual aids, to enhance communication and improve the provider-patient relationship. Pay attention to nonverbal (body language) communication to validate the patient's experience, preferences, and concerns. Working to empower people or groups experiencing stigma, for example, by building skills and efficacy to address internalized stigma and cope with and challenge stigma, and building partnerships
		stress management: behaviours undertaken to reduce stressors or impact of stressors **Planning:** identify component parts of behaviour and make a plan to execute each one or consider when and/or where behaviour will be performed, i.e., schedule behaviours	Practice stress-reducing techniques such as mindfulness training, enhancing awareness of oneself, compsassion for both self and others, improving organizational improving workflow management, organizing services focused on reducing workload, improving interoperability
		Time management: action planning applied to the perceived problem of shortage of time	Improve workflow, organizing services, focused on reducing workload, improving interoperability and use of electronic medical records and telemedicine services.

Modelling	Observe the behaviour of others	**Modelling**: observe the behaviour of others **Imagery**: use planned images (visual, motor, sensory) to implement behaviour change techniques (inc. mental rehearsal)	Video dramatization to demonstrate effective, empathetic interaction with patients

8.6 Conclusion

Drawing on the systematic literature review and the three qualitative studies reported in previous chapters and using the MRC guidelines and related steps of the BCW framework, an intervention has been proposed to address some of the identified barriers to prescribed opioid optimisation. The intervention targets specifically the problem of poor communication and broken relationships between healthcare providers and patients. It uses education, training, persuasion and modelling and related BCTs, delivered in online and video format and face to face lectures to improve communication skills, reduce bias and stereotyping and encourage information provision and shared decision-making. This should lead to more appropriate, individualized prescribing and tapering decisions that make patients feel heard, understood and supported, leading to better compliance with treatment. The following chapter concludes the thesis with assessment of the research contribution and limitations, and suggested directions for further work.

Chapter 9: Conclusion

9.1 Chapter description

This chapter summarises key aims, objectives and findings identified throughout the thesis with emphasis on the theoretical and methodological contributions. Also, research strengths, limitations, implications and reflective account are highlighted.

9.2 Introduction

The aim of this thesis was to study enablers and barriers of prescribed opioid optimisation for CNMP patients and potential interventions to optimise opioids use.

First, we performed a systematic review of the available literature on interventions that aim to optimise the use of prescribed opioids for CNMP patients, including how these interventions have been developed. We also performed a narrative review of the current status of the opioid epidemic in the UK, since most of the studies that were retrieved from the systematic review were from the USA. This review highlighted the difference in the extent of the opioid epidemic and in opioid use, which the research team considered important to understand in order to develop an intervention that might suit the UK context. Following this study, we performed three qualitative studies. Two were based on semi-structured interviews using the Theoretical Domains Framework as a topic guide with community pharmacists and pain clinicians about the barriers and enablers of opioid optimisation for CNMP patients. The third study was also qualitative and used the TDF as a topic guide but involved analysis of chronic pain patients' forums for their perspectives on prescribed opioid optimisation for CNMP. Finally, using available empirical evidence, a psychological model of behaviour change was applied in order to design a theory-based intervention that aims to improve the provider-patient relationship, which eventually may lead to opioid optimisation.

This chapter comments on the main findings of the work and addresses some theoretical and methodological contributions. After an assessment of the studies' strengths and limitations, the chapter closes by presenting some implications for daily practice, ideas for future research and reflections on the learning experience as a whole.

9.3 Summary of the study

9.3.1 Systematic review of prescribed opioid optimisation interventions

The systematic review highlighted that existing literature is not consistent in the definitions of opioid use behaviours. Also, there was substantial heterogeneity in the types of populations being studied, their co-morbidities and medications, which make it difficult to draw a robust conclusion. The interventions were categorised into single-component and multi-component interventions.

The single-component interventions were either educational, behavioural or used opioid contracts and urine drug testing to reduce the targeted medication-taking behaviours. These had a limited effect, as they usually sought to reduce or prevent problematic medication-taking behaviour without taking into consideration patients' physical and psychological states.

The multi-component interventions in this study were frequently based on US chronic pain management recommendations. Such multi-component interventions have been demonstrated to be more effective in detecting and reducing problematic medication-taking behaviour, taking into account patients' physical and psychological conditions, as well as their satisfaction. The complexity of these approaches, however, makes it difficult to determine which components addressed specific behaviours, which is required in order to tailor interventions to the needs of the CNMP population, as these can differ in a variety of ways and from one demographic region to the next.

9.3.2 Community pharmacists' role and perspective on prescribed opioid optimisation.

This study highlighted the limited role that UK community pharmacists currently play in prescribed opioid optimisation, due to multiple barriers. The community pharmacists showed their awareness of the issues around the long-term use of prescribed opioids

for CNMP and expressed concerns about patient safety. Nevertheless, they perceived that they have a very limited role to play as there are no clear guidelines for environmental resources that could enable their involvement in educating patients, checking prescriptions or monitoring opioid use behaviour with patients. The main constraints mentioned were the lack of sufficient patient information and time for through patient education and monitoring. A clearer description of the UK pharmacists' role in prescribed opioid optimisation is needed, as well as more education and training that may enable the community pharmacists to play a wider role in prescribed opioid use for chronic pain.

9.3.3 Patients' perspectives on enablers and barriers of prescribed opioid optimisation.

Patients' posts on online discussion forums showed that CNMP affected every part of patients' life. Their main concern when seeking healthcare was to get rid of the pain and improve their quality of life. Many perceived that the quality of care received did not fulfil their needs. The data showed patients to be knowledge seekers who sought information about their CNMP and various medications and treatments, were aware of the harms associated with opioids, and were willing to cooperate with their providers in order to achieve a better quality of life. However, they expressed a need for support to cope with the physical and emotional difficulties of tapering and withdrawal. Some reported poor communication with healthcare providers, and perceptions of being stigmatized. The results suggested that a better patient-provider relationship that leads to an understanding of the patients' needs may lead to opioid optimisation.

9.3.4 Pain clinicians' perspective of the enablers and barriers to prescribed opioid optimisation.

The pain clinicians demonstrated a high level of scientific knowledge around the use of opioids for CNMP. They emphasised the need for educational interventions for other healthcare providers including GPs and specialists in other fields, who often inappropriately prescribed opioids for patients without taking into consideration the negative consequence of long-term use and limited effectiveness of these medications for patients. They also reported their experience of patients' attitudes and behaviour towards opioids and noted that the complexity of some patients' psycho-social factors can be a barrier to optimisation of prescribed opioid use for CNMP.

9.4 Intervention

The complexity of CNMP patients' psycho-social factors and the importance of their emotions appear to have a critical role in patients' understanding of their conditions and the effect of long-term prescribed opioid use. The endless effect of CNMP on patients' life and their emotions highlight the importance of positive relationships with others in their surroundings, including healthcare providers, psychological or other professionals who involve in the patient's care during their difficult times such as periods of high-intensity pain or opioid tapering, as the key that may lead to reducing their reliance on prescribed opioids as a tool to cope with their pain. The demonstration of patient-centred care and taking their feelings and worries into consideration in their treatment plan could build trust in the healthcare system and the providers, which would eventually lead to reduced reliance on medication as the cornerstone of CNMP patients' journey to reduce the effects of CNMP on their quality of life.

The research team used a theoretical framework and existing evidence on prescribed opioid optimisation to design an intervention that is comprehensive enough to be

effective, targeting multiple factors that may improve healthcare providers' approach to effectively communicate with these patients in order to gain their trust and make them rely less on opioids to reduce the effect of pain on their life. The most important conclusion of this approach was that the key focus of the intervention should be the health care provider, instead of the patient. It was suggested that providers' focus on their professional roles may lead to overlooking patients' needs, which are usually complex due to the massive impact of pain, psychologically and physically on their quality of life. We highlighted the importance of transforming the healthcare providers' focus to more patient-centred care and improving their understanding of patients' needs. The intervention proposed would use education, training, persuasion, and modelling, delivered via a blended learning approach, to help healthcare providers to communicate more effectively with patients, be aware of the impacts of bias and stereotyping, educate patients about their treatment, and involve them in planning and decision making for their care.

9.5 Contributions of the Research

In addressing the research objectives mentioned earlier, the research makes a number of theoretical and methodological contributions.

9.5.1 Theoretical contributions

As far as we know, this is the only qualitative study to have been performed on this subject worldwide. Some of the study findings are similar to those of other studies, such as the negative effect of the CNMP on the patients whole life and the stigmatisation of the patients by their healthcare providers (see Chapter 5,Chapter 6,Chapter 7) However, the unique barriers and enablers of prescribed opioids optimisation for CNMP in the UK have not been described in such depth in the context

before. Moreover, this thesis provides an improved understanding, adding to that from previously quantitative studies that explored the perspectives of healthcare providers and patients about prescribed opioid optimisation. Also, these studies confirmed that prescribed opioid optimisation is a complex behaviour, influenced by various factors including environmental factors, social influences, and lack of training and knowledge of some healthcare providers as well as the overwhelming impact of patients' emotions on their medication use and their perception of their conditions. Mapping the findings of these studies into the Theoretical Domains Framework (TDF) and Behaviour Change Wheel (BCW) to inform intervention development was a unique aspect of this study. This has informed a proposed intervention that can be developed to target improvement of patient-provider relationships, leading to better cooperation between the stakeholders during prescribed opioid optimisation. Because the factors most likely to affect prescribed opioid optimisation (environmental context and resources, professional role, social influences, emotions, and knowledge) have been identified, as well as how these factors can best be addressed, the intervention's chances of success are improved. This improves the chances of any solution created as a consequence of this study being adopted and successful. Co-designing the research with key stakeholders will also boost the chances of success.

9.5.2 Contribution to methodology

This thesis has contributed methodologically by the systematic nature of the search of patients' forums and keyword topic search using keywords suggested by previous literature. As far as we know, this is the first time a systematic review of publicly available data on online forums has been conducted and the TDF framework has been

applied to identify and present key emerging themes, shedding light on patients' perspectives.

9.6 Practical implications

This study has significant implications for policy and practice. There is increasing interest in the understanding of the barriers and enablers of prescribed opioid optimisation. One of the implications for policy and practice that is highlighted by the community pharmacists' study (see Chapter 5) is the need for a clearer definition and guidelines on the use of opioids for CNMP and the optimisation role that community pharmacists should perform for these patients. Also there is a need for training and education on CNMP and prescribed opioid optimisation, consistent with the NHS vision of the expanded role of pharmacists in clinical aspects of patient care. The clinician study highlighted the need for utilizing a comprehensive and systematic way to assess patients before starting tapering. This should include using standardized questionnaires to assess patients as a whole including physical, and psychological aspects of patients' opioid use, before starting tapering, rather than individual practitioners relying on their own clinical judgement (see Chapter 7). An insight from the patients' study is that patients' emotion dominated their life and affected every aspect and should be taken into consideration by their healthcare providers, especially when the patients are going through tapering, which was seen as a traumatic experience for many of these patients (See Chapter 6).

9.7 Strength of the study

This research has provided a holistic evidence-based picture of the complex determinants that may influence prescribed opioid optimisation. This thesis has investigated prescribed opioid optimisation from the perspectives of community

pharmacists, patients, and pain clinicians. There are no other studies that have studied prescribed opioid use drawing on behavioural change theories or studied prescribed opioid optimisation considering the perspectives of patients and their providers. The proposed intervention development process, using the improved patient-provider relationship as an example determinant, illustrates how evidence reported in this thesis may be taken forward. The findings of the empirical studies and the systematic review have been used to develop an intervention that is intended to improve the provider-patient relationship by using education and training for healthcare providers to highlight the importance of considering the patients' emotions and encourage them to involve patients in clinical decision- making. Training would also highlight the importance of healthcare providers 'communication skills, both verbal and non-verbal, as these have a big impact on the patient-provider relationship. In addition to this, considering the interplay of determinants and how they relate to one another will add to the depth of understanding, supporting intervention development

This is believed to be the only study that combines the use of the TDF and taxonomies of behaviour change to inform an intervention aimed at optimising the use of prescribed opioids for CNMP. This research has captured what is considered to be an inclusive range of determinants including barriers and facilitators optimising the use of prescribed opioids for CNMP. Using these findings and the mapping process as outlined, it is now possible to design and pilot different interventions which include components that are considerably more likely to be effective. The utilisation of a theoretical framework promotes a systematic uptake of research findings, ensuring intervention development is evidenced-based and applicable to the settings in which they are to be delivered. Such methods are easily accessible to researchers and give

assurance to those with a non-psychology background that theory is incorporated in a robust and logical manner. This research also adds to the accumulative bank of evidence within the implementation science arena. TDF and BCW, which have been effectively used to develop interventions in health settings, were used to underlie the intervention design. These frameworks are useful since they allowed comprehensive behavioural theories to be used to describe how elements behind enablers and barriers of appropriate opioid use or prescribing among stakeholders could be linked. The COM-B is versatile in that it may include contradictory behaviours and show how capacity, opportunity, and motivation for various behaviours interact to influence observed behaviour. The TDF has been used to inform the methodological designs of the empirical studies reported in the thesis and to provide a consistent, rigorous approach to the analysis of data. Alongside these frameworks, the MAC framework guided the development of the intervention.

9.8 Limitations of the study

Nevertheless, there are limitations to this research which should be taken into consideration when drawing inferences from it. There are other, wider issues within the complex system that can not be solved by developing one intervention. Importantly, how evidence may sit within a whole systems approach to tackling a problem such as the lack of a clear definition of the community pharmacists' role when dispensing prescribed opioids needs to be considered.

Although the intervention development process outlined here is specific in nature, further behavioural exploration at a wider level (drawing upon policy level determinants) is possible using the same methods, and attempts. However, there will

always remain a need to understand determinants at an individual level as this information will ultimately form the building blocks of any systematic approach.

One of the limitations of this thesis is the lack of GPs' perspectives, as GPs are the main healthcare providers who are usually in contact with these patients, and previous studies have suggested that GPs, by inappropriate prescribing, have contributed to the opioid epidemic. Another limitation is the use of patients' forums due to reasons explained in Chapter 3 instead of conducting semi-structured interviews with patients. The interviewing of CNMP patients who are on chronic opioid therapy, these who are going through tapering or former chronic opioid therapy user, based on a TDF topic guide, would enable greater comparability with other studies.

The sample size may also be considered as a drawback of this thesis, since it cannot be assumed that the findings are representative of all UK healthcare providers (community pharmacists, clinical pharmacists and pain consultants). Nevertheless, data saturation was reached, and all participants spoke similarly about their perspectives of prescribed opioid optimisation. Also, previous studies have shown that the perceptive of local and international medical society about the limited use of chronic opioid therapy for CNMP are similar.

Other limitations relate to the use of the TDF and the behaviour change techniques taxonomy (BCTTv1). The TDF is a commonly used framework that has been referenced widely, yet it has been criticised for not including all possible modes of action that may influence behaviours. Connell et al. (2019) identified 12 common mechanisms of action that do not fit within the Theoretical Domains Framework. It is probable that by relying solely on the Theoretical Domains Framework to organise and

analyse the data, crucial behavioural factors and mechanisms of action for inappropriate prescribed opioid use and prescribing were neglected. Also, there was overlap between the TDF domains, as well as difficulty adapting questions during the interview topic guide development. For example, when participants were asked what they perceived to be environmental and resource barriers, and what could hinder their intention to participate more in prescribed opioid optimisation, the answer to both questions was the same.

Also, the behaviour change techniques taxonomy (BCTTv1) was difficult to use. The ambiguous definition and the overlap between techniques make it hard to differentiate between them, and the effect of choosing one over the others could impact the intervention's success and applicability.

9.9 Methodological Reflections

The qualitative research in Chapters 4-6 represents almost all the work in this PhD thesis. The research quality and reliability are detailed Chapter3. A critical realist ontology was integrated with a more constructivist epistemology in the conducting this approach. Critical realism assumes the existence of an objective reality apart from human creation, but that perception of this reality is constrained by one's place within it (e.g., social and economic factors). Because people's views of reality are influenced by their beliefs, experiences, and interpretations, the researcher could not ignore the role of subjectivity during the analytical process. In this respect, a critical realist approach allowed the identification of differences in participants' interpretations, which allowed the understanding of how factors, such as existing Environmental context and resources, Social/professional role and identity, Knowledge and others influenced perceptions and experiences on prescribed opioid optimisation (Chapter 7). However,

the qualitative methodological approach was based solely on the overview of individuals' own perspectives, without considering the possible impact of constraints other than those directly reported. For example, it would be interesting to investigate geographical differences in the perceptions of healthcare providers and patients of the extended use of prescribed opioids for CNMP within the UK. Thematic analysis was chosen as the technique of analysis to both reflect reality and to unpick the surface of that 'reality' in terms of the contexts in which people make sense of their thoughts and feelings. As a result, it's an especially good strategy for a critical realism perspective. Furthermore, researchers who are new to the qualitative approach might use Thematic Analysis (322). Because this was the author's first time performing primary qualitative research, and Thematic Analysis allows for a critical realist perspective, it was decided that this was the most suitable analytical method to use. Thematic analysis identifies and analyses patterns in data. This was facilitated by use of the Framework Approach, which is beneficial for improving data management transparency and accessibility, as well as facilitating discussion and communication of the study research team. Furthermore, Framework Analysis facilitates in-depth, interpretive and linkage of the findings by helping to design an intervention based on these findings. This guarantees that viewpoints are contextualised, as evidenced by the level of analysis in both the exploratory interview research and the qualitative assessment of the intervention in this PhD.

Qualitative research performed from a critical realist viewpoint allows for the most credible interpretations of the data to be acquired through careful interpretation, allowing for some (limited) generalizability (323). The qualitative findings in this thesis could provide valuable insight into similar populations or situations, as is desirable in

qualitative research. For example, the current findings may be transferable patients who are using chronic opioid therapy specific CNMP conditions such as lower back pain, fibromyalgia. Also, the views of the pain consultants, community pharmacists and the clinical pharmacists about the barriers and enablers of prescribed opioids in the UK could be transferable to other healthcare providers such as GPs or nurses. However, it is accepted that a researcher cannot disregard their subjectivity in qualitative analytical processes; therefore, reflexivity is a vital component. The author of this Ph.D. research is an Arab-Muslim female with a background in Pharmacy. The researcher has practised pharmacy in Saudi Arabia, which has a national healthcare system similar to that of the UK, yet due to differences in the religion and culture of both patients and healthcare providers have an effect on the extent of use of chronic opioid therapy for CNMP. For example, patients are reluctant to use narcotics daily for their chronic pain, as it may interfere with their religious rituals such as the five payers which are not allowed to be performed under the influence of drugs or alcohol. The researcher has received various training on qualitative research see Appendix 5, and the research team further consisted of the lead author's two supervisors, both from pharmacy practice backgrounds, who have published many qualitative papers using a variety of analytical methods. With respect to this, the theoretical preconceptions of the researchers, e.g., knowledge of health behaviour change concepts, may have had some degree of influence on the present qualitative findings and interpretations. As well as the influence of academic background, it is also important to reflect upon how the personal background and characteristics of the researcher may have played a role in the research. In this respect, the PhD author also offers the reflective account see (9.9).

