# Modelling factors associated with long-term prescription patterns of analgesia for musculoskeletal conditions in primary care

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# Declaration

This PhD project was funded by the NIHR National School for Primary Care Research for 3 years, and for a further 3 months by the Arthritis Research UK Primary Care Centre, Keele University.

The initial idea was developed by myself in conjunction with my lead supervisor, Dr. Kelvin Jordan. Throughout the course of this PhD project I developed the detailed structure, analytic approach and managed the project with the guidance from my supervisors Dr Kelvin Jordan, Dr John Bedson and Professor Peter Jones. The project is a secondary analysis of two databases, the Consultations in Primary Care Archive (CiPCA) and the North Staffordshire Osteoarthritis Project (NorStOP) administered by the Centre's informatics team and the project teams.

Dr Kelvin Jordan, Dr John Bedson and Professor Peter Jones advised me on the analysis structure, presentation, planning and writing of the thesis chapters. They also helped with the clinical interpretation of the findings. I conducted all the analyses and writing of the thesis. The systematic review was initially conducted and submitted as an assignment in the module Literature Search and Synthesis (Module code: PTY-40038V1) which was done as part fulfilment of the training credits required as a Keele PhD student. Part of the work has been submitted for publication in peer reviewed journals.

# Abstract

Musculoskeletal (MSK) pain is a major reason why people consult their general practitioner. Analgesia plays a central role in its treatment but do not always work, resulting in the need to switch amongst analgesia potency levels. Stronger analgesia is however associated with increased adverse effects.

The aim was to investigate the use of robust statistical approaches to determine socio-demographic and clinical factors associated with receiving and switching, prescribed analgesia in primary care management of MSK pain.

The first phase reviewed statistical methods previously used in modelling medication switching, and established that Cox proportional hazards and logistic regression models were predominantly used. The second phase investigated the prevalence of prescribed analgesia, factors associated with being prescribed analgesia, and prescription patterns in the management of new MSK conditions using a general practice database. In 3236 incident consulters, 42% were prescribed analgesia, NSAIDs being most prescribed. In a 5 year follow-up period, three prescription patterns were identified: no analgesia or basic analgesia only, use of NSAIDs, and multiple-potency analgesia combinations. The main baseline factors associated with being prescribed analgesia, and stronger analgesia were increasing age and having been previously prescribed analgesia. The third phase used Cox and Weibull frailty models to identify factors associated with switching analgesia and switching to stronger analgesia. The main factors identified were age, gender and initially prescribed analgesia.

The fourth phase used a prevalent cohort of 1610 patients aged 50+ with linked self-reported and medical record data. Patient-reported factors such as level of physical function and pain interference were also associated with switching of analgesia. Using a propensity score approach to modelling outcomes suggested those who switched analgesia did not have better three year outcomes, but further research is required to establish if switching analgesia is beneficial in reducing pain and improving function.

# Contents

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# Chapter 1

## 1 Introduction

This thesis examines analgesia primary care prescription patterns in patients presenting to primary care with musculoskeletal (MSK) conditions, and the patient characteristics associated with variations in prescription patterns including the switching of analgesia. Appropriate statistical methods to determine the pharmacological, clinical and demographic factors associated with starting and switching pharmacological treatment of MSK conditions in primary care are also explored.

The main analysis follows a cohort of patients from initial consultation for a MSK condition for a maximum of 5 years, modelling factors associated with being prescribed analgesia and the potency level prescribed, and the switching of analgesia. The impact of switching analgesia on patient reported outcomes is also explored. The analysis is based on the hierarchical analgesia categorisation (HAC), a previously developed hierarchy of analgesia grouped according to perceived equi-potency when managing a given level of pain (Bedson et al., 2009).

Changing (switching) analgesia is a common feature in the primary care treatment of MSK conditions (Chou et al., 2005; Rahme et al., 2006). In this thesis, switching analgesia is defined as either a record of a prescription of an analgesia of a potency different from that previously prescribed (this may be in place of, or in addition to the initial analgesia), or a record of prescribed analgesia without a previous analgesia prescription on first consultation (Gore et al., 2012, Rahme et al., 2006; Schneider, 2010).

There are several factors that can be associated with the need to start or switch analgesia ranging from the complexity of the medical condition, the severity and chronicity of pain, side effects of current medication and existing co-morbidity or multi-morbidity as well as a natural improvement in the pain resulting from the treatment (Bartsch et al., 2008;

Mercadante and Bruera, 2006). For example the presence of particular co-morbidities such as low back pain, anxiety and irritable bowel syndrome are associated with the initiation of stronger analgesia (opioids) in patients with fibromyalgia (Boulanger et al., 2011; Mercadante and Bruera, 2006), while NSAIDs are not recommended in patients with chronic obstructive pulmonary disease (COPD), cardiovascular, chronic kidney and gastro-intestinal complications (Rahme and Nedjar, 2007; Hunt et al., 2007).

The need to switch to stronger or alternative analgesia primarily occurs in three sets of circumstances. 1) Where the patient's pain or condition is controlled by medication, but they experience intolerable adverse effects. 2) Where pain is not adequately controlled but the dosage of the current medication cannot be increased due to adverse effects. 3) When pain is not adequately controlled, even with a rapid increase in dosage that does not produce adverse effects, (Chou et al., 2005; Rahme et al., 2006). The switching between opioid analgesia can also sometimes be a calculated move by clinicians, as opioid rotation may be an effective strategy in the management of negative effects such as constipation, nausea, dizziness, dependency, hyper-analgesia and cognitive impairment (Joseph et al., 2009; Fitzcharles et al., 2010; Reid et al., 2010).

While stronger analgesia has the potential to alleviate pain and improve the quality of a patient's life, the stronger the analgesia, the more potential there is for the patient to experience adverse side effects such as psychological addiction, dependency, gastric toxicity, hyper-analgesia (increased sensitivity to pain) and restricted therapeutic effect (Benyamin et al., 2008; Reid et al., 2010). Eschewing treatment that is ineffective and striving to maximise the use of more effective analgesia with the least potential for adverse side-effects is beneficial to patients (Kroenke et al., 2009; Schneider, 2010). An improved awareness of analgesic use is however only the starting point, since whatever prescribing algorithms are being used, it is important for the GP to understand what factors they might consider when choosing a therapeutic approach to their patient's pain in order to optimise the cost and benefit of their prescribing.

## 1.1 Musculoskeletal conditions

A musculoskeletal (MSK) condition is described by Littlejohn (2005) as a cardinal symptom of the changes in normal mechanical, physical, and biochemical functions of the joint and muscle processes resulting in tissue damage, disease or dysfunction of the MSK system. Its presence could be a manifestation of a possible underlying disease or condition which may or may not get better with time and medication (Affleck et al., 1999).

The symptoms of MSK conditions include joint pain, joint stiffness, limitation of movement of the joint and swelling, and occur most commonly in the hands, knees, spine, hips and lower back (Main, 2002). MSK pain has a multi-factorial aetiology. Examples of MSK conditions include rheumatoid arthritis and osteoarthritis (OA) (Wood, 1999). However, in most cases, no specific diagnosis can be attributed to the cause of MSK pain, such as that which may occur in low back pain, knee pain and shoulder pain (Littlejohn, 2005). These may result as a manifestation of tendonitis or soft tissue inflammation (Littlejohn, 2005). The pain can be localised to a specific section or region of the body (for example knee) or widespread, due to the nature and cause of the condition. Injuries may contribute to the development of osteoarthritis (OA) of the knee but in the majority of cases, patients often do not attribute their chronic pain to injury (Wood, 1999; Katz, 2002).

MSK pain is associated with increasing age, obesity, female gender, abnormal joint loading during occupations involving repetitive use of joints over prolonged periods, e.g. professional athletes, and manual jobs based on lifting and handling of heavy loads (Wood, 1999; Fitzcharles et al., 2010). Exposure to low social support and low social participation may also be associated with higher levels of MSK pain (Jordan et al., 2008).

Analgesics are often used to alleviate the resultant pain but they do not always work, giving rise to the need to switch between analgesia (Rahme et al., 2006). While switching analgesia can be necessary, it also brings about the complications of adverse effects which may complicate the management of the condition (Moulin, 2001; Bope et al., 2004).

## 1.2 Prevalence of musculoskeletal conditions in the UK

The prevalence of MSK conditions in the UK and the world in general has far reaching health and economic implications (Wood, 1999; Brooks, 2005). MSK conditions were the most frequent self-reported longstanding illness in the UK 1995 General Household Survey, with a rate of 159 per 1000 adult women and 143 per 1000 adult men, with people who live in socially deprived areas having more MSK symptoms, (Urwin et al., 1998). In 2006, an estimated quarter of the general practice registered population consulted at least once with a MSK problem during the course of the year (2405 per 10,000 persons) (Jordan et al., 2010)

In a study by Jordan et al. (2007), the annual consultation prevalence of MSK conditions in the UK in 2001 for adults aged 15 and above was calculated at around 2000 persons per 10000, based on national and regional primary care databases. The prevalence increases steadily with age and is much higher among females. Some of the MSK conditions evaluated for annual consultation prevalence within the population are osteoarthritis (230-280 persons per 10000), arthralgia (400 persons per 10000) and rheumatoid arthritis (44 persons per 10000) (Jordan et al., 2007).

## 1.3 Burdens and health implications of musculoskeletal conditions

MSK pain impacts negatively on society at large as its incidence and prevalence continue to increase in both the developing and the developed world (Main, 2002). It is a major cause of disability, loss of function and emotional stress among individuals (Brooks, 2005). MSK also results in poor quality of life among sufferers and financial constraints among other burdens, posing a significant challenge to the health care system (Wood, 1999; Brooks, 2005). MSK pain has serious consequences, which include the physical and emotional distress of patients and their families as well as resulting in financial consequences for employers in terms of sickness absence and lost productivity (Main, 2002; Brooks, 2006).

The direct health care cost of back pain in the UK in 1998 was estimated to be around £1.6 billion with the cost of informal care and the production losses related to back pain totalling £10.6 billion (Maniadakisa and Gray, 2000). To highlight the impact of MSK pain, back pain, which accounts for about 10% of all MSK conditions consulted for, results in restrictions on individuals' social and physical activities and consequently has a substantial impact on their life style, the health care system and the national economy (Wood, 1999; Brooks, 2005).

## 1.4 Management of musculoskeletal pain: WHO guidelines

The early treatment and management of MSK pain is essential in alleviating disability and the resultant burdens from the MSK conditions (Ehrlich, 2003). Research shows that a holistic approach to managing MSK, where pharmacological and non-pharmacological treatments (exercise, physiotherapy, psychological support) in combination can be effective (Ehrlich, 2003; Kean et al., 2008; Dillard, 2011). Notwithstanding the importance of non-pharmacological therapies, in general practice, the fundamental treatment strategy available to the general practitioner (GP), however, is the prescribing of analgesia (Dillard, 2011; Kean et al., 2008). They are essential to curb or minimise the impact of MSK pain.

In recognition of the social and economic implications, guidelines on the pharmacological management of MSK pain have been formulated to ensure best practice and effective management. In 2003, WHO recognised MSK pain as one of the major reasons why people consulted their general practitioner and consequently offered health care professionals guidance on the use of analgesia in low back pain, which is equally applicable to MSK conditions in general (Ehrlich, 2003).

### 1.4.1 Analgesia use in the management of musculoskeletal pain

The WHO guidelines on the pharmacological management of MSK pain defined an analgesia ladder, whereby doctors were encouraged to use basic analgesia in the first instance (e.g. paracetamol), then step up to using non-steroidal anti-inflammatories

(NSAIDs) if basic analgesia did not control the pain, and where appropriate as a third step, use opioid analgesia such as codeine. The analgesia has varying levels of potency and side effects. Avoiding treatment which is ineffective and maximising the use of those giving better results without adverse side-effects is beneficial to the patients (Kroenke et al., 2009). More potent analgesia that are more likely to give better pain relief are also more likely to have adverse side effects (Benyamin et al., 2008; Fitzcharles et al., 2010; Schneider, 2010; Kroenke et al., 2009).

The WHO guidelines are the guiding principles in the formulation of the aims and structure of this thesis. The guidelines and the analgesia ladder are though open to varying interpretations as there are over 300 formulations in the UK that clinicians can prescribe in isolation or in combination. The most distinguishable categories of analgesia are basic analgesia (including paracetamol), opioids and non-steroidal anti-inflammatory drugs (NSAIDs), but opioids can be further subdivided (weak, moderate and strong analgesia) according to potency (Benyamin et al., 2008; Bedson et al., 2012).

The hierarchical analgesia categorisation (HAC) model which has six distinguishable categories described in chapter 3 is the interpretation of the analgesia ladder used in this thesis. The HAC was used to calculate primary care prescription prevalence of analgesia and the effects of national guidelines on prescribing of analgesia between 2001 and 2009 (Bedson et al., 2012). For example, while the authors showed that analgesia annual prescription prevalence has remained around 3100 patients prescribed analgesia per 10,000 registered population, the prescription of moderate analgesia varied over time, reflecting responses to national guidelines by clinicians.

There is evidence that the analgesia used to control MSK pain do not always work leading to the need to switch to different analgesia or potency levels. There is also evidence that the effectiveness of analgesia in relieving pain is associated with the levels of pain which in turn is associated with emotional, psychosocial and socio-demographic patient

characteristics (Fitzcharles et al., 2010; Schneider, 2010). MSK pain and disease severity is usually characterised by symptoms and distress (which can be subjective) rather than objective clinical measures of disease severity or tissue abnormality (Brown et al., 2010), it is essential to continue to develop ways to overcome the numerous barriers to the effective management of pain including patient related factors.

Considering switching of analgesia as a symptom of the presence of the barriers, evaluating baseline and long term factors associated with analgesia switching can therefore help understand the patient specific barriers, which group of patients is at higher risk of exposure to adverse effects, how clinicians prescribe analgesia and potentially inform the future pharmacological management of MSK conditions.

Switching analgesia is primarily an indication that the current medication is not meeting the expectations of the patient, the patient is not benefiting or its adverse effects exceed the benefits (Brown et al., 2010). In MSK conditions, it is not entirely known how patients come to prefer one treatment over another (Schneider, 2010). While the patient's preferences and expectations of treatment benefit are affected by their experiences and perceptions of the treatment and their level of pain, they are willing to try treatments suggested by their GPs (Sarzi-Puttini et al., 2012). The patient's expectations and general beliefs are strongly associated with subsequent adherence to the treatment, for example, a perceived level of harm such as disruption of normal life leads to taking less medicine, while the perceived extent to which the medicine restores normal life leads to adherence (Brown et al., 2010; Sarzi-Puttini et al., 2012). There are emotional aspects in the perception of pain and medication, for example anxiety or depression (Kroenke et al., 2009), which may emanate from socio-demographic patient characteristics. Switching of analgesia is potentially an indication of poor adherence related to the presence of less favourable perceptions and expectations about the medication.

There is therefore a need to evaluate changes or switching in analgesia use in MSK conditions as identifying associated socio-demographic and clinical factors may help clinicians in understanding their patients better and lead to treatment plans tailored to address adherence, perceptions and beliefs from the onset of consultation for a MSK condition. For example, an awareness session to make the patients 'at risk' of switching analgesia aware of all their long-term treatment alternatives, their potential benefits and associated adverse effects may be effective. The patients may appreciate that there is increased exposure to adverse effects resulting from use of a wide spectrum of analgesia and that the exposure may eventually limit the clinicians' choices from the available drugs or even increase morbidity associated with MSK pain (Lewis et al., 2002; Mercadante and Bruera, 2006). Clinicians may then consider treatments that may alleviate the impact of the adverse effects, recognise and address patients' concerns and misconceptions from onset of treatment.

Although there are prescription guidelines for clinicians, there are few studies that evaluate the different strategies for choosing initial treatment, such that deciding between first line analgesia and subsequent analgesia is more a matter of expert consensus, clinician's experience and patient preference (Kroenke et al., 2009). There is also little evidence that following the recommended stepped approach of starting with weaker analgesia and then later moving to stronger analgesia is the best practice. For example with opioids, their long-term use is not proven to be beneficial as most studies end after 6 months (Franklin et al., 2008; Ashworth et al., 2013) and do not suggest recognisable benefits, but opioid use is increasing in the UK (Bedson et al., 2012). It is also unclear whether this stepped approach is suitable for all patients. Clinicians need to know what is happening in real practice, such that if they have some idea which patients might switch quickly, it may be preferable instead to use a stronger painkiller immediately rather than using a stepped approach which may delay patient pain control.

Understanding the socio-demographic, clinical, pharmacologic and patient-reported factors associated with analgesia prescribed on initial consultation and with switching of analgesia will make clinicians more aware that there are patients potentially at higher risk of switching. This will allow better identification of these groups when they first present their MSK conditions. The pain management regime of such patients may be personalised to ensure it is robust, effective and ensures that patients constantly integrate feedback to successfully cope with their condition.

## 1.5 Aims and Objectives of the thesis

The aims of this thesis are therefore

- **To use robust statistical methods to identify patterns in the pharmacological management of MSK pain in primary care,**
- **To explore and understand the pharmacologic, clinical and demographic factors associated with switching analgesia ,**
- **To undertake an initial evaluation of the long term outcomes associated with switching analgesia**.

The specific objectives are:

**Phase 1 - Previous approaches to modelling medication switching**

- To identify the statistical methods previously used to model switching of medications/drugs in primary care
- To evaluate the applicability of the statistical methods to model analgesia switching in MSK conditions in primary care
- To identify common factors previously identified to be associated with switching of drugs/medication in general.

**Phase 2 - Patterns of analgesia prescribing in new musculoskeletal consulters**

- Establish the percentage of patients prescribed analgesia at the onset of consulting for a MSK problem, which potency of analgesia is used and what factors are associated with this.
- Determine whether latent class analysis is a feasible method for grouping patients newly consulting with MSK problems based on analgesia prescriptions over 5 years
- Determine if distinct clusters of patients can be identified based on the potency of the analgesia they are prescribed, and then assess their association with patient socio-demographic and clinical characteristics.

**Phase 3 - Switching analgesia in primary care**

- Compare Cox and Weibull models in modelling factors associated with switching from initial analgesia to different potency levels over time
- Identify factors associated switching from initial analgesia potency level and establish if the factors associated with time to first switching vary with the potency level of initial analgesia.
- Identify factors associated with switching taking into account successive switches from the initial analgesia potency to different potency levels
- Identify factors associated with change from no or low potency medication (no medication, basic analgesia and weak analgesia analgesia) to higher potency analgesia (moderate, strong analgesia) over time
- Identify factors associated with the incident rate of switching in multiple-event switches

**Phase 4 – Association of patient-reported factors and long term outcomes with switching**

- Assess if the same factors identified previously to be related to switching in an incident MSK consulting group are also the key factors associated with switching in a prevalent MSK consulting group aged 50+ years
- Investigate whether switching or progressing to stronger analgesia and having an increased number of analgesia switches within 3 years is linked to reduced reporting of pain interference and reporting improved physical function at the end of the 3 year period

## 1.6 Structure and Phases of the thesis

**Phase 1:** Chapter 2 presents a systematic review of statistical methods previously used to model medication switching. The medical conditions considered are cancer, MSK conditions, depression, schizophrenia, epilepsy and asthma. Non-musculoskeletal conditions are included in order to generate a larger population of studies for review.

The primary objective of the review is to identify commonly used statistical methods in modelling switching of medication and to compare and contrast the methods in order to understand their relevance, strengths and limitations in delivering the objectives of this thesis. The findings of the review will then inform the methodologies to be used in the phase 3 modelling. Chapter 3 then describes the datasets to be used in the study. The chapter also describes the hierarchical analgesia categorisation (HAC) used in this thesis as the primary interpretation of the WHO analgesia ladder, and looks briefly at the existing clinical relevance of the clinical and socio-demographic factors assessed for their association with switching analgesia.

**Phase 2:** Chapters 4 and 5 are both exploratory and analytic and based on a high quality database of routinely collected consultation and prescription data (CiPCA) (described in Chapter 3). The patients included in the study are those who consulted for any MSK

condition in 2006 with no MSK consultation 12 months prior to their consultation and also had no prescribed pain analgesia in that period. The initial medication prescribed is defined as pain medication prescribed within 2 weeks of their MSK consultation.

In Chapter 4, the data exploration and description includes frequency of prescription for each type of analgesia (HAC categories) at initial consultation and, variation by age, gender, general practice and site of MSK problem, e.g. knee, low back. The factors associated with prescription of any analgesia and with potency level of the initial analgesia are also evaluated. In Chapter 5, patterns of analgesia prescriptions over the 5 year follow-up period in these patients are determined using latent class analysis. Associations of the identified patterns with baseline factors such as patient age, gender, practice, previous MSK consultation and previous prescribed analgesia are examined through multinomial logistic regression.

**Phase 3:** This phase (Chapter 6-7) examines routinely recorded clinical factors including region of pain, comorbidity, number of MSK consultations and prescriptions, and socio-demographic factors like age, gender, and general practice associated with switching. The same cohort is used as in Phase 2 to model time to first switch (both to any and to stronger analgesia) and switching taking into account multiple analgesia switches.

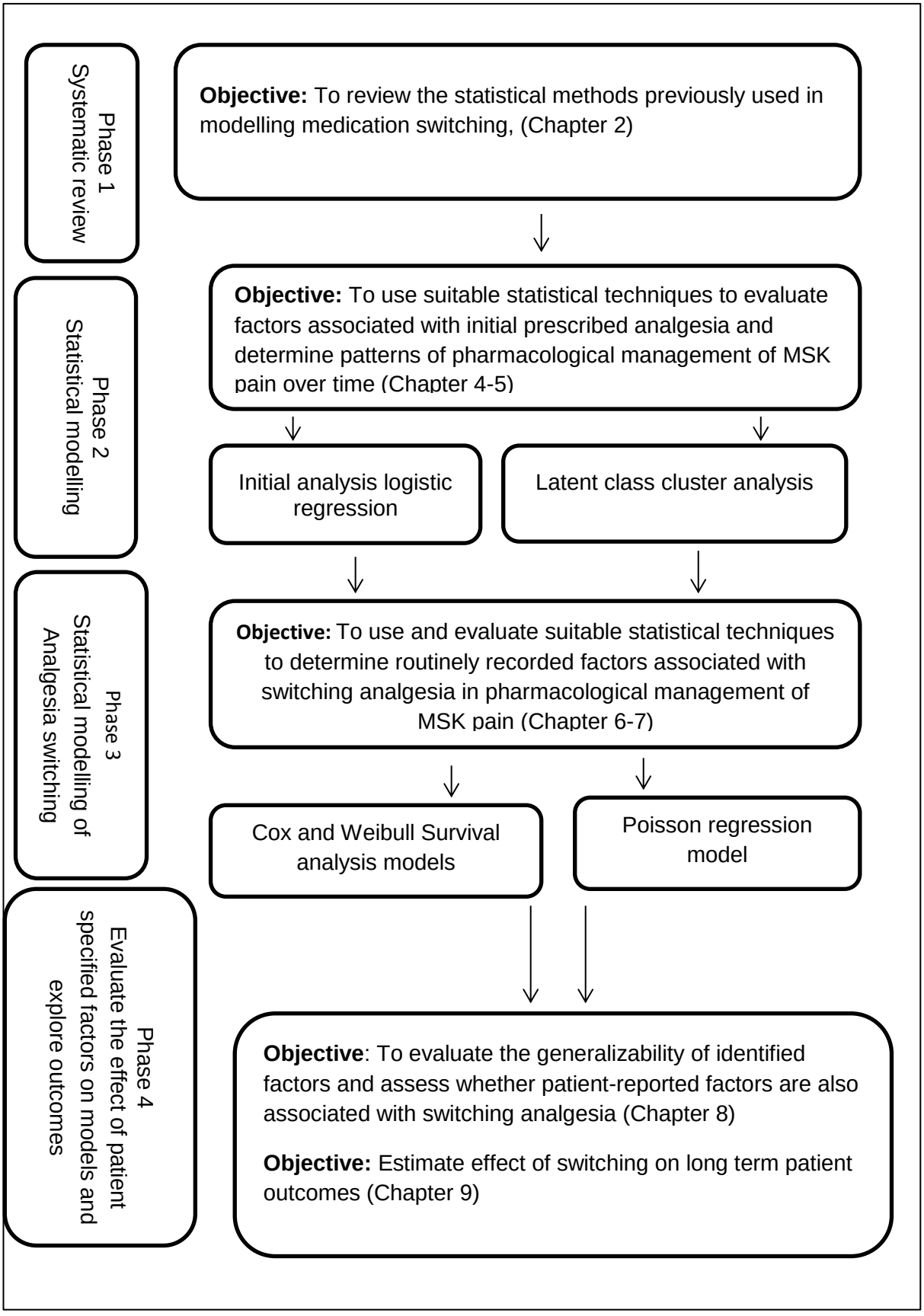
The models used are the Cox proportional hazards model, identified as a possible approach through the systematic review in Phase 1, and Weibull models as an alternative to the Cox. Statistical models are used in various forms, accounting for more than one analgesia switch per person and incorporating frailty (to address variation in switching not accounted for by available variables). Poisson regression is employed to evaluate factors associated with the relative incidence rates of switching among patients with more than one analgesia switch.

**Phase 4:** This phase (chapter 8-9) uses data from an older (50+) cohort (the NorStOP cohort) for which linked medical record and survey data has been collected. In Chapter 8, the objective is to validate and extend the models used in phase 3.

The Weibull model is fitted to evaluate if the clinical and socio-demographic factors associated with analgesia switching identified in phase 3 are also associated in this cohort and when patient-reported variables are included. In Chapter 9 the effect of switching analgesia and the number of switches on long term pain interference and physical function are evaluated, with confounding factors adjusted for through application of propensity score modelling.

A schematic overview summarising the objectives, structure and statistical methods of the thesis is illustrated in Figure 1.5.1 below. The next chapter is a systematic review of statistical methods used in modelling medication switching in medical research, while the data, analysis tools and variables considered in this thesis are introduced in chapter 3.

Figure 1.5.1 Schematic overview of the thesis



# Chapter 2

## 2 Statistical methods for modelling switching of medication: a systematic review

### 2.1 Introduction

This Chapter details a systematic review examining statistical methods previously used to model medication switching. Medication switching in this review is defined as the act of changing from one medication to another, taking additional medication, or stopping use of current medication. In my initial literature search, only one study (Rahme et al., 2005) modelling drug switching in MSK conditions in primary care was found, and no studies reviewing statistical methods applicable to modelling switching in medication generally were found. Other medical conditions where switching of medication are common were therefore considered for inclusion in the systematic review to enable a larger literature base that will allow a comprehensive review of statistical methods used in the modelling of medication switching. The medical conditions are cancer, epilepsy, depression, hypertension and MSK pain.

Some of the medical conditions like MSK pain, depression and cancer tend to co-occur (Bartsch et al., 2009), which may widen the spectrum of common factors associated with medication switching. Inevitably each medical condition will have its own set of significant factors but identifying common factors for a set of conditions may help in further understanding the switching process.

The need to quantify clearly the risks of switching makes the choice and use of statistical methods fundamental in modelling switching. The statistical modelling of socio-demographic and clinical factors associated with switching analgesia in primary care treatment of MSK conditions has not been widely performed; hence a systematic review of

the most applicable statistical methods is necessary. The review will inform the choice of statistical methods to be used in later chapters of the thesis.

The objectives of the systematic review presented in this chapter are:

1. To identify the statistical methods previously used to model switching of medications/drugs in primary care
2. To evaluate the applicability of the statistical methods to model analgesia switching in MSK conditions in primary care
3. To identify common factors previously identified to be associated with switching of drugs/medication in general.

## 2.2 Methods

### 2.2.1 Literature search Strategy

The initial search strategy was limited to EBSCOhost databases and health databases: which are AMED (Alternative & Complementary Medicine), British Nursing Index, CINAHL, MEDLINE, SPORTDiscus and PsycINFO. A manual search of the Statistics in Medicine journal was also conducted as it is a relevant journal which may have statistical papers related to modelling switching. The search was centred on publications in the years between 2000 and 2010 inclusive, in order to limit the modelling approaches to those used in the recent past. A selection of papers that had been previously identified opportunistically through Google Scholar was used to identify initial key words and subject headings as suggested by Scott et al. (2002). The reference lists of the identified papers were searched in attempt to locate further articles.

The key words were the synonyms and related phrases of each medical condition, switching, medication and modelling or statistical analysis. Alternative spellings, acronyms and any closely related words were used. Some key word have asterisks, for example model* to allow the search engine to consider all possible derivatives of the word, while

some phrases are put in quotes, for example “pharmacological treatment” to enable the phrase to be considered as a single word. This was done because in the preliminary search of Google Scholar the words were found to have variations within the desired context and the phrases were more meaningful within the context if considered as a single word.

**Example search terms were:**

1. Statistical Modelling OR Model* OR Statistical Analysis
2. Medication OR Drugs OR Analgesia OR “Pharmacological treatment”
3. Switching OR Switch* OR Changing OR Change*
4. “Musculoskeletal pain” OR “Musculoskeletal disorders” OR “Musculoskeletal conditions”
5. Cancer OR “Cancer pain” OR “Chronic pain”
6. Epilepsy
7. Depression OR Depress*
8. Hypertension OR “High blood pressure”
9. 1 AND 2 AND 3 AND 4
10. 1 AND 2 AND 3 AND 5
11. 1 AND 2 AND 3 AND 6
12. 1 AND 2 AND 3 AND 7
13. 1 AND 2 AND 3 AND 8
14. 9 OR 10 OR 11 OR 12 OR 13

**Inclusion criteria**

The inclusion criteria was formulated with the view that it was not feasible to translate non-English articles into English and that the statistical methods used should be applicable to retrospective or prospective analyses allowing adjusting for multiple patient characteristics. The diseases chosen (cancer, MSK conditions, hypertension, depression

and epilepsy) were those where changing medications is a common feature in the primary care management of, and treatment of associated chronic pain (Chou et al., 2005; Rahme et al., 2005). They are sensible choices since each involves the use of medications that are switched to attain some degree of control and therefore have commonality, e.g. hypertension drugs are often used hierarchically as in the current NICE guidelines, and often different drugs are targeted at different age groups, as may be the case in the treatment of MSK. There are several factors that can be associated with the need to switch medications ranging from the complexity of the medical condition, resultant pain and symptoms of the condition, side effects, effectiveness, co-morbidity or multi-morbidity and patient preference (Sarzi-Puttini et al., 2005, Lewis et al., 2002). The use of several common chronic problems will enable a wider selection of studies and more factors associated with switching to be identified. The inclusion criteria can be summarised as:

i. English language journals or those with English translation available
ii. Full text available
iii. Observational, prospective or retrospective studies
iv. Cohort studies
v. Studies that used statistical modelling to model the switching of medications
vi. Treatment or management of cancer, epilepsy, depression, hypertension and MSK pain.

**Exclusion criteria**

The exclusion criteria were conceived from the realisation that medication changes or switching in clinical trials are planned and usually specific to a particular drug or medication, while in this thesis some of the changes or switches to be evaluated are not pre-planned and are not specific to medications. The objectives of the chapter are primarily to identify statistical modelling techniques applicable to switching; hence the

studies should have comprehensive text describing the statistical modelling approaches. The exclusion criteria can be summarised as:

i. Clinical trials and other randomised studies
ii. Studies reported only in abstracts as they do not detail the modelling procedure employed

### 2.2.2 Assessment of the quality of the studies.

Table 2.2.1: Study quality assessment criteria

| **Assessment criteria** | **Outcome** |
|---|---|
| **A. Validity of study design** | Y N N/A |
| 1. Were study objectives stated/ described? | |
| 2. Were sampling methods clearly described? | |
| 3. Was sample size stated and adequate for the analysis? | |
| 4. Were participants inclusion/exclusion criteria clearly described? | |
| **B. Statistical Methods** | |
| 1. Were the statistical methods used adequately stated or referenced? | |
| 2. Were the statistical methods used appropriate for the data? | |
| 3. Were the statistical methods applied correctly in data analysis? | |
| 4. Were model assumptions reported/ tested (e.g. Cox Proportional Hazards) | |
| 5. Were additional analysis and tests used (e.g. K-M plots, bootstrap, log rank)? | |
| 6. Were models validated with different datasets/bootstrap? | |
| **C. Data description and Model presentation** | |
| 1. Were outcomes and relevant characteristics of the participants adequately summarised? | |
| 2. Were graphical illustrations used (e.g. Kaplan-Meier plots)? | |
| 3. Were model development steps and final models stated? | |
| 4. Were model parameters given with confidence intervals? | |
| 5. Were missing data accounted for? | |
| 6. Were model goodness-of-fit measures given (e.g. -2logL) | |
| 7. Were conclusions drawn from the statistical analyses justified? | |
| 8. Were statistical packages used stated? | |

The quality of the studies identified was assessed narratively though an assessment criteria derived from Mallet et al., (2010) in attempt to ensure that the synthesis process is credible. There is no standard tool to assess the quality of studies for the purposes of establishing the suitability of statistical approaches used, but there is need for a systematic approach to synthesising research evidence to establish relevance and applicability of statistical modelling approaches used in the past in modelling medication switching. It is essential to establish that the use of the statistical model is credible within the context of the research, for the outcome of the synthesis to be trusted (Rodgers et al., 2009).

The systematic review by Mallet et al. (2010) assessed 47 articles on prognostic models using time to event data with the aim of developing a new prognostic model and prognostic index to predict patient outcome in cancer patients. Prognostic models are clinical prediction models that allow multiple risk factors to be assessed systematically. The review found that models developed with poor methods and reporting compromise the reliability and clinical relevance of models derived from them. While the purpose of the review by Mallet et al. (2010) was different from the purpose of this review, the process of establishing that published statistical models have been developed through poor or good methods and are well reported is important in establishing the quality of the studies. A further similarity is that the review was dealing with studies modelling time to event data, which is also the core aspect of this thesis.

A poorly developed and reported model raises doubts about the suitability of the statistical approach used, while well developed and reported models give credibility. The objectives of the study, the sample size, the type of the outcome measures and the patient characteristics, and available information on the patients can inform on the choice of statistical model to be used. For example, in order to use the Cox proportional hazards model, one needs to have the precise data on time to an event.

The study quality assessment criteria used in this review is given in Table 2.2.1 above. The studies were rated as satisfying the assessment items or not, or whether the item is not applicable to the study. Studies satisfying more than 50% (author's choice) of the applicable items were considered of reasonable quality. The results were extracted, summarised and tabulated with columns including authors, objective, disease, population, data source (e.g. medical records, survey), outcome variable, risk factors assessed and statistical method used. The study authors' justification for the choice of method and comments are discussed in the discussion section.

## 2.3 Results

401 papers were identified in the search of which 9 met the inclusion/exclusion criteria (see Figure 2.3.1). Of the nine studies used in this review, four used only logistic regression to identify the factors associated with switching of medications while four used only the Cox proportional hazards model. The final study (Bartch et al., 2009) used both the logistic and the Cox model. Three of the studies modelled medication switching in schizophrenia, two in MSK conditions, one in cancer, one in epilepsy, one in depression and one in hypertension.

Table 2.3.1 below is a summary of the aspects of papers considered for this review which might help in understanding what influenced the authors' choice of the statistical methods used in the modelling procedure. The factors that were not statistically significant in the models are in italics.

Figure 2.3.1: Flow chart of selecting studies for review

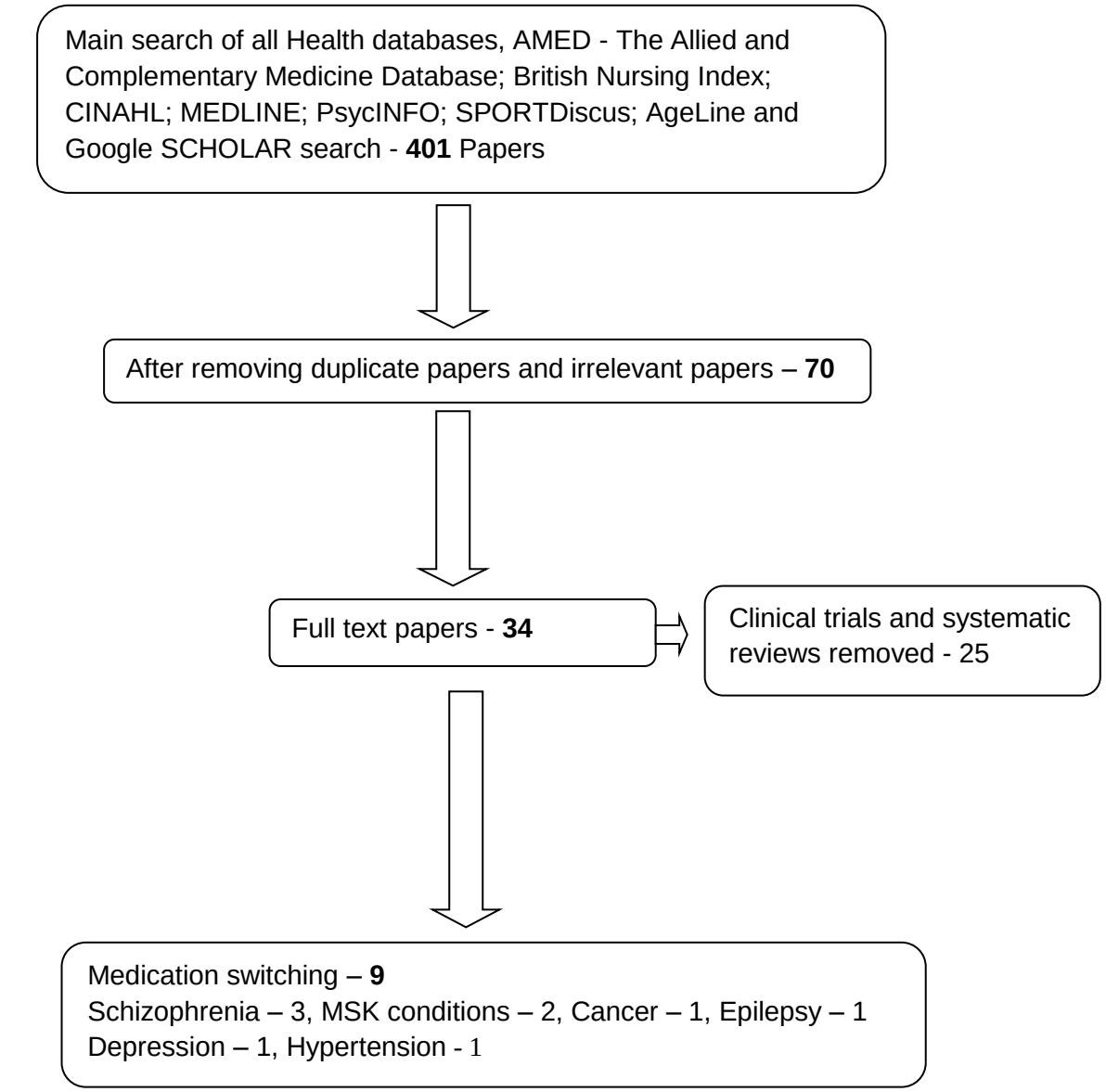


Table 2.3.1: Summary of the papers used in the review

| **Author** | **Study Objective** | **Data source (n=)** | **Disease** | **Risk factors assessed** | **Statistical method** |
|---|---|---|---|---|---|
| 1. Ascher-Svanum et al. (2006) | To determine time to all-cause discontinuation of medication and associated factors | Observational study (n=2327) | Schizophrenia | Age, gender, *ethnicity*, comorbidity, prior hospitalisation, *enrolment site*, *insurance type*, substance use, scores in the Positive and Negative Syndrome Scale | Cox proportional hazards model/ Kaplan-Meier |
| 2. Bartch et al. (2009) | To determine factors predicting activity of second line therapy | Retrospective study of females (n=97) | Cancer | Age, hormone receptor status, brain metastases, more than one metastatic site, first-line therapy | Cox proportional hazards model/ Kaplan-Meier logistic model |
| 3. Bennett et al. (2003) | To determine the degree of switching from NSAIDS to COX2 and factors associated with switching | Cohort study from General Medical Services (n=480573) | Musculoskeletal Pain | Age, gender, *dose*, co-prescribing of anti-peptic ulcer drugs, drug type | logistic model |
| 4. Chou et al. (2 005) | To explore factors influencing the switch in the use of anti-hypertensive medications | Cohort study on Taiwan National Health Insurance database (n=565048) | Hypertension | Age, gender, *Initial practitioner*, last practitioner, *practitioner's age*, clinic change, Medication type, *last physician age*, | logistic model |

| Author | Study Objective | Data source (n=) | Disease | Risk factors assessed | Statistical method |
|---|---|---|---|---|---|
| 5. Essock et al. (2006) | To explore whether it is more advantageous to continue taking the medication being received at baseline or to switch to different antipsychotic | Case-control study (n=1432) | Schizophrenia | Age, Drug type, Positive and Negative Syndrome Scale score | Cox proportional hazards model/ Kaplan-Meier |
| 6. Hansen et al. (2009) | Investigating the association between A-rated antiepileptic drugs (AEDs) and epilepsy-related events | Case-control study (n=44217) | Epilepsy | Age, *gender* , region, type of seizure, number of prescriptions in 6 months | logistic model, chi-squared test |
| 7. Marcus et al (2009) | Examining the pharmacologic, clinical and demographic factors associated with switching antidepressants | Cohort study on patients and PharMetrics administrative data (n=56521) | Depression | Age, gender, depressive disorder, co-morbid metal condition, general medical illness, anti-depressant class, initial dose | logistic model |
| 8. Marshall et al. (2009) | Comparison of time to all cause discontinuation across antipsychotic drug therapies | Retrospective database analyses (n=1191) | Schizophrenia | Age, gender, ethnicity, *drug type*, type of episode | Cox proportional hazards model/ Ordinary least squares model |
| 9. Rahme et al. (2005) | To evaluate drug switching and associated costs among elderly chronic NSAIDS users | Retrospective cohort study on claims database (n=953656) | Musculoskeletal Pain | Age, gender, prior health check, *previous diagnosis*, prior medication, previous switch, drug type, *staff consulted* | Cox proportional hazards model Kaplan-Meier |

Italics –Non-significant factors in the models

## 2.4 Evaluation of the studies

The studies were evaluated for quality using the quality assessment criteria and the results are summarised in Table 2.4.1 below. All studies passed the 50% criteria mentioned in section 2.2.2. In four of the papers, the authors justified the choice of the statistical method used in the modelling while five did not. They all however stated the need to adjust for other variables in the use of either the Cox model or the logistic model. Rahme et al. (2005) stated that the Cox model was used in order to determine hazard ratios for first switch while adjusting for baseline characteristics, and for multiple switches whilst further adjusting for the number of previous switches as well as treatment duration. Essock et al. (2006) stated the use of the Cox model was to compare the discontinuation and future switching rates between patients who switched at study entry and those who stayed on entry medication, while adjusting for other variables and assessing interactions.

Bartch et al. (2009) used both the Cox model and the logistic models. The Cox model was used to evaluate the factors associated with switch to first line and second line treatments and the multinomial logistic model to evaluate variables associated with treatment response to second line treatments. Chou et al. (2005) used the logistic model to identify predictors of patient drop out from treatment regime or switching after 30 days under medication, in which switching was considered to have occurred or not in a fixed time interval.

All the studies had a detailed description of study design, the study size, baseline characteristics and outcome variables. The study objectives and the modelling procedures to be followed were well spelt out with model development detailed step-by-step. The coefficients of the models were stated appropriately as hazard ratios (Cox model), odds ratios (Logistic model). Only two of the nine studies, (Essock et al. (2006) and Chou et al. (2005)) did not state the statistical packages used to fit the models. Three of the four papers that used the Cox regression model (Bartch et al., 2009; Rahme et al., 2005; Ascher-Svanum et al., 2006) stated testing the proportional hazards assumptions of the

models and also evaluated the discrimination and calibration of the models using Kaplan-Meier curves. Only 1 study (Ascher-Svanum et al., 2006) went on to use bootstrap re-sampling to validate the models.

Eight studies had sample sizes over 1000 with the largest having over 900,000 eligible participants. The study with the smallest sample size was by Bartch et al. (2009) which had 97 patients. It was intended to predict the response to second line therapy in the treatment of breast cancer in women. However despite the small sample size of the Bartch study, the study design, baseline characteristics, drug exposure and switching, significant variables and model coefficients together with significance levels were well detailed. The Bartch study used Kaplan-Meier plots to highlight the differences between the risk groups. Model development was detailed step-by-step and the creation of risk groups within the explanatory variables was given medical justification, for example age was categorised as less than 35, 35-64 and 65+ because response to therapy was similar within each age-group and presumably expected to be different between age groups. It is however not reported if the goodness-of-fit tests, model performance and validation with external data or same data through bootstrap methods were done.

Although the studies in this review did not satisfactorily address all the items in the quality assessment criteria (for example in eight studies, models were not validated with different datasets and model goodness-of-fit measures were not given), it can be generally accepted that the quality of the studies with regards to statistical methodology can be taken as satisfactory as they adequately satisfied the 50% criteria on the quality assessment scale and the models can be considered credible. The models identified a wide range of factors associated with medication switching, varying according to the medical conditions and variables in the dataset. Variables associated with switching included age, gender, ethnicity, previous episodes of the condition, type of drug, underlying medical conditions, initial physician consulted, co-morbid conditions treated for, prior use of medication, side effects, initial dosage and the price of the medication.

Table 2.4.1: Satisfaction of the quality assessment criteria by studies

| **Assessment criteria** | **Study** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **A. Validity of study design** | Ascher-Svanum et al. (2006) | Bartch et al. (2009) | Bennett et al. (2003) | Chou et al. (2005) | Essock et al. (2006) | Hansen et al. (2009) | Marcus et al (2009) | Marshall et al. (2009) | Rahme et al. (2005) |
| 1. Were study objectives stated/ described? | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 2. Were sampling methods clearly described? | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 3. Was sample size stated and adequate? | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 4. Were inclusion/exclusion criteria clearly stated? | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **B. Statistical Methods** | | | | | | | | | |
| 1. Were the statistical methods used adequately stated or referenced? | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 2. Were the statistical methods used appropriate? | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 3. Were the statistical methods applied correctly in data analysis? | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 4. Were model assumptions reported/ tested (e.g. Cox Proportional Hazards) | Y | Y | N/A | N/A | N | N/A | N/A | N | Y |
| 5. Were additional analysis and tests used (e.g. K-M plots, bootstrap, log rank)? | Y | Y | N | N | Y | Y | N | Y | Y |
| 6. Were models validated with different datasets? | Y | N | N | N | N | N | N | N | N |

| Assessment criteria | Study | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **A. Validity of study design** | Ascher-Svanum et al. (2006) | Bartch et al. (2009) | Bennett et al. (2003) | Chou et al. (2005) | Essock et al. (2006) | Hansen et al. (2009) | Marcus et al (2009) | Marshall et al. (2009) | Rahme et al. (2005) |
| **C. Data description and Model presentation** | | | | | | | | | |
| 1. Were outcomes and relevant characteristics of the participants adequately summarised? | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 2. Were graphical illustrations used (e.g. Kaplan-Meier plots)? | Y | Y | N/A | N/A | Y | N/A | N/A | Y | Y |
| 3. Were model development steps/final models stated? | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 4. Were model parameters given with confidence intervals? | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 5. Were missing data accounted for? | | Y | Y | Y | Y | Y | Y | Y | Y |
| 6. Were model goodness-of-fit measures given (e.g. -2logL)? | Y | N | N | N | N | N | N | N | N |
| 7. Were conclusions drawn from the statistical analyses justified? | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 8. Were statistical packages used stated? | Y | Y | Y | Y | Y | Y | Y | Y | Y |

Y = Yes, N = No, N/A = not applicable

Although the effects of variables vary from condition to condition in increasing or reducing the risk of switching, age, gender, underlying medical conditions and co-morbid conditions are common important variables linked to switching. In the studies looking at MSK conditions (Bennett et al., 2003, Rahme et al., 2009), for example, older, female patients and those with a history of taking anti-peptic drugs were found to be more likely to be switched from NSAIDs to COX-2 inhibitors.

### 2.4.1 Justification of statistical model choice

Some authors did not specifically state the reasons for their model choice but from their work it can be assumed that the objectives of the study, the type and quality of the data including the variables available influenced the choice of the statistical model to be used. The statistical packages used which include SAS, SPSS and Stata are all compatible with both statistical models used which rules out the possibility that the model choice was influenced by the statistical package at the disposal of the authors.

The Cox and the logistic models have some similarities but the fundamental differences lie with the precision of event time, the proportional hazards assumption and that the logistic model is parametric. The Cox model is a semi-parametric or distribution-free approach that is; it does not assume that the data has a particular underlying distribution. The proportional hazards assumption; the hazards of the different groups are proportional, (Lawless 1982), which means that the unique effect of a unit increase in a covariate is multiplicative with respect to the hazard rate. For example, starting a long term pharmacological management of MSK with drug type A may halve one's hazard rate for a need to switch to more potent drug, compared to type D over time.

To appreciate the differences, Table 2.4.2 briefly describes the similarities and difference between the Cox and Logistic models.

Table 2.4.2: Characteristics of the Cox and the logistic models

| Cox Proportional Hazards Model | Logistic Model |
|---|---|
| Basic model, $h(t, x_i) = h_0(t)\exp\{\boldsymbol{\beta} x_i\}$ $h_0(t)$ is the baseline hazard and a function of time and $\boldsymbol{\beta}$ is a vector of regression coefficients (Section 6.2.3.1) | Basic model, $\pi(x) = \frac{\exp\{a+bx_i\}}{1+\exp\{a+bx_i\}}$ $a + bx_i$ is a linear function: $a$= intercept, $b$ = regression coefficient, $x_i$ =predictor variable |
| Models instantaneous event probability at a given time point | Models event probability in an observation time window |
| Outcome - time to event | Binary response "event occurred: yes |
| Proportional hazards assumption | No proportional hazards assumption |
| Applicable to medical research | Applicable to medical research |
| Analyse the relation of time dependent events to other variables | Analyse the relation of time dependent events to other variables |
| Uses partial likelihood for parameter estimation | Uses maximum likelihood for parameter estimation |
| Semi-parametric | Fully parametric |
| Parameter estimates nearly identical to logistic in case of rare events and short time intervals | Parameter estimates nearly identical to Cox in case of rare events and short time intervals |
| Sample size has no effect on difference in Cox and logistic parameters (D'Agostino et al., 1990) | Sample size has no effect on difference in logistic and Cox parameters (D'Agostino et al., 1990) |

The objectives stated in the studies all suggest that the switching of medication and the factors that can be associated with the process were of importance, meaning that both the Cox and logistic models are applicable in all the studies. However, the definition of time as discrete (fixed time period in which events are evaluated to have occurred or not) or continuous (precise time to each event is measured) separates the studies. The objective of two studies (Ascher-Svanum et al., 2006; Marshall et al., 2009), which were to determine time to all-cause discontinuation of medication and associated factors rule out the logistic model as the objectives suggest the effect of time to each event is essential.

If there is a need to evaluate the time until an individual event occurs or the instantaneous event probability at a given time, then the Cox is more appropriate. Hence it can be

postulated that the objectives of the studies did influence the choice of the statistical methods in some of the studies.

## 2.5 Discussion

The studies show that the Cox proportional hazards model and logistic regression are the commonly used methods to model switching of medications and they allow for multivariable modelling of the explanatory variables. Detail on the choice of categorisation in variables, model development and model evaluation depends on the researchers but can be used to validate the model choice as it suggests the researcher understands the appropriateness of the chosen method. The studies give no special justification as to the choice of the method, but it can generally be inferred from the studies and their objectives. The objectives of a study and the definition of the outcome variable can be assumed to significantly influence the statistical model choice among other factors.

Given data that allow for both models, and similar objectives, the Cox proportional hazards model is a better approach than logistic regression as it considers switching also as a function of time to each switching event. The choice of the Cox model over the parametric forms of the time to event analysis modelling techniques such as the Weibull can be justified by the desire to avoid making assumptions about the underlying distributions of the data (Marubini, 1994).

The selected studies highlight lack of efficacy and tolerability as some of the reasons that medication switching becomes a necessity. The lack of efficacy can be considered to be failure in achieving a desirable response to medication within an expected time frame. This makes the use of the logistic model appropriate for modelling factors associated with switching in which time to each switching event is not considered of importance (Berkhof, 2009).

Tolerance is a state of reduced sensitivity of drug to the body resulting in lower threshold pharmacological effect of the drug at normal dose (Joseph et al., 2009; Fitzcharles et al.,

2010; Reid et al., 2010). It can be assumed to be associated with the time elapsed on that medication although the medical history of the patient and other factors can be associated too. This means that the switching under such circumstances is a function of time; hence the time to event models, in this case the proportional hazards model will be most appropriate. It therefore remains for individuals, in light of the available data, to select either the semi-parametric or fully parametric form of the model (Marubini, 1994). The choice should not be made without due consideration of the data and analysis objectives.

The logistic model is suitable for discrete survival data or where the times to each event are not available (Berkhof et al., 2009). Both methods can handle continuous and categorical explanatory variables and allow multiple risk factors to be used systematically and reproducibly. They can be used as prognostic models (Mallet, 2010). In general, the outcomes in the Cox model are usually presented as hazard ratios while in logistic regression the outcomes are usually presented as odds ratios. For both the logistic regression and Cox model, the lack of model fit may be expressed by the deviance and evaluation of residuals (Dobson and Barnett, 2008).

The limitations of this analysis are that the design of the systematic review, the conduct of literature search, the evaluation of the quality of the studies were all done by one person which leave room for errors and a person-specific interpretation of the findings. However this review was initially submitted in fulfilment of a module assessment for the training module Literature Synthesis and Systematic review. The feedback from the module lecturer and the feedback from my supervisors identified most of the weaknesses that lead to an improvement in the review process, which was developing study quality assessment criteria. The other limitation could be that a quality assessment criterion of the studies was derived from the assessment criterion by Mallet (2010) which was meant to assess the quality of studies in the development of prognostic models for cancer research. This makes the assessment subjective in that it is not a universally accepted criterion.

The review only considered published papers with full text. There is therefore likelihood that not all relevant studies were identified, therefore excluding other modelling approaches in the analysis. The review considered a range of medical conditions to enable a larger population of the studies to be used in the review. Treatment regimens vary according to each medical condition so that the choice of the statistical modelling approaches is determined by the type of data and the research questions being answered. No similar reviews were found in available literature to enable comparison of this review to what is already known.

## 2.6 Conclusion

The choice of statistical methods used in modelling medication switching seems to be influenced by among other factors: the objectives of the study, the type and quality of the data, but most importantly the perception or definition of time as discrete or continuous. The Cox model seems to be more informative of switching and associated factors as it incorporates the effect of time to each event. Notwithstanding other possible statistical modelling techniques that can be used, the Weibull model (section 6.2.2.2) may also be relevant and applicable for the main analysis in this thesis as it can be used in a similar way to the Cox model. Age, gender and prior medication use are commonly associated with medication switching. The data, variables, outcomes and the necessary analytic tools used in this thesis are introduced in the next chapter.

