DURING PATIENTS' TREATMENT AT A CHRONIC PAIN CLINIC, WHAT INFLUENCE DOES THE EDUCATIONAL ROLE OF A SPECIALIST PHARMACIST HAVE ON THEIR ANALGESIA AND PERCEPTIONS ABOUT THEIR PAIN MEDICINES?

By

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ABSTRACT

Aims

This research aimed to determine whether education and advice from a specialist pharmacist in a chronic pain team (CPT) improved patient's analgesia.

Methods

55 patients referred to a chronic pain service in Staffordshire, UK were reviewed, educated and advised by a specialist pharmacist, four months apart. Medication and pain scores were recorded using validated tools (BPI and S-LANSS). Data were compared and analysed for significant changes. Ethical approval was obtained.

Results

Significant changes between visits were identified in some areas of medicine taking behaviour (BPI). Patients' mean 'worst pain' score improved (8.4 to 7.9, $p=0.023$), perceived percentage of 'relief from treatment' increased (41% to 51%, $p<0.001$), fewer patients reported analgesia as 'ineffective' (43% to 13%, $p=0.003$), perceived duration of effective analgesia increased ($p=0.004$) finally more patients reported their mild/moderate opioids 'effective'($p=0.006$).

Between visits, patient attitudes to medication taking changed. Overall fewer patients required: stronger analgesia (57% to 37%, P=0.002); more analgesia than prescribed (33% to 21%, p=0.004) more analgesic information (76% to 45%, p=0.004). Fewer considered they were taking ‘too much’ analgesia (46% to 31%, p=0.004)

Conclusion

Results suggest that education about analgesia by a specialist pharmacist working in a CPT can positively impact on patient’s pain scores.

DEDICATION

The late Mr D. S. Rawson, friend, companion and general life coach.

ACKNOWLEDGEMENTS

The process of getting to this point has been a long and winding path, aided and encouraged by many people who believed in me, including:

My wife who has sat through so many quiet evenings disturbed only by the rattle of my keyboard and latterly my sighs of exasperation.

Dr Christine Hirsch, my supervisor who, throughout the years, was unfailingly positive.

Professor John Marriott, who suggested “give it a try?”

Mr James Hodson, the Statistician who revealed the ‘significance’ of my results

Dr Brian Hebron, a friend

Dr Julian Smith, who started all of this

Mr Ashish Khiloshiya, my manager in the South Staffordshire Chronic Pain Service, the other members of the team and the patients who made this research possible

Finally, my children who were bold enough to give back to me my mantra from their studies – ‘there’s no such thing as can’t!’

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CHAPTER 1 INTRODUCTION

I’ve learned that people will forget what you said, people will forget what you did, but people will never forget how you made them feel.

Maya Angelou (1928-2014)

1.1. Overall layout of this thesis

The aim of this research was to investigate the effect that a pharmacist had in a Chronic Pain Team (CPT) in relation to changes in pain scores and patient medicine taking behaviour. It will firstly introduce the background of this research along with the medicinal treatment of chronic pain. It will then cover the systematic review, the aims and objectives, the methods used in this research and the results. The layout of the discussion follows the same format as that of the results and the discussion of each group of results finishes with its own conclusion. The thesis then closes with the conclusion, appendices and references.

1.2. Introduction

This chapter commences with the audit basis for this research. It then outlines the context of the chronic pain service within Staffordshire and the role of the pharmacist within that service. It sets out the problems associated with chronic pain, its definition, epidemiology and background for the need to treat pain. It concludes with an outline of the medicines used in the treatment of this condition.

1.3. Audit basis for this research

In 2013 an audit was carried out in the South Staffordshire chronic pain service (CPS) by the researcher to ascertain the use of medicines recommended for the treatment of neuropathic pain by General Practitioners (GPs). One hundred sequential patients attending the pharmacist's clinic were asked to self-complete the Leeds assessment of neuropathic symptoms and signs – short form (S-LANSS)

questionnaire prior to arrival at the clinic. As part of the patient's medicines use review (MUR) during the appointment a record was made of the medicines prescribed to treat the patient's chronic pain. The medicines prescribed by the patients' GP were then analysed in relation to their S-LANSS score using the accepted S-LANSS score of >=12 as the definition for the presence of elements of neuropathic pain within the patients' pain (Bennett *et al.*, 2005).

Fifty seven patients in this audit group reported an S-LANSS score of >=12 and of these 21 (37%) were not taking medicines which NICE recommends are appropriate for treating neuropathic pain (NICE, 2013a). In addition, of the 21 not taking these medicines, 9 (43%) were taking strong opioids. Cochrane reviews (McNicol, Midbari and Eisenberg, 2013; Els *et al.*, 2017a) and the Faculty of Pain Medicine (FOPM) (NHS, 2015) all recommend that strong opioids may not be effective in the treatment of this condition. As a result, it was decided to explore the use of medicines for neuropathic pain and strong opioids in the treatment of chronic pain.

1.4. South Staffordshire chronic pain service

The South Staffordshire chronic pain service (CPS) treats patients at five centres, Burton, Lichfield, Rugeley, Stafford and Tamworth. Patients from each of these locations were included in this research.

Figure 1.1 Map of Staffordshire

Map from the Trust Website

1.4.1. Initiation and administration of the Chronic Pain Service

In 2010 the South Staffordshire Primary Care Trust (PCT) sought providers for a biopsychosocial CPS. This treatment modal suggests that at least some of a patients' pain is self-manageable (Kamper *et al.*, 2015; Cheatle, 2016; Kress *et al.*, 2015; BPS, 2013; NICE, 2013a) and the efficacy of this model has been demonstrated (Gatchel *et al.*, 2007). A Cochrane Review reported that there was moderate evidence to support this approach to the treatment of chronic pain (Kamper *et al.*, 2015). This was supported by a later analysis of the benefits that patients' reported after being treated by an interdisciplinary pain team (Hapidou and Horst, 2016).

This represented a change from earlier treatments for chronic pain where the emphasis had been upon the biomedical model of treatment (Engel, 1977; Bendelow, 2013). In this model of care patients' awaited treatment to be given to them by others.

The South Staffordshire CPS was originally commissioned as a referral service to offer guidance to GP's and their patients on the treatment and self-management of chronic pain. The commissioners explicitly required the CPS to encourage patient self-management. The aim was to minimise referrals for chronic pain into Secondary Care. The service continues to date.

The biopsychosocial model of treatment, which developed slowly from its origins (Engel, 1977), was predicated on the principle that the experience of chronic pain could be managed by a combination of biomedical, psychological and social factors. The aim of treatment was twofold. Firstly, to empower patients to accept that their condition was to some extent self-manageable and take the knowledge which was offered by the CPS and apply it to their lives. Secondly, to provide patients with the knowledge and skills to manage their own pain in ways which facilitated their lives, albeit with some residual pain. Much of the teaching necessary for such empowerment and self-management takes place during a Pain management program (PMP) course. This means that patients need to be prepared to engage with the concept of self-management before being considered (eligible) for this course. Without this acceptance and engagement, patients may not be able to move on from constantly seeking a biomedical solution for their pain. Many patients find this approach difficult, at least initially.

1.4.2. PROCESS FOR REFERRAL OF PATIENTS TO AND WITHIN THE CHRONIC PAIN SERVICE

Patients' are referred to the CPS by their GP, by letter. These letters are reviewed and triaged by one of two Extended-Scope Physiotherapist (ESP), one of whom also has an additional prescribing qualification. Following on from this triage, accepted patients are reviewed either by a multi-professional group (MPG) within the CPS or an individual physiotherapist. The pharmacist is involved with some of the MPG reviews. At their initial appointment patients are involved in a discussion about the

available therapeutic options, a treatment pathway agreed and their GP informed by letter. A flow chart setting out patients' movements within the CPS is set out in Fig 1.2.

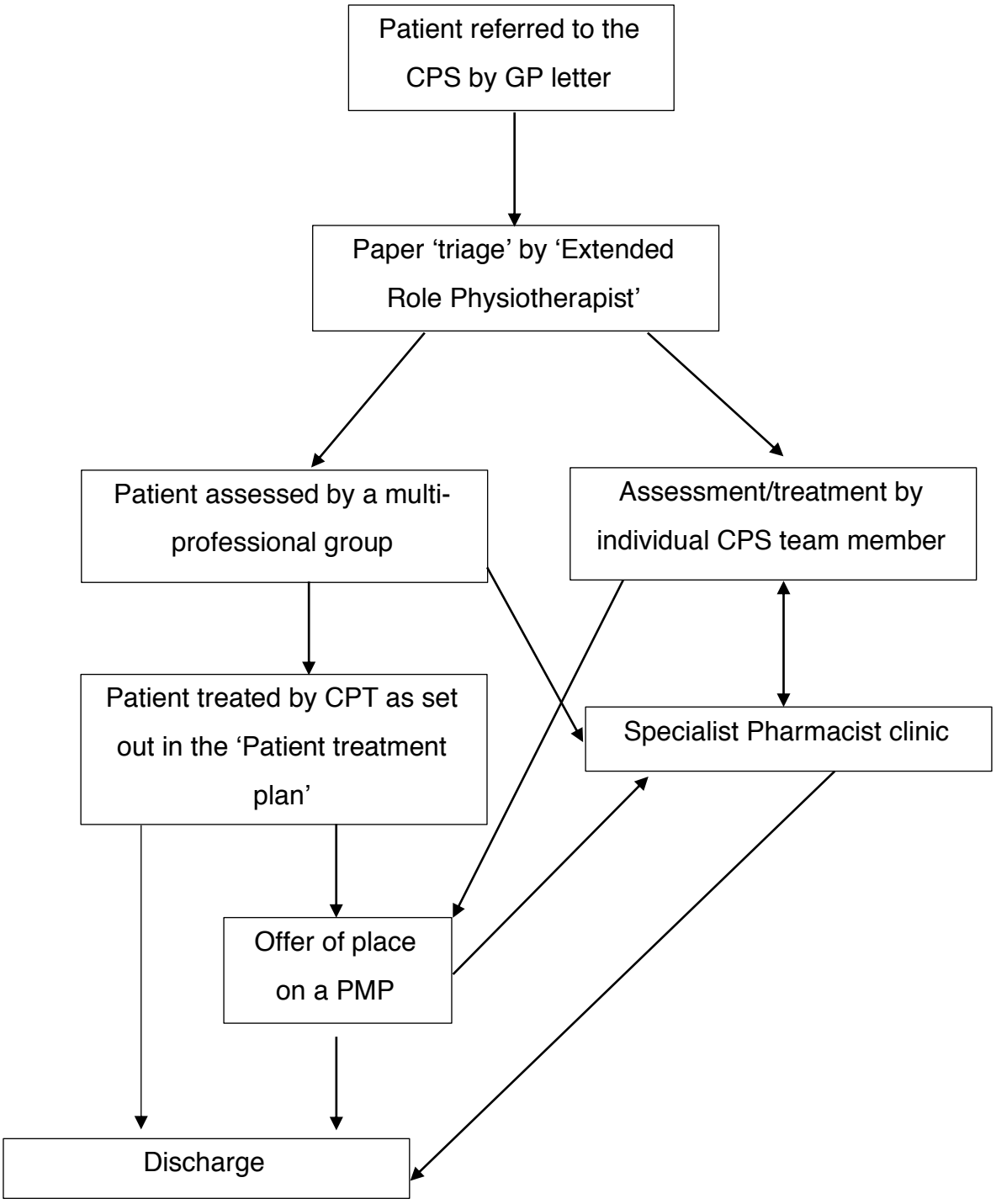

Figure 1.2 Flow diagram of referral process into the pharmacist clinic

The consultation options that are available across the CPS for inclusion in the individual patients' treatment plans include Physiotherapy, Occupational Therapy, Clinical Psychology, Pharmacy and Consultant medical staff. The treatments offered include exercise guidance, cognitive behavioural therapy, eye movement desensitisation and reprogramming (EMDR), transcutaneous electric nerve stimulation (TENS), spinal and local injections and nerve ablations and medicines optimisation. X-rays and scans can also be ordered if this would aid diagnosis and facilitate appropriate treatment.

The pharmacist offers an initial appointment of one hour where an MUR is undertaken. After this 'medicines optimization advice' is offered to the patient and as appropriate included within the post clinic letter for the GP. Subsequent appointments are offered, if this is agreed with the patient to be appropriate either for the correct initiation of a complex medicinal intervention or the gradual reduction of inappropriate medicines.

Over six, three-hour sessions, the PMP covers the physiological and psychological aspects of chronic pain and there are discussions about flare up management, pacing, problem solving and sleep hygiene. The program explored various relaxation techniques, visualisation, distraction and breathing to allow patients to determine which was beneficial for them. Lastly, participants were instructed in graded exercises or basic Tai Chi.

The pharmacist's presentation occupies half of one session, approximately 90 minutes. The aim is to guide patients towards the appropriate and optimal use of their pain medicines. Time is also allocated to counter any of the misinformation that the participants have about their pain medicines.

1.5. Definitions and understandings

There are three well recognised and accepted definitions of pain, which are important when talking to patients about their chronic pain.

i. "*Pain is whatever the experiencing person says it is, existing whenever or wherever the person says it does"* (McCaffery, 1968).

ii. (Pain is) "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in such terms".*
International Association for the Study of Pain (IASP, 2018)

iii. (Neuropathic pain is) *"Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system"* (IASP, 2015)

Acute pain can be divided into two groups. Firstly, it occurs as a short-lived response when local nociceptive pain receptors send a message to the central nervous system (CNS) reporting tissue damage or injury. It is a survival trait initially involved in the removal of the affected area from the possibility of further harm. Secondly, there are a group of conditions which result in repeated nociceptive stimulation and which can be of unknown duration. Included in this group are post-surgical pain, inflammatory

bowel disease or cancer pain. Each of these pains relate to a specific condition. These conditions are treated in the same way as acute pain but over a longer period.

Chronic pain or persistent pain, on the other hand, as seen in the CPS is much more difficult to define, except as a counterpoint to acute pain and often varies with the emotional state of the patient. Unlike acute pain, the expected duration is often unknown and is independent of any underlying illness or injury (McAllister, 2015). Rather than being a single disease it is an immense and diverse range of disease conditions, which present with the similar clinical symptoms of pain (Treede *et al.*, 2015). It was suggested by Grichnik and Ferrante (1991) that chronic pain should be regarded as a disease of its own. The full list of conditions included within the overall definition of 'Chronic Pain' is available from the IASP website (IASP, 2012). The positive survival traits of acute pain appear to have transmuted into inappropriate perceptions, which are harmful to the individual. This transmutation may lead to pain unrelated to any discernible cause, with symptoms, which are often associated with the symptoms of neuropathic pain.

Because the diagnosis and treatment of chronic or persistent pain does not relate to an underlying illness there has been a tendency to question the reality of the patients' suffering. It was recognition of this which led McCaffery (1968) to define pain in the way that she did.

The differentiation between acute and chronic pain is therefore important in order to provide appropriate management and treatment. Analgesia for acute pain is generally administered on a regular basis and can be very effective. As healing occurs the analgesia can be stepped down and stopped. Drug therapy for chronic pain on the other hand is often not very effective and once started it may continue, at some level, for an unspecified length of time (Ballantyne, Kalso and Stannard, 2016).

There is no consensus of opinion on the length of time before acute pain becomes chronic pain (Mifflin and Kerr, 2014; Feizerfan and Sheh, 2015). In discussions with patients' it is often helpful to describe it as "*pain that extends beyond the expected period of healing*" (Loeser and Bonica, 2001).

For a pharmacist, the vagaries of this pain bifurcation are important. Chronic pain is not simply continuing acute pain because, over a period of time, the body changes in response to the experience (Section 1.5.1). It is generally accepted with acute pain that "*analgesia is more effective at keeping pain away then making it go away"*, but once a patient has chronic pain, therapy may continue for a long time. This extended duration of treatment should lead to a different risk-benefit analysis of efficacy versus side effects to determine which pain medicines are more appropriate for long term therapy. Those side effects which take longer to develop such as opioid effects on the endocrine system and possibility of pregabalin induced weight gain need to be considered differently. The potential for decreased patient wellbeing needs to be balanced appropriately against any recorded analgesic benefit.

The Brief Pain Inventory tool, which was used during this research, uses the term 'pain medication' rather than analgesic. Therefore, throughout this thesis, the term 'pain medication' or 'pain medicine' is used where it is regarded as more appropriate to the context than analgesic or analgesia

1.5.1. CLASSIFICATION OF PAIN

The classification of pain can be helpful in providing a basis for choice of therapy. At its simplest level there are only two types of pain: pain generated by damage to tissues (nociceptive pain) or pain resulting from damage to nerves (neuropathic pain) and patients can have either or both at the same time (Parker, Acland and Swire, 2008).

A more comprehensive classification divides pain into three groups

i. Nociceptive pain – the body's normal response to injury or trauma. It results from direct stimulation of the nociceptive receptor e.g. broken bones, burns or post-surgery pain. The quality of nociceptive pain was often described by patients as 'deep', 'gnawing', 'throbbing' or 'aching'.
ii. Inflammatory pain – resulted from activation or sensitisation of the nociceptive pain system by a variety of physiologically active compounds released at the site of an inflammatory reaction, symptoms included redness, swelling and warmth to the touch.

iii. Neuropathic pain – pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. Patients may describe these pains as 'burning', 'shooting' or 'stabbing'. They may also express symptoms of numbness, hypersensitivity, paraesthesia or other unusual sensations.

These three types of pain are defined by sets of symptoms, which in turn, suggest treatment options, but for any individual, the situation is more complicated than this.

In a study by Hashmi *et al.* (2013) colleagues reported that if nociceptive stimulation is ongoing, the area of the brain which is activated by these stimuli moves from the area of the brain normally associated with pain to an area which is usually associated with emotion. These changes are similar with pain from different locations or causes (Roussel *et al.*, 2013). These changes are classified as 'sensitisation' (Latremoliere and Woolf, 2009) and are often involved in the 'chronification' of pain which can result in perceptions of pain that are totally out of proportion with the extent of any physical damage (Woolf, 2014). Secondly, pain may also result from previous injury or trauma, which had not resolved as normally expected. For physical injury or surgery, the pain should have resolved by the end of the trauma or wound healing process (Macrae, 2008; Tinastepe and Oral, 2013; Bruce and Quinlan, 2011) (Section 1.5). Following psychological damage or trauma, the pain may be a somatic expression of something long repressed or denied (Afari *et al.*, 2014; Burke *et al.*, 2017) and such hidden suffering has been associated with fibromyalgia (Hauser *et al.*, 2011; Gerber *et al.*, 2018)

Each patient's pain may contain varying proportions of all three types of pain: nociceptive, inflammatory and neuropathic. Yunus (1984) suggested that such pain could probably be most easily visualised in terms of a Venn diagram (Figure 1.3). The points where the circles intersect represents the pain of that patient and this may suggest treatment options. This pain picture varies between patients and for an individual patient, as their pain flares and wanes.

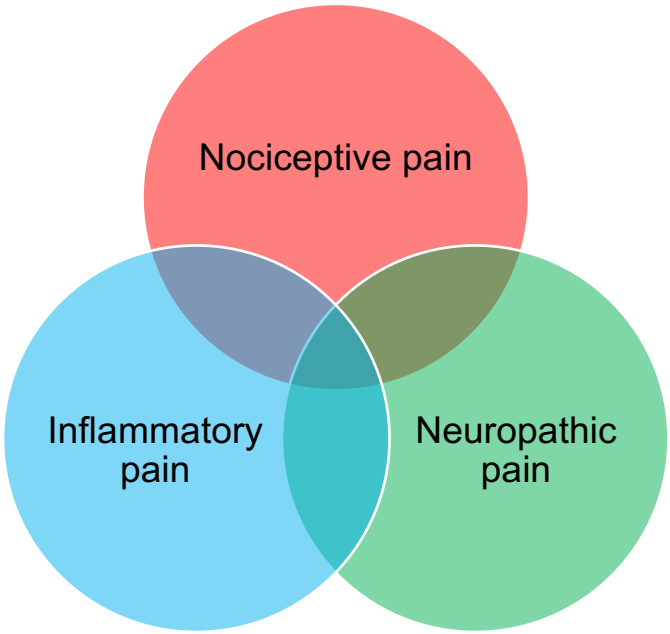

Figure 1.3 Suggested Venn diagram of a patient's pain

Based on Yunis (1984)

The dichotomy of patients' perceived pain and suffering, coupled with the possibility that it may have a significant psychological component, which often predominates (Cruccu and Truini, 2009) complicates treatment. Many patients find it challenging to understand that the pain, with which they may have lived for many years, may not result from actual damage to their bodies (O'Sullivan, 2015).

We should not be surprised if ongoing pain changed the brain. The brain changes when we learn anything: juggling (Driemeyer *et al.*, 2008), the taxi drivers 'knowledge' (Maguire, Woollett and Spiers, 2006) or pirouetting (Hanggi *et al.*, 2010). Such is the plasticity of the brain that it has been suggested: *"'we only use one particular brain once, because the next time we use it, it will have been changed."* (Villringer, 2010).

If this is the case it is be difficult to escape the conclusion that much chronic pain is likely to be of mixed origin. Therefore, patients who have chronic pain, resisting nociceptive analgesic therapy or which results in a reduced quality of life, should probably be assessed for the possibility of treatment with medicines used for the treatment of neuropathic pain (Freynhagen and Bennett, 2009).

Figure 1.4 sets out the major divisions of acute and chronic pain incorporating the definitions above.

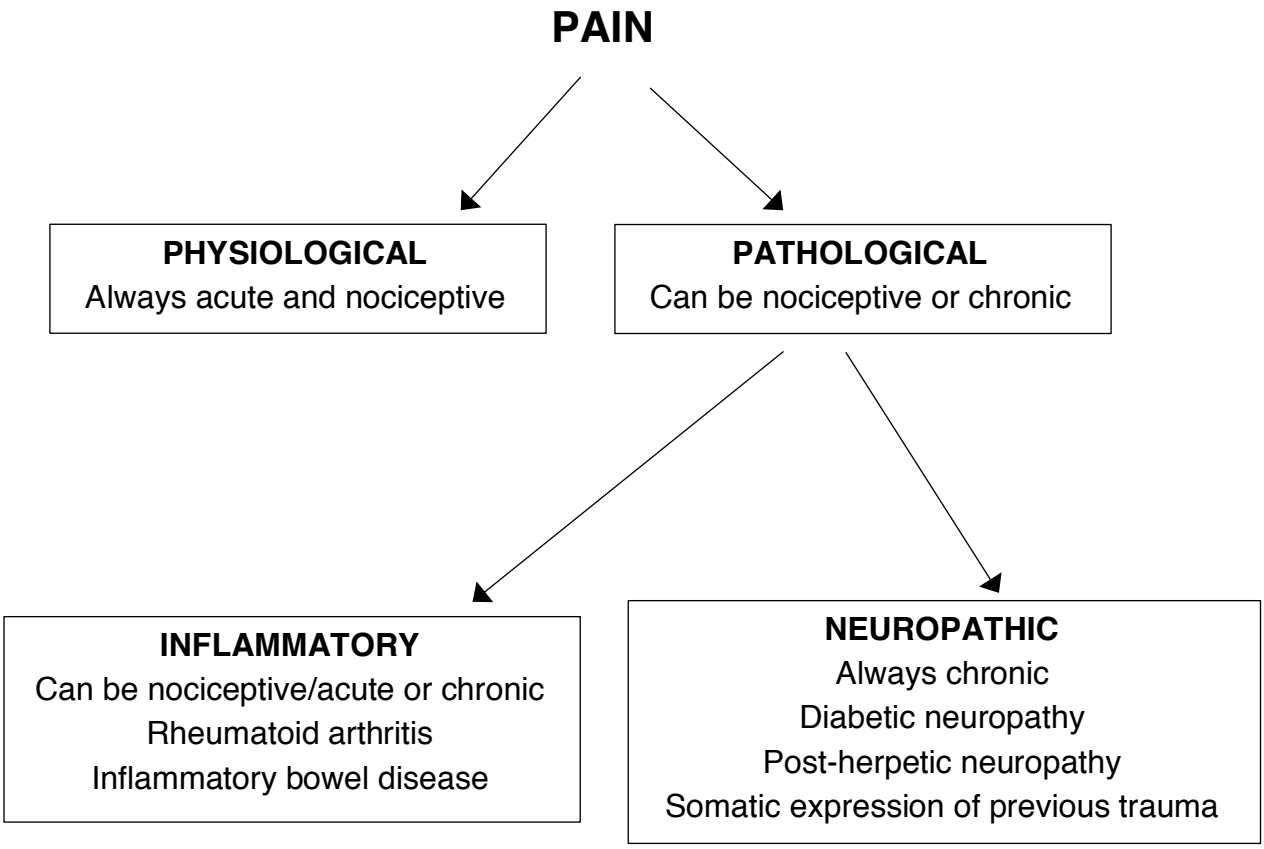

Figure 1.4 A diagrammatic representation of the types of pain.

1.5.2. AN OUTLINE OF THE PHYSIOLOGY OF PAIN

Written accounts about the theory of pain go back as far as Epicurus (347-270BC) who suggested that there was a direct pain pathway from the wound to the brain via the spinal column with pain being proportional to the size of the wound. There was no room in his proposals for pain without an obvious cause; this was regarded as not real; '*plus ça change'.*

By the end of the first millennium Avicenna (980-1037AD) was proposing that there should be 15 adjectives to describe pain. This proposition disappeared until relatively recently when researchers began to re-examine the subjective nature of pain (Melzack, 1975).

During the Second World War at the battles for Monte Cassino and Anzio the pain responses of severely wounded soldiers were recorded by Beecher (1946). Some of those with the most severe wounds were clearly not in pain. This led to a questioning of Epicurus' suggestion that the intensity of the pain was related to the size of the wound and the proposal that in some way pain was modulated by the body.

More recently Melzack and Wall (1965) proposed that there was a lower limit to pain transmission and any impulses which crossed that threshold would be subject to modulation and control. Their proposal also suggested that non-painful stimuli could close a 'gate' to a more painful stimulus. This gave a theoretical basis to the

observation that a patient with pain is less aware of their pain when they are completely engaged in a distracting task.

It is now understood that in common with many physiological systems, the body's response to pain is a balance between excitation and inhibition within the overall central nervous system (CNS). The upward transmission of excitatory pain impulses is via the dorsal horn into the CNS and is glutamate mediated. This is balanced by descending controls from the brain which exert strong inhibition on the dorsal horn and is mediated in the main by endogenous opioids, 5-HT/serotonin, nor-adrenaline and adenosine, in different locations within the spinal cord.

Pain pathways in the CNS are illustrated in Figure 1.5. Ascending nerve routes from the periphery via the 'dorsal horn' of the spinal cord and descending modulating nerve pathways. Painful stimuli terminate in the Somatosensory cortex. Modulating messages originate in the Somatosensory cortex and the Hypothalamus and exert their influences in the Rostral Medulla and in the Spinal cord. Pain medicines exert their effects in various places depending upon the mode of action of the individual medicine.

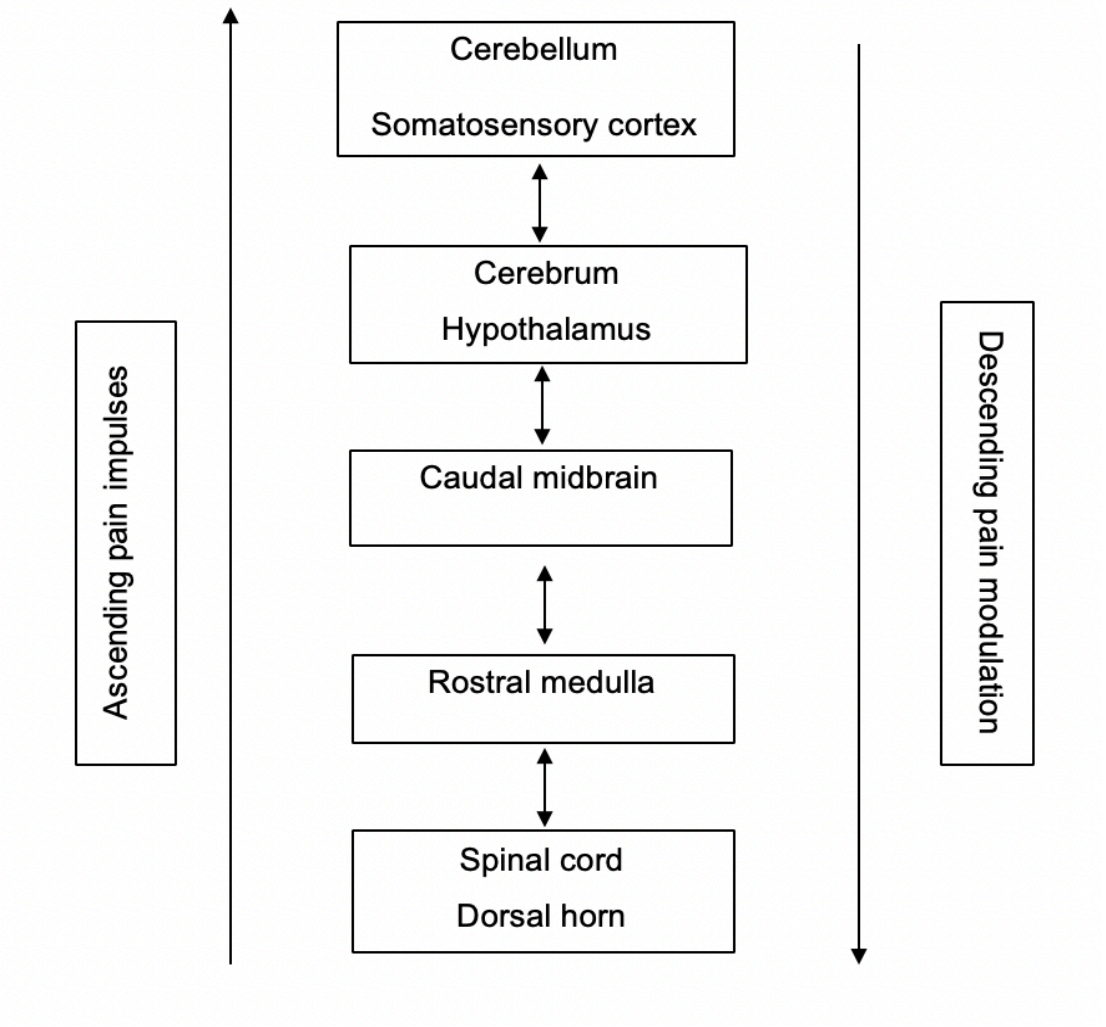

Figure 1.5 Schema of pain/modulation pathways

1.5.3. EPIDEMIOLOGY OF CHRONIC PAIN

Accurately determining the number of people with pain, nociceptive, neuropathic or chronic, is difficult. Pain is subjective, often transient and modulated by personal circumstances and therefore difficult to measure consistently and objectively. In Europe one in four people aged 15 and over "*experienced chronic pain in the past week of a magnitude sufficient to restrict activities"* (EU, 2007). The Scottish Intercollegiate Guidelines Network (SIGN) report that 18% of the population in Western Europe suffered with moderate to severe chronic pain (Colvin, 2013). Within England, the Health Survey 2011 reported that 31% of men and 37% of women suffered with chronic pain. This rose to 53% and 59% respectively for patients aged 75 and over (Bridges, 2011). A systematic review in the UK (Fayaz *et al.*, 2016) suggested that between a third and a half of the population suffered with some form of chronic pain and that between 10.4% and 14.3% of the population suffered with disabling chronic pain that was either moderately or severely limiting (Von Korff grades 3 & 4,) (Von Korff *et al.*, 1992). This equated to more than seven million people in the UK. These figures were higher than those reported in the National Pain Audit (Price *et al.*, 2012), which suggested that 6.4% of the population suffered with chronic pain with "*a high expressed level of need"* (Smith *et al.*, 2001)

In a randomly generated sample of 6,000 patients from six General Practices, 48% of patients suffered with chronic pain and 8% had pain which was predominantly of neuropathic origin as defined by the S-LANSS questionnaire (Torrance *et al.*, 2006). A review of world data by van Hecke *et al.* (2014) reported a population prevalence

for pain with neuropathic elements of between 6.9% and 10%. A postal survey was undertaken in France and analysed 23,000 replies. This reported 31.7% of the patients surveyed suffered with chronic pain and 19.9% regarded their pain as moderate to severe. This survey used the DN4 questionnaire for neuropathic pain which suggested that 6.9% of patients suffered with neuropathic pain and in 5.1% of the sample this was regarded as moderate to severe (Bouhassira *et al.*, 2008).

The relationship between chronic pain and neuropathic pain is complex. Research has suggested that up to 50% of patients with chronic lower back pain have elements of neuropathic pain (Freynhagen and Baron, 2009; El Sissi *et al.*, 2010; Kaki, El-Yaski and Youseif, 2005; Fishbain *et al.*, 2014). In addition, patients with neuropathic elements in their pain report higher pain intensities (Torrance *et al.*, 2006) and poorer quality of life (Smith *et al.*, 2007) than those with chronic pain without neuropathic elements. It is also reported that the complexity of the relationship between chronic pain and neuropathic pain is increased by the fact that the proportion of chronic pain patients who are regarded as suffering with neuropathic pain changes with the diagnostic tool used (Harrisson *et al.*, 2017). Another facet of the difficulty of measuring pain objectively and consistently.

The extent of the problem of chronic pain is exemplified, on a more localised scale, by the work of the CPS in South Staffordshire. The culmination of the therapeutic journey for many of the patients is the offer of a place on a PMP. The CPS offers these courses back-to back in five locations. On each course up to 15 places are

offered. Therefore, in a twelve-month period up to 600 patients are offered the opportunity to attend a PMP. The exact numbers who attend these courses at each location was not readily available because Trust records are filed by referring GP practices rather than by location of treatment.

1.5.4. THE NEED TO ACHIEVE CHRONIC PAIN CONTROL

Chronic pain is one of the commonest reason for a person to seek medical care (Hotchkiss, 2006). The UK Chief Medical Officer's report in 2008 suggested that the overall cost of chronic pain was approaching 1% of Gross Domestic Product (CMO, 2008). The total healthcare costs of UK patients with chronic lower back pain were double those of matched controls (Hong *et al.*, 2013). Patients with chronic pain were five times more likely to visit an Accident and Emergency (A&E) department than matched controls (Hadi and Alldred, 2015). Similar figures are not available for the costs of neuropathic pain in the UK (O'Connor, 2009). In the US in 2000 the healthcare costs of patients with 'Painful Neuropathic Disorders' were more than three times the costs of matched controls (Berger, Dukes and Oster, 2004).

The need to achieve an overall improvement in pain control is therefore twofold: reduce personal suffering and reduce the cost of treatment and associated societal costs. As a result, there needs to be an effective and efficient service for the treatment of people suffering with chronic pain. In times of financial restriction, it is easy to focus on the cost of the medicines used and overlook the costs to the individual and society (RCGP, 2013).

1.5.5. GUIDANCE FOR TREATING CHRONIC PAIN

Evidence-based guidance is the best way to ensure that pain medicines are used appropriately -

i. The World Health Organisation (WHO) Pain Ladder sets out, in three easily understandable steps, how pain medicines should be used to achieve the greatest possible reduction in pain (WHO, 1986). (This is laid out in more detail below)

ii. The National Institute for Health and Care Excellence (NICE) Guidelines, lays out best practice guidelines for all aspects of health care pointing practitioners toward evidence-based practice.

iii. The Cochrane Organisation – sets out to organise medical literature in a way, which facilitates evidence-based treatments.

iv. *'At a glance guide to prescribing analgesics for non-malignant chronic pain'* A guidelines published by the Staffordshire Area Prescribing Committee to offer guidance to local GPs (Appendix 8.1).

v. The Oxford League Table of Analgesics in Acute Pain sets out the comparable efficacies of a number of analgesics in the treatment of acute pain based on their number needed to treat (NNT) (FOPM, 2007). This table does not relate to chronic pain but this information may be helpful as an indication of the likelihood that a particular analgesic would be effective for the nociceptive elements of the patients' pain.

Each of these guidelines offers an insight into an aspect of the treatment of chronic pain. Taken together they represent the best route available towards the successful treatment of chronic pain.

1.5.5.1. WHO Pain ladder

In 1986 the WHO promulgated a logical framework for the treatment of cancer pain, the Analgesic Ladder (WHO, 1986) (Figure 1.6). It suggested that when a small number of medicines were used appropriately, sequentially and progressively as pain increased in severity, the analgesic results were better (Ventafridda *et al.*, 1987). This treatment plan become the foundation for many subsequent guidelines used in the treatment of different types of pain.

Step one of the WHO analgesic ladder, suggests that patients, presenting with mild to moderate pain, should start with regular paracetamol or if the pain involves inflammation an NSAID. For neuropathic pain this should be bolstered with an adjuvant such as a tricyclic anti-depressant or a gabapentinoid, as necessary. Patients whose pain is not controlled with these medicines or presenting with more severe pain would be offered the same combinations with the addition of a 'mild/moderate opioid'. Patients with even more severe pain would be offered a 'strong opioid'. Initial assessment is essential for correctly identifying appropriate pain medicines with regular ongoing reviews equally important especially in situations where pain levels very.

Figure 1.6 illustrates the three step WHO pain ladder and the medicines that are included in each step.

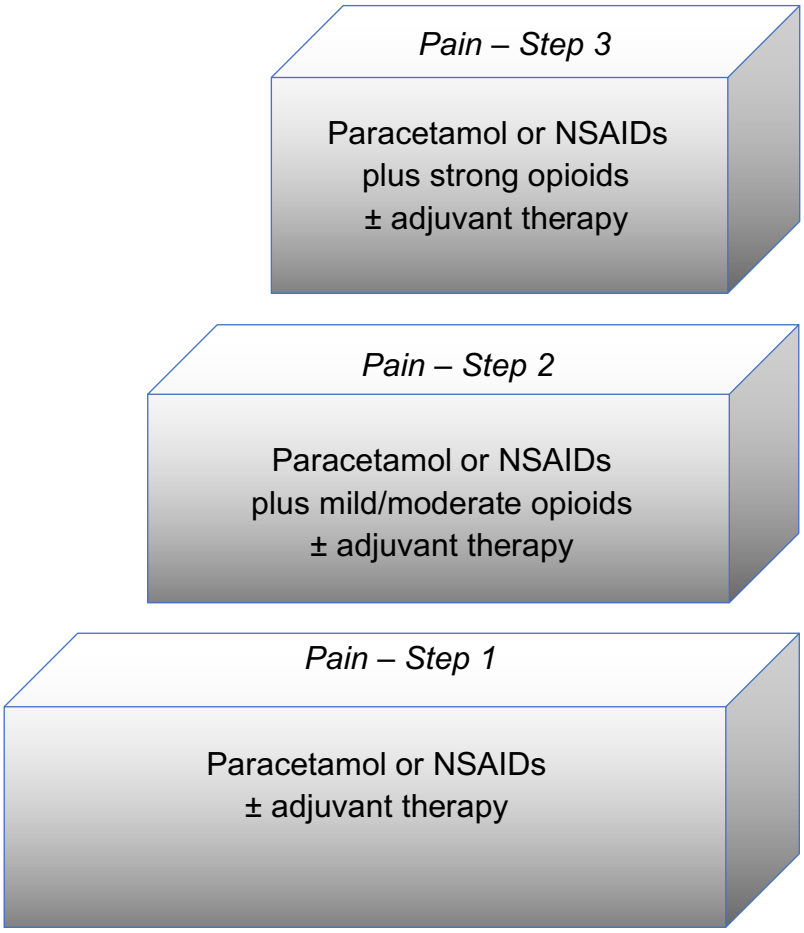

Figure 1.6 The WHO pain treatment ladder

As suggested by WHO (1986)

The WHO also set out the rules for how analgesics should be taken, if they are to give the benefits claimed (Reid and Davies, 2004). They should be taken 'by mouth', 'by the clock' i.e. regularly, if appropriate, 'by the ladder' i.e. additive, and progressive following the increments suggested, 'for the individual' because each patients' pain is

unique to them and 'with attention to detail' because only the patient understands their pain' (Manias, Botti and Bucknall, 2006). These comments are incorporated into the advice from the CPS with one addition. Chronic pain flares and wanes constantly, therefore regimens for pain medicines must somehow allow for this.

By following the three steps of the WHO pain treatment ladder, it is reported that adequate pain relief could be achieved with nociceptive pain for between 70% and 80% of patients (Vargas-Schaffer, 2010). Partial relief for neuropathic pain could be achieved for between 40% and 60% of patients (Dworkin *et al.*, 2007).

1.5.5.2. Application of guidance for the treatment of chronic pain

Within the South Staffordshire CPS, the WHO Pain Ladder is used as originally promulgated, with the following four provisos

i. Many patients with chronic pain find NSAIDs helpful. The Oxford League Table ranks many of these as having NNT's of less than 2 (FOPM, 2007). However, these medicines carry the possibility of side effects, which worsen with age (Pirmohamed *et al.*, 2004) and many of the patients that attend the CPS are in older age groups. The British National Formulary (BNF) (JFC, 2017) recommends using the 'lowest dose' for the 'shortest possible time'. Because of this it is suggested to patients, for whom these medicines were effective and appropriate, that if possible they reserve NSAIDs for use either

when their pain flared or for pre-emptive use when they were going to engage in an essential activity, which they knew will cause them pain.

ii. The consistent use of any opioid therapy leads to a rightward shift in the dose response curve *i.e.* the development of tolerance (Collett, 1998; Freye and Latasch, 2003; Chu *et al.*, 2012). It is reported that varying the dose on an ongoing basis delays the development of this tolerance (Duttaroy and Yoburn, 1995; Dighe *et al.*, 2009; Brennan, 2013; Sullivan, 2014). Therefore, patients were advised to seek an opportunity to vary the dose of their opioids with the intensity of their pain. Suggestions include varying doses in anticipation of the pain likely to be caused by their plans for the day, avoiding the maximum dose if possible and aiming for an 'opioid free' time as frequently as possible.

iii. Strong opioids are retained for use only as a last resort. Their use in the treatment of chronic pain is controversial (NHS, 2015). They create multiple overt and covert side effects and above a morphine equivalent dose of more than120mg daily it is suggested that the side effects are likely to outweigh any benefits (NHS, 2015).

iv. Treatment is generally additive, one drug in addition to the previous regimen. Paracetamol is reported to offer dose sparing effects for opioids (Colvin, 2013; Valentine *et al.*, 2015; Zeidan *et al.*, 2014) and synergism with NSAIDs (Miranda *et al.*, 2006). The relative safety of paracetamol and NSAIDs are discussed in Section 1.6.1 and Section 1.6.4. Additive therapy is premised upon the suggestion that higher potency analgesics will generally have greater

side effects and therefore it is important to take advantage of as much benefit a possible from lower potency medicines, with possibly fewer side effects.

1.6. Drugs used for the treatment of pain

The aim of this section is to outline the context for the use of medicines to treat chronic pain because medicines used for the treatment of nociceptive pain may not be effective in the treatment of chronic or neuropathic pain (Colvin, 2013). It will then highlight those aspects of pharmacology and pharmacokinetics, which are relevant to the treatment of chronic pain.

Our understanding about, and the treatment of chronic pain, is moving towards a more guidance based, multi-professional approach. Medicines have a role in the treatment and management of chronic pain but they are rarely an answer in themselves. Pain medicines will not, usually, create a chronic pain free state, but their appropriately targeted use by patients can help to facilitate the achievement of necessary everyday tasks, which are known to be painful. The significance of any benefit varies with the particular condition and patient being treated.