9.10 Areas for future research

Using frameworks such as the TDF to explore the pain healthcare providers and patients as adopted in this research is relatively new, and further exploration is needed to determine its usability and effectiveness.

The reports of the stakeholders participating in these studies suggested that GPs play a much larger role in provision than expected. Further research to explore the role of GPs (and other primary healthcare providers such as nurses) needs to be carried out to understand how they might best support CNMP patients. This will also allow for the development of interventions that target these providers and their patients, which seems sensible in the current situation, where many CNMP patients who have been on prescribed opioids for the long term are required to wean completely from these medications.

Following evidence pertaining to the role of family, friends, and other individuals in the patients' surroundings, there is a need for further research with this population to explore how these individuals could be employed to help in reduce CNMP suffering and optimise the use of prescribed opioids. Additionally, how patients' surroundings could potentially support opioids optimisation is worth further exploration.

The following research priorities and recommendations can be made based upon the findings of this research:

1. The perspectives of other healthcare providers including GPs and nurses, on prescribed opioid optimisation, should be investigated
2. The perspectives of healthcare providers and CNMP patients from deprived UK area where patients rely solely on their pain medications to relieve pain due to economic

issues should be investigated and compared to those reported in this thesis and compare their views to this thesis studies result.

3. The perspective of policymakers prescribed opioid optimisation could also be explained.
4. Specifically, it would be worthwhile to explore the perceptive of policymakers on expanding the role of community pharmacists to be involved more in prescribed opioid optimisation.
5. A feasibility study should be developed using evidence on behavioural determinants generated from this research. This should include relevant intervention components and appropriate behaviour change techniques which are theoretically underpinned.
6. Research is needed to explore the experiences and skills of former CNMP and long-term prescribed opioid patients who have been successfully weaned from opioids and manage to live with CNMP without chronic use of any type of analgesic.
7. More research is needed to explore the expansion of community pharmacists' role to play a bigger role in prescribed opioid optimisation, using different research approaches or different frameworks.
8. All interventions should include components that address patients' emotions as a barrier to prescribed opioids optimisation. Researchers should consider the role of GPs to inform any future intervention development as this will increase the depth of understanding of determinants surrounding GP's perspective of enablers and barriers of opioid optimisation.
9. Employing implementation science and the use of theoretical frameworks, such as the TDF should be utilised more widely to explore system-level barriers and facilitators to

behaviour change. This is particularly true for researchers with minimal or no psychological training, to ensure a theoretical grounding.

The researcher future work will continue exploring the possible intervention to optimise the use of prescribed opioids for CNMP. This thesis has addressed previous interventions and highlighted the enablers and barriers to opioid use for CNMP that patients and healthcare providers experience. It has proposed intervention that has been designed based on the found evidence on using TDF and WBC, which give the direction for further work in these areas.

The first is continuing to design the intervention by looking at each domain of the intervention and what change needs to be done to improve communication between healthcare providers and patients to optimise the clinic's time to build a positive relationship. The two parties can have a better understanding based on the messages and concerns they share clearly. Achieving this objective may require conducting a systematic review of the best way to communicate with patients with chronic pain, those undergoing tapering, opioid use disorder, and those with distress, anxiety, and depression. It is important to look for the unmet needs of CNMP patients who are on opioids for the long-term in literature.

As a Saudi pharmacist, I believe it is important to find ways to address chronic pain in patients using appropriately prescribed opioids. The status of chronic pain management and the appropriate use of opioids is not clearly defined in the Saudi context. There is a dearth in the literature regarding the prevalence of chronic pain, type of CNMP, its severity, and the trend of using prescribed opioids. A few studies have highlighted that CNMP is one of the most treated conditions in the Saudi health care system. Therefore, there is a need for further studies to explore the subject in depth.

9.11 Reflective account

I have learned a lot about chronic pain, medicine optimisation, prescribed opioids, qualitative research, behaviour change psychology, and myself as a result of my PhD. The discipline of research, a field in which I had always been fascinated, has been a steep learning curve for me. The skills I learned during this research, such as how to do a literature review, qualitative interviews, data analysis, academic writing and other technical skills will be useful throughout my career as I continue to try to understand my surroundings and understand why individuals act in the way they do. The multiple training courses I have taken (PhD profile) have given me a strong foundation in research techniques. The TDF, COM-B, and other tools I have learned in behaviour change psychology and the Behaviour Change Wheel will also assist with this mission wherever I choose to work. Professionally, I have a deeper understanding of clinical practice and the importance of patient-centred care and recognize that those things are not as easy as it may seem at the first glance. I have discovered that positive interprofessional relationships and provider-patient relationships are critical to growing personally and professionally. I have learned resilience and how resilient I am, as well as when to take a step back, rest, and seek assistance. Conducting research has put me to the test mentally and emotionally, and I believe I have grown as a person as a result of it. I am more conscious of my limitations, more patient, and ultimately more confident in myself today than I was when the project began. In particular, one of the experiences that made me grow emotionally was reading the patients' posts. This, in the beginning, affected my mental and emotional well-being and was not an easy feeling that I could overcome easily. However, because I was determined to be a knowledge contributor and help others who suffer, I was determined to do this research to help humanity. This made me keep working on the projects, strive to publish some

of my work and have a positive impact on CNMP patients' life. I learned how important it is to deal with others based on human-to-human concepts. I had always thought that we are all driven by our nature to put humanity first in everything we do, but in real life, this is not always the case, as some of us are in various ways affected by modern society, education, the media, customs, rule and regulations, history and even ethnicity. As a result, we focus on materialistic needs and may become less connected to our main purpose. Being human means that one has emotions towards oneself. It means having a deep sense of empathy and being caring. It means to not be perfect, to make many mistakes, and to grow every moment, as we are all driven by curiosity and must explore.

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Appendics

Appendix 1

Copy of published paper

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COMMENTARY

Current status of opioid epidemic in the United Kingdom and strategies for treatment optimisation in chronic pain

Aziza Alenezi[1] · Asma Yahyouche[1] · Vibhu Paudyal[1]

Received: 1 April 2020 / Accepted: 17 November 2020
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Abstract
The increase in opioid prescriptions in the United States has been accompanied by an increase in misuse as well as overdose and toxicity related morbidity and mortality. However, the extent of the increased opioid use, including misuse in the United Kingdom, currently remains less debated. Recent studies in the United Kingdom have shown a rise in opioid use and attributed deaths, particularly in areas with higher deprivation. There are also large variations amongst the devolved nations; Scotland has the highest drug-related deaths and year-on-year increase within Europe. Better clinical guidelines that can enable person-centred management of chronic pain, medicines optimisation, and early diagnosis and treatment of opioid use disorder are crucial to addressing opioid-related morbidity and mortality in the United Kingdom.

Keywords Chronic non-malignant pain · Chronic opioid therapy · Opioid use disorder · United Kingdom

Impacts on practice

- Triangulation of currently available data from multiple sources confirms that opioid crisis is deepening in the United Kingdom which needs urgent policy and practice focus on patient pathways to opioid misuse.
- Clinical guidelines and innovative service models that can enable person-centred management of chronic pain, medicines optimisation, and early diagnosis and treatment of opioid use disorder are needed.
- There is a need for better linkage of data across sectors to enable epidemiological surveillance and monitoring of prescribed and illicit opioids use.

Introduction

The term 'opioid epidemic' specifically refers to increased deaths and hospitalisations due to prescribed and illicit opioids and their analogues. The opioid epidemic in the United States (US), [1] has led to calls internationally regarding rational prescribing and use of prescribed opioids as well as the need to address the misuse of illicit opioids (for instance, heroin and opium) and diverted pharmaceutical opioids (such as buprenorphine, methadone, and morphine). The aim of this paper is to critically discuss current practice and research regarding the extent of prescribed opioid use, particularly in the context of chronic non-malignant pain (CNMP) management, and identify how rising opioid (both prescribed and illicit use) related morbidity and mortality can be addressed.

Chronic opioid therapy (COT) in the management of CNMP

COT defined as the use of opioids on most days for more than three months, remains the mainstay of CNMP [2]. CNMP is a condition where patients persistently or recurrently experience pain for at least three months [3]. CNMP affects 20% of adults worldwide. In the United Kingdom (UK), studies suggest that up to half of the population (about 28 million adults) may be living with CNMP [4]. There is, however, a lack of evidence of improved patient outcomes in relation to the use of COT in CNMP. A recent randomised clinical trial has shown adverse effects and notably worse pain intensity in opioid users compared to non-opioid users, with no difference in pain interference [5]. Evidence also suggests that discontinuing COT in CNMP does not

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2 The systematic review paper

European Journal of Clinical Pharmacology
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REVIEW

Interventions to optimize prescribed medicines and reduce their misuse in chronic non-malignant pain: a systematic review

Aziza Alenezi[1] · Asma Yahyouche[1] · Vibhu Paudyal[1]

Received: 20 March 2020 / Accepted: 15 October 2020
© The Author(s) 2020

Abstract

Purpose Sub-optimal opioid prescribing and use is viewed as a major contributor to the growing opioid crisis. This study aims to systematically review the nature, process and outcomes of interventions to optimize prescribed medicines and reduce their misuse in chronic non-malignant pain (CNMP) with a particular focus on minimizing misuse of opiates.

Methods A systematic review of literature was undertaken. Search of literature using Medline, EMBASE and CINAHL databases from 2000 onwards was conducted. Screening and selection, data extraction and risk of bias assessments were undertaken by two independent reviewers. Narrative synthesis of the data was conducted.

Results A total of 21 studies were included in the review, of which three were RCTs. Interventions included clinical (e.g. urine drug testing, opioid treatment contract, pill count), behavioural (e.g. electrical diaries about craving), cognitive behavioural treatment and/or educational interventions for patients and healthcare providers delivered as a single or as a multi-component intervention. Medication optimization outcomes included aspects of misuse, abuse, aberrant drug behaviour, adherence and non-adherence. Although all evaluations showed improvement in medication optimization outcomes, multi-component interventions were more likely to consider and to have shown improvement in clinical outcomes such as pain intensity, quality of life, psychological states and functional improvement compared to single-component interventions.

Conclusions A well-structured CNMP management programme to promote medicines optimization should include multi-component interventions delivered by a multidisciplinary team of healthcare professionals and target both healthcare professionals and patients. There was heterogeneity in definitions applied and interventions evaluated. There is a need for the development of clear and consistent terminology and measurement criteria to facilitate better comparisons of research evidence.

Keywords Chronic non-malignant pain · Chronic pain · Medication optimization · Opioid use

Introduction

Chronic non-malignant pain (CNMP) is defined by the International Association for the Study of Pain as persistent pain regardless of normal tissue healing, for 3 months or more [1]. CNMP is a complex and variable interplay between biological, psychological and social factors. It is categorized by the World Health Organization (WHO) as a chronic disease because, it may last a lifetime, can lead to functional impairment, is irreversible and requires patient rehabilitation, frequent medical care and supervision [1]. CNMP prevalence estimates greatly vary, ranging from 8% to 60% in the general population [2, 3]. Adverse clinical, humanistic and economic consequences for patients, families and society have been reported [4].

Medication optimization is defined 'as a person-centred approach to safe and effective medication usage and to guarantee that patients get the optimal outcomes from their medications' [5]. Analgesics including opioids are cornerstone in CNMP treatment. Optimizing medicines use in CNMP includes preventing and mitigating 'problematic behaviour' in relation to the use of opioids and gabapentinoids in addition to

A protocol developed as per the PRISMA-P guideline is registered under PROSPERO ID=CRD42018111569.

Supplementary Information The online version of this article (https://doi.org/10.1007/s00228-020-03026-4) contains supplementary material, which is available to authorized users.

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promoting adherence to the prescribed regimen [5]. 'Problematic behaviour' is aberrant behaviour suggestive of addiction, misuse or abuse of prescribed opioids for use or administration other than intended by the prescriber and is commonly reported among CNMP patients [6]. A previous literature review demonstrates that up to 50% of CNMP patients are known to demonstrate problematic behaviours [6].

Healthcare professionals face the problem of effectively treating CNMP while preventing inappropriate medications use and as well as promoting appropriate prescribing and deprescribing. Therefore, clinicians need strategies and assessment tools to help them weigh the risks and benefits of CNMP treatment. Previous systematic reviews have looked at interventions to prevent or reduce opioids misuse [7, 8]. The concept of medicines optimization as a whole has not been investigated. The aim of this study was to systematically review the nature, process and outcomes of interventions used to optimize prescribed medicines use and reduce their misuse in CNMP patients.

Methods

This study was conducted based on the Cochrane Guideline and reported as per Preferred Reporting Items for Systematic Review and Meta-analysis (Electronic supplement 1) [4]. Systematic reviews are protocol driven reviews based on priori objectives and plans for literature search, data collection and analyses. Structured approach to identifying, appraising, and synthesizing all relevant studies on a given topic enables researchers to avoid bias in the review process [9]. The protocol was developed as per the PRISMA-P (PRISMA-Protocol) guideline (registered PROSPERO ID = CRD42018111569).

Literature search

Electronic searches were conducted in Medline, EMBASE and CINAHL databases using medical subject headings (MeSH) and free text keyword, including medication adherence, patient compliance, adherent, adherence, non-compliant, noncompliance, non-adherent, non-adherence, chronic pain, chronic non-malignant pain and chronic non-cancer pain. The search was limited to 2000 onwards.

Inclusion and exclusion criteria

Studies in the English language using an intervention aimed at optimizing the appropriate usage of prescribed pain medication among adults with CNMP using pain medication for 3 months or more were included. The following concepts were included in medicines optimization: medication adherence, drug misuse, patient compliance to prescribed treatment, including deviation and misuse, adherence/ non-adherence, compliance/non-compliance or safe and effective use of medicines. Studies eligible for inclusion included randomized controlled trials (RCTs), nonrandomized and quasi experimental studies, case-control, cohort and cross-sectional studies published in the English language. Eligible participants were 18+ years with CNMP. Studies involving participants from care homes, residential homes or hospices were excluded as these patients were assumed not to be self-administering their medicines. Both medicines optimization outcomes such as misuse of opioid and clinical outcomes such as pain score, depression and anxiety scale and functional interference were considered.

Screening and selection

Two independent investigators (AA and VP) screened the study abstracts according to the inclusion and exclusion criteria. Any conflicts arising regarding the selection were resolved by a third investigator (AY), by discussion or by obtaining the study's full text.

Data extraction and quality assessment

A data extraction form was developed. Data on study characteristics, intervention types and outcome measures were extracted. The two authors independently extracted the data and any disagreement was resolved through discussion or by a third reviewer. For studies utilizing RCT designs, the risk of bias was assessed using the outline criteria of the Cochrane Handbook for Systematic Reviews of Interventions [9]. The critical appraisal skills programme (CASP) was used for the quality assessment for the rest of the studies.

Two authors (AA and VP) independently performed the assessment, any disagreements were resolved through discussion with a third author (AY). Narrative synthesis of the data was conducted because the studies were heterogeneity in definitions, types of interventions, and measurements and reporting methods such as meta-analysis should be conducted when included studies are sufficiently homogeneous in participants involved, interventions, terminology and outcomes to provide a precise summary [10].

Results

From 952 records initially identified, 21 studies met the inclusion criteria (Fig. 1). The reasons for study exclusion are detailed in the Supplementary Material. Of the 21 included studies, three were RCTs and 18 were observational designs.

3 The community pharmacists' study

International Journal of Clinical Pharmacy
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RESEARCH ARTICLE

Roles, barriers and behavioral determinants related to community pharmacists' involvement in optimizing opioid therapy for chronic pain: a qualitative study

Aziza Alenezi[1] · Asma Yahyouche[1] · Vibhu Paudyal[1]

Received: 30 March 2021 / Accepted: 15 September 2021
© The Author(s) 2021

Abstract
Background Opioid are currently widely used to manage chronic non-malignant pain (CNMP), but there is a growing concern about harm resulting from opioid misuse and the need for medicine optimization, in which pharmacists could potentially play a key role. *Objective* This study explored pharmacists' roles, barriers and determinants related to their involvement in optimizing prescribed opioids for patients with chronic pain. *Setting* Community pharmacies in the United Kingdom. *Method* Semi-structured interviews based on the Theoretical Domains Framework were conducted between January and May 2020 with 20 community pharmacists recruited through professional networks. Data were analysed thematically. *Main outcome measure:* Pharmacists' perceived roles, barriers and behavioural determinants in relation to opioid therapy optimization. *Result* Pharmacists demonstrated desire to contribute to opioid therapy optimization. However, they described that they were often challenged by the lack of relevant knowledge, skills and training, inadequate time and resources, systemic constraints (such as lack of access to medical records and information about diagnosis), and other barriers including relationships with doctors and patients. *Conclusion* The contribution of community pharmacists to optimize opioid therapy in CNMP is unclear and impeded by lack of appropriate training and systemic constraints. There is a need to develop innovative practice models by addressing the barriers identified in this study to enhance the contribution of community pharmacists in optimization of opioid therapy for chronic pain.

Keywords Chronic pain · Community pharmacists · Medicine optimization · Opioid · Qualitative · Theoretical domains framework

Impacts on practice

- Pharmacists are keen to contribute to opioid optimization by educating patients, managing their expectations, monitoring and referring problems, as part of a patient-centred approach.
- Constraints impeding community pharmacists' potential role in prescribed opioid optimization such as lack of training, and system-related barriers should be addressed.

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Published online: 02 October 2021

Introduction

Chronic pain is defined as pain that persists for more than three months [1]. The World Health Organization (WHO) data suggest that the prevalence of chronic pain is 22% of the world population [2] and in the UK 46% of the population suffer from chronic non-malignant pain (CNMP) [3]. The concerns about prescribed opioid and chronic opioid therapy (COT) effectiveness, safety, and abuse in CNMP have grown, especially with the alarming death rate related to medical and illicit use of opioid in North America [4]. The extent of the increased opioid use, including misuse, remains less debated in the UK. Yet, UK based studies indicate an upward trend in the use of prescribed opioid in the National Health Services (NHS) parallel to that in the US [5].

Medicine optimization, which means ensuring safe, effective, and efficient medicine use, is becoming a key priority in the UK's NHS to manage long-term conditions

4.