# Chapter 3

## 3 The hierarchical analgesia categorisation and data sources for the thesis

The aims and objectives of the thesis stated in chapter 1 will be achieved using a previously derived categorisation of analgesia, the hierarchical analgesia categorisation (HAC) developed by Bedson et al. (2009).

The thesis concerns the analysis of two distinct datasets. The first dataset of routinely recorded primary care data (the Consultations in Primary Care Archive (CiPCA)) will be used to study patients presenting with new episode (incident) MSK conditions. The second dataset, a linked medical record and survey dataset in a cohort of the general population aged 50 and over (the North Staffordshire Osteoarthritis Project (NorStOP)), will be used to study older patients with new or on-going consultations for MSK conditions. Both databases are held at the Keele University Arthritis Research UK Primary Care Centre.

Chapter 3 aims to describe in more detail the HAC, the use of different potency levels of analgesia, the quality of the data used, use of Read codes in identifying MSK conditions and the rationale of the socio-demographic and clinical factors selected for investigation for their association with switching throughout the thesis.

The objectives of the chapter are to:

1. Introduce the HAC as a viable interpretation of the WHO guidelines on analgesia use in the management of MSK conditions
2. Briefly describe the use of analgesia in primary care and their associated adverse effects

3. Introduce and highlight the quality of the data to be used in the thesis and the use of Read codes in identifying MSK conditions
4. Give a brief rationale of the factors selected for investigation in the thesis

## 3.1 The HAC model of drug groups

In the United Kingdom (UK) there are over 300 analgesia formulations available to general practitioners (GPs) to prescribe from (BNF 65 2013). Bedson and colleagues, using GPs in a consensus exercise, derived a hierarchical analgesia categorisation (HAC) where all analgesia formulations were categorised into six groups according to equipotency when treating varying levels of perceived pain (Bedson et al., 2012). Figure 3.1.1 shows the categorisation. Group 1 comprises basic analgesia e.g. paracetamol or topical NSAIDs, whilst groups 2-5 are made up of increasingly potent opioids either alone or in combination with other medications such as paracetamol, e.g. co-codamol. Group 6 comprises non-steroidal anti-inflammatory drugs (NSAIDs) which the consensus exercise did not rank in the potency ladder but were considered as an adjunct to analgesia prescribing.

The HAC is essentially a research tool which simplifies the examination of large numbers of analgesia. Additionally it provides ordered groups of increasingly potent analgesia which reflects the way in which the WHO prescription ladders present a framework of increasingly potent analgesia for use in the management of MSK pain. Consequently, the HAC's analgesia groupings can now be used as reference points in understanding and evaluating the current prescription patterns of GPs when managing MSK pain, instead of attempting to compare the 300 or more individual analgesia formulations found in the BNF (BNF 65 2013) (Figure 3.1.1). The HAC has been used successfully to evaluate factors associated with the prescription of opioids for joint pain (Green et al., 2012) and association of opioid use with disability among low back pain consulters in primary care (Muller et al., 2012).

Figure 3.1.1: Hierarchical Analgesia Categorisation model for prescribing analgesia and NSAIDs in primary care

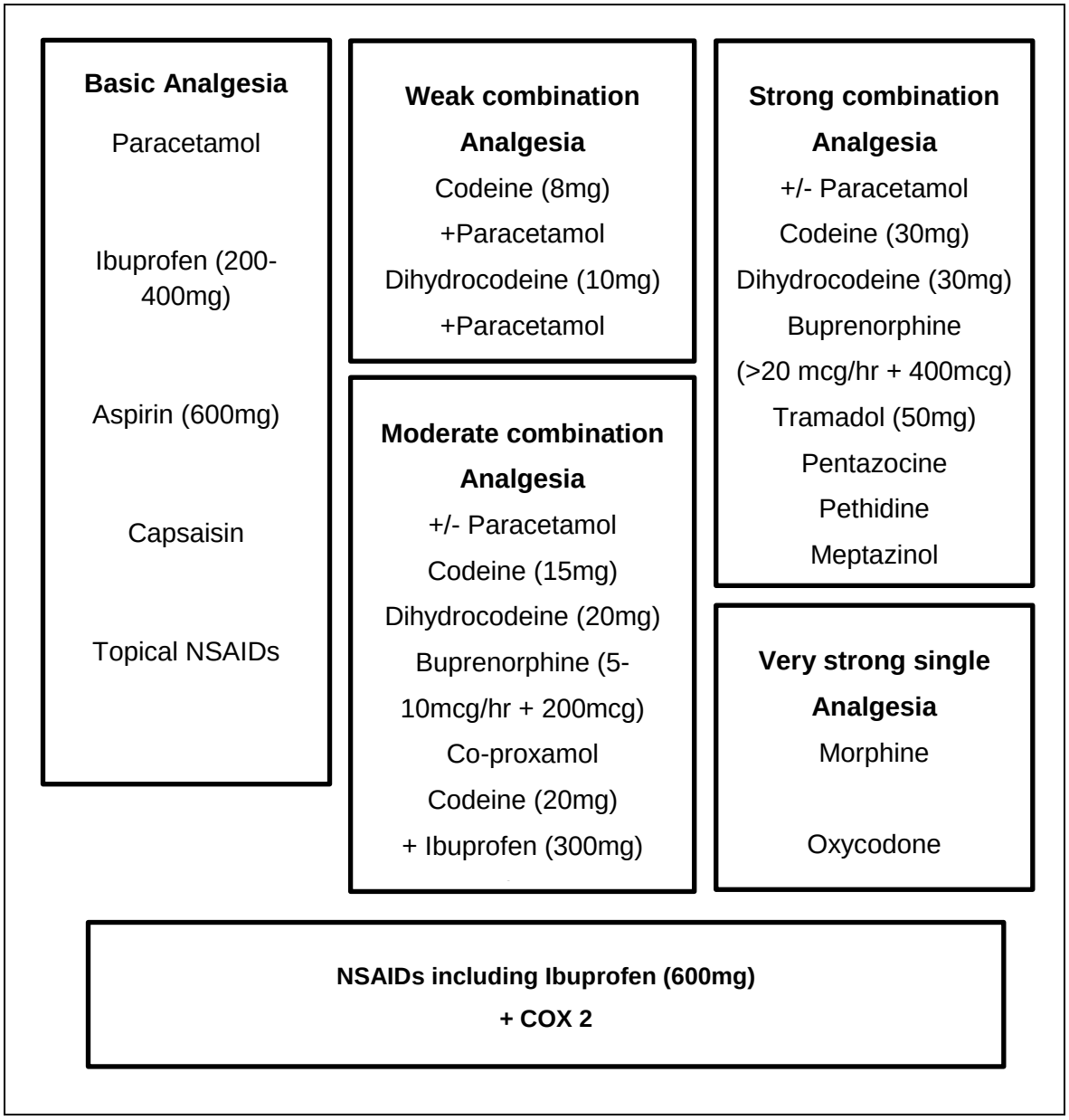
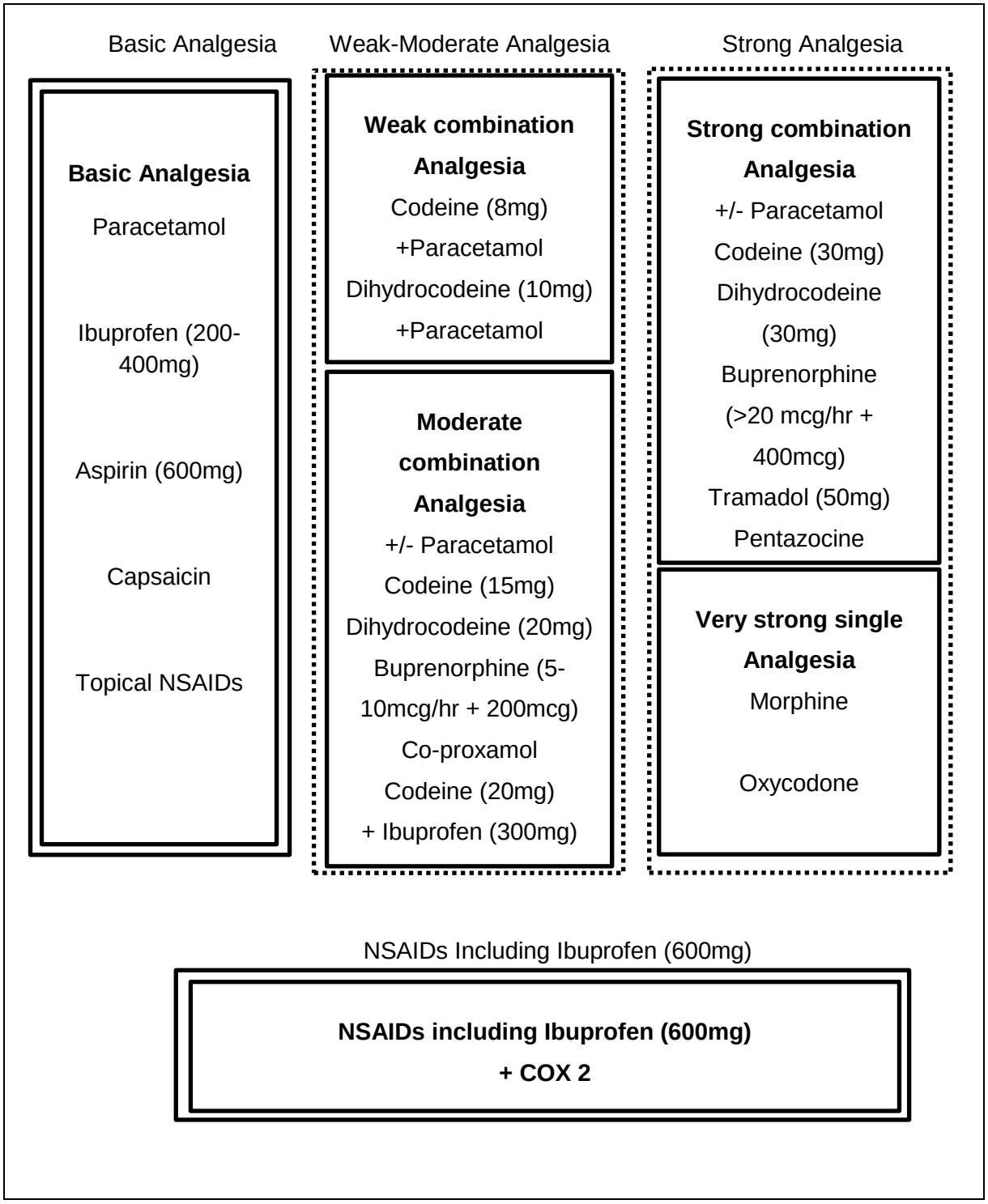


Figure 3.1.2: Flexible Hierarchical Analgesia Categorisation model for prescribing analgesia and NSAIDs in primary care




**Solid boxes** – The initial categorisations in the HAC model, **Dotted boxes** – Categorisations used in the analysis

For this thesis, due to the low prevalence of prescriptions from, in particular, the very strong analgesia category of the HAC and to aid interpretation, the HAC groupings are simplified by combining closely similar categories of analgesia equipotency. In the

analysis of initially prescribed analgesia in new MSK consulters (Chapter 4), the categories are reduced into four main groups of basic analgesia, weak-moderate analgesia, strong analgesia and NSAIDs, by combining weak and moderate analgesia (weak-moderate analgesia), and strong analgesia with very strong analgesia (strong analgesia). In chapter 5-9, five main categories of basic analgesia, weak analgesia, moderate analgesia, strong analgesia and NSAIDs are used (Figure 3.1.2).

While it was intended to use the HAC in its original form, the low prevalence of prescribing from some categories as outlined above prompted the reduction to four groups in Chapter 4. However due to the longer follow-up period used from Chapter 5 onwards, and hence increasing number of patients' prescribed weak and moderate analgesia, these were considered separately in these Chapters.

### 3.1.1 Basic analgesia

Basic analgesia are non-opioids; their possible side effects are toxicity when excessive dosages are consumed or in patients with impaired liver function, malnutrition or dehydration (Ehrlich, 2003; Fitzcharles et al., 2010). The majority of basic analgesia can be bought over the counter without a prescription (paracetamol, lower strength ibuprofen, topical NSAIDs, and aspirin) whilst all of them, including capsaicin, are available on prescription.

According to the WHO analgesia ladder, basic analgesia, for example, paracetamol and ibuprofen are the first-line therapy for mild to moderate pain. They should be considered as the initial and on-going pharmacotherapy for the treatment of persistent pain, particularly MSK pain (Ehrlich, 2003; Fitzcharles et al., 2010).

### 3.1.2 Opioids

Within this thesis, opioid potency is determined through the use of the HAC. As seen in this categorisation, opioids can be considered in four categories depending on potency (Bedson et al., 2013). The first category of weak opioids (weak analgesia) (e.g. codeine

8mg and tramadol 37.5mg) is stronger than basic analgesia, moderate opioids (moderate analgesia) (e.g. codeine 15mg and nefopam) are stronger than weak opioids, and strong combination plus strong single opioids (strong analgesia) are stronger than moderate opioids.

Nefopam, for example, is a painkiller which reduces moderate pain. Exactly how it does this is not fully understood although it is thought to interrupt the way pain messages are sent to your brain from your body (Moulin, 2001). The use of Co-proxamol, a moderate analgesia, is now less prevalent in the UK due to the associated adverse effects recognized by national guidelines for GPs (Bedson et al., 2012).

Opioids are considered for moderate to severe pain, pain related functional impairment and diminished quality of life due to pain (Fitzcharles et al., 2010). They can be used independently or in combination with basic analgesia (Ehrlich, 2003; Moulin, 2001). It is recommended that patients using on-going opioid medications should be assessed regularly for attainment of therapeutic goals, adverse effects and safe and responsible use (Fitzcharles et al., 2010).

The use of opioids has been associated with higher frequency of constipation, nausea, dizziness, cognitive impairment, respiratory problems, depression and urinary retention, overdose, self-poisoning and fractures (Dunn et al., 2010; Saunders et al., 2001; Benyamin et al., 2008; Fitzcharles et al., 2010). For example, constipation is reported among 40 to 95% of patients using opioids and 80% of patients using opioids report at least one of the adverse effects (Benyamin et al., 2008; Saunders et al., 2001).

### 3.1.3 NSAIDs

The NSAIDs category in the HAC consists of non-steroidal anti-inflammatory drugs including Cyclooxygenase 2 (COX-2) which are non-opioids. Within the consensus exercise used to develop the HAC, GPs felt that they could not exactly position NSAIDs and COX-2 within the potency ladder, but they were considered stronger than basic

analgesia. They are deemed as second-line therapy (treatment that is given when initial treatment doesn't work, or stops working), either alone or as an adjunct to basic analgesia in the WHO ladder for management of moderate to severe MSK pain (Ehrlich, 2003; Fitzcharles et al., 2010).

NSAIDs are rarely used, and with much caution, in older patients who do not obtain desired relief from other therapies, but are commonly used in younger patients (Fitzcharles et al., 2010, Oshima et al., 1996). Their potential adverse effects include gastrointestinal complications, acute renal failure, and bleeding disorder, cardiovascular complications (hypertension, congestive heart failure and increased cardiac mortality) (Fitzcharles et al., 2010; Oshima et al., 1996). The prescription of COX-2s has been less prevalent in the UK in the recent past (Bedson et al., 2012), due to warnings in national guidelines and directives to clinicians about adverse effects.

## 3.2 Databases

The Consultations in Primary Care Archive (CiPCA) database, used to examine analgesia prescribed in a group of new MSK consulters in Chapters 4 - 7 is described in section 3.2.1. The NorStOP dataset used in chapters 8 and 9 is described briefly in section 3.2.2 and in more detail in chapter 8. The derivation of the socio-demographic and clinical factors to be investigated for association with prescription of analgesia, prescription patterns and switching of analgesia and outcomes is also described in this section.

### 3.2.1 Consultations in Primary Care Archive (CiPCA)

In the UK, over 95% of the population are registered with a general practice, and this is normally the first point of access to the National Health Service (Lis and Mann, 1995). Primary care prescription and consultation data for the period 2004-2010 from the Consultations in Primary Care Archive (CiPCA) is used in Chapters 4-7. Approval for establishing CiPCA for research purposes was granted by the North Staffordshire Research Ethics Committee (Jordan et al., 2007; Jordan et al., 2010).

CiPCA is a high quality database of consultation information from 13 general practices in North Staffordshire. It is similar to other national databases such as the National Survey of Morbidity in General Practice (MSGP4) in terms of percentage composition of registered patients by age group and sex, and the annual prevalence of persons consulting for MSK conditions (Jordan et al., 2007). The practices contributing to CiPCA cover a range of areas in terms of deprivation although generally North Staffordshire is more deprived than England as a whole (Jordan et al., 2010).

The high quality of the database is ensured through an annual cycle of assessment, feedback and training in morbidity coding of the general practices conducted by the Keele Research Centre (Porcheret 2004; Jordan et al., 2007). The database contains consultation and prescription records for over 100,000 patients from 13 general practices in North Staffordshire from 1998 onwards. 12 practices contributed continuously in the time frame of the study reported here. The information contained in the database includes a unique patient identifier, date of birth, gender, member of staff consulted, consultation text (up to the first 250 text characters), their registered practice and Read codes. Read codes (NHS Clinical Terminology Service (2005)) are a hierarchy of morbidity, disease symptoms and process codes. They become more specific or precise to a condition consulted for further down the hierarchy (Jordan et al., 2007; Jordan et al., 2010).

The prescription data is contained in a sister dataset (Prescriptions in Primary Care Archive (PiPCA)) to the consultation data and linkage is made using the unique patient identifiers. Data includes the BNF chapter, the drug item, issue date, quantity prescribed and price. Prescription data should be complete as clinicians must record the details electronically in order to prescribe medication (Porcheret 2004; Jordan et al., 2007; Jordan et al., 2010).

CiPCA / PiPCA has been used in primary care research studies that has led to, as of 9th October 2013, 16 peer-reviewed publications. A previous study in PiPCA utilised the HAC

categorisation of analgesia and found that significant changes to prescribing occur at times when national advice and guidelines are issued to GPs (Bedson et al., 2012). CiPCA has also been used to examine prevalence of regional (knee, back, foot, etc) MSK problems in primary care (Jordan et al., 2010; Menz et al., 2010), compare MSK prevalence cross-nationally (Jordan et al., 2013), determine current management of morbidity (for example, gout, Roddy et al., 2010) and the associations between pairs of morbidities (Roddy et al., 2013; Burton et al., 2010). The potential limitations of CiPCA are that it is based on a regional dataset, is limited to patients from general practices in Staffordshire. However, the quality of CiPCA as a primary care database and comparability to national and international databases means that the findings of this thesis should be generalizable to a broader population than North Staffordshire.

### 3.2.2 North Staffordshire Osteoarthritis Project (NorStOP)

The North Staffordshire Osteoarthritis Project (NorStOP) was a longitudinal general population survey between 2001 and 2011, of those aged 50 and over in the general practice registered population (Thomas et al., 2004). There are three study cohorts, NorStOP1, NorStOP2 and NorStOP3. This thesis uses the first two cohorts for which six year data had been collected at the time of analysis. The survey consisted of health questionnaires that collected information on several areas of life including socio-demographics, general health, bodily pain and interference of pain in their daily lives (Thomas et al., 2004). Similar questionnaires at baseline, three and six year follow-up were used in collecting the data and consent to view medical records was requested (Thomas et al., 2004).

NorStOP was designed to describe the prevalence of pain and pain interference with activities, determine the course of joint (hand, knee, hip and foot) pain and related disability over 6 years, and determine the factors associated with their onset and persistence. It has also been used to describe the prevalence of participation restriction. The baseline population mailed the health survey in NorStOP1 and NorStOP2 combined

was 20214 and 13986 (69%) responded to the survey. This thesis used those who consented to medical record review and responded to baseline and 3 year surveys. The medical record data contains the same information as for CiPCA.

More than 25 publications in peer reviewed journals have used the NorStOP data, for example, a study by Wilkie et al. (2008) found that both the onset and persistence of person-perceived participation restriction are more common in the older age-groups. Factors associated with future primary care prescription of opioids in those self-reporting joint pain have been evaluated using NorStOP based on the hierarchical analgesia categorisation (HAC), in which it was found that those most likely to receive a high-strength analgesia were younger aged, males, and those overweight or obese (Green et al., 2012). NorStOP has also been used to investigate the association between hand arthritis and disability (Myers et al., 2007), the effect of age on the onset of pain interference in older adults (Thomas et al., 2007) and factors associated with persistently reporting pain that does not interfere with life (Jordan et al., 2012).

Ethical approval for the NorStOP study was obtained from the North Staffordshire Local Research Ethics Committee (Thomas et al., 2004). A further description of the database and relevant variables is available in chapter 8.

## 3.3 Data management

The CiPCA database is a collection of routinely recorded medical information, and the data was not initially collected for statistical analysis, as such the data had to be cleaned and variables formulated for analysis as described below.

The inclusion criterion for the MSK consulters in the final dataset is described in detail in Chapter 4. Year on year prescription and consultation records from 2004 to 2010 were merged to create the complete dataset. All analgesia that can be prescribed for MSK pain then had to be categorised according to the HAC categories such that the 300+ analgesia

and combinations could be identified as basic analgesia, weak analgesia, moderate analgesia, strong analgesia, very strong analgesia and NSAIDs.

The identification of MSK conditions from consultation data to identify patients fitting the inclusion criteria is described below. Socio-demographic and clinical factors to be investigated for association with prescription of analgesia, prescription patterns and switching of analgesia were derived from the information available in the database.

### 3.3.1 Sample size

The sample sizes were dictated largely by the databases from which the study is based; hence the exact sample size required for the study was not calculated. However to ensure that the results derived from the study are credible, the minimum number of patients required was determined by reference to available literature from studies determining minimum sample sizes needed for Cox regression analysis in order to determine associated variables with outcomes in cohort studies within medical research.

Mallet et al. (2010) in a systematic review study evaluating the development of prognostic models in cancer research observed that a sample size of 500 patients or above was less likely to produce asymptotically biased parameter estimates. Hsieh and Philip (2000) in a simulation study to derive an appropriate sample size for a Cox proportional hazards regression model within medical research established that a sample size of 717 patients was adequate to fit a model with 90% power at 5% significance level with covariates' parameter estimates of 0.2 or a hazard ratio (HR) of 1.22, if the number of events was 215. Alternatively, a sample of 510 patients was adequate to fit a model with 80% power at 5% significance level with covariates' parameter estimate of 0.35 or a HR of 1.42, if the number of events was 51. It was therefore assumed that a cohort consisting of at least 720 patients will be adequate for this study, considering that switching analgesia is a common event in the management of MSK pain, implying a potentially large number of events. In main analyses of this study, the minimum sample size used is 1309.

### 3.3.2 Identification of conditions from consultation data through Read Codes

The first task was to identify patients who had consulted for MSK conditions through the Read codes and Read terms entered by their GPs at their consultations. Read codes are a hierarchical classification commonly used in UK general practice to record medical conditions (NHS Clinical Terminology Service: Clinical Terms Version 3 (Read Codes); (Jordan et al., 2010; Bedson et al., 2007; Benson 2011), while Read terms are a brief description of the condition and location.

The Read Code classification has five digit alpha-numeric codes using the numerals 0–9 (indicating process of care), and the letters A–Z (indicating diagnostic Chapter), The first character relates to level 1 (for letters A-Z, the Read Chapter, broadly categorised morbidity, for example, N = musculoskeletal), the second to level 2 (Type of condition) and so on (Jordan et al., 2010; Benson, 2011). This makes the Read codes more disease and location specific as one moves down the levels, (for example, Read Code N05z6 has the Read Terms "osteoarthritis of the lower leg" and "osteoarthritis of the knee") (Jordan et al., 2010). The Read code together with the Read Terms therefore identifies the precise MSK condition and location.

The Read codes were also used to categorise MSK consultations by body region (back, hip, knee, shoulder, arm, neck, ankle and foot and other/unspecified) using a previously derived classification (Jordan et al., 2010). "Unspecified" problems tended to be codes where either no region was described in the associated Read Term (e.g. the term simply specified "arthralgia") or the problem covered more than one region (Jordan et al., 2010). The existence of co-morbidity and previous MSK consultations were also identified through the Read Codes.

For this thesis, all codes under Chapter N “MSK and connective tissue diseases”, Chapter R, “Symptoms, signs and ill-defined conditions” and Chapter 1 "History/Symptoms" were

selected as they include codes deemed to be predominantly MSK and have been used in previous research by Jordan et al. (2010). Chapter S, “Injury and Poisoning” can be classified as including MSK conditions (injuries) but was excluded for reasons described in Chapter 4. Jordan et al. (2010) derived all morbidity Read codes potentially relating to pain or MSK conditions within the database CiPCA. Snapshots of the first 45 Read Codes for each of chapter 1, N and R, together with the Read Terms and region of pain are included in Appendix A.

### 3.3.3 Socio-demographic and clinical factors assessed for association with analgesia prescribing

Medical record databases contain a wide range of patient information which may or may not be related to the progression and management of MSK conditions. The socio-demographic, clinical factors routinely recorded in primary care being evaluated in the thesis are age, gender, deprivation, registered practice, staff consulted, region of pain, previous MSK consultation, previous prescribed analgesia, and co-morbidity. These factors, selected for investigation in this study for their association with medication management, are those that have been found in the literature or are assumed to be related to pain, MSK conditions and specifically the prescription of specific analgesia.

For instance increasing age and female gender are associated with higher prevalence of MSK conditions, while the prescription of NSAIDs is more prevalent in younger patients and not recommended among the elderly (Wood 1999; Fitzcharles et al., 2010). Exposure to low social support and low social participation which are a common feature among deprived localities are also associated with higher levels of MSK pain (Jordan et al., 2008). In the UK, low income families do not pay for their prescriptions, hence it can be hypothesised that the prescription patterns and utilisation of health services will vary with varying levels of deprivation. It can also be assumed that variables that can be closely linked to individuals’ life-style can have an impact on the prescription patterns too.

General practices have different staffing levels in terms of numbers and in diversity (experience, prescribing habits) of health practitioners, it is therefore logical to assume that even though clinicians are guided by national guidelines, there are aspects of prescribing that are open to individual interpretation depending on the clinician's interest in the MSK condition. For example different general practitioners may manage MSK conditions differently (Richette et al., 2011). The prevalence of pain and pain interference vary by location of pain (Thomas et al., 2004), while stronger analgesia is recommended for moderate to severe pain that restricts movement and reduce the quality of life (Fitzcharles et al., 2010). It can therefore be assumed that the pain location may be an important determinant of the prescription patterns in MSK conditions.

The previous MSK consultation and previous prescribed analgesia give a brief medical and analgesia history of the patient which GPs may consider in deciding whether to give medication or not, and which medication to prescribe (Schneider, 2010). GPs are also known to consider the existence of co-morbidities when they decide which analgesia to prescribe (Richette et al., 2011, Fitzcharles et al., 2010).The prescription of NSAIDs is not recommended among patients known to have diabetic related complications such as vascular disease, chronic obstructive pulmonary disease (COPD), cardiovascular, chronic kidney and gastro-intestinal complications (Fitzcharles et al., 2010).

The detailed definition and description of all the socio-demographic and clinical characteristics evaluated for association with initial analgesia, prescription patterns and analgesia switching is given in the next chapter.

# Chapter 4

## 4 Pain medication prescriptions issued at first musculoskeletal consultation

### 4.1 Introduction

WHO guidelines on the management of MSK pain recommend clinicians administer basic analgesia like paracetamol or topical NSAIDS for pain relief prior to considering other alternatives (Ehrlich, 2003). Chapter 3 outlined the close relationship between the WHO guidelines and the categorisations by Bedson et al. (2009) of analgesia available for prescription. The adverse effects associated with analgesia use were highlighted as well as the factors which may be associated with analgesia use. It also described the CiPCA general practice database, the proposed use of Read codes in identifying MSK conditions and the rationale for the factors selected as potentially associated with the initiation and prescription of analgesia.

Chapter 4 aims to evaluate the current practices in the pharmacological management of MSK conditions at the onset of seeking or accessing medical care and evaluate whether patients are prescribed medication on their first consultation, what medication is prescribed, and the factors associated with being prescribed pain medication and the medications used. The chapter sets the reference point for the future analyses assessing switching from one group of analgesia to another.

The specific objectives of this chapter are to:

1. Establish if patients are prescribed pain medication at the onset of consulting for a MSK condition.
2. Establish which groups of analgesia are prescribed at the initial consultation.
3. Determine characteristics associated with being prescribed any analgesia.

4. Determine factors associated with being prescribed higher potency analgesia rather than basic analgesia.

## 4.2 Methods

### 4.2.1 Data management and study population

The Consultations in Primary Care Archive (CiPCA) for the period 2004-2006 served as the source of the data. Data from the 12 general practices with complete information for that period was used. The information contained in the database includes unique anonymised patient identifier, date of birth, gender, deprivation of the patient's local neighbourhood, member of staff consulted, their registered practice and Read morbidity codes. The prescription data includes the BNF chapter, the drug item, and issue date. A full description of CiPCA is given in Chapter 3.

The patients included in the analysis consisted of those who;

- Had a record of any MSK condition (MSK) in 2006,
- Had no prior MSK consultation and no prescribed analgesia medication within 12 months preceding their first MSK consultation in 2006,
- Were aged 15 and above at time of consultation in 2006.

Injuries were excluded from the definition of a MSK consultation based on the objectives of the main study (Chapter 1), to follow MSK conditions over time, as in the majority of cases injuries tend to be self-limiting and of relatively short duration.

The inclusion criteria are defined in this way since it is reasonable to assume that any patient who does not consult for, and does not receive prescribed analgesia medication for 12 months, does not have a chronic or persistent MSK condition that is currently considered by the patient as a troublesome (Moulin, 2001).

### 4.2.2 Outcome measures

The two dependent variables were i) receiving prescribed analgesia within 14 days of first MSK consultation in 2006 and ii) the analgesia group (1-6) of the medication prescribed at this time. However due to the small numbers of patients prescribed moderate analgesia and strong single analgesia, weak analgesia were combined with moderate analgesia, and strong combination analgesia were combined with very strong single analgesia. This meant that the analgesia groups were reduced to: 1- basic analgesia, 2 - weak-moderate analgesia, 3 - strong analgesia and 4 - NSAIDs.

### 4.2.3 Socio-demographic and clinical characteristics

The factors being evaluated for their association with pain medication prescription on first consultation were age, gender, deprivation, co-morbidity, registered practice, staff consulted, region of pain, previous consultation and medication history. Age is considered both as a continuous and categorical variable while all other variables are categorical. The age of the patients was calculated as of the 1st of July 2006 and grouped into the following categories: 15-29, 30-44, 45-59, 60-74, and 75+. The age group 30-44 is used as the reference category as the prevalence of MSK conditions increases with age as observed in the study by Jordan et al. (2007); a recognisable upward trend starts from this age group. Using the age group 15-29 where the prevalence is very low will mean a very high disparity with the older age groups leading to overinflated parameter estimates.

Neighbourhood deprivation was based on the Index of Multiple Deprivation 2007. This is linked to the postcodes of patient addresses (Department for Communities and Local Government, 2007). The deprivation ranks range from 1 to 32,482, with 1 being the most deprived neighbourhood and 32,482 least deprived in England. This variable was categorised into 3 levels with patients in the lower third based on deprivation rank being the most deprived, the middle third moderately deprived and the top third least deprived. The staff member consulted was categorised into GPs and all other medical staff (such as practice nurses and nurse practitioners).

The region of pain was categorised as back, knee, hip, neck, foot and ankle, arm (hand, wrist, arm, elbow and upper limb), shoulder, and other or unspecified. The specified areas are the most common locations of MSK pain (Littlejohn, 2005). Identification of pain region used a previously derived classification by Jordan et al. (2010) which is described in Chapter 3. Previous consultation for a MSK problem was defined as having a recorded MSK consultation in the period 12 to 24 months before the baseline MSK consultation. Similarly, previous prescribed analgesia was defined as receiving any prescribed analgesia 12 to 24 months before the baseline MSK consultation. These variables give a brief medical history of the patient which clinicians may consider in deciding whether to give medication or not and which medication to prescribe (Sullivan et al., 2005).

Co-morbidity was defined as the presence in the primary care records of one or more specified disorders or diseases in the period 0-24 months before the baseline MSK consultation. The specific comorbidities were diabetes, chronic obstructive pulmonary disease (COPD), depression, cardiovascular disease, chronic kidney disease, gastro-intestinal, and neoplasm. These are long term comorbidities which clinicians take into consideration when deciding which type of analgesia to prescribe (Sullivan et al., 2005), and some have been discussed in section 3.3.2.

The Read Codes were selected after discussion with a clinician (John Bedson) who is also my supervisor. The Read Codes of the selected comorbidities are C10… for diabetes, H3… for COPD, E2… for depression, G2…, G6… and G8… for cardiovascular diseases, 1Z1… for chronic kidney, J… for gastro-intestinal and B… for neoplasms. The registered general practices are anonymously coded as 1 – 12; hence this variable has 12 levels.

### 4.2.4 Statistical Methods

The analyses were designed to evaluate which factors are associated with being prescribed pain medication on first consultation and, if prescribed medication, which factors are associated with the potency level of medication prescribed. For the first analysis, multilevel logistic regression was used to evaluate the association of being prescribed any pain medication on first consultation with the patient and practice characteristics listed above.

A second analysis was performed on only those receiving a pain medication. A multilevel multinomial logistic regression model with the analgesia group as the outcome variable was used to assess associations of patient characteristics with receiving analgesia from each of the analgesia groups. The reference category was group 1 (basic analgesia).

The general practice (level 2) variable was included as a random variable (a variable accounting for between practice variations), while patient characteristics (level 1) were fixed effects in both analyses.

Both adjusted and unadjusted multilevel logistic and multilevel multinomial models were fitted with statistical significance evaluated at the 5% level using the statistical package Stata. The adjusted model is the model in which all clinical and socio-demographic variables are included in the model, while the unadjusted model is the model in which only one variable is included at a time.

It was not necessary to incorporate methods to address missing data in the analyses. The outcome variables had no missing values. Of the independent variables, only pain location had potentially missing data. Within the dataset, the Read Terms (described in Chapter 3) were sometimes ambiguous in the location of pain, such as “sports injury”, making it impossible to identify the exact region. The category of the pain location variable labelled “other/unspecified” accounts for these non-specific regions (about 2% of patients).

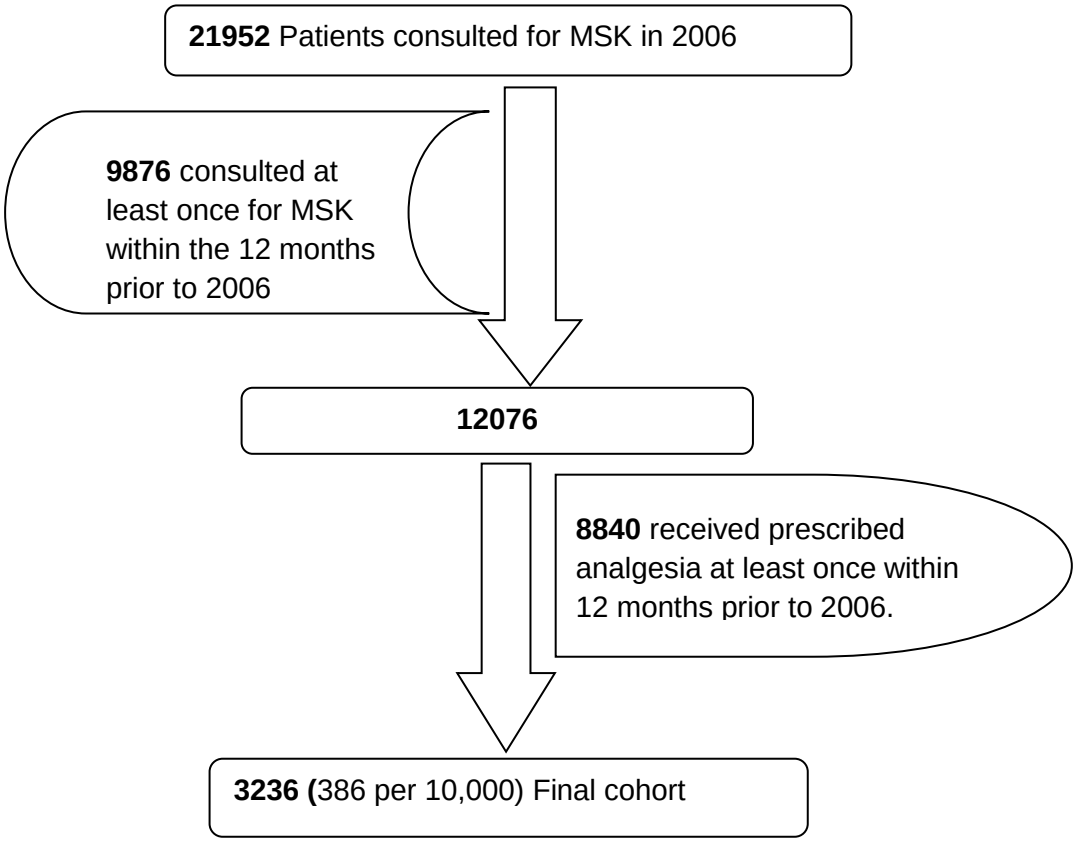
## 4.3 Results

The results show the number of patients who consulted for MSK conditions, the number fitting the inclusion criteria and the number prescribed analgesia on first consultation. The proportions of the patients prescribed each analgesia category according to the socio-demographic and clinical characteristics are given, together with the characteristics associated with being prescribed analgesia and the potency category.

### 4.3.1 New consulters for musculoskeletal conditions

In 2006, there were 83,875 patients aged 15 and over registered at the 12 practices. 3236 (386 per 10,000) patients were identified as fitting the study inclusion criteria (section 4.2.1), that is having a new consultation for a MSK problem in 2006 and aged 15+.

Figure 4.3.1: Flowchart of patients consulting for MSK problem



### 4.3.2 Patients consulting for a new MSK conditions

The mean age of these 3236 patients was 43 years (SD 15.8), and 1916 were males with mean age 44 years (SD 17.3), while 1320 were females with mean age 42 years (SD 14.8). The mean age of the 1344 prescribed analgesia on first consultation was 45 years (SD 15.8). Age is summarised in Table 4.3.1.

Table 4.3.1: Mean (SD) age of patients with new consulting episode of musculoskeletal pain in 2006

| | **Overall** | | | **Prescribed analgesia** | | |
|---|---|---|---|---|---|---|
| **Variable** | N | Mean | SD | n | Mean | SD |
| All | 3236 | 43 | 15.8 | 1344 | 45 | 15.8 |
| Females | 1320 | 42 | 14.8 | 551 | 46 | 17.3 |
| Males | 1916 | 44 | 17.3 | 793 | 44 | 14.7 |

The age group 30-44 made up 33% of the patients consulting for a new MSK problem in 2006; while the age group 75+ made up the least, 3%. 59% were males while 41% were females. The back was the most common site of the MSK problem (26%), followed by the knee (11%). Least commonly affected was the hip (6%), with other or unspecified regions accounting for 26% (Table 4.3.2).

13% had a recent history of consulting for a MSK problem, albeit not within the previous 12 months, and 16% had received pain medication 12-24 months before their 2006 consultation. Eighty-one per cent were seen by General Practitioners, 19% by other staff members including nurse practitioners and practice nurses. A detailed description of patients by each characteristic is given in Table 4.3.2.

Table 4.3.2: Socio-demographic and clinical characteristics of patients with new consulting episode of musculoskeletal pain in 2006

| Variable | | | Prescribed analgesia | |
|---|---|---|---|---|
| | N | Column % | n | Row % |
| **Total** | 3236 | - | 1344 | 42 |
| **Age (years)** | | | | |
| 15-29 | 710 | 22 | 224 | 32 |
| 30-44 | 1081 | 33 | 448 | 41 |
| 45-59 | 963 | 30 | 428 | 44 |
| 60-74 | 374 | 12 | 181 | 48 |
| 75+ | 108 | 3 | 63 | 58 |
| **Gender** | | | | |
| Females | 1320 | 41 | 551 | 42 |
| Males | 1916 | 59 | 793 | 41 |
| **Previous musculoskeletal consultation** | | | | |
| Yes | 413 | 13 | 163 | 39 |
| No | 2823 | 87 | 1181 | 42 |
| **Previous analgesia prescription** | | | | |
| Yes | 512 | 16 | 244 | 48 |
| No | 2724 | 84 | 1100 | 40 |
| **Region of Pain** | | | | |
| Back | 838 | 26 | 465 | 55 |
| Knee | 341 | 11 | 144 | 42 |
| Hip | 203 | 6 | 68 | 33 |
| Foot and Ankle | 223 | 7 | 94 | 42 |
| Arm | 314 | 10 | 105 | 33 |
| Shoulder | 245 | 8 | 129 | 53 |
| Neck | 218 | 7 | 93 | 43 |
| Other/unspecified | 854 | 26 | 246 | 29 |
| **Co-morbidity** | | | | |
| Selected | 119 | 4 | 63 | 53 |
| None | 3117 | 96 | 1281 | 41 |
| **Deprivation** | | | | |
| Most | 1430 | 44 | 624 | 44 |
| Moderate | 1263 | 39 | 508 | 40 |
| Least | 543 | 17 | 212 | 39 |
| **Staff category** | | | | |
| GPs | 2616 | 81 | 1117 | 43 |
| Other | 620 | 19 | 227 | 37 |
| **Practice** | | | | |
| 1 | 254 | 8 | 79 | 31 |
| 2 | 224 | 7 | 78 | 35 |
| 3 | 219 | 7 | 77 | 35 |
| 4 | 253 | 8 | 76 | 30 |
| 5 | 161 | 5 | 59 | 37 |
| 6 | 283 | 9 | 115 | 41 |
| 7 | 420 | 13 | 241 | 57 |
| 8 | 324 | 10 | 143 | 44 |
| 9 | 288 | 9 | 130 | 45 |
| 10 | 327 | 10 | 166 | 51 |
| 11 | 143 | 4 | 57 | 40 |
| 12 | 340 | 11 | 123 | 36 |

### 4.3.3 Analgesia prescriptions

Table 4.3.3: Socio-demographic and clinical characteristics of patients prescribed each group of analgesia

| | Pain medication prescribed | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | **Basic Analgesia** | | **Moderate Analgesia** | | **NSAIDs** | | **Strong Analgesia** | |
| **Total** | **n** | **% [c]** | **n** | **% [c]** | **n** | **% [c]** | **n** | **% [c]** |
| | **321** | 24 | **239** | 18 | **637** | 47 | **147** | 11 |
| **Age (years)** | | | | | | | | |
| 15-29 | 85 | 26 | 28 | 12 | 96 | 15 | 15 | 10 |
| 30-44 | 73 | 23 | 66 | 28 | 250 | 39 | 59 | 40 |
| 45-59 | 79 | 24 | 77 | 32 | 221 | 35 | 51 | 35 |
| 60-74 | 53 | 17 | 44 | 18 | 65 | 10 | 19 | 13 |
| 75+ | 31 | 10 | 24 | 10 | 5 | 1 | 3 | 2 |
| **Gender** | | | | | | | | |
| Females | 137 | 43 | 118 | 49 | 230 | 36 | 66 | 45 |
| Males | 184 | 57 | 121 | 51 | 407 | 64 | 81 | 55 |
| **Previous musculoskeletal consultation** | | | | | | | | |
| Yes | 33 | 10 | 28 | 12 | 83 | 13 | 19 | 13 |
| No | 288 | 90 | 211 | 88 | 554 | 87 | 128 | 87 |
| **Previous analgesia prescription** | | | | | | | | |
| Yes | 40 | 12 | 49 | 21 | 127 | 20 | 28 | 19 |
| No | 281 | 88 | 190 | 79 | 510 | 80 | 119 | 81 |
| **Region of Pain** | | | | | | | | |
| Back | 64 | 20 | 114 | 48 | 203 | 32 | 84 | 57 |
| Knee | 44 | 14 | 11 | 5 | 84 | 13 | 5 | 3 |
| Hip | 10 | 3 | 13 | 5 | 38 | 6 | 7 | 5 |
| Foot and Ankle | 26 | 8 | 10 | 4 | 54 | 9 | 4 | 3 |
| Arm | 31 | 10 | 8 | 3 | 47 | 7 | 1 | 1 |
| Shoulder | 34 | 10 | 14 | 6 | 71 | 11 | 10 | 7 |
| Neck | 17 | 5 | 15 | 6 | 44 | 7 | 17 | 12 |
| Other/unspecified | 95 | 30 | 54 | 23 | 96 | 15 | 19 | 13 |
| **Co-morbidity** | | | | | | | | |
| Selected | 20 | 6 | 13 | 5 | 22 | 3 | 8 | 5 |
| None | 301 | 94 | 226 | 95 | 615 | 97 | 139 | 95 |
| **Deprivation** | | | | | | | | |
| Most | 146 | 46 | 123 | 52 | 277 | 43 | 78 | 53 |
| Moderate | 120 | 37 | 82 | 34 | 254 | 40 | 52 | 35 |
| Least | 55 | 17 | 34 | 14 | 106 | 17 | 17 | 12 |
| **Staff category** | | | | | | | | |
| GPs | 273 | 85 | 210 | 88 | 523 | 82 | 111 | 76 |
| Other | 48 | 15 | 29 | 12 | 114 | 18 | 36 | 24 |

**c = Column %**

1344 (42%) patients received prescribed analgesia within 14 days of their new MSK consultation (Table 4.3.2). Of those who received prescribed pain medication, 24% received basic analgesia, 18% weak or moderate analgesia, 11% strong analgesia and 47% NSAIDs (Table 4.3.3). Socio-demographic and clinical characteristics of those prescribed the different types of analgesia are detailed in Table 4.3.3.

### 4.3.4 Factors associated with prescription of analgesia

The associations of prescribing any analgesia with socio-demographic and clinical factors are shown in Table 4.3.4. Both adjusted and unadjusted odds ratios (OR) are included in the Table but only adjusted odds ratios are interpreted below. There was significant practice variation in the decision to prescribe (range across practices of 30% to 57% of patients receiving analgesia) with variation between practices accounting for 9% of unexplained variation in patients being prescribed analgesia in the multivariable model with all patient characteristics included.

Compared to the 30-44 year old age group, the odds of being prescribed an analgesia on first consultation were significantly less in those aged 15 to 29 (OR 0.69 95% CI [0.56, 0.85]) but higher in those aged 45 to 59 (1.23 [1.02, 1.49]), 60 to 74 (1.51 [1.17, 1.95]), and those aged over 75 (2.28 [1.49, 3.49]). Those in the least deprived areas were least likely to receive an analgesia prescription (0.69 [0.55, 0.86]). Analgesia were most likely to be prescribed for those with pain in the back; however, no difference was apparent between those with shoulder and back problems. Those who had received prescribed analgesia in the past were more likely to be prescribed analgesia at this new consultation (1.24 [1.01, 1.54]).

There were no significant relationships of being prescribed analgesia with comorbidity, gender or whether the patient saw a GP or other medical staff.

Table 4.3.4: Associations with prescription of any analgesia at new consultation for musculoskeletal pain

| | OR [95% CI] | | |
|---|---|---|---|
| **Model** | **Unadjusted** | **Adjusted** | **Adjusted P-value** |
| **Fixed effects** | | | |
| **Age Group** | | | |
| 30-44 | 1.00 | 1.00 | - |
| 15-29 | 0.65 [0.53, 0.80] | **0.69 [0.56, 0.85]** | < 0.001 |
| 45-59 | 1.12 [0.94, 1.34] | **1.23 [1.02, 1.49]** | 0.025 |
| 60-74 | 1.28 [1.01, 1.64] | **1.51 [1.17, 1.95]** | 0.002 |
| 75+ | 1.85 [1.23, 2.78] | **2.28 [1.49, 3.49]** | < 0.001 |
| **Gender** | | | |
| Male | 1.00 | 1.00 | - |
| Female | 1.00 [0.87, 1.15] | 1.02 [0.88, 1.19] | 0.780 |
| **Previous musculoskeletal consultation** | | | |
| No | 1.00 | 1.00 | - |
| Yes | 0.89 [0.72, 1.09] | 0.83 [0.66, 1.05] | 0.119 |
| **Previous analgesia prescription** | | | |
| No | 1.00 | 1.00 | - |
| Yes | 1.24 [1.03, 1.49] | **1.24 [1.01, 1.54]** | 0.045 |
| **Pain Region** | | | |
| Back | 1.00 | 1.00 | - |
| Knee | 0.59 [0.46, 0.77] | **0.56 [0.43, 0.72]** | < 0.001 |
| Hip | 0.38 [0.27, 0.52] | **0.35 [0.25, 0.49]** | < 0.001 |
| Foot and Ankle | 0.55 [0.40, 0.74] | **0.52 [0.38, 0.71]** | < 0.001 |
| Arm | 0.40 [0.30, 0.54] | **0.39 [0.29, 0.53]** | < 0.001 |
| Shoulder | 0.90 [0.67, 1.20] | **0.81 [0.60, 1.08]** | 0.155 |
| Neck | 0.58 [0.43, 0.79] | **0.57 [0.42, 0.78]** | < 0.001 |
| Other/unspecified | 0.32 [0.26, 0.39] | **0.29 [0.24, 0.37]** | < 0.001 |
| **Comorbidity** | | | |
| Selected | 1.00 | 1.00 | - |
| None | 0.64 [0.44, 0.92] | 0.77 [0.52, 1.13] | 0.217 |
| **Deprivation** | | | |
| Most | 1.00 | 1.00 | - |
| medium | 0.85 [0.73, 1.01] | **0.80 [0.67, 0.95]** | 0.012 |
| least | 0.77 [0.63, 0.95] | **0.69 [0.55, 0.86]** | 0.001 |
| **Staff category** | | | |
| Other | 1.00 | 1.00 | - |
| GP | 0.85 [0.70, 1.02] | 0.85 [0.69, 1.04] | 0.108 |
| **Random effect** | **VARIANCE** | | |
| **Practice** | 0.08 [0.03, 0.21] | **0.09[0.03, 0.23]** | < 0.001 |

**Unadjusted model =** Individual variable in the model, **Adjusted model =** All variables included simultaneously

### 4.3.5 Factors associated with type of analgesia prescribed

In the 1344 patients prescribed analgesia, there was wide variation between practices in type of analgesia prescribed. Variation between practices accounted for 27% of all remaining variation in type of medication prescribed in the multivariable model including all patient and practice characteristics.

Table 4.3.5 shows the associations of socio-demographic and clinical factors with type of analgesia in those prescribed analgesia. Compared to those aged 30-44, patients aged 15-29 were more likely to receive basic analgesia than weak-moderate analgesia, strong analgesia or NSAIDs. In the case of NSAIDs for example, for patients aged 15-29 the adjusted relative risk ratio (RRR) was (0.30 95% CI [0.20, 0.46]) compared to the 30-44 age group. Also a decreased chance of NSAID prescription was also evident in those aged over 60 (for example, aged 75 and above, RRR 0.05 [0.02, 0.13]). Females were more likely than males to be prescribed weak-moderate analgesia compared to basic analgesia (RRR 1.45 [1.02, 2.09]). A previous history of analgesia prescription was associated with the prescribing of stronger analgesia compared to basic analgesia (for example, weak-moderate analgesia, RRR 1.88 [1.11, 3.10]). Strong analgesia were less likely to be prescribed than basic analgesia to those living in the least deprived areas (RRR 0.45 [0.23, 0.88]). There was a non-significant increased likelihood of being prescribed NSAIDs if the patient did not have comorbidity (RRR 1.89 [0.96, 3.73])

Those with back pain were more likely to be prescribed weak-moderate analgesia, strong analgesia and NSAIDs than basic analgesia compared to those presenting with MSK problems in other regions. Those who were seen by GPs were more likely to be prescribed strong analgesia than basic analgesia (RRR 1.74 [1.01, 3.02]).