When a medicine is used to treat any condition there is always a balance to be struck between benefit and the possibility of side effects. As a result, any discussion between the pharmacist or any other Health Care Professional (HCP) and the patient about their pain and medicines must fully explore the following questions. Does the medicine elicit a therapeutic response? Are the side effects, acceptable? Are the

directions for their use understandable and achievable? Finally, regardless of the efficacy, tolerability or practicality is the patient willing or likely to take the medicine?

The drug groups currently used in the treatment of chronic pain, with the commonly used examples within the CPS are:

i. Paracetamol
ii. Opioids
    a. Mild/moderate – codeine, dihydrocodeine, tramadol
    b. Strong - morphine, oxycodone, fentanyl, buprenorphine, tapentadol
iii. Anti-depressants – amitriptyline, nortriptyline, duloxetine.
iv. Gabapentinoids – gabapentin, pregabalin.
v. Non-steroidal anti-inflammatories (NSAIDs) – ibuprofen, naproxen, diclofenac
vi. Topical applications – NSAID gel, lidocaine plaster (very occasionally), capsaicin cream

Each of these groups, except the opioid subdivision, exhibit different mechanisms of action. The examples within each group will have slightly different efficacy and side effect profiles and it is a combination of these two factors, which determine the ability of an individual medicine to affect a reduction in pain for a specific patient with an acceptable level of side effects. As a result, it is important to remember that failure with any one medicine does not necessarily imply failure with any other (Moore *et al.*, 2015b).

1.6.1. PARACETAMOL

Paracetamol is classified as a mild/moderate analgesic and is widely available, being regarded as safe enough to be allowed unrestricted sale in a pack of 16 tablets. The adult dose is 1g up to a maximum of four times a day i.e. one dose is effective for about six hours, with no flexibility for additional doses. At this dose it is normally, but not uncontroversially, regarded as a safe, first line analgesic therapy for patients with normal liver function (Wise, 2015; Hall, 2016; Machado *et al.*, 2015). For acute lower back pain Bandolier suggests an NNT of 3.5 (FOPM, 2007), but for chronic lower back pain a Cochrane review suggested that it is probably ineffective (Saragiotto *et al.*, 2016).

As outlined above (Section 1.5.3) up to 50% of chronic lower back pain may contain elements of neuropathic pain. To investigate the place of paracetamol in the treatment of neuropathic pain, either with or without codeine, Wiffen *et al.* (2016) undertook a systematic review and concluded that there was insufficient evidence to determine whether or not paracetamol provides effective analgesia. Regardless of this, patients often actively report benefit when taking paracetamol for their pain.

The balance of evidence about whether or not paracetamol should be regarded as suitable for first line therapy in chronic pain is constantly being reviewed. In particular its effectiveness in the treatment of low back pain and osteoarthritis was questioned (Zhang, Jones and Doherty, 2004; Shamoon and Hochberg, 2001; Abdulla *et al.*, 2013; Machado *et al.*, 2015; Roberts *et al.*, 2015). Paracetamol, as

with all medicines has the potential to cause side effects and therefore there must be some benefit to balance against this possibility. Most recently it has been suggested that paracetamol should be regarded as first line therapy with or without codeine because the alternatives, NSAIDs are generally regarded as less safe (Kress and Untersteiner, 2017). In the treatment of mild to moderate pain the Drug and Therapeutics Bulletin suggests that paracetamol should be regarded as a first line therapy, with an analgesic efficacy similar to aspirin but with less gastro-intestinal irritation because of its different mechanism of action (DTB, 2018).

In the treatment of osteoarthritis a systematic review by Zhang, Jones and Doherty (2004) suggests that paracetamol is effective but not as effective as NSAIDs, but because NSAIDs are not as safe as paracetamol these medicines should be reserved for patients for whom paracetamol is ineffective. There is also support from Kress and Untersteiner (2017) for the use of paracetamol before NSAIDs, in vulnerable groups such as, the elderly, pregnant women and patients with gastro-intestinal and cardiovascular conditions

The mode of action of Paracetamol is not fully understood. The main mechanism of action is the inhibition of the Cyclooxygenase system, more specifically a selective COX-2 inhibitor (Derry, Derry and Moore, 2013; Twycross *et al.*, 2013). Evidence of this inhibition has been observed in the CNS, spleen and lungs. However, this cannot be the entire picture because paracetamol exhibits synergy with NSAIDs (Derry, Derry and Moore, 2013) and synergy demands a second mechanism of

action. There is evidence that paracetamol also influences serotonin, opioid, nitric oxide (NO) and cannabinoid pathways (Jozwiak-Bebenista and Nowak, 2014; Sharma and Mehta, 2014). These modes of action may account for some of the unusual paracetamol side effects reported by patients in this research *e.g.* sedation, nausea/vomiting and dry eyes.

Paracetamol is metabolised in the liver, mainly by two bio-transformational pathways. The majority is converted either to a glucuronide (~55%) or a sulfonate (~35%), which are then excreted via the kidneys. Both of these metabolic steps are 'rate limited'. Less than 5% is excreted unchanged (Mazaleuskaya *et al.*, 2015). Between 5% and 10% is converted along the cytochrome P450 (CYP) CYP2E1 pathway to the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). At therapeutic doses of paracetamol, the NAPQI which is produced conjugates with glutathione (GHS) and is rendered safe. During paracetamol over dosage, either acute or chronic, the quantity of paracetamol which remains after the glucuronide and sulfonation transformations are maximised increases. This increased availability of paracetamol leads to an increase in the amount of NAPQI created. The protective glutathione conjugation is then overwhelmed and toxic damage to the liver results (Buclin, Nicod and Kellenberger, 2009).

Chronically malnourished patients may have diminished body stores of glutathione. This reduces the liver's ability to undertake the GSH conjugation of the NAPQI. The interaction of alcohol and or alcohol induced liver damage and paracetamol is not at

all clear. There is no good evidence to support the suggestion that alcoholics are at increased risk of liver damage from therapeutic or toxic doses of paracetamol. (Rumack, 2004; Prescott, 2000)

A Drug Safety Update from NICE (2010) reviewed the dosage recommendations for intravenous (IV) paracetamol. The BNF contains a warning that there is an increased risk of toxicity with a daily IV dose of 4g of paracetamol for adult patients with a body weight of under 50kg and who have risk factors for hepatic damage. It is also suggested that clinical judgement should be used to adjust oral doses of paracetamol for such patients (DTB, 2018). At least one hospital formulary committee has formalised this by suggesting that for patients with a body weight between 41kg and 49kg the oral dose of paracetamol should be 750mg four times a day and between 31kg and 40kg, 500mg four times a day (NHS, 2018a). However NICE reports no evidence that low body weight alone would lead to increased paracetamol toxicity (NICE, 2015a).

1.6.2. OPIOIDS

Opioid is the generic term used to describe medicinal compounds which produce an effect similar to the dried latex which exudes from the seed pods of Opium poppies. Almost all opioids have the ability to create analgesia and at the same time cause tolerance, dependence and addiction.

Opioids are commonly classified according to their potency. Head to head comparisons of different opioids in equipotent doses failed to show any difference in their side effect burden (Drewes *et al.*, 2013).

- Mild/moderate opioids *viz.* codeine, dihydrocodeine and tramadol (NICE, 2015b). Doses of opioids are expressed in terms of their morphine equivalence, but this can vary depending upon the route and frequency of administration. Mild/moderate opioids are regarded as having a potency of between one eighth and one tenth of morphine (NHS, 2012; NICE, 2015b).
- Strong opioids *viz.* morphine, oxycodone, buprenorphine, fentanyl and tapentadol.

Both tramadol and tapentadol sometimes demonstrate additional analgesic efficacy in the treatment of neuropathic pain over and above their nominal morphine equivalent dose. They both act on other receptors in addition to their Mu opioid activity. Tramadol inhibits the reuptake of both serotonin and noradrenalin and tapentadol inhibits the reuptake of noradrenaline.

Opioids have two major therapeutic effects. Within the dorsal horn they cause the inhibition of the upward transmission of pain. Centrally they offer downward modulation of pain. In addition, it has been reported that opioid receptors are expressed in the periphery as part of the inflammatory response and therefore opioids may also act in this location (Sawynok, 2005; Smith, 2012).

Some opioids, *e.g.* codeine, tramadol and to some extent oxycodone must undergo biotransformation either to make them effective or to increase their effectiveness. These transformations are undertaken via the CYP enzyme pathway in the liver. The necessity for this transformation means that the time from administration to achieving an active blood level may be altered.

Table 1.1 Variants of CYP enzymes involved in opioid bio-transformations (Ma, Woo and McLeod, 2002; Smith, 2009; Kapur, Lala and Shaw, 2014).

Converted from	Converted to	Variant of CYP involved
Codeine	Active morphine	2D6
Tramadol	Active O-desmethyl tramadol	3A4, 2D6
Some oxycodone	Some active oxymorphone	2D6

The levels of expression of CYP enzymes in an individual are under the control of more than one gene which is described as polymorphism. As a result, the level of their activity of these systems can vary between individuals. It Is reported that 6-10% of Caucasians, 2-5% of African Americans and 1% of Asians are classified as having lower levels of the 2D6 variant. Such people are classified as slow metabolisers and may be poorly served by analgesics which require these transformation (Ma, Woo and McLeod, 2002). In addition, the MHRA suggests that between 3% and 6% of Caucasian patients are ultra-rapid metabolisers (MHRA, 2013).

The influence of inter-patient variation in opioid metabolism and effect that this has on analgesia has long been reported, (Smith, 2009). There is no reason to suspect that patients who were being treated for chronic pain would be exempt from these variations. Therefore, for patients who receive no benefit from a dose of codeine, tramadol or to a lesser extent oxycodone, is this because the patient's pain is resistant to these medicines, because the necessary bio-transformation has not taken place or they really just haven't taken their medicine. The lack of biotransformation may be tested by a trial with an alternative which has its own innate activity *e.g.* 'switching' from codeine to dihydrocodeine

All opioids carry a side effects burden, which is related to their potency and the dose used. The common opioid side effects are drowsiness, sedation, nausea, sickness, constipation and respiratory depression. The FOPM (2018) suggested that in normal clinical practice more than 80% of patients will experience at least one side effect from opioid therapy. Between 20% and 33% of patients are expected to experience nausea on initiation of opioid therapy and half of these will experience frank vomiting (Swegle and Logemann, 2006; Smith and Laufer, 2014). Even with mild/moderate opioids such as codeine some patients will discontinue therapy because of side effects (Straube *et al.*, 2014). Constipation should always be expected with opioid therapy because tolerance to this effect develops much more slowly (Collett, 1998). Those patients who are able to tolerate the nausea, sickness and drowsiness until tolerance to these symptoms develops will probably experience them again if and

when the dose is increased. Overall it is suggested that between a quarter and a half of patients will withdraw from opioid therapy because of adverse effects (Moore and McQuay, 2005; Kalso *et al.*, 2004).

Opioids also have a range of other significant but less obvious side effects. These include cognitive impairment, sleep disturbance, effects on the immune system – itching, effects on the endocrine system – fertility, sex drive (hypogonadism), cortisol production and reduction in bone density (Baldini, Von Korff and Lin, 2012; Benyamin *et al.*, 2008).

There is one other point which is possibly relevant to opioid prescribing in the treatment of chronic pain. It is reported that when equivalent doses of sustained release (S/R) and immediate release (I/R) opioid formulations are used to treat chronic pain S/R preparations are a greater driver towards hypogonadism than I/R formulations (Rubinstein, Carpenter and Minkoff, 2013). This suggests that opioid side effects are not only related to the medication itself but also to the dosing regimen used.

Opioid tolerance (OT) is an inevitable neuroadaptation of continuous and/or long-term opioid therapy and it may even start with the first dose (Kornetsky and Bain, 1968). It is defined as the gradual loss of analgesic efficacy over time. (Collett, 1998; Freye and Latasch, 2003; Chu *et al.*, 2012; Morgan and Christie, 2011). The effects of tolerance to the different opioid side effects i.e. nausea, analgesia, respiratory

depression and constipation can be observed developing at varying speeds (Hayhurst and Durieux, 2016; Steinberg, 2017; Volkow, Benveniste and McLellan, 2018). This can be advantageous in clinical practice where tolerance to respiratory depression develops more quickly than to analgesia. It is suggested that opioid tolerance can be reduced by 'switching' between different opioids (CADTH, 2017; Mitra *et al.*, 2013; Gatti *et al.*, 2010; Quigley, 2004)

In some patients ongoing opioid therapy can also lead to opioid induced hyperalgesia (OIH). This is a clinical condition in which the patient's nociceptive receptors are sensitised in some way by exposure to opioids, thereby, paradoxically, causing them to feel greater pain (Lee *et al.*, 2011; Ballantyne and Mao, 2003; Hayhurst and Durieux, 2016). The differential diagnosis between OT and OIH can be difficult and is out with the scope of this thesis. Either can lead to an apparent decrease in the efficacy of opioid analgesia and therefore an increase in the patient's pain (Tawfic, Faris and Date, 2013).

Opioid tolerance is specifically reported as a problem for chronic pain patients where there is an aspiration that a reduction in pain would lead to improved physical functionality (McAllister, 2016). In such patients the continuous dose escalation, needed to overcome the development of tolerance/hyperalgesia, is not a real therapeutic option because of the increase in dose related opioid side effects (Baldini, Von Korff and Lin, 2012; Brennan, 2013). As an alternative to ever

increasing doses others have reported phasing out the opioid therapy can lead to a reduction in pain (Baron and McDonald, 2006).

The development of tolerance may not be inevitable and it is reported that continuous exposure caused greater tolerance than intermittent exposure (Duttaroy and Yoburn, 1995; Morgan and Christie, 2011). Ballantyne (2017) suggested that in the treatment of chronic pain occasional or intermittent use of opioids may provide equivalent or better analgesia, with the development of less tolerance. In addition, patients often report a preference for intermittent therapy, because it allows them to tailor their analgesia more closely to their needs, enabling them to focus on their life rather than their pain (Fine, Mahajan and McPherson, 2009). The availability of both I/R and S/R formulations within an individual's analgesic regimen can facilitate an equi-analgesic state with a lower overall opioid dose (Ghodke *et al.*, 2017).

High efficacy opioids are reported to demonstrate less tolerance than low-efficacy opioids (Morgan and Christie, 2011) but this is not necessarily the case in practice. When used as transdermal formulations the use of the high-efficacy fentanyl demonstrates a greater development of tolerance than the low-efficacy buprenorphine (Sittl, Nuijten and Poulsen Nautrup, 2006). It is suggested that this apparent contradiction may be due to the buprenorphine's lower potential for down regulation of the Mu opioid receptor (Morgan and Christie, 2011; Hans and Robert, 2009)

Prescribed opioids also carry the on-going risk of dependence and addiction (Morgan and Christie, 2011). Patients frequently ask about the addiction potential of all pain medicines, not just opioids, because they conflated messages about opioids with other groups of medicines. Such misinformation makes the job of educating patients about the possible side effects of their pain medicines even more challenging.

1.6.2.1. Codeine

Codeine is generally classified as a mild/moderate opioid analgesic. When used for analgesia the BNF suggests a dose of 30mg-60mg up to four times a day as required. It has a potency of approximately one tenth of morphine.

Codeine is inactive and needs to be bio-transformed by CYP2D6 enzymes into active compounds such as morphine before it is effective. For patients who are slow metabolisers (Table 1.1) the analgesic response would develop slowly, if at all. For those who are ultra-rapid metaboliser the effect would peak very quickly and then fade.

1.6.2.2. Dihydrocodeine

Dihydrocodeine has similar analgesic properties to codeine but does not require bio-transformation. When used for analgesia the BNF suggests is a maximum daily dose of 240mg. The frequency of dosing and the size of the individual dose are dependent upon the formulation being used. The potency is approximately one tenth of morphine.

There is a perception that dihydrocodeine may be more addictive than codeine. Roussin, Plalmaro and Lapeyre-Mestre (2016) reviewed this and reported that there had been no evaluation of experimental data regarding its abuse potential.

1.6.2.3. Tramadol

The BNF describes tramadol as an opioid for moderate to severe pain, but NICE classifies it as a mild/moderate opioid analgesic (NICE, 2015b) and recommends it as a rescue pain medicine in the treatment of neuropathic pain (NICE, 2013b). It is included in the local Stoke guidance for the treatment of chronic non-malignant pain as a moderate analgesic (Njoku, Rosam and Ashworth, 2017). McQuay *et al.* (1997) report from a meta-analysis that the NNT for a 50% reduction in pain using tramadol 50mg (NNT = 8) is about half that of codeine 60mg (NNT = 17).

NICE Clinical Knowledge Summaries (CKS) report that there is evidence that tramadol is effective for treating back pain and osteoarthritis. The side effects are similar to codeine or dihydrocodeine but the possibility of drug interactions are greater (NICE, 2015b)

The marketed tramadol product is a racemic mixture of (+) and (-) enantiomers. These enantiomers act directly upon two different receptor systems. The (+) enantiomer is more selective for inhibiting serotonin reuptake whilst the (-) enantiomer is more selective for inhibiting the reuptake of noradrenaline. The Mu

opioid activity was almost entirely due to the o-desmethyltramadol metabolite. The bio-transformed (+) enantiomer showing more analgesic potency than its (-) partner (Gibbison, Bailey and Klein, 2015; Dayer, Desmeules and Collart, 1997; Grond *et al.*, 1999). The biotransformation of tramadol to the active O-desmethyltramadol uses the polymorphic CYP2D6 pathway. This effect is not quite as clear-cut as with codeine because of tramadol's other actions (Smith, 2011). Therefore, in a similar way to codeine patients who are slow metabolisers may be poorly served by tramadol.

Only about 30% of the analgesic action of tramadol are reversed by naloxone (Gibbison, Bailey and Klein, 2015). Therefore, other mechanisms must be involved. The effects on serotonin and noradrenaline have already been mentioned. In addition, it is suggested that tramadol has some activity at the N-methyl-D-aspartate (NMDA) receptor and that this action contributes to tramadol's reported effectiveness in the treatment of neuropathic pain (Hollingshead, Duhmke and Cornblath, 2006; Hara, Minami and Sata, 2005).

Tramadol's effect on serotonin and noradrenaline reuptake increases the potential range and severity of side effects up to and including serotonin syndrome (Duehmke *et al.*, 2017). When used for analgesia the BNF suggested a licensed maximum daily dose of 400mg. In the treatment of neuropathic pain NICE suggests that tramadol be used for acute rescue therapy (NICE, 2019).

1.6.2.4. Morphine

Morphine is the standard against which the potency of all other opioid analgesics are equated/measured. It may be prescribed orally as liquid, I/R or S/R preparations.

The main routes of metabolism and excretion for morphine are glucuronide conjugation at the 3- or 6- hydroxyl groups (Christrup, 1997). Morphine glucuronides are excreted via the kidneys. Morphine-6- glucuronide (M6G) is 10-20 times more potent than its parent compound. It has been reported that the majority of the analgesic effect of a dose of morphine results from the action of the M6G and therefore a patient's optimum dose of morphine may, in some way, be related to their kidney function (Klimas and Mikus, 2014). Therefore the dose of morphine should be reviewed regularly in patients with kidney failure (Neerkin, Brennan and Jamal, 2006). A proportion of the M6G passes out with bile into the intestine, from where it may be recirculated. Between 7% and 10% of a dose of morphine is excreted in the faeces (Stain-Texier, Sandouk and Scherrmann, 1998; FDA, 2012).

1.6.2.5. Oxycodone

Oxycodone is a partial pro-drug. The parent compound is responsible for the largest proportion of the analgesia. Some of the dose is bio-transformed by CYP2D6 to oxymorphone, which exhibited significant analgesic activity. Therefore, it is suggested that patients who are slow metabolisers may have an altered response to Oxycodone (Smith, 2011; Trescot *et al.*, 2008a; Trescot *et al.*, 2008b).

On occasions it is necessary to change from one opioid to another and approximately equivalent doses were required. For example, the BNF recommends that for oral dosing 10mg of morphine equates to 6.6mg of oxycodone. On the other hand, the manufacturers suggest 10mg of morphine equated to 5mg of oxycodone and this particular ratio is supported by the West Midlands Palliative Care Physicians (NHS, 2012). Such conversion factors need to be approached with care. Arbitrary equi-analgesic dose ratios cannot take account of the genetic make-up, other metabolic differences and the tolerance status of individual patients.

1.6.2.6. Buprenorphine

Buprenorphine is used both as a transdermal patch and as a buccal/sublingual tablet. As a transdermal formulation its potency is approximately 80 times morphine. The time to steady state depends upon the formulation used and is up to 60 hours and half-life after removal up to 36 hours. For sublingual use its potency is approximately 50 times morphine. The buccal tablet had a bioavailability of 50% and is initially effective in about 30min. This time increases significantly on repeat dosing. Such a delay means that this formulation is not ideal for treating breakthrough pain (Foster *et al.*, 2013).

Buprenorphine is a partial agonist – antagonist and it is suggested that this combination has advantages in reducing some of the side effects associated with strong opioids. It is claimed that buprenorphine is safe for use in renal impairment

(Boger, 2006; Forrest and Kuczynska, 2016). Therefore the transdermal formulation is often regarded as appropriate for elderly patients (Vadivelu and Hines, 2008).

For those who can tolerate the systemic effects of buprenorphine, there is one additional adverse effect with the transdermal formulation, which can be troublesome *i.e.* a localised allergic reaction to patch. This can be sufficiently acute to generate a blister and therefore termination of therapy. Although the adhesive has been blamed for some of these occurrences, there are reports of a delayed hypersensitivity reaction to buprenorphine (Kyrklund, Hyry and Alanko, 2013).

The major metabolite of buprenorphine is norbuprenorphine. This and the parent compound are conjugated prior to excretion (Smith, 2011). There is evidence of some enterohepatic circulation of buprenorphine (Cone *et al.*, 1984; Foster *et al.*, 2013) which helps maintain its steady plasma levels and long biological half-life.

1.6.2.7. Fentanyl

Fentanyl is available as a transdermal patch, and as nasal spray and buccal preparations for more immediate effects. The transdermal formulation has a potency of about 100 times morphine. Time to steady state blood levels from a patch is 12-16 hours with half-life of 16-22 hours after removal (Kornick *et al.*, 2003) shorter that for a buprenorphine patch. Bioavailability of the nasal spray is approximately 90% reaching an effective dose within 11-20minutes. This makes the nasal route for fentanyl suitable for acute breakthrough pain. For buccal preparations the

bioavailability varies between 50% and 70% with a much longer time to an effective dose 30-240minutes (Kuip *et al.*, 2012). The buccal preparations contain sucrose and therefore appropriate oral care is necessary.

Fentanyl patches do not generally cause a local dermal allergenic response, but there are on-going problems with the adhesion of the patch. Absorption of the drug from the patch varies with body temperature, skin type and placement. Therefore, patients sometime experience variance in their dose after exercise, bathing or sitting in the sun, which was case reported as significant (Sindali *et al.*, 2012).

Fentanyl is more than 99% metabolised to norfentanyl by the CYP3A4 system but there is no evidence that any of the metabolites were active. Therefore, conditions or medicines which alter the enzymatic profile of the liver have the potential to alter clearance of fentanyl (Smith, 2009).

1.6.2.8. Tapentadol

Tapentadol has a dual mode of action. It interacts with the Mu opioid receptor and inhibits the reuptake of noradrenaline, neither of which require any bio-transformation (Langford *et al.*, 2016). It has an analgesic potency somewhere between Tramadol and Morphine.

The double action of tapentadol, suggests that, as with tramadol, it may be effective in the treatment of neuropathic pain (Sugiyama *et al.*, 2018). Early reports indicate

that it will probably have a place in therapy but evidence is still scarce (Baron *et al.*, 2016; Langford *et al.*, 2016; Vranken, 2015; Coluzzi *et al.*, 2017; Reimer *et al.*, 2017; Sugiyama *et al.*, 2018). It is licensed for use 'third line' in treatment of painful diabetic neuropathy in the US in 2013 (Games and Hutchison, 2013). It has recently been added to local Stoke chronic pain guidance (Njoku, Rosam and Ashworth, 2017) as a suggested treatment for neuropathic pain and is therefore beginning to be prescribed by local GPs in Staffordshire.

1.6.3. DRUGS USED FOR THE TREATMENT OF NEUROPATHIC PAIN

This section will address the available adjuvant medicines prescribed for the treatment of neuropathic pain.

There are five medicines recommended in the BNF which may be used for the treatment of neuropathic pain; amitriptyline, nortriptyline, pregabalin, gabapentin and duloxetine. The reported NNTs and NNHs for these medicines (Table 1.2) provide an interesting insight into their relative efficacy and potential for harm.

Table 1.2 NNT & of NNH medicines used in the treatment of neuropathic pain

With placebo and tramadol included for comparison (Haroutounian and Finnerup, 2018).

Type of pain medicine	NNT (95%CI*)	NNH (95%CI*)	Achieved analgesia with placebo (%)
Tricyclic antidepressants	3.6 (3.0-4.4)	13.4 (9.3-24)	85/475 (18%)
Serotonin/noradrenaline antidepressants (e.g. duloxetine)	6.4 (5.2-8.3)	11.8 (9.6-15)	278/982 (28%)
Gabapentin	7.2 (5.9-9.1)	25.6(15-79)	291/1430 (20%)
Pregabalin	7.7 (6.5-9.4)	13.9 (12-17)	578/2410 (24%)
Tramadol	4.7 (3.6-6.7)	12.6 (8.4-19)	96/361 (27%)

* Confidence limits

Overall, tricyclic antidepressants (TCAs) have the lowest NNT and a similar NNH to others in this group. Tramadol has the second lowest NNT with an NNH in line with other medicines. Gabapentin stands out as having the best NNH, much better than pregabalin. For clinical practice this would suggests that the initial therapeutic option should be either a TCA or gabapentin. The final choice between the two then being made by other factors such as medicines interactions with TCAs, the possibility of side effects and the much larger number of dose units required for gabapentin treatment.

These figures also highlight that in the treatment of neuropathic pain, the recommended medicines were demonstrably effective in only a minority of patients. This table also includes data from trials which included a placebo arm.

These data presuppose that all neuropathic conditions are treatable in the same way and this may or may not be the case. Mendlik and Uritsky (2015) suggested that varying the medicine can sometimes bring unexpected benefits and needs further explanation. This also gives support to Smith *et al.* (2012) whose Delphi study reported that at least four different medicines should be assessed before any neuropathic condition can be regarded as resistant to treatment.

1.6.3.1. Tricyclic anti-depressants (TCA)

There are two TCAs which are included in guidance for the treatment of neuropathic pain, amitriptyline a tertiary amine and the secondary amine nortriptyline. They are differentiated pharmacologically by the ratio of 5-HT to noradrenaline reuptake inhibition. Amitriptyline is regarded as a non-selective inhibitor whereas nortriptyline is noradrenaline selective. Amitriptyline is licensed for the treatment of chronic pain (NICE, 2018). If this demonstrates too much sedation then nortriptyline may be more acceptable. In 2010 the International Association for the Study of Pain suggested that secondary amines, such as nortriptyline could be used in preference to the earlier tertiary products such as amitriptyline in an effort to minimise some of the side effects (Dworkin *et al.*, 2010). A Cochrane review in 2015 found no evidence that

nortriptyline was effective in the treatment of chronic pain in adults (Derry *et al.*, 2015).

The side effects of both these TCAs relate to their antimuscarinic activity including dry mouth, sedation, blurred vision and vivid dreams (Bryson and Wilde, 1996). Paradoxically, some patients who take amitriptyline regarded the sedation as a bonus, because after a good night's sleep they are better able to face their pain the following day.

The mechanism of action of TCAs in the treatment of chronic pain is still not fully understood. The major effect appears to be related to an increase of inhibitory serotonin neurotransmitters in the spinal column. There is also some evidence that these medicines exert a direct effect on opioid and NMDA receptors (Onali, Dedoni and Olianas, 2010; Lawson, 2017).

The major metabolic pathway for these TCAs is via the liver and as with opioids involves both 2D6 and 2C19 variants of the CYP pathway. Therefore, the polymorphic state of individual patient may make it difficult to find the optimal therapeutic dose. The ethnic variation in the 2D6 variant was mentioned above (Section 1.6.2) *i.e.* 6-10% of Caucasians, 2-5% of African Americans and 1% of Asians are classified as slow metabolisers. For the 2C19 variant 3-5% of Caucasians and 12-23% of Asians are regarded as slow metabolisers (Ma, Woo and McLeod, 2002). The situation becomes more complicated in older people. The CYP

transformation of these medicines results in the formation of polar compounds, to facilitate renal excretion. As patients age, renal clearance may become an issue (Rudorfer and Potter, 1999).

In the treatment of chronic pain TCAs are usually taken once a day in the early evening to minimise sedation the following morning. The half-life varies between 12 hours and 36 hours (Bryson and Wilde, 1996). The possibility of genetic variations in the rate of metabolism and excretion of TCAs may explain why the timing of the dose can be crucial to the tolerability of these medicines (Rudorfer and Potter, 1999; Ingelman-Sundberg, 2011).

All medicines in this group can have cardiac side effects and in overdose can cause cardiac arrest. They should therefore be avoided in patients with concomitant cardiac disease.

1.6.3.2. Gabapentinoids

Pregabalin and gabapentin are both licensed for the treatment of neuropathic pain. They are structural analogues of gamma amino butyric acid (GABA) but do not appear to exert their analgesia via this system. They selectively bind to the $\alpha 2\alpha 1$ and $\alpha 2\alpha 2$ subunits of the voltage activated calcium channels (Bockbrader *et al.*, 2010) and act as calcium channel modulators, reducing the entry of calcium into the cell. The action at this receptor increased the levels of L-glutamic acid decarboxylase, which in turn increased the level of extracellular GABA. They act in

several different places in the CNS, but how these actions mediate the analgesic effects of these medicines is not fully understood (Baillie and Power, 2006; Patel and Dickenson, 2016). NICE guidance indicates that if pain control is poor, therapy should be switched between all four medicines recommended for the treatment of neuropathic pain (amitriptyline, duloxetine, gabapentin and pregabalin) until an effective therapy has been found or all four have been tried (NICE, 2019).

The bioavailability and pharmacokinetics of these two medicines are different. Gabapentin is only absorbed in a short section of the duodenum: therefore, the bioavailability goes down as the dose increases (FDA, 2009). Pregabalin is absorbed throughout the small intestine, which leads to a more consistent outcome (Narayanan, Venkantaraju and Jennings, 2015). They both bear a structural similarity to L leucine, which allows for facilitated transport across cellular membranes.

The metabolism of both of these drugs is independent of liver enzymes. They are excreted almost entirely (98%) unchanged via the kidneys. This means that there are less opportunities for drug interactions, but care is necessary in patients with reduced kidney function.

Side effects that patients reported for both medicines included weight gain, sedation, memory loss, visual effects, irritability and erectile dysfunction. However, clinical

practice suggests that there are many interpatient differences between the efficacy and tolerance of these two medicines.

It is recommended that the doses of these two gabapentinoids be increased slowly and titrated to the patient's response starting from 25 or 50mg pregabalin and 100 or 300mg gabapentin depending upon the initial side effects. The onset of analgesia is slow and so there appears to be little need for a rapid dose escalation (Hall, 2016). Some published guidelines for the treatment of chronic pain suggested that dose increases of gabapentin beyond 50% of the maximum should be done after consultation with a member of a chronic pain team (NHS, 2016; NHS, 2019c). Other guidelines specifically suggest that if there is no response after titration to 50% of the maximum dose, the therapeutic choice should be reconsidered (Njoku, Rosam and Ashworth, 2017). Evidence for these recommendations is lacking and therefore they are included as generalised local comments.

1.6.3.3. Duloxetine

Duloxetine is a serotonin and nor-adrenaline re-uptake inhibitor antidepressant, which is licensed for the treatment of diabetic neuropathy. Duloxetine has an NNT of 6.4 in the treatment of diabetic neuropathy (Haroutounian and Finnerup, 2018) and 8 in the treatment of fibromyalgia (Lunn, Hughes and Wiffen, 2014). This report goes on to suggest that the benefit for fibromyalgia sufferers may be more related to an improvement in their mood rather than a specific treatment for their pain.

The major metabolism of duloxetine was to 4, 5 or 6 hydroxy duloxetine via CYP1A2 and CYP2D6 pathways. The 2D6 pathway is polymorphic but any variation would be too small to be clinically significant (Knadler *et al.*, 2011).

Duloxetine is effective in the treatment of neuropathic pain, but trials comparing it with other anti-depressants such as venlafaxine have not suggested which might be best (Saarto and Wiffen, 2007; Lunn, Hughes and Wiffen, 2014). Most patients who are treated with this medicine will suffer with at least one side effect such as dizziness, drowsiness and constipation (Lunn, Hughes and Wiffen, 2014).

1.6.4. NON-STEROIDAL ANTI-INFLAMMATORY MEDICINES (NSAIDS)

NSAIDs are classified as mild/moderate analgesics, with antipyretic and anti-inflammatory effects. They elicit more side effects than paracetamol both with regard to frequency and severity (Davis and Robson, 2016; Day and Graham, 2013). Because of their similarity, these medicines will be considered together rather than individually

NSAIDs act mainly by inhibiting the actions of the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzyme pathways. Most of the medicines in this class are non-selective and effect both COX-1 and COX-2 but a few *e.g.* celecoxib and etoricoxib are regarded as selective for COX-2 enzyme systems.

Cyclooxygenase enzymes are responsible for the transformation of arachidonic acid into prostanoids: prostaglandin, prostacyclin and thromboxane, which are short lived and therefore act either at the point of generation or initiated a signal from that location. Therapeutic treatment with NSAIDs therefore reduces the formation of these active moieties in areas where the COX enzymes systems are extant (Cashman, 1996). In addition, there are reports which indicate that the benefits of NSAIDs may also involve the, cannabinoid, nitric oxide (NO), noradrenaline, serotonin and cholinergic receptor systems (Hamza and Dionne, 2009). The COX-1 enzyme system is present in most bodily systems and the side effects of NSAIDs with this mechanism of action include irritation of the gastric lining and an increase risk of renal failure. The COX-2 enzyme, on the other hand, is 'induced' in response to injury and the NSAIDs which are selective for this mode of action are much less likely to cause gastric irritation but the risk of renal failure remains the same and they are associated with an increased risk of heart attack and stroke.

The overall analgesic effect of these medicines probably depends upon the way that they interact with COX systems in the painful areas of each individual. This mode of action means that they will have maximal effect where inflammation is involved and limited efficacy against neuropathic pain (Hall, 2016; Moore *et al.*, 2015a; Hamza and Dionne, 2009; Cashman, 1996).

When diclofenac was taken in combination with paracetamol in a double-blind study of patients 120 patient with moderate to strong pain the analgesic efficacy was better

than either medicine alone (Breivik, Barkvoll and Skovlund, 1999). Such a result would suggest that there is more than one mechanism at work. However, it is also reported that their use in this way causes an increased incidence of side effects: increases in blood pressure and the incidence of cardiovascular events. Therefore their use in this way should probably be avoided (Brune and Hinz, 2011).

Non-specific COX inhibitors such as ibuprofen or naproxen will cross the blood-brain barrier and will therefore exert an influence on the levels of brain prostaglandins, which will be part of their mechanism of action (Burian and Geisslinger, 2005; Ajmone-Cat *et al.*, 2010).

Most NSAIDs are metabolised in the liver by oxidation and conjugation and excreted, mainly via the kidneys. The polymorphic CYP2C9 enzyme system is involved in the metabolism of NSAIDs. Up to 8% of Caucasians have variants, which mean that dose adjustment may be necessary (Ma *et al.*, 2016). The BNF recommends that if one NSAID is ineffective then it is worth assessing a second.

The number and range of side effects associated with these medicines (Day and Graham, 2013; Davis and Robson, 2016) are related to the importance and distribution of the COX enzyme system within the body. Cardiovascular side effects include an increase in systolic blood pressure and a doubling of hospital admissions for heart failure (Davis and Robson, 2016). In patients with cardio-vascular disease it

is reported that they caused more deaths than road traffic accidents (Davis and Robson, 2016).

NSAIDs are often regarded as contraindicated in patients with asthma (Sturtevant, 1999). Further work is required to understand the full extent of this problem. 21% of patients are reported as suffering with aspirin induced asthma that is cross sensitive with up to 100% of NSAID treated patients (Jenkins, Costello and Hodge, 2004). Others have suggested that only 10% of patients would suffer with aspirin induced asthma and between 80 and 90% of adult asthma patients would be able to tolerate aspirin and NSAIDs with appropriate warnings (Wan, 2012).

Renal side effects of NSAIDs included changes in renal function and rarely, papillary necrosis (Whelton and Hamilton, 1991) especially when taken in combination with other analgesics (Elseviers and De Broe, 1998). Systematic reviews have tried to assess the risks and prescribers have been reminded that NSAIDs can accelerate the progression of chronic kidney disease and to prescribe the lowest effective doses (Nderitu *et al.*, 2013). More recently, because of the widespread use of these medicines, there have been calls for further research to determine the absolute risk of using NSIADs, especially in older people (Zhang *et al.*, 2017; Davis and Robson, 2016). An NHS Medication safety dashboard (NHS, 2018b) reported that from amongst 1,000 patients over 65 who were prescribed an NSAID without some form of gastric protection approximately one will be admitted to hospital with a ‘gastric

bleed'. More recently still the NHS has set out an action plan to improve medicines safety and NSAIDs are the 1st to be considered (NHS, 2019a).

For patients with chronic pain who were also taking a prophylactic dose of aspirin 75mg the addition of an NSAID needs to be considered even more carefully. The action of the NSAID may inhibit the cardio-protective role of the aspirin and increase the risk of intestinal bleeding (Rodriguez *et al.*, 2016; Nalamachu *et al.*, 2014). Catella-Lawson *et al.* (2001) reported that ibuprofen but not diclofenac antagonises the benefit of low dose aspirin. A report in 2014 suggested that the most common cause of a drug-drug interaction, between an 'over the counter' (OTC) (Section 8.2) and a prescribed medicine, in the elderly was between aspirin and diclofenac (Schmiedl *et al.*, 2014). A prospective analysis of 18,820 hospital admissions on Merseyside was published in 2004. It reported that two medicines, which caused the greatest number of adverse reactions warranting an admission to hospital were NSAIDs and Aspirin. (Pirmohamed *et al.*, 2004) and this become more significant as the patients age increases (Seager and Hawkey, 2001). As a result, because the majority of patients suffering with chronic pain were in older age groups, the selection of these medicines should be considered carefully and Hall (2016) suggests that their use should probably be restricted to when pain flares. Such a use would be in line with the NICE guidance of lowest dose for the shortest possible time (NICE, 2015c).

1.6.5. TOPICAL TREATMENTS FOR PAIN

If pain is limited to one particular site such as a knee, a post-herpetic area or the soles of the feet, there may be benefit in treating that area with a topical agent rather than by systemic administration. There are potentially three agents to choose from, NSAID gels, lidocaine plasters and capsaicin creams and plasters, depending upon the type of pain being treated.

A Cochrane review (Derry *et al.*, 2016) reports that for a minority of patients with chronic osteoarthritis NSAID topical gels provide a good levels of pain relief but there is no evidence for their use in non-arthritic conditions. The authors also noted that there is an apparent placebo effect from the gel itself. It is important with these preparations to calculate the total dose of active ingredient which is applied to ensure that it remains below that which would have been taken orally. Medicines, which are applied to the skin are perforce absorbed systemically, *en-route* to elimination. Patients for whom NSAIDs are truly contraindicated should avoid these medicines.

Lidocaine 5% medicated plaster is licensed for pain due to 'Post-herpetic neuralgia' (PHN) (NHS, 2017b; Goddard and Reaney, 2018). Patches should be applied to the skin for 12 hours and then removed for 12 hours.

Capsaicin 0.075% cream is licensed to treat pain due to 'Post-herpetic neuralgia' and under expert supervision painful diabetic neuropathy (NICE, 2011). Care is always necessary with these products to ensure that the active medication is not transferred

to ‘personal’ mucus membranes or superficially to (significant) others, from and to unprotected areas. There is also a capsaicin plaster 8% which is licensed for focal neuropathic pain in an ‘expert centre’.

CHAPTER 2 SYSTEMATIC REVIEW

2.1. Introduction

This chapter will set out the methodology of the systematic review, its search terms, the robustness of the results returned and the possibility of bias. The application of the selection criteria to the papers returned will then be addressed. The papers in the exiting systematic reviews will then be examined in detail. This will be followed by a detailed examination of the papers selected to be included in this systematic review, the determination of the topics for the narrative synthesis and their contribution to this research topic.

2.2. The rationale for this systematic review

Background reading for the research pharmacist's place in the CPT revealed that the literature about this role had been reviewed twice in the relatively recent past. Firstly, 'Educational interventions by pharmacists to patients with chronic pain' (Bennett *et al.*, 2011) and secondly, 'Effectiveness of pharmacist-led medication review in chronic pain' (Hadi *et al.*, 2014a). Most of the references reported in these two reviews related to pain with a specific diagnosis. Therefore, this systematic review aims to update those reviews by searching for literature, not previously included, about the role of a pharmacist working in a chronic pain team, with patients whose pain is generally without a diagnosable cause. This systematic review will then consider whether the medicines advice, which can be offered by a pharmacist in a

CPS, results in any improvements in the patient's pain and through an educational intervention, their understanding of pain medicines.

2.3. The systematic review

2.3.1. METHODOLOGY

2.3.1.1. The search terms

The search terms were chosen to represent the type of role and intervention carried out by the researcher and other pharmacists working with patients in a face to face role within a CPT.

The context for the intervention in this research is patients being treated for their chronic pain by a multi-professional CPT in face to face consultations. The selection of patients and the problems that they reported to the pharmacist, were to some extent driven by the referral (to the pharmacist) criteria extant within the CPT (Section 4.4).

The explanation of the role of medicines in the treatment of chronic pain is carried out in the South Staffordshire CPS by the research pharmacist but in other CPTs this may be undertaken by other HCPs e.g. physiotherapists, therefore the search terms needed to include this possibility.

The focus of the pharmacist's intervention is around medicines education and change in medicine taking behaviour, therefore medicines and analgesia were included.

The target cohort of patients in this research were suffering with chronic pain and who were attending a clinic based chronic pain service. This was covered by the search terms.

The search terms used were

- Pharmacist* OR physiotherapy* OR multi*
- Medicine* OR analgesi*
- Chronic AND pain AND clinic

A model search using these search terms is included at Appendix 8.5. The same search terms were used for each data base.

A general literature search together with an appreciation of the historical development of pain services for patients had demonstrated few publications relating to this type of clinical pharmacy role prior to 2000. It was therefore decided that the searches would be undertaken from 1990 to the present day.

Seven data bases were searched CINHAL, Cochrane, Embase, International Pharmacy Abstracts (searched up to the date of termination) Ovid Medline, Ovid Psychinfo and Web of Science. Searches were also undertaken on OpenGrey and Bielefeld Academic Search Engine (BASE). At the same time a weekly Google Scholar alert' with the terms for 'pharmacist' and 'chronic pain' was initiated.

The inclusion criteria for titles was based upon the practice of the research pharmacist as set out above - a medicines review for patients with chronic pain, with no detectable damage or illness or whose pain intensity bore no relation to the extent of any detectable damage or illness, referred to the pharmacist's clinic, for a face-to-face clinic consultation.

The exclusion criteria were non-English texts and papers that did not relate to adults (18 years and over). No research papers returned by the search process was rejected for either of these two reasons.