Patient study

From: [redacted]
Sent: 10 April 2022 23:45
To: Aziza Alenezi (PhD Pharmacy FT Non-Lab (B230))
Subject: Dove Medical Press: Submission accepted for publication

Dear Mrs Alenezi,

I am pleased to inform you that the submission, "Patient Perspectives on the Appropriate Use of Prescribed Opioids in Chronic Non-Malignant Pain: Analysis of Online Forums Using Theoretical Domains Framework", has been accepted for publication in "Journal of Pain Research". The article publishing charge is now payable before the paper can be progressed any further and an invoice is accessible here: https://www.dovepress.com/invoice.php?i_key=vAgxDK1TBcdVhbfRG8Pzm05y58579
(If you require any amendments to your invoice please reply to this email. Please note invoices cannot be amended once a payment has been made)

The above acceptance for publication is conditional upon the required copyright permissions being obtained, if applicable.

5 The clinicians' study submission

Dear Dr. Yahyouche,

Your submission entitled "ORIGINAL RESEARCH
Roles, barriers and behavioural determinants related to pain healthcare providers' involvement in optimising opioid therapy for chronic pain: a qualitative study" has been received by journal European Journal of Pain

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author. The URL is https://www.editorialmanager.com/eurjpain/.

Your manuscript will be given a reference number once an Editor has been assigned.

Thank you for submitting your work to this journal.

Kind regards,

Dr. Bettina Haake-Weber
Editorial Assistant
European Journal of Pain

Please be aware that if you ask to have your user record removed, we will retain your name in the records concerning manuscripts for which yo were an author, reviewer, or editor.

Appendix 2

Interview Protocol Worksheets

Community pharmacists interview schedules

neral Information				
ite the participant ID in the audio recording before starting.				
e	□ (25-35)	□ (36-45)	□ (46-60)	□ Other
nder	□ Male	□ Female		
ecialty and role				
cation				
perience, years	□0–5	□5.1–10	□10.1–15	□15.1–20	20+

General statement: *I think you are aware of the increased of prescription opioid inappropriate prescribing, misuse and abuse. I am interested to find out how you, as a community pharmacist, view this situation, how you see your role in relation to dispensing and monitoring of these medications, and the factors you think influence what you do in this regard.*

What are your general thoughts about dispensing opioid prescriptions?

Prompt: How can pharmacists contribute in recognizing the various forms of opioid toxicity and in preventing inappropriate prescribing and diversion of opioids?

What does chronic opioid therapy optimisation mean to you?

Prompt: - How can the role of community pharmacists in the prevention, surveillance, and treatment of opioids misuse/ opioid use disorders be leveraged?

What are the knowledge barriers to optimising chronic opioid therapy for chronic pain?

Prompt: - What training have you had in how to appropriately review opioid prescription and identify opioid-related abuse and misuse?

How often do you encounter patients with what you perceive to be inappropriate chronic opioid therapy?

Prompt: - How common do you think prescribed opioids misuse and abuse in the UK?

When considering filling a prescription for a controlled substance, how do you evaluate patient risk for misuse?

Prompt: - What reasons might prompt you to decide to carefully assess opioid-related abuse and misuse and review an opioid prescription?

Is there anything that could help you and your colleagues to focus om performing a careful review of opioid prescription / identify problematic medication behaviour? (e.g. organisational or workflow procedures)

Prompt: - What specific guidelines or policies does your pharmacy have on when to hold an opioid prescription or when you need to call a clinician?

What are the obstacles that prevent you from being more involved in opioid optimising for CNMP?

Prompt: - Tell me about your communication with providers regarding opioid prescription. When you need to contact the provider, are they accessible? What you do if you cannot reach the prescriber?

How confident are you when dispensing high dose opioids?

Prompt: - How optimistic are you, that the use of e-prescription or prescription monitoring program will reduce inappropriate us of opioids?

What do you think of evaluating the patient's expectation of using Chronic Opioid Therapy before initiating the therapy?

Prompt: - What do you think of educating patients to accept that chronic pain is an ongoing condition that needs to be managed, rather than an acute issue that can be treated and "cured"?

Prompt: - How can we educate patients who are already depending on opioids to relieve their chronic pain?

Do you intend to review each opioid prescription and assess misuse use and abuse? Why do you feel this way?

Prompt: - Ideally, would you like to review them?

Do you think optimising chronic opioid therapy is a personal goal or an institutional goal?

Prompt: - What factors may interfere with the goal?

Do you see careful assessment misuse and abuse behaviour as part of your job?

Prompt: - Who else's role is it?

What do you think should be done to make the situation better?

Prompt: - What are your suggestions for an intervention that might mitigate inappropriate opioid use among CNMP patients?

Sponsor: University of Birmingham

Interview Protocol Worksheet Healthcare Professionals

Research title: Barriers and enablers to the prescribing and use of opioids in patients with chronic non-malignant pain.

Introduction

Thank you for coming today.

Informed consent

PAUSE: Ask if participant has any questions or concerns about:

Confirm permission to record the session.

Before starting the interview make sure to highlight that:

All ideas are equally valid

There are no right or wrong answers—we are interested in your experiences

Everyone's views should be heard and respected

ONE MORE TIME any questions or concerns?

General Information					
Write the participant ID in the audio recording before starting.					
Age	□ (25-35)	□ (36-45)	□ (46-60)	□ Other	
Gender	□ Male	□ Female			
Speciality and role					
Experience, years: / /					
Time at a hospital, years:	□0–5	□5.1–10	□10.1–15	□15.1–20	20+

Healthcare providers' questions

General question:

How was your day at work today?

What types of chronic pain are most common among your patients? Most challenging to treat?

What are the biggest barriers and challenges in working with your pain patients?

What types of opioids are most prescribed for chronic patients?

What are the biggest barriers and challenges in prescribing these or tapering these medications?

Please could you briefly describe your experience, attitude, and belief about prescribing COT, and could you describe the patients who are using it?

What approach do you take when working with your most challenging chronic opioid therapy patients?

Overall, are there factors that would lead you to NOT recommend or prescribe, taper chronic opioid therapy for a patient?

Do you think you can judge who/when should start the chronic opioid therapy and who is not? How?

How do you think that explaining the risk of opioids will affect patients with severe pain when using opioids?

Can you describe a set of behaviours that you distinguish between CNMP patients who are using chronic opioid therapy compared to chronic pain patients who are not using or refuse to use chronic opioids therapy?

What measures prevent the problematic taking of medication behaviours and the side effects of opioids?

How is the patient involved in the decision of starting /tapering opioids?

Is there anything that could help you and your colleagues to focus on appropriate opioid prescribing and appropriate assessment of the risk of problematic opioid use/cessation?

How does patient satisfaction in your relationship with patients affect the way that you prescribe, deprescribe opioids or assess patients?

Do you think that there is somebody in the team who expects you to follow the guidelines or risk assessments? Who are they? Prob [How important are their expectations to you?

Is optimum opioid use among CNMP patients one of your primary goals?

Are there external incentives in place to encourage you to try to optimise chronic opioid therapy for chronic pain?

How do you think the chronic opioid therapy and chronic pain could be improved in the future?

is there anything else you would like to add?

Close-up

Thank you for coming today

Sponsor: University of Birmingham

Interview Protocol Worksheet patients

Research title: Optimising medication use in chronic non-malignant pain (CNMP) patients, Healthcare professionals and patients' perspectives of barriers and enablers to the appropriate use of prescribed long-term opioids in CNMP patients' management using Theoretical Domain Framework.

Introduction

Thank you for coming today

Informed consent

PAUSE: Ask if the participant has any questions or concerns about:

Before starting the interview, make sure to highlight that:

All ideas are equally valid

There are no right or wrong answers—we are interested in your experiences

Everyone's views should be heard and respected

General Information				
Registered the participant code on the audio recording				
Age	□ (25-35)	□ (36-45)	□ (46-60)	□ Other
Gender	□ Male	□ Female		
Pain type :				
Medication name and dose:				
How long you have been using opioids				
Pain intensity:				

ONE MORE TIME any questions or concerns?

May you please tell us how and why started using opioids to control pain?
Can you remember the first time that you used opioids either prescribed or OTC? (early exposure to opioids)?

Patients' interview guide

Can you tell me about your day?

Can you tell me the name of the medication that you are taking for pain?

Tell me about your experiences of dealing with chronic pain

What is it like to be a patient taking long-term opioids for chronic non-malignant pain?

What problems have you encountered?

How well is your pain controlled using chronic opioid therapy?

What is the worst thing about having chronic pain and chronic opioid therpay ?

What social barriers do chronic pain patients using chronic opioid therapy encounter from employers and colleagues in the workplace?

Are there any unique challenges from using these medications?

How do you describe yourself/life before and after using opioids to manage your pain?

What are advantages of using these medications compared to other medications or other interventions such as physiotherapy? What are the disadvantages?

What can chronic pain patients do to help themselves (reduce pain intensity and use less analgesic), that no one else can do for them?

What effect do people around you have on your pain management or using opioids?

Can you tell me what barriers you encounter when you get your medication from the pharmacy?

Please could you tell us how and why you started using opioids to control pain?

As a chronic pain patient using chronic opioid therapy, can you tell me how your healthcare providers or the NHS system can play a better role in improving your experience?

Finally, is there anything else you would like to add?

Appendix 3

Participant information sheet



Sponsor: University of Birmingham

Participant information sheet for Community pharmacists.

Title of study: Community pharmacists' perspectives of the barriers and enablers of their role to optimise chronic opioids therapy for chronic non-malignant pain patients

Why am I being given this form?

You are being asked to participate in this research study because you are a community pharmacist. We would like to know your perspectives of the barriers and enablers of your role as community pharmacists to optimise chronic opioids therapy for chronic non-malignant pain patients.

Why is this study being done?
This study aims to explore the Community pharmacists' perspectives of the barriers and enablers of their role to optimise chronic opioids therapy for chronic non-malignant pain patients. The findings of this study could inform other studies to develop an intervention to improve appropriate opioid use for CNMP. This study will recruit community pharmacists who are willing to be contacted by the research team.

Who is funding the study?
The study is funded by the Royal Embassy of Saudi Arabia Cultural Bureau in London for a PhD student (Researcher).

How is the study designed?
This study is looking at community pharmacists' beliefs and experiences of the barriers and enablers of their role to optimise chronic opioid therapy for chronic non-malignant pain. Community pharmacists' will be interviewed individually.

What is expected of me?
You will be asked to participate in a single face to face or by phone interview at your pharmacy or at University of Birmingham. The interview will be conducted face to face or by phone at a time that is convenient to you. The interview will last about 45-60 minutes, the interview will be recorded using password secure recorder and transcribed to help the researchers record your thoughts correctly. In the interview, you

will be asked about your knowledge and beliefs about barriers and enablers for appropriate opioids prescribing for CNMP.

How long will I be involved in the study?
The entire study will last approximately 3-6 months. Your participation in the study will consist of a single interview which will take about 45-60 minutes.

What are the potential risks I may experience?
There are no known risks to you as a participant. The interview will be confidential, but there are limits to confidentiality. For example, if you were to tell me something new that could put someone at risk of harm, or unsafe practice, I may have to inform a relevant person. If this happened, I would discuss this with you, and tell you what I was going to do.

Can I expect to benefit from participating in this research study?
You may not receive any direct benefit from taking part in this study. Your participation in this research will help to understand pharmacists' perspective and may underscore a need for interventions to mitigate the issue. This study also aim to inform the development of an intervention that will be used to optimise long term opioids use in CNMP management.

.

Do I have to participate? What alternatives do I have? If I agree now, can I change my mind and withdraw later?

Your participation in this study is voluntary and you are free to withdraw 14 days after the interview without giving any reason. If you choose to withdraw, the audio recorded interview and all other relevant study documents will be destroyed.

Will I be paid for my participation or will there be any additional costs to me?
Unfortunately, we will not be able to reimburse participants for their time or any additional costs incurred.

How is my personal information being protected?
All investigators will comply with the requirements of the General Data Protection Regulation (GDPR) and the Data Protection Act 2018 with regards to collection, storage, processing and disclosure of personal information and uphold the Act's core principles. All personal identifiable data (signed consent form) will be securely held in the Birmingham Treatment Centre. The audio recorded interview be will identified only using the study ID. The link between your study ID and indefinable data will be stored securely and separate from your study records at University of Birmingham. The audio recorded interview will be analysed on encrypted laptop or University of Birmingham hard drives. Only the research team will have access to details and coding. The audio recorded interview and data collected during the study may be looked at by the

researchers and representative from the University of Birmingham (sponsor), from regulatory authorities. Study documentation and data will be archived for 10 years after completion of the study at the University of Birmingham. If the regulatory authorities make inquires, then study records will be provided to them, while maintaining participant confidentiality.

How can I know what is the study outcome?
The full study report including anonymised quotations will be made publicly available in the research thesis, which is due for submission at the end of the study, or published articles.

Questions about the Study
If you have any questions about this study, please contact the research team as follows:

Chief investigator: Dr Asma Yahyouche. **E-mail**: [redacted] **Tel:** [redacted]
Chief investigator: Dr Vibhu Paudyal E-mail: [redacted] **Tel:** [redacted]
Researcher: Aziza Alenezi E-mail: [redacted]
For any complaint: Birgit Whitman, the University's Head of Research Integrity and Governance, who is an independent point of contact for participants/parents/legal guardians:

E-mail: researchgovernance@contacts.bham.ac.uk Phone: 0121 415 8011

Sponsor: University of Birmingham

Participant Information Sheet- patient

Title of study: Barriers and enablers to the prescribing and use of opioids in patients with chronic non-malignant pain.

Invitation

We would like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. I would advise you to tale at least 24 hours to read though this information sheet and discuss this other if you wish. If there is anything that is not clear, or if you would like more information, please contact us using the research team contact details at the end of this sheet.

Your opinion is very important to us.

Why am I being given this form?

We are interested to speak to anyone who are currently using or in the past have used painkillers called “opioids” such as Tramadol, Morphine and Oxycodone for more than three months to manage chronic pain. We would like to know, what is it like to be a patient taking opioids for long time to manage chronic pain?

What is the purpose of this research?

This research is being undertaken as part of a PhD study by Aziza Alenezi. The study aims to understand barriers to managing chronic pain through the use of opioids. We aim to interview 20 patients and 20 healthcare professionals.

Who is funding and organising the research?

This research is conducted as part of a doctoral degree for Aziza Alenezi whose PhD studentship is funded by the Saudi Royal Embassy; however, the funder is solely

funding the student and has no involvement in the study or conflict of interests with the study outcomes. The study is organised by the University of Birmingham (UoB).

Do I have to take part?

It is entirely up to you to decide whether or not you participate. If you change your mind and do not wish to participate, you can withdraw from the study at any time, and you do not have to give us any reason. We will destroy all data, recording and your consent forms.If you would like to join the study, to ask questions or to tell us you have changed your mind, please contact us using the research team contact details at the end of this sheet.

If I want to take part what do I need to do?

If you would like to take part, please contact the researcher (Aziza)who will talk to you about the study and answer your queries. If you are still happy to take part you will be asked to sign the consent form and complete the questionnaire . The questionnaire will take between 10 to 20 minutes to complete and includes questions on how you are using your pain management opioid medication. You will be provided with a pre-paid envelope to return your signed consent form and completed questionnaire to us. Please remember to keep a copy of the consent form for yourself.

With your consent you will also be asked to take part in an interview, this will be arranged by the research team and is explained further in the next section.

What does participation in this research involve?

Your participation in the study will consist of a single interview at a time that is convenient for you, either face to face at Birmingham Treatment Centre, via phone or online (Zoom). The interview will last about 20-35 minutes and will be audio recorded using a password-protected recorder and transcribed to help the researchers record your thoughts correctly. The interview will be like a conversation. You will be asked to talk about your experience and perspective as chronic pain patients who are using chronic opioid therapy to control their pain.

The interview will be strictly confidential. However, if during or after the interview, you share information that indicates you may be at risk of harm to yourself or others, then for your safety, confidentiality may have to be broken and I may have to tell someone in your care team, so help can be given.

What are the potential risks I may experience?

The topics of using opioids to manage chronic pain might be sensitive to talk about and could bring back negative thoughts or feelings and it is possible that it could be upsetting for you. You can request to stop the interview at any time. You are welcome to take a break or stop your participation if you wish to, without giving us any reason. If your feelings of distress persist, we recommend that you visit your GP or other healthcare worker of usual contact.

Can I expect to benefit from participating in this research study?

There might be no immediate or direct benefits to you. This research will help us understand how we can improve care of patients with chronic pain, and we hope that healthcare providers will use our findings when treating future patients.

Will I be paid for my participation or will there be any additional costs to me?

You will be given a £10 voucher for taking the time to participate in the study. You will be paid the cost of day rider bus pass ticket if you come for face to face interview to Birmingham Treatment Centre or the University of Birmingham to take part in the research.

How is my personal information being protected?

All investigators will comply with the requirements of the General Data Protection Regulation (GDPR) and the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and uphold the Act's core principles. All personal identifiable data (signed consent form) will be securely held in the University of Birmingham and will remain strictly confidential. Your name and other identifying details will not appear on any report or publication which arises from this research. Any quotation from your interview any demographic data that could identify you, we will assign you a study ID (for example QW4) to keep you unidentifiable. The audio recorded interview will be identified only using the study ID. The link between your study ID and indefinable data will be stored securely and separate from your study records in a locked cabinet at a locked room in the University of Birmingham. The audio recorded interview will be anonymised, transcribed and analysed on an encrypted laptop or UoB hard drive. Only the research team will have access to your personal information and interview details.

Audio-recordings and anonymised transcripts will be securely stored at UoB for the duration of the study. Your information including the consent form, audio-recorded interview and data collected during the study may be looked at by the researchers and representatives from UoB (sponsor), from regulatory authorities or the NHS trust. This is to check that the research is being conducted properly. Study documentation and data will be archived for 10 years after completion of the study at UoB. At the end of this period, all the study documents, including the interview recordings, will be destroyed.

In case you withdraw from the study within 14 days of the interview, your research data will be destroyed, and subsequently, your data will not be included in any publications. In case a transcript was submitted for publication, and you decided to withdraw from the study, we can destroy all your documents and your personal data will be destroyed as appropriate.

If you choose the phone interview option, your contact details will be stored as paper-based documents, separately from other study documents. They will be kept in a locked cabinet in the researcher's office and will be destroyed immediately after your interview.

How will we use information about you?

We will need to use information from you and your medical records for this research project. This information includes:

- Your name and contact details
- Information about how long you have been using opioids for pain management from your medical records as accessed by your care team only.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

What are your choices about how your information is used?

In case you withdraw from the study within 14 days of the interview, your research data will be destroyed, and subsequently, your data will not be included in any publications.

If you withdraw after 14 days your data collected up to that point may already be submitted for publication and it won't be possible to withdraw the anonymised transcript, we can destroy all data collected on paper and your personal data will be destroyed as appropriate.