Table 4.3.5: Associations with type of analgesia prescribed at new consultation for musculoskeletal pain in those prescribed an analgesia

| MODEL | RRR [95% CI] | | | | | |
|---|---|---|---|---|---|---|
| **Fixed effects** | **Weak-moderate Analgesia** | | **Strong Analgesia** | | **NSAIDs** | |
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| **Age Group** | | | | | | |
| 30-44 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 15-29 | 0.33 [0.19, 0.57] | **0.32 [0.18, 0.57]** | 0.20 [0.10, 0.38] | **0.20 [0.10, 0.40]** | 0.30 [0.20, 0.45] | **0.30 [0.20, 0.46]** |
| 45-59 | 1.07 [0.67, 1.17] | 1.32 [0.81, 2.15] | 0.79 [0.48, 1.30] | 1.04 [0.62, 1.78] | 0.81 [0.56, 1.18] | 0.83 [0.54, 1.22] |
| 60-74 | 0.87 [0.51, 1.46] | 1.19 [0.67, 2.13] | 0.42 [0.22, 0.78] | 0.71 [0.35, 1.42] | 0.34 [0.21, 0.53] | **0.35 [0.22, 0.57]** |
| 75+ | 0.76 [0.40, 1.47] | 1.01 [0.50, 2.05] | 0.11 [0.03, 0.37] | **0.18 [0.05, 0.64]** | 0.04 [0.02, 0.11] | **0.05 [0.02, 0.13]** |
| **Gender** | | | | | | |
| Male | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Female | 1.32 [0.94, 1.86] | **1.45[1.02, 2.09]** | 1.10 [0.74, 1.62] | 1.31 [0.85, 2.01] | 0.77 [0.58, 1.01] | 0.95 [0.70, 1.28] |
| **Previous musculoskeletal consultation** | | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.10[0.64, 1.90] | 0.86 [0.47, 1.58] | 1.23[0.67, 2.27] | 0.98[0.49, 1.95] | 1.24 [0.80, 1.93] | 0.93 [0.57, 1.54] |
| **Previous analgesia prescription** | | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.64 [1.03, 2.61] | **1.88 [1.11, 3.10]** | 1.49 [0.88, 2.56] | 1.72 [0.94, 3.16] | 1.58 [1.07, 2.35] | **1.74 [1.11, 2.71]** |

| MODEL | RRR [95% CI] | | MODEL | | RRR [95% CI] | |
|---|---|---|---|---|---|---|
| **Fixed effects** | **Weak-moderate Analgesia** | | **Strong Analgesia** | | **NSAIDs** | |
| | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Pain Region** | | | | | | |
| Back | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Knee | 0.13 [0.06, 0.26] | **0.11 [0.05, 0.23]** | 0.08 [0.03, 0.21] | **0.08 [0.03, 0.23]** | 0.54 [0.34, 0.87] | 0.65 [0.40, 1.08] |
| Hip | 0.72 [0.29, 1.77] | 0.61 [0.24, 1.55] | 0.53 [0.19, 1.48] | 0.62 [0.21, 1.81] | 1.18 [0.55, 2.56] | 1.59 [0.71, 3.55] |
| Foot and Ankle | 0.21 [0.09, 0.47] | **0.17 [0.07, 0.39]** | 0.11 [0.04, 0.35] | **0.10 [0.03, 0.32]** | 0.63 [0.37, 1.12] | 0.61 [0.34, 1.10] |
| Arm | 0.12 [0.05, 0.26] | **0.10 [0.05, 0.23]** | 0.02 [0.00, 0.14] | **0.02 [0.00, 0.13]** | 0.40 [0.24, 0.67] | **0.40 [0.24, 0.69]** |
| Shoulder | 0.22 [0.11, 0.45] | **0.18 [0.09, 0.37]** | 0.21 [0.10, 0.47] | **0.18 [0.08, 0.40]** | 0.62 [0.38, 1.05] | **0.56 [0.33, 0.96]** |
| Neck | 0.49 [0.23, 1.06] | 0.50 [0.23, 1.12] | 0.76 [0.35, 1.61] | 0.83 [0.37, 1.84] | 0.81 [0.43, 1.54] | 0.82 [0.42, 1.62] |
| Other/unspecified | 0.36 [0.22, 0.57] | **0.32 [0.20, 0.53]** | 0.17 [0.10, 0.32] | **0.18 [0.10, 0.34]** | 0.34 [0.22, 0.51] | **0.38 [0.25, 0.59]** |
| **Comorbidity** | | | | | | |
| Selected | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| None | 1.18 [0.57, 2.44] | 1.49[0.68, 3.26] | 1.18 [0.50, 2.76] | 1.40 [0.56, 3.53**]** | 1.89 [1.30, 3..57] | 1.89 [0.96, 3.73] |
| **Deprivation** | | | | | | |
| Most | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Medium | 0.85 [0.58, 1.26] | 0.75 [0.49, 1.13] | 0.85 [0.58, 1.33] | 0.76 [0.47, 1.22] | 1.17 [0.86, 1.61] | 1.19 [0.85, 1.67] |
| least | 0.74 [0.44, 1.23] | 0.58 [0.33, 1.01] | 0.58 [0.31, 1.09] | **0.45 [0.23, 0.88]** | 1.02 [0.68, 1.54] | 1.00 [0.64, 1.56] |
| **Staff category** | | | | | | |
| Other | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| GP | 0.79[0.47, 1.04] | 0.81[0.47, 1.39] | 1.86 [1.12, 3.09] | **1.74 [1.01, 3.02]** | 1.25 [0.84, 1.86] | 1.17 [0.77, 1.79] |
| **Random effect** | | | | | | |
| Practice | 0.27 [0.13] | | | | | |

**Unadjusted model** = Individual variable in the model**, Adjusted model** = All variables included simultaneously

## 4.4 Discussion

On first consultation for MSK conditions, 42% of the patients were prescribed analgesia. NSAIDs were most frequently prescribed followed by basic analgesia while opioids alone or in combination with other analgesia were the least prescribed. The higher potency opioids were less commonly prescribed. There was variation in prescription rates by different factors. Being prescribed any analgesia on first consultation was associated with the age of the patient, their level of neighbourhood deprivation, the body region in which they experienced pain and their registered general practice.

The chances of being prescribed weak-moderate analgesia over basic analgesia were associated with patient age, whether they are female, having received any analgesia in the past, the location of pain and the registered practice. The prescription of strong analgesia over basic analgesia is associated with patient age, level of deprivation, region of pain and registered practice. The chances of prescribing NSAIDs over basic analgesia are associated with patient age, region of pain, having received analgesia in the past, and registered practice.

Table 4.4.1 below gives a summary of the significant socio-demographic and clinical variables associated with being prescribed weak-moderate analgesia, strong analgesia and NSAIDs instead of basic analgesia, after adjusting for all possible variables.

Table 4.4.1: Summary of the factors associated with type of prescribed analgesia

| Variable | Weak - moderate Analgesia | Strong Analgesia | NSAIDS |
|---|---|---|---|
| **Age** | | | |
| 15-29 | <Yes | <Yes | <Yes |
| 30-44 | - | - | - |
| 45-59 | No | No | No |
| 60-74 | No | No | <Yes |
| 75+ | No | <Yes | <Yes |
| **Gender** | | | |
| Female | >Yes | No | No |
| **Previous musculoskeletal consultation** | | | |
| Yes | No | No | No |
| **Previous Analgesia prescription** | | | |
| Yes | >Yes | No | > Yes |
| **Pain region** | | | |
| Back | **-** | - | - |
| Knee | <Yes | <Yes | No |
| Hip | No | No | No |
| Foot and ankle | <Yes | <Yes | No |
| Hand and wrist | <Yes | <Yes | <Yes |
| Shoulder | <Yes | <Yes | <Yes |
| Neck | No | No | No |
| Other/Unspecified | <Yes | <Yes | <Yes |
| **Deprivation** | | | |
| Least | **-** | - | - |
| Medium | No | No | No |
| Least | No | <Yes | No |
| **Co-morbidity** | | | |
| Selected conditions | - | - | - |
| None | No | No | No |
| **Staff category** | | | |
| GPs | **-** | - | - |
| Other staff | No | >Yes | No |

Reference group = -, Significant increased likelihood of having analgesia = >Yes, Significant decreased likelihood of having analgesia = <Yes
Non-significant = No

The adherence to the WHO guidelines in starting pharmacological management of MSK pain is to some extent evident in that 58% of the patients consulting for the first time were not prescribed any pain medication while medications at the higher end of potency were less commonly prescribed (Bope et al., 2004). A previous study of those aged over 50 consulting in primary care for MSK pain, and who had not consulted in the previous 30 days, also reported that less than half were prescribed analgesia (Muller et al., 2012). The strongest opioid analgesia was prescribed less than basic analgesia on first consultation. Higher potency drugs are more likely to have adverse side effects while starting at low potency minimises exposure to side effects (Dunn et al., 2010; Saunders et al., 2001; Benyamin et al., 2008; Fitzcharles et al., 2010; Schneider, 2010). Hence it can be assumed that in addition to following the guidelines, clinicians do consider the risk of adverse effects.

Doctors consider whether a patient is young or elderly (Garbez and Puntillo, 2005; Benyamin et al., 2008) when deciding whether to prescribe analgesia or not and the level of potency to prescribe. Older age groups appear more likely to be prescribed analgesia which mirrors the consultation prevalence for MSK pain increasing with age (Jordan et al., 2007; Fitzcharles et al., 2010) such that for example, despite fewer patients being aged 75+, they are the most likely to be prescribed pain medication. It is likely that older patients had consulted previously for MSK pain and are able to communicate their pain and hence may be perceived by providers as experiencing more pain (Garbez and Puntillo, 2005; Saunders et al., 2001). The patient's communication of pain is regarded as the strongest predictor of the amount and strength of medication given (Eder et al., 2003) and a patient's experience gives meaning to their pain (Manias et al., 2002).

Patients aged over 75 were twice as likely to receive analgesia as younger age groups, but were less likely to be prescribed NSAIDs. This finding is in keeping with current advice on NSAID use in older patients who might be considered more likely to experience adverse effects such as renal toxicity (Sullivan et al., 2005; Wood, 1999) and

gastrointestinal haemorrhage (Akarca, 2005; Schneider, 2010; Fitzcharles et al., 2010) with NSAIDs. Stronger analgesia were less likely to be used in those aged over 75, a finding that has also been described previously (Benyamin et al., 2008; Edlund et al., 2007; Green et al., 2012; Walker-Bone et al., 2000). This would make clinical sense since using more potent opioid type drugs in the elderly has been associated with increased rates of falls and bone fractures (Dunn et al., 2010; Saunders et al., 2001; Benyamin et al., 2008; Fitzcharles et al., 2010; Schneider, 2010). Comorbidity was linked to a lower likelihood of being prescribed NSAIDs which also reflects the possibility that clinicians are avoiding using these drugs in patients more vulnerable to side effects (Schaffer et al., 2006). However, this finding was non-significant and the prevalence of our selected comorbidities in this group with new MSK problems was low.

Younger adults (15-29) were more likely to be prescribed basic analgesia, perhaps reflecting the less severe nature of pain in younger people with MSK problems (and are a possible reflection of adherence to analgesia guidelines). Due to their age, this group is less likely to have previous exposure to prescribed analgesia medication. Therefore where it is used, the first level of analgesia as suggested in these guidelines is most commonly prescribed (Sarzi-Puttini et al., 2005). Female patients were more likely to be prescribed weak- moderate analgesia over basic analgesia compared to male patients. Females are often perceived by GPs as experiencing more pain than males and females are better than males at communicating their pain (Garbez and Puntillo, 2005; Curatolo and Bogduk, 2001), which may influence the decision to prescribe more potent medication than basic analgesia.

GPs' knowledge of previous medication affects their prescribing; a patient with a record of previous medication is more likely to be given weak-moderate analgesia. GPs will generally inquire from the patient about their medication use prior to consultation (Garbez and Puntillo, 2005; Fitzcharles et al., 2010) which makes a potential case for the use of weak-moderate analgesia over previously used basic analgesia. Basic analgesia are

available over the counter without prescription, and patients first seen in primary care may already be using these medications.

Patients from the most deprived areas were more likely to be prescribed pain medication than patients from medium and least deprived areas. Patients from least deprived areas were less likely to be prescribed strong analgesia compared to most and medium deprivation patients. The association of level of deprivation with prescription of analgesia is closely related to findings by (Jordan et al., 2008; Berkman, 2004) that social characteristics such as neighbourhood level of unemployment have an additional detrimental effect on health.

The level of pain is associated with emotional distress, low social support and low social participation (Katz, 2002; Garbez and Puntillo, 2005). This high level of emotional distress may inflate the GP's perceived level of pain (Katz, 2002). People who live in socially deprived areas have more MSK symptoms (Urwin et al., 1998) which probably leads to them being prescribed analgesia due to potentially higher perceived levels of pain.

Patients in more deprived areas may rely on prescribed medication even for pain that can be eased with over the counter medications as prescriptions are free for low income patients in the UK. Patients from least deprived areas may prefer to purchase over the counter medications as they pay for their prescriptions, which is similar to findings by (Bedson et al., 2001) on factors affecting over the counter use of aspirin in cardiovascular diseases.

Patients with pain in the knee, hip, foot and ankle, hand and wrist, neck and other or unspecified parts were less likely to be prescribed pain medication than pain in the back. Pain in the knee, foot, ankle, hand, wrist, shoulder and other or unspecified parts was less likely to be prescribed weak or moderate analgesia and strong single or combination analgesia. Doctors use NSAIDs less for pain in the hand, wrist and shoulder and use strong analgesia less for pain in the knee, foot, ankle, hand, wrist, neck and shoulder.

Back pain limits the functional reach of limbs and the ability to rotate the trunk repetitively which is essential for mobility, and results in restrictions on individuals' social and physical activities and have a substantial impact on their life style (Rudy et al., 2007; Fitzcharles et al., 2010). Back pain also constitutes about 10% of all MSK conditions consulted for and is a leading cause of disability (Main 2002; Brooks, 2006). Therefore, the GPs may be more likely to perceive back pain as limiting in the day to day activities that a person has to perform hence the need to prescribe stronger pain medication for back pain. GPs may perceive pain differently in varying regions, in terms of the handicap it causes, back, knee and hip pain being debilitating in terms of mobility and shoulder, wrist and hand pain limiting daily activities such as washing, cooking, cleaning (Littlejohn, 2005).

The potential limitations of the study include that it is based on a regional dataset, is limited to patients selected over a 12 month consultation period, and the inclusion criteria may include patients with MSK pain episodes with a periodicity of more than 12 months and those who have been taking over the counter medications. Their initial consultation of 2006 and subsequent medication prescribed may not be a true reflection of the starting point of their pharmacological management for MSK pain. However the inclusion criteria ensures that it is reasonable to consider the patients as having no chronic pain prior to consulting as chronic pain is often defined as pain lasting more than three months, (Kraoenke et al., 2008). The inclusion criteria may eliminate patients who may have been treated for non-MSK conditions which are treatable with analgesia, leading to potential loss of co-morbidity or multi-morbidity patients.

GPs consider multiple factors including co-morbidity in deciding the medication and appropriate potency level (Bope et al., 2004); Garbez and Puntillo, 2005; Schneider, 2010). There may be other unmeasured variables like other contraindications for whether one may or may not be prescribed a certain drug although relevant comorbidities were examined. Pain severity, weight, alcohol misuse and ethnicity might also impact on

prescription of analgesia (Breckenridge and Clark, 2004) and these are not evaluated in the analysis.

Despite the limitations of the study, the important associations found have previously been observed in other related but different studies such as Muller et al. (2012). A study sample greater than 500 can adequately give reliable parameter estimates in logistic regression (Mallett, 2010) hence a sample of 3236 and 1344 can be assumed to be adequate in the multilevel logistic and multilevel multinomial logistic model respectively.

The data used in the study is drawn from a high quality data set, CiPCA, which gives comparable consultation prevalence Figures for MSK problems as the larger national datasets (Jordan et al., 2007). The study provides a good starting point for further research into the pharmacological management of MSK pain over time as it identifies baseline factors associated with prescription of analgesia.

## 4.5 Conclusion

The study is an evaluation of initial pain management strategies in the treatment of MSK pain and suggests that the HAC model of prescribing in general practice is a valuable tool in describing prescription dynamics. Not all patients consulting for a new episode of a MSK condition are prescribed analgesia. A variety of factors appear to be taken into account which also appear to influence, which category of analgesia is deemed suitable. The prescription profiles or pathways followed by different patients over time are investigated in the next chapter.

# Chapter 5

## 5 Prescription patterns of analgesia in musculoskeletal conditions in primary care over five years: A latent class analysis

### 5.1 Introduction

Chapter 4 identified socio-demographic and clinical characteristics associated with analgesia prescribing at the time of a new MSK consultation. The chapter demonstrated that the hierarchical analgesia categorisation (HAC) model has potential as a tool in describing prescribed analgesia issued at first consultation for MSK pain. That chapter highlighted that while some patients consulting for the first time are not prescribed pain medication, factors such as age of the patient, gender and previous prescribed analgesia seem to be taken into consideration when deciding to prescribe and the initial potency level given.

Changing analgesia is an essential feature of long term treatment of MSK pain in primary care (Ehrlich, 2003). There are several factors that may influence the need to change analgesia ranging from the pain intensity which may seriously limit mobility, side effects, effectiveness of the analgesia, co-morbidity and patient preference (Chou et al., 2005; Rahme et al., 2006). The use of stronger medication over time may be a marker for the severity of the pain and its effect on everyday activities (Hunt et al., 2007).

Changing or switching analgesia leads to patients having different prescribed medication profiles or pathways over time. A patient's medication profile over time can be a proxy for the severity of their MSK condition. The starting point for measuring management success or failure may be identifying the changes in prescribed analgesia based on the interpretation of the HAC analgesia ladder (Chapter 3), which reflects the World Health Organisation (WHO) (Ehrlich, 2003) guidelines for the treatment of MSK conditions.

As seen in Chapter 3, the WHO ladder suggests starting with non-opioid analgesia before moving up the potency ladder. The potency levels of the HAC prescribed over time can therefore define a medication pathway, enabling evaluation of what medication pathways or profiles that the patients are consigned to, based on their baseline characteristics. One hypothesis is that patient characteristics at the onset of pharmacological treatment are predictive of their eventual pathway. Additionally the predictive characteristics, if any, might help clinicians identify patients at risk of switching to more potent analgesia and accordingly 'flag' these patients for special monitoring.

The aim of the analysis set out in this chapter, therefore, is to use latent class analysis to identify common medication profiles defined by varying degrees of analgesia potency levels prescribed to MSK consulters over time and examine the socio-demographic and clinical variables associated with membership of each medication profile.

The specific objectives of the chapter are:

1. To determine if patients newly consulting with MSK problems can be grouped into a small number of distinct clusters based on the potency levels of their analgesia prescribed in primary care over 5 years
2. To assess the association of patient socio-demographic and clinical characteristics with the identified prescribing patterns
3. To determine whether latent class analysis is a feasible method for grouping patients based on analgesia prescriptions

Classifying patients using their prescribed analgesia potency levels over time and identifying the associations with clinical and socio-demographic factors have the potential to give a valuable insight into the current analgesia prescribing patterns in MSK conditions.

## 5.2 Methods

The pain analgesia profiles among MSK patients were identified through latent class analysis. The underlying principle of latent class analysis (Vermunt and Magidson, 2000) is that the pain medication profiles for the MSK consulters are assumed to be finite in number, are mutually exclusive combinations of the six potency levels within the HAC that are prescribed to the patients over time, and the patients within each cluster profile are homogenous with respect to medication potency levels received. The resulting medication profiles are then characterised by socio-demographic and clinical characteristics of patients using descriptive statistics and multilevel multinomial logistic regression.

### 5.2.1 Data management and study population

All the patients identified and included in the analysis in chapter 4, were considered in this analysis. A further addition to the inclusion criteria was that the patients remained registered throughout the five year period under consideration. Patients were excluded from the analysis if their registration records showed them as not registered in any of the years after 2006 up to the end of 2010. This was designed to ensure the patients were comparable in terms of exposure time or follow-up period, so that a comparison of those lost to follow-up and those followed to the end could be avoided as it is hypothesised that the prescription patterns are dependent on time. Pain medication profiles were therefore based on primary care prescription records from the first MSK consultation of 2006 up to the end of 2010.

### 5.2.2 Outcome measures

The outcome measures (the “indicator” variables) were the potency levels defined by the HAC model, which means there were six possible potency levels that patients can be prescribed under the HAC model over time. These were basic analgesia (BA), weak combination analgesia (WCA), moderate combination analgesia (MCA), strong combination analgesia (SCA) and very strong single analgesia (VSSA) and NSAIDs. The indicator variables were defined as binary variables, “prescribed” or “not prescribed”.

### 5.2.3 Socio-demographic and clinical characteristics

The baseline variables investigated for association with medication profiles over the 5 years were age, gender, deprivation, co-morbidity, registered practice, staff consulted (GP or other), region of pain at first MSK consultation (e.g. knee, back), previous MSK consultation and previous prescribed analgesia. All variables were used as categorical variables with age having five categories, deprivation with three categories of most, medium and least deprivation (Chapter 4). As in Chapter 4, comorbidity was also used as a binary variable: having at least one of the selected co-morbidities (diabetes, chronic obstructive pulmonary disease (COPD), depression, cardiovascular, chronic kidney, gastro-intestinal and neoplasm) or none.

### 5.2.4 Latent class analysis

The fundamental principle of latent class analysis (LCA) is that the responses to observed variables in a population can be grouped into finite distinct mutually exclusive and exhaustive unobserved sub-populations called latent classes (Henry and Muthen, 2010; Vermunt and Magidson, 2008). LCA assumes that that each patient belongs to one and only one latent class (or cluster) and that the response variables are mutually independent of each other within each latent class.

LCA has the potential to find clinically homogenous groups which can then be compared on baseline socio-demographic and clinical variables (Ahn et al 2008; Nylund et al., 2007). For example, a group prescribed only NSAIDs may be found to have common characteristics such as initial body region of pain and age group, which may confirm the known association of NSAID prescription and age, but highlight the importance of the region of pain in the decision making after age has been taken into consideration.

In this study LCA was used to determine groups of patients with similar analgesia potencies prescribed over five years. The potency levels are defined according to the HAC model, and they are as described above (section 5.2.2).

Let $Y_{ij}$ denote whether individual $i$ was prescribed category $j$ of the hierarchical analgesic categorisation (HAC), the response variable, where $1 \leq i \leq N, 1 \leq j \leq J$. $N$ is the total number of individuals, $J$ is the total number of response variables. In this case there are six observed binary response variables (the potency levels) (1=basic analgesics, 2=weak analgesics, 3=moderate analgesics, 4=strong combination analgesics, 5=strong single analgesics and 6=NSAIDs). $Y_{ij}$= 1 represents being prescribed the potency level *j* at least once during follow-up and 0 otherwise. Each patient is characterised by the vector $\mathbf{Y}_i=(Y_{i1}, Y_{i2}, Y_{i3}, Y_{i4}, Y_{i5}\, Y_{i6})$ which represents their prescribing pattern across the six potency levels

Let $X$ represent a single nominal variable consisting of $K$ distinct latent classes or clusters, $x = k: k = 1, 2, \dots, K$, which cannot be observed directly from the data. The basic idea underlying the latent class model is that the probability of an individual to have a prescription pattern $\boldsymbol{y}$, $P(\boldsymbol{Y_i} = \boldsymbol{y})$, is an average of the $K$ cluster-specific probabilities of having a prescription pattern given membership of cluster $k$. The assumption of local independence (the $J$ response variables are assumed to be independent within clusters) leads to the general form of LCA (based on notation of Vermunt and Magidson, 2008):

$$P(\boldsymbol{Y_i} = \boldsymbol{y}) = \sum_{k=1}^{K} P(X = k) \prod_{j=1}^{6} P(Y_{ij} = y_j | X = k)$$

$P(\boldsymbol{Y_i} = \boldsymbol{y})$ is the probability of an individual $i$ having a prescription pattern $\boldsymbol{y}$, $P(X = k)$ is the probability that a randomly selected individual belongs to cluster $k$ and specifies the estimated size of the cluster. $P(Y_{ij} = \mathrm{y}_j | \mathrm{X} = k)$ is the probability of receiving category $j$ given cluster membership of $k$. The multiplication of the six HAC category conditional probabilities, $\prod_{j=1}^{6} P(Y_{ij} = y_j | X = k)$ is a result of the underlying assumption of LCA that within a cluster $k$, the observed variables are mutually independent.

After estimating the conditional prescription probabilities $P(Y_{ij} = \mathrm{y}_j|\mathrm{X} = k)$, the comparison of the cluster-specific probabilities of prescribing each potency level shows how the clusters differ from each other in prescription patterns. The clusters may then be named according to the dominant potency levels (HAC) in the cluster, for example a cluster of patients with a high probability of receiving basic analgesics and low probability of receiving analgesics from the other categories could be labelled as “Basic analgesics”.

The assumption of local independence cannot be investigated a priori but can be evaluated through examining the bivariate residuals after model fitting. Bivariate residuals less than 1 suggest the assumption is not likely to be violated while values greater than 1 suggest a violation of the independence assumption (Vermunt and Magidson, 2008). The violation of the assumption suggests the model has difficulty in discriminating between the corresponding variable pairs of indicator variables (i.e. the pair of analgesia categories with bivariate residual greater than 1) in the model. There is no specific single way of dealing with the violation of the assumption (Nylund et al., 2007); hence the statistician has to make a subjective choice among the possible ways which include fitting a multilevel model or joint modelling of the variables for which the bivariate residual is greater than 1.

In this study any violation was addressed by merging adjacent categories of analgesia (joint modelling of the analgesia categories where necessary, for example strong combination analgesia are clinically similar to very strong single analgesia, hence a single variable of strong analgesia could be considered if the bivariate residual for these two categories was greater than 1). Weak and moderate combination analgesia can be combined as weak/moderate analgesia.

#### 5.2.4.1 Posterior probability

In latent class analysis it is assumed that each individual belongs to only one cluster and the appropriate cluster membership is defined by their posterior membership probabilities for each cluster. The posterior membership probabilities for any individual are obtained using Bayes theorem as follows:

$$P(X = k|\boldsymbol{Y_i} = \boldsymbol{y}) = \frac{P(X = k)P(\boldsymbol{Y_i} = \boldsymbol{y}|X = k)}{\boldsymbol{P}(\boldsymbol{Y_i} = \boldsymbol{y})}$$

The higher the conditional probability of cluster membership given their prescription pattern, $P(X = k|\boldsymbol{Y_i} = \boldsymbol{y})$, the more likely the individual belongs to that cluster. Individuals are allocated to the cluster for which their posterior probability is highest.

#### 5.2.4.2 Model goodness-of-fit analysis

The difficulty in latent class analysis is identifying the optimal number of clusters as there is no dominant criterion for choosing the best model. Models are fitted successively starting from a 1-cluster model and adding a further cluster each time. The most statistically significant model, in latent class analysis also known as the parsimonious model, can be determined through a variety of goodness-of-fit statistics (Ahn et al., 2008; Nylund et al., 2007) and for this study, the Akaike's Information Criterion (AIC), Bayes Information Criterion (BIC) and the Constant Akaike's Information Criterion (CAIC) and the likelihood ratio test were used.

**The Akaike Information Criterion (AIC)**

The AIC is based on the log-likelihood of the model; hence for a k-cluster model it is defined as: $AIC_{LL_k} = -2\log L_k + 2p$ where $p$ is the number of parameters to be estimated (Vermunt and Magidson, 2008; Nylund et al., 2007). The AIC is used to compare across several plausible models reflecting different numbers of clusters and the lowest value indicates the optimal number of clusters.

**Bayes Information Criterion (BIC)**

The BIC is also based on the log likelihood of the model and takes into account the sample size $n$; hence for a *k*-cluster model it is defined as: $BIC_{LL_k} = -2logL_k + p(\ln(n))$ where $p$ is the number of parameters to be estimated and $n$ is the sample size (Nylund et al 2007; Bozdogan, 2000). The BIC is used to compare across several plausible models and the lowest value indicates the optimal number of clusters.

**Constant Akaike Information Criterion (CAIC)**

The CAIC is a derivative of the AIC which penalises models that have a large number of parameters like the BIC, by incorporating the natural logarithm of the sample size plus 1. It is defined as: $CAIC_{LL_k} = -2logL_k + p(\ln(n) + 1)$ where $p$ is the number of free model parameters or parameters to be estimated and $n$ is the sample size (Nylund et al., 2007; Bozdogan 2000). The CAIC is used to compare across several plausible models and the lowest value indicates the optimal number of clusters.

**Likelihood ratio test**

The likelihood ratio test compares the improvement in the fit between neighbouring class models through their log likelihoods and provides a *p*-value that can be used to determine if there is a statistically significant improvement in fit by inclusion of one more cluster (Nylund et al., 2007). The likelihood ratio test follows a chi-squared distribution. Consider a *k*-cluster model, then the neighbouring class model is *(k-1)*-class, the difference between log likelihoods of the models can be expressed as $LR = -2\left(LL_k - LL_{(k-1)}\right)$ (Nylund et al., 2007; Bozdogan, 2000). A *p*-value less than 0.05 indicates that the model is not a good fit hence adding another cluster improves model fit.

**5.2.5 Model validation**

The best model in this study is that which is both clinically and statistically justifiable. While it is essential to establish a model choice through statistical evaluation techniques,

the clinical interpretation of the model is equally important. The goodness-of-fit statistics discussed above are not always conclusive especially when clinical importance is factored into model selection. The posterior probabilities also complement and validate model choice.

While there is no specific probability cut off point, the higher the posterior probability the better, as low posterior probabilities indicate that the model has difficulty in distinguishing between combinations of analgesia and allocating cluster membership (Henry and Muthen 2010; Nylund et al., 2007; Bozdogan, 2000; Vermunt and Magidson, 2008). In this study the minimum, maximum and mean posterior probabilities for patients within each cluster were considered as a means to evaluate and choose the final model in addition to the goodness-of-fit statistics.

There is no agreed specific cut-off point to indicate satisfactory posterior probabilities. Here, the proportions of the posterior probabilities above 0.7 and below 0.55 were compared. The 0.7 mark was used to indicate patients with a very high likelihood of being in their allocated cluster while probabilities below 0.55 indicate the patients have almost equal probabilities of being in another cluster. The goal of latent class analysis is to determine the smallest number of latent clusters that is sufficient to explain or account for associations among the observed variables (Henry and Muthen 2010; Vermunt and Magidson, 2008). Models with fewer clusters will take priority over models with more clusters in deciding the final model in the event of inconclusive goodness-of-fit measures.

The final model should be clinically meaningful and interpretable in line with knowledge of prescription patterns of pain analgesia from published studies. There are known prescription trends by age, gender, pain location, medication history and co-morbidity for different potency levels of analgesia. For example NSAIDs are the mainstay of drug treatment of acute and chronic pain, but their side effects make them less suitable for the elderly and they should be less used for patients with comorbidity (for example, bowel or

gastrointestinal problems) (Main, 2002; Brooks, 2006) Garbez and Puntillo, 2005), and Curatolo and Bogduk, 2001).

Factoring in clinical knowledge ensures that the final model is not only statistically valid but clinically useful and informative too. The model should help describe prescription patterns of analgesia in primary care treatment of MSK conditions over time and help establish factors associated with the prescription patterns.

### 5.2.6 Model evaluation and final model selection

The full clinical meaning and interpretation of the final model can be appreciated by establishing links to the clinical and socio-demographic patient variables available at baseline (onset of seeking medical care). The clinical importance of the model was evaluated by considering the prescription profiles of the clusters and comparing socio-demographic and clinical characteristics associated with the clusters to those related to analgesia prescribing identified from published papers and with discussion with a clinician (Dr John Bedson) and a biostatistician (Dr Kelvin Jordan) who have thorough knowledge through extensive research in MSK conditions. Two models were evaluated before the final model was chosen.

Descriptive comparison of the clusters by the analgesia categories and baseline variables were used to assess the magnitude of homogeneity of patients in each cluster and extent of heterogeneity between clusters. A multilevel (patient (level 1) and practice (level 2)) multinomial logistic model with cluster membership as the dependent variable was used to determine associations with socio-demographic and clinical characteristics. The model uses relative risk ratios (RRR) to compare and evaluate how different from the reference cluster are the other clusters. The reference cluster in the regression models was the cluster thought to have the least potent drugs prescribed. RRRs were reported with their 95% confidence interval (95%CI).

Only the adjusted models were discussed in detail to illustrate the heterogeneity between the clusters. The probability of being in a given cluster may vary from one individual to the other, and hence the multilevel multinomial logistic model was fitted with the probability of being in a cluster for each individual used as weighting in the model. Weighting accounts for the level of uncertainty in cluster membership. It also ensures the contribution of characteristics of an individual to the estimation of the model parameters is related to the probability of them being in the cluster. The latent class model was fitted using Latent Gold 4.0 while the multilevel multinomial logistic model was fitted using STATA.

Conclusions and discussion points were drawn from the detailed analysis and comparison of the best two models fitted. The two models were examined closely to consolidate the conclusions to be drawn about the suitability of latent class analysis in analysing prescribed pain medication profiles among primary care MSK consulters. The final preferred model from the two was selected after consideration of their goodness-of-fit statistics, posterior probabilities, clinical interpretability and validity, homogeneity of individuals within each cluster and heterogeneity across clusters.

## 5.3 Results

### 5.3.1 Data description

Of the 3236 patients who were identified in Chapter 4 as having consulted for a new MSK condition, 370 (11%) were lost to follow-up. Since the specific reason for loss to follow-up could not be ascertained, and the aim of the analysis was to characterise long-term prescription patterns over time, these 370 were excluded from the analysis. A total of 2866 patients were registered throughout the five year period under consideration which is 89% of the cohort that consulted for new MSK pain in 2006.

The excluded patients were similar to the overall cohort by age and gender composition. There were 214 (58%) males in the excluded group with a mean age of 42 years with a standard deviation of 21.2. The mean age of the 2866 patients included in the study in

years was 40.7 with a standard deviation of 17.2 and a median age of 40. The ages of the patients ranged from 15 to 92 years. 60% of the participants were male. Not all the patients received prescribed pain medication during the 5 years.

A total of 1992 (70%) received at least one category of the HAC in terms of pain medication prescribed over the five years. The mean follow up period was 4.5 years (as first consultation could be anytime during 2006). NSAIDs were the most commonly prescribed (to 62% of the patients over the 5 years) followed by basic analgesia (31%) and weak analgesia (21%). Very strong single analgesia was rarely prescribed (<1%), Table 5.3.1.

As in Chapter 4, the outcome variables were complete with no missing values and the only independent variable with missing data (categorised as “other/unspecified”) was pain location.

**Indicator variables**

Table 5.3.1: Number (%) of patients prescribed analgesia from each category

| Indicator | Number of patients | % of total patients |
|---|---|---|
| Basic Analgesia | 892 | 31 |
| Weak combination analgesia | 602 | 21 |
| Moderate combination analgesia | 198 | 7 |
| NSAIDs | 1771 | 62 |
| Strong combination analgesia | 544 | 19 |
| Very strong single analgesia | 16 | <0.01 |

**5.3.2 Six indicator variable models**

Models based on all 6 indicator variables were fitted. The chi-squared p-values for the log-likelihood ratio test which were not statistically significant at 5% level, the Akaike’s Information Criterion (AIC), the Bayes Information Criterion (BIC) and the Constant Akaike’s Information Criterion (CAIC) suggested a choice between the 3-cluster and the 4-cluster models seemed reasonable, see Table 5.3.2. The *p*-values of 0.10 for the 3-cluster model and 0.38 for the 4-cluster model indicate good fit for both models. The CAIC

(14512.76) and the BIC (14492.76) were at their lowest in the 3-cluster model. The AIC (14370.27) was lowest in the 4-cluster model. Therefore both the 3-cluster and the 4-cluster model are justifiable choices; hence both were evaluated for the assumption of local independence.

Table 5.3.2: Goodness of fit statistics for the cluster models with 6 indicators

| | LL | BIC (LL) | AIC (LL) | CAIC (LL) | $L^2$ | p-value |
|---|---|---|---|---|---|---|
| 1-Cluster | -7401.89 | 14851.54 | 14815.78 | 14857.54 | 525.38 | 5.5e-7 |
| 2-Cluster | -7206.56 | 14516.62 | 14439.13 | 14529.62 | 134.74 | 1.0e-9 |
| 3-Cluster | -7166.77 | **14492.76** | 14373.54 | **14512.76** | **55.15** | **0.10** |
| 4-Cluster | -7158.13 | 14531.21 | **14370.27** | 14558.21 | **37.88** | **0.38** |
| 5-Cluster | -7156.69 | 14584.06 | 14381.39 | 14618.06 | 35.00 | 0.20 |
| 6-Cluster | -7149.88 | 14626.15 | 14381.77 | 14667.15 | 21.37 | 0.50 |

**Evaluation of the local independence assumption**

The bivariate residuals (BVR) for the 4-cluster model and the 3-cluster model in Table 5.3.3 suggest that for both models, the assumption of local independence is violated as some of the residuals are greater than 1. The BVR of (1.3176) in the 3-cluster model for the pair of very strong single analgesia and NSAIDs indicate the 3-cluster model has difficulty in discriminating between these two potency levels. The BVRs of (2.0489), (2.2661) and (6.9140) in the 4-cluster model indicate that the model has difficulty in discriminating very strong single analgesia from basic analgesia, NSAIDs and strong combination analgesia respectively. The best models using 6-indicator variables were therefore in violation of the local independence assumption.

Table 5.3.3: Bivariate residual output for the 4-cluster and 3-cluster models

| **Indicators** | Basic analgesia | Weak combination analgesia | Moderate combination analgesia | NSAIDs | Strong combination analgesia | Very strong single analgesia |
|---|---|---|---|---|---|---|
| **4-cluster model** | | | | | | |
| Basic analgesia | - | | | | | |
| Weak combination analgesia | 0.1740 | - | | | | |
| Moderate combination analgesia | 0.1055 | 0.0646 | - | | | |
| NSAIDs | 0.0015 | 0.0745 | 0.2712 | - | | |
| Strong combination analgesia | 0.0246 | 0.0089 | 0.0003 | 0.1329 | - | |
| Very strong single analgesia | 0.0002 | 0.1266 | 0.6675 | **1.3176** | 0.1339 | - |
| **3-cluster model** | | | | | | |
| Basic analgesia | - | | | | | |
| Weak combination analgesia | 0.5868 | - | | | | |
| Moderate combination analgesia | 0.0591 | 0.0102 | - | | | |
| NSAIDs | 0.0285 | 0.0222 | 0.3599 | - | | |
| Strong combination analgesia | 0.0027 | 0.0210 | 0.0660 | 0.0189 | - | |
| Very strong single analgesia | **2.0489** | 0.0904 | 0.0945 | **2.2661** | **6.9140** | - |

### 5.3.3 Five indicator variable models

The strong combination and very strong single analgesia categories were merged into a single indicator variable named strong analgesia. The five indicators were therefore basic analgesia, weak analgesia, moderate analgesia, strong analgesia and NSAIDs. The 5-indicator variable model was fitted and the 3-cluster and 4-cluster models were selected based on the goodness-of-fit statistics.

The BIC (14316.46), AIC (14215.13) and the CAIC (14333.46) are at their lowest in the 3-cluster model but the differences in these measures for the 3 cluster and the 4 cluster models are marginal. The p-values for both models, 0.11 for the 3-cluster and 0.054 for the 4-cluster model are greater than 0.05. The change in the log likelihood from the 3-cluster to the 4-cluster model is very small as shown in the graph in Figure 5.3.1 which shows why the likelihood ratio test identifies the two models as likely candidates. Further evaluation of the 5 indicator model is explored with the evaluation of the local independence assumption.

Figure 5.3.1: Illustration of change in log likelihood with increasing number of clusters

Table 5.3.4: Goodness of fit statistics for the 5-indicator model

| | LL | BIC (LL) | AIC (LL) | CAIC (LL) | $L^2$ | p-value |
|---|---|---|---|---|---|---|
| 1-Cluster | -7305.82 | 14651.45 | 14621.64 | 14656.45 | 451.15 | 4.1e-79 |
| 2-Cluster | -7127.17 | 14341.91 | 14276.34 | 14352.91 | 93.85 | 1.6e-11 |
| 3-Cluster | -7090.56 | **14316.46** | **14215.13** | **14333.46** | 20.64 | **0.11** |
| 4-Cluster | -7087.87 | 14358.85 | 14221.75 | 14381.85 | 15.26 | 0.054 |
| 5-Cluster | -7083.11 | 14397.08 | 14224.22 | 14426.08 | 5.73 | 0.057 |

**Evaluation of local independence assumption in the 5 indicator models**

The bivariate residuals for all the pairs of indicator variables are substantially less than one in both the 3-cluster and 4-cluster models (Table 5.3.5). This suggests that the models do not have difficulty in discriminating between any of the variable pairs. The assumption of local independence is not violated for both the 3-cluster and the 4-cluster models.

Table 5.3.5: Bivariate residuals between variable pairs for the 3 and 4-cluster models

| **Indicators** | Basic analgesia | Weak analgesia | Moderate analgesia | NSAIDs | Strong analgesia |
|---|---|---|---|---|---|
| **4-cluster model** | | | | | |
| Basic analgesia | - | | | | |
| Weak analgesia | 0.3604 | - | | | |
| Moderate analgesia | 0.0019 | 0.0163 | - | | |
| NSAIDs | 0.0619 | 0.0044 | 0.3055 | - | |
| Strong analgesia | 0.0162 | 0.0025 | 0.1305 | 0.1458 | - |
| **3-cluster model** | | | | | |
| Basic analgesia | - | | | | |
| Weak analgesia | 0.0000 | - | | | |
| Moderate analgesia | 0.0018 | 0.0799 | - | | |
| NSAIDs | 0.0064 | 0.0237 | 0.1914 | - | |
| Strong analgesia | 0.0137 | 0.0009 | 0.0000 | 0.0369 | - |

### 5.3.4 Cluster properties

**The 3-cluster model**

The clusters are labelled according to the evidently dominant analgesia within each cluster as follows; Cluster 1 – Basic analgesia, Cluster 2 – NSAIDs and Cluster 3 – Multiple-potency. The cluster properties are illustrated in Table 5.3.6 and Table 5.3.7.

**Basic Analgesia cluster**: The cluster contains 40% of all the patients in this analysis and consists of patients who received mainly no pain medication or basic analgesia. The patients have a 0.34 probability of being prescribed basic analgesia and a 0.11 probability of being prescribed weak analgesia. The cluster has minimum, maximum and mean posterior probabilities of 0.52, 0.86 and 0.70 respectively. 86% of the patients are classified in this cluster as belonging to the cluster with probability 0.70 or above while less than 1% was classified with probability less than 0.55.

**NSAIDs cluster**: The cluster contains 37% of all the patients in the analysis and consists of patients who received predominantly NSAIDs only within the five year period. The patients have a 0.61 probability of being prescribed NSAIDs, 0.14 probability of being prescribed weak analgesia and 0.19 probability of being prescribed strong analgesia. The cluster has minimum, maximum and mean posterior probabilities of 0.44, 0.82 and 0.76 respectively. 84% of the patients in this cluster are classified with probability 0.70 or above while less than 1% was classified with probability less than 0.55.

**Multiple-potency cluster**: The cluster contains 23% of all the patients in the analysis and they received combinations of the five potency levels without any potency level clearly dominating the cluster. The patients have probabilities 0.65 of being prescribed basic analgesia, 0.50 of being prescribed weak analgesia, 0.20 of being prescribed moderate analgesia, 0.62 of being prescribed NSAIDs and 0.51 of being prescribed strong analgesia. The minimum, maximum and mean posterior probabilities are 0.45, 0.99 and

0.77 respectively. 61% of the patients in this cluster were classified with probability 0.70 or above while 22% were classified with probability less than 0.55.

**The 4-cluster model**

The 4-cluster model is an extension of the 3-cluster model described above. It splits the Basic analgesia cluster into two clusters: no medication cluster and a basic analgesia cluster. The clusters are labelled according to the evidently dominant analgesia within each cluster as follows; Cluster 1 – NSAIDs, Cluster 2 – No Medication, Cluster 3 – Basic analgesia and Cluster 4 – Multiple-potency. The cluster properties are illustrated in Table 5.3.6 and Table 5.3.7.

**Basic Analgesia cluster**: The cluster contains 23% of the patients in the analysis and consists of patients who were predominantly prescribed basic analgesia throughout the follow-up period. The patients have a probability 0.16 of receiving weak analgesia. The minimum, maximum and mean posterior probabilities are 0.36, 0.82 and 0.69 respectively. 63% of the patients in this cluster are classified with probability 0.70 or above while 21% were classified with probability less than 0.55.

**NSAIDs cluster**: The cluster contains 32% of the patients in this analysis and consists of patients predominantly prescribed NSAIDs throughout the follow-up period. The patients have probabilities 0.65 of receiving NSAIDs, 0.22 of receiving weak analgesia and 0.27 of receiving strong analgesia. The minimum, maximum and mean posterior probabilities are 0.43, 0.80 and 0.59 respectively. 21% of the patients in this cluster are classified with probability 0.70 or above while 16% were classified with probability less than 0.55.

**Multiple-potency cluster**: The cluster contains 17% of the patients in this analysis who received combinations of the five potency levels without any potency level clearly dominating the cluster. The patients have probabilities 0.72 of being prescribed basic analgesia, 0.52 of being prescribed weak analgesia, 0.23 of being prescribed moderate analgesia, 0.63 of being prescribed NSAIDs and 0.56 of being prescribed strong

analgesia. The minimum, maximum and mean posterior probabilities are 0.40, 0.98 and 0.78 respectively. 78% of the patients in this cluster are classified with probability 0.70 or above while 21% was classified with probability less than 0.55.

**No medication cluster**: The cluster contains 28% of the patients in the analysis who received no prescribed medication throughout the follow-up period. The minimum, maximum and mean posterior probabilities are 0.46, 0.57 and 0.57 respectively. None of the patients were classified with probability 0.70 or above while 3% was classified with probability less than 0.55.

The mean posterior cluster probabilities were higher in the three-cluster than the four-cluster model for the basic analgesia and NSAIDs clusters, but similar for the Multiple-potency clusters.

Table 5.3.6: Within cluster probability of receiving analgesia medication

| | 3-Cluster model | | | 4-Cluster model | | | |
|---|---|---|---|---|---|---|---|
| | Basic Analgesia | NSAIDs | Multiple-Potency | Basic Analgesia | NSAIDs | Multiple-Potency | No Medication |
| **Cluster Size** | **0.3971** | **0.3717** | **0.2313** | **0.2332** | **0.3208** | **0.1674** | **0.2786** |
| **Indicators** | | | | | | | |
| Basic analgesia | | | | | | | |
| No | 0.6589 | 0.9309 | 0.3509 | 0.4379 | 0.8440 | 0.2804 | 0.9654 |
| Yes | **0.3411** | 0.069 | **0.6491** | **0.5621** | 0.1560 | **0.7196** | 0.0346 |
| Weak analgesia | | | | | | | |
| No | 0.8890 | 0.8642 | 0.4990 | 0.8374 | 0.7799 | 0.4761 | 0.9492 |
| Yes | 0.1110 | 0.1358 | **0.5010** | 0.1626 | 0.2201 | **0.5239** | 0.0508 |
| Moderate analgesia | | | | | | | |
| No | 0.9816 | 0.9566 | 0.8026 | 0.9839 | 0.9395 | 0.7688 | 0.9741 |
| Yes | 0.0184 | 0.0434 | 0.1974 | 0.0161 | 0.0605 | 0.2312 | 0.0259 |
| NSAIDs | | | | | | | |
| No | 0.9006 | 0.3927 | 0.3801 | 0.9165 | 0.3523 | 0.3740 | 0.7252 |
| Yes | 0.0994 | **0.6073** | **0.6199** | 0.0835 | **0.6477** | **0.6260** | 0.2748 |
| Strong analgesia | | | | | | | |
| No | 0.9969 | 0.8080 | 0.4902 | 0.9963 | 0.7325 | 0.4379 | 0.9650 |
| Yes | 0.0031 | 0.1920 | **0.5098** | 0.0037 | 0.2675 | **0.5621** | 0.0350 |

Table 5.3.7: Summary of posterior probabilities by cluster

| | 3-Cluster model | | | 4-Cluster model | | | |
|---|---|---|---|---|---|---|---|
| **Cluster** | Basic Analgesia | NSAIDs | Multiple-Potency | Basic Analgesia | NSAIDs | Multiple-Potency | No medication |
| **Summary statistic** | | | | | | | |
| Size (n) | 1428 | 858 | 580 | 554 | 1049 | 360 | 903 |
| Minimum | 0.52 | 0.44 | 0.45 | 0.36 | 0.43 | 0.40 | 0.46 |
| Mean | 0.70 | 0.76 | 0.77 | 0.69 | 0.59 | 0.78 | 0.57 |
| Maximum | 0.86 | 0.82 | 0.99 | 0.82 | 0.80 | 0.98 | 0.57 |
| % > 0.70 | 86 | 84 | 61 | 63 | 21 | 78 | 0 |
| % < 0.55 | <0.1 | <0.1 | 22 | 21 | 16 | 21 | 3 |

### 5.3.5 Cluster description by baseline characteristics

In the 3-cluster model, of the 2866 patients, 1428 were in the basic analgesia, 858 in the NSAIDs and 580 in the multiple-potency clusters while in the 4-cluster model 554 were in the basic analgesia, 1049 in the NSAIDs, 360 in the multiple-potency and 903 in the no medication clusters. These cluster compositions are as observed from the data and not model estimated.

Table 5.3.8 describes the prevalence of the patients in each cluster according to the categories of the baseline characteristics. For example in the 3-cluster model, 56% of the 15-29 age group were in the basic analgesia cluster, 29% in the NSAIDs cluster and 15% in the multiple-potency cluster, while 18%, 34%, 10% and 38% of this age group were in the basic analgesia cluster, NSAIDs cluster, multiple-potency cluster and no medication cluster respectively, in the 4-cluster model.

In the 3-cluster model, the age groups with the highest prevalence in the basic analgesia cluster were the 15-29 (56%) and 75+ (60%), while in the NSAIDs cluster it was the 30-44 group (41%), and 60-74 (35%) and the 75+ (34%)in the multiple-potency cluster. In the 4-cluster model, the age group with the highest prevalence in the basic analgesia cluster was the 75+ (54%), while in the NSAIDs cluster it was the 30-44 (48%), the 75+ (34%) in the multiple-potency and the 15-29 (38%) in the no medication cluster.

Table 5.3.8: Cluster description by baseline variables

| Variable | Total (n) | 3-Cluster model | | | 4-Cluster model | | | |
|---|---|---|---|---|---|---|---|---|
| | | Basic Analgesia | NSAIDs | Multiple-Potency | Basic Analgesia | NSAIDs | Multiple-Potency | No medication |
| **Age group** | | **% Col** | **% Col** | **% Col** | **% Col** | **% Col** | **% Col** | **% Col** |
| 15-29 | 539 | 56 | 29 | 15 | 18 | 34 | 10 | 38 |
| 30-44 | 933 | 42 | 41 | 17 | 12 | 48 | 9 | 31 |
| 45-59 | 908 | 44 | 33 | 23 | 15 | 42 | 14 | 29 |
| 60-74 | 386 | 47 | 18 | 35 | 25 | 25 | 26 | 24 |
| 75+ | 100 | 60 | 6 | 34 | 54 | 4 | 34 | 10 |
| **Gender** | | | | | | | | |
| Female | 1154 | 50 | 25 | 25 | 22 | 33 | 15 | 30 |
| Male | 1712 | 50 | 33 | 17 | 18 | 39 | 11 | 32 |
| **Previous musculoskeletal consultation** | | | | | | | | |
| Yes | 407 | 49 | 31 | 20 | 19 | 38 | 13 | 30 |
| No | 2459 | 50 | 30 | 20 | 19 | 36 | 13 | 32 |
| **Previous Analgesia prescription** | | | | | | | | |
| Yes | 475 | 38 | 32 | 30 | 18 | 41 | 19 | 22 |
| No | 2391 | 52 | 30 | 18 | 20 | 36 | 11 | 33 |
| **Pain location** | | | | | | | | |
| Back | 690 | 38 | 39 | 23 | 16 | 45 | 15 | 23 |
| Knee | 311 | 53 | 31 | 16 | 21 | 37 | 9 | 33 |
| Hip | 188 | 49 | 28 | 23 | 19 | 35 | 16 | 30 |
| Foot and ankle | 226 | 53 | 29 | 18 | 21 | 35 | 12 | 32 |
| Hand and wrist | 219 | 54 | 28 | 18 | 17 | 35 | 9 | 39 |
| Shoulder | 216 | 40 | 36 | 24 | 15 | 45 | 15 | 25 |
| Neck | 203 | 51 | 29 | 20 | 29 | 40 | 9 | 31 |
| Other/Unspecified | 813 | 59 | 22 | 19 | 23 | 27 | 13 | 37 |

| Variable | Total (n) | 3-Cluster model | | | 4-Cluster model | | | |
|---|---|---|---|---|---|---|---|---|
| | | Basic Analgesia | NSAIDs | Multiple-Potency | Basic Analgesia | NSAIDs | Multiple-Potency | No medication |
| **Deprivation** | | | | | | | | |
| Most | 1212 | 48 | 31 | 21 | 21 | 38 | 14 | 28 |
| Medium | 1141 | 51 | 30 | 19 | 18 | 36 | 12 | 35 |
| Least | 513 | 52 | 29 | 19 | 19 | 36 | 12 | 34 |
| **Comorbidity** | | | | | | | | |
| Selected | 107 | 47 | 28 | 25 | 22 | 36 | 16 | 26 |
| None | 2749 | 38 | 36 | 26 | 24 | 35 | 16 | 25 |
| **Staff category** | | | | | | | | |
| GP | 2296 | 50 | 29 | 21 | 20 | 36 | 13 | 31 |
| Other | 570 | 51 | 33 | 17 | 17 | 38 | 10 | 35 |
| **General practice** | | | | | | | | |
| 1 | 215 | 65 | 18 | 17 | 19 | 24 | 11 | 46 |
| 2 | 210 | 55 | 29 | 16 | 17 | 37 | 8 | 38 |
| 3 | 175 | 62 | 20 | 18 | 30 | 25 | 13 | 32 |
| 4 | 230 | 53 | 30 | 16 | 16 | 37 | 9 | 38 |
| 5 | 145 | 43 | 34 | 23 | 12 | 43 | 13 | 32 |
| 6 | 225 | 60 | 17 | 23 | 31 | 20 | 18 | 31 |
| 7 | 372 | 31 | 45 | 24 | 13 | 56 | 12 | 18 |
| 8 | 290 | 49 | 33 | 18 | 18 | 41 | 10 | 32 |
| 9 | 242 | 48 | 28 | 24 | 20 | 35 | 14 | 31 |
| 10 | 312 | 47 | 29 | 24 | 21 | 38 | 16 | 26 |
| 11 | 152 | 53 | 34 | 14 | 21 | 37 | 11 | 32 |
| 12 | 298 | 48 | 32 | 20 | 18 | 34 | 15 | 33 |

**$\%_{Col}$ = Column %**

### 5.3.6 Cluster comparison by baseline variables: Multinomial logistic models

The unadjusted and adjusted multilevel-multinomial logistic models were fitted to compare clusters in: i) the 3-cluster model and ii) 4-cluster model and the relative risk ratios (RRR) show which baseline factors were significantly associated with cluster membership in each model.

**Multinomial logistic model on the 3-cluster model**

The unadjusted model showed that NSAIDs cluster and the Multiple-potency cluster were significantly different from the Basic analgesia cluster by age, gender, previous prescribed analgesia and pain location and not by deprivation, consultation history, co-morbidity and staff category. The adjusted model showed significant difference by age, gender, medication history, deprivation, comorbidity and pain location. There was variation by practice as shown in Table 5.3.9. General practice accounted for 12% of the unexplained variation.

Compared to those aged 30-44, the youngest age group (15-29) and oldest age groups (60-74 and over 75) were less likely to be classified in the NSAIDs cluster than in the basic analgesia cluster. For example, for patients aged 15-29 the adjusted relative risk ratio (RRR 0.55 95% CI [0.41, 0.74]) compared to the 30-44 age group. Those aged 60-74, (RRR 0.42 [0.28, 0.63]) and those aged 75+ (RRR 0.08 [0.02, 0.40]) were also less likely to be in the NSAIDs cluster. The patients who previously received prescribed analgesia in the past, (RRR 1.47 [1.10, 1.97]) were more likely to be in the NSAIDs cluster than in the basic analgesics cluster. Patients presenting at the initial consultation with a MSK problem in the knee, (RRR 0.61 [0.42, 0.89]), hand and wrist, (RRR 0.48 [0.31, 0.73]), neck (RRR 0.57 [0.37, 0.89]) or unspecified locations (RRR 0.41 [0.30, 0.55]) were less likely to be in the NSAIDs cluster when compared to those presenting with a back problem.