In the United States there is an increasing problem with the abuse of prescription opioid analgesics with the pharmacist becoming involved in maintaining the security of the supply of opioid analgesics to patients with chronic pain. Those papers which related solely or mainly to this process were also discarded.

2.3.1.2. Robustness of the results

Each of the papers which came through into the final selection were then assessed for robustness of the evidence which it might contribute to this systematic review. Only two of the papers, which covered different aspects of the same research, involved a randomised controlled trial (RCT). In addition, there was no new robust data which added to our knowledge about the benefits which a pharmacist could bring to a CPS and which could reasonably be considered suitable for meta-analysis. Therefore, the decision was taken that this work would be presented as a Systematic Review with a Narrative Synthesis.

The UK Economic and Social Research Council (ERSC) has proposed a method to improve the quality of narrative approaches to evidence synthesis, which is widely used including in Cochrane reviews (Popay *et al.*, 2006). Within this guidance there is use of the Jadad scale (Jadad *et al.*, 1996) which uses three yes:no answer questions to grade published papers into five groups. The patients must be randomised, the research must be double blinded and there must be information about withdrawals and dropouts. Additional points are awarded for appropriateness of the randomisation and the blinding and points withdrawn if these are not appropriate. The scores range from 0-very poor to 5-rigorous. A Jadad score was determined for each of the papers in this systematic review.

The simplicity of this approach has been criticised because it makes no mention of allocation concealment which is necessary to minimise the subconscious allocation

of patients to appropriate groups and which Cochrane considers important (Popay *et al.*, 2006). Other systems for grading the robustness of clinical trial data are available such as the Delphi expert consensus route or the CONSORT checklist. Neither of these systems claim that they are suitable for rating the quality of research evidence, but have on occasions been used for this purpose. (Berger and Alperson, 2009).

The methodology for incorporating research results into reviews needs to be more structured (Docherty and Smith, 1999). But if it is to increase the quality of research outcomes being incorporated into reviews or other guidelines and thereby improve the evidence base of therapy it must depend upon some type of scoring system. The robustness of any rating score used in a systematic review and/or meta-analysis will always depend upon the extent and validity of the information contained within the papers, the rigorousness of the execution in the original research as well the interpretation of the reporting by the reviewer (Berger and Alperson, 2009). Berger and Alperson (2009) conclude with suggestions for the points which should be considered in any evaluation system: each trial outcome must be analysed effectively and comprehensively, scores allocated only when scores are justified and differences in scores accentuated by using a multiplier rather than an additional sequence. Then because it is very important to stop results which are less reliable from being carried forward they suggested that any assessment tool should be updated regularly.

2.3.1.3. Risk of bias

Cochrane promulgates a set of eight questions, each with a four point answer yes, maybe yes, maybe no and no, to determine the extent of the bias in a research project (Cochrane, 2018). Each paper in this systematic review was rated from the information available for the risk of bias.

2.4. The results

A flow diagram of the process for inclusion and exclusion is included below Figure 2.1. The titles of the 585 papers returned from the seven data bases were examined for duplications and 244 were removed. Titles of papers were scanned initially for 'pharmacist' and 'pain' and then for 'chronic pain'. Where there was doubt about the type of pain involved further information was sought from the abstract. Those papers which related solely to pain from a physically attributable cause *e.g.* arthritis or cancer pain were discarded as they were not representative of the cohort seen by the researcher. Where there was doubt the full text was examined to determine the presence or absence of chronic pain of unknown origin. As a result, 268 papers were removed.

The titles and abstracts of the remaining 73 papers were then examined in more detail for how the pharmacists' interacted with the patient. If the context of the pharmacist patient interaction was not clear the full text was examined. Only those reporting a face-to-face encounter were retained. This resulted in a further 63 articles being rejected leaving 10 reports.

Efforts were made to obtain further information from ‘conference’ reports. No further information was forthcoming, related to authors’ pending publications. The searches of the grey literature did not reveal any new publications.

The bibliographies of the papers which came through this selection process were also scanned for any additional reports which had not been returned to minimise the chance of relevant material being missed. There were two reports from bibliographies, which complied with the selection criteria. These were included, increasing the final total to 12.

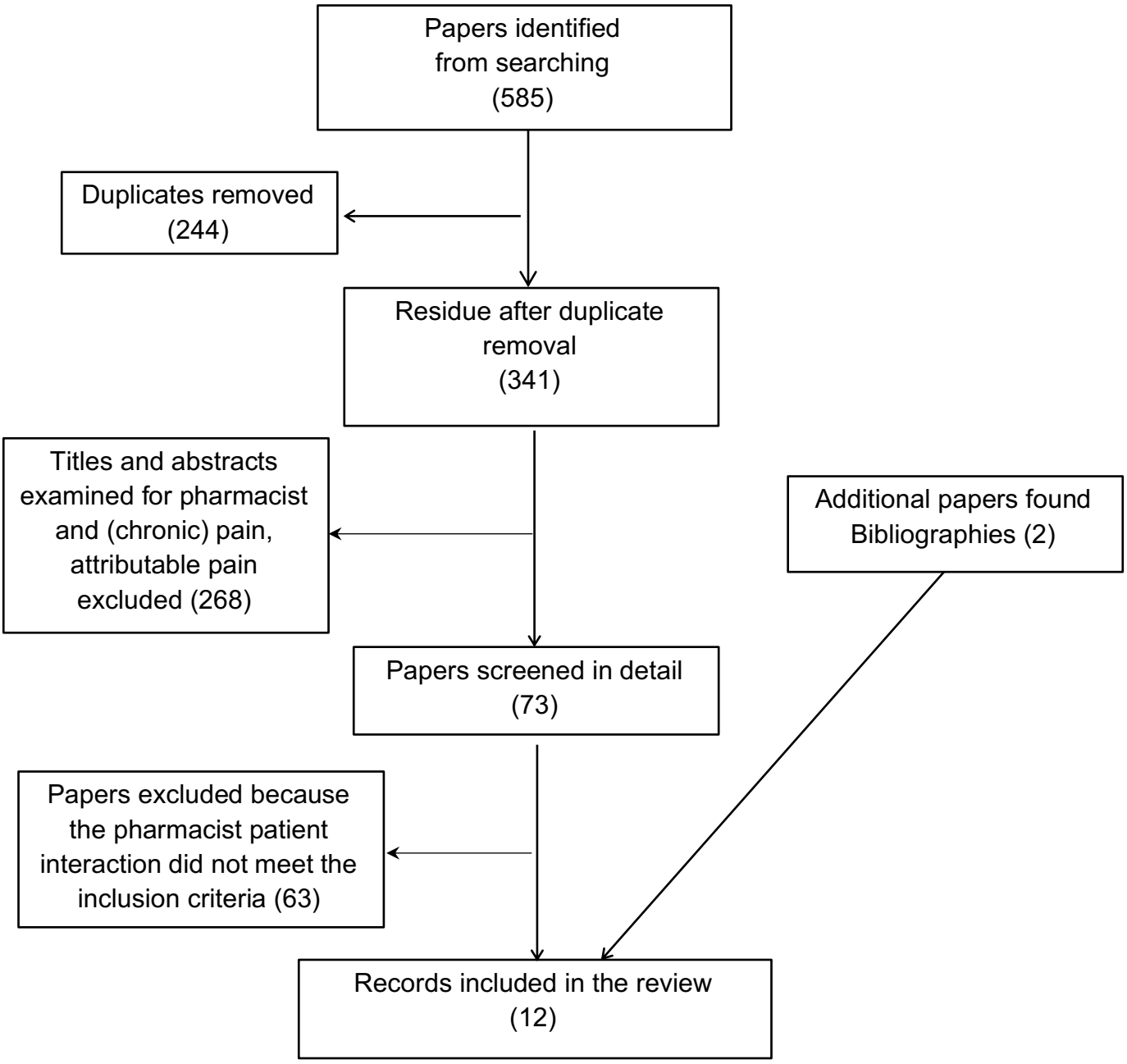

Figure 2.1 Diagram of the review process

2.5. Narrative synthesis

This section will outline the details of the two existing systematic reviews. It will then address those papers from these reviews which were included in this systematic review. Finally, the twelve retrieved papers in this systematic review will be discussed.

2.5.1. PAPERS INCLUDED IN THE EXISTING SYSTEMATIC REVIEWS

The two previous systematic reviews were retrieved during the search process, Bennett *et al.* (2011) and Hadi *et al.* (2014a) and the papers which they included were reviewed in the same way as all of the other papers returned by the systematic review searches.

The first review by Bennett and colleagues (2011) reviewed four papers which met their search criteria of an RCT with a control group who received usual care or attention, including patients with chronic pain of any aetiology, who underwent an educational intervention and had changes in pain score measured.

The second review by Hadi and colleagues (2014a) reviewed five papers which met their search criteria. Their focus was on RCTs and nonrandomized studies with controls. The intervention of interest was a medication review delivered independently by the pharmacist or as part of a multi-disciplinary team. They

included patients with chronic pain as defined by the IASP but excluded patients with cancer pain.

An assessment of these two reviews using the NIHR Study Quality Assessment Tool of Systematic Reviews and Meta-analysis (NIH, 2018) revealed that the answers to each of the eight questions in this tool had been addressed appropriately. Therefore, both systematic reviews met the quality criteria.

The search terms for these two reviews were different to those used for this systematic review. Firstly, both had a requirement for an RCT. Secondly, there were differences in their definitions of pain. Bennett *et al.* (2011) included pain of any aetiology. The results published by Hadi *et al.* (2014a) demonstrated an accent upon pain which related to a physically discernible cause even though the search criteria suggested pain without apparent biological value.

These systematic reviews only included two papers which were common to both. Table 2.1 includes the papers listed in the same order as the original publications, with duplicates removed and lays out details of the recorded pain aetiology, patient population, pain scores and the specified pharmacist intervention.

Table 2.1 Articles included in the Bennett *et al.* (2011) and Hadi *et al.* (2014a) reviews

Reference	Title	Pain aetiology	Sample size	Pain score 0-10 scale	Pharmacist intervention
Powers, Hamilton and Roberts (1983)	Pharmacist intervention in methadone administration to cancer patients with pain.	Cancer	N=20 I=11 (8) C=9 (8)	I=8.75 C=8.45	Face to face review days 1 and 8 then phone
Gammaitoni *et al.* (2000)	Palliative pharmaceutical care: a randomized, prospective study of telephone-based prescription and medication counselling services for treating patients attending a chronic pain clinic	Multiple	N=74 I=38 (20) C=36 (21)	I=6.43 C=6.57	Telephone review, mean 1.2 calls per patient
Hay *et al.* (2006)	Effectiveness of community physiotherapy and enhanced pharmacy review for knee pain in people aged over 55 presenting to primary care: pragmatic randomised trial	Knee pain	N=216* I=108 (100) C=108 (92)	I=6.0 C=6.0	3 to 6 sessions of approximately 20mins over 10 weeks
Petkova (2009)	Education for patients with painful arthritis: a community pharmacy-based pilot project	Arthritis	N=90 I=45 (43) C=45 (43)	I=9.4 C=9.74	Group sessions led by pharmacist educator and assistants, 4 sessions over 16 weeks

Hoffmann *et al.* (2008)	Pharmaceutical care for migraine and headache patients: a community-based, randomized intervention	Headache & migraine	N=410 I=201 (163) C=209 (194)	Not available	Face to face average 2 hours per patient
Bruhn *et al.* (2013)	Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial	Multiple	N=196** I=70 (60,58) C=63 (54,55)	Not available	Pharmacist review and prescribe, pharmacist review and refer back to GP and treatment as usual
Marra *et al.* (2012)	Pharmacist-initiated intervention trial in osteoarthritis: a multidisciplinary intervention for knee osteoarthritis	Knee pain	N=139 I=73 (72) C=66 (65)	Not available	Pharmacist and physiotherapist. Face to face consultation

N = number, I = intervention group, C = control group, ( ) number completing,

*Pharmacist and physiotherapy arm.

**Prescribing pharmacist review and treatment and non-prescribing pharmacist referral

All of these papers included references to a Medicines Utilisation Review (MUR). This is a generic term which relates to an interaction between a pharmacist and a patient where the benefits of medicinal treatment are discussed, treatment optimised, possible side effects minimised and the possibility of waste from unused medicines or the inappropriate use of medicines reduced. The literature contains various definitions or interpretations of the MUR process (RPS, 2018; NICE, 2016; PCNE, 2017; Blenkinsopp, Bond and Raynor, 2012). The details of the specific MUR process used was not always clear in the papers retrieved by these systematic reviews.

2.5.2. RESULTS FROM EXISTING SYSTEMATIC REVIEWS

Bennett *et al.* (2011) systematic review studied the effects of an "*educational intervention*" defined as "*information, behavioural instruction or advice in relation to the management of chronic pain*" of at least two and a half hours and reported that this was worthwhile, resulting in a pain reduction of 0.5 on a 0 to 10 scale. The review also reported that addressing drug related problems helped to reduce adverse (drug) events by 50%.

The Hadi *et al.* (2014a) systematic review concluded that a *"pharmacist led medication review"* led to a slightly larger pain reduction of 0.8 on a 0 to 10 scale. There was no mention of side effects. In addition, it reported a significant improvement in patient satisfaction equivalent to a 'small to moderate' effect.

There was no consistency or detail of what was undertaken during the MURs mentioned in any of the papers in either of these two systematic reviews.

Out of the seven papers included in these two reviews only Gammaitoni *et al.* (2000) related to patients attending a chronic pain clinic and one paper Bruhn *et al.* (2013) included patients with chronic pain of unknown origin. Gammaitoni *et al.* (2000) research used a telephone-based service and therefore was not carried over to this systematic review because it did not meet the requirement for face-to-face communication. The research reported by Bruhn *et al.* (2013) involved an RCT with three arms undertaken in six GP practices, three in East Anglia and three in Grampian, Scotland. The three arms were pharmacist prescribing, pharmacist paper review with referral back to the GP and treatment as usual. The two arms involving pharmacists both recorded reductions in pain intensity scores, but only in the pharmacist prescriber group was the reduction significant. The scale used to record changes in pain was the seven-point Chronic pain grade scale (CPG) rather than the more commonly used 0 - 10 scale. The use of this tool was justified *"based on our judgement following an earlier feasibility study".* Because it met the inclusion criteria this paper was included in this review. No other papers from Bennett *et al.* (2011) or Hadi *et al.* (2014a) were included in this systematic review.

2.5.3. PAPERS INCLUDED IN THIS SYSTEMATIC REVIEW

The criteria for inclusion in this systematic review were 'a medicines review for patients with chronic pain, with no diagnosable cause, referred to the pharmacist's clinic, for a face-to-face clinic consultation' (Section 2.3.1.1).

All the included papers were assessed for quality and bias (Cochrane, 2018; Jadad *et al.*, 1996) and summary details along with pain scores were presented in Table 2.2. The papers were ordered firstly by the quality of the evidence (green) and then according to the perceived relevance to the pharmacists' practice.

Table 2.2 Listing of the articles retrieved by this search

No	Reference	Title	Brief overview	Article outline	Risk of bias	Jadad score
1	Bruhn *et al.* (2013)	Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial	UK, medicinal treatment for chronic pain with three intervention arms. Pharmacists prescribing group 70, pharmacist paper review group 63, treatment as usual group 63.	RCT six General Practices with prescribing pharmacists, three in Scotland and three in England.	Medium	2
2	Neilson *et al.* (2015)	Pharmacist-led management of chronic pain in primary care: costs and benefits in a pilot randomised controlled trial	UK, medicinal treatment for chronic pain with three intervention arms. Pharmacists prescribing group 70, pharmacist paper review group 63, treatment as usual group 63	A further paper on the Bruhn, H. research listed above, reporting the costs of the separate intervention arms	Medium	2
3	Hadi *et al.* (2016)	Effectiveness of a community-based nurse-pharmacist managed pain clinic	UK 79 patients enrolled and 35 returned. Mixed-method study	A community-based, nurse-pharmacist pain clinic for adults in the north of England	High	0
4	Gill, Taylor and Knaggs (2013)	Less pain - the result of a community pharmacy pilot pain service evaluation	UK pilot 176 enhanced medication reviews resulting in 182 interventions. Only one interaction between each patient and a pharmacist	A community pharmacy-based study aimed at providing an increased level of service and information to patients suffering with chronic pain in London	High	0

5	Dougall, Harrison and Lowrie (2015)	Community Pharmacy based pharmacist, independent prescribing clinic for people receiving painkillers	UK pilot 91 patients enrolled and 22 returners. Before and after study	A community pharmacy-based study involving one pharmacy and on one GP in the Greater Glasgow area.	High	0
6	Harrison (2015)	Improving the quality and access of care for people living with chronic pain – development of a new model of care with Community Pharmacy	UK pilot 20 patients enrolled for an extended medication review	A community pharmacy-based study aimed at providing increased levels of service	High	0
7	Thomas (2012)	Is pharmacist prescribing a painless alternative in chronic pain management	UK prescribing pharmacist seconded to a multidisciplinary clinic, three months pilot, 29 patients, 43 appointments	A hospital pharmacy-based study in conjunction with Gateshead pain management team, effectiveness, cost and formulary compliance	High	0
8	Coleman, Yangphaibul and Begovic (2013)	A pilot study to assess a new role for a pharmacist in a multidisciplinary chronic pain team in primary care	UK prescribing pharmacist seconded to an MSK clinic. 32 patients attending an MSK clinic. Mean 2.5 interventions per patient	Addition of a pharmacist to a primary Care MSK chronic pain clinic.	High	0
9	Dumbreck and Cameron (2011)	The Role of the Pharmacist Prescriber within a Community-based Pain Management Service: A Case Study	UK case report, pharmacist advice sought for one patient	Patient attending the Fife integrated pain management service	High	0
10	Bauters, Devulder and Robays (2008)	Clinical pharmacy in a multidisciplinary team for chronic pain in adults	93 patients attending an out-patient multidisciplinary reference centre for chronic pain in adults (Europe)	Pharmacist working in a hospital out-patient pain centre.	High	0

11	Cosio and Lin (2014)	Efficacy of an outpatient, multidisciplinary VA pain management clinic: findings from a one-year outcome study	Conference report, 546 veterans who were opioid users and who attended a multidisciplinary pain management clinic (US)	Pharmacist working with a multi-disciplinary pain team	High	0
12	Norman (2015)	Implementation and evaluation of a pharmacist-managed chronic pain clinic in a primary care setting	Conference report, 39 patients attended a pharmacist led chronic pain clinic in primary care (US)	Pharmacist managed pain clinic aimed at improving chronic pain-related outcomes particularly in relation to opioids	High	0

2.5.4. SUMMARY OF THE PAPERS SELECTED BY THIS SYSTEMATIC REVIEW

This section provides a summary of the significant details of the papers included in this systematic review (Table 2.2). At the start of the review process it was hoped that more data would have been reported since the publication of the Bennett *et al.* (2011) and Hadi *et al.* (2014a) systematic reviews. The twelve articles which are included in this systematic review include one (Bruhn *et al.*, 2013) which was included in the Hadi *et al.* (2014a) systematic review. In addition, there was one paper (Bauters, Devulder and Robays, 2008) which, from the date would have been available to the two earlier reviewers but which did not meet their inclusion criteria.

Only two of the papers, Bruhn *et al.* (2013) and Neilson *et al.* (2015) included in this systematic review had a Jadad (Jadad *et al.*, 1996) score of greater than zero, because that research involved a random allocation into different treatment groups. These two papers were reports of different aspects of the same research. Bruhn *et al.* (2013) investigated whether there were any differences in outcomes between a pharmacist prescriber, pharmacist paper review and referral and treatment as usual (TAU) on patients' pain and the benefits that they created. Neilson *et al.* (2015) investigated the differing cost benefit of these interventions. These findings are discussed further in Section 2.5.6.

The research reported in the Bruhn *et al.* (2013) papers was not strictly comparable to the researcher's clinical practice for two reasons. Firstly, the exclusion criteria excluded medicines *"that can be used for analgesia but whose primary indication is not chronic pain (e.g. triptans, antiepileptics or antidepressants)".* These groups included almost all of the medicines used in the treatment of neuropathic pain and it was noted in Section 1.5.3 that for patients with lower back pain up to 50% reported some elements of neuropathic pain. Therefore, their exclusion would significantly reduce the options available for effectively treating chronic pain. Secondly, the inclusion criteria for the Bruhn *et al.* (2013) review included patients who had *"either two or more acute prescriptions, and/or one repeat prescription within the last 120 days, for an analgesic"*. One repeat prescription for a pain medicines would not necessarily support the level of analgesia required for the treatment of chronic pain similar to that reported by the patients seen by the researcher. The mean number of pain medicines reported by the patients in the researcher's cohort was 2.8. These two criteria would have excluded many patients seen by the researcher.

Table 2.3 Details of the articles retrieved by this search

No	Study	Condition	Participants	Intervention	Primary study outcome	Notes	Clinician
1	Bruhn *et al.* (2013)	Chronic pain	196 patients in three arms	Enhanced MUR, postal follow up	CPG significant improvement in pharmacist prescribing arm from 66.1 to 58.1	Pharmacists 2 days training. Some GP's thought some recommendations trivial	Pharmacist
2	Neilson *et al.* (2015)	Chronic pain	196 patients in three arms	N/A	Involvement of pharmacist in treatment of chronic pain in GP practice probably not cost-effective	Pharmacists 2 days training. Some GP thought some recommendations trivial	Pharmacist
3	Hadi *et al.* (2016)	Chronic pain	36 patients seen twice	Enhanced MUR and education ~ 40 minutes	BPI-PSS* Worst pain reduced from 8.0 to 7.5 Average pain reduced from 7.0 to 6.0 BPI-PIS** Average pain reduced from 7.1 to 6.1	No additional training for pharmacist, specific training for the nurse about problems associated with chronic pain	Pharmacist & nurse
4	Gill, Taylor and Knaggs (2013)	Pain	176 patients seen once	Enhanced MUR, including BPI and painDETECT	9 (5%) patients referred back to GP for possible undiagnosed neuropathic pain	Half day training for 10 community pharmacists in undertaking enhanced pain related MUR. Undiagnosed neuropathic pain and poor compliance	Pharmacist
5	Dougall, Harrison and Lowrie (2015)	Pain patients referred from GP	21 patients seen twice	Enhanced MUR including VAS	VAS reduced from 5.6 to 4	Prescribing pharmacist made changes to patient pain medication, no additional training	Pharmacist

6	Harrison (2015)	Chronic pain	20 patients seen once	MUR – no other details	Mean VAS = 7 No 2nd visit, no VAS changes recorded	Pain waiting times recorded	Pharmacist
7	Thomas (2012)	Chronic pain	29 patients 17 seen twice	MUR – no other details	Mean VAS, reduction 2.7	MUR, clinic extended beyond initial pilot, because of drug cost saving. Poor compliance mentioned	Pharmacist
8	Coleman, Yangphaibul and Begovic (2013)	Chronic pain	32 patients seen once	MUR – no other details	No pain scores recorded	Clinic extended beyond initial pilot in MSK clinic, because of added value.	Clinical pharmacist
9	Dumbreck and Cameron (2011)	Chronic pain	1 patient	MUR on one patient	BPI-PSS Worst pain reduced from 7 to 5 Best pain reduced from 3 to 2	Overcame reluctance to take pain medicines	Pharmacist
10	Bauters, Devulder and Robays (2008)	Chronic pain	93 patients	MUR – no other details	No pain scores recorded	Clinical pharmacist input in hospital clinic setting.	
11	Cosio and Lin (2014)	Chronic pain	546 patients	Pre and post clinic questionnaires	Unspecified significant reduction in pain	Multidisciplinary Veterans pain management facility	Pharmacist
12	Norman (2015)	Chronic pain	25 patients two visits	Extended MUR	NRS reduced from 6.2 to 5.8	Pharmacist led CPS	Pharmacist

*BPI-PSS – Brief pain inventory – Pain severity scale

**BPI-PIS – Brief pain inventory – Pain interference scale

Looking at the remaining papers in this systematic review in more detail, they all returned a Jadad (Jadad *et al.*, 1996) score of zero. Therefore, they would be regarded as low-quality evidence, but they combined to contribute to the narrative synthesis (Section 2.5.5).

Hadi *et al.* (2016) conducted a qualitative and quasi-experimental study with 35 patients returning for a second visit. Gill, Taylor and Knaggs (2013) reported on a study in north London where 10 community pharmacists who had been specially trained, undertook 176 enhanced medicine reviews (Appendix 8.2) and referred nine patients back to their GP for suggested undiagnosed neuropathic pain.

Dougall, Harrison and Lowrie (2015) and Harrison (2015) described outcomes of MURs undertaken by community pharmacists with the aim of suggesting improvements in analgesic prescribing and or signposting to other services. Dougall, Harrison and Lowrie (2015) noted that the patients who had been seen twice by the pharmacist recorded a reduction in their mean VAS score from 5.3 to 4.0. In the paper by Harrison (2015) the pharmacist only saw patients on one occasion and therefore was not able to record any changes in pain scores. The paper by Harrison (2015) did observe poor compliance, report that a number of patients who reported symptoms of neuropathic pain did not appear to be receiving treatment and comment the overall duration of the patients' pain.

Thomas (2012) and Coleman, Yangphaibul and Begovic (2013) studied the outcomes of a hospital pharmacist's involvement in a chronic pain team. Thomas (2012) reported that *"of the patients who had one or more pharmacological interventions from the pharmacist a mean reduction in the VAS pain score of 2.7 or 33% was achieved*". There was no mention of pain scores in patients who had not had a pharmacological intervention. On the other hand Coleman, Yangphaibul and Begovic (2013) made no mention of pain scores, their report concentrated upon the therapeutic interventions made by the pharmacist. Thirty-two MURs were undertaken by the pharmacist, and a total of 80 actions were recorded. Of these 64 were for medicine optimisation and 13 for the reduction of adverse effects. In the list of actions reported was the suggestion that prescribers should prescribe adjuvant medicinal treatment for neuropathic pain, specifically amitriptyline.

There was one (anecdotal) case report, which was therefore probably not generisable, as well being very low level evidence (Dumbreck and Cameron, 2011). This described benefits from a pharmacist consultation in terms of improved pain control resulting from the use of co-codamol. The patient also accepted treatment with gabapentin which led to a reduction in side effects and to a reduction in the overall number of medicines taken. No pain scores were reported.

Bauters, Devulder and Robays (2008) studied the effects if a pharmacist in a hospital out-patient pain clinic who undertook 93 MURs and recorded a total of 107 clinical interventions. No pain scores were recorded only the fact that 21 medicines stopped,

22 medicine regimens amended and 21 medicines started. Of the started medicines 33% were for anti-depressants or anti-epileptics, which within a pain clinic would most likely be prescribed to treat neuropathic elements of chronic pain. Cost benefit of involving pharmacists' in this form of treatment of chronic pain was mentioned but not discussed in any detail.

The Cosio and Lin (2014) and Norman (2015) reports were both abstracts from conference reports and were regarded as very low level evidence. Efforts were made to contact the authors but no details were available other than those included in the conference abstract. Cosio and Lin (2014) described the treatment of 546 patients with chronic pain in a multidisciplinary outpatient clinic, including a pharmacist. No pain scores were presented but it was reported that patients showed a significant improvement in their pain along with improvements in mobility and activities of daily living (ADL). Norman (2015) reported on a pharmacist led chronic pain clinic in primary care aiming to improve pain and reduce opioid use. Twenty-five patients were seen on at least twice and these patients reported a mean improvement in pain score, from 6.2 to 5.8 and a mean decrease in morphine equivalent opioid dose from 70.6mg to 66.6mg.

2.5.5. THE DETERMINATION OF THE TOPICS FOR THE 'NARRATIVE SYNTHESIS'

The themes for which this Systematic Review sought research papers, was the success or otherwise of a pharmacist's intervention in the treatment of chronic pain. They emerged from the retrieved publications, which revealed beneficial outcomes in

the treatment of chronic pain. Their inclusion in the retrieved papers was outlined in Table 2.4 table below and then considered later in more detail.

As discussed in Section 2.3.1.2 a narrative synthesis of the data has been chosen due to the diverse nature of the quality of the papers published covering the educational involvement of a pharmacist specialising in pain in the treatment of chronic pain. The synthesis was carried out in accordance with guidelines (Ryan, 2013; Popay *et al.*, 2006) eliciting significant themes from the findings of the individually published papers included in the systematic review.

- Impact of intervention upon the patients' pain
- Neuropathic pain
- Patients' understanding of their pain medicines
- Cost implications of the pharmacists' intervention.

The twelve papers included in the narrative review are summarised and the contribution of each to the themes are presented in Table 2.4

Table 2.4 Themed summary of the papers with the topics for synthesis.

No	Reference	Changes in pain scores and how these changes were measured	Neuropathic pain	Patients understanding of their pain medicines	Cost implications of pharmacist intervention
1	Bruhn, H. 2013	Pain intensity improved (CPG), significantly in the pharmacist prescribing arm and non-significantly in the pharmacist review arm	Not mentioned	*A priori* hypothesis that in patients with chronic pain pharmacist advice would lead to better pain control or better functioning	Some practice colleagues' question whether the addition of a pharmacist was cost effective
2	Neilson, A. 2015	As set out in Bruhn, H 2013 above. Research into the 'cost effectiveness of a pharmacist intervention	Not mentioned	Not mentioned	Report suggests that pharmacist intervention was not cost effective
3	Hadi, M. 2016	BPI pain severity reduced from 8 to 7.5, BPI average pain reduced from 7 to 6 and BPI pain interference reduced from 7.1 to 6.1	Not mentioned	Problems with adherence were mentioned in passing	Author suggest that cost effectiveness of the intervention requires further investigation
4	Gill, J. 2013	101 patients completed a painDETECT questionnaire. Resulted in 28 possible and 23 likely patients with neuropathic pain.	Out of 76 MURs 9 (5%) were referred back to their GP for possible undiagnosed neuropathic pain	Patient reluctance to take analgesia was mentioned - even when patients knew pain increased as a result	Suggestion that the detection of undertreated pain in community is cost effective

5	Dougall, C. 2015	16 of 21 patients recorded a decrease in VAS from 5.6 to 4.0	Not mentioned	Pharmacists MUR included a check of compliance and understanding	Author suggests costs require further investigation
6	Harrison, H. 2015	Mean baseline VAS pain score is 7.0 (no other pain scores mentioned)	11/20 reported symptoms of neuropathic pain, 10/11 were not taking appropriate medicines	35% (8/23) took their analgesics at doses lower than recommended by their prescriber	Medicine costs increasing year on year, would pharmacist involvement help with controlling costs?
7	Thomas, M. 2012	Pain VAS reduction of 2.7 or 33% in those patients who had a pharmacological intervention	Some patients did not understand dose titrations, an indication that neuropathic pain may be being undertreated	Patients do not take medicines optimally, lack of direction clarity, complexity of therapy and fear of side effects	Additional cost justified by medicine saving from formulary adherence
8	Coleman, B. 2013	No measures of pain undertaken – aim to 'add value' to the service	Report notes that amitriptyline was added to some patients' prescription, a possible indication of neuropathic pain	Pharmacists were able to offer advice about optimising therapy and enhancing adherence	Other members of the team reported that pharmacists added value to patient care
9	Dumbreck, S. 2011	Case report – pain scale 1-10 Worst improved from 7 to 5 Best improved from 3 to 2	Patient had untreated neuropathic pain. Pharmacist initiated treatment	Patient reported a greater understanding of the use of their analgesia after research completed	
10	Bauters, T. G. 2008	None recorded – report about the efficacy of clinical pharmacy	Text includes references to medicines used in the treatment of neuropathic pain	Not mentioned	Authors opined that this was not cost effective
11	Cosio, D. 2014	Stated as a significant reduction in pain	Not mentioned	Reported reduction in levels of fear about taking medicines	Conference report No mention of cost

12	Norman, J. 2015	Pain score decreased from 6.2 to 5.8, scale not mentioned Morphine equivalent dose from 70.6mg to 66.6mg	Opioid use declined and mean non-opioid prescriptions increased from 1.8 to 2.0	Compliance increased	Conference report No mention of cost

2.5.6. THEMES WHICH EMERGED FROM THIS SYSTEMATIC REVIEW.

The themes identified were then examined in detail for contributions to this narrative synthesis and discussed in the section below.

2.5.6.1. Impact of intervention upon patients' pain.

The pharmacist interventions set out in the 12 papers highlighted by this review generally fall into two groups: pharmacists as prescribers and pharmacists as reviewers with referral back to the prescriber for any suggested changes in therapy. The Bruhn *et al.* (2013) paper reported on research with one arm in each of these groups. Four papers involve pharmacist prescribing for chronic pain patients (Dougall, Harrison and Lowrie, 2015; Thomas, 2012; Coleman, Yangphaibul and Begovic, 2013; Dumbreck and Cameron, 2011). In the remaining reports the pharmacists reviewed the patients' therapy and made recommendations for suggested changes to the patients' prescriber or there were insufficient details to determine the role of the pharmacist.

All of the papers included by this systematic review reported that the pharmacist's intervention was an MUR of some sort. The papers then went on to report on the effect which this intervention had had on the patient's pain.

An MUR is defined by the RPharmS as

'a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication related problems and reducing waste'

(RPS, 2018).

Prior to this Blenkinsopp, Bond and Raynor (2012) had made a more general point

'Medication review is, at heart, a diagnostic intervention which aims to identify problems for action by the prescriber, the clinician conducting the review, the patient or all three but can also be regarded as an educational intervention to support patient knowledge and adherence.'

These two definitions reveal differences in interpretation of the role of an MUR. It can either be a discussion with the aim of optimising medicinal treatment or a discussion aimed at educating the patient, which as a by-product will optimise medicinal treatment. For many of the papers included in this systematic review there was no indication of what were the priorities of the researchers during their MUR interventions.

Three of the research projects included this systematic review specified that the pharmacist undertook training to undertake an enhanced MUR. This was aimed at improving the consistency of the intervention

Harrison (2015) reported on a research study in west Dunbartonshire, in which pharmacists were to undertake an enhanced MUR with patients suffering with chronic pain. All of the local community pharmacies volunteered to participate and participation required them to complete a 2 x 3hours training course, consisting of presentations, role play and case studies. This was undertaken to ensure that the pharmacist understood how to administer the STarT questionnaire (Section 8.2) as well as learning about chronic pain so that they would be able to refer patients on for further advice and treatment as appropriate. The research did not go to plan and only 20 of the projected 400 MURs were completed. At the debriefing meeting one of the comments noted was that pharmacists did not feel confident to undertake these MURs with their chronic pain patients. This posed questions about the adequacy and appropriateness of the training provided.

In the Gill, Taylor and Knaggs (2013) report, pharmacists undertook a half day training. This included instruction about the BPI questionnaire, neuropathic pain and the painDETECT (Section 8.2) questionnaire as well as the LESS PAIN (Section 8.2) format for questioning (Gill, Taylor and Knaggs, 2013; Gill, Taylor and Knaggs, 2012).

All of the pharmacists in the Bruhn *et al.* (2013) undertook a two day course prior to the commencement of the research. This aimed to familiarise them with the problems associated with chronic pain and to agree a common approach to the treatment being recommended in the two arms of the trial in which they were involved.

The MUR undertaken by Dougall, Harrison and Lowrie (2015) included recording a VAS pain score. There was no mention in the report of training to undertake this task.

The notes recorded about the MURs undertaken by Hadi *et al.* (2016), Thomas (2012) and Coleman, Yangphaibul and Begovic (2013) suggest that they would be encapsulated by the definition promulgated by the RPharmS. In the remaining papers comments were restricted to reporting that an MUR was undertaken.

Bruhn *et al.* (2013) reported on an RCT which recruited 196 patients suffering with chronic pain and who were randomly divided into three comparative treatment groups: pharmacist review and prescribing, pharmacist paper review with referral back to the GP for prescribing and TAU, ongoing care by their GP. This research used the CPG, which scores 0 to 100. The CPG aims to enumerate the patient's pain intensity in combination with their pain related disability. This method of scoring is complex and time consuming and insufficient research has been undertaken to relate the scores obtained to the more usual 11-point VAS and BPI scales. In the

pharmacist review and prescribing group, the CPG mean intensity score reduced from 66.1 to 58.1 (P=0.002) at the six-month follow-up. This contrasted with the pharmacist paper review and referral to the GP for prescribing group who only reported a non-significant overall mean reduction in pain from 68.4 to 67.4. There were no reported changes in the pain scores of the TAU group. The changes at six months in all three arms for pain related disability were similar but smaller. The questionnaires were sent to participants at 3 months and 6 months after the research had been completed included questions about their satisfaction with the research process. In the 'review and referral' group patients questioned why the pharmacist was not able to prescribe thereby avoiding another appointment and a longer wait for treatment. All participating pharmacists and GPs were invited to take part in a semi-structured interview and their responses recorded.

Dougall, Harrison and Lowrie (2015) reported on the success of a prescribing pharmacist in this community pharmacy scheme. Sixty-four patients were referred by a local GP for an MUR of the medicines used to treat their chronic pain in the consulting room of the community pharmacy. Patients were seen initially and invited to return for a second appointment. Twenty-two patients returned for at least one follow-up appointment and of these 21 recorded two sequential VAS scores. The mean VAS reduced from 5.6 to 4.0, a reduction of 1.6 (29%). This reduction suggested that an MUR under these circumstances could be worthwhile and the authors suggest that this work should be expanded. This paper made specific mention of the difficulty of obtaining patient follow up data.

In Gateshead hospital a prescribing pharmacist was invited to join the pain management team for a trial period of three months (Thomas, 2012). The mean pain reduction reported for the cohort that were treated (n=29) with a pharmacological intervention was a reduction in the pain score of 2.7 or 33%. There were no details of how this improvement was achieved nor any mention of any pain changes in those patients who did not receive a pharmacological intervention therefore it would not be possible to make any general inferences from these results. The baseline pain score was not reported but a calculation from the details reported suggested that the mean baseline pain score was 8.2. The reduction in pain of (2.7) 33% was not dissimilar to the (1.6) 29% reported by Dougall, Harrison and Lowrie (2015) from a much lower starting pain score level. The author claimed that the cost savings on the medicines used was sufficient to justify the long-term continuation of this service beyond three months.

A prescribing pharmacist was invited to join the CPT at the Whittington Hospital in London to assess the contribution which a pharmacist could make to a multi-disciplinary team (Coleman, Yangphaibul and Begovic, 2013). The report outlines the types of therapeutic changes made but made no mention of pain scores.

The case report published by Dumbreck and Cameron (2011) outlined a reduction of pain for a patient attending a chronic pain clinic. The patient reported significant side effects with co-codamol in the past and was reluctant to even consider the possibility

of benefit from taking medicines, the aim was to minimise the use of pain medicines. The prescribing pharmacist was invited by the team to review this patient to see whether it was possible to overcome this resistance. On discharge the number of medicines taken by the patient had reduced from seven to four and the patient's VAS scores had improved 'worst' from 7 to 5 and 'best' from 3 to 2. The prescribing pharmacist's intervention appeared to have facilitated a reduction in both the patient's pain and the number of medicines being taken.

A community-based nurse-pharmacist pain clinic was described by Hadi *et al.* (2012) and Hadi *et al.* (2016). In this research the pharmacist undertook an MUR and the nurse concentrated on the educating the patient about the use of their pain medicines. A combined report was then sent to the GP with suggestions for improving the patient's therapy. The effect on pain scores were reported for a cohort of 35 who were seen twice and the BPI-PSS 'worst pain' reduced by 6% from 8.0 to 7.5 ($p=0.02$), the 'average pain' reduced by 14% from 7.0 to 6.0 ($p=0.02$) and the average BPI-PIS score reduced by 14% from 7.1 to 6.1 ($p=0.02$). These significant improvements were, larger than that non-significant reduction in the CPG recorded for the paper review and referral group in the Bruhn *et al.* (2013) study, but not as large as that reported by the pharmacist prescribers in Thomas (2012) and Dougall, Harrison and Lowrie (2015). These differences may be related to the face to face component of the interventions. Comparisons with the Bruhn *et al.* (2013) study, prescribing arm, were difficult because of the use of the CPCS rather than the 11 point NRS or BPI scales.

The three final papers were conference overviews. Harrison (2015) reported a mean baseline pain score of 7.0, Norman (2015) reported an overall pain score reduced from 6.2 to 5.8 and Cosio and Lin (2014) reported a significant reduction in pain severity. None of these reports gave any details about the pain scores used and there were insufficient details to allow any other comparisons.

An overview of these results with regard to pain suggests that those pharmacists who were prescribers achieved a greater reduction in pain than those who undertook a review and referred back to the GP. Much more date would be needed before such an impression could be confirmed.

In several of these papers the pharmacists were working as part of a CPT. Systematic reviews have reported that multidisciplinary CPTs are the most effective means of treating chronic pain (BPS, 2013; Kress *et al.*, 2015; Cheatle, 2016) and rehabilitation (Kamper *et al.*, 2015). The possibility that at least some of the benefit reported might have been as a result of the team effort was not addressed and should be addressed in any future research.

The reported role of placebos in the medicinal treatment of pain (Muller *et al.*, 2016; McCartney, 2015) was not mentioned in any of these papers even though it is reported that in clinical trials involving analgesics the placebo effect is always observed (Vachon-Presseau *et al.*, 2018). A Cochrane review has suggests that

research trials for pain treatments should contain three arms, treatment, placebo and treatment as usual (Hrobjartsson and Gotzsche, 2010).

2.5.6.2. Neuropathic pain

Seven of the twelve reports suggest that patients attending these consultations arrived with pain identifiable as neuropathic, but were not currently receiving appropriate therapy. The treatment of neuropathic pain is complex and there are many reasons why this proportion of patients with chronic pain may not be receiving treatment for suspected neuropathic pain. The complex interrelationship between chronic pain and neuropathic pain was outlined in Section 1.5.3 (van Hecke *et al.*, 2014; Bouhassira *et al.*, 2008; Freynhagen and Bennett, 2009).

Gill, Taylor and Knaggs (2013) reported that of the 176 patients involved in their research, 101 completed the painDETECT questionnaire (Freynhagen *et al.*, 2006) which was aimed at elucidating lower back pain with neuropathic elements in community or hospital. Of these 101 patients 23 returned a painDETECT score of between 19 and 38 suggesting that they had a component of neuropathic pain within their overall pain. Nine patients were referred back to their GP for possible undiagnosed neuropathic pain. The authors went on to suggest that if these results were extrapolated nationwide, community pharmacists could identify 50,000 cases of neuropathic pain in a year. This figure depends upon the validity of the questionnaire being used. Cruccu and Truini (2009) suggest that the questionnaires which include

some form of appraisal for allodynia (DN4 and S-LANSS) achieve the greatest sensitivity and specificity. On the other hand Bisaga *et al.* (2010) reported that the S-LANSS was the least sensitive of DN4, S-LANSS and painDETECT at detecting neuropathic pain. In a more recent review Harrisson *et al.* (2017) reported that the frequency of diagnosis of neuropathic pain based upon a questionnaire depended upon the questionnaire used. But this should not distract from the comment by Cruccu and Truini (2009) that we badly need an objective means to measure pain and pain intensity as well as response to treatment. This variation would not be too problematic if the medicines that are used in the treatment of chronic pain were effective. Unfortunately, the NNTs for a 50% reduction in pain with medicines used in the treatment of neuropathic pain vary between 2.2 and 5.0. (McQuay *et al.*, 1996; Haroutounian and Finnerup, 2018; Beniczky *et al.*, 2005) and therefore it is likely that for some patients no treatment will ever be very effective. To make up for this lack of efficacy it is suggested that at least four different therapeutic options for neuropathic pain should be explored (Smith *et al.*, 2012). Notwithstanding these difficulties if pharmacological treatment could be given to the suggested 50,000 patients, this could lead to an improvement in their wellbeing. On the other hand such treatment is difficult to initiate successfully, requiring close review and monitoring and the side effects at therapeutic doses which can be significant, would need to be balanced carefully against any benefit.