We need to manage your records in specific ways for the results to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information;

- At www.hra.nhs.uk/information-about-patients
- By asking a member of the research team
- By contacting the University of Birmingham's Data Protection Officer via dataprotection@contacts.bham.ac.uk
- By contacting the sponsor representative Dr Birgit Whitman via researchgovernance@contacts.bham.ac.uk or telephone 01214158011.

Who has sponsored and insured this study?

This study is sponsored by the University of Birmingham. The University has in force a Public Liability Policy and/or Clinical Trials policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage.

The NHS indemnity scheme will cover potential legal liability arising from the conduct of the research as this will be conducted at Birmingham Treatment Centre.

Who has approved the study?

The study's protocol has been reviewed and approved by xxx the NHS Research Ethics Committee

How can I know what is the study outcome?

The full study report, including anonymised quotations, will be made publicly available in the research thesis, which is due for submission at the end of the study or published articles. You will not be identified in any report or publication, but we may wish to use your anonymised quotations.

If you feel you would like to be involved in our study, please contact

Researcher: Mrs Aziza Alenezi E-mail: [redacted] Mobile:

Chief investigator: Dr Asma Yahyouche E-mail: [redacted] Tel: [redacted]

Chief investigator: Dr Vibhu Paudyal E-mail: [redacted] Tel: [redacted]

For any complaint:

Birgit Whitman, the University's Head of Research Integrity and Governance, who is an independent point of contact for participants/parents/legal guardians: E-mail: researchgovernance@contacts.bham.ac.uk Phone: 0121 415 8011

OR Sandwell and West Birmingham Hospitals NHS Trust PALS (Patient advice and liaison service), Phone: 0121 507 6440 or, 0121 507 4080 or 0121 507 5892, 10 am – 4 pm, Monday – Friday. Email: swbh.complaints@nhs.net.

If you want to complain about how researchers have handled your information you should contact the research team. If you are not happy after that, you can contact the Data Protection Officer on dataprotection@contacts.bham.ac.uk

If you are not happy with their response or believe they are processing your data in a way that is not right or lawful, you can complain to the Information Commissioner's Office (ICO) via their website www.ico.org.uk or telephone 0303 123 1113.

Sponsor: University of Birmingham

Participant information sheet for healthcare provider

Title of study: Barriers and enablers to the prescribing and use of opioids in patients with chronic non-malignant pain.

Invitation

We would like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. I would advise you to tale at least 24 hours to read though this information sheet and discuss this with others if you wish. If there is anything that is not clear, or if you would like more information, please contact us using the research team contact details at the end of this sheet. Your opinion is very important to us.

Why am I being given this form?

You are being asked to participate in this research study because you are a healthcare professional with current experience of prescribing, treating or managing patients who are using long term opioids to manage their pain. We would like to know your views, knowledge and beliefs about what can help you to assess if you are appropriately prescribing or monitoring chronic opioid therapy for chronic non-malignant pain (CNMP) patients, whether or not you assess their suitability for chronic opioid therapy and if so, how you do it.

What is the purpose of this research?

This study aims to explore what helps or prevents you in appropriate opioids prescribing for chronic non-malignant pain (CNMP) patients, and how healthcare providers decide to initiate or maintain chronic opioid therapy and how they identify and monitor patients' aberrant medication-related behaviours throughout treatment.

The findings of this study will help healthcare providers to have a better understanding and improve the practice of chronic opioid therapy prescribing and monitoring its use for CNMP. We aim to interview 20 patients and 20 healthcare professionals.

Who is funding and organising the research?

This research is conducted as part of a doctoral degree for Aziza Alenezi whose PhD studentship is funded by the Saudi Royal Embassy; however, the funder is solely funding the student and has no involvement in the study or conflict of interests with the study outcomes. The study is organised by the University of Birmingham (UoB).

Do I have to take part?

It is entirely up to you to decide whether or not you participate. If you change your mind and do not wish to participate, you can withdraw from the study at any time, and you do not have to give us any reason. We will destroy all data, recording and your consent forms.If you would like to join the study, to ask questions or to tell us you have changed your mind, please contact us using the research team contact details at the end of this sheet.

What does participation in this research involve?

Your participation in the study will consist of a single interview at a time that is convenient for you, either face to face at Birmingham Treatment Centre or via phone. The interview will last about 30-45 minutes and will be audio recorded using a password-protected recorder and transcribed to help the researchers record your thoughts correctly. The interview will be like a conversation. You will be asked to talk about your experience and perspective as a healthcare provider who encounters patients with chronic pain patients who are using chronic opioid therapy to control their pain.

The interview will be strictly confidential. However, if you disclose information about any person being at risk of harm or of any unprofessional practice (e.g. prescription of an inappropriate treatment) confidentiality may have to be broken.

What are the potential risks I may experience?

There is a minimal risk of harm as a result of participation in this study. We consider the greatest disadvantage for you to be the time you invest in our study. The interview will take up to 45 mins of your time. If you have any concerns about the study or

anything is unclear in this leaflet, please discuss any concerns with a member of the research team in the first instance.

Can I expect to benefit from participating in this research study?

You may not receive any direct benefit from taking part in this study. By taking part, you will be providing valuable insight into your experience as a chronic pain healthcare provider which will help us reach a better understanding of healthcare providers' knowledge and beliefs about barriers and enablers for appropriate opioid prescribing. This might us help to improve future practice by formulating a plan to decide on the best strategies to improve opioid use for CNMP. Also, £2000 will be paid to the clinic as a grant.

Will I be paid for my participation or will there be any additional costs to me?

Unfortunately, we will not be able to reimburse participants for their time or any additional costs incurred.

How is my personal information being protected?

All investigators will comply with the requirements of the General Data Protection Regulation (GDPR) and the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and uphold the Act's core principles. All personal identifiable data (signed consent form) will be securely held in the University of Birmingham and will remain strictly confidential. Your name and other identifying details will not appear on any report or publication which arises from this research. Any quotation from your interview any demographic data that could identify you, we will assign you a study ID (for example nurse 1A, Dr QW4) to keep you unidentifiable. The audio recorded interview will be identified only using the study ID. The link between your study ID and indefinable data will be stored securely and separate from your study records in a locked cabinet at a locked room in the University of Birmingham. The audio recorded interview will be anonymised, transcribed and analysed on an encrypted laptop or UoB hard drive. Only the research team will have access to your personal information and interview details.

Audio-recordings and anonymised transcripts will be securely stored at UoB for the duration of the study. Your information including the consent form, audio-recorded interview and data collected during the study may be looked at by the researchers and

representatives from UoB (sponsor), from regulatory authorities or the NHS trust. This is to check that the research is being conducted properly. Study documentation and data will be archived for 10 years after completion of the study at UoB. At the end of this period, all the study documents, including the interview recordings, will be destroyed.

If you choose the phone interview option, your contact details will be stored as paper-based documents, separately from other study documents. They will be kept in a locked cabinet in the researcher's office and will be destroyed immediately after your interview.

How will we use information about you?

We will need to use information from you and your medical records for this research project. This information includes:

Your name and contact details
People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

What are your choices about how your information is used?

In case you withdraw from the study within 14 days of the interview, your research data will be destroyed, and subsequently, your data will not be included in any publications. If you withdraw after 14 days your data collected up to that point may already be submitted for publication and it won't be possible to withdraw the anonymised transcript, we can destroy all data collected on paper and your personal data will be destroyed as appropriate.

We need to manage your records in specific ways for the results to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Who has sponsored and insured this study?
This study is sponsored by the University of Birmingham. The University has in force a Public Liability Policy and/or Clinical Trials policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage.

The NHS indemnity scheme will cover potential legal liability arising from the conduct of the research as this will be conducted at Birmingham Treatment Centre.

Who has approved the study?

The study's protocol has been reviewed and approved by the NHS Research Ethics Committee

How can I know what is the study outcome?

The full study report, including anonymised quotations, will be made publicly available in the research thesis, which is due for submission at the end of the study or published articles. You will not be identified in any report or publication, but we may wish to use your anonymised quotations.

If you feel you would like to be involved in our study, please contact

Researcher: Mrs Aziza Alenezi E-mail: [redacted] Mobile:

Chief investigator: Dr Asma Yahyouche E-mail: [redacted] Tel: [redacted]

Co-Chief investigator: Dr Vibhu Paudyal E-mail: [redacted] Tel: [redacted]

For any complaint:

Birgit Whitman, the University's Head of Research Integrity and Governance, as the sponsor's independent point of contact: E-mail: researchgovernance@contacts.bham.ac.uk Phone: 0121 415 8011

OR Sandwell and West Birmingham Hospitals NHS Trust PALS (Patient advice and liaison service), Phone: 0121 507 6440 or, 0121 507 4080 or 0121 507 5892, 10 am – 4 pm, Monday – Friday. Email: swbh.complaints@nhs.net.

If you want to complain about how researchers have handled your information you should contact the research team. If you are not happy after that, you can contact the Data Protection Officer on dataprotection@contacts.bham.ac.uk

If you are not happy with their response or believe they are processing your data in a way that is not right or lawful, you can complain to the Information Commissioner's Office (ICO) via their website www.ico.org.uk or telephone 0303 123 1113.

Appendix 4

Consent forms

UNIVERSITY OF BIRMINGHAM

Sponsor: University of Birmingham **Community pharmacists' Consent Form**

Participant name: Identification number for this study:

Name of researcher: Aziza Alenezi

Title of project: Community pharmacist's perspectives of othe barriers and enablers of their role and challenges to optimise chronic opioids therapy for chronic non-malignant pain patients: Study protocol

Note: Please read each statement carefully and initial each statement in the box provided **Initial**

I confirm that I have read and understood the Participant Information sheet for healthcare providers (version _____) (dated __/___/____) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. In this case my legal rights will not be affected in any way. If I do choose to withdraw from the study my recorded interview and all other relevant study documents will be destroyed. ☐

I understand that my consent form, audio recorded interview and data collected during the study may be looked at by the researchers and representatives from the University of Birmingham (sponsor), from regulatory authoritie. I give permission for these individuals relevant to the study to have access to my records. ☐

I understand that my data will be stored for 10 years after the study is completed. A record of my personal details will be kept on a secure at the Birmingham Treatment Centre. Pseudo-anonymised results may be stored on a University of Birmingham computer and linked by study ID to my personal details. Only the research team and representatives from the sponsor will have access to them. ☐

I give permission to use anonymised quotations from my interviews in relevant publications, and I understand that my identity will not be revealed, and such information will not be traced back to me. ☐

I agree to take part in the interview. ☐

OPTIONAL

I understand that my contact details will be securely stored at the University of Birmingham with access restricted to members of the research team. My contact details will be deleted after the interview and not used again ☐

I agree to share my contact details with the research team to contact me at my convenience to arrange a time for the interview or to interview me via phone only. ☐

I agree to conduct the interview by phone. ☐

Name of Patient	**Date**	**Signature**
Name of person taking consent	**Date**	**Signature**

UNIVERSITY OF BIRMINGHAM

Sponsor: University of Birmingham Study dentification number

Consent Form for patients

Chief Investigators: Asma Yahyouche **Name researcher**: Aziza Alenezi

Title of project: Barriers and enablers to the prescribing and use of opioids in patients with chronic non-malignant pain

In

Note: Please read each statement carefully and initial each statement in the box provided

I confirm that I have read and understood the information sheet for the above study (version _____) (dated___ __/___/____). I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. In this case, my medical care or legal rights will not be affected in any way. If I do choose to withdraw from the study, my audio-recorded interview and all other study documents will be destroyed

I agree to the audio recording of my interview.

I understand that my consent form, audio-recorded interview and data collected during the study may be looked at by the researchers and representatives from the University of Birmingham (sponsor), from regulatory authorities or the NHS trust. I give permission for these individuals relevant to the study to have access to my records.

I understand that my data will be stored for 10 years after the study is completed. A record of my personal details will be kept on a secure hospital server. Pseudonymised results may be stored on a University of Birmingham computer and linked by study ID to my personal details. Only the research team and representatives from the sponsor will have access to them.

I give permission to use anonymised quotations from my audio recorded interviews in relevant publications, and I understand that my identity will not be revealed, and such information will not be traced back to me.

I understand that I need to complete a questionnaire first to check my eligibility for the study audio recoded interview and I agree to complete the questionnaire.

I understand that if I disclose information about any person being at risk of harm or of any unprofessional practice (e.g. prescription of an inappropriate treatment) confidentiality may have to be broken.

I understand that my contact details will be securely stored at the University of Birmingham with access restricted to members of the research team. My contact details will be deleted after the interview and not used again

I agree to share my contact details with the research team so they can contact me at my convenience to arrange a time for the interview.

I agree to share my contact details with the research team so they can contact me to conduct the audio recorded interview by phone.

I agree to take part in this study.

Name of Participant	**Date**	**Signature**

Name of person taking consent	**Date**	**Signature**

Sponsor: University of Birmingham

Consent form for Healthcare professionals

Participant name: Identification number for this study:

Chief Investigators name: Asma Yahyouche **Researcher name:** Aziza Alenezi

Title of project: Barriers and enablers to the prescribing and use of opioids in patients with chronic non-malignant pain

Note: Please read each statement carefully and initial each statement in the box provided **Initial box**

I confirm that I have read and understood the Participant Information sheet for staff (version _____) (dated __/___/____) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. In this case, my legal rights will not be affected in any way. If I do choose to withdraw from the study my audio-recorded interview and all other relevant study documents will be destroyed. ☐

I understand that my consent form, audio-recorded interview and data collected during the study may be looked at by the researchers and representatives from the University of Birmingham (sponsor), from regulatory authorities or from the NHS trust. I give permission for these individuals relevant to the study to have access to my records. ☐

I understand that my data will be stored for 10 years after the study is completed. A record of my personal details will be kept on a secure server at the Birmingham Treatment Centre. Pseudo-anonymised results may be stored on a University of Birmingham computer and linked by study ID to my personal details. Only the research team and representatives from the sponsor will have access to them. ☐

I give permission to use anonymised quotations from my audio-recorded interview in relevant publications, and I understand that my identity will not be revealed, and such information will not be traced back to me. ☐

I understand that if I disclose information about any person being at risk of harm or of any unprofessional practice (e.g. prescription of an inappropriate treatment) confidentiality may have to be broken. ☐

I agree to the audio recording of my interview. ☐

I agree to take part in this study. ☐

Name of Participant	**Date**	**Signature**
Name of person taking consent	**Date**	**Signature**

Appendix 5

Ph.D. Portfolio

Name PhD student: Aziza Ali Alenezi
University of Birmingham, College of Medical and Dental Sciences

PhD period: Nov-2017 to April 2022
1st Supervisors: Dr. Asma Yahyouche,
2nd Supervisor: Dr. Vibhu Paudyal

Courses	***Year***
Statistics theory course at University of Birmingham	2018
Systematic Review Training course for two weeks at University of Hull	2018
Scriptoria Scientific writing workshops for a full day at the University of Birmingham	2018
Using EndNote to manage your references at the University of Birmingham	2018
Searching & finding information workshop at University of Hull	2018
Writing critically workshop at University of Hull	2018
Getting started with NVivo parts 1&2 for one week at the University of Hull	2018
Advanced NVivo part 1&2 for one week at the University of Hull	2018
Using NVivo and Endnote for literature review workshop at the University of Hull	2018
Basic techniques for creating presentations workshop	2018
Creating & delivering conference presentations workshop	2018
Academic poster presentation	2018
Formatting your dissertation	
Using Microsoft Word training workshop	2019
Qualitative Research Methods for one week at the University of Birmingham	2019
Good Clinical Practice (GCP) training for a full day at St James University Hospital	2019
Informed Consent Training workshop for a full day at St James University Hospital	2019
Clinical Research workshop a full day training at University of Birmingham	2019
One to one training with Clinical Research Compliance team at university of Birmingham (5 sessions)	2019
	2020

An introduction to Microsoft team

The basics of teaching, inclusive teaching, large and small group teaching (labs and seminars), assessment and feedback, and more (ILT) training online workshops (5 sessions) with wining the HEFI Horizon Award winner	2021

Conferences and Abstracts	***Year***
HSRPP 2019 poster presentation	2019
HSRPP 2019 Pechakucha session	2019
ESCP 2021 poster presentation	2021
ESCP 2021 poster presentation	2021
ESCP 2022 oral presentation	2022

Publication paper	***Year***
Alenezi, A., Yahyouche, A. & Paudyal, V. Interventions to optimize prescribed medicines and reduce their misuse in chronic non-malignant pain: a systematic review. *Eur J Clin Pharmacol* **77,** 467–490 (2021). https://doi.org/10.1007/s00228-020-03026-4	2021
Alenezi, A., Yahyouche, A. & Paudyal, V. Current status of opioid epidemic in the United Kingdom and strategies for treatment optimisation in chronic pain. *Int J Clin Pharm* **43,** 318–322 (2021). https://doi.org/10.1007/s11096-020-01205-y	2021
Alenezi, A., Yahyouche, A. & Paudyal, V. Roles, barriers and behavioral determinants related to community pharmacists' involvement in optimizing opioid therapy for chronic pain: a qualitative study. *Int J Clin Pharm* **44,** 180–191 (2022). https://doi.org/10.1007/s11096-021-01331-1	2021

Appendix 6

Ethical approval letters

(community pharmacists)

Application for Ethical Review ERN_19-1922
Susan Cottam (Research Support Group)
Sent: 31 January 2020 15:31
To:
Cc:

Dear Dr Yahyouche

Re: "Community pharmacists' perspectives of the barriers and enablers of their role to optimise opioids therapy for chronic non-malignant pain patients: Study protocol"
Application for Ethical Review ERN_19-1922

Thank you for your application for ethical review for the above project, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I confirm that this study now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as described in the Application for Ethical Review, and/or any adverse events occurring during the study should be promptly brought to the Committee's attention by the Principal Investigator and may necessitate further ethical review.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

Kind regards

Susan Cottam
Research Ethics Manager
Research Support Group
C Block Dome
Aston Webb Building
University of Birmingham
Edgbaston B15 2TT
Tel:

Appendix 7

the patients' forum ethical approval letter

Application for Ethical Review ERN_19-1922
Susan Cottam (Research Support Group)

Sent: 31 January 2020 15:31
To:
Cc:

Dear Dr Yahyouche

Re: "Community pharmacists' perspectives of the barriers and enablers of their role to optimise opioids therapy for chronic non-malignant pain patients: Study protocol"
Application for Ethical Review ERN_19-1922

Thank you for your application for ethical review for the above project, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I confirm that this study now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as described in the Application for Ethical Review, and/or any adverse events occurring during the study should be promptly brought to the Committee's attention by the Principal Investigator and may necessitate further ethical review.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

Kind regards

Susan Cottam
Research Ethics Manager
Research Support Group
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Aston Webb Building
University of Birmingham
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Appendix 8HRA approval letter

Ymchwil lechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Asma Yahyouche
Lecturer in Clinical Pharmacy
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University of Birmingham
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05 October 2020

Dear Dr Yahyouche

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Barriers and enablers to the prescribing and use of opioids in patients with chronic non-malignant pain**
IRAS project ID:	**270017**
Protocol number:	**RG_19-160**
REC reference:	**20/WA/0232**
Sponsor	**University of Birmingham**

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.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

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 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) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

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 standard conditions 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.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **270017**. Please quote this on all correspondence.