Table 5.3.9: Unadjusted and adjusted multinomial logistic models that examines the association of baseline variables with cluster membership in the 3-cluster model

| **Model** | **RRR Estimates [95% CI]** | | | |
|---|---|---|---|---|
| **Reference cluster- Basic analgesia** | **NSAIDs Cluster** | | **Multiple-potency Cluster** | |
| | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Age Group** | | | | |
| 30-44 | 1.00 | 1.00 | 1.00 | 1.00 |
| 15-29 | 0.51 [0.38, 0.69] | **0.55 [0.41, 0.74]** | 0.69 [0.48, 0.99] | 0.69 [0.48, 1.01] |
| 45-59 | 0.77 [0.60, 0.99] | 0.83 [0.65, 1.08] | 1.34 [0.99, 1.81] | **1.44 [1.05, 1.95]** |
| 60-74 | 0.38 [0.26, 0.56] | **0.42 [0.28, 0.63]** | 2.01 [1.41, 2.86] | **2.20 [1.52, 3.18]** |
| 75+ | 0.07 [0.01, 0.36] | **0.08 [0.02, 0.40]** | 1.64 [0.81, 3.31] | 1.54 [0.74, 3.19] |
| **Gender** | | | | |
| Male | 1.00 | 1.00 | 1.00 | 1.00 |
| Female | 0.74 [0.60, 0.90] | 0.82 [0.67, 1.03] | 1.40 [1.11, 1.75] | **1.45 [1.15, 1.85]** |
| **Previous musculoskeletal consultation** | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.10 [0.81, 1.42] | 1.08 [0.81, 1.44] | 1.04 [0.81, 1.53] | 0.82 [0.59, 1.14] |
| **Previous Analgesia prescription** | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.47 [1.12, 1.94] | **1.47 [1.10, 1.97]** | 2.37 [1.79, 3.15] | **2.27 [1.68, 3.06]** |
| **Region of Pain** | | | | |
| **Back** | 1.00 | 1.00 | 1.00 | 1.00 |
| Knee | 0.55 [0.39, 0.79] | **0.61 [0.42, 0.89]** | 0.46 [0.30, 0.72] | **0.46 [0.29, 0.72]** |
| Hip | 0.55 [0.35, 0.85] | 0.70 [0.44, 1.12] | 0.74 [0.47, 1.20] | 0.76 [0.46, 1.25] |
| Foot and Ankle | 0.54 [0.36, 0.81] | 0.73 [0.47, 1.13] | 0.55 [0.34, 0.88] | 0.66 [0.40, 1.09] |
| Hand and Wrist | 0.49 [0.33, 0.74] | **0.48 [0.31, 0.73]** | 0.49 [0.30, 0.79] | **0.45 [0.27, 0.74]** |
| Shoulder | 0.88 [0.58, 1.32] | 0.84 [0.55, 1.28] | 0.92 [0.58, 1.46] | 0.78 [0.48, 1.26] |
| Neck | 0.54 [0.35, 0.82] | **0.57 [0.37, 0.89]** | 0.59 [0.36, 0.95] | 0.60 [0.36, 1.00] |
| Other/unspecified | 0.35 [0.26, 0.47] | **0.41 [0.30, 0.55]** | 0.52 [0.38, 0.71] | **0.51 [0.37, 0.71]** |

| Model<br>Reference cluster- Basic analgesia | RRR Estimates [95% CI]<br>NSAIDs Cluster | | <br>Multiple-potency Cluster | |
|---|---|---|---|---|
| | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Deprivation** | | | | |
| Most | 1.00 | 1.00 | 1.00 | 1.00 |
| Medium | 0.91 [0.73, 1.13] | 0.83 [0.66, 1.03] | 0.83 [0.65, 1.06] | **0.68 [0.52, 0.88]** |
| Least | 0.87 [0.66, 1.15] | 0.82 [0.61, 1.11] | 0.81 [0.59, 1.11] | **0.62 [0.45, 0.88]** |
| **Co-morbidity** | | | | |
| Selected | 1.00 | 1.00 | 1.00 | 1.00 |
| Other | 1.03 [0.44, 1.61] | **1.38 [1.02, 1.88]** | 0.69 [0.39, 1.32] | **0.60 [0.44, 0.83]** |
| **Staff category** | | | | |
| GP | 1.00 | 1.00 | 1.00 | 1.00 |
| Other | 1.10 [0.89, 1.42] | **1.13 [0.89, 1.43]** | 0.72 [0.64, 1.03] | 0.84 [0.63, 1.11] |
| **Random effect** | **Variance [SD]** | | | |
| General Practice | **0.12 [0.06]** | | | |

**Unadjusted model =** Individual variable in the model, **Adjusted model =** All variables included simultaneously

The age groups 45-59 and 60-74 with (RRR 1.44 [1.05, 1.95]) and (RRR 2.20 [1.52, 3.18]) respectively were more likely to be in the Multiple-potency cluster. Females (RRR 1.45 [1.15, 1.85]) and patients who previously received prescribed analgesia in the past (RRR 2.27 [1.68, 3.06]) were more likely to be in the Multiple-potency cluster. Patients from medium and least deprived areas (RRR 0.68 [0.52, 0.88] and 0.62 [0.45, 0.88]) respectively are less likely to be in the Multiple-potency cluster when compared to those living in the most deprived areas. Patients presenting at the initial consultation with a MSK problem in the knee (RRR 0.46 [0.29, 0.72]), hand and wrist (RRR 0.45 [0.27, 0.74]), and unspecified locations (RRR 0.51 [0.37, 0.71]) are less likely to be in the Multiple-potency cluster compared to those experiencing back problems.

**Multinomial logistic model on the 4-cluster model**

The unadjusted model showed that the NSAIDs cluster, the Basic analgesia cluster and the Multiple-potency clusters were significantly different from the No pain medication cluster by age, gender, medication history, pain location and by deprivation but not by previous MSK consultation, co-morbidity and staff category. The adjusted model showed significant differences by age, gender, medication history, comorbidity, deprivation and pain location (Table 5.3.10).

With the No pain medication cluster as the reference cluster, the age group 15-29 with (RRR 0.60 95% CI [0.42, 0.85]) was less likely to be in the NSAIDs cluster when compared to those aged 30-44. Patients who received prescribed analgesia in the past (RRR 1.77 [1.25, 2.51]) were more likely to be in the NSAIDs cluster. Patients experiencing pain in the knee (RRR 0.57 [0.37, 0.87]), hand and wrist (RRR 0.41 [0.26, 0.67]) and unspecified locations (RRR 0.38 [0.27, 0.53]) were less likely to be in the NSAIDs cluster when compared to those consulting initially for pain in the back. Those from medium deprivation (RRR 0.69 [0.53, 0.91]) were also less likely to in the NSAIDs cluster.

Also, age groups 60-74 and over 75 with (RRR 3.11 [1.89, 5.10]) and (RRR 16.2 [4.28, 61.4]) respectively are more likely to be in the Basic analgesia cluster than no medication cluster compared to those aged 30-44. Patients from medium deprivation (RRR 0.69 [0.51, 0.94]) are less likely to be in the Basic analgesia cluster. The age groups 45-59, 60-74 and over 75 with (RRR 1.71 [1.14, 2.57], 4.27 [2.60, 7.01] and 11.8 [2.97, 46.9]) respectively are more likely to be in the Multiple-potency cluster. Females (RRR 1.54 [1.13, 2.10]) and patients who previously received prescribed analgesia in the past (RRR 2.48 [1.66, 3.69]) are more likely to be prescribed multiple potency levels.

Patients from medium and least deprivation neighbourhoods (RRR 0.55 [0.39, 0.77] and 0.52 [0.33, 0.80]) respectively are less likely to be in the Multiple-potency cluster when compared to the most deprived. Patients experiencing pain in the knee (RRR 0.36 [0.19, 0.65]), hand and wrist (RRR 0.33 [0.17, 0.63]), neck (RRR 0.42 [0.21, 0.85]) and unspecified locations (RRR 0.46 [0.30, 0.70]) are less likely to be in the Multiple-potency cluster compared to those experiencing back pain. With practice considered as a random effect in the multilevel model, a statistically significant variance of 0.093 [SD 0.047] shows that there is practice variation in cluster membership. Practice accounts for 9% of the unexplained variation.

Table 5.3.10: Unadjusted and adjusted multinomial logistic models that examine the association of baseline variables with cluster membership in the 4-cluster model

| **Model** (*Reference cluster - No medication*) | **RRR Estimates [95% CI** | | | | | |
|---|---|---|---|---|---|---|
| | **(Basic analgesia)** | | **(NSAIDs)** | | **(Multiple-potency)** | |
| | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Age Group** | | | | | | |
| 30-44 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 15-29 | 1.42 [0.87, 2.11] | 1.32 [0.86, 2.03] | 0.57 [0.40, 0.81] | **0.60 [0.42, 0.85]** | 0.86 [0.60, 1.42] | 0.88 [0.54, 1.41] |
| 45-59 | 1.39 [0.88, 2.01] | 1.42 [0.96, 2.12] | 0.91 [0.72, 1.22] | 0.99 [0.74, 1.34] | 1.54 [1.04, 2.32] | **1.71 [1.14, 2.57]** |
| 60-74 | 2.87 [1.83, 4.80] | **3.11 [1.89, 5.10]** | 0.72 [0.42, 1.14] | 0.77 [0.49, 1.23] | 3.70 [2.33, 6.01] | **4.27 [2.60, 7.01]** |
| 75+ | 16.0 [4.33, 60.0] | **16.2 [4.28, 61.4]** | 0.33 [0.03, 2.41] | 0.31 [0.04, 2.66] | 12.2 [3.09, 46.0] | **11.8 [2.97, 46.9]** |
| **Gender** | | | | | | |
| Male | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Female | 1.32 [1.01, 1.74] | 1.17 [0.88, 1.55] | 1.02 [0.70, 1.22] | 1.03 [0.80, 1.32] | 1.60 [1.21, 2.14] | **1.54 [1.13, 2.10]** |
| **Previous musculoskeletal consultation** | | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.12 [0.74, 1.54] | 1.05 [0.72, 1.54] | 1.11 [0.82, 1.53] | 1.04 [0.77, 1.41] | 1.00 [0.66., 3.91] | 0.92 [0.61, 1.39] |
| **Previous analgesia prescription** | | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.34 [0.89, 2.00] | 1.28 [0.85, 1.97] | 1.78 [1.33, 2.51] | **1.77 [1.25, 2.51]** | 2.68 [1.77, 3.85] | **2.48 [1.66, 3.69]** |

| **Model** (*Reference cluster - No medication*) | **RRR Estimates [95% CI (Basic analgesia)** | | **(NSAIDs)** | | **(Multiple-potency)** | |
|---|---|---|---|---|---|---|
| | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Region of Pain** | | | | | | |
| Back | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Knee | 1.02 [0.57, 1.56] | 0.84 [0.50, 1.41] | 0.52 [0.43, 0.81] | **0.57 [0.37, 0.87]** | 0.38 [0.22, 0.72] | **0.36 [0.19, 0.65]** |
| Hip | 1.09 [0.58, 1.90] | 0.79 [0.42, 1.47] | 0.64 [0.32, 0.90] | 0.63 [0.37, 1.09] | 0.80 [0.44, 1.41] | 0.67 [0.35, 1.28] |
| Foot and Ankle | 1.12 [0.61, 1.93] | 0.79 [0.44, 1.42] | 0.54 [0.32, 0.84] | 0.61 [0.37, 1.02] | 0.64 [.033, 1.00] | 0.59 [0.31, 1.11] |
| Hand and Wrist | 0.69 [0.44, 1.22] | 0.68 [0.38, 1.22] | 0.41 [0.34, 0.70] | **0.41 [0.26, 0.67]** | 0.41 [0.21, 0.74] | **0.33 [0.17, 0.63]** |
| Shoulder | 1.01 [0.48, 1.86] | 0.96 [0.51, 1.82] | 0.88 [0.54, 1.53] | 0.83 [0.50, 1.39] | 0.90 [0.54, 1.56] | 0.71 [0.37, 1.33] |
| Neck | 1.04 [0.62, 1.77] | 0.88 [0.48, 1.62] | 0.63 [0.43, 1.02] | 0.63 [0.39, 1.01] | 0.39 [0.23, 0.94] | **0.42 [0.21, 0.85]** |
| Other/unspecified | 1.00 [0.66, 1.45] | 0.83 [0.56, 1.24] | 0.43 [0.34, 0.53] | **0.38 [0.27, 0.53]** | 0.54 [0.44, 0.77] | **0.46 [0.30, 0.70]** |
| **Deprivation** | | | | | | |
| Most | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Medium | 0.72 [0.53, 0.88] | **0.69 [0.51, 0.94]** | 0.76 [0.64, 0.92] | **0.69 [0.53, 0.91]** | 0.70 [0.49, 0.85] | **0.55 [0.39, 0.77]** |
| Least | 0.82 [0.51, 1.14] | 0.71 [0.48, 1.05] | 0.80 [0.63, 1.14] | 0.71 [0.51, 1.01] | 0.66 [0.54, 1.13] | **0.52 [0.33, 0.80]** |
| **Co-morbidity** | | | | | | |
| Selected | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| None | 0.82 [0.43, 1.64] | **0.64 [0.45, 0.90]** | 0.78 [0.42, 1.64] | **2.27 [1.67, 3.07]** | 0.67 [0.34, 1.06] | 0.70 [0.49, 1.00] |
| **Staff category** | | | | | | |
| GP | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Other | 0.83 [0.64, 1.13] | 0.83 [0.60, 1.15] | 0.89 [0.70, 1.24] | 1.10 [0.86, 1.41] | 0.68 [0.45, 0.70] | **0.80 [0.56, 1.14]** |
| **Random effect** | | | **Variance [SD]** | | | |
| General Practice | | | **0.093 [0.047]** | | | |

**Unadjusted model =** Individual variable in the model, **Adjusted model =** All variables included simultaneously

### 5.3.7 Final model choice

The goodness-of-fit statistics BIC (14316.46), AIC (14215.13) and CAIC (14333.46) in the 3-cluster model are lower than in the 4-cluster model, BIC (14358.85), AIC (14221.75) and CAIC (14381.85). The cluster mean posterior probabilities in the 3-cluster model of 0.70 (basic analgesia cluster), 0.76 (NSAIDs), and 0.77 (multiple-potency) compared to 0.69 (basic analgesia cluster), 0.59 (NSAIDs), 0.78 (multiple-potency), and 0.57 (no medication) in the 4-cluster model indicate that there is more uncertainty in discriminating between cluster memberships between the no medication and the basic analgesia clusters in the 4-cluster model. Only 41% of the subjects in the 4-cluster model compared to 86% in the 3-cluster model are classified with probability of 0.70 or above. If the mean cluster posterior probabilities are considered as a measure of homogeneity within the clusters and heterogeneity across clusters, then clusters in the 3-cluster model are more heterogeneous and members in each cluster are more homogeneous.

The current WHO guidelines on how general practitioners should prescribe in the pharmacological management of MSK problems suggest a stepped approach (Ehrlich, 2003). The guidelines suggest that clinicians start with a basic analgesia such as paracetamol and then consider NSAIDs before prescribing strong analgesia if pain persists. Hence it can be said that the 3 cluster model reflects what current advice advocates making it a suitable choice.

The model shows that there are three categories of prescription profiles over time, namely basic analgesia only or no medication, NSAIDs, and mixture of analgesia including stronger analgesia. Based on the model it can be assumed that those prescribed NSAIDs generally needed something stronger than basic analgesia but less than stronger analgesia and those on a mixture of analgesia or stronger analgesia can no longer be treated adequately with NSAIDs or basic analgesia only. The opinions of the clinician Dr

John Bedson and the biostatistician Dr Kelvin Jordan concur that the 3-cluster model was more clinically interpretable in line with current guidelines.

After universal consideration of the goodness-of-fit statistics, posterior probabilities, the cluster sizes, homogeneity of individuals within each cluster and heterogeneity across clusters, the 3-cluster model is statistically superior to the 4-cluster model.

**Three cluster model analgesia prevalence summary**

In the basic analgesia cluster, 61% received no medication, 25% received basic analgesics only and 14% basic analgesia and weak combination analgesia. In the NSAIDs cluster, 57% received NSAIDs only, 12% a combination of NSAIDs-WCA, 3% a combination of NSAIDs-MCA and 25% a combination of NSAIDs-SA. In the multiple-potency cluster there were many combinations of the five potency levels, but prominently, 4% received all five potency levels, 14% a combination of four potency levels, 54% a combination of three potency levels and 14% a combination of two potency levels including strong analgesia.

**Model Similarities: 3-cluster v 4-cluster model**

Cluster comparison by baseline characteristics suggest similar clinical conclusions can be drawn from both models. Both models highlight similar subgroups of patients, a group dominated by NSAIDs prescriptions and a group dominated by prescription of multiple potency levels. In the 3-cluster model, the Basic analgesia cluster is dominated by those receiving basic analgesia even though there were some patients with no medication; this is similar to a combination of the No medication and the Basic analgesia clusters in the 4-cluster model. Similar conclusions can be drawn from both models on the association of the combinations of medication potency levels and age, gender, medication history, pain location and deprivation.

Over the course of five years following a new MSK consultation, the observations highlighted by both model classifications were that compared to only receiving basic analgesia or no analgesia:

1. NSAIDs were less likely to be prescribed to the elderly, but were more likely to be prescribed to the working age groups.
2. NSAIDs were more likely to be prescribed to males, people who have been prescribed pain medication in the past and people experiencing pain in the back.
3. Multiple potency prescriptions were more likely in over 60 age groups.
4. Multiple potency prescriptions were most common among females, people with prescribed medication in the past and those presenting initially with back pain

The 4-cluster model adds some observations about the people who were not prescribed any pain medication in contrast to those prescribed any pain medication:

1. The prevalence of people who were not prescribed any pain medication over 5 years declines with increasing age from a peak amongst 15-29 to a low among the over 75.
2. People with back pain and people with previously prescribed analgesia in the past were more likely to be prescribed pain medication than no medication at all.
3. People from most deprived backgrounds were more likely to be prescribed pain medication than no medication at all.
4. Adults over 60 years were more likely to be prescribed basic analgesia than no medication at all

## 5.4 Discussion

The use of latent class analysis has uncovered distinct subpopulations characterised by prescribed analgesia potency levels within a cohort of new MSK consulters which are both clinically relevant and supported by findings from different research settings. The first cluster which comprises those prescribed no pain medication or basic analgesia and occasionally weak analgesia may reflect the initial steps in the hierarchical treatment of MSK pain where patient concerns can be addressed through non-pharmacological means or basic analgesia.

The second cluster which comprises patients prescribed predominantly NSAIDs and to a lesser extent stronger analgesia, may reflect cases where stronger analgesia are deemed necessary but non-steroidal anti-inflammatory drugs (NSAIDs) have precedence over opioids. However in some patients, stronger analgesia is also tried. The third cluster of patients with high probability of all potency levels reflect possibly patients returning with severe conditions and intolerable levels of pain leading to combinations of potency levels or quick ascendency up the potency levels due to lack of effectiveness of weaker analgesia .

This analysis has not assessed the order of the analgesia prescribed as this will be the focus of Chapters 6-7. However, the clusters do not contradict the medication pathways related to the WHO analgesia ladder for the management of low back pain. This ladder suggests that pharmacological therapy starts with low potency non-opioid analgesia (hence the emergence here of a basic analgesia cluster) and a gradual addition of weak opioids before addition of stronger opioids (Ehrlich, 2003).

There is a link between pain intensity and the analgesia potency level received as well as side effects (Muller et al., 2011). The variation of cluster membership may be attributed to pain intensity or side effects. The multiple potency prescriptions in the third cluster may be

reflective of higher pain intensity that varies over time leading to prescription of multiple potency levels.

The association of living in less deprived areas being less likely to be prescribed multiple analgesia may reflect that patients from more deprived backgrounds are more likely to be prescribed analgesia free of charge whilst those in more affluent areas may prefer to purchase some medications over the counter. It can also be assumed that the less deprived are healthier and require less intervention. This analysis has concentrated on prescribed medications and the use of over the counter analgesia in this cohort is unknown, though 90% of prescriptions issued within the NHS are free of charge suggesting we are likely to have identified the majority of analgesia being used in primary care (House of Commons Committee of Public Accounts, 2008).

Latent class analysis has never been used in this context before but the results suggest it can be a valuable method in understanding prescription patterns in the pharmacological management of MSK conditions. Latent class analysis has a distinct advantage over other clustering methodologies in that the statistical model is based on the underlying probability distributions that generate the data hence the choice of cluster criterion is probability based (Vermunt and Magidson, 2002). This enables maximum likelihood estimation, rigorous statistical tests and goodness-of-fit measures in determining the best model. For example, in the initial six indicator model, the bivariate residuals identified the violation of the local independence assumption. One of the potential causes of the violation is a large number of indicator variables resulting in data becoming sparse and the parameter estimation process lacking precision (Popper, 2004; Vermunt and Magidson, 2000). The final model in this study was supported by four goodness-of-fit measures, the likelihood ratio test, the BIC, AIC and the CAIC. The high average posterior probabilities suggest low misclassification rates and that statistically the model is good quality while the clinical interpretation of the model was substantiated by a clinician’s evaluation.

The highly statistically significant variables in the multilevel multinomial logistic model show that the established clusters do not contradict the known guidelines and trends in the management of MSK pain, for example NSAIDs are known to be less likely to be prescribed for the 75+ age group due to the associated adverse effects for this age group (Fitzcharles et al., 2010, Oshima et al., 1996).

The prescription rate of NSAIDs in these patients is 62% over the period and they are prescribed mostly to age groups between 30 and 45 years reinforcing the view that NSAIDs are the mainstay of drug treatment of acute and chronic pain, but their side effects make them less suitable for the elderly (Main, 2002; Brooks, 2006; Garbez and Puntillo, 2005; Curatolo and Bogduk, 2001). The multiple-potency cluster suggests combination therapies which may be necessitated by the need to contain intolerable levels of pain while controlling the resultant side effects. Hunt et al. (2007) observed that combined use of NSAIDs and other analgesia is associated with fewer gastro-intestinal complications than treatment with NSAIDs alone, which might be the case in this cluster.

The study highlights that there are three distinct treatment profiles, associated with patient baseline characteristics over 5 years in patients consulting with new MSK problems, which can be described as no or basic analgesia, mainly NSAIDs or multiple pain analgesia. The intriguing group is the multiple analgesia group, which is the smallest group of 23% and has a high exposure to medication side effects. It could be postulated that if in a period of five years they have received at least three out of five potency levels (over 70%) or potency combinations including strong analgesia, they may have limited further viable medication options in the long run. This group consists mostly of females and the age distribution is skewed towards the older age group which is of concern given MSK conditions and their severity increase with age (Jordan et al., 2007), and that this is the age group with highest levels of comorbidity.

Despite the findings the study has its limitations. Although the designs incorporates five years of follow-up, the analysis is essentially a cross-sectional analysis and the likelihood is that analgesia prescriptions and potency level decided upon by GPs has time dependence and this analysis does not observe the sequence of the prescriptions. We are associating baseline factors with prescription patterns over five years and it is possible some baseline factors (e.g. comorbidity) may change. However despite the limitations, the latent class models provide a valuable insight into the prescription patterns of analgesia by potency levels among MSK consulters which provides strong foundations for further research. The older age group with multiple medications might be one that GPs should carefully follow up or be aware of since they may need greater clinical input that might avoid multiple drug use.

## 5.5 Conclusion

There are distinct latent classes of pain analgesia prescribing profiles for patients over a 5 year period. The existence of patient clusters that differ by demographic and clinical characteristics suggests that general practitioners may consider a number of factors including age and previous analgesia potency in deciding the potency level to prescribe next. Further research may be able to identify the group of patients at risk of high potency combinations.

The HAC model provides a reasonably good understanding of prescription patterns in the pharmacological treatment of MSK conditions as observed from current practices. Some patients because of their characteristics at the onset of seeking medical care are more likely to progress through the medication potency levels over time than others. The next chapter will examine the factors associated with time to changes or progression through the potency levels.

# Chapter 6

## 6 Factors associated with time to any switch of analgesia potency level among new musculoskeletal consulters

### 6.1 Introduction

Chapters 4 and 5 suggested that the HAC can provide a practical tool for describing the pharmacological management of MSK conditions with respect to using analgesia. Chapter 5 highlighted that there are three distinct prescription profiles within MSK consulters over time which consist of those prescribed Basic analgesia, NSAIDs and Multiple-potency (analgesia from across all potency levels). There are baseline factors associated with the prescription patterns which include age, gender, pain location, level of locality deprivation and previous prescribed analgesia. The potential group of interest is the 580 patients (23% of all new MSK consulters) who evidently use analgesia from several potency levels over time, despite the fact that the risk of adverse effects of analgesia becomes more likely.

There are numerous reasons which might be related to changes in analgesia. These include full or temporary recovery, deterioration of their condition, lack of efficacy, or patient decision (or choice). As a consequence, some patients will continue with the analgesia they started with, some will stop using analgesia permanently or for a while, while some change to higher potency analgesia or alternate between potency levels. This suggests that the analgesia switching process should be considered as a function of time, hence statistical models incorporating time to event in determining the factors associated with switching analgesia can add further information to the understanding of the switching process.

The association of time when a particular type of switch occurs, and the factors associated with switching may help to evaluate how general practitioners use analgesia to manage MSK pain over time and the potential risk of exposure to adverse effects. The time between subsequent switches will vary across and within individuals over time, but evaluating socio-demographic and clinical factors associated with switching may help clinicians to make therapeutic choices that might limit switching because the drugs used will suit the patient better.

As seen in the systematic review for statistical methods (Chapter 2), the Cox proportional hazards, a semi-parametric model, is suitable as it incorporates the effect of time, but parametric models (Weibull for example) could also be considered in any quest to obtain the best fit. The choice between semi-parametric or fully parametric form of the model is difficult, but consideration of the sample size, study objectives and potential benefits of each model can be a guiding principle (Marubini, 1994). The suitability of the statistical methods used should also be evaluated to ensure that the conclusions drawn from the study are applicable, informative and add to the existing knowledge of pharmacological management of MSK conditions.

The aim of this chapter is therefore to use semi-parametric and parametric statistical methods to evaluate both socio-demographic and clinical factors associated with time to switching analgesia in the pharmacological management of MSK conditions. This will further highlight the patients at higher risk of switching analgesia and therefore potentially exposure to potential adverse effects.

The specific objectives of the chapter are:

1. To model factors associated with change from initial analgesia potency level
2. To establish if factors associated with switch from initial analgesia vary with the potency level of initial analgesia

3. To model factors associated with switching taking into account successive switches from the initial analgesia potency to different potency levels over time
4. To model factors associated with the rate of switching
5. To compare semi-parametric and parametric models in modelling factors associated with switching from initial analgesia to different potency levels

The Cox model, the Weibull model and the Poisson model were employed to achieve the above objectives. The Cox model was identified through the literature review (Chapter 2) as the most commonly used approach in medication switch analysis. The first phase of analysis (Analysis 1) used both Cox and Weibull methods to model time to the first change from the initial potency level, ($1^{st}$, $2^{nd}$ and $5^{th}$ objectives), while the second phase (Analysis 2) models all switches in potency levels ($3^{rd}$ and $5^{th}$ objectives) using the multivariate versions of the same models. To account for unmeasured covariates, Weibull models with gamma frailty were also evaluated in both analyses 1 and 2. The third phase used Poisson and negative binomial regression to evaluate rates of switching over the 5 year follow-up period and associations with the clinical and socio-demographic covariates ($4^{th}$ and $5^{th}$ objectives, Analysis 3).

## 6.2 Analysis 1 - Modelling time to the first change from initial medication potency

### 6.2.1 Methods

The analysis of time to the first switch (change) is considered in two steps to enable iterative model building and evaluation. Switching analgesia, as defined in chapter 1, is defined as either a record of a prescription of an analgesia of a potency different from that previously prescribed (this may be in place of, or in addition to the initial analgesia), or a record of prescribed analgesia without a previous analgesia prescription on first consultation (Gore et al., 2012, Rahme et al., 2006). Stopping medication is not considered as a switch as the precise time to stopping cannot be ascertained. The

statistical approaches are defined in brief, to highlight the differences between the models, and their detailed descriptions can be found in in a wide range of literature including Dobson and Barnett (2008).

**Step 1**: The event of interest (outcome variable) was the first switch of analgesia potency level. Analysis of time to the first change will establish if there was any relationship between change in analgesia potency from the initially prescribed analgesia and baseline clinical, socio-demographic and time-varying covariates.

**Step 2**: In the second step, the analysis was repeated but with the individual strata (HAC categories) of the initial analgesia potency level analysed separately. Analysis of time to first change stratified on the initial medication potency assumed that each category (initial analgesia potency level) had a different likelihood of switching and associated factors which may not be identified when modelled jointly. The Weibull and the Cox models were fitted on each initial analgesia stratum separately to establish if the factors associated with a switch varied by initial medication potency.

A descriptive analysis was conducted initially on the types of changes, that is, for patients in each potency category initially, to what potency level they changed to on first switch, if they switched.

### 6.2.2 Data management and study population

All the patients identified and included in the analysis in Chapter 4 were considered in this analysis but with a slight variation. Patients whose registration records showed them as not registered any time after their initial 2006 consultation were censored at their last registration date (date of leaving the practice). Those whose last registration date after the first consultation could not be established were excluded from the analysis. The time to first switch was derived from the initial consultation date and issue date of prescriptions. Those who did not switch medications had their times censored at the end of 2010 or end of registration.

**Outcome variables:** The outcome variable was time to the first switch from the initial analgesia potency level. The time, in days, is the time between the date of first consultation in 2006 to the date when an analgesia was prescribed of a potency level (based on the HAC) different from initially prescribed, as it is considered they are at risk of starting or changing analgesia from the onset of consultation. The switch from initial analgesia potency was defined as first prescription of analgesia on a different potency level (less or more potent) in the HAC than that prescribed at initial consultation, or first prescription for analgesia in those not prescribed analgesia at initial consultation.

**Censoring**: Inevitably some patients left their practices before the end of follow-up. These individuals therefore have censored times, censored on the dates when they became unregistered (e.g. left or died) from their practices. Registration data for CiPCA though was only available at the mid and end dates of years, so censoring for those leaving their practice was at last date of recorded registration or last recorded prescription date, whichever was later.

**Baseline covariates:** The variables measured at time of initial consultation and considered in this analysis were age, gender, deprivation, co-morbidity, registered practice, staff consulted (GP or other), region of pain (e.g. knee, back) at onset of consultation, previous MSK consultation and previous prescribed analgesia as described in Chapter 4. The initial analgesia received within two weeks of first consultation was also included (basic analgesia, weak analgesia, moderate analgesia, strong analgesia, NSAIDs and no medication). As described in Chapter 5, strong combination analgesia and very strong single analgesia were combined to a single category of strong analgesia. General practice was considered as a clustering variable (section 6.1.2).

**Time-varying covariates**: Time-varying covariates are variables that change during follow-up. The time-varying variables were based on information to the earliest of the first switch, end of follow-up (end of 2010) or date of censorship. They were the number of

analgesia prescriptions for the analgesia category prescribed at initial consultation, number of further MSK consultations after first consultation date, and consulting for pain in more than one location over time. The covariates are evaluated as products of the variables and the natural log of time (Maller and Zhou, 1996). Including the time-varying covariates in the model as the product of the log of time to the event and the measured variable minimises the risk of over or under inflated parameter estimates resulting from the influence of outlying observations.

### 6.2.3 Statistical analyses

Kaplan-Meier survival curves, the Cox model and Weibull model were used. The use of proportional hazards models was considered, but the statistical significance of the time-varying covariates meant that the proportional hazards assumption was no longer valid (Dobson and Barnett, 2008); hence just the Cox and Weibull models assuming non-proportional hazards were used. Kaplan-Meier curves were used as an exploratory analysis to decide if the times to first change are different between categories of the independent variables, with particular interest in the initial medication potency levels. Weibull models with a gamma frailty were used to model the dependence of time to first switch on the socio-demographic and clinical factors. Frailty modelling was used to deal with the possibility of unaccounted variation in switching due to unmeasured covariates.

Comparison of the deviance (-2logL) values were further used to evaluate whether the inclusion of a cluster variable (practice) improved model efficiency, and whether the Cox model or the Weibull model is more suitable in the analysis of analgesia switching. The statistical package Stata was used.

#### 6.2.3.1 Cox proportional hazards model

The basic model is defined by Cox (1972), Marubini (1994) and by Crowder et al. (1991) among several other authors as follows:

Consider a study with N individuals, each with the observed vector $(t_i, \delta_i, \boldsymbol{x_i})$, where $x_i$ is a vector of covariates of $q$ dimension, $\boldsymbol{x_i} = (x_1, x_2, \dots x_q)$, for individual $i$ and $\delta_i$ is the switch or censoring indicator (1=switch, 0=censor) Consider in this case failure to be defined by switching from one medication potency level to another and time to failure to be the time to switching. Then the hazard function (the instantaneous rate of switching) $h(t, x_i)$ for the time to switch *t* for an individual $i$ is defined as:

$$h(t, x_i) = h_0(t) \exp\{\boldsymbol{\beta x_i}\} ,$$

Where $h_0(t)$ is the baseline hazard and is an arbitrary function of time only, $h_0(t)$ is the same for all subjects and **β** is a vector of regression coefficients.

The Cox model is a semi-parametric or distribution-free model; that is, it does not assume that the data has a particular underlying distribution, but its major assumption is that the hazards of the different groups are proportional (Lawless, 1982). Proportional hazards cannot be assumed in models with time-varying covariates, which is the case in this thesis.

Cluster and strata variables can also be used in the Cox model. A cluster variable accounts for correlation of failure times within and between the clusters in which the data is partitioned in the estimation of the model parameters (Collet, 2003). The data can be partitioned into 12 general practices, and so including general practice as a cluster variable in the model enables the model to account for the variation or the correlation of switch times within practices in the final model and enables testing to see if practice has an influence on model parameters. By contrast, strata variables enable the modelling process to consider stratum-specific hazards in estimating model parameters, for example if initially prescribed analgesia was included as a strata variable, the model will consider baseline hazards for potency level different and account for that in model parameter estimation.

The hazard ratios associated with a covariate are estimated through the partial likelihood function (Cox (1972)) which is

$$L_j(\beta) = \prod_{j=1}^{K} \frac{e^{\beta x_j}}{\sum_{l \epsilon R(\theta_j)} e^{\beta x_l}}$$

It works as an ordinary likelihood for making inferences about coefficients of the covariates in the model.

#### 6.2.3.2 The Weibull model

The Weibull model is based on the assumption that the baseline survivor function follows a Weibull distribution. Consider the Weibull distribution as defined by Crowder et al. (1991) as a function of time as follows:

$$f(t) = \lambda p(\lambda t)^{p-1} \exp\{-(\lambda t)^p\}, \lambda > 0, p > 0, t > 0$$

Where $\lambda$ is the scale parameter and $p$ is the shape parameter, the hazard function (the instantaneous rate of switching)

$$h(t) = \lambda p(\lambda t)^{p-1}$$

The scale parameter $\lambda$ controls the spread of the Weibull distribution such that the larger the value of $\lambda$, the more spread is the distribution. The shape parameter $p$ controls the shape of the distribution, for example how skewed the distribution is. To illustrate the effect of the scale and shape parameters, a Weibull distribution with parameters $\lambda = 1, p = 1$ gives a constant hazard rate and an exponential distribution (Lee and Wang, 2003). For $3 \leq p \leq 4$, it is close to the Normal distribution and when $p$ is large, say $p \geq 10$ it is close to the smallest extreme value distribution (Nelson, 1982). The hazard rate increases over time when $p > 1$ and decreases when $p < 1$ as time increases (Lee and Wang, 2003).

For an individual with time to switching medication $t$ and a covariate vector of $q$ variables, $\boldsymbol{x_i} = (x_1, x_2, \ldots x_q)$, the Weibull hazard may be expressed as;

$$h(t, x_i) = \lambda p(\lambda t)^{p-1} \exp\{\beta x_i\}$$

The log of the Weibull likelihood function $l(\theta)$ is

$$l(\theta) = \delta \log p + \delta p \log \lambda + (p-1) \sum_{1}^{n} \delta_i \log t_i - \sum_{1}^{n} (\lambda t)^p$$

$\delta_i$ is the switch or censoring indicator. The parameter estimates obtained that maximise the log likelihood function can then be used to calculate estimated covariate coefficients, standard errors and confidence intervals (Marubini et al., 1995).

The main difference between the Weibull and the Cox model is that the Cox model estimates the baseline survivor function without any reference to a theoretical distribution. They can yield similar results if the data indeed follows a Weibull distribution or if the proportional hazards assumption is true. The Weibull model may yield smaller standard errors due to the parametric form of the baseline hazard instead of estimating hazard rates at every event time (Marubini et al., 1995). The Weibull can also yield smaller standard errors than the Cox if the sample sizes are small, for example less than 30, but there is little difference with larger samples. If the distributional assumptions can be met, the Weibull model will fit the data better than the Cox (Lee and Wang, 2003).

#### 6.2.3.3 Assessing model fit and Goodness-of-fit tests

The evaluation of the fitted model is achieved through residual analysis and the analysis of the survival or hazard functions. These are best illustrated through graphical plots. The residuals commonly used for assessing model fit are Cox-Snell, Martingale and Schoenfeld residuals (Marubini et al., 1995). The evaluation of the proportional hazards assumption is also an essential aspect of model evaluation. However time-varying covariates allow for changing hazard ratios over time, which means the proportional hazards assumption can be relaxed and is no longer a necessary condition in assessing model fit (Collet, 2003).

#### 6.2.3.4 Gamma frailty model

The concept of frailty is based on the heterogeneity amongst individuals (Collet, 2003), that is, not all individuals are the same. High risk or frail individuals will tend to have shorter times before switching medication and lower risk ones will take much longer. Frailty models therefore attempts to account for some of the possible unobserved or unmeasured covariates which may influence switching, and for within group correlations.

If we consider a Weibull model as above, but include a random variable (the frailty element) $z$ the hazard becomes;

$$h(t,x) = \mathrm{z}\lambda p(\lambda t)^{p-1}\exp\{\beta x_i\}$$

The frailty distribution in this analysis is assumed to be gamma but can take any form in general. The gamma distribution is responsive to non-monotonic hazard functions over time and best suited in models with time-varying covariates, (Marubini et al., 1995).

### 6.2.4 Results

#### Data description

Of the original 3236 patients, 57 (2%) ceased to be registered with a last date known to be registered prior to their index consultation, hence time to event could not be determined nor was censoring possible. Most of the independent variables were complete except for pain location (see Chapter 4). The excluded patients were not very different from the main cohort by age and gender, 34 (60%) were males and their mean age was 44 years with a standard deviation of 19.6.

There were 3179 people considered in the analysis with mean age 45 years, (SD 15.9), of which 59% were males. 1629 (51%) people switched from the analgesia prescribed in their first consultation in 2006 or started analgesia. Very high proportions of those initially prescribed weak (70%), moderate (62%) and strong analgesia (70%) switched from initially prescribed analgesia over the five years of follow-up. Over 50% of those aged over

45, females, those with prior MSK consultations, previous prescribed analgesia, pain in the back and hip and selected co-morbidities switched (Table 6.2.1).

Table 6.2.1: Baseline socio-demographic and clinical characteristics of patients switching analgesia

| | | Switch Analgesia | |
|---|---|---|---|
| **Variable** | **N** | **No (Row %)** | **Yes (Row %)** |
| Total | 3179 | 1550(49) | 1629(51) |
| **Age (years)** | | | |
| 15-29 | 688 | 392(57) | 296(43) |
| 30-44 | 1068 | 556(52) | 512(48) |
| 45-59 | 953 | 435(46) | 518(54) |
| 60-74 | 369 | 132(36) | 237(64) |
| Over 75 | 101 | 35(35) | 66(65) |
| **Gender** | | | |
| Females | 1293 | 580(45) | 713(55) |
| Males | 1886 | 970(51) | 916(49) |
| **Previous musculoskeletal consultation** | | | |
| Yes | 409 | 179(44) | 230(56) |
| No | 2770 | 1371(49) | 1399(51) |
| **Previous prescribed analgesia** | | | |
| Yes | 509 | 145(28) | 364(72) |
| No | 2670 | 1405(53) | 1265(47) |
| **Region of Pain** | | | |
| Back | 818 | 376(46) | 442(54) |
| Knee | 388 | 177(52) | 161(48) |
| Hip | 199 | 88(44) | 111(56) |
| Foot and Ankle | 219 | 104(47) | 115(53) |
| Hand/upper limb | 256 | 129(50) | 127(50) |
| Shoulder | 244 | 114(47) | 130(53) |
| Neck | 215 | 114(53) | 101(47) |
| Other/unspecified | 890 | 448(50) | 442(50) |
| **Co-morbidity** | | | |
| Selected conditions | 118 | 53(45) | 65(55) |
| Other conditions/none | 3061 | 1497(49) | 1564(51) |
| **Deprivation** | | | |
| Most | 1402 | 657(47) | 745(53) |
| Moderate | 1239 | 624(50) | 615(50) |
| Least | 538 | 269(50) | 269(50) |
| **Staff category** | | | |
| GPs | 2575 | 1255(49) | 1320(51) |
| Other | 604 | 295(49) | 309(51) |

| Variable | N | Switch Analgesia No (Row %) | Yes (Row %) |
|---|---|---|---|
| **Number of pain locations** | | | |
| One | 2472 | 1053(43) | 1419(57) |
| More | 707 | 497(70) | 210(30) |
| **Analgesia group (1st consultation)** | | | |
| Basic analgesia | 346 | 159(46) | 187(54) |
| Weak analgesia | 223 | 66(30) | 157(70) |
| Moderate analgesia | 47 | 18(38) | 29(62) |
| Strong analgesia | 160 | 47(30) | 113(70) |
| NSAIDs | 687 | 321(47) | 366(53) |
| No medication | 1716 | 939(55) | 777(45) |

Of those switching analgesia, at least 30% first switched to or added NSAIDs from all initial potency levels, the highest number being from strong analgesia (53%). More than 30% also switched to or added basic analgesia from all potency levels, with 53% of those initially on NSAIDs and 48% on weak analgesia first switching to basic analgesia. Less than 20% from all initial potency levels switched to strong analgesia. Those with no medication prescribed at initial consultation were more likely to be prescribed NSAIDs (38%) or basic analgesia (35%) during follow-up (Table 6.2.2).

Table 6.2.2: First switch from initial analgesia potency in those switching

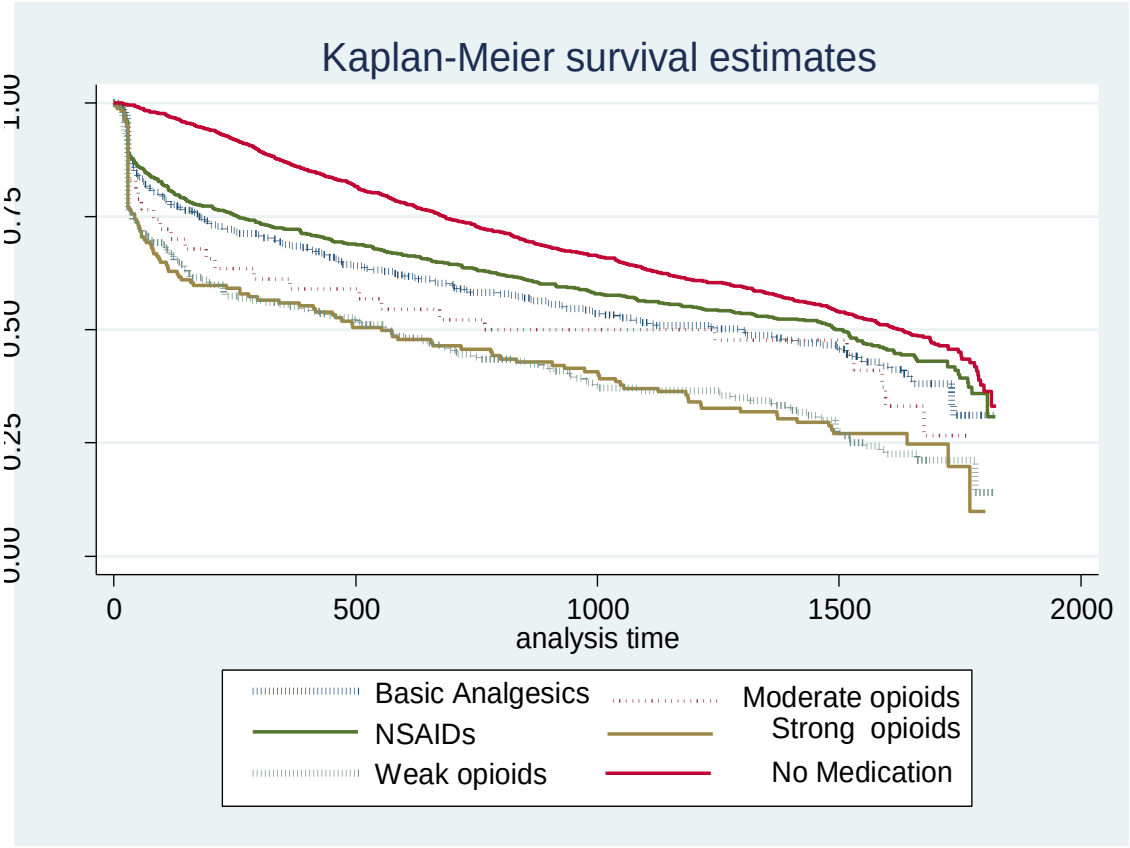
| **Analgesia prescribed on 1st consultation** | | **Group Switched to** Basic analgesia | Weak analgesia | Moderate analgesia | Strong analgesia | NSAIDs |
|---|---|---|---|---|---|---|
| | N | **n (row%)** | **n (row%)** | **n (row%)** | **n (row%)** | **n (row%)** |
| Basic analgesia | 187 | - | 50(27) | 64(34) | 17(9) | 56(30) |
| Weak analgesia | 157 | 76(48) | - | 7(5) | 27(17) | 47(30) |
| Moderate analgesia | 29 | 13(44) | 2(7) | - | 5(17) | 9(31) |
| Strong analgesia | 113 | 35(31) | 12(11) | 6(5) | - | 60(53) |
| NSAIDs | 366 | 193(53) | 80(22) | 23(6) | 70(19) | - |
| No medication | 777 | 272(35) | 106(13) | 32(4) | 75(10) | 292(38) |

Of those who switched analgesia, the mean time to switch was 606 days; the median switch time was 485 days and interquartile range (IQR) (118, 1002).

**Rates of analgesia switching**

The Kaplan-Meier survival curves suggested evidence of different rates of analgesia switching between some age groups, by gender and by medication history. Some covariates showed no evidence of difference, that is, co-morbidity, location of pain, consultation history and staff consulted. The Kaplan-Meier curves showed that, there are more people switching within the first 30 days of starting analgesia for all potency levels. There is evidence of variation in the rates of switching by the initially prescribed analgesia over time (Figure 6.1.1).

Figure 6.2.1: Analgesia switching estimates by initial analgesia prescribed



### 6.2.4.1 Time to first analgesia switch models

The time-varying covariates were statistically significant in the final models meaning that the proportional hazards assumption no longer holds for the model. The -2logL of the models also showed that the inclusion of practice as a cluster variable does not improve model fit; hence the practice variable was left out of the final models. Both the adjusted and the unadjusted models were fitted and the hazard ratios reported with 95% confidence intervals (HR [95%CI]) for both the statistically significant and non-significant variables (Table 6.2.3). The statistically significant variables from these two models are highlighted in bold.

The models show that the baseline variables of age, gender, previous medication history, and analgesia potency at onset of consultation are all statistically significantly related to switching analgesia potency level. Number of MSK consultations and number of analgesia prescriptions of same potency as at initial consultation over follow-up are also associated with switching. Consulting for pain in more than one location over time also significantly increases the risk of switching analgesia. The hazard ratios are similar for Cox and Weibull models with minor variations in some cases. The hazard ratios can be interpreted as the average hazards associated with each variable over time.

**The Cox model**

**Baseline variables:** The model shows that when compared to the 30-44, the age groups 60-74 (adjusted hazard ratio ((HR) 1.31; 95% CI [1.11, 1.53]), and 75 plus (HR 1.45 [1.11, 1.90]) were more likely to experience an analgesia switch when all other factors are held constant. Females were more likely than males to experience analgesia switch (HR 1.14 [1.03, 1.26]). Patients prescribed pain medication 12-24 months prior to their first consultation in 2006, with hazard ratio (HR 1.57 [1.38, 1.78]) also had an increased risk of experiencing a medication switch.

Those who started with no medication at initial consultation (HR 0.74 [0.63, 0.88]) were less likely to change medication status while those starting on weak analgesia (HR 1.34 [1.08, 1.67]), and those starting on strong analgesia (HR 1.34 [1.04, 1.72]) were more likely to switch medication, compared to those starting on basic analgesia. Prior history of MSK consultations, level of deprivation, comorbidity, pain location at initial consultation and staff consulted were not significantly related to time to first analgesia switch.

**Time Varying Covariates:** Patients who consulted for pain in more than one location over time (HR 1.03 [1.02, 1.06]) were more likely to switch analgesia. The hazard ratios of (HR 0.90 [0.88, 0.91]) for number of consultations over time and (HR 1.01 [1.001, 1.02]) for number of analgesia prescribed over time shows that each consultation for MSK reduced the risk of switching analgesia by 10% but each extra prescription increases the risk of analgesia change by 1%, respectively (Table 6.2.3).

**The Weibull model**

The Weibull model identified significant covariates similar to those identified by the Cox model with slightly lower hazard ratios in some instances, for example (HR 1.28 [1.09, 1.51] for the 60-74 and 1.43 [1.10, 1.88]) for the 75+ age groups (Table 6.1.3). The Weibull shape parameter of 0.85 [0.81, 0.88] suggests that the underlying hazard rate decreases as time increases. The -2logL of 7980 suggests the Weibull model is a better fit than the Cox model.

Table 6.2.3: Unadjusted and Adjusted Cox and Weibull models that examine factors associated with time to 1st medication switch

| Variable | Hazard Ratio [95% CI] | | | |
|---|---|---|---|---|
| | Cox Model | | Weibull Model | |
| | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Age Group** | | | | |
| 30-44 | 1.00 | 1.00 | 1.00 | 1.00 |
| 15-29 | 0.92[0.80, 1.07] | 0.92[0.79, 1.06] | 0.92[0.79, 1.06] | 0.91[0.78, 1.06] |
| 45-59 | 1.11[0.98, 1.25] | 1.03[0.91, 1.17] | 1.11[0.98, 1.25] | 1.03[0.91, 1.17] |
| 60-74 | 1.50[1.29, 1.75] | **1.31[1.11, 1.53]** | 1.48[1.27, 1.72] | **1.28[1.09, 1.51]** |
| 75+ | 2.19[1.70, 2.83] | **1.45[1.11, 1.90]** | 2.17[1.68, 2.80] | **1.43[1.10, 1.88]** |
| **Gender** | | | | |
| Male | 1.00 | 1.00 | 1.00 | 1.00 |
| Female | 1.28[1.16, 1.41] | **1.14[1.03, 1.26]** | 1.271.15, 1.40] | **1.12[1.01, 1.24]** |
| **Previous prescribed analgesia** | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.69[1.51, 1.90] | **1.57[1.38, 1.78]** | 1.68[1.49, 1.88] | **1.54[1.36, 1.75]** |
| **Previous musculoskeletal consultation** | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.09[0.96, 1.25] | 0.92[0.79, 1.07] | 1.09[0.95, 1.26] | 0.93[0.80, 1.08] |
| **Comorbidity** | | | | |
| Selected | 1.00 | 1.00 | 1.00 | 1.00 |
| None | 0.91[0.71, 1.16 | 1.14[0.89, 1.47] | 0.93[0.72, 1.19] | 1.17[0.92, 1.52] |
| **Staff category** | | | | |
| GP | 1.00 | 1.00 | 1.00 | 1.00 |
| Other | 1.02[0.90, 1.15] | 1.02[0.90, 1.15] | 1.02[0.90, 1.15] | 1.03[0.91, 1.17] |
| **Deprivation** | | | | |
| Most | 1.00 | 1.00 | 1.00 | 1.00 |
| Medium | 0.87[0.78, 0.96] | 0.95[0.85, 1.06] | 0.86[0.78, 0.96] | 0.94[0.85, 1.06] |
| Least | 0.83[0.72, 0.96] | 0.91[0.79, 1.05] | 0.83[0.73, 0.96] | 0.91[0.80, 1.06] |

| Variable | Hazard Ratio [95% CI] | | | |
|---|---|---|---|---|
| | Cox Model | | Weibull Model | |
| | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Pain Region** | | | | |
| Back | 1.00 | 1.00 | 1.00 | 1.00 |
| Knee | 0.82[0.69, 0.99] | 0.95[0.79, 1.15] | 0.82[0.68, 0.98] | 0.96[0.80, 1.15] |
| Hip | 1.05[0.85, 1.29] | 1.05[0.84, 1.30] | 1.06[0.86, 1.30] | 1.08[0.87, 1.33] |
| Foot and Ankle | 0.92[0.75, 1.13] | 1.02[0.83, 1.27] | 0.91[0.74, 1.12] | 1.02[0.83, 1.26] |
| Hand/upper limb | 0.82[0.68, 1.00] | 0.97[0.79, 1.18] | 0.83[0.68, 1.01] | 0.97[0.79, 1.19] |
| Shoulder | 0.94[0.78, 1.15] | 1.00[0.82, 1.22] | 0.94[0.78, 1.15] | 1.00[0.82, 1.22] |
| Neck | 0.77[0.62, 0.96] | 0.86[0.69, 1.07] | 0.76[0.61, 0.94] | 0.84[0.68, 1.05] |
| Other/unspecified | 0.88[0.77, 1.01] | 0.97[0.85, 1.12] | 0.88[0.77, 0.99] | 0.97[0.84, 1.11] |
| **Initial analgesia (1st consultation)** | | | | |
| Basic analgesia | 1.00 | 1.00 | 1.00 | 1.00 |
| Weak analgesia | 1.66[1.34, 2.04] | **1.34[1.08, 1.67]** | 1.66[1.34, 2.05] | **1.33[1.07, 1.66]** |
| Moderate analgesia | 1.16[0.79. 1.72] | 0.99[0.66, 1.46] | 1.17[0.79, 1.73] | 1.02[0.69, 1.52] |
| NSAIDs | 0.87[0.73, 1.04] | 1.01[0.84, 1.21] | 0.88[0.74, 1.05] | 1.01[0.84, 1.21] |
| Strong analgesia | 1.63[1.29, 2.06] | **1.34[1.04, 1.72]** | 1.63[1.29, 2.06] | **1.34[1.05, 1.72]** |
| No medication | 0.68[0.58,0.80] | **0.74[0.63, 0.88]** | 0.68[0.58, 0.79] | **0.73[0.62, 0.86]** |
| **Time-varying** | | | | |
| **Multiple location** | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 0.86[0.84, 0.87] | **1.03[1.02, 1.06]** | 0.86[0.84, 0.87] | **1.03[1.02, 1.06]** |
| **No. of consultations** | 0.91[0.90, 0.92] | **0.90[0.88, 0.91]** | 0.91[0.90, 0.92] | **0.89[0.88, 0.91]** |
| **No. of Prescriptions** | 1.00[1.00, 1.01] | **1.01[1.001, 1.02]** | 1.00[1.00,1.03] | **1.01[1.001, 1.02]** |
| **-2logL** | | 23690 | | 7980 |
| **Weibull shape parameter** | - | - | - | **0.85[0.81, 0.88]** |

**Unadjusted model =** Individual variable in the model, **Adjusted model =** All variables included simultaneously

### 6.2.4.2 Initial analgesia strata-specific models

The Cox and Weibull models were fitted on each strata of the initial analgesia potency separately. The Cox and Weibull models identified similar variables associated with time to switching for each potency level. For those on basic analgesia initially, time to switch was associated with age, gender, pain location on first consultation, staff initially consulted (GP or other), number of MSK consultations and number of prescriptions received. For those on weak analgesia initially, medication history, pain location, pain in more than one location over time, number of MSK consultations and number of prescriptions were associated with time to switch, while for those on moderate analgesia age and number of MSK consultations were associated with switching.