Harrison (2015) reported on a pilot project to investigate the feasibility of community pharmacists undertaking chronic pain reviews. During the extended MURs, which

included the STarT back questionnaire (Traeger and McAuley, 2013), with the 20 patients in this cohort 11 patients reported symptoms of neuropathic pain. Of these 11, only one was taking medicines which were considered appropriate for the treatment of neuropathic pain. The others were referred back to their GP with recommendations to start appropriate therapy.

Four of the other reports allude to undiagnosed neuropathic pain. Suggestions by the pharmacist for the optimisation of pain therapy for the cohort reported by Coleman, Yangphaibul and Begovic (2013) specifically included adding amitriptyline. In the case report presented by Dumbreck and Cameron (2011) the patient reported symptoms to the pharmacist that suggested neuropathic pain and which reduced after the addition of gabapentin to the patients' therapy. Bauters, Devulder and Robays (2008) reported on a pharmacist's suggestions for improving pain control in this cohort of 93 patients attending a hospital out-patient chronic pain clinic. One third of the suggestions made by the pharmacist were for medicines, which would be appropriate for the treatment of neuropathic pain. Finally the Norman (2015) abstract summarised the changes found in this cohort of 39 patients attending a pharmacist led chronic pain clinic. Pain scores and morphine equivalent doses went down but the mean number of non-opioid adjuvant pain therapies i.e. treatments for neuropathic pain (Pergolizzi, 2016) increased from 1.8 up to 2.0.

Clearly, none of these provide any robust research evidence about the frequency of neuropathic pain in patients with chronic pain. In total of the 12 papers included in

this systematic review seven refer in some way to improving therapy for neuropathic pain. Any opportunities which pharmacist have to improve the therapy of patients with neuropathic pain needs to be explored further, because patients with neuropathic elements in their pain report higher pain intensities (Torrance *et al.*, 2006) and poorer quality of life (Smith *et al.*, 2007) than those without neuropathic elements.

2.5.6.3. Patients understanding of their pain medicines

Patient adherence to medicinal therapy in all chronic conditions is poor, about 50% in 'developed' countries (Yach, 2003) and this was famously commented on by C. Everett Koop, one-time US surgeon general: "*Drugs don't work in patients who don't take them"* (Osterberg and Blaschke, 2005).

Poor adherence/compliance and concordance with medicines in general have been widely examined. There is more understanding for this reluctance where there is little relationship between a therapy and the possible benefits as has been reported in the treatment of hypertension (Anker *et al.*, 2019). But in the treatment of pain, patients were often aware that less medication means more pain (Broekmans *et al.*, 2009). The reasons for this reluctance, which included failure to comply with their pain prescriptions were not clear. Some patients were reluctant to take their pain medicines because of a fear of unwanted side effects or concerns about addiction (Pound *et al.*, 2005; Horne *et al.*, 2013). For others the reasons were more complex, taking pain medicines in some way ceded aspect of control over their lives to their

pain (Pellino and Ward, 1998). However, pharmacists have a responsibility to ensure that patients understand how to take their medicines to maximise any benefit and minimise any adverse effects (Graham and Brookey, 2008; Praska *et al.*, 2005; Kripalani *et al.*, 2007) because some patients will struggle both with understanding dispensing labels and/or the initiation and maintenance of complex dosage regimens (Young *et al.*, 2018). During a clinic consultation there is the opportunity to address some of these concerns. Four papers retrieved by this systematic review (Dougall, Harrison and Lowrie, 2015; Gill, Taylor and Knaggs, 2013; Thomas, 2012; Dumbreck and Cameron, 2011) specifically reported that initially patients did not take their analgesics as prescribed or recommended and that advice from the pharmacist led to better outcomes for their pain. In addition, (Coleman, Yangphaibul and Begovic, 2013; Bauters, Devulder and Robays, 2008) both reported working with patients to optimise their analgesia even though neither include any pain scores which would have confirmed such a claim.

NICE reports that controlling chronic pain is challenging and that prescriber's focus should be on reducing pain in a way which improves the patients quality of life (NICE, 2017). But, pain medicines come with a multiplicity of side effects as discussed in Section 1.5: opioid induced nausea (Moore and McQuay, 2005), constipation (Collett, 1998), NSAIDs and gastric ulceration (Davis and Robson, 2016), gabapentinoid induced brain fog (Zaccara *et al.*, 2011) and TCA induced dry mouth (Cookson, 1993). An MUR provides a pharmacist with the opportunity discuss the dilemma of efficacy versus side effects with the patient. This discussion should lead patients to a

better understanding of their pain medicines about how to improve efficacy and minimise side effects.

The role of the pharmacist has changed and expanded as the use and efficacy of medicines in health care has been transformed. All such changes are aimed at better utilisation of the knowledge, which pharmacists have about medicines and medical conditions and attempting to ensure that patients got the best benefit from their medicines. The contribution that a pharmacist can make in the treatment of chronic pain is recognized by some patients. In the report of their research Gill, Taylor and Knaggs (2013) included 'individual statements' from the satisfaction surveys that patients were asked to complete: '*The pharmacist helped me understand how my medication would improve my pain*' and '*The pharmacist helped me address possible side-effects*'.

2.5.6.4. Cost implications of pharmacist intervention

The supporting data in the papers included in this systematic review about the costs associated with pharmacists' interventions beyond dispensing prescriptions for pain medicines were very limited. In a pilot study which was aimed at determining whether a pharmacist would add value to an MSK chronic pain service (Coleman, Yangphaibul and Begovic, 2013), four physiotherapists were interviewed, in a semi-structured way, after the pharmacist's interventions were completed. The reported summary presented the opinion that pharmacist added value to the service by

providing specialist advice for the patients, which maximized adherence and improved the patient experience. At the end of the pilot, the service was continued and expanded from one to two days a week, but the cost benefits were not discussed further.

Another report was not as positive. An the end of the Bruhn *et al.* (2013) research all participating pharmacists and GPs were invited to take part in a semi-structured interview and their responses recorded verbatim. Comments made by GPs about the pharmacists' suggestions in the 'paper review and refer group' included *"tinkering around the edges"*, *"tried this before"* and *"when we are short of cash, is this an appropriate use of resources?"*.

The total cost of the individual arms of this research were investigated separately (Neilson *et al.*, 2015). Medicine costs were taken from the BNF, appointment costs from the Scottish Health Service Cost Book and pharmacist and GP time from the Personal Social Serviced Research Unit. These were balanced against the gain in quality-adjusted life years (QALY). The final account suggested that the intervention of a pharmacist was probably not cost effective but the numbers were too small to give a definitive answer.

The Neilson *et al.* (2015) paper specifically excluded from their accounting any costs borne by the patients, travel, carer costs and loss of employment as well as the associated societal losses because these were not relevant to the health service

costs. Such omissions are however apposite because Maniadakis and Gray (2000) reported that the total cost of back pain for the UK in 1998 was at least £6.650b, £1.632b (25%) for direct health care costs and £5.018b (75%) for informal care and lost productivity. If the difference between the costs of the three arms was not certain after excluding none NHS costs it would be interesting to see the results recalculated in a way which included the additional costs as calculated by Maniadakis and Gray (2000). Many of the costings used by Neilson *et al.* (2015) were from the same sources used by Maniadakis and Gray (2000). Therefore, it should not be difficult to recast the comparative costs in a way which included the non-NHS costs or some agreed proportion of them. There is ongoing debate about the appropriateness of the basis upon which QALYs (Section 8.2) are calculated (Kirkdale *et al.*, 2010). On the other hand, Harrison (2015) and Thomas (2012) suggest that the additional costs associated with a pharmacists interventions could be offset by savings from within the drugs budget. This is not completely fanciful because Neilson *et al.* (2015) did comment that the most significant part of the expenditure in any of the three arms of this study were the costs of the medicines being prescribed.

Dougall, Harrison and Lowrie (2015) suggests that the cost effectiveness of a pharmacists' intervention into the treatment of chronic pain needs further investigation. This finding was contrary to the report by Bauters, Devulder and Robays (2008) which specifically stated that the intervention of a clinical pharmacist

in this way in the treatment of chronic pain was not cost effective. The remaining reports made no mention of costs.

In times of financial constraint, it is important that costs are investigated. However, given the difficulty of treating chronic pain it is important that effective therapy is not constrained by the cost of the medicines (RCGP, 2013). This highlights the significance of the Maniadakis and Gray (2000) report and the comment about medicine costs in the Neilson *et al.* (2015) report. Overall, the papers retrieved by this systematic review, reported that a pharmacist in a CPS led to a reduction in pain, but the cost benefit was as yet undefined.

2.6. Conclusion

A systematic review of the literature was undertaken to ascertain the extent of the published data about the benefit that a pharmacist working as a member of the CPT can bring to the treatment of chronic pain. The small number of new research papers which had been published indicated that the pharmacist had made a positive contribution to the patients' pain, however the evidence base for this assumption was generally of poor quality, based upon four papers, three brief reports and one RCT (NIH, 2018; Jadad *et al.*, 1996).

It is reported that the best outcomes in the treatment of chronic pain result from a multi-disciplinary team effort (BPS, 2013; Kress *et al.*, 2015; Cheatle, 2016). As most

of this research took place within a CPT it is difficult to truly separate out the pharmacists' contribution.

These research projects were undertaken in community pharmacies, hospitals, clinics and GP surgeries. A key intervention was the pharmacists MUR either face to face or paper based. In future, greater effort needs to be he made to specify in detail this part of the research in order to clarify the impact factor of the intervention.

From these papers it would appear that there are indications that amongst patients suffering with chronic pain there is some unsatisfied need for the appropriate treatment of neuropathic pain. The diagnosis of neuropathic pain is problematic and its treatment difficult. Therefore, it was unclear what was the cause of this unmet need: was it lack of diagnosis, a failure of therapy resulting from ineffective medicines or a lack of treatment or a reluctance on the part of the patient to engage with their treatment.

Many of these papers reported either a lack of compliance with prescribed pain medicines or lack of understanding about how to take their medicines. There was no indication in these papers about whether the pharmacist's intervention resulted in an improvement in the patients' pain scores because the patient's prescriber improved the patient's therapy or because the patient better used the therapy they had been prescribed.

The additional cost of the inclusion of a pharmacist in a CPT is not insignificant. The opinions from the staff and patients who interacted with the pharmacist were largely, but not completely supportive. The analysis of costing which was done indicated that this addition was not cost effective, but this analysis was not free from bias and it did close with the suggestion that the analysis was too small to be certain of the outcome.

CHAPTER 3 AIMS & OBJECTIVES

3.1. Aims

This research set out to determine whether a consultation with the pharmacist, within the multidisciplinary CPT in South Staffordshire and any resulting medicines advice and education changed patient use of their pain medication. If so, did this improve their use of their pain medicines, pain scores or medicine side effects.

3.2. Objectives

Patients were seen at normal CPS pharmacist clinic appointments on two occasions separated by four months. The following objectives were assessed and recorded at both appointments

i. Assess and characterise the patients pain using the BPI questionnaire (Appendix 8.4.2)
ii. Assess and characterise the patients neuropathic pain using the S-LANSS questionnaire (Appendix 8.4.3)
iii. Take a full medication history using the Researchers Drug Dataset questionnaire (Appendix 8.4.4) to determine medicines actually taken and any resulting benefit
iv. Explore patients attitudes towards compliance with their pain medicine therapy with the help of the BPI questionnaire

The differences between the results at the 1st and 2nd appointments were then compared for any changes.

CHAPTER 4 METHOD

4.1. Introduction

This chapter will commence with the ethical approvals obtained before this research commenced and the subsequent protocol amendment. It will then lay out the detail of the patient recruitment, the inclusion and exclusion criteria and the research processes including the intervention. It will conclude with details of the data handling and statistical review.

4.2. Ethical approval

Ethical approval for this research was sought and received from

i. University of Birmingham approval ERG Reference: RG 14-049 dated 6th January 2016.
ii. NHS ethical approval from Brighton and Sussex NRS Committee – 16/LO/0353 – IRAS 181743 – NHS SSI 287948

It was anticipated at the commencement of the research period that sufficient patients would be recruited through the normal clinic appointment system. Unfortunately, whilst this research was extant a new Patient Administration System became operational within the Trust and there was concern that this might create a problem with recall appointments. In anticipation of such a shortfall in numbers, a Protocol amendment was sought and approved, seeking permission to contact patients by phone if necessary, to complete the research project. This proved

unnecessary and all the patients who had been enrolled were offered a 2nd appointment except for those who had been discharged from the CPS

4.3. Patient recruitment

The referral pathway of patients to the pharmacist's clinic is summarised in Figure 4.1.

Patients always arrived at their first full appointment with the pharmacist by one of two routes.

i. Patient referral from another member of the CPT.

Any other member of the CPT was able to refer a patient to the pharmacist's clinic. Such a referral would normally occur when member of the team was concerned about one or more of the following aspects of the patient behaviours

a. Taking their medicines incorrectly even after advice.
b. Appeared to have unresponsive central sensitisation or neuropathic pain.
c. Taking doses of strong opioids whilst still reporting high levels of pain
d. Expressed a wish to reduce their use of strong opioids
e. Lacked confidence in the healthcare professional managing their medicines
f. Specifically asked for a second opinion with the pharmacist
g. Demonstrated a lack of understanding about their medication
h. Expressed anxiety about addiction

These referral criteria encourage team members to make appropriate patient referrals to the pharmacist when they believe that advice about their pain medicines would give them benefit, irrespective of any other facet of their treatment. The pain of the patients in the research cohort was no different, overall, to those seen prior to the commencement of the research. Patients with pain associated with a painful physical condition such as arthritis were only referred to the pharmacist where this had caused pain which was disproportionate to that which would be expected for that particular condition. The referrals to the pharmacist's clinic therefore contained a disproportionate number of patients suffering with pain 'wind-up' or 'central sensitisation' (Appendix 8.2). Referrals also included patients who demonstrate a lack of understanding of the role of pain medicines in their treatment or who were reluctant to become involved with the use of pain medicines.

ii. Patient self-requested an appointment following pharmacist's presentation at a PMP.

The pharmacist's presentation and subsequent discussion at the PMP occupied half of one three-hour session (90 minutes). At that time the role of medicines, in the treatment of chronic pain were outlined along with suggestions for how pain medicines could best be used. At the end of the presentation/discussion patients were offered the opportunity for an informal conversation over coffee or a later individual clinic appointment.

All patients in this research cohort were recruited in one of these two ways

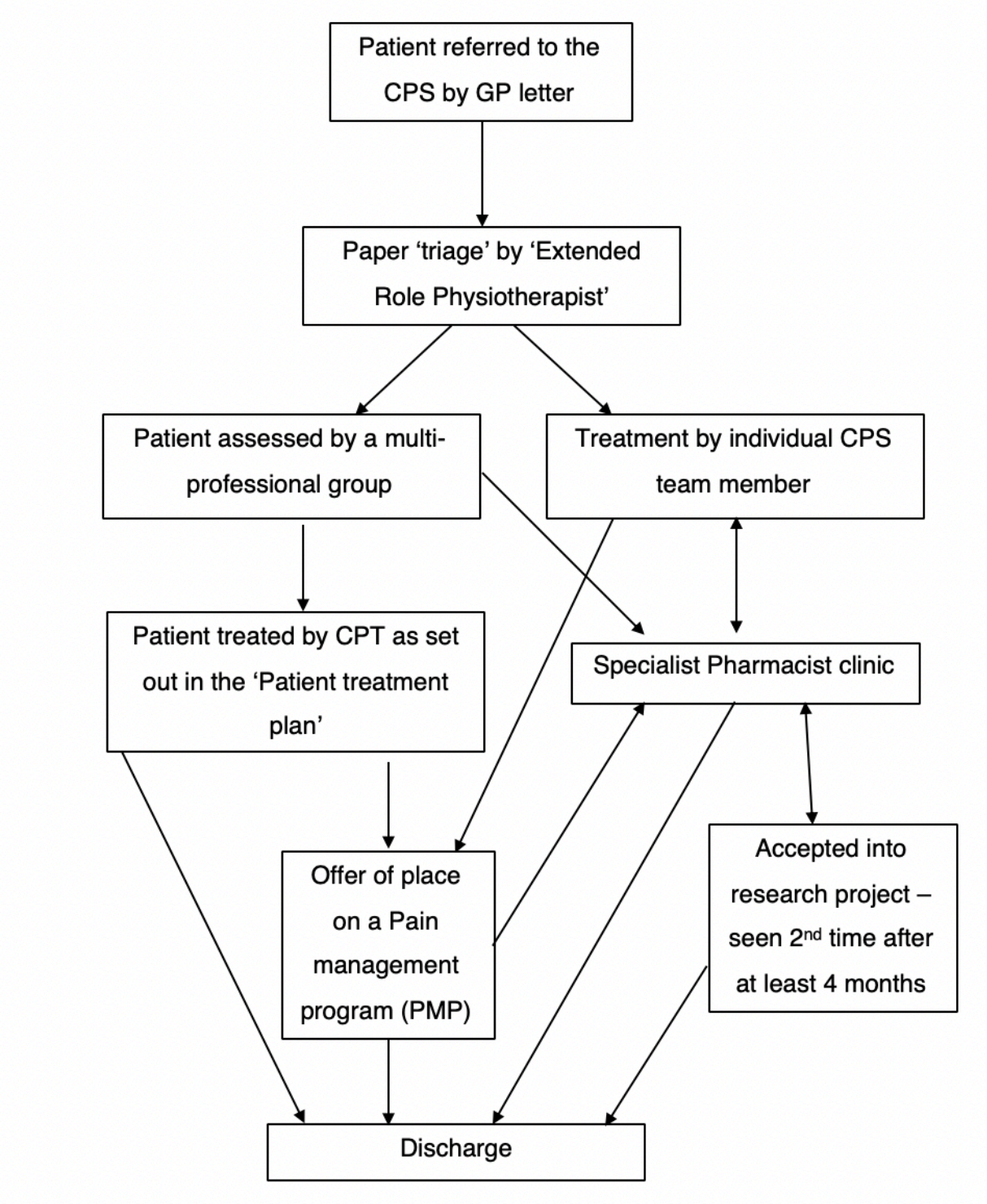

Figure 4.1 Flow diagram of referral process into the pharmacist clinic, including the research appointments

4.4. Research process

Prior to the commencement of the research all members of the CPT were briefed about the protocol and the consent process. Therefore, once the research had commenced when a member of the CPT referred a patient to the pharmacist they explained the pharmacist was undertaking a research project, provided patients with verbal information about the project and began the consent process, emphasising that participation was voluntary and would not influence their care in any way.

During the research period all patients attending for a pharmacist's appointment were offered the opportunity to participate in the research. The letters inviting patients to attend the pharmacist's clinic were sent at least two weeks prior to the clinic appointment and contained, in addition to the normal appointment letter the following paperwork, which had been approved by the Brighton and Sussex NRS Committee NHS ethics committee.

i. Patient Information Sheet (PIS) (Appendix 8.3.1).
ii. Patient Consent Form (PCF) (Appendix 8.3.2).
iii. Patient's Pain Medicine Question (PMQ) (Appendix 8.4.1). A bespoke questionnaire asking about the pain medicines patients were currently taking or had taken in the past.
iv. The BPI (Appendix 8.4.2). A self-completion questionnaire, which included questions about pain intensity, pain medicines and the patients' attitude towards the use of pain medicines. This was validated for use in Chronic non-cancer pain by Keller *et al.* (2004) who collected data on 250 patients with

arthritis and low back pain at two time points and compared this with other generic pain scales.

v. The S-LANSS questionnaires (Appendix 8.4.3). A self-completion questionnaire to determine the presence of neuropathic pain. This was validated for self-assessment and postal research by comparing results from interviews with results from the questionnaire for the same groups of patients (Bennett *et al*., 2005).

After enquiries by the researcher it was understood that both the BPI and S-LANSS questionnaires were freely available for NHS research. The S-LANSS questionnaire had been issued to the patients attending the pharmacist's clinic for a number of years. This was used to inform the pharmacist's approach to the discussion about the type of pain from which the patient was suffering. The BPI short form is a standard outcome measure used by the CPS. This was changed for the pharmacist research because the complete BPI includes questions about the patient's use of medicines in relation to their pain.

Additional copies of all the paperwork were available in clinic if required.

All patients in this research cohort undertook the same, minimum, intervention and the same questionnaires were used. The same records were made for each patient.

Letters offering appointments were issued at least two weeks in advance of the clinic date. Therefore, patients would have two weeks to consider whether they wished to enter into a discussion with the pharmacist about participating in the research.

At the 1st appointment, the opening discussion determined whether the patient was prepared to consider participating in this research project. If the patient was willing to participate the pharmacist would:

i. Ensure that the patient understood the PIS.
ii. Ensure that the patient was given the opportunity to ask any questions.
iii. Confirm with the patient that their treatment would be exactly the same whether or not they agree to participate in the research.
iv. Confirm with the patient that they were free to withdraw from the research at any time without any change to their treatment
v. Confirm with the patient that the research process would only involve looking at the information, which was the same in every way as a normal clinic session, with the exception of the complete rather than short version of the BPI.
vi. Agreed with the patient that if they were willing to participate then together the patient and the researcher would sign the PCF.
vii. Record a 'Patient Identification Number', to ensure patient anonymity in subsequent data analysis. This number was stored securely, separate from any other information.

Once the patient had agreed to participate, the clinic appointment followed the normal format *viz*. characterisation of their pain, a full medical history, understanding of the effectiveness of each pain medicine used and pain medicine optimisation advice. At the end of the appointment an agreement was reached about any suggested changes to therapy and a follow-up appointment was arranged.

Patients were asked to complete the questionnaires sent with their appointment letter prior to attending for their 1st and 2nd clinic appointments. These included the following quantitative pain scales.

i. The eleven-point (0-10) NRS
ii. The BPI pain severity scale (BPI-PSS) comprised four, eleven-point scales *viz.* worst, best, average and now. The information which accompanied the BPI suggested that each of these scores was valid of itself as was the mean overall PSS if all four scores are available (Cleeland, 2009).
iii. The BPI pain interference scale (BPI-PIS) comprised seven, eleven-point scales *viz.* general activity, mood, walking ability, normal pain, relationships, sleep and enjoyment of life. The information which accompanied the BPI suggested that each of these scores was valid of itself as was the mean overall PIS. The mean was also as regarded as valid if four or more scores were included (Cleeland, 2009).
iv. The S-LANSS scale.

Following the 1st appointment, regardless of whether the patient was participating in this research a letter was sent to the GP, with copy to the patient, outlining any agreed suggestions for improving their treatment.

All of the data collected during each clinic appointment from both the questionnaires and the conversation was recorded on the Researchers Drug Datasheet (Appendix 8.4.4). These data were then used to create a spread sheet which became the basis for subsequent analysis.

Letters inviting patients for their follow-up appointment, at least four months after the initial appointment contained the same documents and questionnaires as their original invitation letter. Four months was chosen to allow the pharmacist letters to be prepared, posted and delivered, for patients to arrange an appointment with their GP to discuss and agree any new medicine plan and finally time for any changes in. therapy to become effective.

At their 2nd appointment all research participants were asked to re-confirm their willingness to proceed as before even though continued attendance was regarded as indicative of implied consent. The datasets collected for both the 1st and 2nd appointments were based upon the same questions.

Following the 2nd appointment, regardless of whether the patient was participating in this study, a letter was sent to the GP, with copy to the patient. If a third appointment was necessary this took place outwith the research according to normal clinical practice

The datasets from the two clinic appointments, comprising S-LANSS and BPI information as well as a detailed resume of pain medicines used and their effectiveness were them examined for any (statistically significant) changes including

i. Pain scores
ii. Pain medicines used
iii. Perceived effectiveness of pain medicines used
iv. Answers to questions 24-30 in the complete BPI (Appendix 8.4.2)

Each patient who agreed to participate in the research was asked if they were willing for their GP to be approached by the researcher as part of the study. If the patient consented the Practice Manager of the patient's General Practice was informed about the on-going research. In addition, the practice manager was approached later for information about any extant protocols used by the Practice for the treatment of Chronic Pain.

4.5. The intervention

The intervention, took place during each clinic appointment and lasted between 45mins and one hour. Firstly, an MUR was undertaken. As full a history, as

possible, of the patient's pain medicines to date and the effectiveness of individual pain medicines was recorded. Other medications, including OTC products, were also reviewed because of the possibility of drug duplications or interactions. Explanations were then given to the patients about how their pain medicines could best be used to treat their pain. Two points were always included. Firstly, the patient needed to be aware of whether the pain medicines being take were helpful. Secondly, that they should have an action plan for using their pain medicines when their pain flared or to facilitate important necessary life events which had the potential to cause pain. The agreed salient points were included in the letter to the patients GP.

4.6. Research guidelines

4.6.1. CHECKLIST FOR COHORT STUDIES

The STROBE Statement (Strengthening the reporting of observational studies in epidemiology) set out a suggested checklist of items that should be included in a cohort study (ISPM, 2014). This guidance was followed during the planning of this research.

4.6.2. CHECKLIST FOR BIAS CONTROL

A checklist promulgated by the Cochrane Collaboration to minimise bias in cohort, observational studies was published in 2018 (Cochrane, 2018). This includes eight points which should be considered when undertaking such studies to minimise bias in any results and ranked each between 'definitely yes' and 'definitely no'.

Comparison of this research process with the Cochrane bias tool revealed that there was a chance of bias in this research. All patients included in this research were suffering with chronic pain and were expected to have high pain scores at presentation. The sub-group who were referred to the pharmacist's clinic were at approximately the same point in their care and within the same time frame. They were all exposed to the same processes during consultations with the pharmacist and similar data were recorded for each patient. The data for patients who were seen once and those who were seen twice was kept separate and used either as total data or paired data.

4.7. Inclusion and exclusion Criteria

The following Inclusion and Exclusion criteria were applied to this research.

4.7.1. INCLUSION CRITERIA

i. Adult patients attending the Chronic Pain Service in the South Division of the Staffordshire and Stoke on Trent Partnership NHS Trust
ii. Patients who were willing and able to give full, voluntary, informed consent.

4.7.2. EXCLUSION CRITERIA

i. Patients who were not willing or not able to give full, voluntary informed consent
ii. Patients who were not able to fully comprehend the paperwork through age, incapacity or insufficient literacy in English

iii. For patients' not able to read the research paperwork because of insufficient literacy in English. If a translator was advised for the patient's clinic appointment and was available then an effort was made to include these patients. As a researcher self-funded study there were no funds for the translation of any paperwork into other languages.

iv. Patients taking medicines in a separate clinical trial, which may confound the results of this research.

4.8. Data handling and security

All the data collected for this study was handled in accordance with Trust and University procedures.

All data from the 'Researchers Drug Datasheet' was transferred to Excel and Software Package for Social Science (SPSS) version 19.0 research spreadsheets for analysis.

Each patient attending the Chronic Pain Service had a unique set of notes, relating solely to the CPS. These records were accessible only to the staff employed within the CPS.

All patients who were entered into this study were given a unique sequential number starting with M(ale) or F(emale). The file linking these numbers and the patient's name was stored separately.

During this study, all patient research data was stored on Trust encrypted computers, which were controlled by the Trust's governance policies. Any paper records were stored in a Trust office along with other patient records in a locked filling cabinet in a locked office.

4.9. Statistical review

4.9.1. STATISTICAL ANALYSIS

Prior to the commencement of data analysis statistical advice was sought from James Hodson (Hodson, 2017), Institute of Clinical Sciences, Medicine and Medical Education, University of Birmingham.

This study cohort was made up of patients suffering with chronic pain who had been referred to the pharmacist's clinic. As a result, it was highly likely that their pain would be skewed towards higher results on a 0-10 NRS pain scale and a 0-24 S-LANSS scale, resulting in a non-normal distribution. Therefore, prior to any analysis, pain scores were assessed for normality.

4.9.2. POWER CALCULATION

No data were available to estimate the degree of improvement that would be expected from any intervention, nor what distribution these improvements would take. For this reason, the power calculation was performed based on a sign test, using the assumptions set out below by the statistician.

'The recruitment target for this research was for 100 patients to be recruited between April 2016 and August 2017. Assuming that 80 patients returned for a second appointment after four months, the minimum detectable difference would be that 66% of patients show some degree of improvement in their VAS or S-LANSS pain scores at their four months follow up, based on 5% alpha and 80% power' (Hodson, 2017).

CHAPTER 5 RESULTS

5.1. Introduction

This chapter will set out the demographics of the patients involved in this research. It will then record the patients NRS and S-LANSS pain scores and the pain medicines, which they reported using at their 1st visit. It will then examine any changes in pain scores and perceptions of the effectiveness of their pain medicines, which the patients reported between their two clinic visits. It will conclude with any changes in patients' attitude towards their pain medicines.

5.2. Baseline information about the research cohort

The aim was to recruit 100 patients between April 2016 and August 2017

Much of these data were extracted from the BPI and S-LANSS questionnaires. These are relatively complex questionnaires to complete, unsupervised and not every patient provided an answer to every question. There was insufficient clinic time to go through each questionnaire with each patient.

5.2.1. DEMOGRAPHICS OF PATIENTS AT ENROLMENT

Every patient referred to the pharmacist was offered the opportunity to participate in this research and Table 5.1 shows the distribution of the patients recruited between

each centre. Because of the way that patients were recruited to this research (Section 4.3) no inferences can be drawn from the overall numbers at each clinic.

The English Indices of Deprivation 2015 divides the country into small areas from 1, the most deprived to 32,844 the least deprived. This index is based upon aliquots of 1,500 people and ranks then according to seven domains: income, employment, education, health, crime, housing and environment. These data can be used to track individual areas over time or compare areas geographically (GOV-UK, 2015).

5.2.1.1. Distribution of cohort across clinics and relative deprivation of each clinic locations

Table 5.1 Distribution of the research cohort between the five centres (n=100)

Clinic location	**Rank position out of 32,844** (where 1 is most deprived)	**Deprivation level at this location**	**Male (n=27) (%)***	**Female (n=73) (%)***	**Total (100)**
Burton	4,393	20% most deprived	5 (19%)	12 (16%)	17
Lichfield	11,524	40% most deprived	6 (22%)	11 (15%)	17
Tamworth	16,701	50% least deprived	3 (11%)	11 (15%)	14
Rugeley	8,589	30% most deprived	8 (30%)	18 (25%)	26
Stafford	8,272	50% most deprived	5 (19%)	21 (29%)	26
Total			27 (100%)	73 (100%)	100

* percentage at this location

The literature suggests that there may be a relationship between social deprivation and chronic pain. Therefore, the UK Index of Deprivation 2015 metric for the five centres areas were included. (GOV-UK, 2015).

5.2.1.2. Age distribution of research cohort

A systematic review by Fayaz *et al.* (2016) reported that chronic pain increases with age. This normally collected data were included to compare this research cohort with the Fayaz *et al.* (2016) results. The age distribution was set out in Figure 5.1.

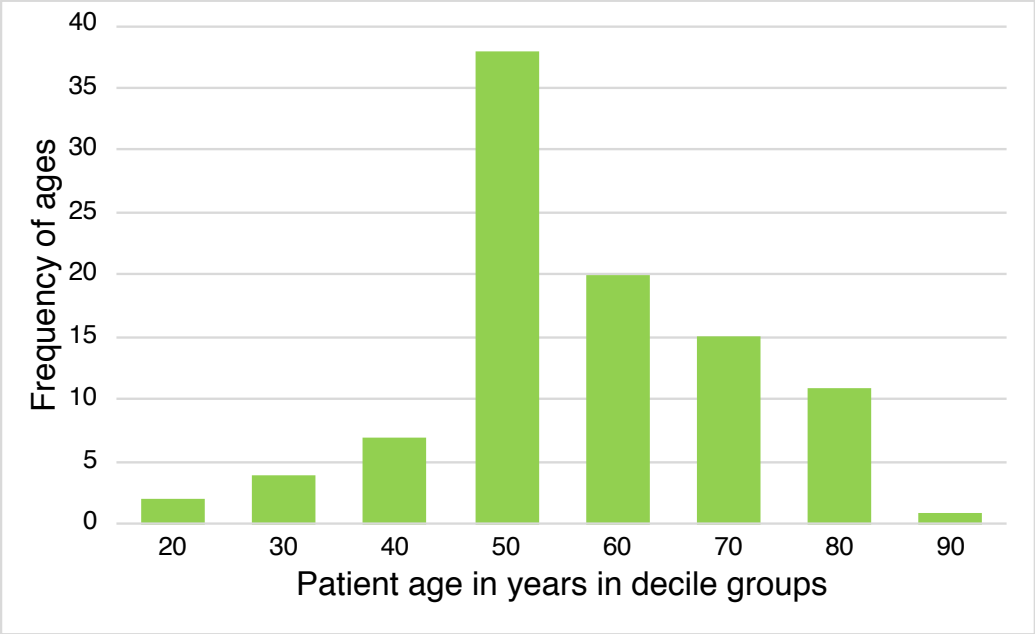

Figure 5.1 Distribution of the ages by deciles of member of the cohort at enrolment (n=100)

There was a wide distribution of ages. The greater proportion of males were aged over 50 years with the largest decile in females being between 40 and 49 years. The mean age was 51.

The numbers of patients in each major decile are set out in Table 5.2. The table also includes the number of patients with NRS>=7 and S-LANSS>=12 pain scores in the same decile groups.

In all age groups over 82% of patients presented with severe pain, defined by Breivik *et al.* (2008) as NRS >=7 and more than 49% of patients reported an S LANSS score of >=12 which Bennett (2001) suggested as indicative of elements of neuropathic pain. Not all patients who had an NRS>=7 had an S-LANSS score >=12 and vice versa.

Table 5.2 Age of patients in the cohort with NRS>=7 & S-LANSS>=12 (n=100)

Age at 1st appointment (years)	Male (n=27) (%)*	Female (n=73) (%)*	Total (100)	Total with NRS>=7**	Total with S-LANSS>=12**	Total with both NRS>=7 & S-LANSS>=12**
Up to 39	1 (4%)	11 (15%)	12	10 (83%)	6 (50%)	5 (42%)
40 < 49	7 (26%)	31 (42%)	38	34 (89%)	23 (61%)	22 (58%)
50 < 59	10 (37%)	13 (18%)	23	19 (83%	13 (57%)	11 (48%)
60 < 69	5 (19%)	8 (11%)	13	12 (92%)	9 (69%)	8 (62%)
> 70	4 (15%)	10 (14%)	14	13 (93%)	7 50%)	7 (50%)
Total	27 (100%)	73 (100%)	100	88 (88%)	58 (58%)	53 (53%)

* Percentages are of the total in this group - male or female

** Percentages are the number in this age group with this pain score

5.2.1.3. Time since receiving their diagnosis (BPI question 6)

In order to take account of any impact the period of time patients had waited prior to being referred to the CPS and then seen in the pharmacist's clinic, the waiting time was recorded.

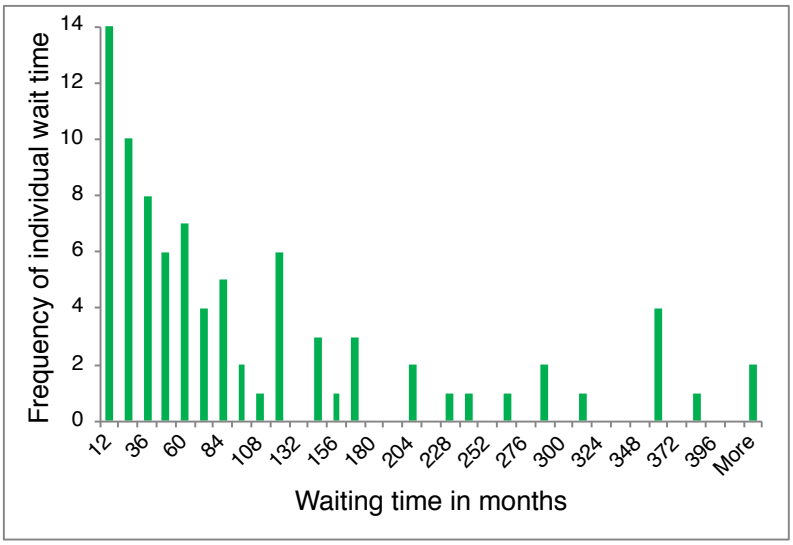

Figure 5.2 Time that patients reported waiting (months) (n=85).

The BPI questionnaire asks patients to record the time since diagnosis in months. Some patients did not have a (remembered) diagnosis or a definite start point for their chronic pain. Most were reporting the time since the commencement of their pain.

More than half of the patients had experienced their pain symptoms for more than 36 months. The mean waiting time for males was 105.9 and for females 106.1. The

median for male patients was 67.5 months and for female patients 60 months. The range of waiting times was one month up to 47 years.

5.2.1.4. Educational achievement, employment and relationship status of the research cohort

In order to compare the demographics of this cohort with previous research, and to set markers for the future the educational status, employment status and patient relationships as recorded in the BPI are tabulate below. Most members of the cohort had some level of educational achievement, the largest employment groups were retired or unemployed and the majority of the cohort were married. The number of patients with the worst pain (NRS>=7 and S-LANSS>=12) were also included in Tables 5.3, 5.4 and 5.5.

Table 5.3 Baseline, patients' educational achievements with NRS>=7 and S-LANSS>=12 (n=100)

Educational status at 1st appointment	Male 27 (%)*	Female 73 (%)*	Total 100	Education with NRS>=7 & S-LANSS>=12 (%)**
Left school with no formal qualifications!	9 (33%)	14 (19%)	23	16 (70%)
GCSE or equivalent	10 (37%)	33 (45%)	43	21 (49%)
A level or equivalent	2 (7%)	10 (14%)	12	6 (50%)
Degree or equivalent	5 (19%)	12 (16%)	17	8 (47%)
Not stated	1 (4%)	4 (5%)	5	2 (40%)
Total	27	73	100	53

* Percentage with this qualification in this group
** Percentage with this pain score in this educational group
! These titles equate as nearly as possible with those in the BPI

Table 5.4 Baseline, patients' employment status with NRS>=7 & S-LANSS>=12 (n=100)

Employment status! at 1st appointment	Male 27 (%)*	Female 73 (%)*	Total 100	Employment with NRS>=7 & S-LANSS>=12 (%)**
Employed f/t	2 (7%)	7 (10%)	9	5 (56%)
Employed p/t	0	7 (10%)	7	4 (57%)
Homemaker	0	9 (12%)	9	5 (56%)
Retired	11 (41%)	19 (26%)	30	15 (50%)
Unemployed	9 (33%)	16 (22%)	25	14 (56%)
Not stated	5 (19%)	15 (20%)	20	10 (50%)
Total	27	73	100	53

* Percentage with this employment status in this group

** Percentage with this pain score in this employment group

! These titles equate as nearly as possible with those in the BPI

Table 5.5 Baseline patients relationship status with NRS>=7 & S-LANSS>=12 (n=100)

Relationship status! at 1st appointment	Male 27 (%)*	Female 73 (%)*	Total 100	Relationship with NRS>=7 & S-LANSS>=12 (%)**
Married	13 (48%)	38 (52%)	51	28 (55%)
Single	6 (22%)	10 (14%)	16	7 (44%)
Divorced/separated	5 (19%)	15 (21%)	20	12 (60%)
Co-habiting	0	3 (4%)	3	1 (33%)
Widowed	2 (7%)	5 (7%)	7	3 (43%)
Not stated	1 (4%)	2 (3%)	3	2 (67%)
Total	27	73	100	53

* Percentage with this relationship status in this group

** Percentage with this pain score in this relationship group

! These titles equate as nearly as possible with those in the BPI

5.2.1.5. NRS and S-LANSS scores at enrolment

Pain scores represented by NRS and S-LANSS scales were recorded at 1st and 2nd visits to determine any changes between appointment. As predicted patients referred to the CPS had high initial NRS scores with a skewed distribution towards higher pain scores. (Figure 5.3).

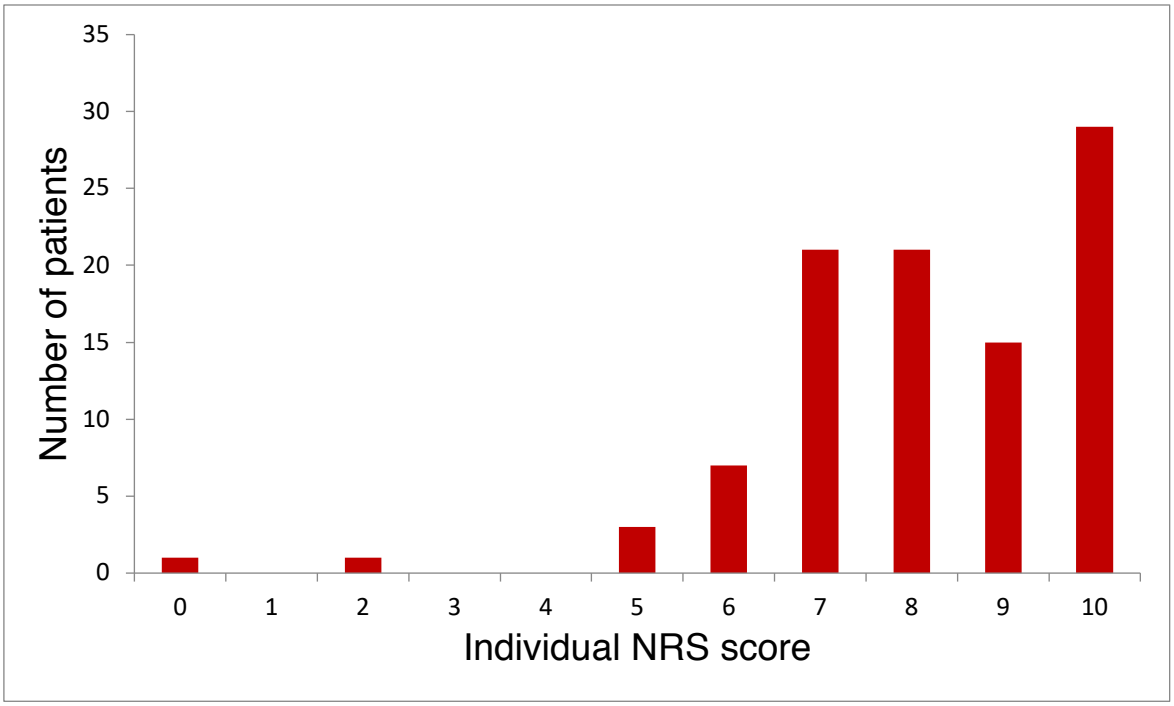

Figure 5.3 Initial NRS pain score for each member of the cohort (n=100)

These results indicated that the NRS pain scores were not normally distributed.