Yours sincerely,
Ann Parry

Email: Wales.REC3@wales.nhs.uk

Copy to: *Dr Birgit Whitman*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Costing template (commercial projects) [Confirmation sponsor insurance]	Version 1	27 January 2020
Covering letter on headed paper [Cover letter]	Version 1	08 July 2020
Covering letter on headed paper [Cover letter]	2	01 October 2020
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
Interview schedules or topic guides for participants [interview questions]	Version 1	06 July 2020
Interview schedules or topic guides for participants [HCP]	1	19 June 2020
IRAS Application Form [IRAS_Form_27072020]		27 July 2020
Letter from sponsor		
Organisation Information Document	V1	17 June 2020
Participant consent form [HCP]	2	15 June 2020
Participant consent form [Patients]	2	15 May 2020
Participant information sheet (PIS) [Participants information sheet]	Version 1	06 July 2020
Participant information sheet (PIS) [HCP]	1	15 June 2020
Research protocol or project proposal [Study protocol]	Version 1	06 July 2020
Schedule of Events or SoECAT [SoE]	Version 1	06 July 2020
Summary CV for Chief Investigator (CI) [-cv (3)Dr Asma]	30/10/2019	30 October 2019
Summary CV for student [Aziza CV]		11 February 2020
Summary CV for supervisor (student research) [Vibhu CV]	29.11.2019	29 November 2019
Summary of any applicable exclusions to sponsor insurance (non-NHS sponsors only)	V1	27 January 2020
Summary, synopsis or diagram (flowchart) of protocol in non technical language	V1	15 June 2020
Validated questionnaire [COMM questionnaire]	Version 1	06 July 2020

IRAS project ID	270017

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is only one participating NHS organisation therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	Study funding will be provided to sites as per the Organisational Information Document	A Principal Investigator should be appointed at study sites	No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application 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

Appendix 9

Study protocol



Optimising medication use in chronic non-malignant pain (CNMP) patients, Healthcare professionals and patients' perspectives of barriers and enablers to the appropriate use of prescribed long-term opioids in CNMP patients' management using Theoretical Domain Framework.

Study protocol

Aziza Alenezi

Barriers and enablers to the prescribing and use of opioids in patients with chronic non-malignant pain.

Protocol version (2) 16 May 2020

Research reference number	
IRAS Number	270017
Sponsor reference Number	RG_19-160
REC reference number	20/WA/0096

This protocol has regard for the HRA guidance

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to adhere to the signed University of Birmingham's Sponsorship CI declaration.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigators: Dr Asma Yahyouche

Signature:……

Date:……..

Name: (please print):

Sponsor statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

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Key study contacts

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Chief Investigator

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Sponsor

University of Birmingham

Funder(s)

Royal Embassy of Saudi Arabia, Cultural Bureau in London

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Key Protocol Contributors

As above

Study summary

Long title: Optimising medication use in chronic non-malignant pain (CNMP) patients, Healthcare professionals and patients' perspectives of barriers and enablers to the appropriate use of prescribed long-term opioids in CNMP patients' management using Theoretical Domain Framework

Short title: Barriers and enablers to the prescribing and use of opioids in patients with chronic non-malignant pain.

Aim

The research aims to identify the barriers and enablers to prescribing and use of chronic opioid therapy for chronic non-malignant pain (CNMP) from the perspectives of healthcare professionals and patients.

Study Design

This research will utilise a qualitative study design based on semi-structured interviews with healthcare professionals and patients with CNMP who are prescribed chronic opioid therapy.

Study Participants

1. Healthcare professionals currently treating or managing patients with chronic non-malignant pain receiving chronic opioids therapy.
2. CNMP patients who are receiving chronic opioids therapy.

The planned size of the recruitment target: We aim to interview approximately 15 chronic pain healthcare professionals and 20 patients.

Participant recruitment

B. Healthcare professionals' recruitment

The research team will distribute the study pack (participant information sheet and consent form) to the healthcare professionals at the recruitment sites. Those who are interested in participating in the study can contact the research team for further information before consenting. In addition, the health care professionals who

participate in the study will be encouraged to give the researcher's contact details to other chronic pain healthcare professionals. We will also recruit healthcare professionals through the acquaintance of the research team and using local practice forums of doctors, pharmacists and nurses.

C. Patient recruitment

2. **Contact via chronic pain clinic staff:** CNMP Patients who use opioids long term will be identified by the pain clinic nurse from their medical records during their clinic visit. They will be given a brief description of the study by one of the healthcare professionals. Those who show interest will be given the study pack by a member of the healthcare team that contains the research team contact information (e-mails and contact telephone). Interested patients can contact the research team using the contact details provided in the participant information sheet. Patients who agree to take part in the study will be asked to tell their relatives, friends or colleagues who meet the inclusion criteria about the project, and to provide the researcher's contact details to any other eligible patients who might be interested in potential participation.

N.B. The researcher will not directly approach patients first. This will eliminate any risk of coercion. The clinical staff and the researcher will stress that there will be no obligation to participate and that patient's care will not be affected if they decide not to take part.

Planned Study Period

Six months

Funding and support in kind

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
University of Birmingham	PhD studentship is offered to Aziza Alenezi by the Royal Embassy of Saudi Arabia.

Role of study sponsor and funder

This research is conducted as part of the doctoral degree for Aziza Alenezi.

The funding body have no role in the study design, conduct, data analysis and interpretation and manuscript writing. They will not be involved in the dissemination of the results of the study.

Roles and responsibilities of study management committees/groups and individuals

The study will be managed by the Chief Investigator(CI) and research team. There will not be any management committees/groups for this study

Patient & Public Involvement:

This study followed the National Institute of Health Research guideline on patient and public involvement in research (1). The following activities were conducted in relation to patient and public involvement:

2. The proposal and recruitment materials including study protocol, participant information sheets and consent forms were shared with Expert Citizens Charity (CIC). Expert Citizens Charity is an independent group of people who have experienced multiple needs including combinations of mental ill-health, homelessness, addiction and offending behaviour who uses their unique skills and experiences to be a voice for others . We held a one-hour meeting on the 29th of April 2020 with Darren Murinas, chief executive of Expert Citizens CIC and with Rachel Hine responsible for supporting research studies with Expert Citizens.

The expert Citizens team considered that the research will be beneficial in supporting healthcare professionals and patients on chronic opioid therapy. Based on the advice of this public involvement event, we have developed detailed information sheet, giving patients access to full details about the study. The team also recommended taking verbal consent at various stages of research to ensure continued consent.

3. The proposal and recruitment materials including study protocol, participant information sheets and consent form were shared with Homeless Link. Homeless Link is a national charity supporting organisations working directly with homeless people in England. We then held a one-hour meeting with one of the organisation's managers on 20th April 2020. The outcome of this meeting led us to revise our participant recruitment, sampling and inclusion criteria. In particular, we now plan to include patients who have successfully come out of chronic opioid therapy and compare their perspectives with those of current chronic opioids users. Also, we discussed how we can deal with distressed participants. The manager has provided us with a link to the organisation's webinar about safeguarding and other training courses for their employees who deal with multiple needs individuals.

4. We conducted a meeting with the Healthcare team at Birmingham Treatment Centre (BTC) on May 2019. The aim of the meeting was to introduce the research team to the chronic pain clinic team, seek their opinion about the study protocol, and potential participants, and have an overview of how the chronic pain clinic is operated. The BTC chronic pain clinic is a multidisciplinary clinic that manages patients with multiple types of pain who are using chronic opioids therapy to manage their pain. The outcome of this meeting led us to choose BTC as the primary study setting.

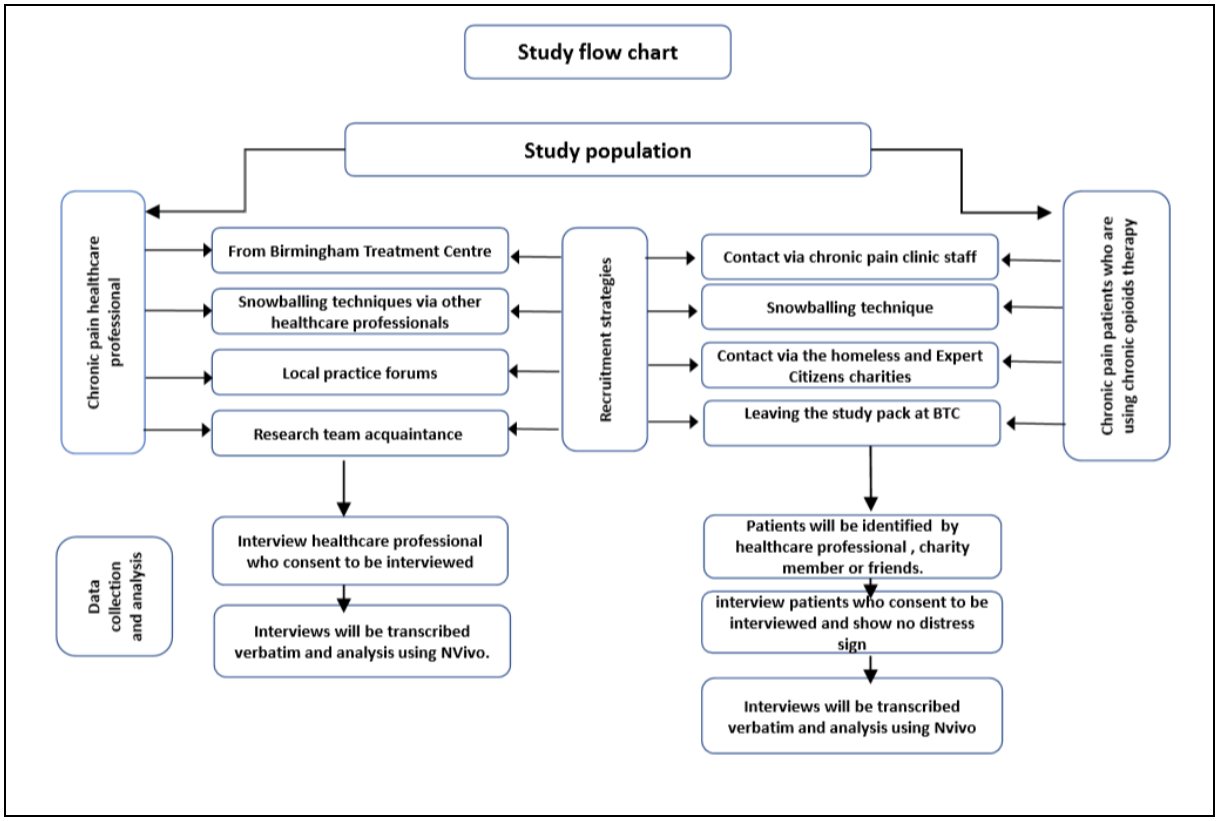
Patients with chronic lower back pain who used chronic opioid therapy has read all the study documents (protocol, participant information sheet, consent form, interview questions). The patients confirmed that participant information sheet and consent form are informative, easy to understand and have suggested some questions for patients and healthcare providers.

Protocol contributors

The protocol was designed and written by the research team. The research output will contain a disclaimer reflecting the fact that results and related interpretation are those of the researchers and not the funder**.**

KEYWORDS: Chronic non-malignant pain, Medicine Optimisation, Appropriate use of opioids. Appropriate prescribing of opioids. Theoretical Domains Framework, Semi-structured interviews.

Study flow chart



Abbreviations:

BTC – Birmingham Treatment Centre

CI –Chief Investigator

CNMP – Chronic Non-Malignant Pain

COMM – Current Medication Misuse Measure

GP – General Practitioner

ICF Informed Consent Form

NHS – National Health Service

NICE – the National Institute for Health and Clinical Excellence

PIS – Participant Information Sheet

PI – principal Investigator

UK – United Kingdom

TDF – Theoretical Domains Framework

Background

Chronic non-malignant pain (CNMP) is a prevalent long-term health problem that might lead to disability and high medical and societal costs [1,2]. Twenty per cent of the European population suffer from CNMP [3] and also, CNMP affects approximately one-third of the UK population and 10-14% per cent of these patients are categorised as severely disabled. Patients usually require a multidisciplinary treatment, yet medications remain a cornerstone of its treatment [4,5]. Opioid medicines, which became popular as medication for pain management in the 1990s, are usually prescribed for the treatment of moderate to severe pain [6,8]. Incidence of CNMP has increased dramatically in the last decade, leading to an increase in the use of analgesics, including opioids, to manage chronic pain. This has led to increasing prescribed opioid-related harms. Opioid use disorder and problematic medication-taking behaviours linked to pain medication taking, including underuse, overuse, misuse, abuse and addiction can reach 40 per cent [10]. Furthermore, clinicians are faced with uncertainty regarding the effects of chronic opioid therapy. The process of effectively assessing, predicting and preventing the occurrence of problematic medication-taking behaviours and opioid use disorder, and optimising medication usage amongst these patients is a challenging task [6]. The opioids dilemma has been around for the last three or so decades, yet up to this day, the number of people dying from overdosing on opioids is still on the increase, and there is no radical solution to it, despite the extensive research and investment that have been undertaken.

An important aspect of medicine optimisation in chronic pain management is that all health care professionals must have knowledge of the tools used to help treat pain, optimise the medication use and reduce the negative consequences of chronic opioids therapy [12]. Their role should involve appropriate prescribing and regular assessment of the chronic opioids therapy and other controlled substances, as well as the education of their patients. Moreover, they must understand the magnitude of chronic pain and treatment barriers that must be surmounted to ensure adequate care. Patients with CNMP vary widely in their needs due to the subjectivity and complexity of pain; therefore, healthcare professionals need to be knowledgeable about different guidelines and risk assessment tools, and carefully consider the appropriateness of opioids and possible alternatives in each case.

Opioid misuse and abuse are prevalent among CNMP patients, and various types of interventions have been used to improve the appropriate long-term use of opioids, Yet the barriers and enablers to appropriate long-term use of opioids are poorly understood. We aim to understand the barriers and enablers to prescribing and use of chronic opioids therapy for chronic non-malignant from healthcare professional and patient perspectives.

Rationale

To understand how stakeholders have tried to reduce the effects of inappropriate use of pain medications and optimise their use, our team conducted a systematic review on the nature, process, and outcomes of interventions for medicine optimisation in CNMP patients. The systematic review identified complex medication-taking behaviour among these patients, including underuse [16], overuse [16], misuse [17-20], abuse [18,21,22] and aberrant drug behaviour [17] adherence [17,23,24] and non-adherence [16,25,25]. There was variability in medication-taking behaviour definitions among the studies; some studies defined and targeted more than one behaviour. There was substantial heterogeneity in the definition of medication-taking behaviours among study populations. Therefore, some of the included studies aimed to reduce problematic medication-taking behaviours (abuse, misuse) [17-22] and others aimed to enhance appropriate medication use (medication adherence, reduction in patient's reliance on opioids) [16,22,23,25,26].

A number of varied interventions have been used, singly or in combination to detect, assess, prevent, predict or identify problematic medication-taking behaviours. Approaches used include clinical practice interventions a treatment agreement contract , urine drug testing/screening, a monthly assessment in the clinic or over the phone, , pill count [17, 19, 20, 23-25, 27, 28,] disease management programmes[17, 22, 29-31], technological interventions (electronic diaries, prescription monitoring programmes [17, 19, 20, 24, 25, 30, 32], educational interventions [16-19, 24, 31], behavioural interventions (motivational interviewing theory, attachment theory, craving theory)[18, 20, 21, 26, 28], and healthcare provider (HCP)-led interventions (pharmacist, nurse ,physiologist [16, 18, 30, 32]. The main limitation of most of the included studies is the varied ways of combining interventions, which makes it challenging to determine what is the most effective component or combination. Also,

there is inadequate information that can positively support data accuracy and recruitment efficacy.

Furthermore, the systematic review investigated how researchers decided to choose a particular type of intervention and the use of theories/theoretical frameworks in the design, implementation and evaluation of interventions for medication optimisation in CNMP patients. The choice of the type of interventions seems to be influenced by the research background. The use of theory was limited to only four studies out of 22 studies [20, 21, 26, 34].

The impact of clinical outcomes, adaptability and feasibility of most interventions in different settings remains unclear; therefore, most of the interventions seem to lack significant value without stronger evidence. Moreover, their practicality in non-research settings was not clear, as well as their adaptability and efficacy in situations of scarce healthcare resources, due to the high cost usually associated with the use of these types of interventions. As a result, it is difficult to identify which interventions are most likely, in particular settings, to be useful or efficient for medicine optimisation in CNMP patients.

The prescribing and using of medications are complex processes involving both clinical and non-clinical behaviours. Also, there is a need to optimise opioids use for CNMP and reduce its harms. Expert guidelines suggest that opioids only be started as a final choice and be stopped if the risks outweigh the benefit [12]. Theoretically, guidelines do exist to manage CNMP. However, once a prescriber has considered the ratio of risk to the benefit of chronic opioids therapy and determined that the patient is not sufficiently benefiting, only a few tools exist to help the provider and patient follow a different therapeutic path. Therefore, a significant challenge facing prescribers across all specialisms is what to do with patients who were on chronic opioids therapy for therapeutic use (i.e., pain relief), but continue to use opioids when the benefit is not apparent. Determining how to support opioid initiation and cessation in CNMP patients is complicated by knowledge gaps between expert guidelines and clinical practice. This lack of understanding may lead to unintended clinical consequences of inappropriate prescribing, such as early initiation, inadequate support for opioids cessation, patient dissatisfaction, problematic medication-taking behaviour, non-adherence, and conflictual prescriber–patient relationships. Therefore, research is needed to identify

the potential barriers and facilitators to the appropriate use of chronic opioids therapy from the perspectives of CNMP patients and their healthcare providers.

In summary, the barriers and enablers to opioids' long-term appropriate use and prescribing for CNMP have not been well explored. To our knowledge, no studies have specifically explored barriers and enablers to optimising long-term prescribing and use of opioids for CNMP. This study will utilise a framework of behavioural theory, the Theoretical Domains Framework (TDF) to explore barriers and enablers to the prescribing and use of opioids in CNMP.