For those initially on strong analgesia, only pain location on first consultation, pain in more than one location over time, and number of MSK consultations over time were associated with medication switching. For those initially on NSAIDs, gender (female), previous prescribed analgesia, pain in more than one location over time, number of MSK consultations and number of prescriptions were associated with time to switch. Those who were prescribed no pain analgesia initially had age, gender, previous prescribed analgesia, and pain in more than one location over time, and number of MSK consultations associated with time to starting medication (Table 6.2.4 and 6.2.5).

Both the Cox and the Weibull stratified models are characterised by large hazard ratios accompanied by very wide confidence intervals. This is expected as fewer individuals contribute to the estimation process due to low numbers at risk in the individual categories of the initial analgesia potency. The adjusted Cox and Weibull models in Table 6.2.3 are therefore better fits to the data than the stratified models.

Table 6.2.4: Initial analgesia stratified Cox models that examine factors associated with time to 1st medication switch

| Variable | Hazard Ratio [95% CI] - Cox | | | | | |
|---|---|---|---|---|---|---|
| | **Basic Analgesia** | **Weak Analgesia** | **Moderate Analgesia** | **Strong Analgesia** | **NSAIDs** | **No medication** |
| **Age Group** | | | | | | |
| 30-44 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 15-29 | 0.86[0.54,1.36] | 1.20[0.69,2.07] | 0.72[0.15,3.40] | 0.84[0.40,1.76] | 1.06[0.76,1.48] | 0.90[0.74,1.10] |
| 45-59 | 1.04[0.66,1.65] | 0.75[0.47,1.18] | **0.08[0.01,0.62]** | 0.92[0.56,1.49] | 1.13[0.88,1.45] | 0.99[0.83,1.19] |
| 60-74 | **1.93[1.17,3.18]** | 0.88[0.51,1.52] | 0.39[0.04,3.12] | 0.77[0.39,1.53] | 1.37[0.97,1.94] | **1.43[1.12,1.82]** |
| 75+ | 1.46[0.83,2.57] | 0.50[0.23,1.08] | 0.58[0.04,8.03] | 0.66[0.07,5.60] | 2.23[0.89,5.59] | **2.74[1.77,4.23]** |
| **Gender** | | | | | | |
| Male | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Female | **0.70[0.51,0.96]** | 1.17[0.81,1.68] | 1.95[0.41,9.10] | 0.93[0.60,1.45] | **1.42[1.15,1.76]** | **1.21[1.05,1.40]** |
| **Previous prescribed analgesia** | | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.49[0.95,2.34] | **1.93[1.28,2.91]** | 0.07[0.01,0.60] | 1.35[0.81,2.26] | **1.40[1.08,1.82]** | **1.72[1.43,2.08]** |
| **Previous musculoskeletal consultation** | | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 0.63[0.37,1.06] | 0.59[0.34,1.02] | 2.58[0.20,32.9] | 1.48[0.80,2.75] | 0.75[0.53,1.05] | 1.02[0.82,1.26] |
| **Comorbidity** | | | | | | |
| Selected | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| None | 1.15[0.62,2.13] | 2.02[0.95,4.28] | 0.67[0.05,7.97] | 0.98[0.40,2.38] | 0.96[0.53,1.73] | 0.95[0.63,1.42] |
| **Staff category** | | | | | | |
| GP | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Other | **0.54[0.34,0.87]** | 1.43[0.88,2.34] | 0.66[0.16,2.74] | 1.40[0.86,2.27] | 1.14[0.86,1.52] | 0.99[0.83,1.18] |

| Variable | Hazard Ratio [95% CI] - Cox | | | | | |
|---|---|---|---|---|---|---|
| | **Basic Analgesia** | **Weak Analgesia** | **Moderate Analgesia** | **Strong Analgesia** | **NSAIDs** | **No medication** |
| **Deprivation** | | | | | | |
| Most | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Medium | 1.13[0.79,1.62] | 1.01[0.69,1.48] | 0.41[0.12,1.38] | 1.04[0.65,1.65] | 0.93[0.74,1.18] | 0.89[0.76,1.04] |
| Least | 1.41[0.93,2.15] | 0.96[0.58,1.61] | 0.51[0.05,4.94] | 0.95[0.46,1.96] | 0.92[0.67,1.25] | 0.85[0.69,1.05] |
| **Pain Region** | | | | | | |
| Back | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Knee | **0.45[0.25,0.79]** | 1.07[0.52,2.22] | 2.16[0.05,80.0] | 1.62[0.63,4.20] | 0.98[0.69,1.38] | 0.99[0.75,1.32] |
| Hip | 1.24[0.55,2.76] | 1.79[0.90,3.55] | 9.56[0.17,510] | **3.34[1.57,7.10]** | 0.64[0.39,1.06] | 0.99[0.73,1.34] |
| Foot and Ankle | 1.03[0.57,1.88] | 1.82[0.77,4.29] | - | 0.91[0.21,4.00] | 0.99[0.66,1.50] | 1.00[0.75,1.32] |
| Hand/upper limb | 0.80[0.46,1.40] | **2.82[1.25,6.40]** | - | **12.5[1.28,122]** | 0.76[0.48,1.20] | 0.92[0.67,1.25] |
| Shoulder | 0.69[0.39,1.21] | **2.79[1.44,5.39]** | - | 1.16[0.51,2.67] | 0.98[0.69,1.40] | 0.87[0.61,1.24] |
| Neck | **0.41[0.19,0.89]** | 0.70[0.28,1.73] | - | 0.90[0.48,1.68] | 0.75[0.44,1.27] | 0.72[0.52,1.01] |
| Other/unspecified | **0.60[0.38,0.94]** | 0.86[0.56,1.34] | 4.88[0.57,41.3] | 1.08[0.59,2.00] | 1.01[0.74,1.38] | 1.00[0.82,1.22] |
| **Time-varying** | | | | | | |
| **Multiple location** | | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.11[0.58,2.14] | **3.69[1.16,11.7]** | 8.68[0.51,146] | **7.72[2.07,28.8]** | **1.58[1.00,2.49]** | 1.28[0.97,1.67] |
| **No. of Consultations** | **0.88[0.84,0.92]** | **0.75[0.67,0.83]** | **0.78[0.65,0.94]** | **0.77[0.68,0.87]** | **0.88[0.85,0.91]** | **0.93[0.92,0.95]** |
| **No. of Prescriptions** | **1.00[1.00,1.01]** | **1.00[1.00,1.01]** | 0.99[0.96,1.01] | 1.00[0.99,1.01] | **1.00[1.00,1.01]** | **-** |

**Unadjusted model =** Individual variable in the model, **Adjusted model =** All variables included simultaneously

Table 6.2.5: Initial analgesia stratified Weibull models that examine factors associated with time to 1st medication switch

| Variable | Hazard Ratio [95% CI] - Weibull | | | | | |
|---|---|---|---|---|---|---|
| | **Basic Analgesia** | **Weak Analgesia** | **Moderate Analgesia** | **Strong Analgesia** | **NSAIDs** | **No medication** |
| **Age Group** | | | | | | |
| 30-44 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 15-29 | 0.84[0.53,1.33] | 1.27[0.74,2.18] | 0.42[0.09,1.88] | 0.94[0.45,1.95] | 1.06[0.76,1.47] | 0.91[0.75,1.11] |
| 45-59 | 1.01[0.65,1.59] | 0.76[0.48,1.20] | **0.03[0.01,0.29]** | 0.94[0.58,1.53] | 1.11[0.87,1.43] | 1.01[0.84,1.21] |
| 60-74 | **2.07[1.25,3.40]** | 0.81[0.47,1.41] | 0.12[0.01,1.02] | 0.90[0.46,1.77] | 1.31[0.92,1.85] | **1.43[1.12,1.83]** |
| 75+ | 1.39[0.79,2.42] | 0.52[0.24,1.12] | 0.24[0.01,3.59] | 0.95[0.11,8.15] | 2.12[0.85,5.31] | **2.69[1.74,4.15]** |
| **Gender** | | | | | | |
| Male | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Female | **0.68[0.49,0.94]** | 1.25[0.87,1.78] | 2.68[0.58,12.4] | 0.87[0.55,1.36] | **1.37[1.11,1.70]** | **1.20[1.04,1.39]** |
| **Previous prescribed analgesia** | | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.47[0.94,2.15] | **1.95[1.29,2.95]** | **0.03[0.01,0.30]** | 1.46[0.87,2.45] | **1.35[1.03,1.75]** | **1.73[1.43,2.08]** |
| **Previous musculoskeletal consultation** | | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 0.65[0.38,1.08] | 0.60[0.34,1.06] | 4.97[0.41,59.6] | 1.40[0.76,2.59] | 0.75[0.53,1.06] | 1.02[0.83,1.26] |
| **Comorbidity** | | | | | | |
| Selected | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| None | 1.19[0.64,2.20] | **2.22[1.04,4.71]** | 1.01[0.09,10.6] | 0.98[0.40,2.39] | 0.99[0.55,1.80] | 0.96[0.64,1.44] |
| **Staff category** | | | | | | |
| GP | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Other | **0.52[0.32,0.84]** | 1.42[0.87,2.32] | 0.46[0.10,2.08] | 1.57[0.96,2.57] | 1.13[0.85,1.50] | 0.98[0.82,1.17] |

| Variable | Hazard Ratio [95% CI] - Weibull | | | | | |
|---|---|---|---|---|---|---|
| | **Basic Analgesia** | **Weak Analgesia** | **Moderate Analgesia** | **Strong Analgesia** | **NSAIDs** | **No medication** |
| **Deprivation** | | | | | | |
| Most | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Medium | 1.14[0.80,1.63] | 1.02[0.70,1.49] | **0.27[0.08,0.90]** | 1.08[0.68,1.72] | 0.95[0.75,1.20] | 0.88[0.75,1.03] |
| Least | 1.42[0.94,2.15] | 1.02[0.61,1.70] | 0.60[0.05,7.10] | 0.99[0.48,2.04] | 0.95[0.69,1.30] | 0.84[0.68,1.03] |
| **Pain Region** | | | | | | |
| Back | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Knee | **0.42[0.24,0.74]** | 1.04[0.51,2.14] | 14.5[0.35,598] | 1.64[0.63,4.28] | 1.01[0.72,1.42] | 0.99[0.75,1.32] |
| Hip | 1.23[0.55,2.74] | 1.73[0.88,3.43] | - | **3.04[1.45,6.36]** | 0.66[0.40,1.09] | 1.01[0.74,1.36] |
| Foot and Ankle | 1.04[0.57,1.89] | 2.01[0.84,4.80] | - | 0.81[0.18,3.56] | 0.94[0.62,1.43] | 0.93[0.68,1.27] |
| Hand/upper limb | 0.79[0.45,1.36] | **2.24[1.01,5.03]** | - | 2.63[0.31,22.3] | 0.74[0.47,1.17] | 1.01[0.76,1.33] |
| Shoulder | 0.67[0.38,1.19] | **3.12[1.61,6.06]** | - | 1.13[0.49,2.63] | 0.96[0.67,1.37] | 0.86[0.61,1.22] |
| Neck | **0.37[0.17,0.81]** | 0.76[0.31,1.84] | - | 0.77[0.41,1.46] | 0.74[0.44,1.25] | **0.71[0.51,0.99]** |
| Other/unspecified | **0.58[0.37,0.92]** | 0.80[0.52,1.24] | 16.8[1.57,184] | 1.01[0.54,1.84] | 1.00[0.73,1.37] | 1.00[0.81,1.22] |
| **Time-varying** | | | | | | |
| **Multiple location** | | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.19[0.61,2.32] | **8.15[2.24,29.6]** | 1.75[0.16,18.7] | **11.4[3.10,42.5]** | **1.64[1.03,2.60]** | 1.27[0.96,1.66] |
| **No. of Consultations** | **0.87[0.83,0.91]** | **0.67[0.58,0.76]** | **0.82[0.70,0.97]** | **0.70[0.61,0.81]** | **0.87[0.85,0.90]** | **0.93[0.92,0.95]** |
| **No. of Prescriptions** | **1.00[1.00,1.01]** | 1.00[0.99,1.01] | 0.98[0.96,1.01] | 1.00[0.99,1.01] | **1.01[1.00,1.02]** | **-** |

#### 6.2.4.3 Gamma frailty Weibull model time to first-switch

The Weibull model with gamma frailty shows that there was a statistically significant effect of frailty on the model. The frailty parameter with a value of (HR 0.57 [0.32, 0.99]) suggests that the effect of frailty is declining with time. The Weibull shape parameter (HR 0.97 [0.89, 1.05]) is not statistically significantly different from 1 suggesting a constant hazard. The model identified similar associated covariates as the Weibull model without frailty (shown in Table 6.1.3) but with slightly higher hazard ratios, for example (HR 1.17 [1.04, 1.33]) for females, for the frailty model and (HR 1.12 [1.01, 1.24]) for the Weibull without frailty model (Table 6.2.6).

Table 6.2.6: Gamma frailty Weibull and Weibull models that examine factors associated with time to 1st medication switch

| Variable | Hazard Ratio [95% CI] | |
|---|---|---|
| | **Gamma frailty Weibull** | **Weibull** |
| **Age Group** | | |
| 30-44 | 1.00 | 1.00 |
| 15-29 | 0.91[0.76, 1.08] | 0.91[0.78, 1.06] |
| 45-59 | 1.01[0.86, 1.18] | 1.03[0.91, 1.17] |
| 60-74 | **1.34[1.09, 1.64]** | **1.28[1.09, 1.51]** |
| 75+ | **1.49[1.05, 2.12]** | **1.43[1.10, 1.88]** |
| **Gender** | | |
| Male | 1.00 | 1.00 |
| Female | **1.17[1.04, 1.33]** | **1.12[1.01, 1.24]** |
| **Previous prescribed analgesia** | | |
| No | 1.00 | 1.00 |
| Yes | **1.65[1.39, 1.94]** | **1.54[1.36, 1.75]** |
| **Previous musculoskeletal consultation** | 1.00 | 1.00 |
| No | | |
| Yes | 0.93[0.77, 1.13] | 0.93[0.80, 1.08] |
| **Comorbidity** | | |
| Selected | 1.00 | 1.00 |
| None | 1.22[0.88, 1.68] | 1.17[0.92, 1.52] |
| **Staff category** | | |
| GP | 1.00 | 1.00 |
| Other | 1.04[0.89, 1.22] | 1.03[0.91, 1.17] |
| **Deprivation** | | |
| Most | 1.00 | 1.00 |
| Medium | 0.94[0.82, 1.08] | 0.94[0.85, 1.06] |
| Least | 0.91[0.76, 1.09] | 0.91[0.80, 1.06] |
| **Pain Region** | | |
| Back | 1.00 | 1.00 |
| Knee | 0.94[0.74, 1.18] | 0.96[0.80, 1.15] |
| Hip | 1.05[0.80, 1.36] | 1.08[0.87, 1.33] |
| Foot and Ankle | 0.98[0.75, 1.26] | 1.02[0.83, 1.26] |
| Hand/upper limb | 0.93[0.72, 1.19] | 0.97[0.79, 1.19] |
| Shoulder | 0.99[0.76, 1.27] | 1.00[0.82, 1.22] |
| Neck | **0.75[0.57, 0.99]** | 0.84[0.68, 1.05] |
| Other/unspecified | 0.93[0.78, 1.11] | 0.97[0.84, 1.11] |

| Variable | Hazard Ratio [95% CI] | |
|---|---|---|
| | **Gamma frailty Weibull** | **Weibull** |
| **Initial analgesia (1st consultation)** | | |
| Basic analgesia | 1.00 | 1.00 |
| Weak analgesia | **1.41[1.05, 1.89]** | **1.33[1.07, 1.66]** |
| Moderate analgesia | 1.16[0.67, 1.99] | 1.02[0.69, 1.52] |
| NSAIDs | 0.97[0.76, 1.22] | 1.01[0.84, 1.21] |
| Strong analgesia | **1.53[1.09, 2.15]** | **1.34[1.05, 1.72]** |
| No medication | **0.61[0.48, 0.77]** | **0.73[0.62, 0.86]** |
| **Time-varying** | | |
| **Multiple location** | | |
| No | 1.00 | 1.00 |
| Yes | **1.40[1.09, 1.78]** | **1.03[1.02, 1.06]** |
| **No. of consultations** | **0.89[0.87, 0.91]** | **0.89[0.88, 0.91]** |
| **No. of Prescriptions** | **1.01[1.00, 1.02]** | **1.01[1.001, 1.02]** |
| **-2logL** | 7996 | 7980 |
| **Weibull shape parameter** | 0.97[0.89, 1.05] | **0.85[0.81, 0.88]** |
| **Frailty parameter** | **0.57[0.32, 0.99]** | **-** |

## 6.3 Analysis 2 - Modelling analgesia switching taking into account multiple-event switches over time

### 6.3.1 Methods

In the analysis of factors associated with time to first analgesia switch the Weibull and the Cox models show that the baseline variables of age, gender, previous prescribed analgesia, and analgesia potency at onset of consultation are all statistically associated with switching. Number of MSK consultations and number of analgesia prescriptions over follow-up are also associated with switching. Consulting for pain in more than one location over time also increases the risk of switching analgesia. The Cox and Weibull model parameters are similar with minor variations in some cases.

In the long term management of MSK conditions it is inevitable that individuals will switch across analgesia potency levels on more than one occasion. As in section 6.2.1, switching analgesia is defined as either a record of a prescription of an analgesia of a potency different from that previously prescribed (this may be in place of, or in addition to the initial analgesia), or a record of prescribed analgesia without a previous analgesia prescription on first consultation (Gore et al., 2012, Rahme et al., 2006; Schneider, 2010). Stoppages between the multiple switches are not considered in the analysis as only precise prescription dates and not stopping dates can be ascertained.

The analgesia potency categories as defined by the hierarchical analgesia categorisation (HAC) implies that individuals can switch up to five times without repetition of a category, for example, assuming they started with no medication the order could be: basic analgesia, weak analgesia, moderate analgesia, strong analgesia and NSAIDs. However, there is a possibility the prescription pattern may follow fluctuating switches, for example, NSAIDs, weak analgesia , moderate analgesia , NSAIDs, basic analgesia, NSAIDs.

Different analgesia or potency levels of analgesia have potential for different adverse effects, which implies that the multiple-event switches may be of clinical importance as a

risk of exposure to the adverse effects of analgesia changes as switches occur. Analysing time to individual switches or just adjusting for the number of switching events over time would neglect the correlation between the switch times for an individual. The switching event for each individual should be considered as correlated as switching between analgesia is informed by the preceding analgesia. For this reason, the presence of multiple-event switches in the analgesia switching process should be included in the analysis of switching.

As a reminder, the objectives of this section were to;

1. Determine clinical and socio-demographic factors associated with switching analgesia taking into account if an individual switches more than once
2. Determine if the inclusion of frailty in the models improves model fit

The factors associated with higher risks of switching analgesia taking into account the possibility of multiple switches can be modelled as in the previous section; however the Cox and Weibull models need to account for correlation and dependence among successive switch times for each individual. This can be achieved through the use of the multivariate Cox and Weibull models.

### 6.3.2 Data management and study population

All the patients identified and included in the analysis in the previous section were considered in this analysis. The socio-demographic and clinical variables are as defined in section 6.2.1, while the time-varying covariates are defined up to the first switch date. The number of analgesia changes will be determined for the entire period under review and the time between successive switches was determined through the issue dates of the successive potency levels. The counting process approach was used in defining time to the events as described below.

**Outcome variables**

Due to the nature of pharmacological management of MSK pain it is logical to consider that from the onset of seeking medical care for a MSK condition, the individual is at risk of changing their medication status. The time when an individual is at risk of switching analgesia is the risk interval (Ezell et al., 2001). The risk interval can be considered as the time between events (time from last switch) or the entire time before the event (time from initial consultation), which leads to the definition of time by either the counting process or the total time process. The total time approach considers time from first consultation up to each switch while the counting process considers time from the previous switch (Ezell et al., 2001). The counting process was used in this analysis.

The first switch is defined as the first change in potency level or point of addition of a different potency level to the initial analgesia potency level for the subject. The second switch is the second change or addition of a new analgesia, the third is the third change or addition of another potency level.

**Counting process approach**

The time of only the first switch is calculated from first consultation while subsequent switches are calculated from the point of the previous switch. For example, considering a patient prescribed NSAIDs at first consultation, who is later prescribed strong analgesia, and later weak analgesia. The time to the first switch is the time between the initial consultation date and the first prescription date of strong analgesia; the second switch time is calculated as the time from the first prescription date of strong analgesia to the first prescription date of weak analgesia. If a patient is not prescribed analgesia at first consultation, but later receives an NSAID, and later weak analgesia, the first switch time is the time between the initial consultation date and the first prescription date of NSAIDs, while the second switch time is the time between first date of NSAIDs prescription and the first weak analgesia prescription date.

As in section 6.2.1 censoring for those leaving their practice was at last date of recorded registration or last recorded prescription date, whichever was later.

### 6.3.3 Statistical Analysis

The multivariate Cox and Weibull models were used to model the factors associated with switching analgesia taking into account multiple switches. The proportional hazards will not be assumed in modelling switching taking into account multiple switch times as time-varying covariates are included in the model. The multivariate Cox and Weibull models discussed below are minor variations of the univariate Cox proportional hazards models and univariate Weibull models. The multivariate Weibull model with a gamma frailty was also used and compared to the Weibull model.

#### 6.3.3.1 The multivariate Cox and Weibull models

As in the univariate models, consider a study with $n$ individuals, each with the observed vector $(t_{ik}, \delta_{ik}, \boldsymbol{x_{ik}})$, $(i = 1, 2, \dots, n)$ where some or all individuals experience more than one event. In this case consider failure to be defined by switching between different analgesia potency levels, and time to failure to be the time to the switching events, then the observed vector represents the $k^{th}$ switch, $(k = 1, \dots, K)$. Then the hazard function $h(t, \boldsymbol{x_{ik}})$ for the $k^{th}$ time to switch $t_{ik}$ for an individual $i$ with covariate vector

$$\boldsymbol{x_{ik}} = (x_{1i}, x_{2i}, \dots x_{ki})$$

with $\delta_{ik}$ being the $k^{th}$ switch or censoring indicator (1=switch, 0=censor) is defined for the Cox proportional hazards model as:

$$h(t, x_{ik}) = h_{0k}(t) \exp\{\boldsymbol{\beta}_k \boldsymbol{x_{ik}}\}$$

Where $h_{0k}(t)$ is the baseline hazard for the $k^{th}$ failure or switch, and is an arbitrary function of time only. $h_{0k}(t)$ is allowed to vary over each of the switch times as an arbitrary function of time and $\boldsymbol{\beta}_k$ is a vector of regression coefficients to be estimated after adjusting for the $k$ failure events that each individual experienced (Ezell et al., 2001).

The Weibull proportional hazards model is as for the Cox model with the only variation being the hazard function, thus;

$$h(t, x_{ik}) = \boldsymbol{\lambda p}(\boldsymbol{\lambda t})^{\boldsymbol{p-1}} \exp\{\boldsymbol{\beta}_k \boldsymbol{x_{ik}}\}$$

With $h_{0k}(t) = \boldsymbol{\lambda p}(\boldsymbol{\lambda t})^{\boldsymbol{p-1}}$, and frailty extension can be included as in the univariate model.

**Likelihood Estimation**

The likelihood estimation is an extension of the partial likelihood estimation in the single event Cox model (Ezell et al., 2001). The partial likelihood therefore becomes:

$$PL(\beta) = \prod_{j=1}^{n} \prod_{k=1}^{K} \left[ \frac{e^{\beta_k x_{jk}}}{\sum_{l \epsilon R(\theta_{jk})} e^{\beta_k x_{lk}}} \right]^{\delta_{ik}}$$

The parameter estimation process considers $k$ sub-models $(k = 1, 2, \ldots K)$ in estimating model parameters. Only patients who are both observed at time $t$ and in the $k^{th}$ switching event as well as the persons who switched at time $t$ contribute information to the stratum-specific (i.e. the $k$ events) likelihood function (Ezell et al., 2001). For example if $k = 3$, patients at risk of switching and those who switched for the third time contribute information to parameter estimation. For the Weibull model the log likelihood function is;

$$l(\theta) = \delta \log p + \delta p \log \lambda + (p-1) \sum_{i=1}^{n} \delta_{ik} \log t_{ik} - \sum_{i=1}^{n} (\lambda t_{ik})^p$$

The log likelihood is formed as a combination of failures and censored observation.

### 6.3.4 Results

**Data description**

Of the 3179 patients, 672 (21%) switched analgesia more than once. The mean number of switches was 2 (SD 4.0) with 1 as the median number of switches, IQR (1,4) and the maximum number of switches for an individual was 31. Of those initially prescribed weak analgesia or strong analgesia, 39% had more than one switch. 25% of those initially

prescribed basic analgesia, 30% of those initially prescribed moderate analgesia, 25% of those initially prescribed NSAIDs and 14% of those initially prescribed no medication switched more than once (Table 6.3.1).

Table 6.3.1: Baseline Socio-demographic and clinical characteristics of patients switching analgesia once and more than once

| | | Switch Analgesia | | |
|---|---|---|---|---|
| **Variable** | **N** | **No (%)** | **At least once (%)** | **More than once (%)** |
| Total | 3179 | 1550(49) | 1629(51) | 672(21) |
| **Age (years)** | | | | |
| 15-29 | 688 | 392(57) | 296(43) | 101(15) |
| 30-44 | 1068 | 556(52) | 512(48) | 186(17) |
| 45-59 | 953 | 435(46) | 518(54) | 220(23) |
| 60-74 | 369 | 132(36) | 237(64) | 126(34) |
| Over 75 | 101 | 35(35) | 66(65) | 39(39) |
| **Gender** | | | | |
| Females | 1293 | 580(45) | 713(55) | 322(25) |
| Males | 1886 | 970(51) | 916(49) | 350(19) |
| **Previous musculoskeletal consultation** | | | | |
| Yes | 409 | 179(44) | 230(56) | 90(22) |
| No | 2770 | 1371(49) | 1399(51) | 582(21) |
| **Previous prescribed analgesia** | | | | |
| Yes | 509 | 145(28) | 364(72) | 153(30) |
| No | 2670 | 1405(53) | 1265(47) | 517(19) |
| **Region of Pain** | | | | |
| Back | 818 | 376(46) | 442(54) | 187(23) |
| Knee | 388 | 177(52) | 161(48) | 65(17) |
| Hip | 199 | 88(44) | 111(56) | 54(27) |
| Foot and Ankle | 219 | 104(47) | 115(53) | 47(21) |
| Hand/upper limb | 256 | 129(50) | 127(50) | 37(14) |
| Shoulder | 244 | 114(47) | 130(53) | 50(20) |
| Neck | 215 | 114(53) | 101(47) | 46(21) |
| Other/unspecified | 890 | 448(50) | 442(50) | 186(21) |
| **Co-morbidity** | | | | |
| Selected conditions | 118 | 53(45) | 65(55) | 28(24) |
| Other conditions/none | 3061 | 1497(49) | 1564(51) | 644(21) |
| **Deprivation** | | | | |
| Most | 1402 | 657(47) | 745(53) | 316(23) |
| Moderate | 1239 | 624(50) | 615(50) | 252(20) |
| Least | 538 | 269(50) | 269(50) | 104(19) |
| **Staff category** | | | | |
| GPs | 2575 | 1255(49) | 1320(51) | 547(21) |
| Other | 604 | 295(49) | 309(51) | 125(21) |

| Variable | N | Switch Analgesia | | |
|---|---|---|---|---|
| | | No (%) | At least once (%) | More than once (%) |
| **Number of pain locations** | | | | |
| One | 2472 | 1053(43) | 1419(57) | 533(22) |
| More | 707 | 497(70) | 210(30) | 139(19) |
| **Initial analgesia (1st consultation)** | | | | |
| Basic analgesia | 346 | 159(46) | 187(54) | 85(25) |
| Weak analgesia | 223 | 66(30) | 157(70) | 87(39) |
| Moderate analgesia | 47 | 18(38) | 29(62) | 14(30) |
| Strong analgesia | 160 | 47(30) | 113(70) | 63(39) |
| NSAIDs | 687 | 321(47) | 366(53) | 169(25) |
| No medication | 1716 | 939(55) | 777(45) | 254(14) |

The Cox and Weibull models modelling factors associated switching using all analgesia switches identified similar factors to those identified in the Cox and Weibull models modelling the risk of first analgesia switch only in the previous section. The factors are age, gender, previously prescribed analgesia, level of deprivation, multiple pain locations, number of prescriptions and initial analgesia potency as statistically significant.

The factors have similar effects on the models, for example older age was associated with the risk of switching when multiple switches are taken into account as well as increased risk of first analgesia switch. The only variations are that pain location is associated with the risk of switching more than once, while it was not associated with a first analgesia switch.

The number of consultations is not associated with the risk of switching once all switches are considered, but was previously associated with risk of a first switch (section 6.2.3.1). The Weibull model with gamma frailty identifies similar factors with the number of consultations associated with declining risk as in the first switch analysis, and the parameter estimates are slightly smaller for the frailty model.

#### 6.3.4.1 The multiple-event switch models

**The Cox model**

The Cox model identified similar statistically significant covariates as the Weibull model with mostly identical hazard ratios.

**The Weibull model**

In the Weibull model, the 15-29 age group is less likely to switch analgesia compared to those aged 30-44 with all things equal (HR 0.81 [0.72, 0.90]), while the 60-74 and over 75 are more likely to, with hazard ratios (HR 1.47 [1.32, 1.64] and 1.95 [1.65, 2.31]) respectively. Females are more likely to switch than males with (HR 1.16 [1.07, 1.25]), while those with previous prescribed analgesia are also more likely to switch analgesia, (HR 1.32 [1.20, 1.45]).

The model also shows patients initially consulting for hip pain as more likely to switch analgesia with (HR 1.33 [1.16, 1.53]), while those with pain in the upper limb and shoulder were less likely compared to those with back pain, (HR 0.74 [0.62, 0.88] and 0.80 [0.69, 0.93]) respectively. Those initially prescribed weak analgesia and strong analgesia with (HR 1.17 [1.01, 1.35] and 1.38 [1.17, 1.62]) respectively are more likely to switch, while those initially with no medication are less likely, HR 0.75 [0.67, 0.85] than those initially prescribed basic analgesia.

The -2logL of 14732 is much smaller than that of the Cox model which suggests the Weibull is a better fit. The Weibull shape parameter of 0.56 [0.54, 0.58] suggests that the hazards of switching decline with time when multiple-event switches are considered in the model (Table 6.3.2).

Table 6.3.2: Cox and Weibull models that examine factors associated with time to switching when multiple-event analgesia switches are accounted for

| | Multiple-event switch models HR [95%CI] | | | |
|---|---|---|---|---|
| | Cox model | | Weibull model | |
| **Variable** | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Age Group** | | | | |
| 30-44 | 1.00 | 1.00 | 1.00 | 1.00 |
| 15-29 | 0.78[0.70, 0.80] | **0.80[0.72, 0.90]** | 0.79[0.71, 0.88] | **0.81[0.72, 0.91]** |
| 45-59 | 1.06[0.97, 1.16] | 1.02[0.93, 1.18] | 1.07[0.98, 1.16] | 1.02[0.93, 1.12] |
| 60-74 | 1.57[1.42, 1.74] | **1.47[1.32, 1.64]** | 1.55[1.40, 1.72] | **1.47[1.31, 1.63]** |
| 75+ | 2.42[2.07, 2.84] | **1.95[1.65, 2.31]** | 2.40[2.05, 2.82] | **1.95[1.64, 2.31]** |
| **Gender** | | | | |
| Male | 1.00 | 1.00 | 1.00 | 1.00 |
| Female | 1.27[1.19, 1.37] | **1.16[1.08, 1.25]** | 1.26[1.18, 1.35] | **1.16[1.07, 1.25]** |
| **Previous prescribed analgesia** | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.38[1.27, 1.51] | **1.33[1.21, 1.46]** | 1.37[1.25, 1.49] | **1.32[1.20, 1.45]** |
| **Previous musculoskeletal consultation** | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 0.97[0.88, 1.08] | 0.90[0.80, 1.01] | 0.97[0.88, 1.08] | 0.90[0.80, 1.01] |
| **Comorbidity** | | | | |
| Selected | 1.00 | 1.00 | 1.00 | 1.00 |
| None | 0.92[0.77, 1.09] | 1.15[0.96, 1.37] | 0.93[0.78, 1.10] | 1.16[0.97, 1.38] |
| **Staff category** | | | | |
| GP | 1.00 | 1.00 | 1.00 | 1.00 |
| Other | 0.98[0.90, 1.07] | 1.01[0.92, 1.11] | 0.98[0.90, 1.07] | 1.01[0.92, 1.11] |

| | Multiple-event switch models HR [95%CI] | | | |
|---|---|---|---|---|
| | Cox model | | Weibull model | |
| **Variable** | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Deprivation** | | | | |
| Most | 1.00 | 1.00 | 1.00 | 1.00 |
| Medium | 0.84[0.78, 0.90] | **0.86[0.79, 0.93]** | 0.83[0.77, 0.90] | **0.86[0.79, 0.93]** |
| Least | 0.78[0.71, 0.87] | **0.79[0.70, 0.87]** | 0.78[0.70, 0.86] | **0.78[0.70, 0.87]** |
| **Pain Region** | | | | |
| Back | 1.00 | 1.00 | 1.00 | 1.00 |
| Knee | 0.95[0.84, 1.07] | 1.05[0.92, 1.19] | 0.98[0.84, 1.06] | 1.05[0.92, 1.19] |
| Hip | 1.26[1.10, 1.44] | **1.32[1.15, 1.52]** | 1.26[1.10, 1.44] | **1.33[1.16, 1.53]** |
| Foot and Ankle | 0.90[0.78, 1.04] | 0.99[0.85, 1.15] | 0.89[0.77, 1.03] | 0.99[0.85, 1.15] |
| Hand/upper limb | 0.62[0.53, 0.74] | **0.74[0.62, 0.87]** | 0.63[0.53, 0.74] | **0.74[0.62, 0.88]** |
| Shoulder | 0.77[0.67, 0.89] | **0.80[0.68, 0.93]** | 0.77[0.66, 0.89] | **0.80[0.69, 0.93]** |
| Neck | 0.86[0.74, 1.01] | 0.94[0.80, 1.10] | 0.85[0.73, 0.99] | 0.94[0.80, 1.10] |
| Other/unspecified | 0.88[0.80, 0.97] | 1.01[0.91, 1.11] | 0.88[0.80, 0.96] | 1.00[0.90, 1.09] |
| **Initial analgesia (1st consultation)** | | | | |
| Basic analgesia | 1.00 | 1.00 | 1.00 | 1.00 |
| Weak analgesia | 1.31[1.14, 1.51] | **1.17[1.01, 1.35]** | 1.31[1.13, 1.50] | **1.17[1.01, 1.35]** |
| Moderate analgesia | 1.20[0.93, 1.54] | 1.08[0.83, 1.39] | 1.18[0.92, 1.52] | 1.06[0.82, 1.08] |
| NSAIDs | 0.89[0.79, 1.01] | 0.96[0.84, 1.09] | 0.89[0.79, 1.00] | 0.96[0.84, 1.08] |
| Strong analgesia | 1.65[1.43, 1.90] | **1.39[1.18, 1.63]** | 1.64[1.42, 1.89] | **1.38[1.17, 1.62]** |
| No medication | 0.66[0.59, 0.74] | **0.76[0.67, 0.85]** | 0.77[0.59, 0.74] | **0.75[0.67, 0.85]** |
| **Multiple location** | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.05[1.03, 1.06] | **1.06[1.04, 1.08]** | 1.05[1.03, 1.06] | **1.06[1.04, 1.08]** |
| **No. of consultations** | 1.00[1.00, 1.01] | 1.00[0.99, 1.01] | 1.00[0.99, 1.01] | 1.00[0.99, 1.01] |
| **No. of Prescriptions** | 1.00[1.00, 1.02] | **1.01[1.00, 1.02]** | 1.00[1.00, 1.01] | **1.01[1.00, 1.02]** |
| **-2logL** | - | 48696 | - | 14732 |
| **Weibull shape parameter** | - | - | **-** | **0.56[0.54, 0.58]** |

### 6.3.4.2 Multiple-event switch Weibull model with Gamma frailty

The multiple- event switch Weibull model with frailty also identified age, gender, medication history, deprivation, initial medication potency, multiple pain location over time, number of consultations and prescriptions as statistically significant covariates associated with the risk of multiple switches in a relatively short time interval.

The hazard ratios are generally higher than those in the Weibull model without frailty and the CI's were wider. The hazard ratios (HR 1.34 [1.08, 1.66] and 1.50[1.02, 2.18]) for the 60-74 and over 75 age groups show an increased risk of switching for the older age groups. Females are more at risk than males (HR 1.40 [1.23, 1.59]), while the (HR 1.21 [1.02, 1.44]) for previous prescribed analgesia also indicates a higher risk.

Patients from medium deprivation (HR 0.81 [0.70, 0.93]) and patients from least deprived (HR 0.78 [0.65, 0.94]) are both at a lesser risk of multiple-event analgesia switches compared to patients from most deprived locations. Patients initially prescribed weak analgesia and moderate analgesia are at higher risk of multiple-event medication switches than those initially on basic analgesia, hazard ratios (HR 1.50 [1.11, 2.03] and 2.33 [1.38, 3.93]) respectively. Pain in multiple location (HR of 1.09 [1.05, 1.13]) is associated with a slightly higher risk, and an increasing number of prescriptions over time (HR 1.04 [1.03, 1.05]) is also associated with a slightly increased risk of switching. Those with higher number of consultations had a marginally reduced risk (HR 0.99 [0.98, 0.99]).

The frailty parameter with a value of 1.01 [0.92, 1.11] indicates that the frailty is not statistically significantly different from 1 suggesting that there is no evidence that frailty improves model fit to the data. The Weibull shape parameter 1.04 [0.99, 1.09] indicate that the hazards associated with the covariates will slightly increase over time if the unmeasured covariates are adjusted for through gamma frailty (Table 6.3.3) but it is not statistically significant.

Table 6.3.3: Weibull model with Gamma frailty that examines factors associated with time to switching when multiple-event analgesia switches are accounted for

| Variable | Hazard Ratio [95% CI] Gamma frailty Weibull model | Weibull model |
|---|---|---|
| **Age Group** | | |
| 30-44 | 1.00 | 1.00 |
| 15-29 | 0.94[0.78, 1.12] | 0.81[0.72, 0.91] |
| 45-59 | 0.99[0.85, 1.16] | 1.02[0.93, 1.12] |
| 60-74 | **1.34[1.08, 1.66]** | **1.47[1.31, 1.63]** |
| 75+ | **1.50[1.02, 2.18]** | **1.95[1.64, 2.31]** |
| **Gender** | | |
| Male | 1.00 | 1.00 |
| Female | **1.40[1.23, 1.59]** | **1.16[1.07, 1.25]** |
| **Previous prescribed analgesia** | | |
| No | 1.00 | 1.00 |
| Yes | **1.21[1.02, 1.44]** | **1.32[1.20, 1.45]** |
| **Previous musculoskeletal consultation** | | |
| No | 1.00 | 1.00 |
| Yes | 0.94[0.77, 1.14] | 0.90[0.80, 1.01] |
| **Comorbidity** | | |
| Selected | 1.00 | 1.00 |
| None | 1.31[0.95, 1.82] | 1.16[0.97, 1.38] |
| **Staff category** | | |
| GP | 1.00 | 1.00 |
| Other | 1.01[0.86, 1.18] | 1.01[0.92, 1.11] |
| **Deprivation** | | |
| Most | 1.00 | 1.00 |
| medium | **0.81[0.70, 0.93]** | **0.86[0.79, 0.93]** |
| least | **0.78[0.65, 0.94]** | **0.78[0.70, 0.87]** |
| **Pain Region** | | |
| Back | 1.00 | 1.00 |
| Knee | 0.86[0.68, 1.07] | 1.05[0.92, 1.19] |
| Hip | 1.08[0.81, 1.41] | **1.33[1.16, 1.53]** |
| Foot and Ankle | 0.89[0.68, 1.16] | 0.99[0.85, 1.15] |
| Hand/upper limb | 0.80[0.61, 1.03] | **0.74[0.62, 0.88]** |
| Shoulder | 0.85[0.66, 1.10] | **0.80[0.69, 0.93]** |
| Neck | 0.79[0.60, 1.04] | 0.94[0.80, 1.10] |
| Other/unspecified | 1.02[0.86, 1.22] | 1.00[0.90, 1.09] |

| Variable | Hazard Ratio [95% CI] Gamma frailty Weibull model | Weibull model |
|---|---|---|
| **Initial analgesia (1st consultation)** | | |
| Basic analgesia | 1.00 | 1.00 |
| Weak analgesia | **1.50[1.11, 2.03]** | **1.17[1.01, 1.35]** |
| Moderate analgesia | **2.33[1.38, 3.93]** | 1.06[0.82, 1.08] |
| NSAIDs | 0.96[0.76, 1.21] | 0.96[0.84, 1.08] |
| Strong analgesia | 1.01[0.72, 1.41] | **1.38[1.17, 1.62]** |
| No medication | 0.94[0.76, 1.16] | **0.75[0.67, 0.85]** |
| **Time-varying** | | |
| **Multiple location** | | |
| No | 1.00 | 1.00 |
| Yes | **1.09[1.05, 1.13]** | **1.06[1.04, 1.08]** |
| **No. of consultations** | **0.99[0.98, 0.99]** | 1.00[0.99, 1.01] |
| **No. of Prescriptions** | **1.04[1.03, 1.05]** | **1.01[1.00, 1.02]** |
| **-2logL** | 12198 | 14732 |
| **Weibull shape parameter** | **1.04[0.99, 1.09]** | **0.56[0.54, 0.58]** |
| **Frailty parameter** | **1.01[0.92, 1.11]** | **-** |

## 6.4 Analysis 3 - Modelling rates of analgesia switching

### 6.4.1 Methods

Section 6.2 and 6.3 evaluated the socio-demographic and clinical factors associated with first analgesia switching and any switching of analgesia. In the analyses both the Weibull and the Cox models show that the baseline variables of age, gender, previous prescribed analgesia, and analgesia potency at onset of consultation are all statistically associated with switching under both circumstances. Fewer numbers of MSK consultations and increased number of analgesia prescriptions and consulting for pain in more than one location over time also increases the risk of switching analgesia. The level of neighbourhood deprivation and pain location become associated with switching if multiple-event switches are accounted for.

The risk of switching (and hence increased likelihood of adverse effects) can also be evaluated by a count of switching events that an individual experiences during follow up. This implies that the medication switches that take place over time can be considered to be a random process as the order in which the switches take place will vary from one individual to the other. While it is informative to quantify the hazards associated with time between the switches in multiple switches, knowing the rates of switching over the follow-up period adds a different but essential dimension to the understanding of the switching process.

The number of analgesia switches increases with time for some individuals but remains constant for some, as seen in Chapter 5 in which some individuals were prescribed all potency categories while some were prescribed a single analgesia throughout their follow-up period. Considering that the study cohort is assumed to be first time consulters or an incident group of MSK consulters, an alternative approach to the first 2 analyses would be to determine the factors associated with the decreasing or increasing average rate of switches for the cohort over the 5 year follow-up period. This may help clinicians identify

for closer monitoring, patients who might have higher rates of switching over time and take that into account when designing their MSK management plan.

The specific objective of this section is to;

1. Determine the socio-demographic and clinical factors associated with rates of switching during follow-up time
2. Assess value of using Poisson regression to model switching.

### 6.4.2 Data management and study population

All the patients identified and included in the analysis in the previous section were considered in this analysis. The number of analgesia potency changes will be determined for the entire period under follow up.

#### Outcome variable

The number of analgesia switches experienced by the patients throughout their follow up time is the dependent variable.

#### Independent variables/ Covariates

The clinical and the socio-demographic variables evaluated were the same as in the previous sections except for the number of prescribed analgesia and the number of MSK consultations. The number of MSK consultations and prescriptions were calculated for the entire follow-up period instead of up to the first switching event.

### 6.4.3 Statistical Analysis

The analgesia switch rate over follow-up time was evaluated, while adjusting for clinical and socio-demographic variables through Poisson regression.

#### 6.4.3.1 Poisson regression

The outcome (dependent) variable is a count of the number of analgesia switches. Poisson regression models the log of the expected count as a function of the independent variables. Strength of association of the independent variables with number of switches is

shown using incident rate ratios (IRR) obtained by exponentiation of the log of the Poisson regression coefficients. See Cameron and Trivedi, (1998) for further description of Poisson regression.

### 6.4.4 Results

As stated in section 6.2.3, of the 3179 patients, 672 (21%) switched analgesia more than once. The mean number of switches was 2 (SD 4.0) with 1 as the median number of switches with an IQR (1, 4) and the maximum number of switches for an individual was 31

The Poisson regression model identified factors associated with the rates of switching analgesia similar to the factors associated with the risk of switching analgesia if multiple switches are accounted for (section 6.3). The factors are age, gender, previous medication history, level of deprivation, initial region of pain consulted for, initial analgesia potency level, multiple pain locations over time and number of prescriptions.

All factors associated with the risk of first analgesia switch are also identified as associated with rates of switching with the variation being that being prescribed weak or strong analgesia is associated with increased risk of first analgesia switch but not associated with number of switches. The other variation is that increasing number of consultations is associated with increased rates of switching. All statistically significant incident rate ratios are highlighted in bold in Table 6.4.1.

The incidence rate ratio (IRR 0.85 [0.76, 0.94]) for the 15-29 age group suggests that for this age group the rate of switching is less than in the 30-44 age group. There were also higher rates of switching for those aged 60-74 (IRR 1.35 [1.21, 1.50]) and 75 and over (IRR 2.04 [1.75, 2.39]. The IRRs of 1.08 [1.01, 1.15] and 1.30 [1.19, 1.42] for gender and medication history respectively, indicate that rates of switching are about 8% higher among females than males and 30% higher among those with previous analgesic medication history than those without. For deprivation, (IRR 0.90 [0.83, 0.96]) for medium deprivation and (IRR 0.79 [0.71, 0.87]) for least deprived indicates that the rates of

switching are 10% and 21% less than in the most deprived group respectively. When compared to initial pain in the back, the rate of multiple switching among those with initial hip pain, (IRR 1.47 [1.29, 1.68)] is higher, while for those with initial upper limb pain, (IRR 0.76 [0.64, 0.89]) and initial shoulder pain (IRR 0.86 [0.74, 0.99]) is less.

The rates were not affected by the type of initial analgesia potency issued except for those prescribed no medication on initial consultation (IRR 0.67 [0.60, 0.75]), which indicates a lesser rate than those initially prescribed basic analgesia. Those experiencing pain in multiple locations over time (IRR 1.41 [1.24, 1.56]) had a higher incidence rate than those who continue to consult for pain in the same location over time. Each extra consultation (IRR 1.06 [1.05, 1.07]) and each extra prescription for the same potency level over time (IRR 1.01 [1.01, 1.02] were associated with a 6% and 1% increase in the incidence rates of switching respectively.

Table 6.4.1: Poisson regression model that examines factors associated with incident rates of switching over unit follow-up time

| **Variable** | **Poisson model Incident Rate Ratios- IRR [95% CI]** | |
|---|---|---|
| | Unadjusted | Adjusted |
| **Age Group** | | |
| 30-44 | 1.00 | 1.00 |
| 15-29 | 0.75[0.68, 0.84] | **0.85[0.76, 0.94]** |
| 45-59 | 1.06[0.97, 1.15] | 0.97[0.89, 1.06] |
| 60-74 | 1.60[1.45, 1.77] | **1.35[1.21, 1.50]** |
| 75+ | 3.03[2.63, 3.50] | **2.04[1.75, 2.39]** |
| **Gender** | | |
| Male | 1.00 | 1.00 |
| Female | 1.30[1.22, 1.39] | **1.08[1.01, 1.15]** |
| **Previous prescribed analgesia** | | |
| No | 1.00 | 1.00 |
| Yes | 1.45[1.34, 1.57] | **1.30[1.19, 1.42]** |
| **Previous musculoskeletal consultation** | | |
| No | 1.00 | 1.00 |
| Yes | 0.98[0.89, 1.08] | 0.93[0.84, 1.03] |
| **Comorbidity** | | |
| Selected | 1.00 | 1.00 |
| None | 0.75[0.64, 0.87] | 0.96[0.82, 1.12] |
| **Staff category** | | |
| GP | 1.00 | 1.00 |
| Other | 1.01[0.93, 1.09] | 0.99[0.90, 1.08] |
| **Deprivation** | | |
| Most | 1.00 | 1.00 |
| medium | 0.82[0.77, 0.88] | **0.90[0.83, 0.96]** |
| least | 0.73[0.67, 0.81] | **0.79[0.71, 0.87]** |
| **Pain Region** | | |
| Back | 1.00 | 1.00 |
| Knee | 0.99[0.95, 1.20] | 1.11[0.98, 1.25] |
| Hip | 1.25[1.11, 1.42] | **1.47[1.29, 1.68]** |
| Foot and Ankle | 0.81[0.71, 0.98] | 0.97[0.83, 1.12] |
| Hand/upper limb | 0.56[0.48, 0.65] | **0.76[0.64, 0.89]** |
| Shoulder | 0.80[0.69, 0.92] | **0.86[0.74, 0.99]** |
| Neck | 0.80[0.70, 0.98] | 0.93[0.80, 1.08] |
| Other/unspecified | 0.91[0.85, 1.00] | 1.04[0.95, 1.15] |

| Variable | Poisson model Incident Rate Ratios- IRR [95% CI] | |
|---|---|---|
| | Unadjusted | Adjusted |
| **Initial Potency level** | | |
| Basic analgesia | 1.00 | 1.00 |
| Weak analgesia | 1.43[1.25, 1.63] | 1.13[0.99, 1.29] |
| Moderate analgesia | 1.10[0.86, 1.40] | 1.03[0.80, 1.31] |
| NSAIDs | 0.82[0.73, 0.91] | 0.90[0.80, 1.01] |
| Strong analgesia | 1.82[1.59, 1.98] | 1.12[0.95, 1.30] |
| No medication | 0.51[0.46, 0.56] | **0.67[0.60, 0.75]** |
| **Multiple location** | | |
| No | 1.00 | 1.00 |
| Yes | 1.77[1.64, 1.92] | **1.41[1.24, 1.56]** |
| **No. of consultations** | 1.08[1.05, 1.09] | **1.06[1.05, 1.07]** |
| **No. of Prescriptions** | 1.01[1.01, 1.02] | **1.01[1.01, 1.02]** |
| **-2logL** | 10194 | 10194 |

**Unadjusted model =** Individual variable in the model, **Adjusted model =** All variables included simultaneously

## 6.5 Discussion

The analysis in the first section (6.2) used the Cox and Weibull models to model factors associated with the risk of a first analgesia switch, the second section (6.3) analyses used the same models to model the factors associated with the risks of switching analgesia if multiple switches are accounted for. The third section (6.4) analysis used the Poisson model to model factors associated with the rates (counts) of switching, and despite some variation in parameter estimates, similar conclusions can be drawn from the results of these different approaches. That is, most of the factors associated with the risk of first analgesia switch are also associated with the risk of switching if multiple analgesia switches are accounted for and modelling rates of switching analgesia.

It is however necessary to base the discussion and conclusions on the best models from each section. These are, for analysis of first-switch and multiple-event switches, the Weibull model with and without frailty, and for modelling rates of switching, the Poisson regression model. The factors are summarised in Table 6.5.1.

Table 6.5.1: Summary of statistically significant variables in all models

| Significant variables in the models | | | | | | | |
|---|---|---|---|---|---|---|---|
| | First switch | | | Multiple-event switch | | | Rates |
| **Variable** | Cox | Weibull | Frailty | Cox | Weibull | Frailty | Poisson |
| **Age Group** | | | | | | | |
| 30-44 | - | - | - | - | - | - | - |
| 15-29 | No | No | No | <Yes | <Yes | No | <Yes |
| 45-59 | No | No | No | No | No | No | No |
| 60-74 | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes |
| 75+ | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes |
| **Gender** | | | | | | | |
| Male | - | - | - | - | - | - | - |
| Female | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes |
| **Previous prescribed analgesia** | | | | | | | |
| No | - | - | - | - | - | - | - |
| Yes | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes |
| **Previous musculoskeletal consultation** | | | | | | | |
| No | - | - | - | - | - | - | - |
| Yes | No | No | No | No | No | No | No |
| **Comorbidity** | | | | | | | |
| Selected | - | - | - | - | - | - | - |
| None | No | No | No | No | No | No | No |
| **Deprivation** | | | | | | | |
| Most | - | - | - | - | - | - | - |
| medium | No | No | No | <Yes | <Yes | <Yes | <Yes |
| least | No | No | No | <Yes | <Yes | <Yes | <Yes |
| **Pain Region** | | | | | | | |
| Back | - | - | - | - | - | - | - |
| Knee | No | No | No | No | No | No | No |
| Hip | No | No | No | >Yes | >Yes | No | >Yes |
| Foot and Ankle | No | No | No | No | No | No | No |
| Hand/upper limb | No | No | No | <Yes | <Yes | No | <Yes |
| Shoulder | No | No | No | <Yes | <Yes | No | <Yes |
| Neck | No | No | No | No | No | No | No |
| Other/unspecified | No | No | No | No | No | No | No |
| **Initial Potency level** | | | | | | | |
| Basic analgesia | - | - | - | - | - | - | - |
| Weak analgesia | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes | No |
| Moderate analgesia | No | No | No | No | No | >Yes | No |
| NSAIDs | No | No | No | No | No | No | No |
| Strong analgesia | >Yes | >Yes | >Yes | >Yes | >Yes | No | No |
| No medication | <Yes | <Yes | <Yes | <Yes | <Yes | No | <Yes |
| **Multiple location** | | | | | | | |
| No | - | - | - | - | - | - | - |
| Yes | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes |
| **No. of consultations** | <Yes | <Yes | <Yes | No | No | <Yes | >Yes |
| **No. of Prescriptions** | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes | >Yes |

No= non-significant, <Yes=decreasing risk of switching, Yes>=increasing risk of switching, Reference category = -

The Weibull models with and without the frailty extension were chosen as they were a better fit to the data compared to the Cox, coupled with some advantages they have over the Cox as modelling techniques. While the Cox model has the property of not making any underlying distributional assumptions, the Weibull distribution is a flexible and versatile distribution (Collet, 2003; Marubini et al., 1995). The Weibull enables extrapolation of what may happen long term with the patients by considering the shape parameter, for example, a shape parameter less than one suggests that the effect of the covariates on the risks of switching declines with time, while a value greater than one suggests otherwise. If the distributional assumptions can be met, the Weibull model will fit the data better than the Cox model (Lee and Wang, 2003).