Initial S-LANSS scores however were variable with no pattern of distribution across the score range of 0 – 24 (Figure 5.4)

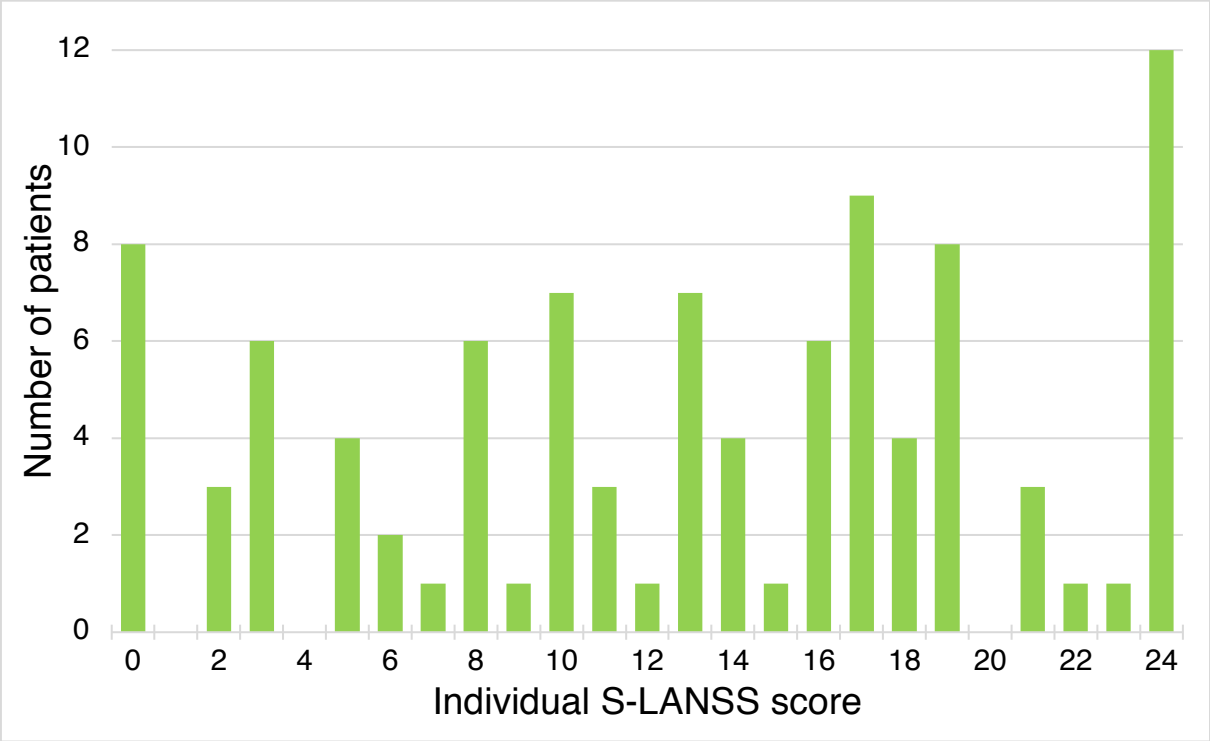

Figure 5.4 Initial S-LANSS score for each member of the cohort (n=100)

These results indicate the S-LANSS scores are not normally distributed

Table 5.6 Baseline patients' mean pain scores for the cohort (n=100)

Baseline pain scores for research cohort	Male 27	Female 73	Total 100
Mean NRS (0-10) pain score	8.3	8.1	8.1
Mean S-LANSS (0-24) if >=0	13.7	14.2	14.1

Mean pain score values are presented in Table 5.6. Although the data were not normally distributed, means pain score values are included for comparison with the mean pain score values presented in published literature.

5.2.1.6. Reluctance of research cohort to take their pain medicines

Objective 4 of this research was to investigate patients' attitudes towards their pain medicines. At their 1st appointment almost one patient in five (Table 5.7) declared that they were reluctant to take their pain medicines, at the outset of their clinic appointment.

Table 5.7 Patients' reluctance to take pain medicines at 1st appointment (n=18)

Expressions of reluctance to take medicines (percentage of 'reluctant' group)	**Male**	**Female**	**Total (%)**
Reluctant to take pain medicines	6	12	18
Reluctant to take pain medicines with NRS >=7	5	11	16 (89%)*
Reluctant to take pain medicines with S-LANSS >=12	5	10	15 (83%)*
Reluctant to take pain medicines with NRS>=7 and S-LANSS >=12	3	9	12 (67%)*

* Percentage with this pain score of 'reluctant' group (n=18)

As shown in Table 5.7 a high percentage of patients with pain scores indicating severe pain and elements of neuropathic pain reported a reluctance to take their pain medicines.

5.2.2. USE OF MAIN GROUPS OF PAIN MEDICINES AT ENROLMENT

The published literature contains suggestions that the severity of pain and the use of pain medicines was related to social class and/or levels of deprivation (Bonathan, Hearn and Williams, 2013; Wakefield *et al.*, 2016; Torrance *et al.*, 2006; Chen *et al.*, 2019; Carr and Moffett, 2005; Morgan, Conway and Currie, 2011). Therefore, in Table 5.8 the use of pain medicines is presented by CPS clinic location and level of deprivation. Table 5.9 expands this to include the use of strong opioids and medicines for neuropathic pain in relation to NRS >=7 and S-LANSS >=12.

In Burton, the most deprived area, the proportion of patients who reported taking of mild/moderate opioids was greater, whilst the proportion of NSAIDs was lower than in the other centres.

Table 5.8 Patients use of pain medicines by location 1st appointment by location

Location	Rank deprivation where 1 is most deprived (of 32,488)	Number in cohort at this location	Taking (%)* paracetamol at each location	Taking (%)* mild/moderate opioids at each location	Taking (%)* strong opioids at each location	Taking (%)* neuropathic meds at each location	Taking (%)* NSAIDs at each location
Burton	4,393	17	14 (82%)	14 (82%)	6 (35%)	13 (76%)	6 (35%)
Lichfield	16,701	17	12 (71%)	8 (47%)	7 (41%)	11 (65%)	10 (59%)
Tamworth	11,524	14	8 (57%)	8 (57%)	5 (36%)	10 (71%)	8 (57%)
Rugeley	8,589	26	17 (65%)	12 (46%)	6 (23%)	18 (69%)	13 (50%)
Stafford	8,272	26	16 (62%)	11 (42%)	12 (46%)	20 (77%)	13 (50%)
Total		100	67	53	36	72	50

* Percentage taking this pain medicine at this location

Table 5.9 Patients with NRS >=7 and S-LANSS >=12 by location and the numbers of these taking 'strong opioids' or neuropathic medicines

	Number in cohort at this location	Number with NRS >=7 (%)*	Number with S-LANSS >=12 (%)*
Burton	17	15 (88%)	12 (71%)
Lichfield	17	14 (82%)	11 (65%)
Tamworth	14	12 (86%)	7 (50%)
Rugeley	26	23 (88%)	13 (50%)
Stafford	26	24 (92%)	15 (58%)
Total	100	88	58
	Number in cohort at this location	**Number with NRS >=7 taking strong opioids (%)****	**Number with S-LANSS >=12 taking neuropathic medicines (%)****
Burton	17	6 (40%)	9 (75%)
Lichfield	17	5 (36%)	8 (73%)
Tamworth	14	5 (42%)	6 (86%)
Rugeley	26	5 (22%)	9 (69%)
Stafford	26	11 (46%)	12 (80%)
Total	100	32 (36%)	44 (76%)

* Percentage with this pain score at this location
** Percentage taking this pain medicine with this pain score at this location

Stafford had the highest proportion of patients with an NRS >=7 and at the same time had the highest proportion of patients taking strong opioids. Burton had the highest proportion of patients with an S-LANSS >=12 and one of the lower proportions of patients taking medicines appropriate for this condition. Overall, a third of patients with an NRS >=7 were taking strong opioids and three quarters of patients with an S-LANSS >=12 were taking medicines appropriate for this condition.

5.3. Changes in pain scores between visits

5.3.1. INTRODUCTION

This section will set out changes in the pain scores recorded in the BPI and S-LANSS between the 1st and 2nd appointments. It will focus on those which changed significantly but mention those that did not.

The number of patients who returned for a 2nd appointment was 55, between July 2016 and November 2017. The number of patients who answered individual questions in the questionnaires used varied from question to question. The following changes in pain scores were from paired patients (n) unless otherwise stated.

The pain score information collected from each of the patients in this research was from four pain scales as described in Section 4.5 (Section 8.4.2 and 8.4.3).

5.3.2. STATISTICAL ANALYSIS

Prior to undertaking any statistical analysis, bar charts were produced of the frequency of occurrence of each NRS and S-LANSS pain scores of the cohort (Figure 5.3 and 5.4). Neither the NRS or S-LANSS scores were normally distributed, therefore, non-parametric statistical tests were applied.

In the event only 55 patients returned for a 2nd appointment. Advice was sought from the statistician, about whether this reduced total was sufficient for meaningful

analysis. The advice was that the statistical tests suggested for use (Wilcoxon Signed Rank test, McNemar test and Fisher exact test) were more powerful than those used in the original calculations and that therefore there was no necessity to change the original statistical basis for the research (Hodson, 2017).

5.3.3. CHANGE IN PAIN SCORES BETWEEN THE 1ST AND 2ND APPOINTMENT

Objectives one and two of this research were to assess and characterise the patients' pain. In order to determine whether changes had occurred between the 1st and 2nd appointments, changes in the main scores from the pain questionnaires were examined. This was followed by a more detailed examination of some of those results. Finally, the other measures of pain reported in the BPI were set out.

5.3.3.1. Changes in the overall NRS, BPI and S-LANSS scores

As shown in Table 5.10, patient's pain scores from BPI and S-LANSS reported from their 1st and 2nd appointment were compared. None of the changes were statistically significant.

Table 5.10 Changes in mean pain scores for paired results between 1st and 2nd visits (n=53)

Pain scale	1st visit			2nd visit		
	Male	Female	Total	Male	Female	Total
Mean NRS score	8.7	7.5	8.1	8.1	7.4	7.7
Mean BPI-PSS*	6.7	7.1	7.0	6.6	6.9	6.8
Mean BPI-PIS**	8.0	7.1	7.6	7.8	7.4	7.6
Mean S-LANSS score	12.3	12.7	12.6	12.5	12.4	12.5

* Brief pain inventory – pain severity score
**Brief pain inventory – pain interference score

The only significant change was reported in Figure 5.5.

5.3.3.2. Pain score changes in relation to attendance at PMP

Fifty-five patients returned for a 2nd appointment. Of these 18 (3 males and 15 females) had attended a PMP course between their 1st and 2nd appointments (Table 5.11). This patient sub-group were a small proportion of the overall cohort. No further analysis of the differences between these two sub-groups was undertaken.

Table 5.11 Changes in mean pain scores between paired patients who had attended PMP and those who had not.

			2nd appointment before PMP sub-group (n=32)*		2nd appointment after PMP sub-group (n=18)*	
Pain scores	**Mean scores 1st appointment (n=55)**	**Mean scores 2nd appointment (n=55)**	**Mean scores 1st appointment (n=32)**	**Mean scores 2nd appointment (n=32)**	**Mean scores 1st appointment (n=18)**	**Mean scores 2nd appointment (n=18)**
Mean NRS score	8.1	7.7	8.3	7.8	8.4	7.5
Mean S-LANSS score	12.6	12.5	12.8	13.4	11.9	11.1

* The before and after status of every patient was not available

5.3.3.3. Changes to the individual elements of the BPI-PSS and BPI-PIS scores

The individual elements of the BPI-PSS and the BPI-PIS, were examined in detail to determine whether any of the individual element scores changed significantly. This revealed that of the 11 elements encompassed by these two overall scores only the 'Worst' element of the BPI-PSS (question 12) reduced significantly, from a mean of 8.4 to a mean of 7.9. (Figure 5.5)

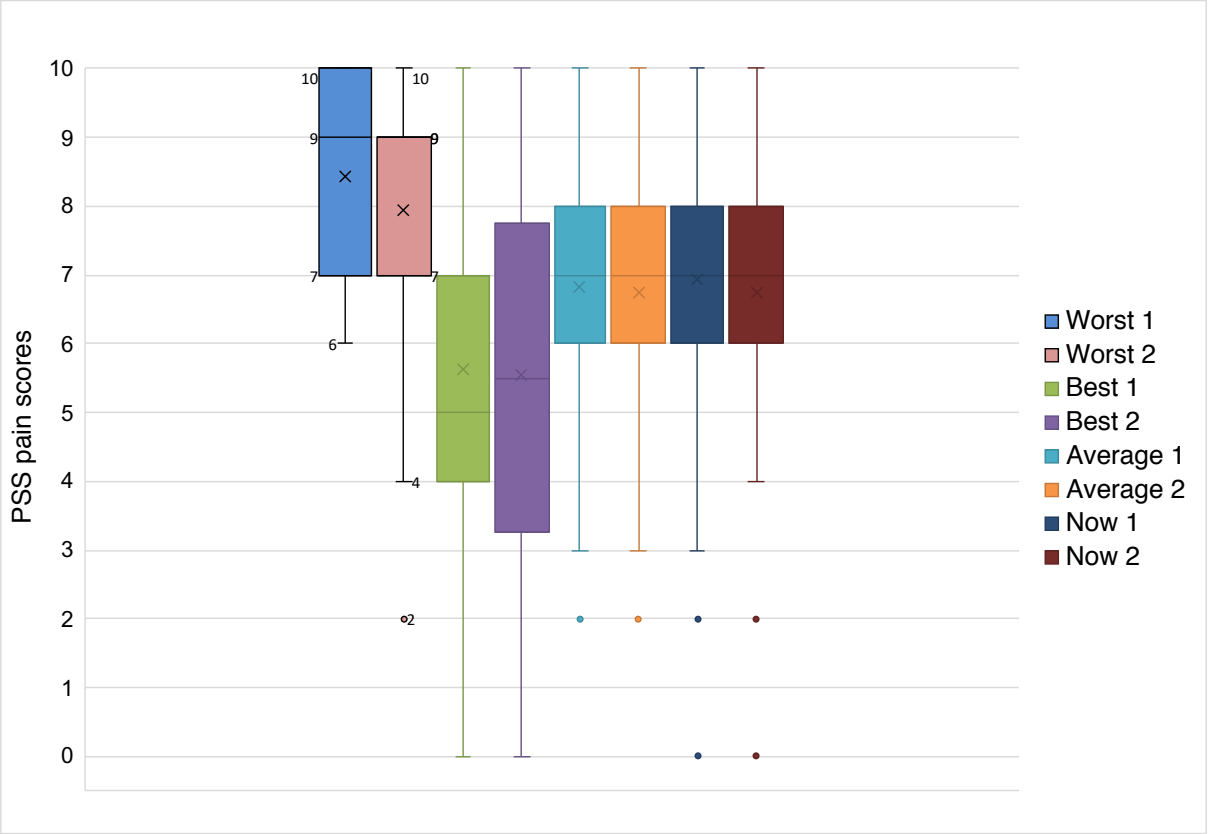

Figure 5.5 Changes in the four elements of the Pain Severity Score (BPI-PSS) for paired results (n=51)

(Wilcoxon signed rank P=0.023)

This result suggested that patients perceived their 'Worst Pain' had improved between the 1st and 2nd clinic visits. An outlier to the results of 2nd visit patients reported low score of 2.

Further analysis of these changes (Table 5.12) revealed that when answering the four questions of the BPI-PSS scores (Section 8.4.2) the number of patients who reported improvements in their pain were similar but overall fewer patients reported an increase in their pain in question 12 than for questions 13-15.

Table 5.12 Further analysis of changes in the BPI-PSS scores between 1st and 2nd appointment for the patients who recorded these scores on both occasions (n=50)

BPI Question number (Q)	Pain score worsened	Pain score remained the same	Pain score improved by 1	Pain score improved by 2 or more
Pain worst (Q 12)	9 (18%)	24 (48%)	9 (18%)	8 (16%)
Pain best (Q 13)	15 (30%)	16 (32%)	10 (20%)	9 (18%)
Pain average (Q 14)	15 (30%)	21 (42%)	5 (10%)	9 (18%)
Pain now (Q 15)	18 (36%)	14 (28%)	9 (18%)	9 (18%)

These results indicate that fewer patients reported a 'worse' pain score when answering question 12 than for any of the other three questions.

5.3.3.4. Changes in percentage pain relief during the previous week resulting from the use of their pain medicines

The BPI question 19 (Section 8.4.2) asked patients to record how much pain relief the use of their pain medicines had provided, as a percentage, during the previous week. The mean % improvement in pain relief increased from 41% at their 1st appointment to 51% at their 2nd appointment *i.e.* patients reported that their pain medicines had given them more pain relief.

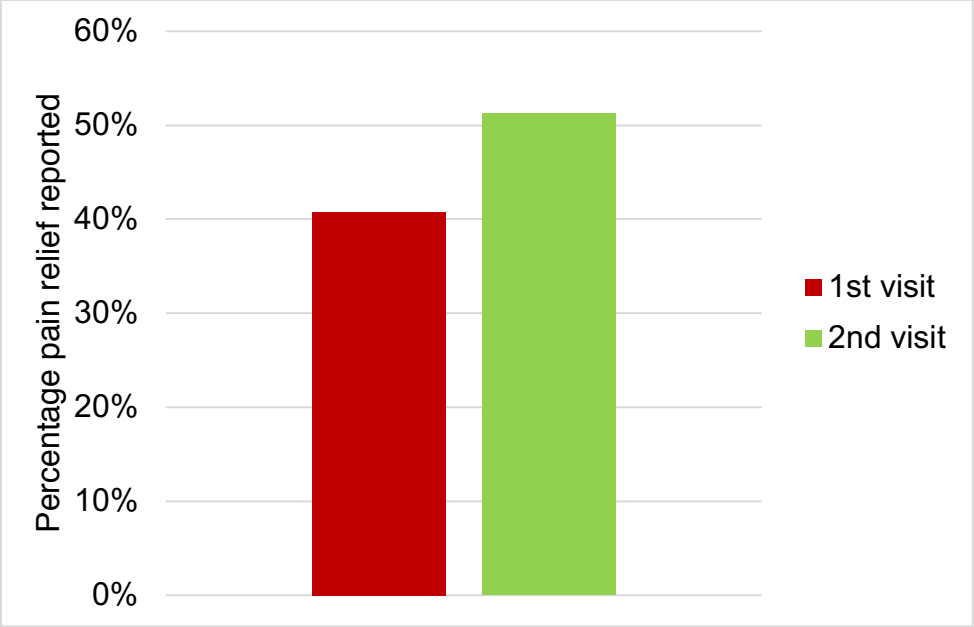

Figure 5.6 Mean percentage pain relief resulting from use of pain medicines (n=50)

(Wilcoxon signed rank P <0.001)

5.3.3.5. How long before pain returns after taking/using pain medicines

Patients were asked to record (BPI question 20) (Section 8.4.2) how many hours before their pain returns after taking/using their pain medicines, by choosing from a range of answers ranging from '*Pain medication doesn't help at all'* up to '*24 hours'*.

The data were analysed in two ways. Firstly, did the percentage of patients who thought that their pain medicines gave them no benefit change between the two appointments? This decreased significantly from 43% to 12% (Figure 5.7)

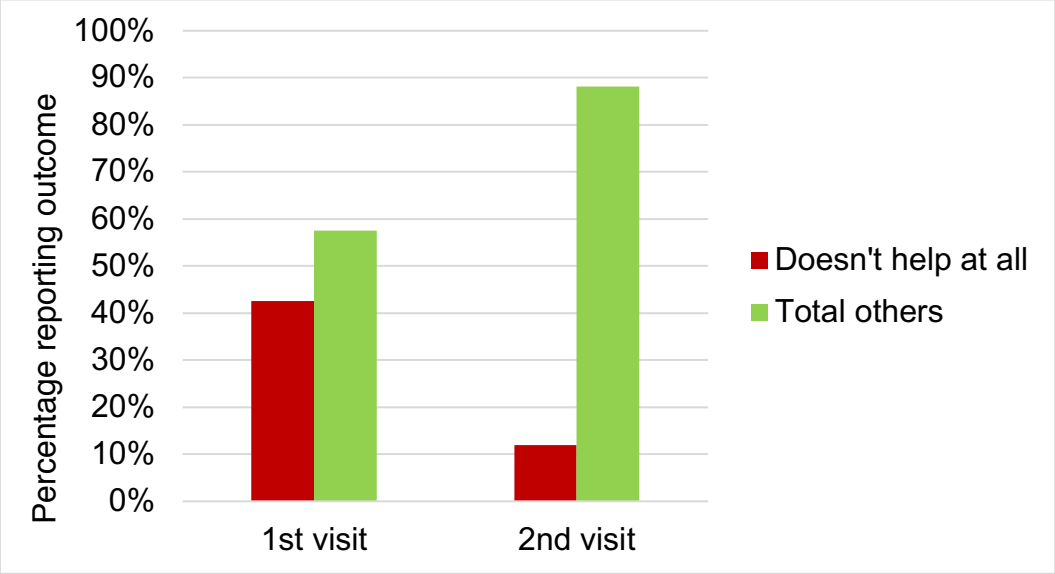

Figure 5.7 Did your pain medicines give you any pain relief? (n=40) (McNemar test P = 0.008).

These results suggested that at their 2nd appointment all but 12% (5) of the patients now believed that their pain medication gave them some relief.

Secondly, how did the reported duration of the relief change? (Figure 5.8)

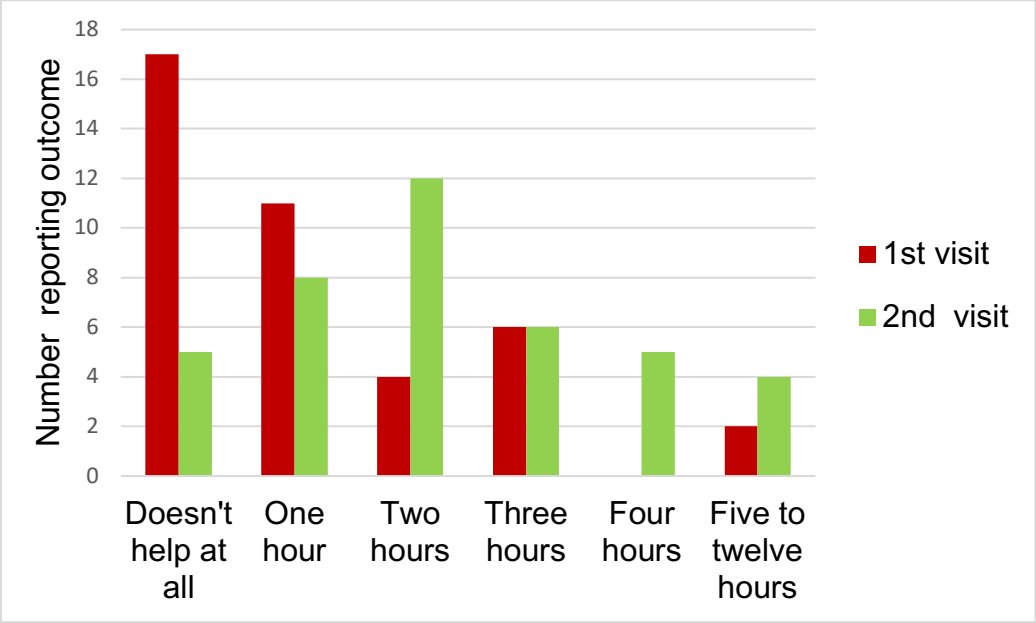

Figure 5.8 Changes in reported duration of pain relief? (n=40)

(Wilcoxon signed rank test P = 0.003)

These results suggested that at their 2nd appointment patients reported that the benefit of their pain medication was lasting longer. The combination of these two analyses suggest that more patients were achieving a significant improvement in their pain, at their 2nd visit which they regarded as clinically noticeable.

5.4. Changes in the reported efficacy of pain medicines between visits

5.4.1. INTRODUCTION

When the pharmacist was undertaking each MUR, patients were asked about each of their pain medicines in turn 'Is this helpful?' with a response of yes/maybe/no? Analysis of the benefits that patients reported for the five groups of pain medicines investigated in this research (paracetamol, mild/moderate opioids, strong opioids, neuropathic medicines and NSAIDs) are based upon the answers to these questions. The results of this analysis are set out sequentially. Firstly, the changes in overall helpfulness of the five analgesic groups and then each medicine/group in more detail.

Analysis of the 'helpfulness' of analgesics was limited to the overall helpfulness of each group. The number of reports for many of the individual medicines was too small to allow for meaningful analysis in any greater detail.

These data 'does this pain medicine help? – yes/maybe/no were relatively complex. Statistical guidance was sought on how the answers to these questions could best be analysed. It was decided that if patients responded with 'unsure' of any benefit that this would be recoded as 'no benefit' (Hodson, 2017). The analysis was then undertaken using binary yes/no data. Two analyses of these data were undertaken initially to check the validity of this approach. Firstly, using the answers from all of

the patients using a medicine at each appointment, the Fisher exact test was used. This test accepts the use of unequal sized groups. Secondly, using only answers from the patients who were using the same medicine at both appointments the McNemar test was used. This test required groups of equal sizes.

Table 5.13 presents two sets of data. Firstly, the overall changes in pain medicine taken between the two visits because patients both stopped and started medication between visits. At the 2nd appointment 19 of 55 patients reported taking a new pain medicine, but 47 of 55 reported stopping a pain medicine. The overall trend was for more pain medicines to be stopped except for neuropathic therapies where more where started. Secondly, changes that patients reported for the perceived effectiveness of their pain medicines between their 1st and 2nd appointments.

Table 5.13 Changes in the overall numbers of patients who used each of pain medicine groups and their reported efficacy between 1st and 2nd visits

			Analysis - patients taking pain medicine at each visit using Fisher exact test (FET)					Analysis - patients taking pain medicines on both visits using McNemar test				
Pain medicine			**visit 1**		**visit 2**		**P value**	**visit 1**		**visit 2**		**P value**
Analgesic	**Start***	**Stop****	**n**	**Helpful (%)+**	**n**	**Helpful (%)+**	**FET!**	**n**	**Helpful (%)+**	**n**	**Helpful (%)+**	**McNemar**
Paracetamol	0	22	41	22 (54%)	33	20 (61%	0.079	31	18 (58%)	31	19 (61%)	1.000
Mild/moderate opioid	5	8	35	18 (51%)	32	26 (81%)	0.010	27	12 (44%)	27	22 (81%)	0.006
Strong opioid	2	5	18	9 (50%)	15	11 (73%)	0.284	13	8 (62%)	13	10 (77%)	0.625
Neuropathic	9	4	39	23 (59%)	44	32 (73%)	0.246	35	22 (63%)	35	23 (65%)	1.000
NSAID	3	8	28	16 (57%)	23	15 (65%)	0.580	20	10 (50%)	20	13 (65%)	0.375
Total	19	47										

* Starting an analgesic between 1st and 2nd appointments

** Stopping an analgesic between 1st and 2nd appointments

! Fisher exact test

+ Percentage of patients taking this medicine who regarded it as helpful.

There was generally little change observed in the perceived helpfulness of pain medicines between visits. The only significant change was that a larger number of patients reported that mild/moderate opioids (codeine, dihydrocodeine and tramadol) were more helpful at their 2nd visit than their 1st (Fisher exact P = 0.01, McNemar P=0.006). The numbers of patients taking mild/moderate opioids were sufficient to allow further examination of these results. At their 1st appointment 9 of 17 (53%) patients reported tramadol as helpful and this increased to 14 of 15 (93%) at the 2nd appointment. Changes in the percentage of patients reporting benefit with codeine increase from 50% to 60%) and with dihydrocodeine the increase was from 25% to 60% based on smaller samples.

5.4.2. THE EFFECTIVENESS OF INDIVIDUAL PAIN MEDICINES

The analysis of whether the individual pain medicines, were regarded as effective, was then expanded in the same way for each group of pain medicines, does this medicine help with your pain yes /maybe/no? The statistical significance of any change was then determined, after conversion to binary data, using a McNemar analysis. The (n) varied with the number taking each medicine.

5.4.2.1. Paracetamol

Paracetamol can be a very effective pain medicine, in some situations, if it is used correctly. On their 2nd visit there was a trend for patients to report that they were clearer about the use of paracetamol and more positive about its effectiveness, but the changes were not statistically significant (Figure 5.9).

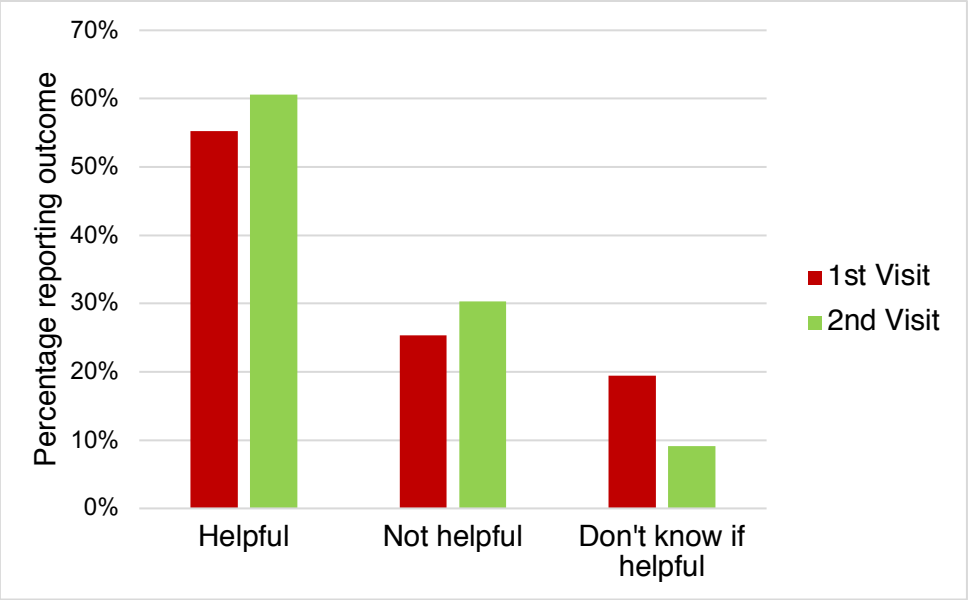

Figure 5.9 Paracetamol, does it help with your pain control? (n=31)

There was still some uncertainty at the 2nd appointment. The proportion of patient taking paracetamol who reported it as not helpful increased, but the proportion who were unsure decreased.

5.4.2.2. Mild moderate opioids

At their 1st appointment a slightly smaller proportion of patients regarded mild/moderate opioids (codeine, dihydrocodeine and tramadol) as effective, compared with paracetamol (Table 5.13). When they returned for their second appointment the percentage of patients who reported that mild moderate opioids were helpful increased from 51% to 81%.

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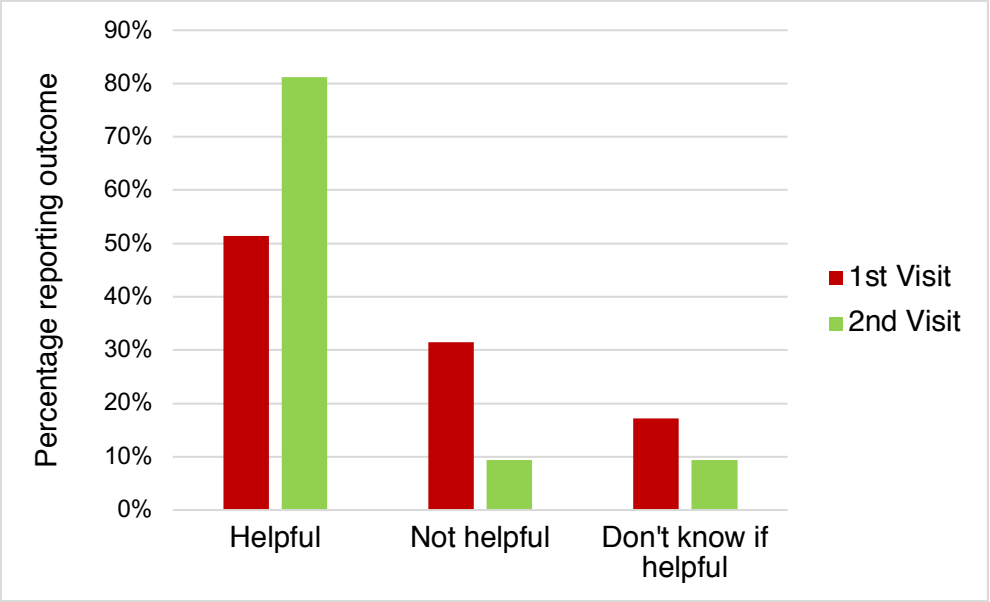


Figure 5.10 Mild moderate opioids, do they help with your pain control? (n=27) (Fischer exact P=0.01 and McNemar P=0.006)

In addition, smaller proportions of patients regarded them as 'not helpful' or were unsure about their helpfulness.

5.4.2.3. Strong opioids

The strong opioids patients reported taking or applying included morphine, oxycodone, buprenorphine and fentanyl. As with paracetamol and mild/moderate opioids just over half of the patients regarded these medicines as helpful at their 1st appointment (Table 5.13). The proportion of patients finding these helpful increased when they returned for their 2nd appointment but the change was not statistically significant (Figure 5.11).

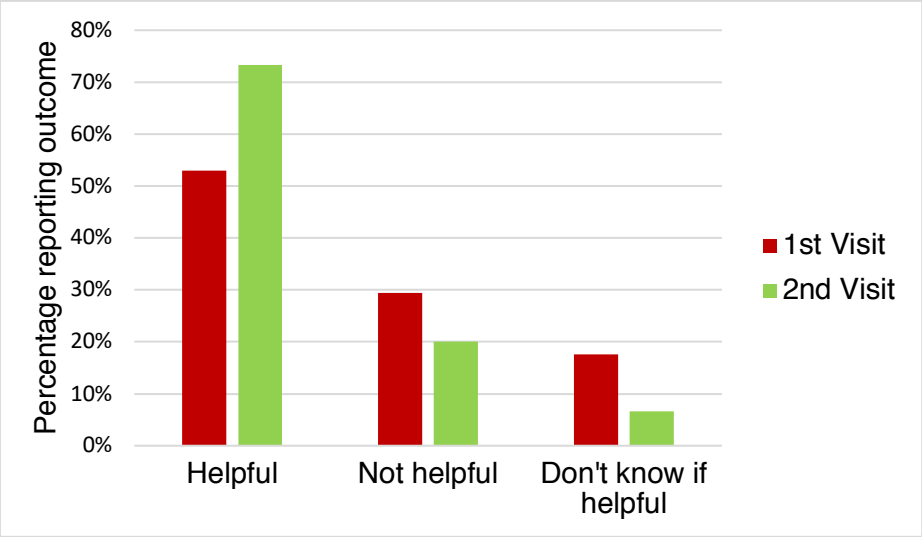


Figure 5.11 Strong opioids, do they help with your pain control? (n=13)

Thirty-six of the patients in this cohort of 100 were taking a strong opioid at their 1st appointment and of these 36 patients, 32 (89%) had an NRS pain score of >=7.

Three patients in this cohort made considerable efforts to reduce their strong opioid dose, including three who were successful. Two patients stopped their buprenorphine patch (20microg/hour) completely with no significant worsening of

pain. The third patient who had been using a Fentanyl patch (50microg/hour) was able to reduce this to 12microcg/hour.

5.4.2.4. Medicines used in the treatment of neuropathic pain.

Thirty-five patients were taking medicines for neuropathic pain (gabapentin, pregabalin, amitriptyline, nortriptyline and duloxetine). The proportion of patients who regarded medicines for neuropathic pain as helpful at their 1st appointment was higher than for strong opioids (Table 5.11). This proportion improved at the 2nd appointment but the change was not statistically significant (Figure 5.12)

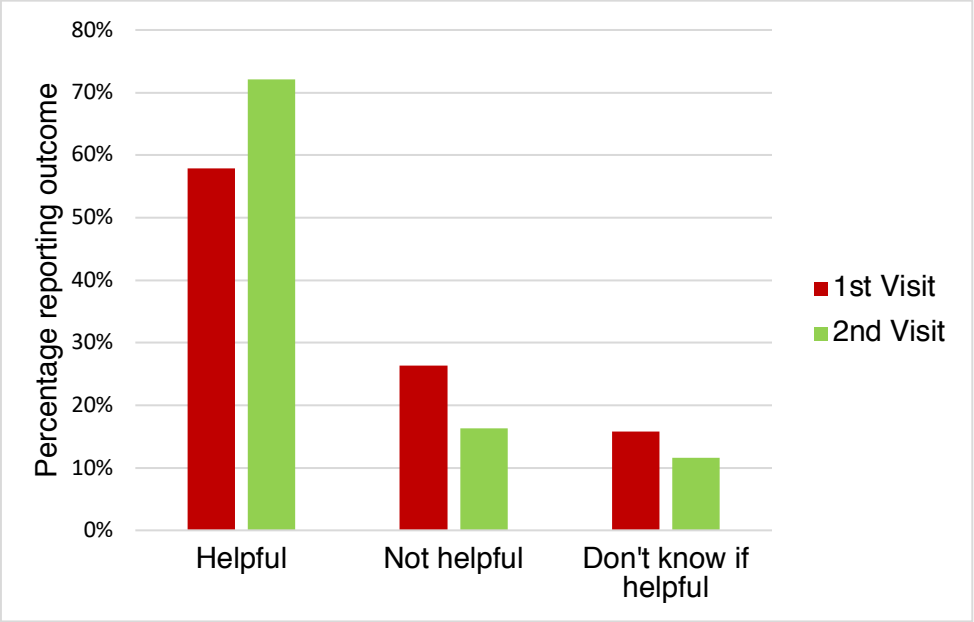


Figure 5.12 Medicines for neuropathic pain, do they help with your pain control? (n=35)

One unexpected finding was that some patients reported, spontaneously, initiating and/or adjusting doses of these medicines on a 'when necessary basis'. These

changes were made either in response to changes in their pain, or the side effects of the medicines were too problematic for continuous therapy.

5.4.2.5. NSAIDs

The Oxford league table of acute pain medicines reported NSAIDs as medicines for acute pain with the lowest NNT (FOPM, 2007). The proportion of patients at their 1st appointment who regarded ibuprofen, naproxen and diclofenac as helpful was almost as high as for therapy for neuropathic pain (Table 5.13). This increased at the 2nd appointment but the change was not statistically significant.

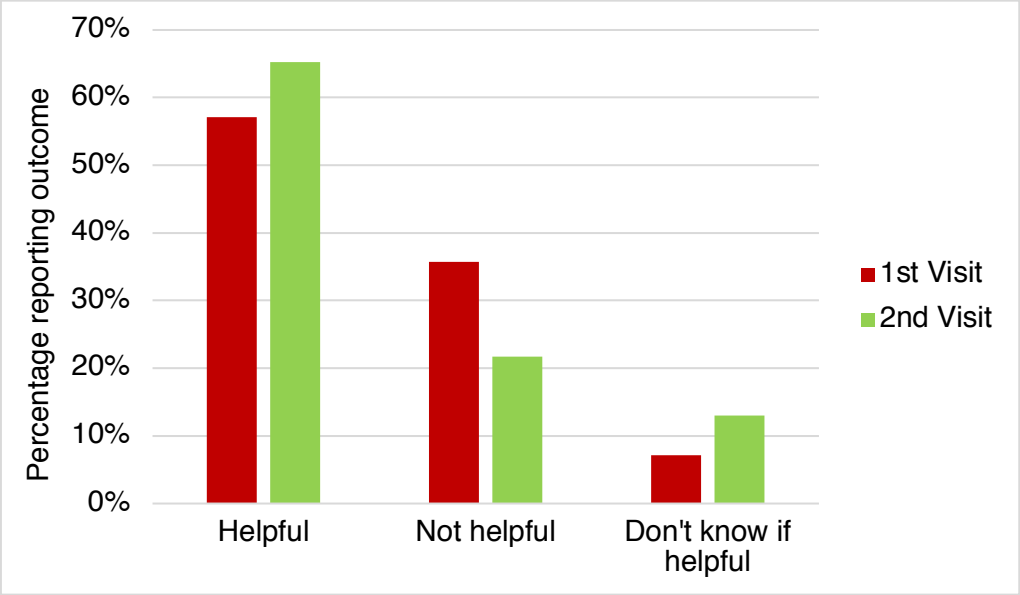


Figure 5.13 NSAIDS, do they help with your pain control? (n=20)

These were the only medicines, where the number of patients who were taking them, without being sure that they were helping, increased at the 2nd appointment.

5.5. Changes in answers to the questions in the Brief Pain Inventory.

5.5.1. INTRODUCTION

The following sections set out the patients' responses to BPI questions 24 -30 (Section 8.4.2) which explore patients' attitude to and understanding of their pain medicines. They are presented as paired results. Not every patient answered all the questions on both appointments in each questionnaire. As a result, the 'n' for each of these questions is different.

As with the answers to the questions about the efficacy of medicines the BPI includes three possible answers yes/maybe/no. These data were transformed into a binary yes/no form for a McNemar significance test.

5.5.1.1. Patient preferences for taking their pain medicines – (BPI Questions 24 and 25)

These two questions ask patients about medicine taking routine and about how frequently they preferred to take their pain medicines. Table 5.14 shows that patients reported few changes in their medicine taking habits between the 1st and 2nd visits. Most were taking their medicines regularly on a three of four times a day basis.

Table 5.14 Answers to BPI questions 24 and 25 at 1st and 2nd appointments

BPI question 24 **I prefer to take my medicines**	**Total 1st appointment***	**Total 2nd appointment***
On a regular basis	35	36
Only when necessary	11	13
Do not take pain medicines	1	1
BPI question 25 **I take my medicines**		
Not every day	2	2
1 to 2 times a day	7	9
3 to 4 times a day	30	38
5 to 6 times a day	6	2
More than 6 times a day	0	0

* Not every patient answered these questions on each occasion

5.5.1.2. Did patients feel they needed stronger pain medicines (BPI question 26)?

It was anticipated that patients who had been referred to a chronic pain clinic would think that they needed stronger pain medicines. At their 1st appointment 57% reported this. At the 2nd appointment this reduced significantly to 37% (Figure 5.14).

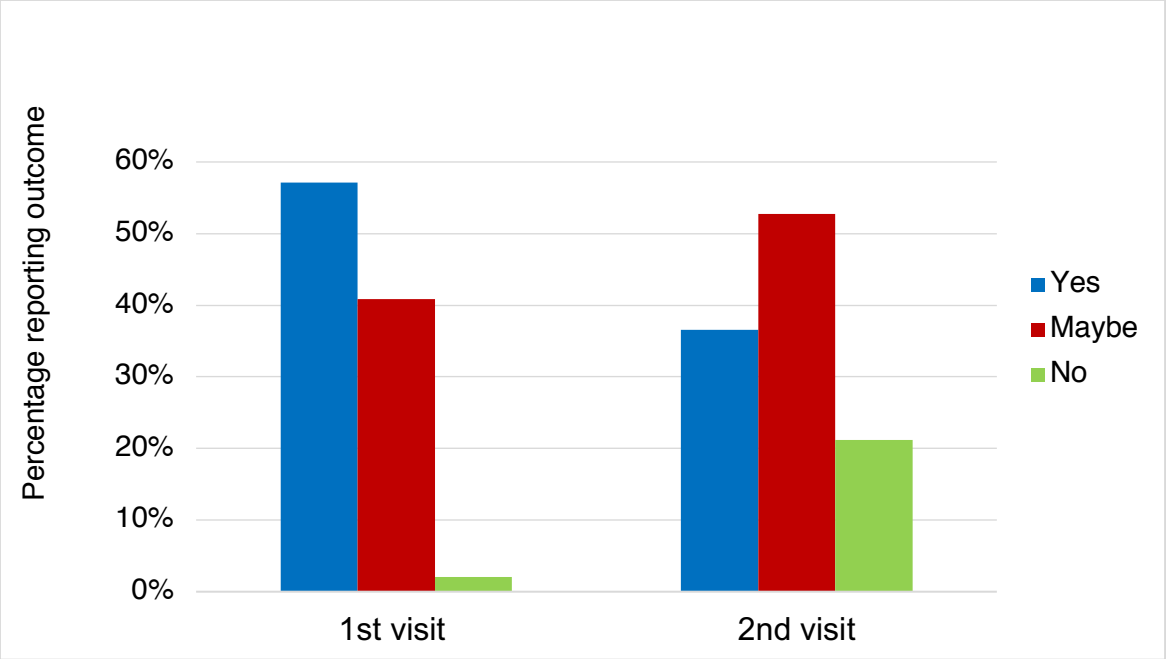


Figure 5.14 Changes in the percentage of patients who think that they need stronger pain medication (n=49)

(McNemar P=0.002)

These changes suggested that at their 2nd visit fewer patients thought that they needed stronger pain medication to control their pain.