Theoretical framework

The study will utilise a qualitative method using semi-structured interviews drawing on constructs and definitions from the Theoretical Domains Framework (TDF) [42]. The framework was judged to be a suitable conceptual tool to guide the design and analysis of the study since it enables an exploration of the full range of potential influences on behaviour and has been validated to facilitate research.[42] The TDF is a framework based on theories of human behaviour and behaviour change and is in line with calls for complex interventions to improve health to be informed by theory[43,44]. The TDF was developed to identify the causes of difficulties and promote understanding about how to change behaviour. The framework was derived from the integration of 33 theories and 128 constructs from behavioural theory, resulting in 12 theoretical domains useful for categorising barriers and enablers to specific behaviours. Therefore, it can be used to understand the factors that might influence the clinical behaviour change being targeted, to underpin possible techniques that could be used to change clinical behaviour [45], and to clarify how such techniques might work. Evidence can inform which clinical behaviours should be changed, and which potential behaviour change techniques and modes of delivery are likely to be effective. The TDF has been used in a number of empirical studies with healthcare professionals to explore problems in clinical areas, supporting its validity as a theoretical framework [42]. Recently, a coding manual has been developed, which lays out 12 theoretical domains used to inform the topic guide of qualitative studies and the analysis of interview transcripts. Questions were designed to explore the domains from the TDF for both stakeholders: healthcare professionals and patients. Key domains will be identified that describe the specific barriers and enablers at a theoretical level, which

may then allow accessing relevant evidence of likely effective behaviour change techniques.

Research aim

This aim of this study is to explore barriers and enablers to long-term prescribing and use of opioids for chronic non-malignant pain (CNMP).

Objectives

2. To explore barriers and enablers to appropriate long-term prescribing and use of opioids for CNMP from the perspectives of healthcare professionals
3. To explore barriers and enablers to appropriate long-term use of opioids from the perspectives of patients.

Outcome

- An in-depth understanding of factors that influence the prescribing, use and optimisation of opioids for CNMP including the related barriers and enablers.

Study design

This study will adopt a qualitative research design using the Theoretical Domains Framework. Qualitative research methods allow a higher degree of flexibility in data collection.

Interviews will be conducted face to face, online or via phone by the researcher and will be audio recorded with written informed consent obtained from the participant.

In our study, we will use the concept of 'data saturation' to determine the sufficient number of key informants from the interviews [46]. We mean by data saturation when no more enablers and barriers to appropriate use and prescribing of opioids are identified. We initially propose to conduct 20 interviews with CNMP patients who are on or have had chronic opioids therapy and 15 interview the healthcare professionals. Also, we will use the stopping criterion by which to decide saturation.

This will allow us to identify determinants of the evidence-practice gap (for example what barriers healthcare professionals face in prescribing opioids for CNMP; what barriers patients face in using opioids and coming off opioids; why some CNMP patients exhibit problematic medication-taking behaviours (misuse); specific behaviours that need changing in order to optimise opioid use in CNMP management). This study will generate an understanding of the healthcare providers' and patients'

perceptions of the multi-level determinants of the behaviours required to optimise chronic opioids therapy.

Study setting

This study will be conducted in Birmingham Treatment Centre, which offers a multidisciplinary team including chronic pain consultants, nurses, physiotherapists and psychiatrists. Participants will also be recruited through charities, professional forums and researcher acquaintances.

Participant recruitment

Eligibility Criteria

Inclusion criteria

Inclusion criteria for healthcare professionals:

- Healthcare professionals who are involved in the care of patients who are using chronic opioids therapy to manage their pain.

Inclusion criteria for patients

- Patients aged 18 or over who have been prescribed opioids for CNMP for 3 months or more.
- Patients who have had chronic prescribed opioid use for 3 months or more in the past but may no longer be using opioid therapy

Exclusion criteria

Exclusion criteria for healthcare professionals

- Healthcare Professionals who are not involved in the care of patients using chronic opioid therapy for pain management.

Exclusion criteria for patients

- Those under the age of 18.
- Patients prescribed opioids for less than three months
- Patients who do not understand and speak English.
- Patients who are not capable to provide informed consent.
- Patients who show emotional distress during presentation at the clinic.

Participant Recruitment

Healthcare professionals' recruitment

We will use convenience sampling, as we aim to interview all pain clinic healthcare professionals working at Birmingham Treatment Centre.

The chief investigator (VP) and researcher (AA) presented and discussed the study with pain clinic healthcare professionals at Birmingham Treatment Centre on May 2019.

From Birmingham Treatment Centre: After obtaining ethical approval, the research team will distribute the study pack (participant information sheet (PIS) and consent form) to the healthcare professionals at the recruitment sitesor the packs will be provided to the site based department managers for distribution to the healthcare professionals, thus eliminating first approach by the research team. Eligible healthcare professionals who are interested to participate in the study can contact the research team for further information before consenting to the interviews. Invitation to participate will also be made during the team meeting, either through remote telephone or video conferencing or face-face if the Covid-19 situation settles.

We will also invite the healthcare professionals by giving a summary pitch of the study in the team meeting. This will be conducted face to face or via video-conference facility available at the clinic.

In addition, the health care professionals who participate in the study will be encouraged to give the researcher's contact details to other chronic pain healthcare professionals. We will also recruit healthcare professionals through the acquaintance of the research team.

Patient recruitment

We will recruit patients with CNMP using the following strategies:

Contact via chronic pain clinic staff: CNMP Patients at Birmingham Treatment Centre who use opioids long term will be identified by the pain clinic nurse from their medical records during their clinic visit. They will be given a brief description of the study by one of the healthcare professionals. Those who show interest will be given the study pack which contain the participants information sheet PIS, consent form and

The Current Opioid Misuse Measure (COMM) questionnaire, and the research team contact information (e-mails and contact telephone).

The researcher, hence, will not directly approach the participants first. This will eliminate any risk of coercion. The clinical staff and the researcher will stress that there will be no obligation to participate and that patients' care will not be affected if they decide not to take part.

Snowballing technique: Patients who agree to take part in the study will be asked to tell their relatives, friends or colleagues who meet the inclusion criteria or other eligible patients about the project, and to provide the researcher's contact details to anyone that might be interested in potential participation.

The researcher, hence, will not directly approach the participants first in any of the recruitment strategies we will be using. This will eliminate any risk of coercion. The charity staff and the researcher will stress that there will be no obligation to participate and that patients' their care will not be affected if they decide not to take part.

All potential participants will be advised to take time (at least 24 hours) to read through the information sheet and discuss it with their healthcare professionals, family or friends before deciding to take part. All participants will be reimbursed for travel expenses a one day bus rider and will be given a £10 Voucher.

Recruitment target

In our study for patients' recruitment, we will use the concept of 'data saturation' to determine the sufficient number of key informants for the interviews [46]. We mean by data saturation when no more enablers and barriers to appropriate use and prescribing of opioids are identified. We initially propose to conduct approximately 20 interviews with CNMP patients who are on or have had chronic opioids therapy and 15 interviews with healthcare professionals. We will use the stopping criterion by which to decide saturation. The plan is to conduct interviews until no new theme/ ideas emerge.

Consent

Interested patients and healthcare professionals will contact the researcher using the contact details provided in the Participant Information Sheet to show their interest in participation. They will be requested to send the consent form using a pre-paid reply

envelope, through e-mail by sending a scanned copy or by contacting the researcher over the phone. Participants who consent to participate through telephone interview will be requested to provide verbal consent via telephone. Prior to the commencement of any interview, participants will be provided with a brief description of the study and reminded that participation in the study is voluntary and that they can withdraw at any time from the study without giving reasons.

If a participant withdraws from the study after being interviewed, their data will be excluded from analysis, which includes destroying audio recordings, transcribed documents and all other documents, pertaining to that participant.

The researcher (AA) will retain overall responsibility for obtaining informed consent of participants for this study. The researcher has attended a training course that was specially designed to train postgraduate students for qualitative research methods at the University of Birmingham as well as an introduction to Good Clinical Practice GCP course and an informed consent training course.

Data collection

We will conduct semi-structured interviews. The interviews will be conducted by the researcher (AA) who has undergone training in interviewing skills at UoB. Interview guides, informed by the Theoretical Domains Framework (TDF)[42], have been developed specifically for healthcare professionals and patients. These will be pilot tested prior to use (See interview guide). We will use the TDF-informed interview guides to probe the participants about barriers and enablers of appropriate long-term prescribing and use of opioids in managing CNMP.

All participating patients will also be asked to fill in the Current Medication Misuse Measure (COMM) (8) questionnaire. The COMM is a 17-item self-report questionnaire that helps to track current aberrant medication-related behaviours during opioid treatment. All items are rated from 0=never to 4=very often (e.g., In the past 30 days, how often have you needed to take pain medications belonging to someone else?) with a total maximum score of 68. Construct validity has been shown to be adequate with positive correlates with urine toxicology results ($p<0.05$). Test-retest reliability was .86 with a 95% CI ranging from .77 to .92. The overall accuracy of the COMM for predicting current aberrant drug-related behaviour, as measured by the area under the curve ratio, was .81 (95% CI, .74–.86; $p < .001$) and coefficient α 86) for the 17 items

suggests adequate reliability. A cut-off score of 8 yielded a sensitivity of 0.75 and specificity of 0.65. An accumulated cut off score of 9 or higher is considered positive.

Data analysis

To improve the quality of the collected data, we will monitor the progress of the interviews by carrying out transcription and analysis concurrently. The audio recordings will be transcribed verbatim by the researcher (AA). The data analysis will be done using NVivo11. The researcher will read and re-read the entire text to get a general sense of the whole perspective of healthcare professionals and patients. The researcher will then divide the significant text segments into “meaning units”, keeping the participants’ own words. The researcher will next eliminate redundancies and relate the meaning units to each other and the overall sense of the experience. The researcher will read all the meaning units again and compare and discuss them with the research team. The research team will convert the raw text, meaning units into agreed NVivo -derived codes that describe significant aspects of the experience. The researcher will categorise the codes into main themes and cluster similar subthemes into the related main themes. Finally, the researcher will develop an overall description of the essence of the participants’ experience by merging the main themes and the subthemes in a flowing narration.

The analysis will follow these steps:

1. Generating specific beliefs

The frequency of similar sub-themes that imply a problem or influence of belief on the targeted behaviour will be counted and categorised.

2. Identifying relevant theoretical domains.

From the earlier step, we can determine which domains can be identified as potential barriers and enablers to healthcare professionals’ or patients’ change. A domain can be identified as an enabler or a barrier if it fulfils the following three criteria: specific beliefs with relatively high frequency; belief with conflict present among the participants; an emphasis on the importance of the belief and evidence of strong beliefs that may impact on the behaviours.

3. Comparing (similarity and difference) the findings from the interviews with healthcare professionals and patients.
4. Data will be verified and checked by the supervisors (AY and VP)who are independent to the study and are not involved in data collection. This will further ensure data validity.

We will compare the findings for both stakeholders to identify how we can achieve chronic opioids therapy optimisation in CNMP.

Safety reporting

Methods (interviews) chosen for this study are unlikely to pose risks to participants.

Ethical and regulatory considerations.

The researcher will make clear to all participants the limits of confidentiality and the confidential method of disclosing information to the research team.

There is no intervention in this study, and it will not affect any care that patients receive in the future.

Risks for participants

Unprofessional practice and maltreatment

For health care providers joining in the study, there is a risk the researcher could be made aware through discussion of unprofessional practice, e.g. prescribing inadequate treatment. For people with CNMP there is a potential risk that during discussions, the researcher could be made aware of maltreatment or abuse.

Any practice that identified as being is potentially detrimental to a vulnerable person will be reported to the individuals direct care team andSandwell and West Birmingham Hospitals NHS Trust PALS (Patient advice and liaison service), Phone: 0121 507 6440 or, 0121 507 4080 or 0121 507 5892, 10 am – 4 pm, Monday – Friday. Email: swbh.complaints@nhs.net.

Incidents deemed to be reportable to the sponsor, such as a serious breach of the protocol, or GCP, identified as likely to affect to a significant degree the physical or mental well being of a participant or the data integrity of the study, will be reported to Dr Birgit Whitman, Head of Research Governance and Integrity at the University of Birmingham and the REC.

All participants will be advised of this in the information sheet provided to them.

Potential risk and harm

The focus of the interviews will be on how the patients use opioids to manage their pain. However, if the researcher suspects that the patients are misusing their medications intentionally or unintentionally, in a way that could put them at risk of overdose, the researcher will report it to the principal investigator. Also, the following statement will be given to all participants as part of the interview introduction: ‘‘What we will talk about today will be confidential, but there are limits to confidentiality. For example, if you were to tell me something new that could put someone at risk of harm, or unsafe practice, I may have to inform a member of your healthcare team and follow local NHS Trust standard procedures for safeguarding. If this happened, I would discuss this with you and tell you what I was going to do.’’

Distress of participants

The main potential risk to the participants is considered to be potential distress from discussing their pain medication-taking behaviours. This study does not aim to explore particularly sensitive or personal aspects. The interview schedule has been reviewed by a patient and public involvement PPI representative from Expert Citizens who leads the organisation’s research and evaluation projects to check that the questions are deemed to be acceptable. To deal with any distress, the researcher will inform all participants they can take a break or reschedule if the topic induces a high stress level, at any time. Participants will be free to withdraw from the study at any time without providing a reason, and their health care will not be affected in any way. They will also be made aware of a confidential method of disclosing information to the research team.

The researcher will state this sentence before starting the interview: “Because the topic of chronic pain and the use of opioids can be sensitive and could make you feel upset, we have measures in place so if you become distressed during the interview we can pause the interview until you feel ready to continue or stop if you feel unable to continue. Anyone identified as being vulnerable may be put in contact with a member of their healthcare team for additional support as required.’

Despite this, it is not possible to predict what each individual may find upsetting and sensitive to discuss.

If a participant shows signs of stress during the research activities, the researcher will advise them to seek professional help regarding the issue (e.g. from their GP or healthcare worker of usual contact).

Contact details of NHS Direct, a mental health charity and the Samaritans will be provided in case people would like to discuss their concerns with an anonymous listening service.

If the level of distress is very intense or the participant shows signs of level 3 of distress, then the distress protocol will be followed. For more details on how the research team will manage distress, see appendix 4 for the distress protocol that will be followed in all distress levels (level 1,2, and 3).

Some participants may wish to share their experience although they find it upsetting, because they believe it is important for the purpose of the research and will be given the opportunity to do this if they wish to. Participants will be made aware during the consent process that direct quotations from their interview may be used but that they will be anonymised, and great care will be taken that they do not include any potentially identifiable information.

The researcher will also report anything that indicates malpractice or neglect to patients, that may be expressed by any of the healthcare professionals to the PI Sandwell and West Birmingham Hospitals NHS Trust PALS (Patient advice and liaison service), Phone: 0121 507 6440 or, 0121 507 4080 or 0121 507 5892, 10 am – 4 pm, Monday – Friday. Email: swbh.complaints@nhs.net. Also, the researcher will tell the participants that if any information is disclosed during the sessions that concern the researcher (e.g. information that a crime is about to be committed or somebody is at risk of significant harm) then confidentiality may have to be broken by contacting the police, 999 or local authorities.

Research Ethics Committee (REC)

Before the start of the study, approval will be sought from the REC for the study protocol, informed consent forms and other relevant documents. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study. All correspondence with the REC will be retained. The Chief Investigator will produce the annual reports as required. The Chief

Investigator will notify the REC of the end of the study. For NHS REC reviewed research, an annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Other regulatory Review & Compliance

The study will be conducted in accordance with the principles of good clinical practice (GCP) and UK Policy Framework for Health and Social Care Research and will have REC approval. In addition to the sponsorship approval (University of Birmingham), a favourable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

Amendments

Any amendments to be made are the responsibility of the Chief Investigator and to make a substantial amendment to the protocol or supporting documentation, the Chief Investigator will submit a valid notice of the amendment to the REC for their consideration. Amendment history will be tracked by strict version numbering of all documents pertaining to the protocol and design of the study such as participant information sheets and consent forms and study protocol.

Peer review

The protocol has been developed by the researcher team and peer reviewed by the Clinical Research Support Office, University of Birmingham.

Patient & Public Involvement.

For the full details of the patient and public involvement in the study, see the summary sections, page 7.

Protocol compliance

Accidental protocol deviation can happen at any time, and this will be adequately documented and reported to the Chief Investigator and Sponsor immediately.

Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

All personal data collected during the course of the study will be either stored electronically on a password protected UoB computer hard drive or as paper files which will be stored in a locked drawer in a locked office with limited access.

Audio recordings and interview transcripts will be pseudonymised using a unique study ID as stated on the consent forms and participants information sheets, will be stored separately from the consent forms that identify participants by name and will be held securely, in a locked cabinet inside a locked room or a room with swipe access, in UoB.

Pseudonymised data will be analysed on a password-protected laptop or UoB hard drive.

Access to details and coding will be limited to the study team via usernames and passwords and data will be kept in a locked cabinet inside a locked room or a room with swipe access in UoB. A file containing linking codes will be held in a separate location from interview transcripts and study field notes using encrypted digital files within password-protected folders. Study documentation and data will be archived for 10 years after completion of the research, in UoB. This information will be held securely for 10 years, according to the University Research Ethics Policy.

Indemnity

The UoB will be the sponsor for the study and will fulfil the insurance/indemnity arrangements should it be needed. The sponsor is responsible for potential legal liability arising from the design and management of the research. Indemnity insurance is in place to cover this liability.

The UoB purchases Clinical Trials Cover, which provides automatic cover for all Clinical Trials including those where the University accepts responsibility as a sponsor, for any harm that comes about due to the University's, or its staff's negligence in relation to the design or management of the trial.

The NHS indemnity scheme will cover potential legal liability arising from the conduct of the research as this will be conducted on site at Birmingham Treatment Centre.

End of study and archiving

The end of study is defined as the submission of the final report. The empirical phase (site involvement) will conclude with the last participant interview. The Sponsor, CI and/or the TSC have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

The study documents will be retained for 10 years and then destroyed. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

Access to the final study dataset

Direct access will be granted to authorised representatives from the sponsor, the host institution and the regulatory authorities to permit study related monitoring, audits and inspection. Access to the final dataset will be controlled by the study team.

Dissemination policy

Dissemination policy

On completion of the study, the data will be analysed, and a final study report will be prepared. In addition, study will be published in a peer reviewed journal with a pain focus.

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Appendices

Appendix 1- Required documentation

Below is a list of requirements for conducting this study:

2. Protocol
3. Participant Information Sheet (PIS) for staff
4. Participant Information Sheet (PIS) for patients
5. Three consent forms for patients (original copy, medical record copy and participant's copy)
6. Two consent forms for the health care providers (original copy and participant's copy)
7. Interview Protocol Worksheet patients
8. Interview Protocol Worksheet healthcare professionals
9. Organisation Information Document
10. Schedule of Events
11. Curriculum Vitae of the research team
12. Software (N vivo) for data analysis
13. A suitable meeting room for interviews.
14. Stationery (pens, paper, flip chart), cards for statements printing, audio recording device
15. Paper for printing the information packs.
16. Money for pain clinic grant, CNMP patients £ 10 voucher, travel expenses for participants.