While frailty can be modelled with the Cox model, if the choice of the Cox model was to avoid distributional assumptions, it is a contradiction to choose the Cox model then assume gamma distributed frailty. In some results presented here, there was a statistically significant frailty effect which declined over time. This may be expected because not all covariates associated with medication switching were measured, and by the nature of medical conditions, some patients are more pre-disposed to switch analgesia than others due to the severity of their conditions. However as time continues the effect of baseline variables, measured or unmeasured may decline as the underlying condition evolves.

Poisson regression has a strong assumption in that the conditional variance equals the conditional mean. If the Poisson model is a good fit, it enables estimation of expected rates of switching across covariates for the exposure period.

Modelling first analgesia switch stratified by initially prescribed analgesia suggests that factors associated with switching were dependent on initially prescribed analgesia. For example being in the age group 60-74 was associated with increased risk of switching if they were initially prescribed basic analgesics or no medication but is not associated with risk of switching if they were initially prescribed moderate or strong analgesia. The smaller

sample sizes make the results however less reliable and hence should be treated with some caution.

The underlying hypothesis of this analysis was that while switching analgesia is acceptable, it can expose patients to risks of adverse effects of analgesia and multiple switches or higher rates of switching imply increased potential for adverse effects. The analysis has highlighted both clinical and demographic factors associated with any switching of analgesia and the rates of switching, and those initially on strong analgesia were more likely to switch which may suggest GPs are aware of risks of adverse events as stated later. The results also suggest an increased risk of switching in the early days of initiation into analgesia treatment, only a small group of patients experience multiple-event switching, and that the risk of multiple-event switching decreases with time.

There was a higher risk and rates of switching medication among the elderly, females, having been prescribed pain medication in the past, consulting for pain in the hip, and for more than one location over time, starting medication with weak or strong analgesia and with increased number of repeat prescriptions received over time. There are declining risks of switching with increasing number of consultation although this is not consistent as the Poisson models of counts of switches suggested an increasing risk. There are declining risks with lower neighbourhood deprivation and receiving no prescribed medication on first consultation. These characteristics may help identify patients at higher risk of switching that clinicians should take note of, when they first present with MSK conditions so that the patients pain management regime may include increased consultation levels.

The difference in the effect of the number of MSK consultations in the time to event Weibull models and the Poisson model may be attributed to that in the Weibull models, the number of consultations were calculated up to the first switch event while in the

Poisson, they were calculated for the entire follow-up period. Therefore in the Poisson model, some consultations may have occurred after switching.

An increase in the number of consultations over time reduces the risk of switching medication. One Cochrane systematic review has shown that regular medical review has previously had a positive outcome on health issues in the primary care setting (Glynn et al., 2010). Potentially, therefore, attending for regular consultations ensures patients use their medication correctly through the GP having the opportunity to advise them to use it as prescribed, thereby maximising the analgesia effect. Conversely, an increase in the number of prescriptions of the same potency over time corresponds to an increased risk of switching to a different potency. Perhaps this is a reflection of pain severity and if GPs use the stepwise (WHO/NICE) approach (Ehrlich, 2003; NICE 2008), failure to control pain means progressing higher up the ladder of analgesia potency as one change does not control pain, so another change occurs. Multiple changes also suggest the patient is no better and requires continued pain relief. With time MSK problems deteriorate so the longer someone keeps getting prescriptions, the more potential for them to worsen, the more likely they might switch.

Medication switching is part of a comprehensive evaluation of pain, adverse side effects and effectiveness of the management of pain procedure (Breckenridge and Clark, 2004; Schneider, 2010). Patients consulting more may have a well-managed regime of pain analgesia with regular feedback and assurance from their general practitioners, making them less likely to switch analgesia. The high number of prescriptions may indicate that the patient relies on medication to alleviate their pain at all times, which may mean that at some point they will need stronger analgesia, or after some time on strong analgesia, they might feel better; hence no need to continue on the stronger medication and they move to a lower potent medication. One of the known side effects of some strong analgesia is dependency (Curatolo and Bogduk, 2001). The higher number of prescriptions over time may be an indication of dependence for some patients.

The higher risk of switching medication among those aged over 60 reflects the increasing severity and discomfort of MSK problems that comes with age whilst MSK conditions also deteriorate with time. A study by Jordan et al. (2009) showed that consultation prevalence for MSK problems was higher among older patients and that they were also more likely to have widespread problems. It is therefore likely that older patients experience more persistent and disabling pain (Thomas et al., 2007). Considering that, a stepped approach to the administration of pain medications is recommended (Ehrlich, 2003). Additionally, general practitioners may consider the side effects associated with prolonged use of analgesia and switch the patients, for example, NSAIDs have adverse gastro-intestinal side effects and increase cardiovascular risks, while opioids may result in constipation among older patients (Kroenke et al., 2009).

The higher risk of females than males in switching analgesia may be attributed to the ability to effectively communicate their perceived pain levels to the general practitioner. The ability of the patient to communicate the level of pain they are experiencing is regarded as the strongest predictor of the strength of medication given (Eder et al., 2003). It is also difficult for the general practitioners to ascertain initial levels of pain, (Blank et al., 2001) which makes it difficult to predict the level of pain relief that specific analgesia will provide. Consequently the patient's communication of pain becomes essential, and female patients more effectively communicate their pain levels than males, (Eder et al., 2003). Females are also perceived by GPs as experiencing more pain than males (Garbez and Puntillo, 2005; Curatolo and Bogduk, 2001). Females may therefore be more likely to have their medication switched, if after the initial or previously prescribed analgesia some level of pain still persists or changes.

GPs will generally inquire from the patient about their medication use prior to consultation (Garbez and Puntillo, 2005). Consequently, in those that they identify as having used analgesia previously, there is subsequently a greater likelihood of them being at a higher risk of switching medication. The patients' experience with the previous medication helps

them appreciate what works and what does not, hence their experience of pain relief, and or side effects, enables them to have an informed input into the decision making process. General practitioners will use their expertise in light of the patient's previous experience, either good or bad, in switching analgesia potency levels (Ehrlich, 2003).

Consulting for pain in multiple locations over time, increases risk of switching and multiple medication switching. Self-evidently, changes in prescribed analgesia are driven by the rationale for switching. The factors that can be associated with the need to switch analgesia range from the complexity of the medical condition or group of medical conditions (co-morbidities), side effects and the level of relief in chronic pain achieved among others (Main, 2002; Brooks, 2006). Experiencing pain in more than one body region at a time might be an indication of widespread pain, leading to the patient having difficulty in coping with the pain, and clinicians may see it necessary to switch the patient to higher potency analgesia. Alternatively, experiencing pain in more than one body region over time may imply that pain levels and severity vary at each point of consultation; hence the potency levels prescribed are determined with respect to the level of pain at the time, leading to switching between potency levels.

Initially consulting for pain in the hip is associated with increasing risk of switches may have a similar interpretation to the finding in Chapter 4, in which those initially consulting for pain in weight bearing joints were most likely to be prescribed analgesia. In this case clinicians will consider quickly changing analgesia if the pain in the hip is not controlled as the hip is a weight bearing joint that may restrict movement and execution of day to day activities.

Those who are not prescribed pain medication on first consultation are less likely to change status over time, while those starting on weak analgesia and strong analgesia are more likely to switch analgesia. GPs consider multiple factors in deciding the analgesia and appropriate dose (Bope et al., 2004). GPs might not use medication in some

individuals since their clinical judgement is that the patient's condition does not require it. Since these patients do not tend to go on in time to receive or switch medication, this would appear to qualify the GPs decision that their condition is not severe enough in the first instance to require prescribed analgesia. These patients may also self-manage with paracetamol or other OTC medications therefore never need a prescription.

Switching from weak and strong analgesia may be related to the known side effects of opioids including dependency and addiction (Saunders et al., 2010; Breckenridge and Clark, 2004). General practitioners will most likely avoid keeping their patients on opioid analgesia for too long (Bhamb et al., 2006). This is particularly so since patients with pain may become depressed because of impact of symptoms on their lives and psychiatric disorders may increase the risk of addiction and dependence (Sullivan et al., 2005; Edlund et al., 2007), which is potentially more likely with opioids (Sproule et al., 2009).

Pain is associated with emotional distress, low social support and low social participation that may be less common in the least deprived areas (Katz, 2002; Garbez and Puntillo, 2005). Consequently, patients from the least deprived areas experience less significant pain and therefore are potentially less likely to switch medication with time compared to patients from most deprived areas. As suggested in Chapter 4, patients from least deprived areas may rely on over the counter medication, while those from deprived areas rely on their GPs' prescriptions.

The study findings however need to be interpreted with due consideration of the potential limitations. As discussed in Chapter 4, the non-randomised sample selection criteria may allow forms of selection bias and other forms of confounding induced by national prescription guidelines available to clinicians (Bedson et al., 2012). GPs may consider multiple factors including all co-morbidities, not evaluated for in this study, in choosing the appropriate analgesia to prescribe (Bope et al., 2004; Garbez and Puntillo, 2005; Schneider, 2010). There may be other variables not captured in the data, which may

influence prescribing and analgesia switching. Pain severity, weight, alcohol misuse and ethnicity might also impact on prescription of analgesia and decisions to switch (Breckenridge and Clark, 2004; Green et al., 2012) and these are not evaluated in the analysis. The study is also not designed to evaluate explicitly the clinical reasons for switching analgesia.

However, the strengths of the study lie primarily in that the data used in the study is drawn from a high quality data set, CiPCA, which gives comparable consultation Figures for MSK problems as the larger national datasets Jordan et al., 2007). The study is naturalistic in that it is based on real-world data, large sample size and uses observational approach without pre-planned treatment changes over time. The inclusion of a frailty effect on the model also partly accounts for variation that unmeasured covariates may have in the models. The inclusion criterion ensures that it is reasonable to consider the patients as having no chronic pain prior to consulting, making it reasonable to assume that no patients with prior chronic conditions are included and that the pain management process unfolds after first consultation of 2006.

## 6.6 Conclusion

This study has found that in the pharmacological management of MSK conditions, the time to switching analgesia is associated with baseline and time-varying factors. Switching analgesia is a comprehensive process which is not only decided by prescription but also by clinical and socio-demographic considerations. While both the Cox model and Weibull model produced similar models, the Weibull model enables identification of the changing effect of covariates over time. The Poisson model suggests that most baseline factors associated with a switch of analgesia are also associated with total number of rates of switching. The factors associated with switching specifically to stronger analgesia (moderate and strong analgesia) are analysed in the next chapter.

# Chapter 7

## 7 Factors associated with time to switching from initially prescribed lower potency analgesia to stronger analgesia

### 7.1 Introduction

Chapter 6 suggested that the time to any analgesia change is associated with factors measured at time of initial MSK consultation (baseline), as well as those measured during follow up time. There is a higher risk and rates of switching analgesia among the elderly, females, having been prescribed analgesia in the past, consulting for pain in more than one location over time, starting medication with weak or strong analgesia and the number of repeat prescriptions received over time. There are declining risks with the increasing number of MSK consultations, low deprivation and receiving no prescribed medication on first consultation. The Weibull model with and without the extension of frailty is a viable alternative to the Cox model in modelling time to analgesia switch.

If patients used the same analgesia potency level over follow up time, it may be assumed that there are negligible negative consequences of using the analgesia. If a patient changes to a lower potency medication; it may be assumed that the condition is not deteriorating further or they have experienced side effects. But if the medication potency level increases to or changes over time to stronger analgesia, it may suggest deterioration of the condition. The patient group subjected to increasing or stronger analgesia potency is also more exposed to potential side effects of analgesia. As indicated in Chapter 3, up to 80% of patients using opioid analgesia experience at least one of the side effects (Benyamin et al., 2008; Fitzcharles et al., 2010), hence clinicians may benefit from identifying patients at the onset of consultation that are at risk of switching to stronger analgesia.

The aim of this chapter is therefore to evaluate which of the identified socio-demographic and clinical factors are associated with higher risk of switching from no, basic and weak analgesia to stronger analgesia over time.

In identifying which baseline characteristics are associated with being more likely to progress up the ladder and switch to stronger analgesia, GPs may be able to identify earlier, patients more at risk of needing stronger medication. Knowing the factors associated with such a switch might help GPs determine which painkiller to use first, that is, if the GP uses a weaker analgesia in a patient who is likely to switch to a stronger analgesia quite quickly, this results in two outcomes: 1) the patient continues to suffer pain unnecessarily and 2), the patient returns for another consultation that might have been avoided if the pain had been initially controlled. Knowing who will switch quickly might help avoid this.

The specific objective of the chapter is therefore:

1. To model factors associated with time to change from initial low medication potency level (no medication, basic analgesia and weak analgesia) to higher potency analgesia (moderate, strong analgesia).

## 7.2 Methods

This analysis considers patients who received lower potency analgesia (no medication, basic analgesia or weak analgesia) at their initial consultation and eventually switched to moderate or strong analgesia.

Switching analgesia is defined as either a record of a prescription of moderate or strong analgesia (this may be in place of, or in addition to the initial analgesia (basic analgesia or weak analgesia)), or a record of moderate or strong analgesia if without a previous analgesia prescription on first consultation (Gore et al., 2012, Rahme et al., 2006; Schneider, 2010). Prescription of NSAIDs is not considered as a switch as NSAIDs cannot

be adequately placed in the potency hierarchy (Chapter 3). Stoppages are not considered in the analysis as only precise prescription dates and not stopping dates can be ascertained.

The analgesia categories (HAC) were as defined in chapter 6, in which strong combination and strong single analgesia are combined to just strong analgesia. Patients prescribed the lower potency analgesia groups in analysis are ‘at the beginning of the treatment ladder’ and therefore potentially the ones that were likely to switch to stronger analgesia if their conditions deteriorated or experienced no pain relief.

### 7.2.1 Data and study population

Of the patients identified and included in the analysis in Chapter 6, only those whose initial medication was no medication, basic analgesia or weak opioids were considered. Patients initially prescribed moderate or strong analgesia and NSAIDs were excluded from the analysis. All variables adjusted for in chapter 6 were considered. The prescription of NSAIDs after initial analgesia but prior to strong analgesia switch was considered as a potential time-varying covariate but was left out of the analysis due to small numbers.

#### Outcome variables

The outcome of interest was time to switching from no medication, basic or weak analgesia to moderate or strong analgesia. The switch or time to the prescription of moderate or strong analgesia was calculated from first consultation date to the first issue date of moderate or strong analgesia. Those who did not switch medications had their times censored at the end of 2010 or deregistration date.

### 7.2.2 Statistical Analysis

Kaplan-Meier curves were used as an exploratory analysis to decide if the times to change are different between categories of the independent variables, with particular interest in the initial analgesia potency levels. The univariate Weibull model with and without gamma frailty was used to model factors associated with time to switch. High risk or frail individuals will tend to have shorter times before switching to higher potency or stronger medication, and lower risk ones tend to take much longer. Frailty therefore accounts for possible unobserved or unmeasured covariates.

The Weibull model was chosen with reference to the previous chapter. In Chapter 6, the Cox and Weibull models tended to produce similar models, and the Weibull was the preferred final choice for reasons stated in Chapter 6. Among them, the Weibull model tended to give a better fit (smaller -2logL values) and the shape parameter helps in understanding the changing effect of the variables in the model on the hazard function over time.

Both models included clinical and socio-demographic variables. Two sets of models were fitted, with (full model) and without (baseline variables only) time-varying covariates. The baseline variable only models were fitted to evaluate the importance of baseline factors which the clinician will have knowledge of at initial consultation. Comparison of the -2logL values were used to evaluate whether the models fitted are different from each other.

## 7.3 Results

### 7.3.1 Data description

A total of 2285 patients were prescribed no medication (75%), basic analgesia (15%) and weak analgesia (10%) as their initial medication. 283 (12%) of the patients eventually switched to higher potency analgesia (moderate and strong analgesia), of which initial medication prescribed was 62% no medication, 18% basic analgesia and 20% weak opioids. The mean time to first switch was 753 days with a standard deviation of 469 days, median time 721, and IQR (354, 1123) days. The shortest switch time was 15 days while the longest was 1777 days. Table 7.3.1 shows a detailed description of patients switching to stronger analgesia by baseline characteristics.

**Survival estimates**

Figure 7.3.1 shows a constant rate of the patients whose initial medication was no medication, basic analgesia or weak analgesia switching to higher potency medication (moderate and strong analgesia) throughout follow up time.

Figure 7.3.1: Overall survival estimates for first switch from no medication, basic analgesia and weak analgesia to moderate or strong analgesia

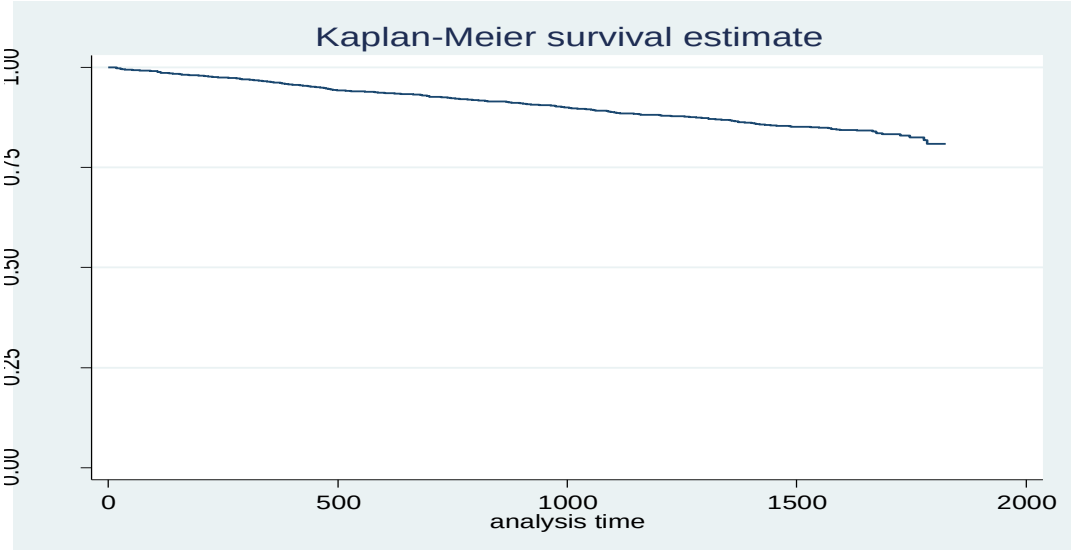


Figure 7.3.2 shows that there were differences in the switching rates for the three categories according to initial analgesia. Those with no medication initially have lower and more constant rates of switching to higher potency analgesia (moderate and strong analgesia) than those initially on basic analgesia, while those with weak analgesia have higher and less constant rates of switching than those initially on basic analgesia.

Figure 7.3.2: Survival estimates for first switch from no medication, basic analgesia and weak analgesia to moderate or strong analgesia by initial analgesia

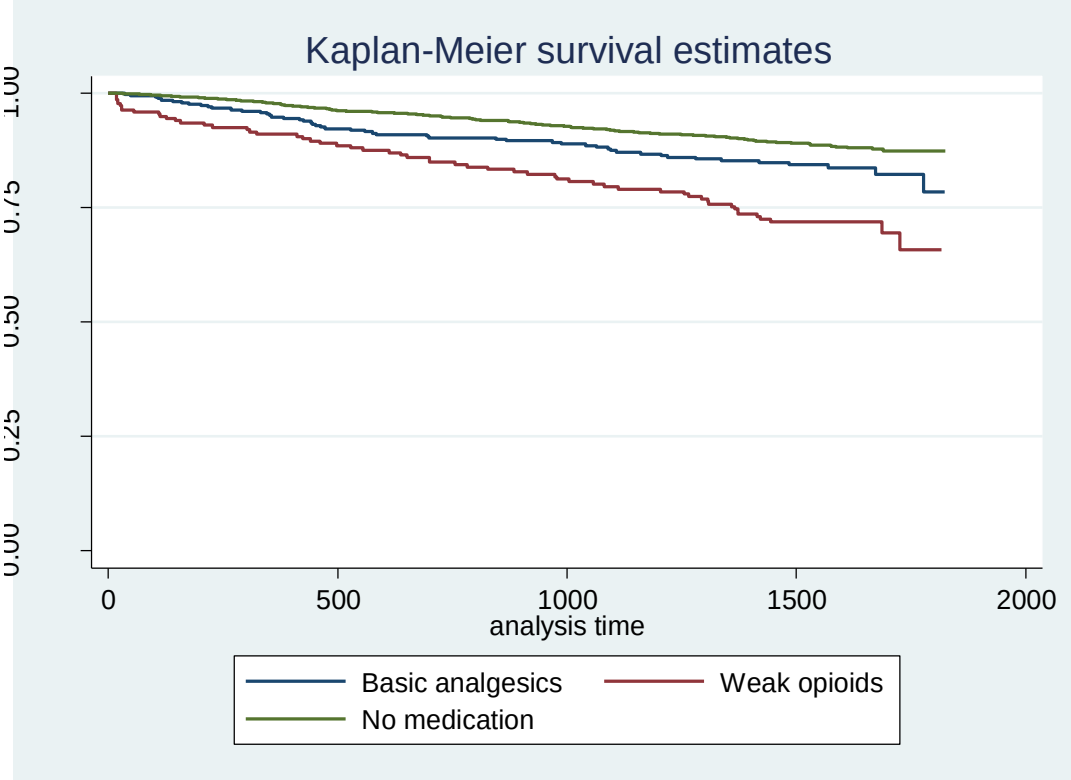


Table 7.3.1: Baseline Socio-demographic and clinical characteristics of patients switching from no medication and basic or weak analgesia to moderate or strong analgesia

| | | Switch to Stronger Analgesia | |
|---|---|---|---|
| **Variable** | **N** | **No (Row %)** | **Yes (Row %)** |
| Total | 2285 | 2002(88) | 283(12) |
| **Age (years)** | | | |
| 15-29 | 566 | 511(90) | 55(10) |
| 30-44 | 716 | 638(89) | 78(11) |
| 45-59 | 643 | 567(88) | 76(12) |
| 60-74 | 271 | 214(79) | 57(21) |
| Over 75 | 89 | 72(80) | 17(20) |
| **Gender** | | | |
| Females | 947 | 813(86) | 134(14) |
| Males | 1338 | 1189(89) | 149(11) |
| **Previous musculoskeletal consultation** | | | |
| Yes | 292 | 252(86) | 40(14) |
| No | 1993 | 1750(88) | 243(12) |
| **Previous prescribed analgesia** | | | |
| Yes | 331 | 269(81) | 62(19) |
| No | 1954 | 1733(89) | 221(11) |
| **Region of Pain** | | | |
| Back | 496 | 430(87) | 66(13) |
| Knee | 240 | 219(91) | 81(9) |
| Hip | 148 | 128(86) | 20(14) |
| Foot and Ankle | 154 | 141(92) | 13(8) |
| Hand/upper limb | 205 | 177(86) | 28(14) |
| Shoulder | 151 | 129(85) | 22(15) |
| Neck | 144 | 131(91) | 13(9) |
| Other/unspecified | 747 | 647(87) | 100(13) |
| **Co-morbidity** | | | |
| Selected conditions | 86 | 74(86) | 12(14) |
| Other conditions/none | 2199 | 1928(88) | 271(12) |
| **Deprivation** | | | |
| Most | 1008 | 907(87) | 133(13) |
| Moderate | 891 | 791(89) | 100(11) |
| Least | 386 | 336(87) | 50(13) |
| **Staff category** | | | |
| GPs | 1855 | 1621(87) | 234(13) |
| Other | 430 | 381(89) | 49(11) |

| Variable | N | Switch to Stronger Analgesia No (Row %) | Switch to Stronger Analgesia Yes (Row %) |
|---|---|---|---|
| **Number of pain locations** | | | |
| One | 21795 | 1526(85) | 269(15) |
| More | 490 | 476(97) | 14(3) |
| **Analgesia group (1st consultation)** | | | |
| Basic analgesia | 346 | 296(86) | 50(14) |
| Weak analgesia | 223 | 166(74) | 57(26) |
| No medication | 1716 | 1540(90) | 176(10) |

### 7.3.2 The Weibull models for baseline variables

The Weibull model and the Weibull model with gamma frailty identified the baseline socio-demographic and clinical factors associated with time to switching from initially prescribed low potency analgesia (no medication, basic analgesia and weak opioids) to higher potency analgesia (moderate analgesia or strong analgesia) as age, having a previous prescribed analgesia, level of deprivation and initial analgesia potency. The models are given in Table 7.3.2 with the statistically significant variables highlighted in bold. All the other factors were not statistically significant at 5% level.

**The Weibull model**

The Weibull model without frailty, (first column of Table 7.3.2) shows that when compared to those aged 30-44, the age groups 60-74, adjusted hazard ratio (HR 1.81; 95% CI [1.26, 2.58]) and 75+ (HR 1.91 [1.10, 3.31]) were more likely to switch to stronger analgesia when all other factors were held constant. Previous prescribed analgesia more than 12 months prior to new MSK consultation in 2006 was associated with increased risk of switching with (HR 1.53 [1.13, 2.07]). Weak analgesia prescribed at the onset of consultation was associated with increased risk of switching to higher potency analgesia over time, (HR 1.77 [1.19, 2.64]) compared to basic analgesia. Patients from medium deprivation neighbourhoods were less likely to be switched to higher potency analgesia, (HR 0.72 [0.55, 0.94]) compared to patients from most deprived neighbourhoods.

**The frailty Weibull model**

The frailty Weibull model, (second column of Table 7.3.2) identified similar variables as the model without frailty but with slightly inflated hazard ratios, whilst gender became significant. The model shows that when compared to the 30-44, the age groups 60-74 (HR 2.29 [1.32, 3.96]) and 75+ (HR 2.23 [1.03, 4.79]) were at higher risk of switching to stronger analgesia. Weak analgesia prescribed at the onset of consultation (HR 2.09 [1.18, 3.72]) were associated with higher risk of switching, while no pain medication at onset of consultation (HR 0.63 [0.39, 0.99]) were associated with decreasing risk when compared to basic analgesia. Females (HR 1.39 [1.03, 1.94]) were more likely than males to switch. Patients from medium deprivation neighbourhoods (HR 0.66 [0.46, 0.94]) were less likely to switch compared to those from most deprived neighbourhoods.

The distribution shape parameters for both models (with and without frailty) suggest that the variables may have an increasing effect on the hazard function over time. The -2loglikelihood values suggest that the frailty model with statistically non-significant frailty parameter (3.05 [0.87, 10.6]) is a slightly better model.

### 7.3.3 Weibull model for baseline and time-varying covariates

The frailty Weibull model including both baseline and time-varying covariates showed that frailty was not statistically significant and was not considered. The Weibull model with baseline and time-varying covariates identified experiencing pain in multiple locations over time, the number of analgesia prescriptions of low potency over time and the number of MSK consultations over time as the only factors associated with the first switch to higher potency analgesia (moderate or strong analgesia). All the other factors were not statistically significant at 5% level.

Experiencing pain in more than one location (HR 2.22 [1.74, 2.85]) was associated with higher risk of switching to stronger analgesia. The increasing number of prescribed analgesia over time (HR 1.04 [1.03, 1.05]) was associated with increased risk of switching

to stronger analgesia. The increasing number of consultations over time was associated with decreasing risk of switching to stronger analgesia (HR 0.40 [0.31, 0.50]).

Although not statistically significant at the 5% level, previous prescribed analgesia (HR 1.34 [0.99, 1.81]) was associated with increased risk of switching at the 10% level. Initially prescribed weak analgesia (HR 1.39 [0.93, 2.08] compared to basic analgesia), although not statistically significant was associated with increased risk of switching. When compared to patients whose initial pain is in the back, patients with initial pain in the knee were less likely to switch to stronger analgesia (HR 0.62 [0.37, 1.03]) although not statistically significant.

The distribution shape parameter (1.27 [1.13, 1.43]) suggests that the variables have increasing effect on the hazard function over time, that is, the risk of switching to stronger analgesia is expected to increase with time.

Table 7.3.2: Weibull models evaluating factors associated with first switches from no medication, basic analgesia and weak analgesia to moderate or strong analgesia

| **Variable** | **HR[95% CI]** | | | | | |
|---|---|---|---|---|---|---|
| | **Baseline variables Weibull Model** | | **Gamma frailty Weibull Model** | | **Baseline + time-varying covariates Weibull model** | |
| | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Age Group** | | | | | | |
| 30-44 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 15-29 | 0.96[0.68, 1.36] | 0.93[0.66, 1.33] | 0.93[0.62, 1.40] | 0.91[0.59, 1.40] | 0.96[0.68, 1.36] | 0.91[0.64, 1.30] |
| 45-59 | 1.01[0.74, 1.39] | 0.97[0.70, 1.34] | 1.01[0.69, 1.46] | 0.93[0.62, 1.39] | 1.01[0.74, 1.39] | 0.90[0.65, 1.25] |
| 60-74 | 1.96[1.39, 2.77] | **1.81[1.26, 2.58]** | 2.38[1.39, 4.07] | **2.29[1.32, 3.96]** | 1.96[1.39, 2.77] | 1.33[0.91, 1.94] |
| 75+ | 2.61[1.54, 4.42] | **1.91[1.10, 3.31]** | 3.32[1.57, 7.04] | **2.23[1.03, 4.79]** | 2.61[1.54, 4.42] | 1.16[0.65, 2.04] |
| **Gender** | | | | | | |
| Male | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Female | 1.36[1.07, 1.71] | 1.24[0.98, 1.57] | 1.45[1.05, 2.00] | **1.39[1.03, 1.94]** | 1.36[1.07, 1.71] | 1.15[0.90, 1.46] |
| **Previous prescribed analgesia** | | | | | | 1.00 |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | |
| Yes | 1.67[1.26, 2.21] | **1.53[1.13, 2.07]** | 1.74[1.19, 2.56] | **1.67[1.10, 2.54]** | 1.67[1.26, 2.21] | 1.34[0.99, 1.81] |
| **Previous musculoskeletal consultation** | | | | | | 1.00 |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | |
| Yes | 1.08[0.77, 1.52] | 0.96[0.67, 1.37] | 1.10[0.76, 1.60] | 1.00[0.63, 1.58] | 1.08[0.77, 1.52] | 1.04[0.73, 1.48] |
| **Comorbidity** | | | | | | |
| Selected | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Other/none | 0.92[0.51, 1.64] | 1.32[0.72, 2.38] | 0.91[0.49, 1.69] | 1.47[0.67, 3.22] | 0.92[0.51, 1.64] | 1.29[0.71, 2.33] |
| **Staff category** | | | | | | |
| GP | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Other | 0.87[0.64, 1.18] | 0.95[0.70, 1.31] | 0.85[0.60, 1.20 | 0.88[0.59, 1.31] | 0.87[0.64, 1.18] | 0.79[0.57, 1.08] |

| Variable | HR[95% CI] | | | | | |
|---|---|---|---|---|---|---|
| | Baseline variables Weibull Model | | Gamma frailty Weibull Model | | Baseline + time-varying covariates Weibull model | |
| | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted |
| **Deprivation** | | | | | | |
| Most | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| medium | 0.70[0.54, 0.92] | **0.72[0.55, 0.94]** | 0.69[0.51, 0.94] | **0.66[0.46, 0.94]** | 0.70[0.54, 0.92] | 0.81[0.62, 1.06] |
| least | 0.81[0.58, 1.12] | 0.76[0.54, 1.06] | 0.80[0.56, 1.13] | 0.69[0.44, 1.06] | 0.81[0.58, 1.12] | 0.91[0.65, 1.27] |
| **Pain Region** | | | | | | |
| Back | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Knee | 0.65[0.40, 1.07] | 0.75[0.45, 1.25] | 0.65[0.40, 1.07] | 0.79[0.43, 1.48] | 0.65[0.40, 1.07] | 0.62[0.37, 1.03] |
| Hip | 1.05[0.63, 1.73] | 1.13[0.68, 1.89] | 1.05[0.63, 1.73] | 1.18[0.61, 2.29] | 1.05[0.63, 1.73] | 0.95[0.57, 1.59] |
| Foot and Ankle | 0.60[0.33, 1.09] | 0.68[0.37, 1.24] | 0.60[0.33, 1.09] | 0.61[0.29, 1.29] | 0.60[0.33, 1.09] | 0.62[0.33, 1.13] |
| Hand/upper limb | 1.04[0.66, 1.62] | 1.27[0.81, 2.01] | 1.04[0.66, 1.62] | 1.42[0.72, 2.57] | 1.04[0.66, 1.62] | 1.10[0.70, 1.73] |
| Shoulder | 1.07[0.66, 1.74] | 1.14[0.69, 1.87] | 1.07[0.66, 1.74] | 1.18[0.63, 2.22] | 1.07[0.66, 1.74] | 1.13[0.69, 1.86] |
| Neck | 0.65[0.35, 1.17] | 0.76[0.41, 1.39] | 0.65[0.35, 1.17] | 0.75[0.36, 1.55] | 0.65[0.35, 1.17] | 0.67[0.37, 1.24] |
| Other/unspecified | 1.04[0.76, 1.42] | 1.16[0.84, 1.60] | 1.04[0.76, 1.42] | 1.25[0.82, 1.91] | 1.04[0.76, 1.42] | 0.90[0.65, 1.23] |
| **Initial Potency** | | | | | | |
| Basic analgesia | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Weak analgesia | 1.89[1.29, 2.76 | **1.77[1.19, 2.64]** | 2.22[1.25, 3.95] | **2.09[1.18, 3.72]** | 1.89[1.29, 2.76 | 1.39[0.93, 2.08] |
| No medication | 0.66[0.48, 0.90] | 0.73[0.52, 1.09] | 0.60[0.39, 0.91] | **0.63[0.39, 0.99]** | 0.66[0.48, 0.90] | 0.91[0.65, 1.27] |
| **Time-varying** | | | | | | |
| **Multiple location** | | | | | | |
| No | - | - | - | - | 1.00 | 1.00 |
| Yes | - | - | - | - | 2.04[1.96, 3.02] | **2.22[1.74, 2.85]** |
| **No. of consultations** | - | - | - | - | 0.72[0.66, 0.79] | **0.40[0.31, 0.50]** |
| **No. of Prescriptions** | - | - | - | - | 1.00[1.00, 1.01] | **1.04[1.03, 1.05]** |
| **-2logL** | - | 2160 | - | 2156 | - | 1882 |
| **Weibull shape parameter** | - | 1.02[0.92, 1.14] | - | 1.18[0.97, 1.43] | - | 1.27[1.13, 1.43] |
| **Frailty parameter** | **-** | **-** | - | 3.05[0.87, 10.6] | - | - |

**Unadjusted model =** Individual variable in the model, **Adjusted model =** All variables included simultaneously

## 7.4 Discussion

The Weibull model has been employed to evaluate the factors associated with switch from no medication, basic analgesia and weak analgesia to moderate or strong analgesia. The models with only variables measured at baseline evaluated the importance of the baseline variables without time-varying covariates while the model with time-varying covariates measured the associations related to the course of the pharmacological management of MSK conditions. Patients who were initially prescribed no medication, basic analgesia and weak analgesia are at higher risk of switching to moderate or strong analgesia if they are 60 or over, if they were previously prescribed analgesia, or if they were prescribed weak analgesia on initial consultation, while those from medium deprivation areas are at lower risk. When time-varying covariates are included in the model, only time-varying covariates (pain in more than one location, number of MSK consultations and number of analgesia prescriptions) are statistically associated with time to switch.

The models were fitted with and without a gamma frailty function. The frailty models showed that the effect of frailty was not statistically significant, with the frailty model with both time-varying and baseline factors not very different from the model without frailty. The frailty model with baseline factors only exhibited higher hazard ratios compared to the non-frailty model and gender was identified as statistically significant. The frailty model is a better fit as seen from the -2logL.

The high risk of older patients, aged 60+, to switch to higher potency analgesia probably reflects that MSK conditions tend to deteriorate and get worse with age (Pergolizzi and Raffa, 2009) hence highlighting the levels of discomfort and severity among this group of patients (Carrington et al., 2010). Clinicians therefore might be inclined to consider a switch to higher potency medication if there is no adequate pain relief. Older patients are more susceptible to co-morbidities (Fitzcharles et al., 2010), hence clinicians may take that into account and decide to switch to stronger analgesia to help control pain. While NSAIDs may provide pain relief better than basic analgesia and weak analgesia, clinicians

may opt for moderate or stronger analgesia due to more frequent occurrence of adverse effects (fluid retention, hypertension, congestive heart failure and possible increased cardiac mortality, acute renal failure) in older patients with NSAIDs (Fitzcharles et al., 2010). The clinicians' judgement could be that NSAIDs associated adverse effects are more likely for this age group than stronger analgesia adverse effects.

The switch from weak analgesia to stronger analgesia could be a calculated move by clinicians as opioid rotation is an effective strategy in the management of negative effects (tolerance and dependence) of opioids (Joseph et al., 2009) and can sometimes improve analgesia success (Pergolizzi and Raffa, 2009). General practitioners will most likely avoid keeping their patients on the same opioid analgesia for too long to avoid negative effects (Bhamb et al., 2006).

Pain that interferes with daily life increases with age and is more prevalent among females. Additionally, older females were also likely to report pain in more than one location (Thomas et al., 2007), which may require stronger analgesia to control (Joseph et al., 2009; Reid et al., 2010). As suggested in Chapter 4, the ability of the patient to communicate the level of pain they are experiencing is regarded as one of the strongest predictors of the strength of medication given, and females have been shown to be better at that, hence the perceived level of pain may lead their clinicians to switch them to stronger analgesia.

Patients with prescribed analgesia history prior to their 2006 consultation and those prescribed weak analgesia on initial consultation were at risk of switching to higher potency analgesia. As suggested in Chapter 4 and 6, clinicians consider patients' response to previous medication. .

Patients from medium deprivation areas were at a lesser risk of switching to stronger analgesia. Patients from least deprived areas had reduced risk but this was not statistically significant. However, there are similarities in the identified association of

deprivation with prescription of analgesia and strength (Chapter 4) and analgesia switching (Chapter 6), It may be that the level of pain associated with emotional distress, low social support and low social participation that may be more common in most deprived areas (Katz, 2002; Garbez and Puntillo, 2005). This potentially leads to higher levels of pain among this group of patients leading to clinicians switching them to stronger analgesia.

The number of analgesia prescriptions and acquiring new pain sites over time increases the risk of switching to moderate and strong analgesia. Pain interference in daily activities is more prevalent among patients with more than one pain location (Thomas et al., 2007) which may require stronger analgesia to alleviate.

The number of MSK consultations over time reduces the risk of switching to higher potency analgesia suggesting that switching to stronger analgesia can be greatly reduced with higher number of consultations. As suggested in the previous chapter , medication switching is part of a comprehensive evaluation of pain, adverse side effects and strategic management of pain (Breckenridge and Clark, 2004; Schneider, 2010), and more consultations may lead to strengthened adherence to the therapeutic plan with regular feedback, assurance, positive reinforcement from their general practitioners or health professionals (Fitzcharles et al., 2010). Routinely and frequently evaluating patients for their degree of analgesia requirements, functional daily activities, adverse events, and adherence to medication routines may minimise switching to stronger analgesia.

Patients with initial pain in the knee were less likely to switch to stronger analgesia although not statistically significant. Knee pain might be more likely to have an inflammatory cause and therefore NSAIDs may be more suited to it than stronger analgesia (Schneider, 2010; Breckenridge and Clark, 2004; Bope et al., 2004). Hence switching to stronger analgesia instead of NSAIDs becomes less likely.

The Weibull shape parameter in the model with time-varying covariates suggests that the risk of switching to stronger analgesia will increase with time in the presence of the measured time-varying covariates. This makes clinical sense, as stated in the previous chapters, MSK conditions tend to deteriorate with time, hence the need to switch to stronger analgesia to control increasing levels of pain.

Limitations of this analysis have been discussed in previous Chapters (for example, unmeasured covariates). The reasons behind switching from lower potency analgesia are not known however, the factors identified as important are logical under the projected possible reasons for switching. Time-varying covariates seem to have more influence in the models than baseline variables. This does not however diminish the fact that the management of MSK is multifaceted, which means that understanding the baseline factors is as important as understanding the time-varying covariates and that there are baseline factors which seem to predispose a patient to being more likely to switch medication. These factors, e.g. age and gender, may also be related to the important time-varying measures (number of consultations and prescriptions). The advantage of the Weibull model is that it is able to indicate that baseline variables may become less important as time progresses but the risk of switching increases with time in the presence of time-varying covariates.

## 7.5 Conclusion

Clinicians need to be more vigilant with patients who at initial consultation are of older age (≥60), female and have received prescribed analgesia in the past as well as those they prescribe weak analgesia as they have higher risks of switching to moderate or strong analgesia. More frequently scheduled MSK consultations may help to minimise the risk of switching, and the implications of this will be discussed in more detail in Chapter 10. While time-varying covariates are most important, modelling baseline factors separately may help identify patients at higher risk of switching at the onset of consultation.

# Chapter 8

## 8 Modelling the effect of patient reported variables on switching analgesia

### 8.1 Introduction

The previous Chapters (6 and 7) have demonstrated that 51% of first time MSK consulters switch from the analgesia they were initially prescribed, with switching most common amongst those initially prescribed weak analgesia (70%). Switching analgesia was associated with socio-demographic variables such as age, gender, level of deprivation as well as initial pain location, initial analgesia potency level and previous medication history. The number of consultations for MSK problems and repeat prescriptions were also associated with switching as was consulting over time for pain in other body regions.

The previous analyses have been on consulters for new (incident) MSK conditions, and have been restricted to assessing association with switching of socio-demographic and clinical characteristics that are routinely recorded in primary care. This chapter aims to utilise a dataset that links self-reported information to medical records to evaluate the generalizability of these findings in a cohort of patients with prevalent MSK conditions aged 50+, the age where MSK problems are most common. The dataset has the benefit of incorporating additional patient-specified variables that might be of clinical importance, for example the level of pain interference and physical function, which were not available in the CiPCA (chapter 6 and 7) database. Pain interference and physical function are a proxy measure of the patient's quality of life in the presence of their MSK condition, as they may indicate the difficulties they have in executing their daily activities.

The aim of the analysis reported in this Chapter is to evaluate the association of clinical and socio-demographic variables with analgesia switching in the presence of patient-

reported variables to help determine the generalizability and limitations of the statistical models derived in Chapter 6 and 7. The patient specific variables are more personal, and therefore more likely to further inform us of the initial characteristics associated with future switching which may give an idea of what input patients have, and the effect of their input in the prescription process. For example, if a patient has used over the counter medication, what effect does it have on the choice of analgesia prescribed.

The specific objectives of the chapter are:

1. To assess if the same factors identified previously to be related to switching in an incident MSK consulting group are also the key factors associated with switching in a prevalent MSK consulting group aged 50+ years.
2. To evaluate whether patient-reported factors are also related to switching analgesia.

These objectives will be achieved through two different analyses, factors associated with, i) switch to stronger analgesia, ii) switching analgesia in which multiple-event, non-ordered switches within the follow up time are accounted for.

## 8.2 Methods

### 8.2.1 Data and study population

The patients were drawn from the North Staffordshire Osteoarthritis Project, cohorts 1 and 2 (NorStOP1 and NorStOP2) described in Chapter 3. The baseline and follow-up data collection surveys were carried out at different times. NorStOP 1 was established through a baseline two stage postal survey in April 2002 and consenting responders followed up in a further two stage postal survey in April 2005. NorStOP 2 was established through a baseline two-stage postal survey from July/August 2002 – July/August 2003 with consenting responders further followed up 3 years later (October 2005 – September 2006).

This therefore was a combined cohort of adults aged 50 years registered with 6 general practices. The baseline survey consisted of health questionnaires that collected information on several areas of life including socio-demographics, physical function and interference of pain in their daily lives (Thomas et al., 2004).

The NorStOP study was designed to describe the prevalence of joint pain and pain interference with activities, to determine the course of joint pain and disability and the factors associated with their onset and persistence, and to describe the prevalence, distribution, and associated features of participation restriction in community-dwelling adults aged 50 years and over (Thomas et al., 2004).

The analysis reported here included respondents who consented to medical record review and responded to baseline and 3 year follow up surveys. As in the CiPCA data, the linked primary care medical record data included prescriptions (BNF chapter, the drug item, issue date) and medical conditions consulted for (see Chapter 4).

For this analysis patients were included who:

i. Responded to baseline and 3 year follow-up surveys and consented to record review,
ii. Had no MSK consultation and no analgesia prescribed in the month before the baseline survey,
iii. Had a MSK consultation within the 6 months after the baseline survey.

The logic in the inclusion criteria was to minimise the influence of prior prescribed analgesia on the patient-reported variables recorded during the baseline survey, e.g. the level of physical function and pain interference. The 6 months period after the survey enabled the establishment of a possible connection between the baseline patient-reported factors with any initial prescription of analgesia. In the evaluation of factors associated with switching to stronger analgesia, only the participants prescribed no

medication, basic analgesia and weak analgesia on first consultation were considered. These switches represent an upward increase in the potency levels of analgesia.

### 8.2.2 Baseline variables

The socio-demographic and clinical variables extracted from the medical records and measured prior to, or at time of baseline survey considered in this analysis were those used previously in the analysis of CiPCA: age, gender, deprivation, co-morbidity, region of pain (e.g. knee, back), MSK consultation history, analgesia prescription history (within the 2 years prior to baseline survey) and the potency level prescribed on first consultation after baseline survey (Chapter 4, section 4.2.3). In modelling the time to switch to stronger analgesia, having been prescribed an NSAID prior to the switch was included in the switching to stronger analgesia model. The socio-demographic and clinical variables were defined and categorised as stated in Chapter 6 and 7 (CiPCA data)

The NorStOP data contains a wide range of patient-reported variables, but the variables used here were marital status, body mass index (BMI), widespread pain, alcohol consumption, smoking history, depression, GP access, physical function, pain interference and over the counter medication (OTC) within 1 month prior to baseline survey date (none, painkillers/creams, natural medicine/glucosamine). The variables were collected through health survey questionnaires at baseline, which contained general health status (SF-36 Physical Function subscale (Ware, 200)), social (Berkman-Syme Social Network Index (Lubben, 1988)), psychological profile (Hospital Anxiety and Depression Scale (Zigmond et al., 1983)), participation restriction (Keele Assessment of Participation (Wilkie et al., 2004)) and regional pain severity (Western Ontario and McMaster Universities Osteoarthritis Index (Ehrich et al., 2000)).

Age was categorised into four groups: 50-59, 60-69, 70-79 and 80+. The marital status was a dichotomous variable, 1 represents those married or cohabiting and 0 otherwise, BMI is a 3-category variable (1, underweight or normal, 2, overweight or obese, 3,

unknown), widespread pain is defined as, 1, axial (back/neck) plus contralateral upper and lower limb and 0 otherwise (Thomas et al., 2004). Also measured were alcohol consumption (1, drinks most of the time or sometimes, 0, no or rarely), and smoking history (1, never smoked, 2, previously smoked, 3, currently smoking).

Depression was measured using the Hospital Anxiety and Depression Scale. This scale has 7 items relating to depression with scores ranging from 0 to 21. Scores of 8 or more indicate possible depression. Physical function was considered as a continuous variable, measured using the SF-36 Physical Function subscale with scores ranging from 0 to 100, higher scores indicating better physical function. Pain interference was measured using the SF-36 which has five ratings for the question on how pain interferes with their daily activities. The ratings were combined into a binary variable: 1 represents pain interferes with life, moderately/quite a bit/extremely and 0 for no/little interference from pain. GP access was coded as 1, adequate access, 0, inadequate access to a GP based on the question asking participants if they have good access to their doctor (GP), as and when they need.

These variables have been shown to be related to pain levels and prescription of analgesia (Green et al., 2012; Meyers et al., 2007; Thomas et al 2004; Thomas et al., 2007). Most of these variables may be perceived to represent a self-assessment of the patient's MSK condition and its impact on the patient's quality of life, their own attempts to manage their condition, as well as the physical and psychological manifestations.

**Outcome variables**

The outcome variables of interest are i) switch from basic analgesia or weak analgesia to moderate or strong analgesia or starting use of a moderate or strong analgesia if initially prescribed no medication (switching defined as in section 7.2); ii) any analgesia switching in which multiple-event switches (more than one switch) are accounted for (section 6.3.1). For the first analysis of switching to a stronger analgesia, time was measured from the

prescription date of the baseline medication (medication prescribed within 14 days of a MSK consultation date in the six months after baseline survey) to the first switch to moderate or strong analgesia. For those who did not switch, time was measured to the end of the 3 year follow-up.

The counting process approach (Chapter 6) was used to calculate time between events in multiple-event switches. Multiple-event switch analysis considers any change in analgesia, regardless of whether the switch is to lower or higher potency analgesia, or back to a previously prescribed analgesia. As such, some individuals incur multiple-events during follow up. All individuals in the analysis were followed up to 3 years.

### 8.2.3 Statistical methods

The Kaplan-Meier curves were used as an exploratory analysis to graphically assess the overall survival estimates and Weibull models used to evaluate the association of baseline factors with time to switching analgesia (described in Chapter 6). For each of the analyses, two models are fitted; one without patient-reported factors to allow comparison to the models reported in Chapters 6 and 7, and then adding patient-reported factors. Frailty models were considered, and as in the previous chapter were found to be not statistically significant, hence left out of the analysis.

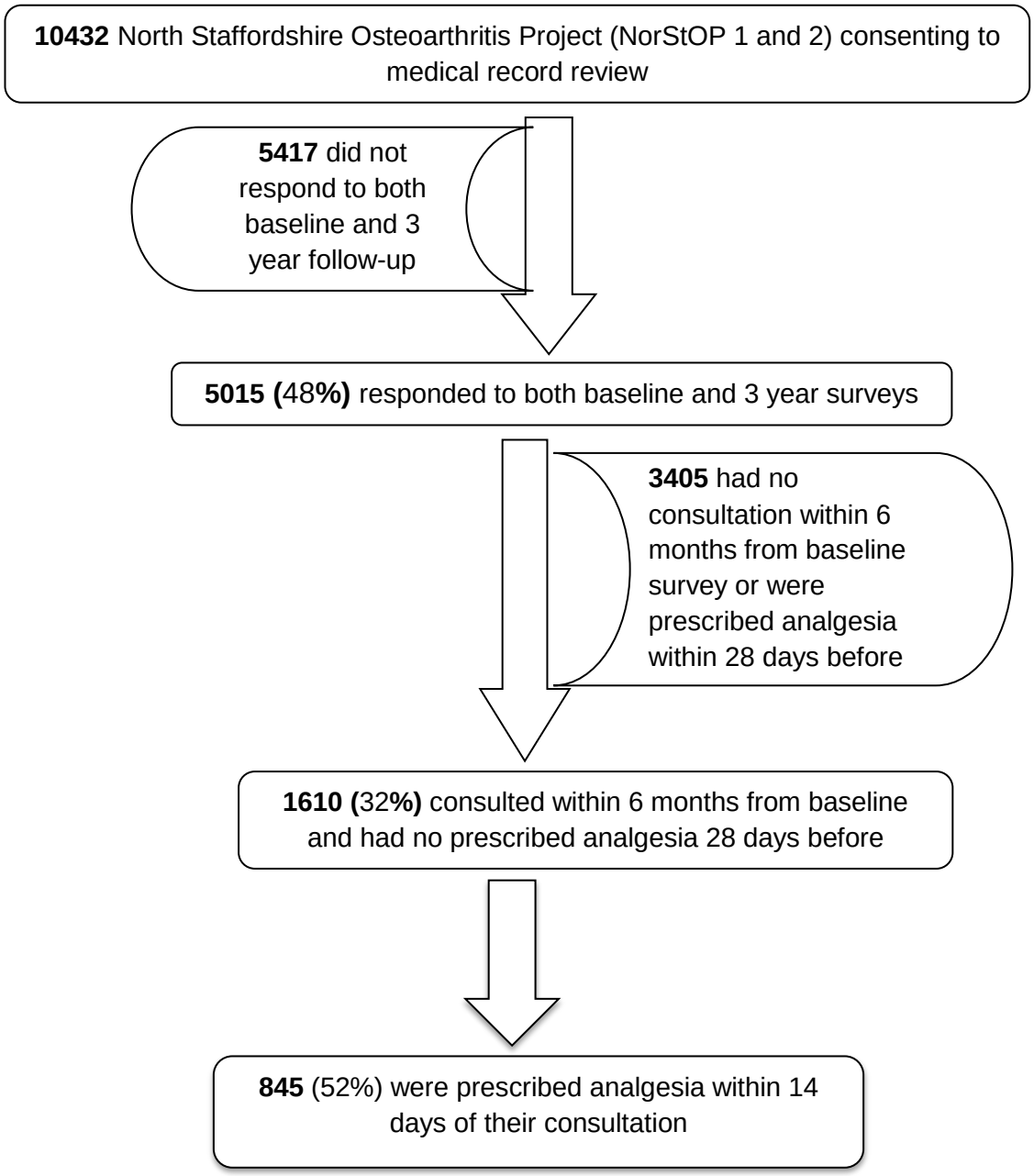
The sensitivity analyses involved fitting two more models, both adjusted and unadjusted and comparing the -2logL to that of the final model. The missing physical function values (continuous) were replaced by the median physical function score. For the categorical variables two extremes were assumed, for example one model assumed that all those with missing values in the depression variable had depression and the other model assumed that they all did not have depression.

## 8.3 Results

### 8.3.1 Study population and Data description

At the onset of data collection, 20214 people were sent health survey questionnaires, of whom 13,986 (69%) responded to the baseline questionnaire. 10,432 (75%) of those who responded at baseline consented to medical record review. 5015 (48%) responded to both baseline and 3 year follow-up survey.