5.5.1.3. Did patients feel they needed to take more pain medicines than prescribed (BPI question 27)?

It was also anticipated that patients who had been referred to a chronic pain clinic would be tempted to take more pain medicine than had been prescribed by their prescriber, if their pain was not adequately controlled. At their 1st appointment 33% reported this. At the 2nd appointment this reduced significantly to 21% (Figure 5.15).

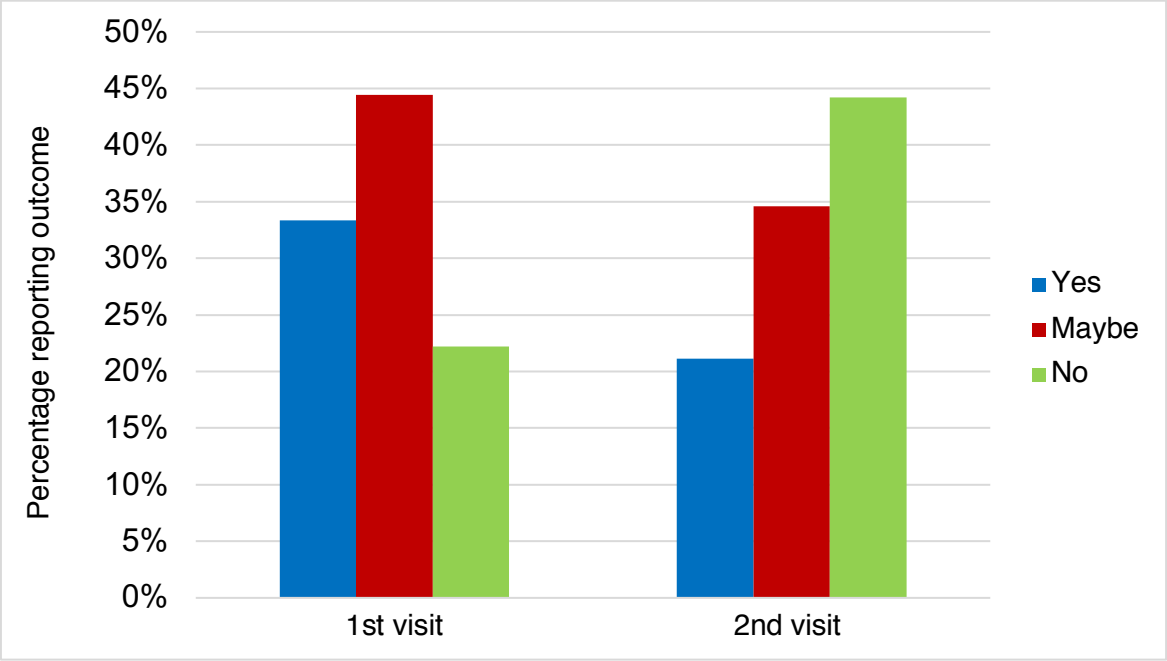


Figure 5.15 Changes in the percentage of patients who think that they need to take more pain medication than had been prescribed (n=45)

(McNemar P=0.004)

These changes suggested that at their 2nd visit fewer patients thought that they needed to take more pain medicine than prescribed by their doctor.

5.5.1.4. Were patients concerned they are using too much pain medicine (BPI question 28)?

Patients often express reluctance to take pain medicines. At their 1st appointment 46% were concerned that they were taking too much pain medicine. At their 2nd appointment this reduced significantly to 31% (Figure 5.16).

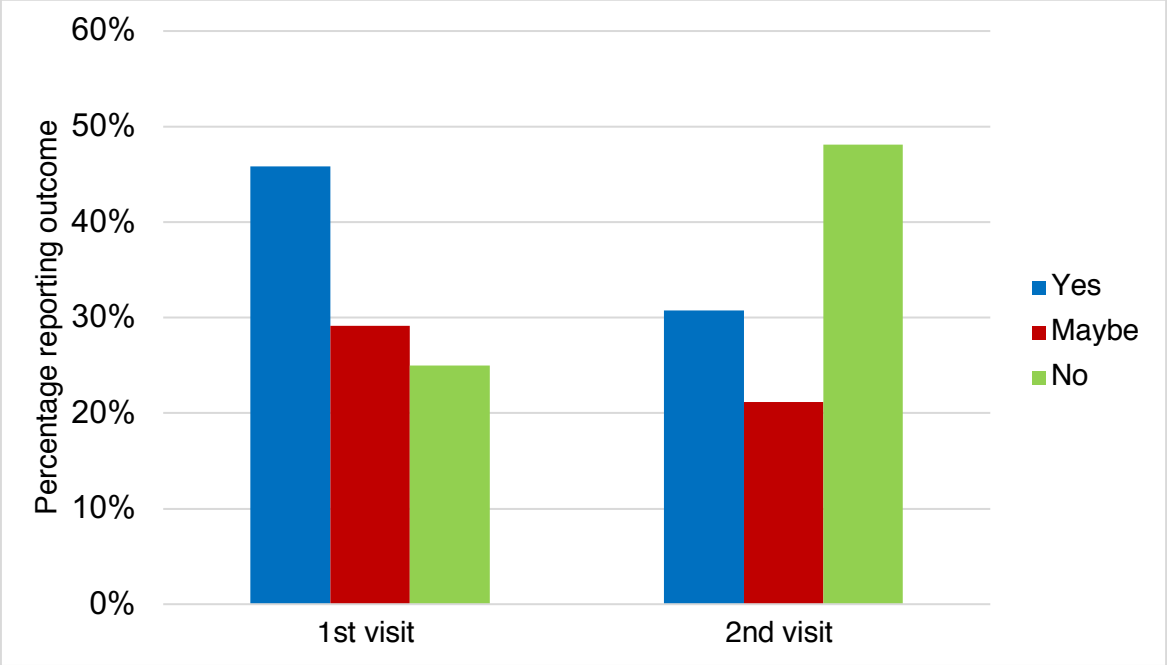


Figure 5.16 Changes in the percentage of patients who think that they are taking too much pain medicine (n=48)

(McNemar P=0.004)

These changes suggested that at their 2nd visit fewer patients thought that they were taking too much pain medication.

5.5.1.5. Did patients feel they needed more information about their pain medicines (BPI question 30)?

In clinic, patients often asked questions about the risks and benefits of their pain medicines. At their 1st appointment 76% of patients recorded that they would like more information about their pain medicines. At their 2nd appointment this reduced significantly to 45% (Figure 5.17).

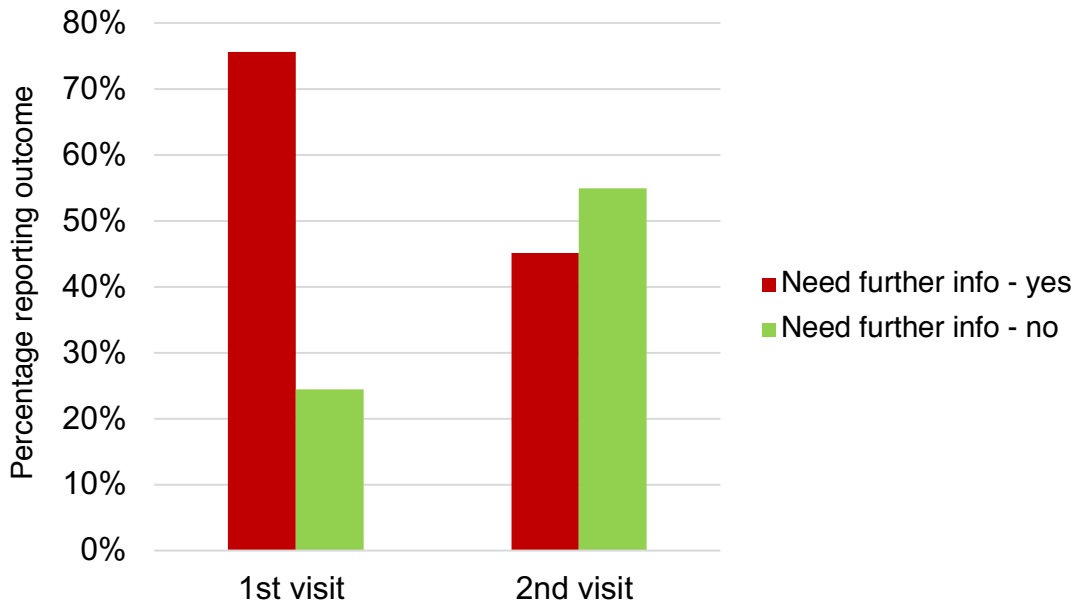


Figure 5.17 Changes in the percentage of patients felt the need for further information about their pain medication (n=45)

(McNemar P=0.001)

These changes suggested that at their 2nd visit fewer patients felt the need for further information about their pain medication.

5.5.1.6. Were patients experiencing problems with side effects (BPI question 29)?

Many patients complained about the side effects of their medicines. At their 1st appointment 64% reported experiencing side effects. At the 2nd appointment this had reduced to 52% (Figure 5.18). This was not a significant change.

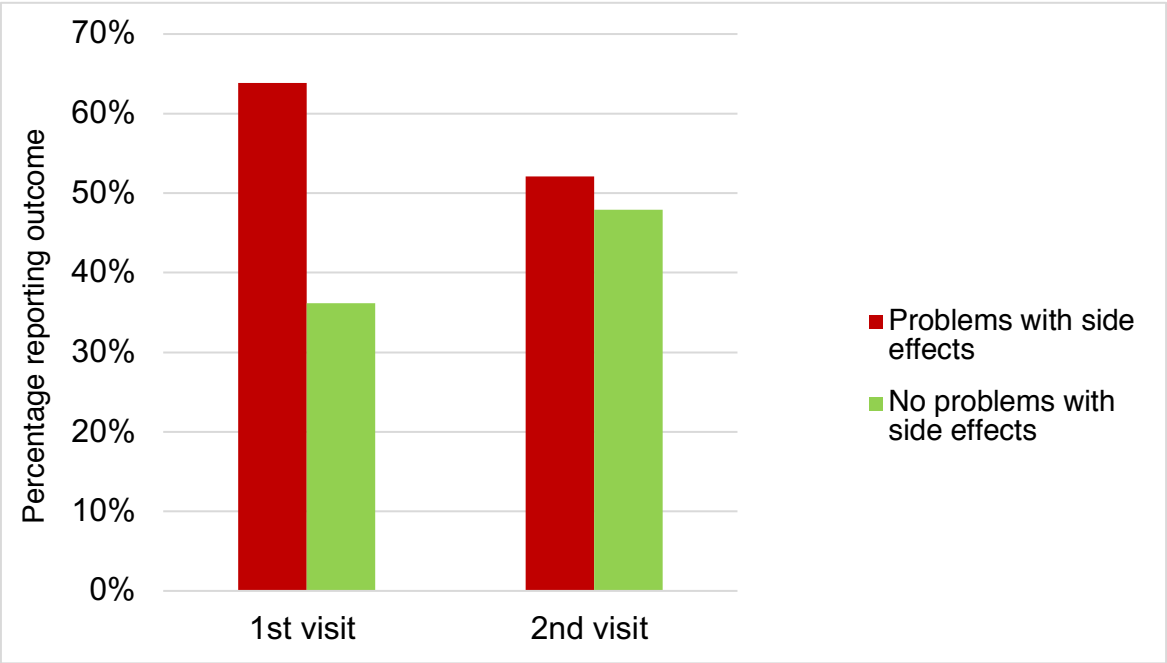


Figure 5.18 Changes in the percentage of patients who experienced side effects with their pain medicines (n=47)

(McNemar P=0.146)

These changes suggest that at their 2nd visit fewer patients experienced side effects from their pain medication but the change was not significant.

5.6. Pharmacist recommendations to GP's about patients' pain medicines.

At the 2nd appointment patients were asked 'what changes had been made to their pain medicines?' If any changes reported were in line with the pharmacist recommendations a record was made. Of the 55 patients who returned for a 2nd appointment 30 (55%) reported that at least one of their pain medicines had been changed along the lines of the pharmacist's recommendations. For many of the patients in this research, the pharmacist made more than one suggestion for improving their pain treatment. Therefore, no attempt was made to correlate the number of suggestions with the number of changes.

5.7. Contact between the research pharmacist and the GP's treating the research patients

One of the subsidiary objectives of this research was to ascertain what systems GPs had in place to assist with the management of chronic pain. This was particularly with regard to referral letters from the chronic pain service and protocols to be used for the treatment of chronic pain

Letters were sent to the Practice Managers of the 80 GP practices which had referred patients to the CPT, unless there was an appropriate email address on the

Practice web page in which case the request was sent via email. Of these 80 practices only three responded.

Because of this paucity of data, no analysis was undertaken.

CHAPTER 6 DISCUSSION

6.1. Introduction

This chapter will discuss the results from this research, addressing each one in turn, with an accent upon those that are most significant. Each section of results will have its own conclusion. The chapter will finish with comments about the limitations of this research, and recommendations about how these might be addressed in future work.

6.2. Baseline information about the research cohort

6.2.1. DEMOGRAPHICS OF THE PATIENTS AT ENROLMENT

The ratio of women to men who were recruited into this cohort was approximately 3:1. Other studies have demonstrated different ratios; Bruhn *et al.* (2013) and Marra *et al.* (2012) ~ 1:1 Petkova (2009) and Hadi *et al.* (2016) ~ 2:1. Epidemiological studies suggest that women suffer more frequently and at greater severity with chronic pain than men (Bartley and Fillingim, 2013). The reasons for this are, as yet, not understood but may include phenotype variations or different hormonal influencers on internal pain modulators (Bartley and Fillingim, 2013). These variations were reported as women having lower pain thresholds and responding differently to analgesia. There were also suggestions that women report higher levels of pain intensity, thermal pain, pressure pain and had greater levels of acceptance (van Hecke, Torrance and Smith, 2013; Rovner *et al.*, 2017). When women and men reported similar levels of pain intensity women were more accepting and maintained higher levels of activity. Men, on the other hand were more subject

to mood disturbance, reported higher kinesiophobia scores and lower activity level (Rovner *et al.*, 2017). Patients pain acceptance and kinesiophobia are behaviourally defined and as a result can be changed (Rovner *et al.*, 2017). This ability to change behaviour was one of the tenets of biopsychosocial chronic pain treatment, where the maintenance of mobility and patient well-being go along with acceptance of some residual pain.

6.2.1.1. Geographic distribution of cohort

The researcher undertook clinic sessions and recruited patients from five locations, Table 5.1 and Figure 1.1.

Risk factors for chronic pain include advancing age, female sex, lower socioeconomic status, lower educational level, obesity, history of a physically strenuous job, childhood trauma, tobacco use, history of injury and depression or anxiety (Reid, Eccleston and Pillemer, 2015b). These factors are also associated with a lesser ability to cope with chronic pain (Bonathan, Hearn and Williams, 2013; Wakefield *et al.*, 2016). The English Indices of Deprivation (GOV-UK, 2015) included domains for income, employment, education and health. It could therefore be suggested that areas with high deprivation are likely to suffer with a higher incidence of chronic pain. The deprivation scores for the five areas of this research were included in Table 5.1 with four of the five areas being in the lower half of the distribution.

The relationship between chronic pain and deprivation, in its widest possible definition, is circular. Chronic pain prevents people from doing the things that they would like/needed to do, such as employment, relationships and activities of daily living. In turn, their (perceived) inability to do such things can make them more withdrawn and more depressed, which in turn can make their pain worse (Bailly *et al.*, 2015; Bonathan, Hearn and Williams, 2013; Mittendorfer-Rutz and Dorner, 2017; Wakefield *et al.*, 2016; Muneer, 2015; Joud *et al.*, 2014). The opposite is also true, if pain is improved significantly then fatigue, depression and sleep interference also improve (Moore *et al.*, 2013).

Table 5.8. sets out the different 'Deprivation scores' for the areas around each clinic location. Tables 5.8 and 5.9 also set out differences between the five research clinics with regard to pain medication use and pain scores. This cohort was too small to determine whether these related to the locale, the idiosyncrasies of individual GP practices in terms of prescribing or coincidence.

The clinic in the area with the lowest 'Deprivation' (0=worst) score was Burton and the highest was Lichfield. In Burton the proportion of patients reporting paracetamol and mild-moderate opioid use were the same (82%), whereas in Lichfield paracetamol use was 71% and mild-moderate opioids 47%. This could be explained by the additional use of strong opioids which were the second highest. Only, Stafford which had the second lowest Deprivation score, reported using more strong opioids.

The clinic with the highest proportion of patients with an NRS>=7 was Stafford which also had the highest proportion taking strong opioids. It ranked lowest for the proportion of patients with S-LANSS>=12 and second best of the use of neuropathic therapy. Evidence has emerged that opioid prescribing was more prevalent in areas of higher deprivations (Chen *et al.*, 2019) at the same time that the benefits of opioids in the treatment of chronic pain was increasingly being questioned (NHS, 2015). Opioids are valuable for the treatment of acute pain and the pain encountered in cancer treatment and palliative care but this usefulness does not extend to chronic pain, where they are associated with serious adverse effects (Stannard, 2018).

The focus on the biopsychosocial model of treatment for chronic pain however introduces the opportunity of other treatment options instead of opioids. Sullivan and Ballantyne (2016) question how important it is, in the treatment of chronic pain and its associated suffering that pain is reduced. At the same time others are reporting that alternative treatment regimens for chronic arthritic pain may offer better overall outcomes than opioids (Krebs *et al.*, 2018). But overarching all of this is the possibility that as a result of the pressure to move the treatment of chronic pain away from opioids their availability may, in some way, be restricted (Alford, 2016) because they are very effective in the treatment of many other painful conditions (Stannard, 2018)

6.2.1.2. Age of the cohort

It is generally reported that the prevalence of chronic pain increases with age (Fayaz *et al.*, 2016; Johannes *et al.*, 2010; Docking *et al.*, 2011; Thomas *et al.*, 2007; BMA, 2017). In a survey of over 17,000 female and male patients suffering with chronic pain, the highest prevalence was in females and males in the 55-59 age group, but the highest proportion was in the 20-24 age group (Blyth *et al.*, 2001). This may not be surprising because people in the 20-24 age group may be more sensitive to anything which interferes with their daily lives or they may be less accepting of unsuccessful therapy.

The mean age of patients at recruitment into this research was 51 years, with the mode decile for males being between 50 and 59 whereas for females it was between 40 and 49 (Table 5.2 and Fig 5.1). This was lower than the ages reported by Bruhn *et al.* (2013) and Marra *et al.* (2012) but higher then Petkova (2009) and Hadi *et al.* (2016). The inclusion criteria for Hay *et al.* (2006) was set at over 55. Overall there was little robust evidence about how the experience of pain changes with age (Taverner, 2005; El Tumi *et al.*, 2017; Schofield, 2018). Therefore, it is probably wrong to suggest that patients should be excluded from research into chronic pain solely on the grounds of their age, but given the lack of published data it should always be recorded.

Table 5.2 also included the proportion of those who reported the most severe pain (NRS>=7 & S-LANSS>=12). In this small cohort the results did not indicate any trends.

6.2.1.3. Waiting time prior to appointment with the pharmacist

The CPS makes strenuous efforts not breach the UK-NHS 18-week rule, for treatment after receiving a referral. It is generally successful, except for those aspects of the service such as spinal injections, where others control the resources.

The lengths of time reported by patients in this research in answer to BPI question 6 (Section 8.4.2), "*how long since you knew your diagnosis"* were recorded. The mean wait was 106 months and almost two thirds reported suffering with their pain for more than 36 months. This was explored graphically in Figure 5.2 and this appears to indicate that patient waiting times for specialist chronic pain treatment are divided into two groups. Firstly, the decreasing numbers waiting over the first few years, possibly whilst the patient and their physician decide that a referral to an expert was deemed necessary. The remainder of the patients were in a group which appears to be waiting an inexplicably long time. The range of patient waits were larger than, but similar to those reported in an audit from the Royal College of Anaesthetists (Black, 2017) followed up by more localised figures from University Hospital Leicester (UHL) (Ingle and Vasu, 2018) (Table 6.1). The questions used in these audits related solely to the times between commencement of pain and referral. This was different to Question 6 of the BPI, used with this cohort, which made

mention of a diagnosis. The length of time that patients had had their pain was reported in one of the papers in the systematic review (Harrison, 2015) and these were also included in Table 6.1.

Table 6.1 Length of time – pain onset, to pain clinic appointment

	UHL[1] data (n=30)	**National[2] data from RCOA (n=197)**	**Harrison[3] data (n=20)**	**This research* (n=85)**
Pain onset to first pain clinic appointment*	Mean 64 months. Range 5 months – 27 years	Mean 74 months. Range 1 month – 35 years	Mean 144 months. Range 2 years - 20 years	Mean 106 months. Range 1 month – 47 years

[1] (Ingle and Vasu, 2018)
[2] (Black, 2017)
[3] (Harrison, 2015)
*This research asked for time from diagnosis

In addition to the wait for a referral there was the wait for an appointment after the referral was made and as mentioned above, for this service, these were generally less than 18 weeks. Waits for a CPS referral appointment are well documented. A Scottish report in Jan 2019 recorded that 399 of 2,798 patients waited for more than 27 weeks (NHS, 2019b). A similar investigation in Australia recorded waits of up to 86 weeks with a national median wait of 15 weeks (Hogg *et al.*, 2012).

Waiting time prior to appointments are relevant because not only is it associated with an increased risk of mortality, independent of other socio-demographic effects (Torrance *et al.*, 2010) it also doubled the suicide risk (Liddy *et al.*, 2017). There are suggestion that some forms of chronic pain and its sequelae can worsen whilst

waiting for treatment within as little as five weeks (Lynch *et al.*, 2008). Furthermore, whilst awaiting referral, fear-avoidance beliefs, where the anticipation of pain resulting from movement inhibits further movement, may contribute to worsening levels of kinesiophobia and poorer overall physical ability (Gatchel *et al.*, 2016).

6.2.1.4. Educational achievements of the research cohort

More than three quarter of patients declared some educational qualifications (Table 5.3). These results were similar to those reported by Hadi *et al.* (2016) but different to those reported by Bruhn *et al.* (2013), who reported a more equal division between those with an education certificate that those with none.

The relationship between educational achievement and chronic pain is complex. There were reports that the prevalence of chronic pain was associated with lower levels of educational achievement (Currow *et al.*, 2010; Saastamoinen *et al.*, 2005). Alternately Roth and Geisser (2002) suggested that the level of educational achievement was unrelated to pain severity and intensity but was inversely related to self-reported disability i.e. as the pain intensity goes up, reporting that pain causes a problem goes down.

Table 5.3 also included the proportion of patients with the most severe type of pain (NRS>=7 & S-LANSS >=12). The results from this small cohort appear to indicate that the proportion of patients with NRS>=7 and S-LANSS >=12 pain reduced as

their education achievements rises. In addition it has been reported that chronic pain intensity decreases as health literacy increases (Koppen *et al.*, 2018) and heath literacy is related to patient's literacy and competences to understand the treatments being offered (Wittink and Oosterhaven, 2018).

6.2.1.5. Employment status of the research cohort

The distribution of employment status of the recruits was set out in Table 5.4. For males, over 40% are 'retired', which was likely to be due to the age distribution of the cohort (Table 5.2) and a third were unemployed. The largest group of females was also 'retired' but with a much smaller percentage (26%). More females were recorded as employed both part time and full time, in addition to being younger.

Overall, this cohort was approximately equally divided between employed, unemployed and retired. For Bruhn *et al.* (2013) the largest group was retired, whilst for Hadi *et al.* (2016) the largest group was unemployed. Unemployment or life on benefits almost inevitably means fewer socio-economic benefits. If this relationship was as reported then the commencement of chronic pain with all of its sequalae could easily lead to a downward spiral of greater disadvantage and more severe pain.

Table 5.4 also includes the proportion of those patients who suffered with the most severe type of pain (NRS>=7 & S-LANSS>=12). These results did not give any indication of variation with employment status.

6.2.1.6. Relationship status of the research cohort

Just over half of the original cohort of patients reported that they were married, Table 5.5. This was similar to the proportions reported by both Bruhn *et al.* (2013) and Hadi *et al.* (2016). It has been widely reported that marriage is associated with improved psychological and physical well-being in both men and women (Shapiro, Lee and Keyes, 2008). However, there was only weak support for the hypothesis that being married helped with pain related emotional suffering (Wade *et al.*, 2013).

Table 5.5 also includes the proportion of those patients who suffered with the most severe form of pain (NRS>=7 & S-LANSS>=12). These results did not give any indication of variation with their relationship status.

6.2.1.7. Reluctance to take (pain) medicines

At their 1st appointment 18 patients expressed openly at the outset that they were resistant to taking pain medicines (Table 5.7). Of these 16 (89%) had an NRS pain score of >=7, 15 (83%) had an S-LANSS score of >=12 and 12 (67%) had both. The reasons why patients with such high pain scores were unwilling to take their analgesia were difficult to ascertain. For some patients it was avoiding side effects, for others it was ineffective therapy. There was also a group of patients who seemed to regard taking medicines as something that they were unwilling to do, almost that acquiescing to treatment gave their pain power over their lives. This might have resulted from a lack of understanding about the correct use of pain medicines.

Alternatively, it might have been belief in inappropriate or wrong facts about their pain medicines.

The relationship between medicine side effects and compliance with therapy has been explored by others (Leporini, De Sarro and Russo, 2014) but the literature, particularly in relation to patients over 65 is very limited (Gellad, Grenard and Marcum, 2011). What is contained in those reports is that a multi-faceted approach to non-adherence is better than focussing solely on the prescriber/patient relationship. Such an approach is practiced by this CPT and may well have contributed to its relative success. It is well documented that many of the medicines used in the treatment of chronic pain had unpleasant side effects *viz.* opioid induced nausea (Moore and McQuay, 2005), gabapentinoid induced brain fog (Zaccara *et al.*, 2011) and tricyclic induced dry mouth (Cookson, 1993) and these will always deter some patients regardless of the severity of their pain. Whatever the reason, these patients may have deprived themselves of potentially effective treatment (Horne *et al.*, 2005).

6.2.1.8. Conclusion

The role of the pharmacist is to empower patients to engage with their chronic pain therapy in ways which enabled them to judge their personal need for the medicine relative to their concerns about the potential adverse consequences (Horne *et al.*, 2013). The improvements in pain scores reported by the patients in this research

would suggest that such empowerment can have benefits in terms of both the extent and duration of analgesia.

Chronic pain and the treatment of chronic pain are context specific (Scott, 2019; Crofford, 2015) and no aspect of chronic pain can be independently and objectively verified. The best quantitative measures that we have are based upon the plethora of extant measuring questionnaires (BPI, S-LANSS or CPG). Unfortunately, research tells us that patients use these as relative scales rather than absolute measures (Robinson-Papp *et al.*, 2015). Therefore, in chronic pain research it is important to record the demographics so that research findings can be related to those which have gone before.

6.2.2. BASELINE S-LANSS SCORES IN RELATION TO EARLIER AUDIT

Tables 5.2 and 5.6 reported that for this research cohort out of 100 patients 58 reported an S-LANSS score >=12 with a mean score of 14.1. These results were similar to those reported from the audit which had initiated this research project. In that audit of 100 patients 57 patients reported an S-LANSS>=12 with a mean of 13.6. The results from these two cohorts suggest a consistent number of patients attending the pharmacist's clinic within the CPS with neuropathic elements in their pain as defined by the S-LANSS questionnaire.

6.3. Changes in pain scores between visits

6.3.1. INTRODUCTION

This section discusses the changes in patients' pain scores between the 1st and 2nd clinic appointments.

Consideration of changes in pain scores often lead to discussions about whether it is possible to define an objective minimum change in a pain score. Some research suggested that regardless of the level of the initial pain score a specific change in the score would result in an effect which the patient regarded as clinically significant (Kelly, 2001). Other reports suggests that the reduction must equate to two points on an 11 point scale (Dworkin *et al.*, 2008). Todd *et al.* (1996) and Kendrick and Strout (2005) suggested that for patients in a trauma unit changes of less than 1.3 VAS were not clinically significant with no attempt to relate this to the patients' original pain score. This was countered by the suggestion that the higher the original pain score the greater the change required before the patient would regard it as clinically significant (Bird and Dickson, 2001). Dworkin *et al.* (2008) and Farrar *et al.* (2001) adopts a different approach and suggested that the clinical significance of any reduction was related to the percentage change and this may need to be 30% before it would be regarded as clinically significant. Other researchers suggesting variation between genders and pain type (Mark *et al.*, 2009), but even this has been refuted, Kelly (1998) reported a lower clinically significant change of 0.9 VAS with no differences between gender, age or cause of pain. Underlying all of this is the

comment in Section 6.2.1.8. that patients regard all of these scales as relative (Robinson-Papp *et al.*, 2015) and therefore any improvements recorded and discussed may relate to something else altogether.

The changes in NRS pain between the 1st and 2nd appointment for this research cohort appeared to be similar to those reported in by Bennett *et al.* (2011). This reported that patients who received a 2.5 hours intensive education program from a pharmacist, recorded an improvement in their pain score of 0.5 on an eleven-point scale. Less intensive intervention was ineffective. In this research patients recorded a mean 0.4 improvement in their NRS score with a 0.5 improvement in their BPI PSS 'worst' pain score (Table 5.10 and Figure 5.5). By the time of their 2nd appointment all patients would have had 1st appointment with the pharmacist which lasted up to an hour. Eighteen of the 55 patients, (Table 5.11) had attended the PMP programme, which includes a 1.5-hour presentation and discussion with the research pharmacist. This would represent an overall total of 2.5 hours of interaction with the pharmacist which was similar to the input suggested by Bennett (2011) as being effective.

The pain scores in Table 5.11 set out the differences in the mean NRS and S-LANSS scores for those patients who had and had not attended a PMP between the two pharmacist appointments. At their 2nd appointment the largest change was in the NRS score of the small group who had attended a PMP. This reduced from 8.4 to 7.5. Of those who had not attended, the S-LANSS increased from 12.8 to 13.4. An indication in the complexity of measuring pain scores. Overall the improvements in

pain scores of the small subgroup who had had the additional intervention appeared larger than those who had not, but the numbers were small.

The mean NRS score of the patients in this research on their 1st visit was 8.1 (Table 5.10). Only two reports retrieved for the Systematic Review dealt with patients who had an NRS score of this magnitude, all others were less. Firstly, Thomas (2012) reported a mean reduction in the NRS score of 2.7 or 33% for those patients who had a pharmacological intervention. There was no record of the actual NRS scores reported, but mathematically, if a reduction of 2.7 is 33% then the baseline NRS score would be 8.1. It would be interesting to discover the analgesic strategies used to achieve such a large reduction in the patients' pain scores. Secondly, Hadi *et al.* (2016) reported that the 'Median BPI 'worst pain' was 8 with a reduction to 7.5 (P=0.02).

6.3.2. CHANGES IN PAIN USING DATA FROM THE BPI AND S-LANSS QUESTIONNAIRES

The overall mean pain scores from the four measures of pain included in this research changed very little (Table 5.10).

More detailed analysis of the data of the total paired group from the two questionnaires revealed three significant changes, reduction in worst pain, increase in perceived pain relief and increased duration of analgesia.

6.3.2.1. Reduction in the 'Worst Pain' element of the PSS

Analysis of the individual elements of the BPI-PSS and BPI-PIS revealed that the worst pain' element reduced significantly from a mean of 8.4 to a mean of 7.9, P=0.023 (Figure 5.5). Out of the 53 patents in this group 8 (16%) reported that their pain reduced by at least 2 points (Table 5.12). Two points in an 11-point pain scale had been reported as clinically significant as discussed previously (Section 6.3.1).

6.3.2.2. What percentage pain relief did patients receive from taking their pain medication in the previous week (BPI question 19)?

The percentage of pain relief recorded by patients after taking their pain medicines in the previous week increased significantly from 41% to 51%, $P < 0.001$ (Figure 5.6). This change was consistent with the reduction in the BPI-PSS worst pain score between the two visits, because benefit might be more noticeable when the pain is worst.

6.3.2.3. How long before the pain returns after taking pain medication (BPI question 20)?

In the treatment of chronic pain, the time period when a patient's pain is reduced by their pain medication is important. Pain medication rarely results in a continuous pain free state, but patients needed to be able to plan their use of pain medicines so

that they can use any benefit to facilitate 'life events' which were essential but which are known to cause or increase pain.

The BPI question 20 (Section 8.4.2) asks 'how long does it take before your pain returns'. This apparently specific question about the duration of pain relief is actually asking a second equally important question at the same time, *i.e.* how many pain medicines were being taken with no perceived benefit? An enquiry about the efficacy of each pain medicine taken by the patient is a routine part of the pharmacist's normal intervention.

Between the 1st and 2nd appointment the number of patients who reported that their analgesia didn't help at all went down significantly, from 42% to 12% P=0.001 (Figure 5.7) leaving12% (5) individuals who may benefit from further optimization of their pain medication. This represented an opportunity for the pharmacist in the CPS, at a subsequent appointment, to continue counselling patients about improving the use of their pain medicines.

It follows that if fewer patients reported no benefit then the periods of time which patients recorded that their analgesia was effective had increased. This change was also significant. More patients reported longer periods of benefit at their 2nd visit, P=0.003 (Figure 5.8).

6.3.3. CONCLUSION

There are several possible explanations for these changes in the patients' pain between the 1st and 2nd appointments. Firstly, had the patients GP taken up one of the pharmacist's suggestions and prescribed a different more effective therapy? Alternatively, did the patients improve the way that they used their pain medicines, as a result of the pharmacist's interventions? If so, the time when they were most likely to notice any benefit would be when their pain is at its worst. The advice from the pharmacist was aimed at improving how patients could use their pain medicines to best advantage. This included reducing the patients' reluctance to take their pain medicines by improving their ability to manage both the benefits and the side effects.

Adherence to medication, particularly for chronic conditions, averages about 50%, less in developing countries (Yach, 2003). Other reports suggest that between a third and two thirds of all US hospital admissions result from poor medicines adherence/compliance possibly because the ability of doctors to recognise non-compliance is poor (Osterberg and Blaschke, 2005). In addition, poor adherence/compliance, such as taking prescribed naproxen and OTC ibuprofen, can lead to adverse drug reactions, which would further discourage patients from taking their pain medicines appropriately (Leporini, De Sarro and Russo, 2014).

However, one point should not be overlooked totally, the power of the placebo (Muller *et al.*, 2016; McCartney, 2015). Table 1.2 includes the proportion of patients who achieved analgesia with a placebo during placebo-controlled trials of medicines

used in the treatment of neuropathic pain. The position of placebo in the treatment of chronic pain is uncertain and Price, Finniss and Benedetti (2008) reported that whilst undertaking a review they noted that the degree of analgesia sometimes varied, with the length of the trial. A later Cochrane review suggested that in clinical trials for pain treatments there should be three arms, treatment, placebo and treatment as usual (Hrobjartsson and Gotzsche, 2010). Such an arrangement might give a better indication of the actual place of the placebo in the treatment of that condition.

In this research the following measures of pain have improved significantly –

i. Mean 'Worst pain' score reduced from 8.4 to 7.9
ii. Mean 'Relief from treatment' improved from 41% to 51%
iii. The proportion of patients taking analgesia from which they perceive no benefit, down from 42% to 12%
iv. The overall duration of analgesia increased

This group of significant results raised one of the fundamental paradoxes of pain therapy. Why did such a small reduction in a pain score create such a large improvement in the perception of benefit? The difficulties of converting changes in pain scores to clinically significant improvements have been addressed previously. in addition, there is research in primary, secondary and A&E care which suggests that reported pain score changes were intertwined with patient satisfaction at the end of an episode of care (Dawson *et al.*, 2002; Shindul-Rothschild *et al.*, 2017; Fallon *et al.*, 2016; Kelly, 2000). If pain scales are relative (Robinson-Papp *et al.*, 2015) are

the patients attending the pharmacist's clinic simply recording satisfaction with the way that they have been treated.

Cochrane reported that attendance at a multi-disciplinary biopsychosocial pain clinic was reported as more effective than usual care in the treatment of chronic low back pain (Kamper *et al.*, 2015). Recommendations for patients to attend such courses are increasing, but there is still some controversy because their greatest benefit seems to be on patient functioning and wellbeing rather than their pain (WIlkinson and Whiteman, 2017; Wilson, 2017). It may be that at least some of the benefits achieved by the patients in this cohort resulted from their involvement with the CPS.

6.4. Changes in the reported efficacy of pain medicines between visits.

6.4.1. INTRODUCTION

At their 1st appointment between 50% and 60% of patients reported that their pain medicines were helpful for all of the five groups of pain medicines (paracetamol, mild/moderate opioids, strong opioids, neuropathic treatments and NSAIDs) with medicines for neuropathic pain showing the greatest benefit at 58%. After the pharmacist's intervention, during the medicines review, when patients returned for their 2nd appointment the proportion of patients who regarded their pain medicines as helpful had increased for all five groups. The only increase which was significant was for mild moderate opioids (Table 5.13).

These results may suggest that the pharmacists' intervention was having a positive influence. The advice both in clinic and at PMP presentations was that no pain medicine was going to make them pain free (NICE, 2017). Therefore, their use of pain medicines should be aimed at facilitating those things in life which are regarded as important but are known in advance to cause pain.

The regular use of opioids is known to rapidly lead to the development of tolerance and that varying the dose prolongs the effective life of these medicines (Yu *et al.*, 1997; McAllister, 2016; Chu *et al.*, 2012). Therefore, it was suggested to patients that they should vary the dose of their mild moderate opioids with the severity of their pain. The point was also made that if a patient's pain had neuropathic elements the mild/moderate opioid of choice should be tramadol if it was tolerable and not contraindicated by other medicines or medical conditions (Ballantyne, 2017).

Considerable effort was also made to try and overcome patients' reluctance to taking pain medicines, particularly opioids, because of the fear of addiction. It may be that enabling patients to take informed decisions about whether or not to take their pain medicines also contributed to improvements in their pain control. Another aim was to encourage patients to obtain the maximum benefit from those medicines which were least harmful for treating their pain before moving to more potent pain medicines as suggested by the WHO Pain Ladder (Reid, Eccleston and Pillemer, 2015a).

In all therapeutic groups there was generally, but not always, a reduction in both the proportion of patients taking medicines which they didn't think were helpful and those who didn't know whether it was helpful. Such changes would also be consistent with the pharmacist's message with this cohort, that because of the possibility of side effects patients should be sure that the pain medicines which they take were beneficial for their pain.

6.4.2. USE AND BENEFIT OF PARACETAMOL

The changes in the use of paracetamol were set out in Figure 5.9. Of the patients who were taking it there was a non-significant increase in the proportion of patients who regarded it as helpful, a surprising increase in those who regarded it as not helpful and a decrease in the proportion of those who did not know if it was helpful. Paracetamol is reported to have different NNTs depending upon the type of pain being treated (FOPM, 2007; Saragiotto *et al.*, 2016; Moore *et al.*, 2015c). These differences in NNT may account for the apparent divisions between effective and non-effective in patients suffering with different types of pain.

The arguments for the use of paracetamol in the treatment of chronic pain are contentious and were set out in Section 1.6.1. Because the current balance of opinion is that paracetamol is safer than a NSAIDs (Kress and Untersteiner, 2017) patients were advised that if paracetamol was effective then in the treatment of their pain it was the *'least worst option'*. This term was used rather than 'better' because there was still the possibility that it might cause harm.

6.4.3. USE AND BENEFIT OF MILD MODERATE OPIOIDS

At their 1st appointment 51% of patients reported mild/moderate opioids were effective. This was slightly smaller than the 55% for paracetamol. By the 2nd appointment this had reversed and 81% regarded mild/moderate opioids as effective compared with 60% for paracetamol

The changes in the use of mild moderate opioids were set out in Figure 5.10. Of those who were taking them, there were significant increases in the proportion of patients who regarded them as helpful and the proportion who thought they were not helpful or didn't know decreased (Table 5.13).

A chronic pain patient's first prescription experience with opioids was often as a combination of Paracetamol with a mild/moderate opioid with many prescriptions being for co-codamol (30/500) two to be taken four times a day. This dose of codeine is equivalent to about 6mg of morphine. For a patient starting opioid therapy, this often resulted in side effects such as nausea, sickness, constipation and dizziness. Up to 10% of patients do not continue because of these side effects (Straube *et al.*, 2014). The requirement for the bio-transformation of codeine before it has any analgesic efficacy also needs to be remembered.

Tramadol is a mild/moderate opioid which has, in addition, the potential to be effective in the treatment of neuropathic pain, making it almost unique in the treatment of chronic pain. Pharmacist referral letters to GPs after 1st clinic

appointments, with this cohort of patients, suggested on 32 occasions that tramadol might be worth an assessment. Because the improvement in the efficacy of mild/moderate opioids was statistically significant these results were examined in more detail. At the second appointment 14 of 15 patients (93%) who were taking tramadol reported it as effective. The proportion of patients who regarded tramadol as effective was more than the 60% reported for both codeine and dihydrocodeine, but these were based on very small numbers (Table 5.13).

6.4.4. USE AND BENEFIT OF STRONG OPIOIDS

At their 1st appointment 52% of users of strong opioids regarded them as effective. The comparative figure for mild/moderate opioids was 51%. There was an increase at the 2nd appointment up to 72%.

Patients would not be attending the CPS if opioids and other analgesics, were able to control their pain. Strong opioids are considered the most effective medicines that are available for the treatment of (nociceptive) pain but this effectiveness does not translate into the treatment of chronic pain (Ballantyne, Kalso and Stannard, 2016).

The changes in the use of strong opioids were set out in Figure 5.11. Of those who were taking them there were non-significant increases in the proportion of patients who regarded them as helpful and the proportion of those who thought it was not helpful or didn't know decreased. The problems associated with opioids and chronic

pain, especially with regard to effectiveness and tolerance were explored earlier (Section 1.6.2).

The role of strong opioids in the treatment of chronic and/or neuropathic pain is controversial (Bostick *et al.*, 2015; Stannard *et al.*, 2016; NHS, 2015). There is insufficient evidence to determine the long-term analgesic effectiveness of opioids (Chou *et al.*, 2015). There are suggestions that opioid side effects often outweigh any long-term benefit, especially at doses >100mg of oral morphine equivalence daily (Anderson, 2015; Stannard, 2012). There is also the suggestion that the use of strong opioids, even if they help with the pain may actually delay improvements in patient function (Ballantyne, 2017). The Faculty of Pain Medicine (FOPM) and NHS England published a report entitled 'Opioids Aware' (NHS, 2015). The Executive Summary from this report included the following points.

'*Opioids are effective analgesics but there is little evidence that they are helpful for long-term or neuropathic pain*'.

'*The risk of harm increases substantially at doses above an oral morphine equivalent of 120mg/day, but there is no increase in benefit'*.

'*If a patient is using opioids, but is still in pain the opioids are not effective and should be discontinued, even if there is no other treatment available*.'

This message was reinforced by two Cochrane reviews. Els *et al.* (2017a) reported that there was no evidence to support the use of large doses of opioids in chronic non-cancer pain because of a shortage of long-term trials at doses used in clinical practice. Els *et al.* (2017b) went on to expand the 'harms' side of opioid therapy and reported that compared to control 78% of patients undergoing opioid treatment suffer with an adverse effect.