Appendix 2 – Schedule of Procedures

Activity	Start Date	End Date	Duration
Meeting with HCP			5
HCP consent & interviews			22
Patient identification/questionnaire			20
Patients Interviews			89
Data analysis			152
Study Report			85

Note: Overall these stages can be done within 6 months after getting the IRAS approval.

Appendix 10

The interview distress protocol

The screening interview and distress protocol

All the screening will be conducted by the researcher.

This is (the researcher name) from the University of Birmingham. Thank you for your interest in our study. Do you have any questions about the study? [if yes, answer questions. If not proceed].

Could you please verify your name and phone number?

Because the topic of chronic pain and the use of opioids can be sensitive and might bring up tough feelings, we are advising individuals who experience a high level of stress or emotional distress or whose participation might put them in danger not to participate at this time.

The following protocol outlines the action of the researcher, if during interview participants exhibit acute distress or safety concern or imminent danger to self or others.

As a researcher remember:

observe the participant for cues that suggest distress

listen carefully for cues (e.g., a lump in the throat; quivering voice).

Remember that you are responsible for getting the interview back on track

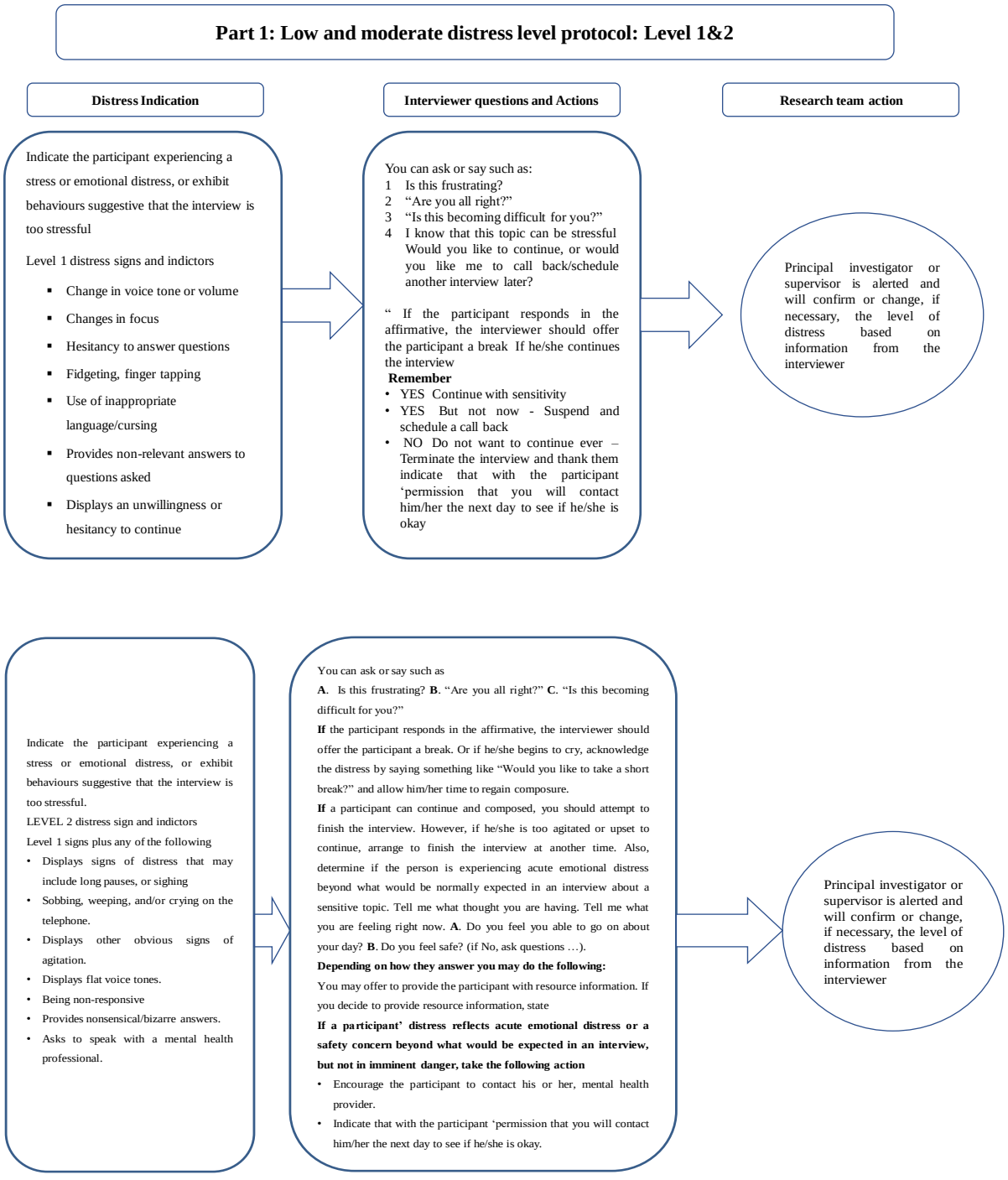
When you feel that the time is right, use a soft, direct manner and say something like, “I have a few more questions

It is important to trust the participant ’s ability to handle personal feelings or emotions. When a participant becomes distressed, it may seem hard to avoid taking on the role of counsellor. Regardless of your background, your function on this job is that of an interviewer, not a counsellor.

Never give advice. Each person has his/her own best answers.

Never tell a person that he/she “should” or “should not” feel a certain way.

Never say that you are “surprised” about something that was said or done. This denotes judgment and criticism.



Note: below is list of helpful telephone numbers, websites and several charity organisations that provide support to people who are in distress or emotional crisis. Please remember that you should contact your GP if your problems persist.

NHS Direct Telephone: 0845 46 47 Lines are open 24-hours every day.

Samaritans: www.samaritans.org.uk Samaritans provide 24-hour confidential emotional support to anyone experiencing feelings of distress.

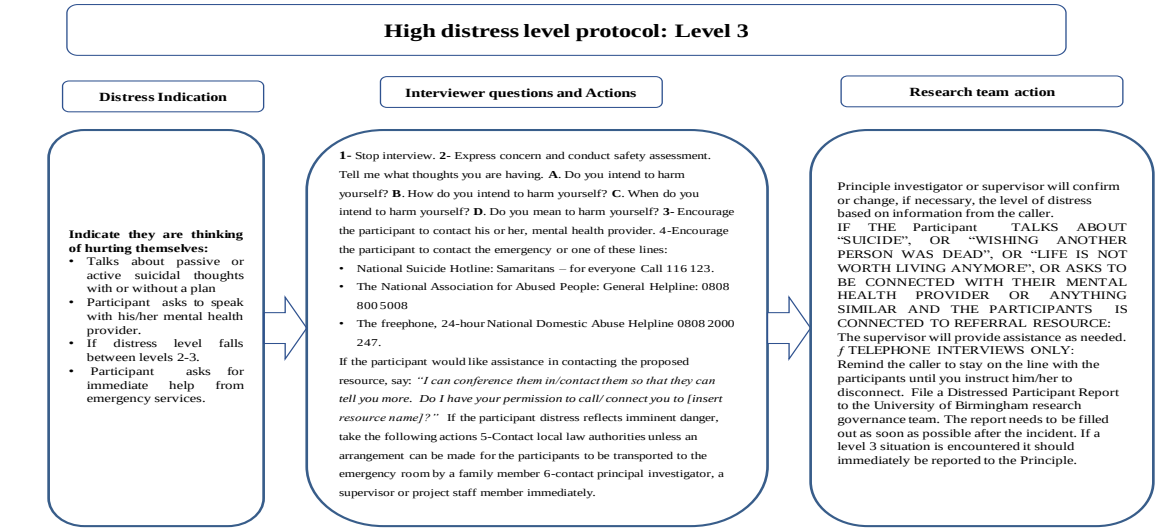
Telephone: 0845 7909 090 Telephone from most mobile providers and some landlines: 116 123

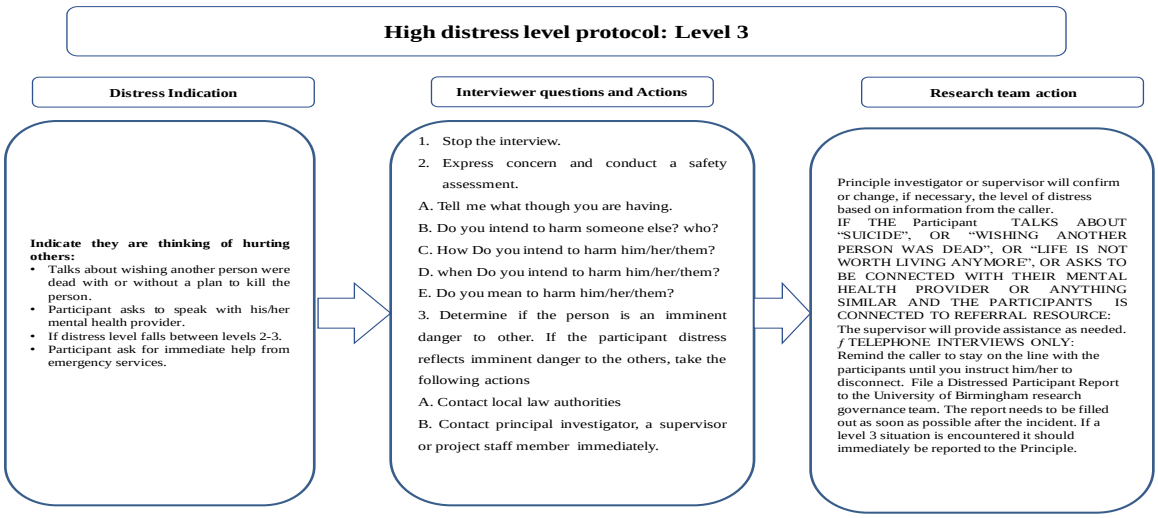
Age UK Norwich: http://www.ageuk.org.uk/norwich/ The Age UK Group works to improve later life for everyone by providing life-enhancing services and vital support.

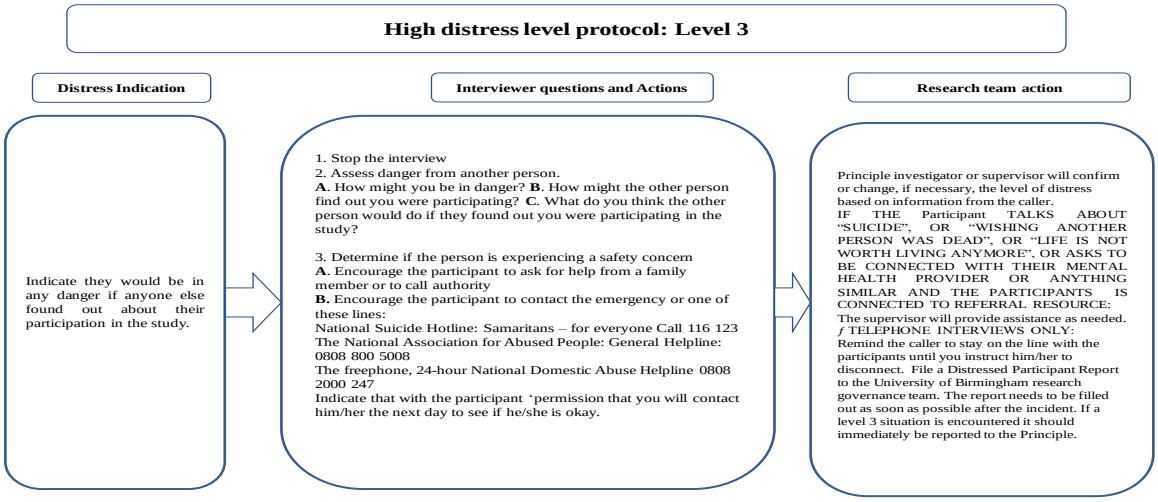
Local Service, telephone: 01603 496333 Lines are open 5 days a week Monday to Friday from 10.00 am to 4.00 pm each day, except Wednesday when they close at 2.00 pm for staff training.

Sane: http://www.sane.org.uk/what_we_do/support/helpline/ SANE runs a national, out-of-hours helpline offering specialist emotional support and information to anyone affected by mental illness, including family, friends and carers. Telephone: 0845 767 8000

Note: for full slide, please double click.







Note: for full power point slide, please double click**.**

Researcher actions

If a participant's distress reflects an emotional response reflective of what would be expected in the interview, offer support and extend the opportunity to;()stop the interview;()regroup;()continue.

If a participant' distress reflects acute emotional distress or a safety concern beyond what would be expected in an interview, but not in imminent danger, take the following action

Encourage the participant to contact his or her mental health provider or to call the emergency room.

Encourage the participant to contact emergency

Indicate that with the participant 'permission that you will contact him/her the next day to see if he/she is okay.

Notify principal investigator or supervisors of the recommendation given to participants

If the participant distress reflects imminent danger, take the following actions

Contact local law authorities unless an arrangement can be made for the participants to be transported to the emergency room by a family member

Indicate that with participants permission to contact him/her the next day to see if he/she is okay.

Immediately notify the principal investigator, supervisor researcher governs team of action taken



Interview Distress Report

Acute emotional distress safety concern? (Y/N)	**Imminent danger (Y/N)**

Study ID: _____

Distress Level (Mild-Level 1, Moderate-Level 2, Severe-Level 3):

_____

Distress Description:

_____

_____

_____

_____

_____

_____

_____

_____

_____

Interviewer Actions:

_____

_____

_____

_____

Supervisor Actions/Comments:

_____

_____

_____

_____

_____

_____

Name of researcher	Date	Signature
Name of research team member	Date	Signature

The researcher will keep a printed copy of these cards and will be given to the patients who show level 1&2 distress will be send via SMS.

UNIVERSITY OF BIRMINGHAM

Helpful telephone numbers and websites Below is a list of several charity organisations that provide support to people who are in distress or emotional crisis.

Please remember that you should contact your GP if your problems persist. NHS Direct Telephone: 0845 46 47 Lines are open 24-hours every day.

Samaritans: www.samaritans.org.uk Samaritans provide 24-hour confidential emotional support to anyone experiencing feelings of distress.

Telephone: 0845 7909 090 Telephone from most mobile providers and some landlines: 116 123

Age UK Norwich:
http://www.ageuk.org.uk/norwich/ The Age UK Group works to improve later life for everyone by providing life-enhancing services and vital support.

Local Service, telephone: 01603 496333 Lines are open 5 days a week Monday to Friday from 10.00 am to 4.00 pm each day, except Wednesday when they close at 2.00 pm for staff training.

Sane:
http://www.sane.org.uk/what_we_do/support/helpline/ SANE runs a national, out-of-hours helpline offering specialist emotional support and information to anyone affected by mental illness, including family, friends and carers. Telephone: 0845 767 8000

***REC reference**: 20/WA/0096*
***Protocol number**: RG_19-160*
***IRAS project ID:** 270017*

UNIVERSITY OF BIRMINGHAM

Helpful telephone numbers and websites Below is a list of several charity organisations that provide support to people who are in distress or emotional crisis.

Please remember that you should contact your GP if your problems persist. NHS Direct Telephone: 0845 46 47 Lines are open 24-hours every day.

Samaritans: www.samaritans.org.uk Samaritans provide 24-hour confidential emotional support to anyone experiencing feelings of distress.

Telephone: 0845 7909 090 Telephone from most mobile providers and some landlines: 116 123

Age UK Norwich:
http://www.ageuk.org.uk/norwich/ The Age UK Group works to improve later life for everyone by providing life-enhancing services and vital support.

Local Service, telephone: 01603 496333 Lines are open 5 days a week Monday to Friday from 10.00 am to 4.00 pm each day, except Wednesday when they close at 2.00 pm for staff training.

Sane:
http://www.sane.org.uk/what_we_do/support/helpline/ SANE runs a national, out-of-hours helpline offering specialist emotional support and information to anyone affected by mental illness, including family, friends and carers. Telephone: 0845 767 8000

***REC reference**: 20/WA/0096*
***Protocol number**: RG_19-160*
***IRAS project ID:** 270017*

The patient who shows distress level 3 will be given the previous sheets and this card or will be send via SMS.



REC reference: 20/WA/0096
Protocol number: RG_19-160
IRAS project ID: 270017

National Suicide Hotline: Samaritans – for everyone Call 116 123

The National Association for Abused People: General Helpline: 0808 800 5008

The freephone, 24-hour National Domestic Abuse Helpline 0808 2000 247



REC reference: 20/WA/0096
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Protocol number: RG_19-160
IRAS project ID: 270017

National Suicide Hotline: Samaritans – for everyone Call 116 123

Appendix 11

Preferred Reporting Items for Systematic Review and Meta-analysis

Appendix 1:
PRISMA Checklist

Section/topic	#	Checklist item	Reported Y/N/NA and page number in the manuscript file
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Y, 3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Y, 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Y, 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Y, 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Y, 5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Y, 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Y, 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Y, Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Y, 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Y, 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Y, 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Y, 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Y, 6, 7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Y, 8,-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Y 7, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Y 10,11 Table 3 page12,13,14
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Y 8,9..Tables 1&2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Y 8, 9 Tables 1&2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Y29,30
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	Y 31
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Y 32
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Y 1

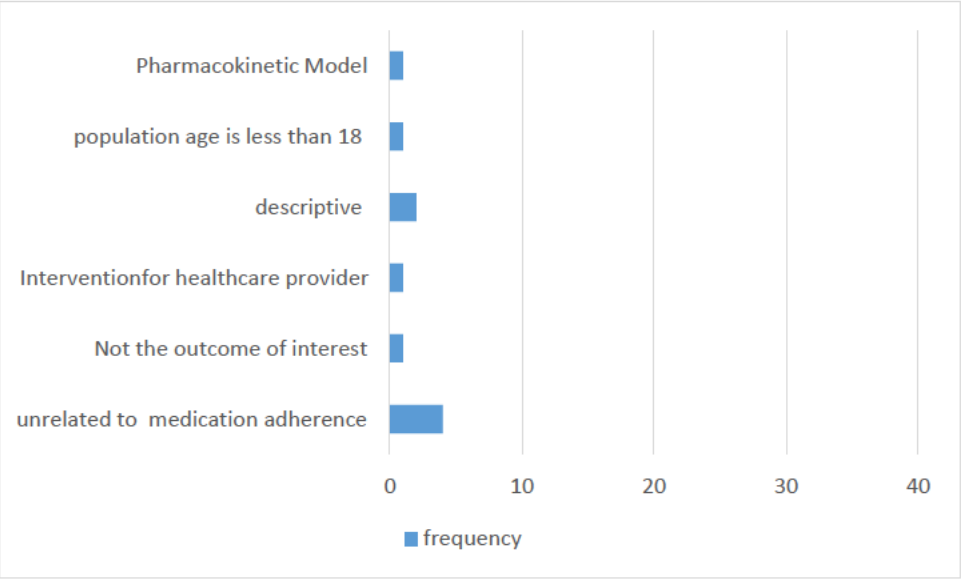
[1]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.doi:10.1371/journal.pmed1000097

NA: Not applicable

Appendix 11

Excluded studies characteristics

STUDY	REASON FOR EXCLUSION
VICTOR,2005	Not the outcome of interest
MARCEAU,2007	Not related to the medication optimisation
BRUHN,2010	Not related to the medication optimisation
HUDSPETH,2010	Not related to the medication optimisation
HUIS IN'TVELD,2010	Not related to the medication optimisation
JAHANSOUZ,2011	Not related to the medication optimisation
LINARES,2013	Pharmacokinetic Model
LEWIS,2014	descriptive of the health provider adherence to the prescribing guideline
WEISS,	Most of the population have patients with addiction
ROBINSON-PAPP,	Descriptive only no enough details about the intervention
SAROYAN,2016	Most of the population age is less than 18 years old
TIMMERMAN,	No intervention



Interventions designed to enhance medication adherence include combinations of more thorough patient instruction and counselling, (intensive) reminders, close follow-up, supervised self-monitoring, rewards for success, family therapy, psychological therapy and telephone follow-up.