Figure 8.3.1: Schematic illustration of the inclusion criteria



Of the 5015 who consented to medical record review and responded to both baseline and 3 year follow-up survey, 1610 (32%) fitted the inclusion criteria of having no prescribed pain medication within the last month prior to the baseline survey and consulting for a MSK condition within 6 months from the baseline survey (Figure 8.3.1).

Studies that have been carried out and compared responders and non-responders within the NorStOP database have found some minor differences.A study by Jordan et al. (2008) investigating social risks for disabling pain in older people found that at baseline, males and the younger aged were less likely to respond but responders at 3 year follow-up were younger than those who were not followed up with a mean difference in age of 4.7 years. In a study by Lacey et al. (2013) which compared consenters and non-consenters to medical record review, slight variations were noted. Compared to those who responded but did not consent to record review, consenters were slightly younger (mean 66.2 years vs. 67.4), had a lower proportion who were female (54% vs. 62%) and reported more joint pain (79% vs. 70%). In a study by Hill et al. (2007) investigating illness perceptions associated with health and behavioural outcomes in people with musculoskeletal hand problems, the study population were on average younger (mean age 65.4 years, S.D. 9.6) than those who reported hand problems but refused further contact (mean age 70.1 years, S.D. 10.6).

### 8.3.2 Initial analgesia prescribing by baseline characteristics

Out of the 1610 patients, 845 (52%) were prescribed analgesia within 14 days of their MSK consultation date. Of all patients prescribed analgesia, basic analgesia were prescribed to 52 (6%) patients, weak analgesia to 492 (58%) patients, moderate analgesia to 27 (3%) patients, strong analgesia to 138 (16%) patients and NSAIDs to 136 (16%) patients. Table 8.3.1 shows the prevalence of analgesia prescription by baseline characteristics.

Table 8.3.1: Baseline socio-demographic, clinical and patient-reported characteristics of patients prescribed analgesia

| Variable | Total | No medication (%)[a] | All analgesia (%)[a] | Basic analgesia (%)[b] | Weak analgesia (%)[b] | Moderate analgesia (%)[b] | Strong analgesia (%)[b] | NSAIDs (%)[b] |
|---|---|---|---|---|---|---|---|---|
| **Total** | 1610 | 765(48) | 845(52) | 52(6) | 492(58) | 27(3) | 138(16) | 136(16) |
| **Age** | | | | | | | | |
| 50-59 | 532 | 293(55) | 239(45) | 19(8) | 112(47) | 3(1) | 55(23) | 50(21) |
| 60-69 | 507 | 241(48) | 266(52) | 14(5) | 165(62) | 10(4) | 35(13) | 42(16) |
| 70-79 | 383 | 160(42) | 223(58) | 11(5) | 141(63) | 12(8) | 32(14) | 27(12) |
| 80+ | 188 | 71(38) | 117(62) | 8(11) | 74(63) | 2(3) | 16(14) | 17(15) |
| **Gender** | | | | | | | | |
| Males | 701 | 336(48) | 365(52) | 26(7) | 201(55) | 8(2) | 61(17) | 69(19) |
| Females | 909 | 429(47) | 480(53) | 26(5) | 291(61) | 19(4) | 77(16) | 67(14) |
| **Married** | | | | | | | | |
| No | 467 | 195(42) | 272(58) | 12(4) | 170(63) | 10(4) | 35(13) | 45(17) |
| Yes | 1443 | 570(60) | 573(40) | 40(7) | 322(56) | 17(3) | 103(18) | 91(16) |
| **Deprivation** | | | | | | | | |
| Most | 713 | 328(46) | 385(54) | 25(6) | 238(62) | 19(5) | 51(13) | 52(13) |
| Medium | 713 | 328(46) | 385(54) | 25(6) | 207(54) | 6(2) | 73(19) | 74(19) |
| Least | 184 | 109(59) | 75(41) | 2(3) | 47(63) | 2(3) | 14(19) | 10(13) |
| **Region of Pain** | | | | | | | | |
| Back | 252 | 79(31) | 173(69) | 6(3) | 97(56) | 9(5) | 37(21) | 24(14) |
| Knee | 192 | 88(46) | 104(54) | 12(12) | 53(51) | 2(2) | 16(15) | 21(20) |
| Hip | 354 | 199(56) | 155(44) | 9(6) | 98(63) | 3(2) | 23(15) | 22(15) |
| Foot/ Ankle | 204 | 106(52) | 98(48) | 6(6) | 59(60) | 4(4) | 9(9) | 20(20) |
| Hand/limb | 186 | 89(48) | 97(52) | 9(9) | 53(55) | 3(3) | 9(9) | 23(24) |
| Shoulder | 199 | 97(49) | 102(51) | 5(5) | 58(57) | 3(3) | 24(24) | 12(12) |
| Neck | 223 | 107(48) | 116(52) | 5(4) | 74(64) | 3(3) | 20(19) | 14(13) |

| Variable | Total | No medication (%)[a] | All analgesia (%)[a] | Basic analgesia (%)[b] | Weak analgesia (%)[b] | Moderate analgesia (%)[b] | Strong analgesia (%)[b] | NSAIDs (%)[b] |
|---|---|---|---|---|---|---|---|---|
| **Co-morbidity** | | | | | | | | |
| Other /none | 916 | 446(49) | 469(51) | 29(6) | 254(54) | 14(3) | 84(18) | 88(19) |
| Select-conditions | 695 | 319(46) | 376(54) | 23(6) | 238(63) | 13(3) | 54(14) | 48(13) |
| **Widespread pain** | | | | | | | | |
| No | 1328 | 643(48) | 685(52) | 41(6) | 396(58) | 21(3) | 110(16) | 117(17) |
| Yes | 282 | 122(43) | 160(57) | 11(7) | 96(60) | 6(4) | 28(18) | 19(12) |
| **Previous musculoskeletal consultation** | | | | | | | | |
| No | 31 | 19(61) | 12(39) | 0(0) | 4(33) | 0(0) | 5(42) | 3 (25) |
| Yes | 1579 | 746(47) | 833(53) | 52(6) | 488(59) | 27(3) | 133(16) | 133(16) |
| **Previous prescribed analgesia** | | | | | | | | |
| No | 717 | 464(65) | 253(35) | 25(10) | 124(49) | 10(4) | 37(15) | 57(23) |
| Yes | 893 | 301(34) | 592(66) | 27(5) | 368(62) | 17(3) | 101(17) | 79(13) |
| **OTC medication** | | | | | | | | |
| None | 252 | 153(61) | 99(39) | 8(8) | 49(49) | 6(6) | 13(13) | 23(23) |
| Painkillers/creams | 733 | 733(44) | 408(56) | 19(5) | 244(60) | 11(3) | 82(20) | 52(13) |
| Glucosamine/other | 625 | 287(38) | 338(62) | 25(10) | 199(59) | 10(3) | 43(13) | 61(18) |
| **BMI** | | | | | | | | |
| Normal /underweight | 579 | 273(47) | 306(53) | 21(7) | 169(55) | 9(3) | 58(19) | 49(16) |
| Overweight /obese | 966 | 465(48) | 501(52) | 29(6) | 298(59) | 18(4) | 76(15) | 80(16) |
| Unknown | 65 | 27(42) | 38(58) | 2(5) | 25(66) | 0(0) | 4(11) | 7(18) |
| **Depression** | | | | | | | | |
| No | 1310 | 653(50) | 657(50) | 40(7) | 377(57) | 17(3) | 107(16) | 116(18) |
| Yes | 300 | 112(37) | 188(63) | 12(6) | 115(61) | 10(5) | 31(16) | 20(11) |

| Variable | Total | No medication (%)[a] | All analgesia (%)[a] | Basic analgesia (%)[b] | Weak analgesia (%)[b] | Moderate analgesia (%)[b] | Strong analgesia (%)[b] | NSAIDs (%)[b] |
|---|---|---|---|---|---|---|---|---|
| **Pain interference** | | | | | | | | |
| None | 748 | 407(54) | 341(46) | 30(9) | 181(53) | 11(3) | 51(15) | 68(20) |
| Yes | 862 | 358(42) | 504(58) | 22(4) | 311(62) | 16(3) | 87(17) | 68(13) |
| **GP Access** | | | | | | | | |
| Yes | 1446 | 680(47) | 766(53) | 48(6) | 441(58) | 22(3) | 129(17) | 126(16) |
| No | 164 | 70(59) | 67(41) | 4(6) | 43(64) | 3(4) | 9(13) | 8(12) |
| **Alcohol** | | | | | | | | |
| Mostly/sometimes | 916 | 313(58) | 381(42) | 18(5 | 242(64) | 17(4) | 50(13) | 54(14) |
| Never/rarely | 694 | 452(33) | 464(67) | 34(7) | 250(54) | 10(2) | 88(19) | 82(18) |
| **Smoke** | | | | | | | | |
| Never smoked | 663 | 341(51) | 322(49) | 18(6) | 192(60) | 10(3) | 49(15) | 53(16) |
| Previously | 733 | 328(45) | 405(55) | 26(6) | 234(58) | 13(3) | 66(16) | 66(16) |
| Currently | 214 | 96(45) | 118(55) | 8(7) | 66(56) | 4(3) | 17(14) | 17(14) |

**a = x/Total, b = x/all analgesia**

The mean age of the 1610 patients fitting the inclusion criteria was 65 years with a standard deviation of 10.2, with 909 (56%) of the participants female. The entire cohort was used in the analysis of switches to any analgesia accounting for multiple switches. The age-group 50-59 constitutes the highest category, 33%, while the 80 and over had the least, 12%, with 60-69 and 70-79 accounting for 31% and 24% respectively (Table 8.3.2).

Altogether, 1309 (81%) of the cohort fitting the inclusion criteria were prescribed no medication, basic analgesia or weak analgesia at their first consultation after baseline survey. These are the participants used in analysing switching to stronger analgesia. Throughout the 3 year follow-up period, 407 (31%) switched to moderate or strong analgesia (Table 8.3.2).

The outcome variables (switching or not and time to switching) were complete with no missing values. This can be attributed to the inclusion criteria which required participants to have responded to both the baseline and 3 year follow-up surveys. The prescription dates used to calculate time to switching were derived from the computerised prescriptions database which is a complete dataset. This means that participants either had a date of switching event or those who did not were censored at 3 year follow-up date.

Some of the baseline variables had missing values, because the survey participants intentionally or erroneously left some of the survey questions unanswered. The variables age, gender, deprivation, co-morbidity, pain location, previous MSK consultation and previous analgesia prescription which were derived from the medical record data were complete except, as previously reported for the CiPCA analysis, for pain location (see Chapter 4). The survey data derived variables (patient-reported) of marital status, over the counter medication (OTC), GP access and widespread pain were also complete.

21 (2%) participants in the cohort of 1309 had missing data in at least one of the remaining self-reported variables: pain interference, depression, physical function, body mass index (BMI), alcohol consumption, and smoking history. Those with missing data were on average slightly older, 67 years versus 65 years with a standard deviation of 13.5. There were more females 54% than males compared to 56% in the entire cohort. All participants with missing self-reported data on any variable were excluded in the final models but sensitivity analyses were done to assess the effect of excluding participants with missing data.

When both models were compared to the final model, both adjusted and unadjusted parameter estimates differed from those of the final model by less than 0.05 and the -2logL were not statistically different from that of the final model.

Table 8.3.2: Baseline Socio-demographic, clinical and patient specified characteristics of patients switching medication

| | Any medication switch | | | Strong analgesia switch |
|---|---|---|---|---|
| **Variable** | **Total** | **No (%)** | **Yes (%)** | **Yes (%)** |
| **Total** | 1610 | 889(55) [a] | 721(45) [a] | 407(31) [b] |
| **Age** | | | | |
| 50-59 | 532(33) | 331(62) | 201(38) | 120(23) |
| 60-69 | 507(31) | 283(56) | 224(44) | 136(27) |
| 70-79 | 383(24) | 190(50) | 193(50) | 110(29) |
| 80+ | 188(12) | 85(45) | 103(55) | 41(22) |
| **Gender** | | | | |
| Males | 701(44) | 412(59) | 289(41) | 150(21) |
| Females | 909(56) | 477(52) | 432(48) | 257(28) |
| **Married** | | | | |
| No | 467(29) | 224(48) | 243(52) | 137(29) |
| Yes | 1443(71) | 665(58) | 478(42) | 270(19) |
| **Deprivation** | | | | |
| Most | 713(44) | 386(54) | 327(46) | 189(27) |
| Medium | 713(44) | 384(54) | 329(46) | 180(25) |
| Least | 184(12) | 119(65) | 65(35) | 38(20) |
| **Region of Pain** | | | | |
| Back | 252(16) | 121(48) | 131(52) | 63(10) |
| Knee | 192(12) | 114(59) | 78(41) | 32(16) |
| Hip | 354(22) | 204(58) | 150(42) | 90(25) |
| Foot/ Ankle | 204(13) | 116(57) | 88(43) | 50(25) |
| Hand/limb | 186(11) | 104(56) | 82(44) | 45(24) |
| Shoulder | 199(12) | 103(52) | 96(48) | 58(29) |
| Neck | 223(14) | 127(57) | 96(43) | 69(31) |
| **Co-morbidity** | | | | |
| Other /none | 916(57) | 532(58) | 383(42) | 201(22) |
| Select-conditions | 695(43) | 357(51) | 338(49) | 206(30) |
| **Widespread pain** | | | | |
| No | 1328(82) | 746(56) | 582(44) | 321(24) |
| Yes | 282(18) | 143(51) | 139(49) | 86(30) |
| **Consultation history** | | | | |
| No | 31(2) | 26(84) | 5(16) | 5(16) |
| Yes | 1579(98) | 863(55) | 716(45) | 402(25) |
| **Medication history** | | | | |
| No | 717(45) | 548(76) | 169(24) | 91(13) |
| Yes | 893(55) | 341(38) | 552(62) | 316(35) |
| **Initial analgesia** | | | | |
| None | 765(47) | 521(77) | 174(23) | 177(23) |
| Basic analgesia | 52(3) | 52(100) | 0 | 0 |
| Weak analgesia | 492(31) | 107(22) | 385(78) | 230(47) |
| Moderate analgesia | 27(2) | 20(74) | 7(26) | - |
| NSAIDs | 136(8) | 80(59) | 56(41) | - |
| Strong analgesia | 138(9) | 39(28) | 99(72) | - |

| | Any medication switch | | | Strong analgesia switch |
|---|---|---|---|---|
| **Variable** | **Total** | **No (%)[a]** | **Yes (%)[a]** | **Yes (%)[b]** |
| **OTC medication** | | | | |
| None | 252(16) | 177(70) | 75(30) | 44(17) |
| Painkillers/creams | 733(45) | 369(50) | 364(50) | 217(30) |
| Glucosamine/other | 625(38) | 343(54) | 282(45) | 146(23) |
| **BMI** | | | | |
| Normal /underweight | 579(36) | 326(56) | 253(44) | 130(22) |
| Overweight /obese | 966(60) | 532(55) | 434(45) | 259(27) |
| Unknown | 65(4) | 31(48) | 34(52) | 18(28) |
| **Depression** | | | | |
| No | 1310(81) | 754(58) | 556(42) | 307(23) |
| Yes | 300(19) | 135(45) | 165(55) | 100(33) |
| **Pain interference** | | | | |
| None | 748(46) | 498(67) | 250(33) | 139(19) |
| Yes | 862(54) | 391(45) | 471(55) | 268(31) |
| **GP Access** | | | | |
| Yes | 1446(91) | 797(55) | 649(45) | 361(25) |
| No | 137(9) | 76(55) | 61(45) | 41(30) |
| **Alcohol** | | | | |
| Mostly/sometimes | 916(57) | 533(58) | 383(42) | 215(23) |
| Never/rarely | 694(43) | 356(51) | 338(49) | 192(28) |
| **Smoke** | | | | |
| Never smoked | 663(41) | 387(58) | 276(42) | 146(22) |
| Previously | 733(46) | 388(53) | 345(47) | 202(28) |
| Currently | 214(15) | 114(53) | 100(47) | 59(28) |

**a = n/1610, b= n/1309, - =excluded**

The mean time to a moderate or strong opioid switch from baseline for those initially prescribed no medication, basic analgesia, or weak analgesia was 715 days (SD 586.62), median 548 days, and IQR (223, 1092) days in those who switched.

The survival estimates are illustrated in Figure 8.3.1. The Kaplan-Meier curve suggests rates of switching to moderate or strong analgesia from low potency (no medication, basic and weak analgesia) was evenly spread over time. Figure 8.3.2 suggests that there was variation in the rates of switching by initial analgesia prescribed. The Kaplan-Meier curves showing switching rates by individual variables are included in Appendix B.

Figure 8.3.1: Overall survival estimates for first switch from no medication, basic analgesia and weak analgesia to moderate or strong analgesia

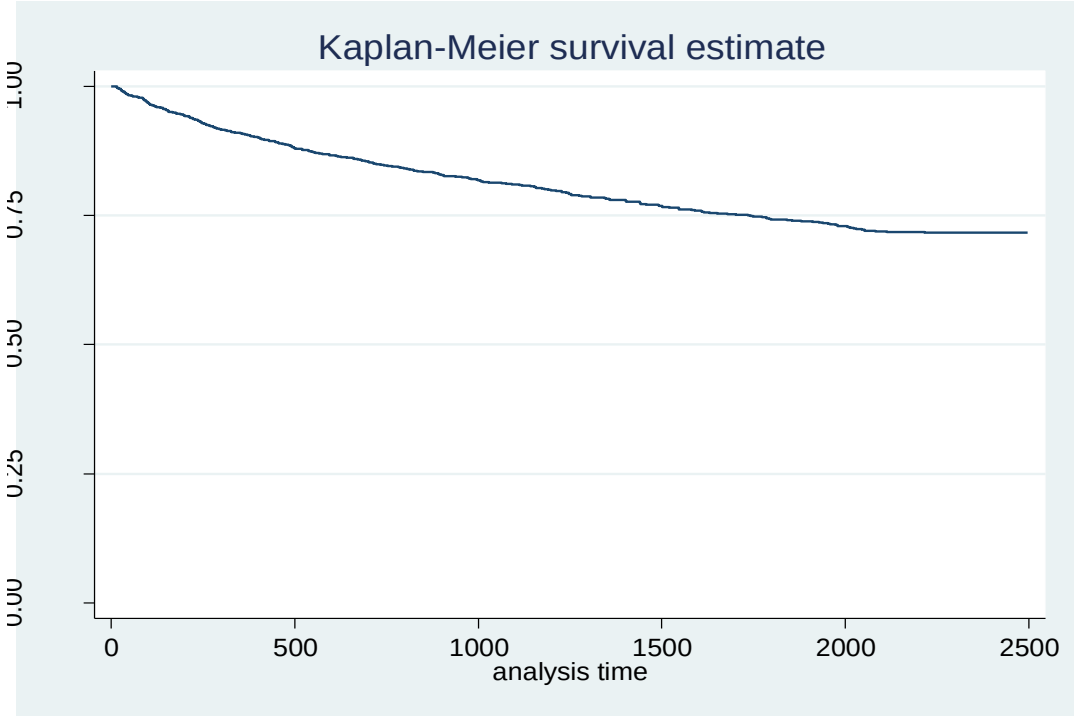
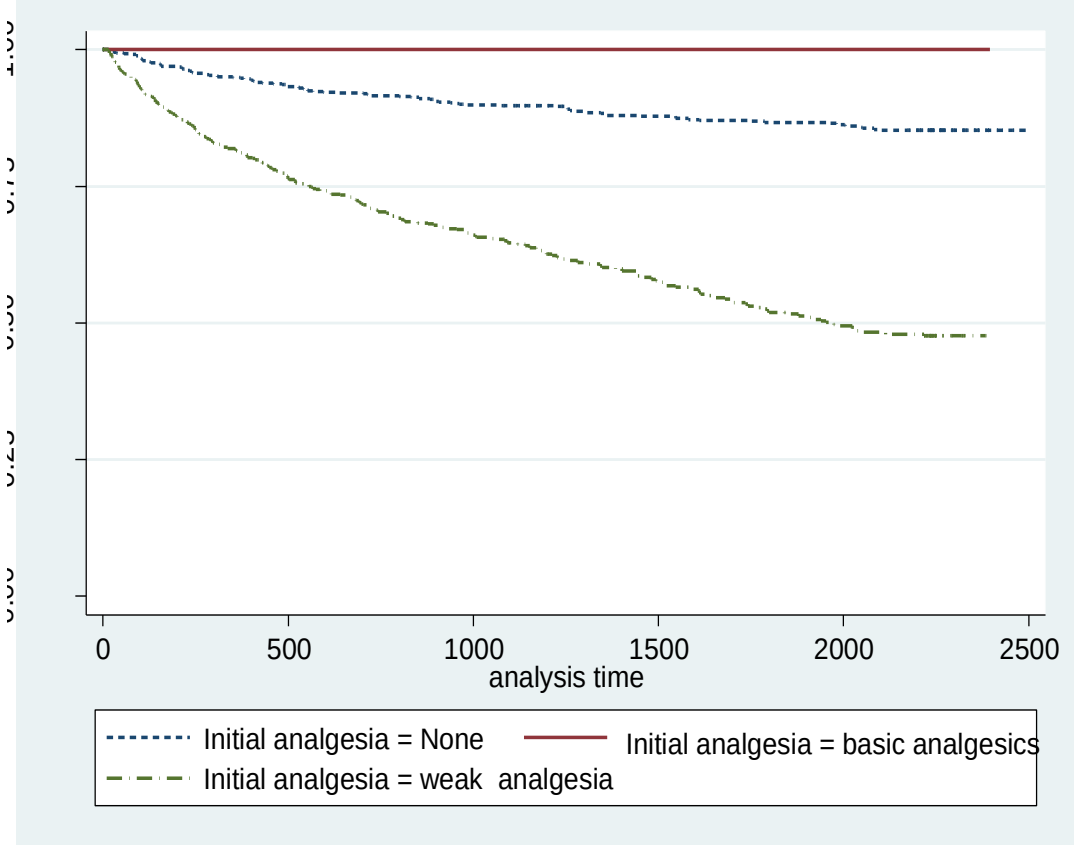



Figure 8.3.2: Survival estimate curves by analgesia prescribed on initial consultation



### 8.3.3 Stronger analgesia switch models

Two models adjusting for baseline variables were fitted to evaluate their association with switching to higher potency analgesia (moderate opioids or strong opioids) for those initially prescribed no medication, basic analgesia or weak analgesia. The first models consisted of only socio-demographic, clinical variables from the medical records; the second, extensions of the first, also included patient-reported variables (Table 8.3.3). The variables statistically significant at 5% level are highlighted in bold in Table 8.3.3.

**Socio-demographic, clinical and patient-reported variables associated with switching to stronger analgesia**

In the model only including clinical and socio-demographic variables identified from the medical records, factors associated with switching to stronger opioids were younger age, for example, for those aged 80 and over compared to those aged 50-59 (HR 0.63; [95% CI [0.42, 0.96]), females (HR 1.30 [1.04, 1.64]), comorbidity (at least one of diabetes, chronic obstructive pulmonary disease (COPD), depression, cardiovascular, chronic kidney, gastro-intestinal and neoplasm), (HR 1.66 [1.32, 2.08]) and having a previously prescribed analgesia (HR 2.62 [1.96, 3.51]). Those initially prescribed a weak opioid were more likely to switch to stronger analgesia (HR 3.47 [2.65, 4.55]) compared to those on no initial analgesia, whilst more MSK consultations over time (HR 0.99 [0.98, 0.99]) and not having a prior NSAID prescribed were related to being less likely to switch, (HR 0.59 [0.45, 0.79]). The Weibull shape parameter (0.96 [0.87, 1.06]) suggests a probable constant hazard function over time.

Age, previous prescribed analgesia and number of MSK consultations were also identified in the analysis of incident MSK consulters in CiPCA in Chapter 7. In Chapter 7, the age group 75 and over was associated with increased risk of switching to opioids compared to those aged 30-44, in contrast with age 80 and over being associated with reduced risk compared to those aged 50-59 seen here. Both medication history and being initially

prescribed weak analgesia were associated with increased risk in the analysis of incident MSK consulters in Chapter 7, while an increased number of MSK consultations were associated with a slightly reduced risk as in this analysis. Co-morbidity and prescribed NSAID were not statistically significant in Chapter 7.

There was no change in the strength of association of socio-demographic and clinical variables with switching to stronger analgesia when the patient-reported variables were added to the model (Table 8.3.3).

The patient-reported variables associated with switching to stronger analgesia were being overweight/obese (HR 1.37 [1.05, 1.78]) compared to normal weight and previously been a smoker (HR 1.70 [1.30, 2.21]) compared to never smoked. A higher (better) baseline physical function score was associated with a reduced likelihood of switching hazard ratio 0.99[0.98, 0.99] per unit score. Unadjusted association of pain interference with switching disappeared in the final adjusted model.

The Weibull shape parameter (0.94 [0.85, 1.03]) suggests the possibility of a constant hazard rate over time. Comparison of the -2logL suggest that the model with added patient specific variables is a better fit to the data.

Table 8.3.3: Models of baseline socio-demographic, clinical and patient-reported variables associated with time to switching to stronger analgesics and to NSAIDs

| | Weibull models without and with patient specified variables Hazard Ratio [95% CI] | | |
|---|---|---|---|
| **Variable** | **Stronger analgesia switch** | **Stronger analgesia switch [a]** | **Stronger analgesia switch [b]** |
| | Unadjusted | Adjusted | Adjusted |
| **Age** | | | |
| 50-59 | 1.00 | 1.00 | 1.00 |
| 60-69 | 1.23[0.96, 1.37] | 0.90[0.68, 1.20] | 0.94[0.69, 1.28] |
| 70-79 | 1.41[1.01, 1.83] | 0.96[0.71, 1.32] | 0.94[0.66, 1.33] |
| 80+ | 1.16[0.81, 1.66] | **0.63[0.42, 0.96]** | **0.58[0.35, 0.95]** |
| **Gender** | | | |
| Males | 1.00 | 1.00 | 1.00 |
| Females | 1.38[1.13, 1.69] | **1.30[1.04, 1.64]** | **1.51[1.16, 1.96]** |
| **Previous musculoskeletal consultation** | | | |
| No | 1.00 | 1.00 | 1.00 |
| Yes | 1.70[0.70, 4.12] | 2.92[0.70, 1.28] | 1.75[0.42, 1.31] |
| **Previous prescribed analgesia** | | | |
| No | 1.00 | 1.00 | 1.00 |
| Yes | 3.38[3.68, 4.27] | **2.62[1.96, 3.51]** | **2.60[190, 3.55]** |
| **Deprivation** | | | |
| Most | 1.00 | 1.00 | 1.00 |
| Medium | 0.92[0.75, 1.12] | 1.05[0.83, 1.32] | 1.09, 0.85, 1.39] |
| Least | 0.69[0.49, 0.98] | 0.82[0.55, 1.21] | 0.87[0.57, 1.33] |
| **Region of Pain** | | | |
| Back | 1.00 | 1.00 | 1.00 |
| Knee | 0.66[0.43, 1.02] | 0.73[0.45, 1.17] | 0.81[0.49, 1.35] |
| Hip | 10.5[0.76, 1.45] | 1.25[0.87, 1.81] | 1.42[0.94, 2.15] |
| Foot/ Ankle | 0.98[0.68, 1.43] | 1.07[0.70, 1.63] | 1.08[0.67, 1.74] |
| Hand/limb | 0.96[0.65, 1.41] | 1.18[0.76, 1.83] | 1.40[0.87, 2.24] |
| Shoulder | 1.24[0.86, 1.77] | 1.09[0.72, 1.66] | 1.27[0.81, 2.01] |
| Neck | 1.27[.090, 1.79] | 1.45[0.98, 2.13] | 1.68[1.10, 2.56] |
| **Co-morbidity** | | | |
| Other /none | 1.00 | 1.00 | 1.00 |
| Select-conditions | 1.46[1.20, 1.78] | **1.66[1.32, 2.08]** | **1.57[1.24, 2.00]** |
| **Initial Analgesic** | | | |
| None | 1.00 | 1.00 | 1.00 |
| Basic | 0 | 0 | 0 |
| Weak opioids | 4.52[3.58, 5.71] | **3.47[2.65, 4.55]** | **3.06[2.29, 4.09]** |
| **NSAID** | | | |
| No | 1.00 | 1.00 | 1.00 |
| Yes | 0.62[0.49, 0.78] | **0.59[0.45, 0.79]** | **0.67[0.49, 0.90]** |
| **No. of MSK consultations** | 0.99[0.98, 1.00] | **0.99[0.98, 0.99]** | **0.99[0.99, 0.99]** |
| **No. of Prescriptions** | 1.00[0.99, 1.01] | 0.99[0.99, 1.01] | 0.99[0.98, 1.01] |

| Variable | Weibull models without and with patient specified variables Hazard Ratio [95% CI] | | |
|---|---|---|---|
| | **Stronger analgesia switch** | **Stronger analgesia switch [a]** | **Stronger analgesia switch [b]** |
| | Unadjusted | Adjusted | Adjusted |
| **Patient-reported** | | | |
| **Married** | | | |
| No | 1.00 | - | 1.00 |
| Yes | 0.71[0.58, 0.88] | **-** | 0.91[0.69, 1.20] |
| **Widespread pain** | | | |
| No | 1.00 | - | 1.00 |
| Yes | 1.26[0.69, 1.60] | - | 0.81[0.59, 1.12] |
| **OTC medication** | | | |
| None | 1.00 | - | 1.00 |
| Painkillers | 1.02[0.62, 1.82] | **-** | 0.85[0.56, 1.27] |
| Glucosamine | 1.03[0.83, 1.84] | **-** | 0.70[0.46, 1.08] |
| **BMI** | | | |
| Normal | 1.00 | - | 1.00 |
| Overweight /obese | 1.17[0.95, 1.45] | **-** | **1.37[1.05, 1.78]** |
| Unknown | 1.38[0.84, 2.27] | - | 1.25[0.68, 2.28] |
| **Depression** | | | |
| No | 1.00 | - | 1.00 |
| Yes | 1.64[1.31, 2.06] | - | 1.09[0.81, 1.46] |
| **Pain interference** | | | |
| None | 1.00 | - | 1.00 |
| Yes | 1.87[1.52, 2.30] | - | 1.06[0.77, 1.45] |
| **GP Access** | | | |
| Yes | 1.00 | - | 1.00 |
| No | 1.25[0.90, 1.72] | - | 1.01[0.69, 1.46] |
| **Alcohol** | | | |
| Mostly | 1.00 | - | 1.00 |
| Never | 0.78[0.64,1.15] | - | 1.16[0.90, 1.49] |
| **Smoke** | | | |
| Never smoked | 1.00 | - | 1.00 |
| Previously | 1.33[1.08, 1.65] | - | **1.70[1.30, 2.21]** |
| Currently | 1.36[1.00, 1.84] | **-** | 1.27[0.87, 1.86] |
| **Physical function** | 0.98[0.98, 0.99] | - | **0.99[0.98, 0.99]** |
| **Weibull shape parameter** | - | 0.94[0.85, 1.03] | 0.96[0.87, 1.06] |
| **-2logL** | **-** | 1886 | 1700 |

**a** Weibull model with patient-reported variables excluded**, b** Weibull model with patient reported factors included

**Unadjusted model =** Individual variable in the model, **Adjusted model =** All variables included simultaneously

### 8.3.4 Any switch models

Two models were fitted to evaluate factors associated with any analgesia switching taking into account time to multiple switches from analgesia prescribed on first consultation. The first model consisted of only socio-demographic and clinical variables recorded in the medical records; the second, an extension of the first, also included patient-reported variables (Table 8.3.4). The variables statistically significant at 5% level are highlighted in bold (Table 8.3.4).The mean number of switches was 4, with a median of 3 and IQR of 5. The maximum number of switches was 47.

**Socio-demographic, clinical and patient-reported variables model**

The first model showed that being aged 70-79, (HR 1.17 [1.06, 1.28]) compared to 50-59, females (HR 1.23 [1.15, 1.32]), having comorbidity (HR 1.26 [1.18, 1.35]) and previous analgesia prescription prior to baseline survey (HR 1.83 [1.87, 2.01]) were associated with increased risk of switching when multiple-event analgesia switches are accounted for. When compared to no initial analgesia, those prescribed initially weak analgesia (HR 1.48 [1.35, 1.63]) and strong analgesia (HR 1.45 [1.28, 1.64]) had an increased risk of switching, while initial prescription of moderate analgesia (HR 0.25 [0.14, 0.43]) and NSAIDs (HR 0.61 [0.51, 0.72]) were associated with reduced risk, as were having a higher number of MSK consultations (HR 0.99 [0.98, 0.99]).

The variables age, gender, medication history, initial analgesia and number of consultations were also identified in the analysis of incident MSK consulters in CiPCA in Chapter 6 as being associated with switching when multiple event switches are accounted for. In Chapter 6, age 75 and over was associated with increased risk compared to age 30-44, similar to the increased risk for those aged 70-79 compared to 50-59 found here. Co-morbidity was not statistically significant in Chapter 6 but significant in this analysis, while number of prescriptions was associated with increased risk and medium and least

deprivation were associated with reduced risk in the CiPCA analysis, but both were non-significant in this analysis.

When adding patient-reported variables to the model, the patient-reported variables associated with increased risk were using over the counter glucosamine/natural medication (HR 1.14 [1.00, 1.32]) compared to no over the counter medication, having interfering pain at baseline (HR 1.13 [1.03, 1.24]), reporting inadequate GP access (HR 1.15 [1.03, 1.30]), and previous smoking (HR 1.70 [1.30, 2.21]) compared to never smoked. Having widespread pain (HR 0.85 [0.77, 0.93]) and higher (better) physical function score, (HR 0.99[0.98, 0.99]) were associated with a reduced risk.

The Weibull shape parameters (0.42 [0.40, 0.43]) for the socio-demographic and clinical variable model, and (0.42 [0.41, 0.43]) for the socio-demographic, clinical and patient-reported variables suggest that the statistically significant covariates have a decreasing effect on the hazard function over time, that is over time, the variables become less associated with switching as multiple-event switches decline with time. The -2logL suggest that the model with patient specific variables is a better fit to the data.

Table 8.3.4: Models of baseline socio-demographic, clinical and patient specified characteristics associated with multiple-events switching to any analgesia

| Weibull models without and with patient specified variables<br>Hazard Ratio [95% CI] | | | |
|---|---|---|---|
| **Variable** | | **Multi-switch [a]** | **Multi-switch [b]** |
| | Unadjusted | Adjusted | Adjusted |
| **Age** | | | |
| 50-59 | 1.00 | 1.00 | 1.00 |
| 60-69 | 1.27[1.17, 1.39] | 1.07[0.98, 1.06] | 1.05[0.96, 1.53] |
| 70-79 | 1.48[1.36, 1.62] | **1.17[1.06, 1.28]** | 1.09[0.99, 1.21] |
| 80+ | 0.98[0.79, 1.01] | 0.91[0.81, 1.03] | **0.83[0.72, 0.96]** |
| **Gender** | | | |
| Males | 1.00 | 1.00 | 1.00 |
| Females | 1.31[1.22, 1.40] | **1.23[1.15, 1.32]** | **1.25[1.15, 1.35]** |
| **Previous musculoskeletal consultation** | | | |
| No | 1.00 | 1.00 | 1.00 |
| Yes | 1.98[1.43, 2.74] | 1.36[0.98, 1.91] | **2.79[1.64, 4.77]** |
| **Previous analgesia prescription** | | | |
| No | 1.00 | 1.00 | 1.00 |
| Yes | 3.55[3.27, 3.86] | **1.83[1.87, 2.01]** | **1.67[1.53, 1.85]** |
| **Deprivation** | | | |
| Most | 1.00 | 1.00 | 1.00 |
| Medium | 1.01[0.94, 1.09] | 1.06[0.99, 1.13] | **1.10[1.02, 1.19]** |
| Least | 0.78[0.69, 0.88] | 0.95[0.84, 1.07] | 0.97[0.85, 1.10] |
| **Region of Pain** | | | |
| Back | 1.00 | 1.00 | 1.00 |
| Knee | 0.97[0.86, 1.11] | 1.09[0.96, 1.23] | 1.05[0.92, 1.21] |
| Hip | 0.92[0.83, 1.12] | 1.05[0.94, 1.18] | 1.11[0.99, 1.25] |
| Foot/ Ankle | 0.90[0.80, 1.02] | 1.01[0.89, 1.15] | 1.00[0.87, 1.15] |
| Hand/limb | 0.93[0.82, 1.05] | 1.08[0.95, 1.23] | 1.14[0.99, 1.30] |
| Shoulder | 1.01[0.89, 1.14] | 1.04[0.92, 1.18] | 1.14[0.99, 1.30] |
| Neck | 1.11[0.98, 1.25] | 1.11[0.99, 1.25] | **1.14[1.01, 1.29]** |
| **1st Analgesia** | | | |
| None | 1.00 | 1.00 | 1.00 |
| Basic | 0 | 0 | 0 |
| Weak analgesia | 3.97[3.67, 4.30] | **1.48[1.35, 1.63]** | **1.42[1.28, 1.56]** |
| Moderate analgesia | 0.47[0.28, 0.81] | **0.25[0.14, 0.43]** | **0.22[0.12, 0.40]** |
| NSAIDs | 1.00[0.86, 1.21] | **0.61[0.51, 0.72]** | **0.65[0.54, 0.78]** |
| Strong analgesia | 3.15[2.81, 3.54] | **1.45[1.28, 1.64]** | **1.43[1.25, 1.62]** |
| **Co-morbidity** | | | |
| Other /none | 1.00 | 1.00 | 1.00 |
| Select-conditions | 1.28[1.20, 1.37] | **1.26[1.18, 1.35]** | **1.20[1.12, 1.29]** |
| **No. of MSK consultations** | 0.98[0.98, 0.99] | **0.99[0.98, 0.99]** | **0.99[0.98, 0.99]** |
| **No. of Prescriptions** | 0.99[0.99, 1.01] | 0.99[0.98, 1.01] | **0.99[0.97, 0.99]** |
| **Weibull models without and with patient specified variables** | | | |

| Hazard Ratio [95% CI] | | | |
|---|---|---|---|
| **Variable** | | **Multi-switch [a]** | **Multi-switch [b]** |
| | Unadjusted | Adjusted | Adjusted |
| **Patient-reported** | | | |
| **Married** | | | |
| No | 1.00 | - | 1.00 |
| Yes | 0.78[0.73, 0.89] | - | 0.97[0.90, 1.06] |
| **Widespread pain** | | | |
| No | 1.00 | - | 1.00 |
| Yes | 0.95[0.71, 0.96] | **-** | **0.85[0.77, 0.93]** |
| **OTC medication** | | | |
| None | 1.00 | - | 1.00 |
| Painkillers | 2.03[1.79, 2.29] | **-** | 1.05[0.92, 1.21] |
| Glucosamine | 2.10[1.86, 2.38] | **-** | **1.14[1.00, 1.32]** |
| **BMI** | | | |
| Normal | 1.00 | - | 1.00 |
| Overweight | 1.18[1.10, 1.26] | **-** | 1.06[0.98, 1.14] |
| Unknown | 1.30[1.10, 1.53] | - | 1.08[0.89, 1.30] |
| **Depression** | | | |
| No | 1.00 | - | 1.00 |
| Yes | 1.47[1.37, 1.59] | - | 1.00[0.92, 1.10] |
| **Pain interference** | | | |
| None | 1.00 | - | 1.00 |
| Yes | 2.00[1.86, 2.14] | - | **1.13[1.03, 1.24]** |
| **GP Access** | | | |
| Yes | 1.00 | - | 1.00 |
| No | 1.17[1.05, 1.31] | **-** | **1.15[1.03, 1.30]** |
| **Alcohol** | | | |
| Mostly | 1.00 | - | 1.00 |
| Never | 0.81[0.76, 1.11] | - | 1.02[0.95, 1.10] |
| **Smoke** | | | |
| Never smoked | 1.00 | - | 1.00 |
| Previously | 1.16[1.08, 1.24] | - | **1.14[1.05, 1.23]** |
| Currently | 0.99[0.89, 1.11] | **-** | 0.98[0.87, 1.10] |
| **Physical function** | 0.99[0.98, 0.99] | - | **0.99[0.98, 0.99]** |
| **Weibull shape parameter** | **-** | **0.42[0.40, 0.43]** | **0.42[0.41, 0.43]** |
| **-2logL** | **-** | 11708 | 10606 |

**a** Weibull model with patient-reported variables excluded**, b** Weibull model with patient reported factors included

**Unadjusted model =** Individual variable in the model, **Adjusted model =** All variables included simultaneously

## 8.4 Discussion

The aim of this analysis was to investigate if factors identified previously to be related to switching in an incident MSK consulting group (Chapters 6 and 7) are also the key factors associated with switching in a prevalent and older aged MSK consulting group, and to determine the importance in the switching process of initial patient-reported factors. The common factors associated with switching between incident and prevalent MSK groups were age, gender, previous prescribed analgesia, initial analgesia (weak and strong analgesia) prescribed and number of MSK consultations. They were associated with switching to stronger analgesia as well as any switch. In contrast to the incident group, co-morbidity was a significant factor in this older aged prevalent group, while the level of deprivation and the number of prescribed analgesia were significant only in the incident group.

The significant patient-reported factors in the presence of socio-demographic and clinical factors were using over the counter medication, BMI (obesity or overweight), pain interference, inadequate access to GP, smoking history and level of physical function. Smoking history was associated with increased risk, while better physical function was also associated with reduced risk of switching to stronger analgesia, or having any switch. Inadequate access to GP increased the risk of switching taking into account multiple-switches, while obesity or overweight increased the risk of stronger opioid switch.

The analysis in this population of prevalent MSK consulters aged 50+ identified common factors, but also some differences to the incident population (Chapter 6 and 7). The variations might be partially explained by that in the CiPCA analysis, only new episode MSK consulters aged 15+ were considered, while the analysis in this chapter included consulters aged 50+ who may have on-going or new MSK episodes and may be well into an episode of care. The original intention was to investigate new consulters but there were inadequate number of cases in this population. Table 8.3.1 summarises variables

associated with switching in this analysis (prevalent) as well as those in the incident cohort analysis.

This analysis also brings out some variables as associated with the risk of switching analgesia that were not in the previous analysis, for example comorbidity associated with an increased risk of switching analgesia and initially prescribed moderate analgesia associated with reduced risk of switching analgesia. While the datasets are different by age and other baseline factors, it is not entirely clear why this is happening, but can only be postulated where possible.

The existence of select comorbidities makes the management of chronic pain a difficult proposition, particularly in the older aged. For example in the presence of cardiovascular and kidney diseases, clinicians have to be cautious and assess absolute risks with medications such as NSAIDs (Adam et al., 2011) and stronger analgesia use (Boulanger et al., 2011). It is possible that in attempting to alleviate pain whilst avoiding causing adverse effects clinicians try to balance the associated risks of medication and the need to control the impact of pain, but the level of pain the patient is experiencing may dictate the use of and switching to stronger analgesia.

The prescription of opioids does not necessarily result in improved outcomes (Ashworth et al., 2013), which implies that switching to stronger analgesia may not necessarily bring about statistically significant improvement on the patient's condition even if the switch to stronger opioids is a better alternative to the previous analgesia. The initial prescription of moderate analgesia was associated with a very low risk of switching in this older-aged population, if a patient's condition is not improving when initially prescribed moderate analgesia, there is not many choices to switch to.

Table 8.4.1: Summary of factors associated with switching analgesia

| | **Prevalent cohort Switching (NorSTOP)** | | **Incident cohort (CiPCA) Switching** | |
|---|---|---|---|---|
| **Variable** | To strong analgesia | Multiple-event Switching | To strong analgesia | Multiple-event Switching |
| **Age** | | | | |
| 50-59 | - | - | - | - |
| 60-69 | No | No | Yes>[a] | Yes>[a] |
| 70-79 | No | No | Yes>[a] | Yes>[a] |
| 80+ | <Yes | <Yes | Yes>[a] | Yes>[a] |
| **Gender** | | | | |
| Males | - | - | - | - |
| Females | Yes> | Yes> | Yes> | Yes> |
| **Previous prescribed analgesia** | | | | |
| No | - | - | - | - |
| Yes | Yes> | No | Yes> | Yes> |
| **Deprivation** | | | | |
| Most | - | - | - | - |
| Medium | No | Yes> | <Yes | <Yes |
| Least | No | No | No | <Yes |
| **Region of Pain** | | | | |
| Back | - | - | - | - |
| Knee | No | No | No | No |
| Hip | No | No | No | Yes> |
| Foot/ Ankle | No | No | No | No |
| Hand/limb | No | No | No | <Yes |
| Shoulder | No | No | No | <Yes |
| Neck | No | Yes> | No | No |
| **Co-morbidity** | | | | |
| Other /none | - | - | - | - |
| Select-conditions | Yes> | Yes> | No | No |
| **Initial analgesia** | | | | |
| No medication | - | - | - | <Yes |
| Basic analgesia | - | - | - | - |
| Weak analgesia | Yes> | Yes> | Yes> | Yes> |
| Moderate analgesia | - | No | - | No |
| Strong analgesia | - | Yes> | - | Yes> |
| **No. of MSK consultations** | <Yes | <Yes | <Yes | <Yes |
| **No. of Prescriptions** | No | <Yes | Yes> | Yes> |

| | Prevalent cohort Switching (NorSTOP) | | Incident cohort (CiPCA) Switching | |
|---|---|---|---|---|
| **Variable** | To strong analgesia | Multiple-event Switching | To strong analgesia | Multiple-event Switching |
| **Patient-reported OTC medication** | | | | |
| None | - | - | - | - |
| Painkillers | No | No | NM | NM |
| Glucosamine | No | Yes> | NM | NM |
| **Pain interference** | | | | |
| None | - | - | - | - |
| Yes | No | Yes> | NM | NM |
| **BMI** | | | | |
| Normal | - | - | - | - |
| Overweight /obese | Yes> | No | NM | NM |
| **Widespread pain** | | | | |
| No | - | - | - | - |
| Yes | No | <Yes | NM | NM |
| **GP Access** | | | | |
| Yes | - | - | - | - |
| No | Yes> | Yes> | NM | NM |
| **Smoke** | | | | |
| Never smoked | - | - | - | - |
| Previously | Yes> | Yes> | NM | NM |
| Currently | No | No | NM | NM |
| **Better Physical function** | <Yes | <Yes | NM | NM |

No= non-significant, <Yes=decreasing risk of switching, Yes>=increasing risk of switching, Reference category= -, Not part of model =NM, a = CiPCA age categories different to NorSTOP

The significance of patient-reported factors which resulted in an improved model fit reinforces the fact that patient input may be essential in GPs considerations prior to deciding whether to prescribe analgesia and what potency level, and can influence the clinicians' perception of pain level (Chapter 4). They added further knowledge about factors associated with prescription patterns and switching to stronger analgesia, but the importance of the socio-demographic and clinical factors identified from medical records previously (Chapter 6 and 7) are not overshadowed as they remain statistically important factors.

Physical function tends to deteriorate with age (Clifton et al., 2011) implying that older age group will have lower physical function levels, and as seen in previous chapters, the

elderly with MSK are more likely to be prescribed stronger analgesia (chapter 4), and once MSK conditions manifest themselves, they may be life-long and get worse with age with increasing levels of pain leading to a poor prognosis (Sarzi-Puttinni et al., 2012). Clinicians' may switch to stronger analgesia to improve or maintain physical function levels.

Access to the GP is essential in the management of MSK conditions as the effectiveness of therapies can be fully realised through frequent re-evaluation of the cause of the chronic pain and its impact on the general physical, emotional as well as the medical state of the patient (Kean, et al., 2008). The management of MSK conditions should be tailored to individual needs (Bergbom et al., 2011) and should address issues of knowledge, beliefs and coping with pain (Brown et al., 2010; Ryan et al., 2007). The more access to clinicians and medical staff patients have through increased consultation schedules, the more likely these issues are to be met. This concurs with the fact that increased rates of consultation and having good access to the GP over time appears to reduce the risk of switching to stronger analgesia.

Smoking history was associated with increased risk of switching analgesia, while overweight or obesity was associated with switching to stronger analgesia. A study by (Green et al., 2012) also found that smoking and obesity was associated with the prescription of opioids in adults aged 50 and above. Smoking and obesity are associated with poor health outcomes, and poor health outcomes increase reliance on professional medical help, hence the prescription of stronger analgesia to alleviate pain may be deemed necessary. Loss of excess weight is a recommended step in the non-pharmacological treatment of MSK pain (Brown et al., 2010). Obesity usually coincides with multi-morbidity which might mean elevated levels of pain in the presence of MSK.

An aim of this analysis was to help determine the generalizability and limitations of the statistical models derived in Chapter 6 and 7. It has shown that baseline socio-

demographic and clinical factors identified as associated with switching analgesia in an incident MSK group are also generally important in a prevalent MSK group even with the inclusion of patient reported factors. The statistical models derived in this analysis and the previous chapters can be generalized to both prevalent and incident MSK groups, with the exception of frailty models. As suggested in Chapter 6, frailty attempts to account for unmeasured variables, hence with a larger number of variables, frailty ceased to be important.

The significance of patient-reported factors suggests patients contribute to the prescription of analgesia in the management of MSK conditions. This suggests that the pharmacological management of MSK conditions is multifaceted, taking into account socio-demographic, clinical and patient-reported variables, and not just about clinicians following prescription guidelines.

This analysis concurs with the previous analysis, that is, there are factors that can be controlled to reduce the risk of switching analgesia in general and switching to stronger analgesia, for example improving access to GPs, increasing consultation frequency in risk groups and reduction of levels of obesity. Reducing the risk of switching to stronger analgesia implies reducing the risk of exposure to a wide spectrum of adverse effects of analgesia.

However, the results should be interpreted with due consideration of the study limitations. The main limitation is that there was a large number of variables adjusted for in the models with a relatively smaller sample size, which may have affected the statistical significance of some variables. The sample size also limits analysis options that may further help in interpreting the results, for example, with a larger sample size; the factors associated with switching from individual potency levels could be explored. For example the fact that there was no one switching from basic analgesics may be attributed to the small number that was prescribed basic analgesia on initial consultation in this cohort. It is

still possible that despite the large number of variables, unmeasured important variables may still exist. The other limitation is that participants with missing data were excluded from the final models. However sensitivity analysis, imputing the extremes of the missing variables did not significantly affect the results of the final model, and the excluded participants were not very different from the entire cohort by gender composition and age.

In comparison to the chapter 6 and 7 analyses, there are variations in follow-up time (5 years versus 3 years) and the composition of the cohorts by age and gender. However despite these variations similar factors were identified as associated with switching analgesia which suggests the studies complement each other, hence despite the limitations, the findings may be generalized to a larger population.

## 8.5 Conclusion

The findings showed that the socio-demographic, clinical as well as patient-reported factors are associated with the analgesia switching process. Despite the differences between the MSK incident and prevalent groups there are common factors identified, which validate findings seen in Chapter 6 and 7. An insight in the impact of the switching processes on the outcomes of patients will be provided by the next chapter which evaluates how switching impacts on changes in physical function and pain interference over time. The strengths and limitations of this chapter are discussed further in the next chapter as the two chapters are interlinked.

# Chapter 9

## 9 The association of switching patients' analgesia with long term physical function and pain interference

### 9.1 Introduction

The previous chapters identified that the time to switching of prescribed analgesia and the use of varying analgesia potency in the treatment of MSK conditions is associated with socio-demographic and clinical variables, as well as variables that may reflect on the lifestyle or quality of life of the patients. For example, low physical function may represent a person's diminished quality of life due to limitations in one's ability to perform their day to day activities without feeling pain.

The main types of switching following the initial MSK consultation examined were: 1) progressing to stronger analgesia, 2) any switching of analgesia which may include multiple switches over time. It is assumed that the predominant reason to switch to stronger analgesia is necessitated primarily by the need to control pain (Mercadante and Bruera, 2012), since stronger analgesia is needed. Switching should aim to improve the quality of life among MSK pain sufferers, which for example may be signified by improved physical function levels and less pain interference with daily activities.

Switching analgesia is an integral aspect of managing long-term MSK, but what the medium to long term impact of switching on controlling pain and improving quality of life is uncertain. It is assumed that stronger analgesia are more likely to be effective but also more likely to yield side effects (Kean et al., 2008). However there is not enough evidence to suggest that the use of stronger analgesia might in the long run be beneficial, as demonstrated in a study by Ashworth et al. (2013) evaluating the association of prescribed stronger analgesia at baseline and self-reported disability. That study found that being

prescribed stronger analgesia was associated with increased Self-reported disability at six months follow-up, but it was also noted that there were baseline differences in those prescribed stronger analgesia and those who were not, suggesting that the prescription of stronger analgesia alone may not be entirely indicative of self-reported future disability.

This chapter concerns the estimation of the association of switching with future quality of life taken into account confounding factors. The quality of life is measured by level of physical function, and pain interference. A lower level of physical function suggests that the patient has increased levels of physical disability which may be a consequence of pain, while pain interference implies that their pain directly limits the activities they can perform in executing their daily routines.

The aim of this chapter was to model the association between switching to stronger analgesia, and any switching, with changes in physical function and pain interference.

The objectives of the chapter are:

1. To investigate whether progressing to stronger analgesia within 3 years is linked to reduced reporting of pain interference and reporting improved physical function at the end of the 3 year period,
2. To investigate whether an increasing number of analgesia switches within 3 years is linked to reporting reduced pain interference and improved physical function at the end of the 3 year period.

## 9.2 Methods

The chapter investigates if switching to stronger analgesia or an increasing number of switches improves the quality of life among patients with MSK problems. However it is unrealistic to assume that there are no confounding factors. Confounding factors, i.e. those believed to be associated with both switching and quality of life, therefore need to

be adjusted for. This was performed here by using a propensity score approach (see statistical methods section 9.2.2.1).

### 9.2.1 Data management and study population

The participants in this chapter were drawn from the North Staffordshire Osteoarthritis Project (NorStOP) using the inclusion criteria described in Chapter 8. This was a cohort of 1610 adults aged 50 years and over registered with 6 general practices. The patients included in this analysis are those who consulted for a MSK condition within 6 months of the baseline survey date and had received no prescribed analgesia in the 28 days prior to the baseline survey (Chapter 8). All 1610 participants were used in modelling the effect of an increased number of analgesia switches, but only the 1309 (81%) who were initially prescribed no medication, basic analgesia and weak analgesia were used to determine the effect of switching to stronger analgesia on quality of life outcomes.