The prescribing of opioids for chronic pain has increased fourfold in the last twenty years. Much of this increase driven by guidelines, which suggest S/R formulations were safer and more effective than I/R formulations (Volkow and McLellan, 2016). Unfortunately, these long acting formulations do not address the patients real analgesic needs, how to cope with the varying level of pain with a constant level of analgesia. Sullivan (2014) suggested that there was insufficient evidence to determine whether there was any real difference between the opioid analgesic efficacy or the incidence of side effects between I/R or S/R formulations. A paper the following year by Miller *et al.* (2015) reported that patients often preferred I/R formulations because this allowed them to match their use of pain medicines with their level of pain and thereby take some control their total opioid dose. A subsequent review by Ballantyne (2017) confirmed that the analgesic benefits of opioids were preserved if they were not used continuously and that intermittent use provided equivalent or better analgesia, which the patients preferred.

Five patients, in this study, who were taking doses of S/R opioids were also taking top-up doses of an I/R opioid. Where patients reported taking mixed duration formulations they mostly acknowledged their therapy was effective. Some were taking the same medicine in two different formulations others were taking different opioids in different duration formulations. This raised two questions. Was one more effective than the other. Alternatively, were they both effective and was it varying the opioid dose which reduced the tendency towards tolerance as has been suggested by Miller *et al.* (2015) and Ballantyne (2017). A much larger cohort of patients taking strong opioid pain medicines would be needed to explore such questions.

Out of the 100 patients in this cohort 36 patients were taking a strong opioid at their 1st appointment. Of these 32 (89%) still had an NRS pain score of >=7. This poses several questions. Were those patients tolerant to their opioid, would their pain be much greater without their opioid or was their opioid truly ineffective for their pain.

Eighteen of the paired patients (33%) arrived at their first clinic appointment using one or more strong opioids medicines. Nine (50%) reported that they were helping with their pain control, 6 (33%) did not think that they were effective and 3 (17%) were not sure. Therefore, 9 (50%) were taking or using a strong opioid preparation from which they perceived uncertain or no benefit. The number taking strong opioids reduced to 15 at the second visit, but of these the proportion of patients who thought that they were effective rose from 53% (8) to 73% (11). Therefore, even after the

pharmacist's intervention four patients taking these potent medicines, which can cause serious adverse effects, without any certainty of benefit.

If there was no real benefit from strong opioids the following possible factors were considered: did the patient's pain include elements of neuropathic pain or was there evidence of opioid induced hyperalgesia. At their 2nd appointment 72% of patients (Table 5.13) reported that medicines for neuropathic pain were reported as effective. If opioid hyperalgesia was suspected the patient was encouraged to undertake a trial of a very gradual reduction in their overall opioid dose, aiming for a downward opioid dose trajectory with minimal withdrawal potential. Baron and McDonald (2006) reported on a group of 23 patients who were taking or using large doses of opioids for chronic pain. Over a period of time these patients were persuaded to eliminate their strong opioid medicines. All patients demonstrated some reduction in pain and the overall mean pain score for these patients went down from NRS 8.0 to NRS 3.5.

For patients hoping to use their opioid therapy to facilitate a return to work the message is equally unhelpful. The use of opioids can delay the return to work (Busse *et al.*, 2015; Deyo, Von Korff and Duhrkoop, 2015; Savych, Neumark and Lea, 2018) and the likelihood of returning to work is reported as inversely proportional to the opioid dose (Nguyen *et al.*, 2011).

Three patients in this cohort made considerable efforts to reduce their strong opioid dose (Section 5.4.2.3). These results suggest that the pharmacist's intervention about the possible dangers of strong opioid therapy had been effective.

There has been a change of tone about the use of strong opioids in the treatment of chronic pain since it was being debated as a 'human right' (Cousins, Brennan and Carr, 2004) and as later expressed in the Montreal Declaration (Cousins and Lynch, 2011). This change has been driven by the realisation of the extent of the opioid misuse problem. In the UK the need for caution with the use of these medicines was acknowledged with the publication of 'Opioids Aware' (NHS, 2015). Advice to prescribers had been issued in various locations on opioid dose reductions (NHS, 2017a; NHS, 2018c) but a Cochrane Review (Eccleston *et al.*, 2017) reported that there was no evidence of the relative safety of any of the proposed opioid reduction schemes.

Tapentadol was added to the local Stoke Guidance on the treatment of chronic pain (Njoku, Rosam and Ashworth, 2017). With a potency between tramadol and morphine this was a useful addition to the range of medicines available for the treatment of chronic pain. There were indications of its effectiveness against neuropathic pain but as yet it had not been accepted by all GP formularies (Langford *et al.*, 2016; Sugiyama *et al.*, 2018)

6.4.5. USE AND BENEFIT OF MEDICINES USED FOR THE TREATMENT OF NEUROPATHIC PAIN

One of the problems involved in the treatment of chronic pain, as discussed in Section 1.5.3 is differentiating nociceptive and neuropathic pain elements, A higher percentage of patients (58%) reported that medicines for neuropathic pain were helpful at the 1st appointment than for any of the other medicines in this research. This proportion increased at the 2nd appointment up to 72% (Figure 5.12). Although these changes were not statistically significant there is an indication that educational advice targeted at careful titration of doses improved patients' outcomes with these medicines. However, given the size of this improvement the mean S-LANSS score only decreased from 12.6 to 12.5 (Table 5.10). Current questionnaires do not facilitate the collection of data which would explore this problem. More accurate historic data is needed to track changes in pain scores with changes in doses. The paradox in the treatment of chronic pain set out in Section 6.3.3 is also relevant here.

Fifty-eight patients in this cohort recorded an S-LANSS score of >=12 (Table 5.9) and therefore were regarded as having elements of neuropathic pain (Bennett, 2001). Of these 44 (76%) were taking an analgesic recommended for this condition in the BNF or NICE (2013a). This leaves 14 (25%) possibly not taking appropriate analgesia. But more patients were taking medicines suitable for neuropathic pain than had an S-LANSS >=12, which may be an indication of successful therapy either known or unrecognised. It may also suggest their use for other therapeutic indications *e.g.* depression coexisting with their pain diagnosis.

The audit which was basis for this research (Section 1.3), found that of the 100 patients who were included, 57 patients recorded an S-LANSS score>=12. Of these only 36 (63%) were taking medicines recommended for the treatment of this condition. The number of patients with an S-LANSS>=12 in the audit was one less than in this research cohort, 58 (Table 5.9). The proportion taking appropriate medicines in the pilot study was 63% compared with 76% (Table 5.9) in this research cohort. Overall these figures indicate some undertreatment of neuropathic pain that could present opportunities for pharmacists to suggest appropriate therapies. The report by Gill, Taylor and Knaggs (2013), outlined in the systematic review suggested that expanding the role of Community pharmacists into the diagnosis, treatment and management of chronic pain could possibly identify 50,000 cases of undiagnosed neuropathic pain in a year.

Sixty-six percent of the patients in this research with an NRS >=7 also had a S-LANSS >=12 and it was suggested by Torrance *et al.* (2007) that patients with chronic pain of predominantly neuropathic origin more difficult to treat. For that investigation a randomly generated list of 6,000 patients from three UK cities were mailed a questionnaire. Three thousand and two were returned. Three groups were identified, patients with no chronic pain and patients who had chronic pain and who were either S-LANSS positive or S-LANSS negative for neuropathic pain elements. The patients who reported neuropathic elements in their pain reported less pain relief from their pain medicines, despite using more, but surprisingly very few were taking

medicines specific for the treatment of neuropathic pain. This report did not include details of whether these patients had assessed neuropathic treatments and failed or whether they had never been offered. Patients who were not taking these medicines could be amongst those being referred for the management of neuropathic pain if greater use were made of community pharmacists (Gill, Taylor and Knaggs, 2013).

The information about the contribution of placebos to the treatment of chronic pain contained in Table 1.2 also needed to be considered seriously. For example both duloxetine and gabapentinoids were recommended for the treatment of fibromyalgia pain. Lunn, Hughes and Wiffen (2014) suggest that any benefit from duloxetine in the treatment of fibromyalgia may result from its anti-depressant effects rather than any direct effect upon the pain. McCartney (2015) reminded us that in the treatment of fibromyalgia about one person in three would receive benefit from pregabalin but in addition one person in five would receive similar benefit from a placebo. Similarly, Wiffen *et al.* (2017) reports that with gabapentin in the treatment of neuropathic pain 3 or 4 of 10 would receive up to 50% pain relief. The comparative figure for placebo was 1 or 2 of 10. Given the potential for harm of these medicines, ongoing assessment for efficacy are important and represented an opportunity for pharmacists to become engaged whilst counselling about the use of pain medicines.

As reported in Section 5.4.2.4 some patients took their neuropathic medication on a when necessary basis because of the sporadic or predictable nature of their pain. For example, patients who experienced pain only during a certain activity did not

require levels of ‘background analgesia’. Their justification for this was they know what was effective but that side effects precluded their use over a longer period. The implication of this method of medicine use was that to achieve the best outcome for themselves, these patients have understood both the benefits and the side effects of their therapy and had balanced that with their daily living.

6.4.6. USE AND BENEFIT OF NSAIDS

The changes in the use of NSAIDs were set out in Figure 5.13. Of those patients who were taking them there was a non-significant increase in the proportion of patients who regarded them as helpful up from 55% to 66%. The proportion who thought they were not helpful decreased. This group of medicines was the only one, in this research, where the proportion of patients who were unsure whether they were helpful increased.

NSAIDs were reported as very effective analgesics in the treatment of acute pain including lower back pain (Enthoven, Roelofs and Koes, 2017). As a group they had amongst the lowest NNTs for the treatment of acute pain as rated by the Oxford League Table of Analgesics (FOPM, 2007) with NNTs of between one and two. Because they are such good analgesics and older people may tend to have more aches and, patients are prescribed more frequently for older than younger patients. This may have resulted in poor quality pain management advice (Ferderman, Litke and Morrison, 2006) because the side effect profile of NSAIDs worsens with age (Seager and Hawkey, 2001).

As set out in Section 1.6.4 NSAIDs can cause a wide range of side effects beyond the widely known gastric irritation. As a result, in older people balancing less pain with the increased risks of morbidity needed to be a real consideration (Wehling, 2014). Given this, at their 1st appointment 43% were taking one of these medicines without any perceived benefit.

NSAIDs have been the medicine of choice in the treatment of inflammatory pain conditions but their mechanism of action there would suggest little rationale for their use in the treatment of neuropathic pain. A Cochrane review reported that there was no evidence to support or refute the use of NSAIDs in the treatment of neuropathic pain (Moore *et al.*, 2015a) . Yet Berger *et al.* (2012) reported that out of a sample of 31,688 patients with a painful neuropathic condition 56% had a prescription for an NSAID compared to 22% in the matched control group. The mean age of the group was 56.1 years and 32.9% (10,434) were in the >=65 age group.

Possession of a prescription and actually taking the medicine are quite different. Compliance figures are difficult to obtain. Many years ago, de Klerk and van der Linden (1996) undertook research into compliance with NSAIDs in the treatment of ankylosing spondylitis using electronic monitors for an average of 225 days. Their results suggested that patients took 81% of the prescribed doses but not necessarily as prescribed. Interestingly, they also reported that there was no correlation between compliance and improvement in reported pain or morning stiffness in a population

where it would be expected that NSAIDs would be effective, which would question the efficacy of this therapy. Similar levels of compliance were reported by (Lanas *et al.*, 2012) who added that compliance to a regular NSAID prescription went up as the pain became more constant.

In this small research cohort, the percentage of patients who thought that their NSAIDs were effective (initially 57%) was approximately the same as the 56% of patients in the Berger *et al.* (2012) report. Given these results and the difficulty of treating patients with chronic pain it would be difficult not to suggest that in any patients' pain NSAIDs should be assessed for efficacy, regardless of the pharmacological logic. However, these were the medicines most likely to lead to an emergency hospital admission (Pirmohamed *et al.*, 2004) therefore they must only be taken if they were perceived to be effective, with appropriate gastric protection (NHS, 2018b), at the lowest dose for the shortest possible time.

6.4.7. CONCLUSION

The improvement in pain resulting from the use of pain medication was only significant for the mild moderate opioid group. Other groups caused apparent improvements but the changes were not significant.

One positive outcome was that overall, more patients reported stopping a pain medication than starting one. This was important because one of the pharmacists' messages was that pain medicines should only be taken when they were perceived

to give benefit. The pharmacist can easily advise on OTC medicines, however not being a prescribing pharmacist in the CPS, any advice about stopping a prescribed medicine would need to be endorsed and changes made by the patient's GP. This additional step for patients to add or change therapy indicates the benefit of an independent prescriber pharmacist (IP) (Section 8.2) in the CPT.

In the Review Synthesis one of the contextual points was that pharmacists had a beneficial role in the treatment of chronic pain and that this was an expression of maximising the use of the pharmacists' basic skill set, *i.e.* knowledge about medicines. From the researchers' clinical practice many patients demonstrated a lack of knowledge about their medicines. As a result, the educational input of the research pharmacist provided patients with an opportunity to understand how to use their pain medicines more appropriately and empowering them to act effectively upon this new knowledge.

Hadi *et al.* (2014b) published an outline of the recommendations made to GPs about the patients who were included in the Hadi *et al.* (2016) research. These included 'stopping n=19', 'adding n=30', 'titrating n=29' and 'substituting n=23' medicine. There was no indication in the text to indicate whether these were prescribed or 'OTC' medicines. Comparable 'medicines optimisation' figures for this research were 'stopping n=44', 'adding n=19'. These included both 'OTC' and prescribed medicines. Overall the number of changes to prescribed therapy as a result of the pharmacist's recommendation were 30 in a cohort of 55 (55%).

6.5. Changes in answers to the questions in the Brief Pain Inventory (Questions 24-30)

6.5.1. INTRODUCTION

The BPI (Section 8.4.2) was designed to explore patient's pain in several ways. It explored the severity of the pain, the effect of the pain on their lives and their understandings of pain medicines. Some patients' are reluctant to take any medicines (Osterberg and Blaschke, 2005) which could be difficult to understand. Sometimes they appeared to conflate information from one group of medicines to another, NSAIDs cause gastric irritation and codeine can be addictive, therefore all pain medicines cause gastric irritation and are addictive. Taken in isolation these statements about NSAIDs and codeine are factually correct, but in the treatment of chronic pain undue concentration on these particular points are not always helpful. For these patients the advice needs to be nuanced with advice about varying the dose to minimise the development of tolerance. For example, tolerance and dependence may go hand in hand and are physiological responses to opioid medicine being taken but addiction is a behavioural response following on from these changes.

Concordance and adherence are recognised problems with any medications. When collecting medicines, pharmacists will usually reinforce the labelled directions. For

example, ‘gabapentin 600mg tds’ is usually translated onto the label as ‘three times a day’. This may be interpreted as “breakfast time, lunch time and bed time” or “breakfast time dinner time and bed time” with no understanding that this relates to every eight hours. Gabapentin, when use for chronic pain should be administered every eight hours for optimal effect, and minimal side effects. Exploring what the patient understands is an important aspect of shared decision making and is certainly a conversation that both specialist and generalist pharmacists, with their understanding of pharmacokinetics, should explore with the patient.

In this research, of the 55 paired patients at the 1st appointment 18 (33%) started off from the stand point that they did not want to take pain medicines (Table 5.7). This went down to 16 (29%) for patients with NRS>=7, 15 (27%) for patients with S-LANSS>=12 and 12 (22%) with both NRS>=7 and S-LANSS>=12. Because pain medicines were so important for the management of chronic pain in this research, it was important to try and understand more about this problem.

The BPI questions 24-30 asks questions about patients’ responses to their pain medicines. The 2nd answers were from patients who were at least four months further along their treatment pathway. The only significant thing, which may have happened within the CPS for some of these patients, since they completed the BPI for the 1st time was the pharmacist intervention and their individual reaction to it. Questions 24 & 25 asked about the frequency with which patients took their pain medication (Table 5.14) and the answers demonstrated little difference between the

1st and 2nd appointments, maybe because they are outwith the pharmacist's purview. The answers to questions 26-30 were sufficiently different to warrant further analysis.

6.5.2. PATIENT INVOLVEMENT WITH THEIR PAIN MEDICINES

6.5.2.1. Did patients feel the need for a stronger type of pain medication (BPI Question 26)?

The percentage of patients who believed that they needed stronger pain medicine reduced significantly down from 57% to 37% (Figure 5.14). Patients' had often waited a long time before arriving at the CPS (Figure 5.2) and therefore it was not surprising that many patients reported, at that time, that they needed stronger pain medication. The significant reduction in the answers at their 2nd appointment was more surprising.

6.5.2.2. Did patients feel the need to take more pain medication than their doctor has prescribed (BPI question 27)?

The percentage of patients who believed that they need to take more pain medicine than was prescribed reduced significantly down from 33% to 21% (Figure 5.15). During clinic consultations some patients mentioned that they took more than the recommended dose of paracetamol. There was also some double dosing with NSAIDs, prescribed naproxen and OTC ibuprofen either deliberately or through lack

of knowledge. There appeared to be a misconception that because these were freely available OTC they were less dangerous.

6.5.2.3. Were patients concerned that they used too much pain medication (BPI question 28)?

The percentage of patients who believe that they are taking too much pain medicine reduced significantly down from 46% to 31% (Figure 5.16). In clinic, patients often demonstrated a tenuous understanding of the rationale for their pain medicine therapy. Some were also intentionally resistant to taking any in pain medicines for complex or personal reasons which have been reported previously (Chen, 1999). This resistance which was explored briefly in Section 6.5.1 and may result from a lack of understanding of the potential complications of the illness being treated or patients may conflate health warnings about different medicines. It may be because the medicines that they had tried previously had given them minimal benefit and intolerable side effects. Many patients reported that they took their medicines because they had been prescribed or they took the ones that didn't make them feel worse.

Patients' attitude to their medicines may be affected by difficulty with understanding the labelling of their medicine or incomplete briefing about a complex medicine regimen. The significance of both of these could be reduced by more concordant prescribing and a greater accent on appropriate counselling when medicines are

issued. Alternatively, the avoidance of analgesia may be perceived as exercising personal control over their pain (Pellino and Ward, 1998) and as such is probably outwith the purview of both the prescriber and the pharmacy

The excess of medicines stopped (47) over medicines started (19) as set out is Table 5.13 was an indication that some patients had heeded the pharmacist's advice during the intervention and were acting upon it. The freedom of action of the research pharmacist with regard to prescribed medicines has been addressed (Section 6.4.7) but if a patient, after consideration, is confident that one of their pain medicines is giving no benefit then this presents an ethical dilemma. The patient should be in concordance with their GP about their pain therapy and therefore it is incumbent upon the patient to agree any changes with their prescriber, otherwise their health records are incomplete.

NICE (2017) suggests that in the treatment of chronic pain the aim is to reduce a person's pain and improve their quality of life. This balance between pain and quality of life is important and not accounted for in the WHO pain ladder because many of the medicines which would then be involved can be associated with serious harm and may not contribute to improving quality of life.

Whatever the reasons for patients believing that they were taking too much pain medicine, each pharmacist-patient interaction was an opportunity to improve the patient's understanding of how to use their pain medicines to improve the quality of

their lives and reduce their concern over the use of these medicines**.** The significant change in the answers to this question may be an indication that the intervention from the pharmacist was having a positive influence upon the patients' use of medicines for their pain.

6.5.2.4. Did patients feel the need to receive further information about their pain medication (BPI question 30)?

The percentage of patients who felt that they needed further information about their pain medicines, reduced significantly from 76% to 45% (Figure 5.17). Often, in clinic patients responded to the pharmacist's explanations about how they could take their medicines differently either to improve benefits or minimise the side effects, in ways which suggested they had not considered this previously. There were two possible explanations for this. They were concepts or ideas that had not been verbalised by their prescriber/pharmacist or they had not been remembered by the patient. Either way this means that some patients may not have received the information that they want and need, to enable them to take their medicines to best advantage. Sometimes the lack of appropriate verbal communication during patient/GP/pharmacist interaction meant that patients only received the information that they needed when they asked for it. (Young *et al.*, 2018). From experience with patients in clinic it would be unwise to assume that all patients had sufficient self-confidence and background information or health literacy to understand the questions that they needed to ask, in addition to the having the intellectual capacity to cope with the information that they were given.

There were also the problems of patients believing inappropriate things about their pain medicines. Whose responsibility was it to ensure that patients understand their pain medicines, the prescriber or the pharmacist? In the absence of real information, we should not be surprised when the void in patient's knowledge was filled with half-truths and erroneous impressions.

The significant change in the answers to this question at the 2nd appointment reflects the importance that the pharmacist placed upon helping the patient to understand their pain medications. One of the roles of the pharmacist's in the CPS was to guide patients towards the optimal use of their pain medicines because the other members of the team would be concentrating on other aspects of the patients' treatment. Other members of the team hear the pharmacist's message during the PMP presentation and are therefore in a position to reinforce this message at appropriate moments.

6.5.2.5. Did patients have problems with side effects from pain medication (BPI question 29)?

The answers to this question (Figure 5.18) did not change significantly between the 1st and 2nd appointments reducing from 64% to 42%.

During this research patients demonstrated poor understanding of their pain medicines and the management of any resulting side effects. Within the Systematic

Review there were four references which mentioned the problem of side effects. Harrison (2015) reported that 35% of patients suffered side effects, Thomas (2012) recorded a much higher proportion of 75% needing advice about side effect management. Gill, Taylor and Knaggs (2013) reported that 20% of patients were referred back to their GP for management of side effects. On the other hand Coleman, Yangphaibul and Begovic (2013) reported that 16% of the actions as an IP related to the management of side effects. All of these publications reported an MUR of some sort but with no real information about what was involved or how this might have influenced the recording and reporting of side effects.

The report by Thomas (2012) recorded that 50% of the cohort needed advice about medicines safety. Safety and side effects are different concepts and there was no mention in the text of how the difference was defined. This differentiation should be explored in any further research.

These four reports suggest that in the treatment of chronic pain the side effects of the medicines can be troublesome both for the patient and the HCP who are involved in their care. Given that chronic pain is a debilitating, widespread condition that may be lifelong, those involved in the treatment of these patients need to be aware of the potential adverse effects of their actions. Additionally, it is essential to ensure that all communications are tailored to the patients' ability to understand. Carter *et al.* (2014) reported that it is critical that either the prescriber or the pharmacist ensure that the patient understands the potential side effects before a pain medicine is prescribed or

dispensed because side effects can lead to a reduction in the appropriate use of a medicine (Dibonaventura *et al.*, 2012).

The decision about whether side effects are serious is, for the patient, a subjective decision and if it is an intensely personal effect then regardless, a patient probably would not disclose the effect unless specifically asked. During any patient clinician interaction this could lead to a divergence of opinion, either overt or covert, about the level or significance of potential side effects (Cooper *et al.*, 2015). The post marketing attribution of serious side effects to a medicines can lead to the withdrawal of its Product Licence (McNaughton, Huet and Shakir, 2014) as exemplified by rofecoxib and valdecoxib. In 2019, a systematic review reported that the discontinuation of antidepressants, including tricyclics and duloxetine both of which are used in the treatment of chronic pain, was more problematic than had been thought heretofore (Davies and Read, 2019). From clinical experience with chronic pain patients the problems associated with the side effects of the medicines used in the treatment of this condition are not always treated with the seriousness that they deserve.

6.5.3. CONCLUSION

The answers to four of the five questions at the end of the BPI questionnaire changed significantly between the 1st and 2nd appointments. These improvements suggest that the input of the pharmacist before the 2nd appointment contributed to patients' better understanding of the use of their pain medicines.

6.6. Conclusion

During this research, conversations between the pharmacist and the patients have consistently explored three ideas. Firstly, the apparent ineffectiveness of many of the pain medicines prescribed for patients. Secondly, the balance that the patient needed to strike between the benefits for their pain and the problems with side effects from their pain medicines. Lastly, what caused the patients reluctance to take medicines and how can this be reduced.

Having explored these three ideas with patients at their 1st appointment and for some also at a PMP presentation this was the group of patients that returned nine significant improvements or changes in four groups.

i. Their pain medicines gave them more benefit
ii. Their analgesia lasted longer.
iii. The benefit for their use of mild/moderate opioids improved
iv. Their attitudes to the use of their pain medicines improved

When taken together these indicate that after discussion with the pharmacist patients had a better understanding of their pain medicines. They engaged with the pharmacist in the CPT in ways which guided them towards using their pain medicines to maximise the benefits and minimise the harms of their medicines *i.e.* right drug, right dose, right time.

6.7. Limitations and recommendations

6.7.1. WAITING TIME FOR PAIN CLINIC APPOINTMENT

Waiting time since the commencement of pain until they received a pain clinic appointment was for some inexplicably long. These were similar but not the same as other reports (Harrison, 2015; Black, 2017; Ingle and Vasu, 2018). Further investigations into the cause of these waiting times and therefore the additional distress caused was both urgent and important.

6.7.2. RECRUITMENT IN RELATION TO ATTENDANCE AT PMP

Eighteen of the 55 patients who returned for a 2nd appointment had attended a PMP during the intervening period. This meant that they would have experienced up to three times the length of pharmacist input time compared with the remaining 38 patients. Because of the small size of this group the only analysis which was undertaken was of the different changes in NRS and S-LANSS between patients who had attended and those who had not (Table 5.11). The NRS of those who had and attended reduced by 0.9 whilst those who had not only reduced by 0.5. The difference between the S-LANSS of the two groups was different. For those who had not attended the S-LANSS increased by 0.6 whilst for those who had the reduction was 0.8.

Attendance at a PMP course between the 1st and 2nd research appointments introduces a potential source of bias because it would potentially increase the time

available of the pharmacist's intervention. Some but not all of the additional intervention would be a duplication and therefore it would need to be controlled in any future research work into this topic.

6.7.3. COMPLETENESS OF PATIENTS' INFORMATION ABOUT THEIR MEDICATIONS

The medicines that patients actually took were recorded and reported, particularly in relation to the benefits that individual medicines gave to the patients. The patient's clinic invitation letter asked them to complete the Patient's Pain Medicine Questionnaire (Appendix 8.4.1), the BPI (Appendix 8.4.2) and the S-LANSS (Appendix 8.4.3) questionnaires and prior to their arrival at the clinic. Patients generally arrived with a completed BPI and S-LANSS questionnaire but they were not so rigorous with completing the Patient's Pain Medicine Questionnaire. Some patients arrived with the 'request' copy of their current FP10, some with a bag of medicines and some with neither. They were generally, but not always, able to be certain about their current medication. The further back the questioning went, the less certain they were of their answers. In the clinic invitation paperwork, they were asked specifically to be prepared to answer questions about their previous medicines. Therefore, this bifurcation in their preparedness was not anticipated. If this research is repeated work would be required to formulate a questionnaire, to be sent out with the invitation letter, to elicit information about the efficacy of previous medicines. It may be that any pre-clinic preparations should be a request for a print-out of the patients' prescription history. This could then form the basis of a

questionnaire to be completed by the patient. In the event of non-completion, time would need to be found to work through this during the clinic.

6.7.4. COMPLETENESS OF PATIENTS' INFORMATION ABOUT SIDE EFFECTS

The balance between side effects and the perceived benefits of pain medications is an important factor in determining optimal therapy for the treatment of chronic pain. Patients were often not able to discuss the side effects of their pain medicines with any certainty even though their invitation letter specifically asked them to prepare for that. Any extension of this research would require work to formulate a questionnaire, to be sent out with the invitation letter, to clarify what side effects previous medicines had caused. It may be that this could also be based upon the prescription history provided by the GP.

This would need to be worked through during the appointment. Some patients demonstrate a tenuous understanding of their side effects and which medicines may be causing these effects but given what has been revealed during this research this is no longer surprising.

6.7.5. COMPLETENESS OF INFORMATION ABOUT MEDICINES FOR NEUROPATHIC PAIN

One of the objectives of this research was posited on an S-LANSS scores (Section 3.2), above or below 12 the guide score for elements of neuropathic pain. One point

was omitted, which was obvious with hindsight. Medicines for neuropathic pain were demonstrably effective for some patients, therefore had existing therapy already given them some benefit and reduced their S-LANSS score from above 12 to below 12. For those patients the appointment would then be about optimisation rather than finding something which gives benefit. Any future research would have to control for this.

There was also a paucity of data relating individual medicines to specific neuropathic conditions as outlined in Section 1.6.3. Therefore, in any future research greater attention needs to be placed on records of diagnosis and the medicines assessed to date.

6.7.6. PSYCHOSOCIAL AND DEPRIVATION DIFFERENCES

The papers from both Bruhn *et al.* (2013) and Hadi *et al.* (2016) were the only two papers returned by this systematic review where societal characteristics of the patients were reported. Societally, they appeared quite different to each other and different again to this cohort. Because chronic pain is treated in a psychosocial context, societal differences need to be explored (Meints and Edwards, 2018) before a full understanding of its initiation, maintenance can promulgated. Such work would require much larger cohorts in areas with different deprivation scores and different societal groups using both qualitative and quantitative methods.

6.7.7. LOCUS OF CONTROL

It became apparent during this research that the patients who were most successful in developing personal strategies to improve their pain control were the ones who were able to understand and engage more fully with managing their medicines. Research has revealed that a high internal locus of control (ILC) was important in predicting improvements in chronic pain control with external controls being mainly negative (Keedy *et al.*, 2014; Nafradi, Nakamoto and Schulz, 2017). Patients with high ILC believe that their outcomes are as a result of their own abilities. Continuing involvement with the CPS and more particularly attendance at a PMP are premised upon the patients' willingness to engage with the concept that at least some of their pain is self-manageable *i.e.* do not have a low locus of control score. Therefore, in any further research it would be important to incorporate some 'locus of control' score such as a Duttweiler (1984) Internal Control Index (ICI).

6.7.8. SHORTFALL IN THE NUMBER OF RETURNERS INTRODUCING THE POSSIBILITY OF BIAS

Of the 100 patients who were enrolled in this study only 55 returned for a second appointment. The small number of returners in this research limited the analysis which could be undertaken, particularly regarding the efficacy of individual medicines.

The introduction of the new Trust computer system made it difficult for the administration staff to book patients and arrange recall appointments for all of the members of the Chronic Pain Team, not just the pharmacist. It also limited the

availability of comparative epidemiological information between the research cohort and the total service.

Lists were generated regularly by the pharmacist to assist the administration staff with the names of those patients who specifically needed to be recalled for this research.

The original power calculation for this research was based upon 80 returners (Hodson, 2017). The difficulty of persuading patients to attend for a second appointment has been mentioned elsewhere (Dougall, Harrison and Lowrie, 2015). The research appointments were stopped four months after 100th patient had been recruited because of the time constraints of the DPharm. timetable. Unfortunately, by that time only 55 patients had been seen for a second time. The reasons for the cessation of recruitment in this research were specific to this project. During any further research, adherence to a Gantt chart would minimise the likelihood of a recurrence of such problems. The loss of so many patients to follow up was one of the two most significant potential source of bias in this research.

The new Trust computer is now well embedded making data about patient bookings more available to interrogation. The patient' pathway of care through the CPS and the length of time that their involvement lasts is individual to them, their pain and their circumstances and patients could be retained within the CPS if the patient was waiting for a research appointment. The full cohort could have been recruited but for the external time constraints.

6.7.9. QUALITATIVE DATA

Pain is a subjective experience that varies on an ongoing basis. Analgesia can be very effective and the use of pain medicine should be closely related, in the patient's mind, to the pain they experience and yet patients often demonstrated not only a lack of understanding on how to use their pain medicines or manage their side effects but also a reluctance to take their pain medicines at all. There are no quantitative measures available which would improve our understanding of this human paradox. But this personal aspect of a patient's involvement with their pain medicines could be explored using qualitative methods. Such research would facilitate the exploration of how patients' pain and their attitude to their pain medicines interrelates with their suffering and their personal circumstances. It would also improve our overall understanding of how the actions of pharmacist interrelate with this situation. Qualitative research into pain is mainly undertaken with chronic pain patients (Osborn and Rodham, 2010) and suggests that patients completion of quantitative pain scales includes experiences and sensations as well as the pain intensity (Robinson-Papp *et al.*, 2015). One report stressed the need to understand the context of a patients pain, which might facilitate our understanding of how patients use qualitative scales (Morse, 2015). From clinical experience with patients during this research for some patients the context of their pain is very important.

Consideration was given at the outset of this research as to whether to include both quantitative and qualitative data. It was decided that this was not an option within the time available.

6.7.10. RECOMMENDATIONS FOR FUTURE WORK

This research has revealed a dearth of new information about how medicines may best be used in the treatment of chronic pain and by extension what should be the role of the pharmacist. It has also revealed during, clinic consultations, how little understanding some patients have about managing their pain control and the misinformation which abounds about many of the individual pain medicines. Chronic pain is so widespread that almost any practising pharmacist is likely to encounter patients who are affected. If opportunities to improve the lives of these patients are not to be missed, consideration needs to be given to what pharmacists are taught about chronic pain and its treatment both at undergraduate level and what is expected of preregistration students. Gill, Taylor and Knaggs (2012) points out the historically pharmacy students have spent eight hours leaning about pain. Comparable figures for doctors are 13 hours, physiotherapists 37 hours and vets 27 hours. The current advice for acute and rehabilitative pain is that regular analgesia is most effective and should be stepped down whilst healing is taking place is correct. In chronic or persistent pain this advice needs to be more nuanced recognising that in chronic pain a pain free state is generally not achievable. Over the lengths of time that patient suffer with chronic pain, the long-term harms of pain medicines are more likely to become overt and the realistic goal for analgesia has to become how to use pain medicines to facilitate those things in life which are necessary but painful. Pharmacists' who are involved in the supply of medicines for patients with pain need be able to differentiate between these two conditions and offer advice appropriately.

The pharmacist works as part of the CPT and any benefit which accrues with regard to better pain control may need to be seen as part of a team effort. The Medicines Research Council (MRC) have developed and updated guidelines as to how the utility of a single intervention within a multi-component package of care can be investigated (Campbell *et al.*, 2000; MRC, 2019).

It would be important to control more rigorously for the second appointment being before or after attending the PMP. There was a difference in both the NRS and S-LANSS scores demonstrated by patients who had or had not attended a PMP.

Further work should be clearer about pain diagnosis, pain medicines used in its treatment. The most difficult results to understand were those that related to the use of medicines for neuropathic pain. Historical changes in S-LANSS scores resulting from medicines already being taken needs to be determined and recorded, as does the diagnosis in relation to the medicines assessed.

It would also be important to control for pain duration. The results in Figure 5.2 and Table 6.1 suggests that there needs to be greater clarity over the questions asked about the commencement and duration of their pain.

The success of some patients in this cohort had with improving their pain may have been based upon greater understanding of how to use their pain medicines to best

effect. Therefore, it would be important to try and tease out changes in patients' understanding to a much greater extent.

Of the answers to BPI questions 26 to 30 only Question 29 about side effects returned a non-significant result. Patients' answer to this question are tied in with their relationship with their pain medicines and understanding this are key element for further work. To achieve this, the research must include a qualitative examination of the patents pain and their medicines.

One final point, in his report Thomas (2012) differentiates between safety advice and side effect management. The difference between the researchers understanding of safety and side effects should be clearly laid out in the MUR.

CHAPTER 7 CONCLUSION

In conclusion this research set out to determine whether a consultation with the pharmacist within the multidisciplinary CPT in South Staffordshire and any resulting medicines advice and education changed patient use of their pain medication. If so did this improve the use of their pain medicines, pain scores or medicine side effects.

There were some significant changes in pain scores between the 1st and 2nd clinic appointment. These were limited to four finding: the BPI-PSS 'worst' pain score went down, the relief which patients recorded after taking their pain medicines improved, fewer patients regarded their pain medicines as ineffective and the benefits which were recorded lasted longer.

Chronic pain is complex and it is difficult to be certain that any particular intervention will be effective, but the pharmacist's intervention in terms of education, specifically regarding timing and optimising of doses is likely to have an important impact. In this research the following four significant changes in patients attitudes to their medicines were recorded: fewer felt that they needed stronger pain medicines, fewer felt that they needed to take more pain medicines than had been prescribed by their GP, fewer thought that they were taking too much pain medicine and fewer felt they needed more information about their pain medicines.

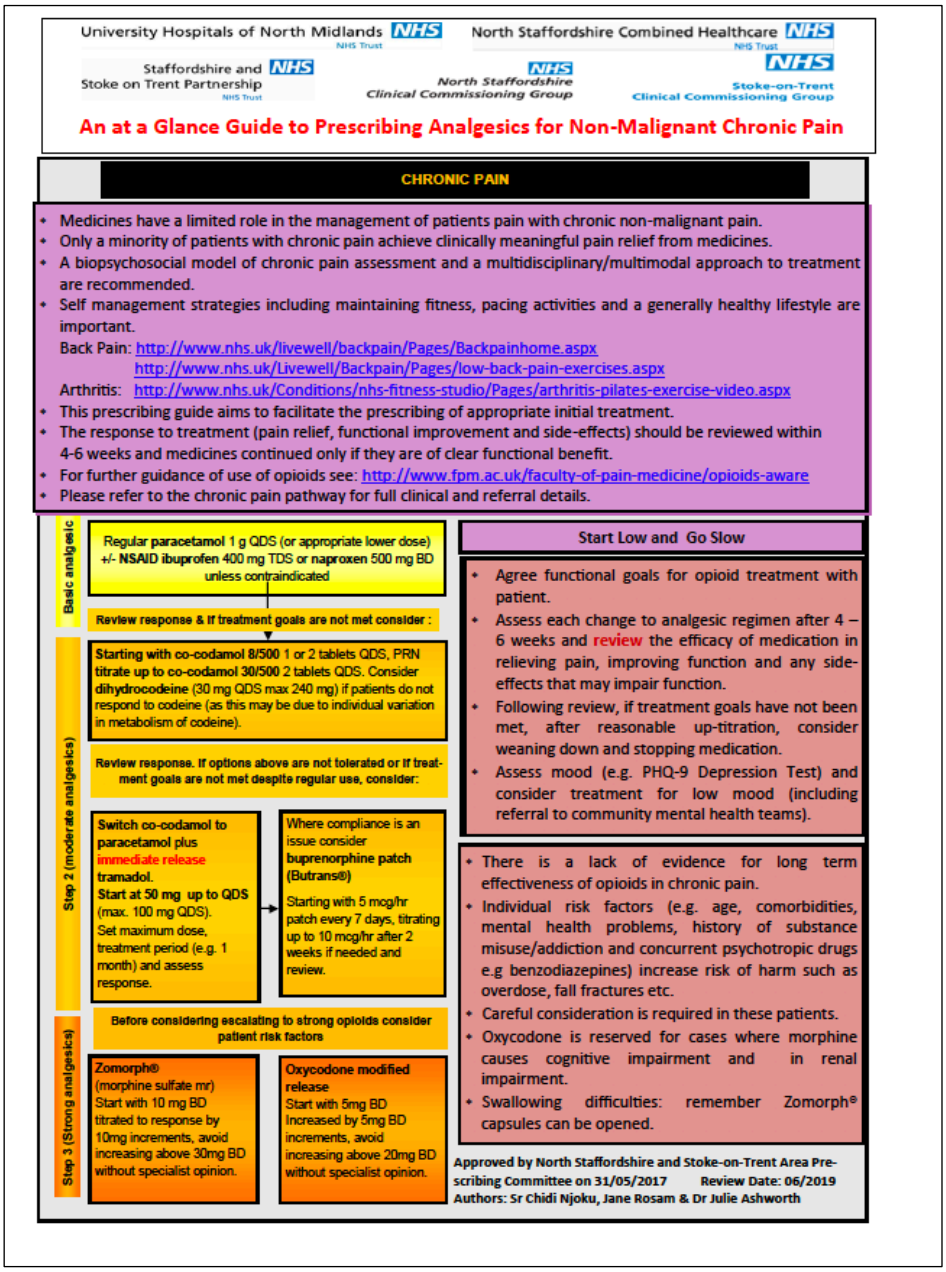
One accepted premise for the treatment of acute pain is that 'pain is easier to keep away than make go away'. This leads to pressure for regular analgesia at predetermined times with the aim of achieving a, largely, pain free state. Chronic pain often cannot be treated in this way, that fact the patients are attending the CPS, with the pain scores they reported, demonstrated that this strategy had been unsuccessful for them.

The interventions undertaken by the pharmacist with patients during this research were twofold. Guiding them, to take more control of their pain medicine therapies and to use them in ways which maximised their benefits and minimised their harms. In addition to accept that their pain will flare and therefore to keep some pain medicine in reserve for when this happened.

The results of this research confirm that by encouraging patients to adopt such an approach, the pharmacist made a demonstrable contribution to the improvement of patients' pain within the context of the chronic pain service.

CHAPTER 8 APPENDICES

8.1. Stoke guidance for the treatment of chronic non-cancer pain



University Hospitals of North Midlands NHS Trust | North Staffordshire Combined Healthcare NHS Trust | Staffordshire and Stoke on Trent Partnership NHS Trust | North Staffordshire Clinical Commissioning Group | Stoke-on-Trent Clinical Commissioning Group

An at a Glance Guide to Prescribing Analgesics for Non-Malignant Chronic Pain

CHRONIC PAIN

- Medicines have a limited role in the management of patients pain with chronic non-malignant pain.
- Only a minority of patients with chronic pain achieve clinically meaningful pain relief from medicines.
- A biopsychosocial model of chronic pain assessment and a multidisciplinary/multimodal approach to treatment are recommended.
- Self management strategies including maintaining fitness, pacing activities and a generally healthy lifestyle are important.
  Back Pain: http://www.nhs.uk/livewell/backpain/Pages/Backpainhome.aspx
  http://www.nhs.uk/Livewell/Backpain/Pages/low-back-pain-exercises.aspx
  Arthritis: http://www.nhs.uk/Conditions/nhs-fitness-studio/Pages/arthritis-pilates-exercise-video.aspx
- This prescribing guide aims to facilitate the prescribing of appropriate initial treatment.
- The response to treatment (pain relief, functional improvement and side-effects) should be reviewed within 4-6 weeks and medicines continued only if they are of clear functional benefit.
- For further guidance of use of opioids see: http://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware
- Please refer to the chronic pain pathway for full clinical and referral details.

Basic analgesic

Regular **paracetamol** 1 g QDS (or appropriate lower dose) +/- **NSAID ibuprofen** 400 mg TDS or **naproxen** 500 mg BD unless contraindicated

Review response & if treatment goals are not met consider :

Step 2 (moderate analgesics)

Starting with co-codamol 8/500 1 or 2 tablets QDS, PRN **titrate up to co-codamol 30/500** 2 tablets QDS. Consider **dihydrocodeine** (30 mg QDS max 240 mg) if patients do not respond to codeine (as this may be due to individual variation in metabolism of codeine).

Review response. If options above are not tolerated or if treatment goals are not met despite regular use, consider:

Switch co-codamol to paracetamol plus immediate release tramadol. **Start at 50 mg up to QDS** (max. 100 mg QDS). Set maximum dose, treatment period (e.g. 1 month) and assess response.

Where compliance is an issue consider **buprenorphine patch (Butrans®)**

Starting with 5 mcg/hr patch every 7 days, titrating up to 10 mcg/hr after 2 weeks if needed and review.

Step 3 (Strong analgesics)

Before considering escalating to strong opioids consider patient risk factors

Zomorph® (morphine sulfate mr) Start with 10 mg BD titrated to response by 10mg increments, avoid increasing above 30mg BD without specialist opinion.