Appendix 12

COREQ (Consolidated criteria for Reporting Qualitative research) Checklist

(community phramacits' study)

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	
Occupation	3	What was their occupation at the time of the study?	
Gender	4	Was the researcher male or female?	
Experience and training	5	What experience or training did the researcher have?	
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	

Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	
Sample size	12	How many participants were in the study?	
Non-participation	13	How many people refused to participate or dropped out? Reasons?	
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	
Presence of nonparticipants	15	Was anyone else present besides the participants and researchers?	
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	

Field notes	20	Were field notes made during and/or after the inter view or focus group?	
Duration	21	What was the duration of the inter views or focus group?	
Data saturation	22	Was data saturation discussed?	
Transcripts returned	23	Were transcripts returned to participants for comment and/or	
Topic	**Item No.**	**Guide Questions/Description**	**Reported on Page No.**
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	
Description of the coding tree	25	Did authors provide a description of the coding tree?	
Derivation of themes	26	Were themes identified in advance or derived from the data?	
Software	27	What software, if applicable, was used to manage the data?	
Participant checking	28	Did participants provide feedback on the findings?	
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	
Data and findings consistent	30	Was there consistency between the data presented and the findings?	
Clarity of major themes	31	Were major themes clearly presented in the findings?	
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

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Standards for Reporting Qualitative Research (SRQR)*(patients' study)

http://www.equator-network.org/reporting-guidelines/srqr/

Page/line no(s).

Title and abstract

Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	Page 1 line 3
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	Page 2 line 20-39

Introduction

Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	Page 4 line 113
Purpose or research question - Purpose of the study and specific objectives or questions	Page 5 line 115

Methods

Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	**Research trustworthiness** Page 9
Context - Setting/site and salient contextual factors; rationale**	Method page 5
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	Method page 5 line 132-145
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	**Ethical considerations** Page 9

Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	Method and data analysis page 5 -7
Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	Method page 5
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	Data analysis page 6-7
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	Data analysis page 6-7
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	**Research trustworthiness** Page 9

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	Result page 9-16
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	Table

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**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist (clinicians' study)

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	
Occupation	3	What was their occupation at the time of the study?	
Gender	4	Was the researcher male or female?	
Experience and training	5	What experience or training did the researcher have?	
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	
Domain 2: Study design			
Theoretical framework			

Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	
Sample size	12	How many participants were in the study?	
Non-participation	13	How many people refused to participate or dropped out? Reasons?	
Setting			
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Appendix 13

Keywords of the CNMP pateints forums study

Please note that the name of online forums and the treads have been reduced OR paraphrased to keep forums users anonymous.

Keywords

Search engine keywords	Patients' forum, chronic pain support, Chronic pain forum, Chronic pain support group, Chronic pain discussion. chronic pain Online community, pain discussion forum

Chronic pain forum search on google sample

Forum's name and link	Exclusion reason
https://forum.....pain	Met the inclusion criteria
https://www.....pain	Non-UK -based forum
www……. Forums	The internal search retrieved old threads only (beyond 2014)
https://.....uk/forum	Met the inclusion criteria
https://www.....	Non-UK -based forum
https://health.....	Registration required
https……pain	Registration required
https://patient.....	Old posts only (inactive)
https://www.....	Registration required
https://.....	Registration required
https://www....._pain	Met the inclusion criteria
https://www.c.....	Registration required
https://.....	Professional Forum
https://www.....	Registration required
https://www.....	Non-UK -based forum
https://www.....	Non-UK -based forum
https://.....	Non-UK -based forum
https://www.....	Forum for professional
https://.....	Non-UK -based forum

https://www.....uk/	Few chronic pain posts
https://.....	Non-UK -based forum
https://forum.....	The internal search retrieved old threads only (beyond 2014)
https://.....pain/	Registration required
https://.....au/	Non-UK -based forum
Many of search on the google using the key words resulted in repetitions of the listed above forum or website for chronic pain with no forum or support group.	

Chronic pain forum search on Bing

Key words	**Reason of exclusion**
Chronic pain forum	
…….. forum	Met the inclusion criteria
Chronic ……com)	Non-UK -based forum
https://www.....pain	Non-UK -based forum
https://www.....pain	Met the inclusion criteria
Forum …….	Old posts only (inactive)
Health……	Non-UK -based forum
Search…….UK	Registration required
https://.....	Registration required
https://www A……t	Old posts only (inactive)
https://www C……)	Educational content only
https://www F……..	Registration required
https://www C……t	Met the inclusion criteria
https://www F…….	professional Forum
https://www L……	Registration required
https://www A……org.uk)	Registration required
https://www C…… y	Non-UK -based forum
https://www C……)um	Carer forum
https://www.....	Non-UK -based forum

Internal search keywords

Internal search keywords	Opioid, opiate, Oxycodone, Other options, codeine morphine, Oramorph Tramadol, fentanyl, Marijuana/ Cannabis, **Emotions;** Depression/anxiety/ frustrated /depressed, stigma, mentally, suicide, withdrawal, coming off, **Medication taking behaviours;** addict dependence misuse addicted abuse relapse, **Pain;** Pain, chronic pain , Worsen pain, living with pain, Suffer, flare up, quality of live**,** Coping with chronic ,accepting pain, Healthcare system (NHS and private) and , healthcare providers, pain clinic

Internal search

Keyword	**Number of Thread Forum name**	**Thread**
Pain medication		

opioid'	1-3 threads forum 1 4 thread forum 3	Mixed Opioids ……. Opioid change …….. Problems ……. buprenorphine ….
opiate	5,6 thread forum 2	.. Long-term Opiates … long term use of pain medication
Oxycodone. Oxycontin	7-10 forum1 11 thread forum2 12-13 threads forum 3	Oxycodone …. Oramorph Oxy……? Oxycodone …… Oxycodone ……. …… Oxycodone …… …….. Oxycodone Oxycodone …….
codeine	14,15 threads forum 3	…….. codeine Dihydrocodeine
morphine Oramorph	16-26, forum1 27-29, forum2 30-31, forum3	Morphine withdrawal Oramorph S……. …….. morphine and gabapentin Zomorph 30- …10mg MST withdrawal …… Morphine withdrawal……? Back ……MST (2 questions) Oramorph……. Aching All Over ...Morphine Is … Normal?? Slow-Release Morphine……. When…. morphine stops working. Starting Morphine……. Morphine question ……. experiences Oramorph Experiences……. Morphine tolerance……. Morphine – does it work for …….?
Tramadol	32-35, forum1 36, forum2 37, forum3	Now more ……. free and off Tramadol Tramadol to …… Tramadol & Dihydrocodeine …… Tramadol……. Now more ……. Advice on ……. Tramadol
Gabapentin	38-40, forum1 41, forum2 42-43, forum3	Lyrica……... gabapentin to ……. Gabapentin……. …….. of gabapentin …. anyone… Gabapentin or Lyrica pregabalin/Lyrica worse pain…….
fentanyl	44-48, forum1 49-51 forum2 52-55 forum 3	1.Fentanyl and ……. 2. Fentanyl ……. Thinking of going back on MS Contin ……. of fentanyl patches……. coming off b……. fentanyl withdrawal Fentanyl causing pain. ……. hyperalgesia? Fentanyl not ……e prescribed length of time Urgent Confirmation/Advice appreciated on ……. Fentanyl……. that vile drug!! …… MS Contin instead of fentanyl patches Warning on … of Fentanyl patches Fentanyl…. Users – Please Reply…….

Marijuana/ Cannabis	56-58 forum1 59 forum3	Cannabis can ……pain Cannabidiol (CBD) CBT – what's …. and does it help? ….. to allow …..s to p… medical marijuana
Other options	60, forum1	…. dose Steroids for c… neuropathic pain?
Strong Pain killer	61 forum 3	is …. patches the strongest
Emotions		
Depression/anxiety/ frustrated /depressed	62-87 forum1 88-105 forum2 106-118 forum3	Embarrassing Problem… Feeling my …is over…… Loneliness, isolation and…. and pain frustrated and ……. AS pain ……. want to end my life Emotions……. Frustrated and don't know … to do … 22 years old, in constant pain … frustrated misunderstood by family and friends and depressed……. Feeling down ……. Feeling so ……. Really ……. Feeling low and …… Feeling So Low…. pain is driving me crazy…… Chronic Pain and Depression Explaining Pain to Partners ab……. Ne…. and depression…. It gets you down, …doesn't it? Acceptance of…… is Hard…. I am angry……. angry, and need help to deal with it……. Difficult Partner ……...? Feeling des……. Frustration, Grief, …… Invalidation from Doctors It's all awful……. Young …… to cope with the mental side of pain How ……. chronic pain to boss? Unsupportive …. doesn't understand my chronic pain……. So Much Pain……. Not Coping with ……. Pain The Invisible ……. oman… Cultivating Hope……. Coping Tips……. Desperation……. please so confused …….and in trouble…. Chronic p…. and small children Grief for …… or celebrating what's passed? Crying……. severe d……. 22, in ……. & Frustrated Terrified……. isolation ……. and pain finally gave in for a ……. stop flare ups Frustration, Grief, and Navigating Invalidation from ……s ….. Anxiety

		pain It's all awful……. so fed up… …… mood swings Feeling overwhelmed with ……. health issues…… Fed up…… So frustrated…… Feeling frightened……. Feeling isolated and …. S…… feeling of sadness & loss?..... Honest …… pain and depression Health anxiety with spinal trouble…… …….. My Pain Relief
stigma	119 thread forum 1	Stigmatized …
mentally	120, forum1 121-123, forum2 124-125, forum	I need help!!.....mentally Fibro sufferers mentally – hope at last? Where To Get Help. mentally Struggling with pain & isolated…. mentally Feeling ill …. mentally Young and struggling to cope with the mental ……
suicide		I can't
suicide	126-129, forum1 130-133 forum3	Feelings of Uselessness…… Losing hope……. Today I am…… I can't ……. being here anymore ……Want to die! Deeply depressed …… …….. suicidal thoughts
withdrawal, coming off		
withdrawal,	134-141, forum1 142-149 forum3	Withdrawal From …….ph Oxycodone withdrawal co-codamol withdrawal Feeling ……. …….. encouragement Withdrawal …… Bad …… Withdrawal …… withdrawal …… withdrawal Stopping ……. Oxy…… withdrawal Difficulty …… reducing opiate …….. morphine stops working……? coming off ……. 2mcg Morphine free……...!! …… …….. withdrawal symptoms show?
Medication taking behaviours		
addict	150, forum1	Addiction ….
dependence	151 forum 1	Dependency on ……..
misuse	152 forum 1	……..
addicted	153, forum 1 154, forum3	…… Addicted to …… …….. being addicted ……. killers
abuse	155, forum 1	…….
relapse	156, frum 1	……..
Pain, chronic pain, Worsen pain		

Pain	157-180 forum1 181-188 forum 2 189- 197 forum 3	Knee pain ……14 months ago …… Pain Relief combinations of meds …….. Can't Get …… Relief ……. pain help 10 years on, ……. pain Back muscle spasm …… “Breakthrough” pain ……. ……. Inflamed bowel disease? …….. Nobody should be in pain…… Back Pain I Need Help…….!!! Pain Pump…… A pain in the butt ……pls …… Pins & needles Constant chronic pain……. Chronic wrist pain, ……. advice needed …….. with severe back problems out there?? Benign Chest Wall Pain Syndrome… trigeminal neuralgia…… nerve problems…… chronic pain and nerve twitching……. Chronic pancreatitis……. Chronic pain for over 15 years…… …… Lumbar Spine OSTEOPOROSIS Trapped sciatic nerve pain ……. ……., sacroiliac joint, ilioinguinal nerve pain …….. pain syndrome&……. prominent pain syndrome Fibromyalgia…… …… degeneration and adolescent scoliosis Struggling with pain …… Any other young people with ……?? Flare up ……. …3 months Cauda Equina Syndrome Post-Surgery……. Disc Replacement…… Complex Regional Pain Syndrome…… Microdiscectomy…… Pain across coccyx, and buttocks……. Lower back pain, ……. legs hips…neck …… pain no answers
Worsen pain	198-211, forum 1 212-213, forum 2 214-224, forum 3	Coming Off ……. And Worsening Pain Unbearable……. Symptom versus…… Pain around/under rib…… excruciating pain……. Hiatus Hernia…… Is Chronic pain syndrome the ……? …… work increasing pain im lost Carpel Tunnel Syndrome……. Sacroiliac fusion in GB……. Arachnoiditis……. failed spinal fusion……. more pain …… infection…. cervical ……. myelopathy tight chest….

		Feeling very unwell……. Chronic Pain Flare Ups…… nerve ……had pain like this in my life! CRPS burning ……. – any tips? …… nerve damage / irritation post fusion Failed back surgery syndrome……. Spinal Stenosis……. Migraines…….. Getting worse……. Really bad pain flare …… Chronic trochanteric …… So angry!..... Low mood, ……. smoking again…
living with pain	225-236, forum 1 237-238 forum2 239-243 forum3	the ……. caused you to have chronic pain Driving ……. back pain Families and Relationships …. regarding our Pain : …. Sexual issues – sorry, … Invisible disability problem…… Struggle ……. or take the meds? pain meds not working…...? ……o the world of pain! Right knee aright Si joint My pain and me…… Having to give up work…… Advice about work…… ……., feeling really low, had enough Unending pain!..... Just about filled the ……. mentally exhausted and the ……. …….. about asking for support at work Dating ……. with chronic pain …pain affects ……. those closest to ……. Positive ……. /End of Day Can't ……y Pain Relief
Suffer, flare up living with pain	244-250, forum1 251-255, forum2 256-266, forum3	shoulder …… Chronic daily ……. …….. get worse with age?? '……. Meaning in life…….' Chronic pain and ……. work : Just thoughts ……. pain : can't sleep…… Difficult Partner Anyone…….? Does ……. feel ill & tired So much pain, no help ……. so alone ……Midnight Battles……. N……. e struggling with knee pain…. Struggling to walk……. Chronic ……. pain, advice needed…… Day after ……. pain and thoughts. Help any advice ……. pain at very high level Ignoring pain……. so ……. confused and in trouble... ……not coping … well

		……. pain forever? Feeling ……exhausted why is life always so ……pain? Flare up pain…. every night
Coping with chronic / accepting pain		
Coping	267-285, forum1 286-289, forum 2 290-301, forum3	Trying …… occupied Exercising ……. help Cold Weather……. pain finally …. pain and to stop flare ups Coping with pain…...! Alternatives……. Alternative / ……. topical products Laughter is the Best Medicine, …….t Accepting the pain…… Alternative methods ……. Physiotherapy exercises…… Pressure, ……. Humidity and Pain……. How to cope with chronic ……. and adjustment to life Which pain coping strategies have you …. successful? Coping with ……Christmas……. What natural……. remedies help you. Chronic…… Pain Tips Do you use…… art as a method of coping with your chronic pain? Chronic …. trochanteric. Medication? Coping……...? Mindful? ……. mindless! Pain Relief ……. Please. Brave……. Coping ……. severe pain? Something …… Laugh Battling…… Acceptance of pain……. Hard to accept……. Mindfulness…… art therapy and……., writing……. Effective ways to cope, please…...? Does Crying Help…?..... Has anyone tried hypnotherapy? Understanding pain…. Acupuncture…… Acceptance……. Coping with school…….
quality of life	302-304, forum 1 305-306, forum3	Not …… diagnosis means? Help? Decompression for. suggested. ….. and in pain and isolated …… and disability affecting quality of life Disabling Pain with …….
Healthcare system (NHS and private) and, healthcare providers		
Pain clinic	308-313 forum1 314, forum2 315-316 form3	What …. pain management clinics offer? Residential ……. Programmes ……. private pain clinic clinical psychology …...? Pain Management P……. Pain Clinics…… Change of ……. clinic

		pain psychol……. Worried about …….
Opiates repeat prescription	317, Forum1	late repeat prescriptions
NHS	318-334 forum1 335, forum2 336-361, forum3	Only l…. e patches work?! Can I use more? Or anything similar? …… on coming off tablets Terrified…… ……. plasters An Update … My Situation …….. experiences? Life after buprenorphine ……. ….. Joint Syndrome advice Mobility aids… Slow-Release M…. Advice on new meds ……. mobility scooter ……. help Has ……. had a spinal nerve block injection Is my physio ……in me off? NHS screw ……. Physio, ……. Good Idea? Repeated l……. Do you ……o what your doctor suggests? Advice Appreciated …… of urgent! Finally got a ……. Please help. ……physiotherapist says I have Not …… this diagnosis means? Help? How to handle ……physiotherapist Advice On …. Meds. Expert … mobility ……. Too much pain……. dentists diff advice Doctors No Help…… Nurses t…….to be doctors. A doctor……. on chronic pain patients Advice on … approach doctor Meds don……. work for Fibromyalgia In pain ……no answers …….. fobbing me off? ……Awkward Doctor ……. pain clinics No pain ……. p from NHS GPs ……. – changing GP After 9 years ……. diagnosis Residential ……. Programmes Fentanyl and ……. no longer prescribed Car crash …… gets diagnosis 4.5 years later! getting fed …… no diagnosis! been called a fake…….

Result

361 threads from three online forums237 forum1 and 2 and 123 forum3.

app