Oxycodone modified release Start with 5mg BD Increased by 5mg BD increments, avoid increasing above 20mg BD without specialist opinion.

Start Low and Go Slow

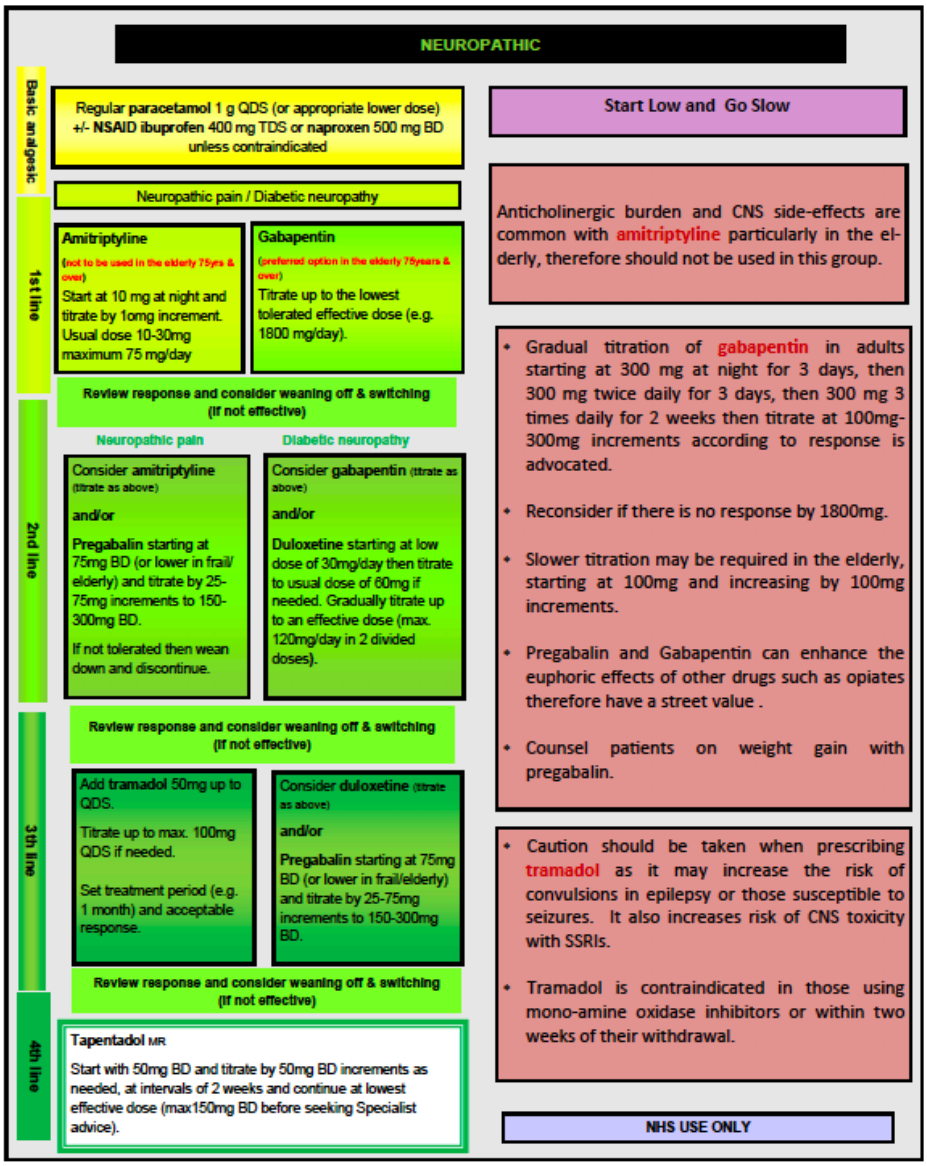
- Agree functional goals for opioid treatment with patient.
- Assess each change to analgesic regimen after 4 – 6 weeks and **review** the efficacy of medication in relieving pain, improving function and any side-effects that may impair function.
- Following review, if treatment goals have not been met, after reasonable up-titration, consider weaning down and stopping medication.
- Assess mood (e.g. PHQ-9 Depression Test) and consider treatment for low mood (including referral to community mental health teams).

- There is a lack of evidence for long term effectiveness of opioids in chronic pain.
- Individual risk factors (e.g. age, comorbidities, mental health problems, history of substance misuse/addiction and concurrent psychotropic drugs e.g benzodiazepines) increase risk of harm such as overdose, fall fractures etc.
- Careful consideration is required in these patients.
- Oxycodone is reserved for cases where morphine causes cognitive impairment and in renal impairment.
- Swallowing difficulties: remember Zomorph® capsules can be opened.

Approved by North Staffordshire and Stoke-on-Trent Area Prescribing Committee on 31/05/2017 Review Date: 06/2019
Authors: Sr Chidi Njoku, Jane Rosam & Dr Julie Ashworth

University Hospitals of North Midlands NHS Trust | North Staffordshire Combined Healthcare NHS Trust | Staffordshire and Stoke on Trent Partnership NHS Trust | NHS North Staffordshire Clinical Commissioning Group | NHS Stoke-on-Trent Clinical Commissioning Group

An at a Glance Guide to Prescribing Analgesics for Non-Malignant Chronic Pain



8.2. Glossary

1 1st pass metabolism – see First Pass

2 5-HT (serotonin, 5-hydroxytriptamine) – a monoamine neurotransmitter, which is involved in both excitatory and inhibitory neurotransmissions. Medicines which alter the availability of this neurotransmitter at its receptor site, can sometimes be effective in the treatment of chronic pain.

3 Acupuncture – This is a type of 'alternative medicine' promulgated for the treatment of many conditions. It involves the insertion of fine needles into the body. In the treatment of chronic pain, the location of the insertion is related to the site of the pain being treated. Reviews of its efficacy are inconsistent. Cochrane suggests that it may be of benefit in chemotherapy induced and post-surgery nausea and vomiting.

4 Addiction – NHS Choices define addiction as – 'not having control over doing, taking or using something to the point where it could be harmful to you'

5 Biomedical model for the treatment of chronic pain. In this treatment model the accent is upon things being done to the patient by other such as injections, surgery and analgesia

6 Biopsychosocial model for the treatment of chronic pain. In this treatment model for the treatment of chronic pain the accent is upon self-management. The patient is equipped with skills, which will hopefully enable them to better manage their own condition. Research has suggested that based on weak/moderate evidence this method gives patients with chronic pain the most likely chance of functional improvement (Cheatle, 2016; Kamper *et al.*, 2015).

7 Bio-transformation – The process by which one organic molecule is transformed, within the body, into another, such as the conversion of an inactive 'Pro-drug' into its active moiety.

8 BPI – Brief pain inventory. This is a questionnaire, which can be self-administered, that was originally compiled to assess the severity of cancer pain. Subsequently, its use has expanded to be a regular tool used in the assessment of many forms of pain as well as in pain research. It asks questions about the pain itself and its effects upon the patient. It also asks about the way medicines are used to treat the pain (Poquet and Lin, 2016). It includes two well used indices for (chronic) pain – Pain Severity Score (PSS) and Pain Interference Score (PIS).

9 BPS – British Pain Society. This organisation defines itself as "An alliance of professionals advancing the understanding and management of pain for the benefit of patients."

10 CBT – Cognitive Behavioural Therapy. This is a psychosocial (*q.v.*) intervention, widely used in the treatment of mental disorders. Guided by research, CBT focuses on developing personal coping strategies that target solving current problems and changing unhelpful thoughts, beliefs, attitudes, behaviours and emotions.

11 CCG - Clinical Commissioning Group. These are the NHS organisations that have been established to organise the delivery of care.

12 Central sensitisation – A medical shorthand for the concept that repetitive nerve impulses from the periphery, in some way, change the way that the brain processes this information. Given the way that the brain demonstrated plasticity in response to learning or memory this is not surprising. Implicit within this concept is the suggestions that as a result of this change there is more pain with less provocation and that this process may be at the root of many painful conditions where there is no identifiable pathology. But as yet there is no certainty over whether the observed brain changes are the cause or effect of any variation in perceived pain levels.

13 Chronic pain – The simplest definition for this is pain that last longer than three or six months. More practically, for the patient, it can be defined as pain lasting longer than would be expected or persisting after healing has taken place. However, its definition also needs to be understood in relation to

- The symptoms of neuropathic pain that are not associated with apparent neuronal damage
- Central sensitisation *q.v.*
- The changes in the brain's focus of neural activity during the transition from acute to chronic pain from the pain centre to those associated with emotion and reward.
- The role of glia in the initiation and maintenance of chronic pain
- The modulation of afferent pain impulses by efferent nerve pathways.

As a result, it is likely that any chronic nociceptive pain will eventually contain elements of neuropathic pain.

14 Cochrane – is the term used as a shorthand for the Cochrane Organisation or a Cochrane Review. This is a worldwide independent, non-profit, non-governmental organisation formed to organise medical research information in a systematic way, which facilitates medical interventions based upon evidence-based practice.

15 COX-1 – Cyclooxygenase 1 enzyme system – also known as prostaglandin-endoperoxide synthase (PTGS). This system is responsible for the conversion of arachidonic acid to prostanoids – prostaglandins, prostacyclins and thromboxanes.

16 COX-2 - Cyclooxygenase 2 enzyme system – also known as prostaglandin-endoperoxide synthase (PTGS). This system is responsible for the conversion of arachidonic acid to prostanoids – prostaglandins, prostacyclins and thromboxanes.

COX1 and COX2 are isoenzyme systems with an isoleucine residue in COX1 substituted with valine in COX2. This minor change removes the steric hindrance to a hydrophobic side pocket thereby facilitating binding to different receptor sites. The COX2 system is generally induced as part of the body's inflammatory response. They are associated with much less gastric irritation, the risk of renal complications remains the same and there are indications of increased risk of heart attacks and strokes.

17 CPGS – Chronic Pain Grade Scale. This is a multidimensional measure, which assesses chronic pain severity in two ways: pain intensity and pain-related disability. It can be used in all chronic pain conditions, including low back pain

18 CPS - Chronic Pain Service. The service set up in South Staffordshire to offer treatment advice to local GPs. It was not set up to manage these patients over the long term.

19 CPT – Chronic Pain Team. The staff who work in the CPS

20 CRPS - Chronic Regional Pain Syndrome. This is a long-term painful condition that often worsens with time. It is characterized by severe pain, out of proportion to the original injury and is often accompanied by sensitivity, swelling, and changes to the skin.

21 CYP – see Cytochrome P450

22 Cytochrome P450 – CYP450 – or CYP. These are 'heme' containing enzymes generally responsible for the insertion of oxygen into an aliphatic moiety in an organic substrate. There are more than 50 enzymes in this group. 90% of drug metabolism involves six members of the group, with the most significant being CYP3A4 and CYP2D6 (Lynch and Price, 2007).

23 Delphi study – a research program involving a group of experts who, having agreed on the ground rules then discuss a problem using a series of 'round robin' questionnaires until a consensus emerges.

24 Dependence – This is specific physical condition where the body has adopted to the presence of a medicine. Sudden cessation of therapy with this medicine will result in predictable, measurable symptoms, known as withdrawal.

25 Deprivation Indices – the use of a series of outcomes measures to concatenate the levels of relative deprivation in small areas in England into an overall whole. The

Index of Multiple Deprivation is the most widely used of these indices. Most of the data used for these statistics are from 2012 to 2013. The information ranks seven domains of deprivation; income, employment, education, health, crime, barriers to housing and living environment. It is used as a measure to compare a small area with another small area in another part of the country.

26 DNA – Did not attend. The term used to describe patients who do not attend their clinic appointment without making contact prior to the date and time.

27 EMDR – Eye movement desensitising and reprocessing. A psychological technique which can be used in appropriate and suitable patients to mitigate some of the worst aspects chronic pain

28 Enhanced medicines review – this is medicines review or MUR *q.v.* into which additional criteria have been added, often requiring specific training.

29 Facilitated transport. The name of one of the means by which molecules are transferred across a cell membrane from outside to inside a cell or vice versa. It is facilitated to differentiate from active transport.

30 Fear-avoidance behaviour. This is the term used to describe a situation often observed in patients suffering with chronic pain. Patients develop pain and then go on to avoid doing things, which they believe will make their pain worse. Unfortunately, this creates a vicious circle where inactivity leads to loss of muscle power, which in turn makes movement more difficult and therefore more painful.

31 First Pass metabolism. This is the term used to define the effect that the intestinal wall and the liver have upon the blood levels of medicines that are absorbed from the intestine and then transported via the Portal Vein through the liver before entering the general circulation. Depending upon the extent of this process the amount of medicine entering the general circulation from an oral dose of medicine can be significantly reduced.

32 Genetic polymorphism – The term used in biology to describe different phenotypes in one population. In this text this is used as a shorthand for the genetic variations between individuals, which result in differing frequency of expression of individual CYP450 enzymes *q.v.* acting at differing levels of efficacy.

33 Glial cells or glia or neuroglia. These are non-neuronal cells that maintain homeostasis, provide support and form myelin in central and peripheral nervous systems. Peripherally they include Schwann cells and centrally astrocytes and microglia. Historically, four functions were associated with glial cells, they support neurones, supply nutrition and oxygen, insulate one neurone from another and remove bacteria and dead neurones.

34 HADs scale – Hospital anxiety and depression score. A scale of 14 questions which aims to avoid measuring somatic symptoms. The aim was to detect and measure anxiety and depression in patients with physical health problems

35 HCP – health care professional. This often has specific connotations but in this document. it refers to individuals who interrelate with patients in some way ether with regard to the treatment of their pain or more particularly about their pain medicines

36 Independent (pharmacist) prescriber (IP) may prescribe autonomously for any condition within their clinical competence.

37 IASP – International Association for the Study of Pain. An international learned society, which brings together researchers, clinicians and caregivers to stimulate and support research into pain and its treatment.

38 I/R – immediate release medicines. Formulations where the release has not been modified to achieve a more prolonged action. See also S/R

39 Kinesiophobia – fear of movement, which may increase during chronic pain, particularly whist waiting for treatment.

40 KTT – Key Therapeutic Topic, occasional statements from NICE suggesting therapeutic treatment options in areas where it is believed that advice would be appropriate.

41 LESS PAIN question format – This approach to questioning was designed to facilitate well informed semi-structured discussions between community pharmacists and service users with pain related problems.

42 Levels of expressed need – a five-point scale defining levels of need in relation to four help seeking behaviour questions *i.e.* pain treatment sought recently or often and painkillers sought recently or often.

43 Median and Interquartile range (MIQ) - an alternative statistical approach for assessing the significance of changes in a 'skewed' data set.

44 Medicines compliance – is the extent to which a patient correctly follows the direction of a doctor issued as expressed on a prescription.

45 Medicines concordance – involves a doctor and a patient making a decision together about a medicine treatment.

46 Medicines review – a consultation between a pharmacist and a patient during which all of the medicines taken or used by a patient are reviewed by a pharmacist with the aim of maximising benefit, minimising harm and avoiding waste.

47 Mild/moderate opioids – A convenient shorthand for the group of analgesics comprising Codeine, Dihydrocodeine and Tramadol.

48 MRC – Medicines Research Council is responsible for the co-ordinating and funding medical research in the UK.

49 MSK – Musculoskeletal clinic. A clinic generally operated within a physiotherapy department, which aims to treat musculoskeletal conditions using physical therapies.

50 MUR – Medicines utilisation review. This is a structured process during which a pharmacist or other health care worker undertakes a review with a patient of the use, efficacy, side effects and compliance of their medicines. This applies in particular to those patients who are taking/using medicines for long-term conditions. This may be 'enhanced' to include additional questions as part of a specific therapeutic or research protocol for which training would be given.

51 Neuropathic pain – one of two types of pain. It is generally associated with two causes

i. A lesion or a disease affecting the somatosensory system *q.v.* and this may be central or peripheral in origin.

ii. Damage to nerve fibres resulting from a physical cause, which then transmit incorrect signals to other pain centres.

It is often described as shooting. This may be constant or episodic. In addition, it may result in inappropriate responses to non-painful stimuli (allodynia). Other symptoms include burning, coldness, 'pins and needles', numbness and itching.

52 NICE – National Institute of Health and Care Excellence. Originally set up as Special Health Authority, the National Institute for Clinical Excellence to reduce variations in the availability of health care across the nation. After merger with the Health Development Agency it became the National Institute for Health and Care Excellence, developing guidance to prevent ill health and promote healthier lifestyles. It offers guidance on all aspects of health care aiming to maximise evidence-based practice.

53 NMDA receptor – N-methyl-D-aspartate receptor. This is a glutamate receptor for an ion channel. Activation allows positively charged ions to flow into the cell. It is important for controlling synaptic plasticity and memory.

54 NNH – Number needed to harm – an epidemiological term. This is the converse of the NNT *q.v.* It is the number of people who need to be treated in a specific way in

order that one will experience an adverse event. In the case of pain how many patients need to be given an analgesic for one patient to experience an untoward event. This is more difficult to calculate than NNT because side effects are less likely to have measurable outcomes i.e. how much constipation is constipation? As with all of science it is more difficult to prove that an event doesn't happen.

55 NNT – Number needed to treat – an epidemiological term. This is the number of people who needed to be treated in a specific way in order that one will receive the anticipated benefit. In the case of pain how many patients need to be given an analgesic for one patient to experience analgesia. This is usually calculated from a measurable outcome such as a 50% reduction in pain.

56 Nociceptive pain – one of two types of pain. It is associated with actual tissue damage and is described as sharp, aching or throbbing.

57 NRS – Numeric Rating Scale. An 11-point pain scale used to assess the level of an adult patient's pain on a scale from 0 to 10 where 0 is no pain and 10 is the worst pain imaginable. With 11 points it does have a mid-point.

58 NSAID(s) – Non-steroidal anti-inflammatory drugs. These are medicines that inhibit the actions of the COX1 and COX2 enzyme systems. The resulting diminution of prostanoid formation reduces the bodies inflammatory response and often therefore pain.

59 OIH – Opioid induced hyperalgesia. A clinical situation where opioid receptors are sensitised to opioids and paradoxically patients feel more pain. The practical result of this is that patients increase the dose of their opioid in an effort to control their pain. This is similar to, but not the same as opioid tolerance.

60 OT - Opioid tolerance – a clinical situation where the efficacy of opioid analgesics fades with repeated doses. Because the patient's response to their opioid dose is not as good as it had been in the past an increase in opioid dose is requested.

61 OTC – Over the counter. A shorthand for those medicines, which patients can buy over the counter from a pharmacist or a pharmacy.

62 PainDETECT questionnaire. This is defined as an easy to use, patient-based questionnaire used to determine the prevalence of lower back pain with neuropathic elements. The answers to the questions score between 0 and 38: 0<12 neuropathic pain unlikely, 13<18 neuropathic pain may be present and 19<38 neuropathic pain is likely.

63 PIS - Pain Interference Score, see BPI.

64 Plastic changes – in biology this is the term used to express the ability of a living organism to change in response to its environment. In this thesis the term is used more specifically to describe changes in the CNS as a result of stimulation from elsewhere within the body. These changes may be normal as in growth and development or the learning of a new skill. Alternatively, they may be abnormal as demonstrated by changes in the CNS in response to continuous painful stimuli.

65 PMP – Pain Management Program. A course where patients who have been referred to the Chronic Pain Service are presented with information about and taught how they might better self-manage their pain rather than waiting for a solution to be given to them by others.

66 Polymorphism – see Genetic Polymorphism.

67 Psychosocial intervention – this looks at individuals in the context of their psychological state and their social environment to determine what effect these are having their physical and mental wellness and their ability to function.

68 PSS - Pain Severity Score, see BPI

69 QALY – Quality-adjusted life year. A measure of the state of health of a person. One QALY is one year of life in perfect health. The measure is used as part of the economic assessment of health planning

70 RCT – randomised controlled trial. A research method which randomly allocates patients to one of two or more groups. This could be active treatment and placebo treatment or it could include a comparator group as well where patients receive a known and tested method of treatment or 'treatment as usual' *q.v.* This may or may not include 'blinding' where the patient and researcher have no knowledge of which group a patient is in until the trial is completed.

71 RPharmS – Royal Pharmaceutical Society

72 Sensitisation – In the context of chronic pain this is a shorthand expression for a patients' pain that is worse than expected from the severity of the lesion or worsened by actions, which would not normally be expected to produce such a response. It has no correlation with the time course of the condition or its severity (Woolf, 2011). See also wind-up.

73 SIGN – Scottish Intercollegiate Guidelines Network. This is a public body set up in Scotland in 1993 to improve healthcare by developing and disseminating evidence based, clinical practice guidelines.

74 S-LANSS an acronym for Short Form – Leeds Assessment of neuropathic symptoms and signs.

75 SNRI – Selective noradrenaline reuptake inhibitors. A group of anti-depressants that have found favour as replacements for TCAs. Their side effect profile is different to TCAs but recently they have been identified as possibly causing occasional, significant and unusual idiopathic effects, which has called into question the perception of their overall safety.

76 Somatic – Relating to the body

77 Somatosensory system – This is an all-encompassing term used to describe the interrelationship between sensory neurones, nerve fibres, their interrelationship with the body.

78 SPSS - Statistical Package for Social Science. A computer program which allows individuals to undertake statistical analysis on their data using the full range of statistical tests.

79 S/R – sustained action medicines. Where the formulation has been modified to prolong the action within the body. This is often done to minimise side effects from a dosage spike or to produce a smooth release curve where ongoing action is required. They are also of benefit where there are problems with patient compliance. See also I/R

80 SSOTP - Staffordshire and Stoke on Trent Partnership Trust, now incorporated in Midlands Partnership Foundation Trust.

81 SSRI – Selective serotonin reuptake inhibitor. A group of anti-depressants that have found favour as replacements for TCAs. Their side effect profile is different to TCAs but recently they have been identified as possibly causing occasional, significant and unusual idiopathic effects, which has called into question the perception of their overall safety.

82 STarT (Subgroups for Targeted Treatment) back Screening Tool is a brief screening questionnaire designed for directing initial treatment for low back pain (LBP) in primary care

83 Strong opioids – A convenient shorthand for the group of analgesics used in the treatment of acute, surgical and terminal pain and whose use in chronic pain is undergoing examination outwith the scope of this research. In the UK this group generally comprises Morphine, Oxycodone, Fentanyl and Buprenorphine.

84 TAU – treatment as usual. In the context of research, this would be a control group for whom nothing changes.

85 TCA – Tricyclic antidepressant (tricyclics). Anti-depressant whose chemical structure in based upon three rings. Newer compounds such as SSRIs and SNRIs have to some extent, overshadowed the use of tricyclic anti-depressants. However,

more recent analysis suggests that one group of side effects may have substituted with another and therefore their possible harms undersold.

86 TENS - Transcutaneous electric nerve stimulation. A treatment for chronic pain, which uses mild electric currents. Conductive pads are attached to the skin, in the area of the pain and a pulsed current is applied. This can either be at a high frequency with a current below that necessary for muscular contraction or at a lower frequency with a current sufficient to produce muscular contraction. Evidence of efficacy is moderate at best.

87 Tolerance – This is the word used to express the decreasing response to a medicine, which results from repeated use. In relation to opioids this would manifest itself as decreasing analgesia. All of the actions of opioids, both therapeutic and side effects demonstrate the development of tolerance over time. These tolerances develop at different rates and may in some therapeutic situations be advantageous for example, tolerance to the opioid induced respiratory depression for patients taking large doses of opioids for palliative care.

88 Van Korff Grading for the severity of pain. This pain grading scale, involving both 'pain intensity' and 'pain disability' using seven questions with answers on in a range 0 – 10 to rapidly calculate the severity of a pain (Von Korff *et al.*, 1992). Some of these measures also feature in the BPI *q.v.*

89 VAS – Visual Analogue Scale. A pain scale used to assess the level of an adult patient's pain. The patient is asked to indicate the position on a 10cm line, which represents their level of pain where 0cm is no pain and 10cm is the worst pain imaginable. The position, which the patient chooses is then transcribed by the observer as a number from 0 to 100. The suggestion being that this gives a more precise outcome that the NRS

90 Venn diagram – a diagrammatic representation of how two or more groups of data interact with each other.

91 WHO – World Health Organisation.

92 WHO Pain ladder – this is a schema originally published in 1986, (WHO, 1996) for the treatment of cancer pain. It suggested that with the appropriate use of a small number of medicines the majority of patients would experience significantly less pain. The actual estimated percentages of the number of patients who would benefit by following this therapeutic regimen have reduced over the intervening years.

93 Wind up - is the increase in pain intensity over time resulting from a repeated stimulus. See also sensitisation.

8.3. Patient Forms

8.3.1. PATIENT INFORMATION SHEET

UNIVERSITY OF BIRMINGHAM

Staffordshire and Stoke on Trent Partnership NHS Trust

Participant Information Sheet

Does a Pharmacist intervention improve analgesic prescribing and pain control?

Peter Farley (Pharmacist)
Research Project for
Doctor of Pharmacy degree

About the Researcher

I am studying for a Doctor of Pharmacy Degree at the University of Birmingham. As a pharmacist I have an interest in how well medicines work. I also have an interest in pain, hence my job with the Chronic Pain Team. I am undertaking this research to enhance our knowledge base and influence current practice.

There is very little research about how effective medicines are in the treatment of chronic pain. Therefore I have chosen to investigate the *Pharmacists' intervention in analgesic prescribing and pain control* as the topic of my research.

(RG 14-049 –Version for submission 3 – 28.02.2016)

About the Research

A member of the Chronic Pain Team is referring you to see me because they think that it would be helpful for you to talk to me about your medicines. This may enable me to make suggestions about how medicines might improve your pain control. They will have told you that every patient who comes to see me is being offered the opportunity to take part in my research project and given you this *Participant Information Sheet* to read.

When you come for your clinic appointment with me, having read this sheet I will ask you whether you are willing to take part in this research. If you agree, the only extra time involved will be a discussion with me, to clarify any questions that you may have, prior to signing the *Consent Form*. This will confirm that you have agreed to participate in the research.

Your appointment will then continue in exactly the same way, as if you were not taking part in the research. The only difference is that some of information that you give me about your condition may be recorded and retained separately for the research project. Once this is completed all of this separate information will be destroyed. However the University of Birmingham will keep a record of my research project.

At the end of the clinic session we will agree whether you need to come for another appointment. This will depend upon how well your pain is responding to the medicines prescribed by your doctor. In addition I will write to your GP and send you a copy, making any suggestions for improvements to you pain medication. If you collect you medicines from a regular pharmacy, I may contact them.

This research work has been sponsored by

1. University of Birmingham
2. The NHS through a National Research Ethics Service Review.
3. The Trust Research and Development Committee

You need to be aware that

- All patients who have an appointment with the pharmacist are being invited to take part in this research
- It is up to you to decide whether or not to take part. If you decide to take part you are still free to withdraw at any time without giving a reason and without any change to your on-going care.
- This research analyses the information, which is routinely collects as part of your consultation with the pharmacist
- If you agree to participate in this research you will be given a *Patient Identification Number,* which will be used instead of your name to identify the research information, which relates to you. The list of names and numbers will be kept separate from all other records.
- GPs who refer patients to the Chronic Pain Service will be contacted as part of the research process.
- All of the information about you will be stored securely within the Trust systems, either with your Pain Clinic notes or on a Tract secured laptop.
- Nothing that would identify you will leave the Trust.
- The results from this research will form part of my submission for a Doctor of Pharmacy Degree. They may also be published in a journal article or presented at a meeting.
- This research will be registered on a national data-base of all research projects

- The information that is used for this purpose will have your name removed so that you cannot be identified.
- If you are taking part in any other medical research, which involves taking medicines, these may interfere with this research. Therefore please will you tell me about this?

Contact details and further information.

Mr Peter Farley, Post Graduate Student, c/o Dr Christine Hirsch, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham. B15 2TT - PJF128@ bham.ac.uk

Supervisor: Dr Christine Hirsch - c.a.hirsch@bham.ac.uk

Patient Advisory and Liaison Service (PALS) – in case you would like to discuss this research project with a third party at any time. customerservice@ssotp.nhs.uk

Telephone 0800 783 2865

Address - Staffordshire and Stoke on Trent Partnership Trust

First Floor, The Medway, Newcastle Under Lyme. ST5 1QG

Results of this research project will be published at http://www.birmingham.ac.uk/staff/profiles/cem/PT/Hirsch-Christine.aspx .

Questions, that you have, to discuss when we meet?

Thank you for reading this, I hope to be speaking to you soon.

8.3.2. PATIENT CONSENT FORM – AS AMENDED

UNIVERSITY OF BIRMINGHAM

Staffordshire and Stoke on Trent Partnership NHS Trust

Informed Consent Form – patient number……..

Title of Study: Does a pharmacist intervention improve analgesic prescribing and pain control?

Name of Investigator: Peter Farley

	Please initial in the boxes below
1. I confirm that I have read and understood the Patient Information Sheet (RG 14-049 - Version for submission 1 – 03.12.2015) for this research. I have had the opportunity to consider this information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without any medical care or legal rights being affected.	☐
3. I understand the appropriate individuals, from the University of Birmingham, may look at research information collected during the study. I give permission for these individuals to have access to this information.	☐
4. I agree to be contacted by phone, if this is necessary for the completion of this research	☐
5. I agree to my GP being informed and approached about my participation in this research.	☐
6. If I have a regular pharmacy, I agree to them being contacted.	☐
7. I agree to take part in this research study.	☐

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

8.4. Patient Questionnaires

8.4.1. PATIENTS' PAIN MEDICINES QUESTIONNAIRE

PATIENTS' PAIN MEDICINE QUESTIONS

Which, if any of these medicines do you take to treat you pain? ID No

It would help with your appointment if you would **please complete this questionnaire before your appointment** and bring it with you.

Will you also **please bring with you a list of all of your current medicines** both prescribed and purchased over the counter?

It would also help if you would try and **remember and make a note of drugs that you have taken in the past** but are not taking any longer.

Do you take one or more of the following medicines? Please circle all appropriate answers.

a. Paracetamol 500mg two, four times a day. Yes No Sometimes
b. Co-codamol 8/500 two, four times a day Yes No Sometimes
c. Co-codamol 30/500 two, four times a day Yes No Sometimes
d. Co-dydramol 10/500 two, four times a day Yes No Sometimes

e. Codeine Yes No S
f. Dihydrocodeine Yes No S
g. Tramadol Yes No S
h. Ibuprofen Yes No S
i. Naproxen Yes No S
j. Diclofenac Yes No S
k. Morphine Yes No S
l. Oxycodone Yes No S
m. Buprenorphine Yes No S

n. Fentanyl Yes No S
o. Pethidine Yes No S
p. Amitriptyline Yes No S
q. Nortriptyline Yes No S
r. Gabapentin Yes No S
s. Pregabalin Yes No S
t. Duloxetine Yes No S
u. Any other?
v. Any other?

Do you buy any medicines for your pain? If so which do you buy?

8.4.2. BPI QUESTIONNAIRE

Brief Pain Inventory

Adapted for to make Question 2 suitable for the patients involved in this research project.
All other details are as close to the original as possible.

Name : _____ Gender : ❑ Male ❑ Female

1) Marital status (at present)

1. ❑ Single
2. ❑ Widowed
3. ❑ Married
4. ❑ Separated/Divorced

2) Education – tick grade or degree completed

1. Left school with no formal qualification
2. A level
3. GCSE/O level/CSE
4. Degree

Please specify professional qualification: _____

3) Current occupation _____
(specify titles; if you are not working, tell us your previous occupation)

4) Spouse's occupation _____

5) Which of the following best describe your current job status?

1. ❑ Employed outside the home, full time
2. ❑ Employed outside the home, part time
3. ❑ Homemaker
4. ❑ Retired
5. ❑ Unemployed
6. ❑ Other

6) How long has it been since you first learned your diagnosis? _____ months

7) Have you ever had pain due to your present disease?

1. ❑ Yes
2. ❑ No
3. ❑ Uncertain

8) When you first received your diagnosis, was pain one of your symptoms?

1. ❑ Yes 2. ❑ No 3. ❑ Uncertain

9) Have you had surgery in the past month?

1. ❑ Yes 2. ❑ No

If yes, what kind? _____

10) Throughout most of our lives we have had pain from time to time (such as minor headache, sprains, toothache). Have you had pain, other then these everyday kinds of pain during the last week?

1. ❑ Yes 2. ❑ No

10a. Did you take pain medications in the last 7 days?

1. ❑ Yes 2. ❑ No

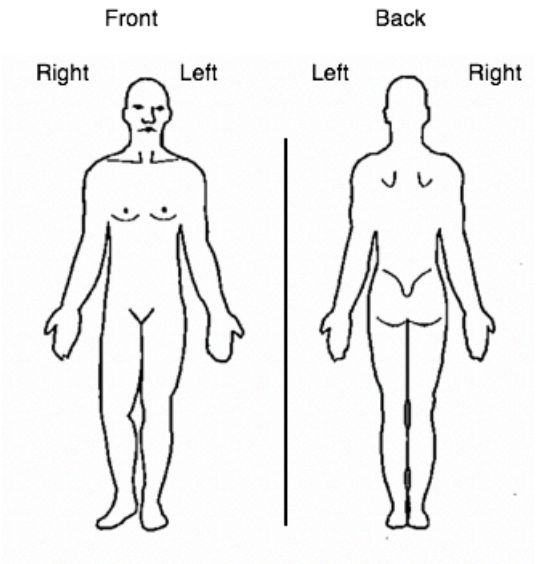
10b. I feel I have some form of pain now that requires medication each and every day.

1. ❑ Yes 2. ❑ No

If your answer to 10, 10a and 10b were all no, please stop here, go to the last page and sign where indicated.

If any of your answers to 10, 10a and 10b were yes, please continue.

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



12) Please rate your pain by circling the one number that best describes your pain at its worst in the last week.

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

13) Please rate your pain by circling the one number that best describes your pain at its least in the last week

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

14) Please rate your pain by circling the one number that best describes your pain on the average

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

15) Please rate your pain by circling the one number that best describes your pain right now

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

16) What kinds of things make your pain feel better (for example heat, medicine, rest)?

_____

_____

17) What kinds of things make your pain worse (for example walking, standing, lifting)?

_____

_____

18) What treatments or medications are you receiving for your pain?

_____

_____

19) In the past week, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received?

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

20) If you take pain medication, how many hours does it take before the pain returns?

1. ❑ Pain medication doesn't help at all
2. ❑ One hour
3. ❑ Two hours
4. ❑ Three hours
5. ❑ Four hours
6. ❑ Five to twelve hours
7. ❑ More than twelve hours
8. ❑ I do not take pain medication

21) Tick the appropriate answer for each item. I believe my pain is due to:

❑ Yes ❑ No No 1. The effect of my treatment (for example medication, surgery, radiation, prosthetic device)?

❑ Yes ❑ No No 2. My primary disease (meaning the disease currently being treated ad evaluated)

❑ Yes ❑ No No 3. A medical condition unrelated to my primary disease (for example arthritis). Please describe condition _____

22) For each of the following words please tick Yes or No if that adjective applies to your pain.

Aching	❑ Yes	❑ No
Throbbing	❑ Yes	❑ No
Shooting	❑ Yes	❑ No
Stabbing	❑ Yes	❑ No
Gnawing	❑ Yes	❑ No
Sharp	❑ Yes	❑ No
Tender	❑ Yes	❑ No
Burning	❑ Yes	❑ No
Exhausting	❑ Yes	❑ No
Tiring	❑ Yes	❑ No
Penetrating	❑ Yes	❑ No
Nagging	❑ Yes	❑ No
Numb	❑ Yes	❑ No
Miserable	❑ Yes	❑ No
Unbearable	❑ Yes	❑ No

23) Please circle the one number that describes how, during the past week, pain has interfered with your:

A. General activity

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

B. Mood

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

C. Walking ability

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

D. Normal pain (including both work outside the home and housework)

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

24) I prefer to take my pain medicines:

1. ❑ On a regular basis
2. ❑ Only when necessary
3. ❑ Do not take pain medicine

25) I take my pain medicine (in a 24 hour period):

1. ❑ Not every day
2. ❑ 1 to 2 times per day
3. ❑ 3 to 4 times per day
4. ❑ 5 to 6 times per day
5. ❑ More then 6 times per day

26) Do you feel you need a stronger type of pain medication?

1. ❑ Yes 2. ❑ No 3. ❑ Uncertain

27) Do you feel you need to take more of the pain medication than your doctor has prescribed?

1. ❑ Yes 2. ❑ No 3. ❑ Uncertain

28) Are you concerned that you use too much pain medication?

1. ❑ Yes 2. ❑ No 3. ❑ Uncertain

If yes, why? _____

_____

_____

29) Are you having problems with side effects from your pain medication?

1. ❑ Yes 2. ❑ No

Which side effects? _____

_____

_____

30) Do you feel you need to receive further information about you pain medication?

1. ❑ Yes 2. ❑ No

31) Other methods that I use to relieve my pain include (please tick all that apply)

❑ Warm compress ❑ Cold compress ❑ Relaxation techniques
❑ Distraction ❑ Biofeedback ❑ Hypnosis
❑ Other (please specify): _____

32) Medicines not prescribed by my doctor that I take for my pain are:

_____

_____

_____

_____

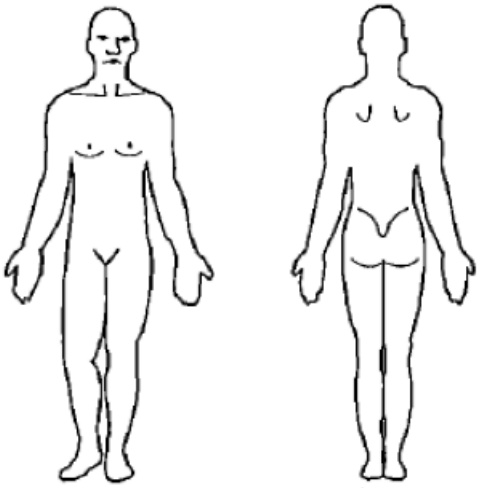
Please sign the questionnaire: _____

8.4.3. S-LANSS QUESTIONNAIRE

THE S-LANSS PAIN SCORE

NAME _____ DATE _____

- This questionnaire can tell us about the type of pain that you may be experiencing. This can help in deciding how best to treat it.
- Please draw on the diagram below where you feel your pain. If you have pain in more than one area, **only shade in the one main area where your worst pain is**.



- On the scale below, please indicate how bad your pain (that you have shown on the above diagram) has been in the last week where:

'0' means no pain and '10' means pain as severe as it could be.

NONE 0 1 2 3 4 5 6 7 8 9 10 SEVERE PAIN

- On the next page are 7 questions about your pain (the one in the diagram)
- Think about how your pain that you showed in the diagram has felt **over the last week**.
- Please circle the descriptions that best match your pain. These descriptions may, or may not, match your pain no matter how severe it feels.
- Only circle the response that describes your pain. **Please continue on the next page.**

S-LANSS

1. In the area where you have pain, do you also have 'pins and needles', tingling or prickling sensations?

a) NO – I don't get these sensations (0)

b) YES – I get these sensations often (5)

2. Does the painful area change colour (perhaps looks mottled or more red) when the pain is particularly bad?

a) NO – The pain does not affect the colour of my skin (0)

b) YES – I have noticed that the pain does make my skin look different from normal (5)

3. Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this.

a) NO – The pain does not make my skin in that area abnormally sensitive to touch (0)

b) YES – My skin in that area is particularly sensitive to touch (3)

4. Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like 'electric shocks', jumping and bursting might describe this.

a) NO – My pain doesn't really feel like this (0)

b) YES – I get these sensations often (2)

5. In areas where you have pain, does your skin feel unusually hot like a burning pain?

a) NO – I don't have burning pain (0)

b) YES – I get burning pain often (1)

6. Gently <u>rub</u> the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?

a) The painful area feels no different from the non-painful area (0)

b) I feel discomfort, like pins and needles, tingling or burning in the painful area that is different from the non-painful area (5)

7. Gently <u>press</u> on the painful area with your finger tip then gently press in the same way onto a non-painful area (the same non-painful area you chose in the last question). How does this feel in the painful area?

a) The painful area does not feel different from the non-painful area (0)

b) I feel numbness or tenderness in the painful area that is different from the non-painful area (3)

8.4.4. RESEARCHER'S DRUG DATASHEET

Does a pharmacist intervention improve analgesic prescribing and pain control?

Researchers Drug Dataset Patient number .....

Name of GP..... Name of Pharmacy.....

Address of GP .....

1.	Pain score	/10		.....	
2.	S-LANSS	/24		Patient DoB	
3.	Weight 50+	y	n	NHS Number	
4.	Age			Consent	y n
5.	Gender	f	m	Date of appointment	
6.	Hepatitis/jaundice	y	n	Clinic where appointment	
7.	Diagnosis – if specific			Entered	y n
8.	1st ; 2nd appointment			Phone number	
9.	Before or after PMP presentation			Butrans = allergy	y n
10.	Cannabis?	y	n		

11. How have you changed the way that you have taken your medicines since .....
    a. PMP y n
    b. 1st clinic appointment y n
12. Did that result from something that I said? y n

13. Are you able to see the see the same GP? y n
    a. If not why not?

14. Does lack of consistency have any effect on your therapy? y n
    a. Can you give me some examples?

15. Has your GP acted on my recommendations? y n

16. **Paracetamol now** y n
- a. Dose
- b. Frequency
- c. Helpful y n
- d. Hours effective
- e. If stopped, why
  - i. Ineffective y n
  - ii. Side effects y n
  - iii. Which
- f. Requested y n
- g. Divide Co-… y n

17. **Moderate opioids now** y n
- a. Which c d t
- b. Dose
- c. Frequency
- d. Helpful y n
- e. Hours effective
- f. If stopped, why
  - i. Which c d t
  - ii. Ineffective y n
  - iii. Side effects y n
  - iv. Which
- g. Requested y n
- h. Which c d t
  - i. Change y n
  - ii. Additional y n
  - iii. Divide Co-… y n

18. **Strong opioids now** y n
- a. Which m o b f
- b. Dose
- c. Frequency
- d. Helpful y m n
- e. How long taken for
- f. Hours effective
- g. If stopped, why
  - i. Which m o b f
  - ii. Ineffective y n
  - iii. Side effects y n
  - iv. Rash y n
- h. Requested y n
- i. Which m o b f
  - i. Change y n
  - ii. Additional y n
  - iii. Dose reduction y n

19. **Neuropathic now** y n
- a. Which a n g p d
- b. Frequency
- c. Dose
- d. Helpful y n
- e. Hours effective
- f. If stopped, why
  - i. Which a n g p d
  - ii. Ineffective y n
  - iii. Side effects y n
  - iv. Which
- g. Requested y n
- h. Which a n g p d
- i. Increase dose existing y n

20. **Non-steroidal now** y n
- a. Which i n d
- b. Dose
- c. Frequency
- d. Taking PPI y n
- e. Helpful y n
- f. Hours effective
- g. If stopped, why
  - i. Which i n d
  - ii. Ineffective y n
  - iii. Side effects y n
- h. Requested y n
- i. Which i n d
- j. PPI y n

8.5. Example of the searches undertaken

Limits 01-01-1990 to 01-01-2019

#1	pharmacist	
#2	physiotherapist	
#3	clinic	
#4	multi-	
#5	chronic	
#6	pain	
#7	analges*	
#8	medicin*	
#9	#1 or #2	Pharmacist or physio
#10	#5 and #6	chronic and pain
#11	#7 or #8	analges* and medicin*
#12	#9 and #3	pharm/physio and clinic
#13	#12 and #10	
#14	#13 and #11	

CHAPTER 9 REFERENCES

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