**Patient Variables**

The baseline variables investigated for association with time to switching in Chapter 8 were considered as confounders (that is potentially related to switching and the outcome variables). The factors considered were age, gender, deprivation, co-morbidity, region of pain (e.g. knee, back), previous MSK consultation and prescription history before baseline survey, marital status, body mass index (BMI), alcohol consumption, smoking history, depression, GP access, baseline pain interference, baseline physical function level, existence of widespread pain and reporting over the counter medication. These variables were selected as they were associated with switching analgesia either in the unadjusted models and/or when adjusted for the other variables (Chapter 8). The variables are as described in Chapter 8.

#### 9.2.1.1 Outcome variables

The outcome variables were physical function score and pain interference measured at the 3 year survey. Physical function was considered as continuous, measured using the SF-36 Physical Function subscale with scores ranging from 0 (worst physical function) to 100 (best). Pain interference was an item from the SF36 measured using the question on how pain interferes with daily activities. The question was: “During the last 4 weeks, how much did pain interfere with your work (including both work outside the home and house work)” and the response choices were; not at all, a little bit, moderately, quite a bit and extremely. The ratings were combined into a binary variable, 1 represents existence of moderate/quite a bit/extreme pain interference and 0 for no/little pain interference as previously defined (Jordan et al. 2008; Thomas et al., 2004).

### 9.2.2 Statistical methods

The potentially confounding effects of the baseline socio-demographic and clinical factors were adjusted for though the use of propensity scores as detailed in Section 9.2.2.1 below. Initially, analyses exploring the relationship between switching analgesia and individual baseline variables (unadjusted models) were carried out to illustrate the importance of each of the variables in estimating the propensity scores. The propensity scores were then estimated using a logistic model adjusting for all baseline variables at the same time.

The propensity score is a measure of the likelihood or propensity of someone to switch given their baseline characteristics. Briefly, in the first stage logistic regression models with switching as the outcome were used to calculate the propensity scores for each patient within the context of the type of switch. The outcomes for these first stage logistic regression models were: 1) progressing to stronger analgesia and 2) any analgesia switch (for the purpose of modelling the effect of number of switches of analgesia).

When analysing the association of number of switches with 3-year outcomes, the propensity to switch to any analgesia was first identified. The choice to use the propensity to switch to any analgesia is based on the assumption that the factors associated with further switches are likely to be similar to those of the first switch.

In the second stage, the propensity scores for each individual were included as an independent variable in the final models modelling the association of switching analgesia with 3 year pain interference and physical function.

#### 9.2.2.1 Propensity score model

Propensity scores are a statistically efficient method of adjusting for multiple baseline factors (confounders) potentially associated with both switching analgesia and physical function and pain interference. In this case it estimates the probability of an individual switching analgesia given their baseline characteristics (Cameron and Trivedi, 1998; Becker and Ichino, 2002). It enables the individual effects of the confounding variables to be collated into a single variable (the propensity score) in the final model.

Using the example of switching from no analgesia, basic analgesia or weak analgesia to stronger analgesia within a three year period from baseline survey, the propensity score $p(X_i)$, can be defined as the conditional probability for individual $i$ of switching to stronger analgesia given their vector of patient covariates (baseline characteristics) $\boldsymbol{X}_i$ recorded at the time of the baseline survey; $p(\boldsymbol{X}_i) \equiv \Pr(\text{Switch} = 1|\boldsymbol{X}_i)$

Where $\text{Switch} = 1$ indicates switching to stronger analgesia occurred, and 0 if not (D'Agostino, 1998). The assumption is that including this propensity score in the model efficiently adjusts for the likelihood of switching and hence should reduce confounding by these observed covariates (Rubin, 2001). This effectively collates the effects of the individual baseline variables into a single measure (propensity score) for each individual.

The propensity scores were estimated using two separate logistic regression models with each of the two types of switch (i.e. stronger analgesia switch and any analgesia switch)

as the outcome variables and the baseline variables as explanatory covariates. Once propensity scores have been estimated, checks should be performed that those who switch and those who do not switch but have similar propensity scores are comparable (balanced) on the baseline characteristics. If not, the propensity scores need to be re-estimated which may include interactions of the “offending” variables which are not balanced (D’Agostino, 1998).

Balancing implies that conditional on the propensity score, the distribution of the measured baseline characteristics is similar between patients who switched and those who did not switch analgesia. The statistical modelling steps to establish the propensity (probability) to switch analgesia for each switching scenario can be summarised as:

1. Fit the logistic model with switching as the outcome and all potential confounders included as explanatory variables.
2. Determine propensity score for each individual (i.e. probability of switching given their baseline characteristics) from the fitted logistic regression model
3. Split the sample into $k$ equally spaced intervals (subclasses) of the propensity scores to assemble $k$ groups. Within each group the distribution of covariates should be balanced between those who switched and those who did not. Balance of covariates within groups allows the attribution of any observed difference in outcomes to be the effect of switching rather than differences in observed covariates. Five or six intervals (subclasses) are usually used initially (Rubin 2001), and this analysis used the software default staring number of intervals, $k$=5.
4. Test (through uses of t-tests) that the mean propensity score of those who switched and those who did not are not different within each interval (balanced), and that the ratio of the variances of the propensity score in those who switched and those who did not is close to one (F-test). If the test fails, return to step 3 to change the number of intervals (for example, from $k$=5 to $k$=6), and test again.

5. If the tests fail within an a priori set number of intervals (usually up to 10) (Rubin 2001), consider including interactions of the variables or higher order terms in the logistic model and repeat the process outlined.

The propensity score estimation steps above can be user specified or executed by default by the statistical package Stata (Becker and Ichino, 2002). The default execution by the statistical package was used in this analysis.

**Propensity score matching**

After derivation of propensity scores, the next stage was to match patients who switched analgesia to those who did not switch but had closely similar propensity scores (Rubin, 2001). Propensity score matched sets mimic randomisation in that those who switch can be assumed to be similar to those who did not switch, by baseline characteristics, such that the difference between the two group outcomes is largely attributed to the effect of switching analgesia.

There are several approaches to matching propensity scores, but this analysis used the nearest-neighbour matching technique. In the matching process, each individual who switched analgesia is paired with one or more comparable (in terms of propensity score) individuals who did not switch analgesia within the same interval from the final logistic regression model (where balance was achieved). A more detailed statistical description of the propensity score model and matching approaches are described by Becker and Ichino (2002) and Rubin (2001).

The nearest-neighbour matching technique (the closest propensity scores within the interval) has the advantage that it can be used with and without replacement, such that it allows a many to one matching, all switched individuals hence find at least one match (Becker and Ichino, 2002).

The matched propensity scores were used as a covariate adjustment (Rubin, 2001). This means that a sub-sample consisting of patients who switched analgesia and those who

did not with similar propensity score were used in the regression model. Those who did not switch and were not matched with those who switched in terms of propensity scores were excluded in the regression model. The outcome variables (physical function and pain interference) were regressed on the binary variable indicating switching status and the matched propensity scores as described in the next sections.

### 9.2.3 Modelling the effect of switching to stronger analgesia

The binary logistic regression model was used with pain interference at 3 years as the outcome variable. The unadjusted model considered only the switch binary variable (switch=0 or 1) as the independent variable and the adjusted model included the matched propensity scores in addition to the switch variable as the independent variables.

The linear regression model was used to examine the association between physical function at three years and switching to stronger analgesia. As in the logistic model, the unadjusted model considered only the switch binary variable as the independent variable and the adjusted model included the matched propensity scores in addition to the switch variable as the independent variables.

### 9.2.4 Modelling the effect of multiple switches

As in section 9.2.3, the binary logistic regression model was used with pain interference at 3 years as the outcome variable. The unadjusted model considered only the number of switches as a continuous variable (number of switches=0, 1, 2 …) as the independent variable, and the adjusted model included the matched propensity scores in addition to the number of switches as the independent variables.

Linear regression model was also used to examine the association between physical function at three years and number of analgesia switches. The unadjusted model considered only the number of switches as the independent variable and the adjusted model included the matched propensity scores in addition, as the independent variables.

## 9.3 Results

### 9.3.1 Data description

The baseline characteristics of the patients included in this analysis are described in Chapter 8.

For evaluating the association of switching to stronger analgesia with 3 year outcomes, 1309 patients on lower potency analgesia at baseline were included. Of these, 13% switched to strong analgesia within 3 years and prior to follow up survey date. At 3 year follow-up, their mean physical function score of those who switched was 42 (SD 30.2) compared to 61 (SD 29.3) for those who did not switch.

The proportion of those switching who reported pain interference at 3 years was 70% compared to 42% of those who did not switch. The mean physical function scores for those who switched to stronger analgesia were lower than those who did not switch at both baseline and 3 year follow-up. For those who switched, the mean scores were slightly lower at follow-up (baseline 44 (SD 30.4) vs follow-up 42 (SD 30.2)).

The prevalence rates of reporting pain interference were lower for those who switched than those who did not at both baseline and follow-up. Of those who switched, the prevalence rate at follow-up was slightly lower than the baseline rate (Table 9.3.1 and Table 9.3.2).

1610 patients were included in the analysis assessing the association of an increasing number of switches with three year outcomes. Of these, 28% had at least 1 any analgesia switch. At 3 year follow-up, the mean physical function scores for those who switched to any analgesia was 48 (SD 30.4) compared to 66 (SD 28.0) for those do did not switch. The proportion of those switching who reported pain interference at 3 years was 63%, compared to 34% of those who did not switch.

Table 9.3.1: Mean follow-up and baseline physical function scores by type of switch

| | Baseline Scores | | | | 3 year Follow-up Scores | | | |
|---|---|---|---|---|---|---|---|---|
| | Switched | | Did not Switch | | Switched | | Did not Switch | |
| **Switch type** | **n** | **Mean (SD)** | **n** | **Mean (SD)** | **n** | **Mean (SD)** | **n** | **Mean (SD)** |
| Any analgesia | 449 | 50 (30.8) | 1161 | 65 (28.8) | 449 | 48 (30.4) | 1161 | 66 (28.0) |
| Strong Analgesia | 169 | 44 (30.4) | 1140 | 61 (29.9) | 169 | 42 (30.2) | 1140 | 61 (29.3) |

Table 9.3.2: Baseline and follow-up pain interference by type of switch

| | Baseline pain interference | | | | 3 year Follow-up pain interference | | | |
|---|---|---|---|---|---|---|---|---|
| | Switched | | Did not Switch | | Switched | | Did not Switch | |
| **Switch type** | **n** | **Yes (%)** | **n** | **Yes (%)** | **n** | **Yes (%)** | **n** | **Yes (%)** |
| Any analgesia | 449 | 65 | 1161 | 43 | 449 | 63 | 1161 | 34 |
| Strong Analgesia | 169 | 70 | 1140 | 50 | 169 | 70 | 1140 | 42 |

The mean physical function scores for those who switched to any analgesia were lower than those who did not switch at both baseline and 3 year follow-up. For those who switched, the mean scores were slightly lower at follow-up (baseline 50 (SD 30.8) vs follow-up 48 (SD 30.4)).

A similar trend to those switching to stronger analgesia in the mean physical function scores was observed, but the prevalence rates of reporting pain interference were similar at baseline and follow-up in this cohort (Table 9.3.1 and Table 9.3.2).

### 9.3.2 Derivation of propensity scores

The baseline factors used to estimate propensity scores for any analgesia switch and strong analgesia switch were older age, female gender, co-morbidity, previous medication history, consultation history, over the counter medication use, depression, pain interference, smoking history, married, less deprivation, pain location, rare or no alcohol consumption and physical function. The unadjusted association of the variables with switching were evaluated to illustrate their individual importance before using them in an adjusted model to estimate the propensity scores (Table 9.3.3).

Table 9.3.3: Unadjusted logistic models of baseline variables with switching as the outcome

| Variable | Unadjusted Logistic models Odds Ratio - OR [95% CI] | |
|---|---|---|
| | Any analgesia switch | Strong Analgesia switch |
| **Age** | | |
| 50-59 | - | - |
| 60-69 | 1.30[1.02, 1.67] | 1.27[0.95, 1.78] |
| 70-79 | 1.67[1.28, 2.18] | 1.60[1.13, 2.27] |
| 80+ | 1.99[1.42, 2.79] | 1.34[0.86, 2.09] |
| **Gender** | | |
| Males | - | - |
| Females | 1.29[1.05, 1.57] | 1.50[1.15, 1.974] |
| **Married** | | |
| No | - | - |
| Yes | 0.66[0.53, 0.82] | 0.68[0.52, 0.90] |
| **Deprivation** | | |
| Most | - | - |
| Medium | 1.01[0.82, 1.24] | 0.89[0.68, 1.16] |
| Least | 0.64[0.46, 0.90] | 0. 55[0.34, 0.91] |
| **Region of Pain** | | |
| Back | - | - |
| Knee | 0.63[0.43, 0.92] | 0.97[0.57, 1.63] |
| Hip | 0.67[0.49, 0.93] | 1.11[0.71, 1.73] |
| Foot/ Ankle | 0.70[0.48, 1.01] | 1.01[0.61, 1.69] |
| Hand/limb | 0.72[0.49, 1.06] | 1.00[0.59, 1.70] |
| Shoulder | 0.86[0.59, 1.24] | 1.50[0.93, 2.43] |
| Neck | 0.69[0.48, 1.03] | 1.38[0.86, 2.21] |
| **Co-morbidity** | | |
| Other /none | - | - |
| Selected conditions | 1.31[1.07, 1.60] | 1.80[1.38, 2.33] |
| **Previous analgesia prescription** | | |
| No | - | - |
| Yes | 5.24[4.21, 6.53] | 3.35[2.47, 4.53] |
| **Previous musculoskeletal consultation** | | |
| No | - | - |
| Yes | 4.31[1.64, 11.2] | 1.95[0.59, 6.49] |
| **Widespread pain** | | |
| No | - | - |
| Yes | 1.24[0.96, 1.61] | 1.20[0.86, 1.67] |
| **OTC medication** | | |
| None | - | - |
| Creams/ Painkillers | 2.32[1.71, 3.16] | 2.07[1.34, 3.19] |
| Glucosamine | 1.94[1.41, 2.65] | 1.48[0.95, 2.32] |

| Variable | Unadjusted Logistic models Odds Ratio - OR [95% CI] | |
|---|---|---|
| | Any analgesia switch | Strong Analgesia switch |
| **BMI** | | |
| Normal / Underweight | - | - |
| Obese/ Overweight | 1.05[0.85, 1.29] | 1.20[0.91, 1.59] |
| Unknown | 1.41[0.84, 2.36] | 1.51[0.80, 2.84] |
| **Depression** | | |
| No | - | - |
| Yes | 1.65 [1.28, 2.13] | 1.78[1.31, 2.41] |
| **Pain interference** | | |
| None | - | - |
| Yes | 2.39 [1.95, 2.93] | 2.42[1.83, 3.20] |
| **GP Access** | | |
| Yes | - | - |
| No | 0.98[0.69, 1.40] | 1.19[0.76, 1.85] |
| **Alcohol** | | |
| Sometimes/mostly | - | - |
| Rarely/Never | 0.75[0.62, 0.92] | 0.77[0.59, 1.00] |
| **Smoke** | | |
| Never smoked | - | - |
| Previously smoked | 1.24[1.01, 1.54] | 1.52[1.14, 2.02] |
| Currently smoking | 1.22[0.90, 1.67] | 1.32[0.87, 2.00] |
| **Physical function** | 0.98[0.97, 0.99] | 0.98[0.97, 0.98] |

**Unadjusted model =** Individual variable in the model

For propensity score estimation for stronger analgesia switching, balancing was achieved with 6 intervals ($k$ =6) and the propensity scores were estimated. The mean propensity score (probability to switch to stronger analgesia) was 0.17 (range 0.01 to 0.61) with a standard deviation of 0.11.

For propensity score estimation of switching to any analgesia, balancing was achieved with 7 intervals ($k$=7). The mean propensity score was 0.45 with a standard deviation of 0.21 (range 0.08 to 0.84). The analysis used the Stata software default starting value of number of intervals ($k$=5) and balancing was achieved without need to include interactions.

### 9.3.3 The effect of switching to stronger analgesia on reported physical function and pain interference

Switching to stronger analgesia was associated with increased risk of reporting pain interference at 3 years follow-up. In The unadjusted odds ratio (OR) for the association of switching to stronger opioids on pain interference at 3 years was 3.20 with 95% CI [2.22, 4.58]. After adjustment for propensity score, the OR fell to 1.50 [1.01, 2.27], but the association of switching to stronger opioids with pain interference remained statistically significant. The adjusted odds ratio was much smaller than the unadjusted coefficient, suggesting there was some confounding.

The unadjusted association of switching to stronger analgesia with 3 year physical function scores was statistically significant (coefficient -19.4; 95% CI -24.33, -14.63) but after adjusting for propensity scores, it was significant only at the 10% level (coefficient -4.35[-9.09, 0.39]). Switching was associated with a reduction in the mean physical function score of 4.35 points on the 0-100 scale.

### 9.3.4 The effect of increasing number of analgesia switches on reported physical function and pain interference

Both the unadjusted analysis (OR 1.37; 95% CI 1.27, 1.48) and the adjusted analysis, (OR 1.17; 95% CI 1.08, 1.27) suggest that an increasing number of switches of analgesia over the follow-up period was associated with increased risk of reporting pain interference at 3 year follow-up. That is, for the adjusted OR, a unit increase in the number of switches is associated with a 17% increase in the odds of reporting pain interference.

The unadjusted coefficient for the association of number of switches with the physical function score was (-4.12 [-4.85, -3.39]). This remained statistically significant after adjusting for the propensity scores (coefficient -2.11[-2.90, -1.33]). A unit increase in the number of analgesia switches before 3 year follow-up is associated with just over a 2 unit reduction on the physical function score at follow-up.

## 9.4 Discussion

Switching to stronger analgesia and multiple switching of analgesia within a three year period was significantly associated with patient-reported pain interference at the end of the 3 years. The results also showed that patients with an increased number of switches to any analgesia were more likely to report worse physical function. However, there was less evidence of an association between switching to stronger analgesia and physical function. To my knowledge, this is the first analysis of the effect of switching analgesia within general MSK conditions and other chronic pain settings.

The switching between opioid analgesia can sometimes be a calculated move by clinicians as opioid rotation is an effective strategy in the management of opioid adverse effects (Joseph et al., 2009), as suggested in Chapter 7. While not all potential benefits of stronger analgesia switching are assessed in this research (for example, pain relief and ability to return to work), the analysis presented here suggests that switching to stronger analgesia prescriptions does not improve physical function or pain interference. However unmeasured confounding (discussed further below), for example interaction of medications or patient adherence to dosage instructions, may have an effect on the conclusions drawn from the results. It is possible that those who switch to stronger analgesia have a very poor prognosis which may be even worse without switching to stronger analgesia. The fact that the explicit reasons for switching to stronger analgesia are not known makes it difficult to rule out the benefits of stronger analgesia switches.

GPs attempt to alleviate the pain their patients experience, but realistically are at best likely to gain some limited control over the painful condition, whilst in some instances will effect no improvement at all. As a part of this, switching to stronger analgesia might be the only feasible option available to them, but this choice is complex and analgesia use has a multifactorial aetiology (Fitzcharles et al., 2010). Their final selection of analgesia is more than just a balance between the need to control pain and the adverse effects. What can

be said is that of those patients who do switch, they do not necessarily have significantly better outcomes.

These findings seem to concur with findings in a study by Ashworth et al. (2013) which aimed to explore in patients with back pain in primary care, the relationship between prescribed stronger analgesia at baseline and self-reported disability at 6 months follow-up. That study also found that being prescribed stronger analgesia at baseline was not associated with improved outcomes at follow-up. These findings also seem to be related to the findings of the study by Franklin et al. (2008). That study examined whether prescription of stronger analgesia within 6 weeks of low back injury is associated with work disability at 1 year and found that the prescription of stronger analgesia for more than 7 days for workers with acute back injuries is a risk factor for long-term disability. This suggests that levels of disability due to chronic pain are not necessarily alleviated by prolonged use of opioids.

The findings of this thesis also highlight the need for further investigation of the long-term consequences of switching to stronger analgesia as the effect of switching to stronger analgesia on patient outcomes are not conclusive. The results appear to suggest that identifying those patients with the highest chances of switching from the onset of medical care, and monitoring them closely through rigorous consultation as well as prolonged use of alternative medication may be the way forward (as discussed in Chapters 7 and 8).

Multiple switches may be an indication of less stable conditions or patients' susceptibility to the adverse effects of analgesia. Consequently the relief brought about by the prescribed analgesia is only short term because of a deteriorating condition, or the change in analgesia becomes necessary to alleviate adverse effects. The findings of this study suggest that quickly switching to the next available option which may lead to multiple switches later does not always produce the desired effects on the patients' physical function and their perception of pain interference.

The strength of this analysis was the use of propensity scores to adjust for confounding. The use of propensity scores to adjust for multiple potential confounders is more efficient than the conventional regression techniques adjusting for multiple covariates (Rubin, 2001). This leads to reduced bias through the matching of those who switched and those who did not, leading to more precise parameter estimates compared to using all baseline variables which may result in unreliable parameter estimates due to sparse data resulting from too many variables (Rubin, 2001).

The propensity scores of those who switched to stronger analgesia and those who did not switch were adequately balanced, meaning that adjusting for propensity to switch makes those who switched and those who did not, statistically comparable to each other, while reducing the number of variables in the final model.

A limitation of our analysis is that is it mixes people who always switch upwards in potency, those who switch downwards and those who move up then down which may be assumed to indicate different reasons for switching. The other limitation is that the analysis considers the propensity to switch to any analgesia then evaluates the impact of multiple switches on the 3 year patient outcomes. However we are concerned with switching as a marker of a changing clinical situation, worse or better, and as such allows us to examine those factors which predominantly influence this process. This allows us to inform doctors of patient characteristics they might need to be aware of when prescribing for patients, such that they might seek to limit the need to switch analgesia and avoid the unnecessary exposure of patients to unwanted adverse events that might drive the process of switching even further.

Physical condition and pain levels can change considerably over a three year period and the measurement at 3 year follow-up may be sometime after the switch occurred. Further, the presence of a prescribed stronger analgesia switch amongst the analgesia used over time could be an indication of the individuals' declining physical function or the increase in

pain interference not as a result of the MSK condition but other co-morbidities. This could also be reflective of that this is an older aged group and findings may be different in younger age groups.

Also as stated earlier, the other limitation is that there may be unobserved or unmeasured confounders which, if included in the estimation of propensity scores, may result in different propensity scores, and in turn result in a different adjusted association of switching with the patient outcomes. Further changes occurring after baseline may be more responsible for the switching, for example, the key associated variables with switching identified in previous chapters were the time-varying factors (e.g. number of consultations) which were not included in this analysis. However, the main aim was to adjust for the available baseline variables that are potential confounders, to investigate the effects of switching analgesia, and to flag patients at higher risk of switching based on baseline characteristics, such that clinicians may be aware of the indicative factors.

The other limitations related to the above are that it is based on an older and prevalent cohort and patients who responded at both baseline and follow-up surveys, such that the results may be different in younger age groups, in patients with new MSK problems and if the non-responders at follow-up were included.

## 9.5 Conclusion

Switching analgesia will always be a fundamental component of the management of pain in MSK conditions, as indicated by the WHO guidelines (Ehrlich, 2003). However, this analysis suggests it may not improve long term patient outcomes. However, further research is necessary on the association of switching analgesia on changes in pain interference and physical function in MSK consulters. The next chapter summarises the main findings of this thesis, the clinical and statistical implications as well as opportunities for future research in assessing long term pharmacological management of MSK conditions in primary care.

# Chapter 10

## 10 Discussion and Conclusion

The aim of this thesis was to use robust statistical methods to evaluate current practices in the pharmacological management of MSK pain in primary care, explore and understand the pharmacologic, clinical and socio-demographic factors associated with switching analgesia, and to evaluate long term success or failure of analgesia switching. The study was designed to examine analgesia prescription patterns and associated patient characteristics in incident and prevalent MSK conditions, as well as reviewing and establishing appropriate statistical methods to model prescription data.

This chapter briefly reviews the main findings of the thesis, what the findings add to the current knowledge of analgesia prescribing in the management of pain in primary care MSK conditions, and reflects on the statistical methodology used in modelling the prescription patterns. The clinical and methodological implications of the research to the treatment of MSK conditions and primary care medical research in general are explored, as well as possible future research.

### 10.1 Summary of main findings

This thesis has contributed to the knowledge base applying a categorisation of analgesia available in primary care (the HAC) to interpret the WHO analgesia prescription ladder in the management of MSK conditions, and findings suggest current prescription practices reflect evidence of adherence to the WHO and NICE guidelines. Profiles of analgesia management over time can be identified from prescription data, which are associated with patient characteristics. Certain patient characteristics were consistently associated with the initial analgesia strength and switching to stronger analgesia over time. With regards to statistical approaches to modelling switching, the Weibull model appeared a preferable alternative to the Cox model for modelling time to switching.

### 10.1.1 Phase 1 - Statistical methods used in modelling medication switching: a systematic review

The systematic review of statistical methods used in modelling medication switching in phase 1 of the thesis revealed that analysing factors associated with switching medication in general is increasing, but is less prevalent within the primary care setting and in MSK diseases. The most commonly used statistical approaches were the logistic regression model if switching is considered as a dichotomous switch / not switch outcome in a set period of time, and the Cox proportional hazards model when time to switch is considered. The reasons for using these approaches are generally not explicitly stated but can be inferred from study objectives. Parametric statistical methods like the Weibull model have not been used in switching medication analyses; hence their appropriateness and feasibility cannot be established from available literature.

### 10.1.2 Phase 2 - Pain medications prescriptions issued at first MSK consultation

The first analysis established that of 3236 new MSK consulters, 47% were not prescribed any analgesia at that initial consultation. Older patients and patients who have been prescribed any analgesia in the past (more than 12 months previously) were more likely to be prescribed analgesia on first consultation. The analgesia prescribed most frequently was NSAIDs followed by basic analgesia (e.g. paracetamol). Patients from medium or least deprived localities and patients experiencing pain in the hand or foot were less likely to be prescribed analgesia, and if they were, it was more likely to be less strong analgesia. There was variation by registered general practice in whether patients were prescribed analgesia, and the potency level prescribed.

### 10.1.3 Phase 2 - Primary care pain medication profiles over five years: A latent class analysis (LCA)

LCA was used to detect the presence of common analgesia prescription profiles over 5 years in new MSK consulters. A three cluster model was identified as the best fitting model for the data. The basic analgesics or no medication cluster consisted of patients

who received mainly either no analgesia or basic analgesia throughout the five year period and a few who received a combination of basic analgesia and weak combination analgesia. Patients in this cluster were predominantly in the age group 15 to 29. No dominant region of pain, for example the back or upper limb was identified in this group.

The NSAIDs cluster consisted of patients who were mostly prescribed NSAIDs. They were predominantly aged 45 to 59, were characterised by a having a higher proportion of males, and significantly more likely to have pain in the back and shoulder. Most had received pain medication on first consultation and had been prescribed some form of analgesia in the past. The oldest age groups (60-74 and over 75) were less likely to be in this cluster. The multiple-potency cluster contained patients who received three or more (more than 70% of the cluster) of the five potency levels (for example, basic analgesia, NSAIDs, moderate strength analgesia). This cluster had a higher proportion of females than males, higher proportions of people with pain in the back, hip and shoulder, and higher proportion aged 45-59 and 60-74 than the other clusters. The first cluster, those prescribed no medication or basic analgesia was the most common, while the third cluster, those prescribed multiple potency levels, was the least common.

### 10.1.4 Phase 3- Modelling time to change of medication potency level among incident musculoskeletal consulters

The objectives of this section were to compare the Cox and Weibull models in evaluating patient characteristics associated with switching to any analgesia, and switching from lower potency analgesia (no medication, basic analgesia and weak analgesia) to stronger analgesia. The gamma frailty extension to the Weibull models was explored. The concept of frailty is based on the heterogeneity amongst individuals, that is, not all individuals are the same due to the nature of their condition or through unmeasured covariates. The Poisson regression model was also used to model patient characteristics associated with rate of switching analgesia. It quantifies the rates of switching across covariates for the period under exposure

The parameter estimates of the Cox and Weibull models were similar but the Weibull models were the final preferred choice as they fitted the data better than the Cox models. Frailty was statistically significant in the time to first switch models (switching from initially prescribed analgesia to stronger analgesia), but not statistically significant in analysing multiple event switches using the Weibull model.

The analysis highlighted both clinical and demographic factors associated with switching analgesia and the rates of switching. There was a higher risk, and increased rates of switching analgesia in general among the elderly, females, those prescribed pain medication in the past, those consulting for pain in more than one location over time, those starting medication with weak or strong analgesia and those with increasing number of prescriptions from their initial analgesia category over time. There is declining risk of switching with increasing number of MSK consultations, low deprivation and receiving no prescribed medication on first consultation.

### 10.1.5 Phase 4 - Modelling time to change of medication potency level among prevalent older aged musculoskeletal consulters

The objectives of this phase were to evaluate if the clinical and socio-demographic factors identified as associated with analgesia switching amongst incident MSK consulters were also associated in a prevalent and older MSK cohort, and also when further adjusted for patient reported factors. Further, to identify self-reported health and demographic factors not recorded routinely in primary care that are associated with switching analgesia. A linked medical record-survey dataset was used for this purpose.

The common factors associated with time to switching analgesia for the incident and prevalent MSK groups were age, gender, previously prescribed medication, initial analgesia (weak and strong analgesia) prescribed and number of MSK consultations. In contrast to within the incident group, co-morbidity was a significant factor in the older aged

prevalent group, while the level of deprivation and the number of prescribed analgesia were significant only in the incident group.

The patient-reported factors related to switching identified in addition to routinely recorded socio-demographic and clinical factors were: using over the counter medication, BMI (obesity or overweight), reporting interference from pain, inadequate access to GP, smoking history and worse physical function. Worse physical function was associated with slightly increased risk of switching to stronger analgesia, and switching taking into account all switches. Reporting inadequate access to GP increased the risk of multiple switches, while obesity or overweight increased the risk of stronger analgesia switch.

### 10.1.6 Phase 4 - Impact of switching analgesia on 3 year pain interference and physical function level

The objectives of this section were to investigate whether switching or progressing to stronger analgesia, and experiencing multiple switches within 3 years is linked to reporting reduced pain interference and improved physical function at the end of the 3 year period.

Potential confounding by baseline variables was adjusted for through use of propensity scores. The analysis suggested that switching to stronger analgesia and multiple switching of analgesia within a three year period was significantly associated with more patient-reported interference from pain at the end of the 3 years. The results also showed that patients with an increased number of switches to any analgesia were more likely to report worse physical function. However, there was no statistical evidence of an association between switching to stronger analgesia and physical function.

## 10.2 Strengths and limitations

The findings of this thesis add to the knowledge of analgesia switching among MSK patients, but the findings need to be interpreted with due consideration of the strengths and limitations of the study.

The strength of the study lies primarily in that the main dataset used a high quality data set, CiPCA, which gives comparable consultation Figures for MSK problems as the larger national datasets (Jordan et al., 2007). The practices contributing data to CiPCA are trained and assessed in morbidity recording (Porcheret, 2004) and prescriptions are complete as clinicians have to use the computer to prescribe medication. The study is naturalistic in that it is based on real-world data, large sample size and uses an observational approach without pre-planned treatment changes over time.

This study used a wide range of complementary statistical methods to thoroughly interrogate the data to highlight the prescription patterns of analgesia in MSK conditions in primary care before drawing conclusions from the results. For example, it used both the Cox and Weibull models before deciding on the approach most suitable in modelling switching.

In multiple event switches the times between successive switches are known to be correlated which may lead to over inflated parameter estimates (Collet, 2003). However the time between event counting processes, employed in the analysis ensures that the correlation is accounted for. The use of the Poisson regression model to evaluate the rates of switching within the total exposure time identified factors associated with higher rates of switching are similar to factors associated with any switching when taking into account all switches from the Cox and Weibull models. The Poisson model validated that the factors identified are indeed associated with multiple switches of analgesia. The study lays a foundation for further research in future in the evaluation of prescription patterns and switching of analgesia through its clinical findings and successful application of statistical methods that have not been used before within the context of MSK condition.

Some of the clinical findings of the thesis on time to switching initially prescribed analgesia are comparable to the study by Gore et al. (2012). The Gore study modelled factors associated with therapy switching, and used The Health Improvement Network (THIN)

database, which is a medical research database of anonymised patient records. The database contains data from 429 practices across the UK and 7.7 million patients. The Gore study found that most switches from initially prescribed therapy occur within the first 100 days and also identified that the patients who were initially prescribed weak analgesia and strong analgesia were at higher risk of switching therapy. These findings are similar to the findings of this thesis.

In comparison with the study by Gore et al. (2012), this thesis explores a wider range of factors associated with prescription patterns and considers patients with incident and prevalent MSK conditions separately. It tackles different switching scenarios separately to account for movement up the analgesia ladder as well as multiple event switching and follows prescription patterns over a longer period of time.

The study by Gore et al. (2012) is the only study that was found to model factors associated with switching analgesia in a similar way to approaches used in this thesis. They found that patients aged above 55 years were less likely to switch therapy. However the Gore study explored age as a binary variable of above or below 55 without clinical justification of their choice and explored few socio-demographic and clinical variables. In contrast this thesis explores age as a five category variable which has highlighted that there are variations in prescription patterns and switching across the five categories, and considers a large pool of socio-demographic, clinical and patient-reported characteristics.

This thesis brings into focus that prescription patterns and analgesia switching in both prevalent and incident MSK consulters is associated with a wide range of factors in contrast to the study by Gore et al. (2012). Amongst the factors adjusted for in this thesis which are not in study by Gore are the regions in which pain was located, number of MSK consultations, presence of co-morbidity and a range of patient-reported variables (such as physical function and pain interference). While it is not possible to measure and adjust for all possible variables, having a wider pool of variables helps as some measured variables

may be strongly related to or proxies for unmeasured ones. For example, the study identified that an increased number of consultations is related to a reduced risk of switching, which may be correlated with adherence to prescribed medication as patients who have regular contact with medical professionals may be more likely to follow their treatment regimens (Schneider, 2010).

Research by Gore et al. (2012) attempted to model switching between differing types of analgesia with varying levels of analgesia effect for MSK conditions but did not examine the full spectrum of available analgesia, adjusted for fewer factors, and did not distinguish patients switching to stronger analgesia, but only considered any change in analgesia. The implication from this approach is that all kinds of switches are of equal importance, which is a contradiction to the fact that stronger analgesia are likely to have more adverse effects even if they do control pain better (Chou et al., 2005; Rahme et al., 2006).

The potential limitation of this study is that the data was not initially designed for medical research but routinely collected as consultation and prescription records and there are only 12 general practices contributing to it. It is therefore possible that some important baseline variables not measured in the database were not included in the analysis, for example patient preference, a better measure of comorbidity, severity of pain and use of over the counter medication among others. The non-randomised sample selection criteria coupled with a small number of participating general practices may allow forms of selection bias due to regional or practice variations such as the population composition within the area covered by the general practices. However the number of participants in the main models was more than the minimum sample size suggested (720) for such a study, making the results more reliable.

The results could also be affected by other forms of confounding induced by national prescription guidelines available to general practitioners, For example advice against use of coproxamol in 2005 resulted in an immediate decline in the use of opioids with a steady

rise there after (Bedson et al., 2012). The prevalence of MSK conditions and average age may vary differently across the wider population. Further, GPs may consider multiple factors in deciding the medication and appropriate potency level (Bope et al., 2004; Garbez and Puntillo, 2005; Schneider, 2010). This study was not designed to evaluate explicitly the clinical reasons for switching analgesia, but to evaluate baseline and time varying factors that clinicians should be aware might be related to a specific prescription pattern or treatment profile eventually.

One limitation of the study could be the presence of missing data in the analyses within the NorStOP dataset and exclusion of those with missing data from the final model. Multiple imputation techniques could have been used to impute missing data. However from the descriptive analysis it can be seen that the overall proportion of missing data is small and the participants with missing data are not very different from the whole cohort by age and gender. Sensitivity analyses assuming those with missing data would have reported the extremes on those variables did not change conclusions.

One major limitation of the findings is that there is potentially a relationship between length of time and some of the variables, for example, the number of consultations before the switching event. An increased number of consultations were associated with a reduced likelihood to switch analgesia. It is possible those generally more likely to switch will do so early before they have had the opportunity to make multiple consultations, whilst those less likely to switch have a longer time in which they can increase their number of consultations. Therefore interpreting the findings to mean that consulting more reduces the likelihood of switching may be a biased interpretation.

Another limitation of the study is lack of pain measurement in the CiPCA cohort with incident MSK conditions; as such we use change of prescription and analgesia potency level as a proxy measure of the changes in pain levels. As discussed earlier, the prescription patterns or switching analgesia may not necessarily be an indication of pain

level or pain resulting from the MSK condition. For example co-morbidity and adverse effects may be the underlying causes of the changes (Rahme et al., 2006). Pain was measured at baseline for the cohort with prevalent MSK, it had less association with switching than physical function levels. However, this was baseline pain and not pain measured within the proximity of the change in analgesia. There are potentially other factors that may influence the level of pain on a day to day basis such that the measured pain may be an exaggeration or underestimation of the actual pain emanating from the MSK condition. Another limitation is the lack of OTC measurement which will be important for basic analgesia, and lack of information on alternative management such as advice to exercise and referral to physiotherapy. Knowing the potency of OTC medication taken by the patients prior to switching and other alternative management strategies will help understanding and interpretation of the reasons for switching analgesia.

This study considers a wide range of MSK conditions amongst the patients selected for analysis without focussing on specific problems. Different MSK conditions have varying levels of pain severity and therefore require different treatment approaches which may account to some extent for the variations in treatment profiles or prescription patterns and time to switching analgesia (Hunt et al., 2007; Schneider, 2010). However, adjusting for pain location accounts for some of the variation in prescription patterns, for example, pain in the hand and wrist is less likely to be related to prescription of stronger analgesia compared to pain in the back.

In evaluating the effect of switching analgesia on the patients' physical function and level of pain interference, the study looks at patient outcomes recorded after three years. There is no conclusive statistical evidence of the effect of switching analgesia on the patient outcomes. Three years is a long time hence it is difficult to link all switching of analgesia with outcome considering that the earliest medication switches occurred just 15 days of initiation into treatment. There is also the potential effect of the unmeasured confounders

on the results. However the use of matching propensity scores ensures that those who switched and those who did not are comparable on measured covariates.

The HAC is a consensus model and is not representative of the entirety of clinicians' views and convictions in classifying analgesia. The HAC classification has six categories by definition but due to inadequate patient numbers in some categories, some had to be combined which may have affected the parameter estimates in the models and the validity of the conclusions drawn from the results. For example strong combination opioids and strong single opioids were combined into a single category of strong analgesia. However, there is clinical evidence that the two categories are similar to each other (Zernikow et al., 2009), such that merging the categories does not affect the clinical interpretation of the results.

The main limitation of LCA is the underlying assumption of local independence which means that the potency categories of analgesia prescribed are assumed to be independent within clusters. Violation of this assumption may lead to patients being placed into incorrect groups (Magidson and Vermunt, 2004). It is possible this may have occurred in this study, even though the results of tests suggest this did not happen to a great extent. The mean posterior probabilities for members in a cluster were greater than 0.7 but not very close to 1 which means there is a small degree of uncertainty in cluster membership. No previous studies using latent class analysis models in analysing prescription patterns and patient profiles were identified which could be compared to this study.

The other limitation of this thesis is that in the systematic review of statistical methods used in modelling medication switching only covered the period 2000-2010, and some papers modelling medication switching were not included, for example the study by Gore et al. (2012). However the study used the Cox model which implies that the conclusions drawn from the review would not have been affected.

The findings interpreted with due consideration of the strengths and limitations of the study illustrates that there are still gaps in the current knowledge of prescription patterns and switching of analgesia in the management of MSK conditions.

## 10.3 Current knowledge gaps in switching analgesia in the management of musculoskeletal conditions

The findings in this research suggest that there is an absence of primary care research evaluating the current prescribing practices and patterns based on the WHO and NICE guidelines for the pharmacological management of MSK conditions. There is also a paucity of relevant literature with respect to the evaluation of factors associated with being prescribed analgesia, the potency level prescribed at the onset of consultation, the explicit relationship between prescription patterns during follow-up and patient characteristics.

The evaluation of factors associated with medication switching in MSK conditions is generally focussed on the clinical aspects and partly on socio-demographic factors. Studies by Rahme et al. (2005) and Bennett et al. (2003) evaluating switching between NSAIDs and COX2s (which is an entirely different context to this thesis) evaluated the association of age, gender, prior health check, previous diagnoses, prior medication and dose and previous switches, while Gore et al. (2012) evaluating therapy switching in chronic low back pain and OA, further looked at co-morbidities such as mental disorders and headaches. The potential effects on pain medication management of using over the counter medication, pain interference, physical function, pain location, the number of consultations prescriptions prior to switching and body weight have never (to our knowledge) been evaluated in switching of analgesia in MSK conditions. However body weight, pain interference and physical function have been shown to be related to prescription of opioids (Green et al., 2012), while deprivation level, income levels and other medications such as anti-depressants have been shown to be predictors of medication selection among patients (Boulanger et al., 2011).

There is evidence of limited use of a wide variety of statistical approaches in analysing and evaluating prescription patterns and switching of analgesia, as seen through the systematic review in Chapter 2. The approaches, if time to switch is the outcome, tend to be heavily reliant on the proportional hazards assumption. Henderson and Oman (1999) analysing the effects of frailty (heterogeneity or unmeasured covariates) in survival analysis models suggested that frailty is always present in most medical data, and if ignored and so the model misspecified, underestimation of the standard errors occurs. The consequences underestimated standard errors are failure of the goodness-of-fit tests to detect departures from assumed model, resulting in unreliable models.

The literature review in Chapter 2 highlighted that switching analgesia has been evaluated only in the context of switching from one specific drug to another, and never from one potency category to another. The existence of over 300 analgesia medications (BNF 65 2013) that clinicians can prescribe made the examination of their use in general practice, a difficult proposition but the development of the hierarchical analgesia categorisation (HAC) by specialist clinicians in the field has laid the foundation of this analysis (Bedson et al., 2012). Previous knowledge on switching analgesia in MSK conditions remains largely specific to individual drugs and have not been generalised according to potency levels of analgesia. The factors associated with the generic change from one category of equipotent analgesia to another have not been rigorously explored but have been based on results from switching between individual drugs within or across potency categories (Chapter 2).

## 10.4 Statistical implications

Latent class analysis is an effective approach to identifying clusters of MSK consulters as defined by prescription patterns. This approach can help in future research in that it can be used to identify groups of patients at high risk of exposure to the adverse effects of analgesia, as seen through the multiple-potency cluster identified in Chapter 5. The LCA approach used here did not take into account the order analgesia were prescribed. The

LCA approach within the context of prescription patterns in MSK can be extended to include longitudinal latent class analysis (LLCA) and latent class growth analysis (LCGA) (Henry and Muthen, 2010; Vermunt and Magidson, 2008). These approaches will enable clustering of patients based on the trajectories of analgesia changes over time, including the order they occur. The follow-up time can be split into smaller discrete time periods so that the potency levels of analgesia can be established for each time period as well for the entire follow-up period.

The main limitation of the Weibull model is that the Weibull is a parametric model which may not always be suitable (Collet, 2003). The parameter estimates of a Weibull and a Cox model are expected to be similar if the probability density function of the data is indeed Weibull (Collet, 2003). However since the Weibull is a good fit to this data, exploiting the advantages of the Weibull model (such as not assuming proportional hazards) over the Cox model can only help to further understand the analgesia switching in MSK conditions, as we can now attach an underlying distribution to the switch times.

The precision of the Weibull model together with the extension of frailty modelling in this thesis could have positive implications in the use of parametric statistical methods in modelling time to switching analgesia in MSK conditions in primary care. The Weibull model is not reliant on the proportional hazards assumption as the Cox model, it summarises the hazard function in a few parameters, model based predictions of survival rates at a given time are not difficult to estimate and model extrapolation is possible. For example in this thesis, the Weibull shape parameter enabled the projection that the risk of switching to stronger analgesia may decrease with time. The Weibull model can now be considered as a viable alternative to the Cox model in this context. The study raises the possibility that some patient clinical and socio-demographic variables are not only associated with time to switching but actually accelerate the time can be explored, considering that most patients switched analgesia within the first 100 days, and the Weibull model has the characteristic of accelerated failure time.

Frailty models account for more variation and changing hazards over time. This may suggest that if there are suspected important unmeasured covariates, frailty model extension should be explored or if the hazard is constant, an exponential model may be explored too.

## 10.5 Clinical implications

The clinical findings from this thesis have implications which may be important to clinicians, practitioners and research, within the context of MSK conditions and prescription of analgesia. Considering that most patients with a new MSK consultation did not get a prescription at first consultation, the majority were initially on low dose prescriptions and switched later to higher strengths analgesia, we can hypothesise that practitioners do seem to follow the WHO and NICE guidelines in the management of MSK, but some patients conditions prove more difficult to deal with. This is seen in the latent class analysis model which shows some groups who prescribed at least three categories, predominantly the over 60 age group. The over 60 group is also associated with the multiple event switches.

Considering among other reasons that switching may be necessitated by the need to alleviate increasing pain (Boulanger et al., 2011; Benyamin et al., 2008), these findings concur with the current knowledge that MSK conditions deteriorate with age and there is higher risk of adverse effects of NSAIDs and stronger opioids in the older patients (Boulanger et al., 2011; Mercadante and Bruera, 2012). The association of increased consultation with reduced risk of switching suggests that while older patients are more vulnerable, there are potentially some underlying issues that need further investigation. For example re-assurance, supervision and individual strategies of coping with pain and their condition may be at play. This suggests that based on baseline characteristics, clinicians should identify and consider recommending more frequent consultations for some patients than others. In the presence of side effects, clinicians may have to prescribe additional medication to control for side effects instead of switching. For

example some patients may experience nausea with stronger opioids. This might lead to non-compliance, but could be avoided if at a timely review this adverse effect was identified and anti-emetics prescribed until the patient develops tolerance to nausea. In the absence of such a review the patient might determine that the medication and side effects are something they are not prepared to tolerate again and so at some future consultation might decide they would prefer an alternative analgesia.

There are patients at higher risk of switching that clinicians should take note of, when they first present with MSK conditions so that their pain management regime may include increased consultation levels. Varying levels of vigilance might be appropriate, the more boxes a patient ticks on the ‘at risk’ of switching factors, the more priority to review should be given. For example, the patients who may be considered at higher risk of switching are females, elderly and lower social class patients.

## 10.6 Future research

The design of a future study could ensure that different pain locations or types of MSK conditions are considered separately. The reasons for the change in the analgesia can be investigated by location or condition. The consistency of risk factors and the effects of frailty across different causes (MSK conditions, pain locations) of switching analgesia can be explored. Prescribed analgesia and change can be additionally analysed in time periods of say 1 year segments over the follow-up period. As such with adequate data, longitudinal and multilevel models could be fitted accounting for either each location or type of MSK condition as a random effect.

With adequate data, the switching of analgesia can followed through to establish which switching combinations are effective in the long term. For example if the patients under observation eventually moved to secondary care, and if moving into secondary care is considered a negative outcome, then the role of switching associated with this outcome can be modelled. More measures, for example physical function and pain interference can

be measured within the time vicinity of the switches in order to capture not only the reason of switching but the immediate effect of switching, and the trajectory of the MSK condition with respect to treatment can be followed and modelled.

In modelling the latent classes of prescription patterns, longitudinal latent class analysis (LLCA) or latent class growth analysis (LCGA) can be employed. Clusters can then be identified and defined by the trajectory (in a longitudinal rather than cross-sectional way) and followed with respect to potency levels at time intervals, for example, potentially a cluster may consist of patients with a trajectory of increasing potency levels in successive time intervals.

The significance of frailty in this thesis suggests the possible presence of accelerated failure time effects. Accelerated failure time models are parametric models for modelling time to event data which consider that the measured covariates are not only associated with time to the event, but actually accelerate the time to the event. The Weibull model has the special characteristic that it can used in both accelerated failure models as well as when proportional hazards are assumed. Hence exploring further the use of parametric failure time models in evaluating time to switching is recommended.

## 10.7 Conclusion

This study has evaluated prescription patterns from first consultation for MSK condition in primary care and followed up over a five year period, accounting for socio-demographic, clinical and patient-specified factors associated with the changes. The study applied a wide range of statistical techniques to establish model and clinical validity and accuracy. The Weibull model is an effective approach to modelling time to medication switching in MSK conditions. It has been shown that there are baseline clinically relevant patient characteristics associated with being prescribed analgesia, the strength of the analgesia prescribed, and the prescribed medication profile over time. GPs might take account of these factors in planning future management.

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# Appendix A

Table A.1: Snapshot of 50 Read Codes under Chapter 1

| | Read_C~e | Read_Term | Region |
|---|---|---|---|
| 1. | 1229 | No FH: Osteoporosis | unspecifie |
| 2. | 1268 | FH: Osteoporosis | unspecifie |
| 3. | 12I | FH: Arthritis | unspecifie |
| 4. | 12I1 | FH: Rheumatoid arthritis | unspecifie |
| 5. | 12I2 | FH: Osteoarthritis | unspecifie |
| 6. | 12IZ | FH: Musculo-skeletal dis. NOS | unspecifie |
| 7. | 14G | H/O: arthritis | unspecifie |
| 8. | 14G1 | H/O: rheumatoid arthritis | unspecifie |
| 9. | 14G2 | H/O: osteoarthritis | unspecifie |
| 10. | 14G3 | H/O: knee problem | knee |
| 11. | 14G4 | H/O: back problem | back |
| 12. | 14G7 | H/O: hip fracture | hip |
| 13. | 14G8 | H/O: vertebral fracture | neck & bac |
| 14. | 14GZ | H/O: musculo-skeletal dis. NOS | unspecifie |
| 15. | 14H5 | H/O: cong. dislocation - hip | hip |
| 16. | 14J | H/O: injury | unspecifie |
| 17. | 14J1 | H/O: head injury | head |
| 18. | 14J2 | H/O: facial injury | head |
| 19. | 14N30 | H/O Spinal surgery | back |
| 20. | 14O9 | At risk of osteoporosis | unspecifie |
| 21. | 14OD | At risk of osteoporotic fracture | unspecifie |
| 22. | 14T5 | H/O: artificial joint | unspecifie |
| 23. | 14V5 | H/O: arthrodesis | unspecifie |
| 24. | 14V50 | H/0: arthrodesis toe | foot |
| 25. | 16A | Stiff neck symptom | neck |
| 26. | 16A1 | No stiff neck | neck |
| 27. | 16A2 | Stiff neck | neck |
| 28. | 16A3 | Wry neck/torticollis | neck |
| 29. | 16A3 | Torticollis - symptom | neck |
| 30. | 16A3 | Wry neck symptom | neck |
| 31. | 16AZ | Stiff neck symptom NOS | neck |
| 32. | 16B | Bruising symptom | unspecifie |
| 33. | 16B2 | Bruises easily | unspecifie |
| 34. | 16B3 | Spontaneous bruising | unspecifie |
| 35. | 16B4 | Post-traumatic bruising | unspecifie |
| 36. | 16BZ | Bruising symptom NOS | unspecifie |
| 37. | 16C | Backache symptom | back |
| 38. | 16C1 | No backache | back |
| 39. | 16C2 | Backache | back |
| 40. | 16C3 | Backache with radiation | back |
| 41. | 16C4 | Back pain worse on sneezing | back |
| 42. | 16C5 | C/O - low back pain | lower back |
| 43. | 16C6 | Back pain without radiat NOS | back |
| 44. | 16C6 | Back pain without radiation NOS | back |
| 45. | 16C7 | C/O - upper back ache | upper back |
| 46. | 16C9 | Chronic low back pain | lower back |
| 47. | 16CA | Mechanical low back pain | lower back |
| 48. | 16CZ | Backache symptom NOS | back |
| 49. | 16J0 | Swollen calf | lower leg |
| 50. | 16J1 | Swollen toe | foot |

Table A.2: Snapshot of 50 Read Codes under Chapter N

| | Read_C~e | Read_Term | Region |
|---|---|---|---|
| 165. | N | Musculoskelet/connectiv tissue | unspecifie |
| 166. | N | Connective tissue diseases | unspecifie |
| 167. | N0 | Arthropathies and related dis. | unspecifie |
| 168. | N0 | Arthritis/arthrosis | unspecifie |
| 169. | N0-99 | Arthritis/arthrosis | unspecifie |
| 170. | N00 | Diffuse connective tissue dis. | unspecifie |
| 171. | N000 | Systemic lupus erythematosus | unspecifie |
| 172. | N0000 | Disseminated lupus erythemat. | unspecifie |
| 173. | N0001 | Libman-Sacks disease | unspecifie |
| 174. | N0002 | Drug-ind systemic lupus eryth | unspecifie |
| 175. | N0003 | Syst lup eryth + organ/sys inv | unspecifie |
| 176. | N0004 | SLE with pericarditis | unspecifie |
| 177. | N000z | Systemic lupus erythematos.NOS | unspecifie |
| 178. | N000z | Systemic lupus erythematosus NOS | unspecifie |
| 179. | N001 | Scleroderma | unspecifie |
| 180. | N001 | Systemic sclerosis | unspecifie |
| 181. | N0010 | Progressive systemic sclerosis | unspecifie |
| 182. | N0011 | CREST syndrome | unspecifie |
| 183. | N0012 | Syst scleros induc drugs/chems | unspecifie |
| 184. | N002 | Sicca (Sjogren's) syndrome | unspecifie |
| 185. | N002 | Keratoconjunctivitis sicca | unspecifie |
| 186. | N002 | Sicca (Sjogrens) syndrome | unspecifie |
| 187. | N003 | Poikilodermatomyositis | unspecifie |
| 188. | N0030 | Juvenile dermatomyositis | unspecifie |
| 189. | N0031 | Dermatopolymyosit,neoplast dis | unspecifie |
| 190. | N003X | Dermatopolymyositis, unspec | unspecifie |
| 191. | N004 | Polymyositis | unspecifie |
| 192. | N005 | Adult Still's Disease | unspecifie |
| 193. | N006 | Antiphospholipid syndrome | unspecifie |
| 194. | N00y | Other spec.diff.collagen dis. | unspecifie |
| 195. | N00y0 | Eosinophilic fasciitis | unspecifie |
| 196. | N00y1 | Fibrosclerosis systemic | unspecifie |
| 197. | N00z | Collagen disease NOS | unspecifie |
| 198. | N01 | Arthropathy with infections | unspecifie |
| 199. | N010 | Septic arthritis | unspecifie |
| 200. | N0100 | Pyogenic arthr.-site unspecif. | unspecifie |
| 201. | N0101 | Pyogenic arthr.-shoulder regn. | shoulder |
| 202. | N0102 | Pyogenic arthr.-upper arm | upper arm |
| 203. | N0103 | Wrist pyogenic arthritis | forearm |
| 204. | N0104 | Pyogenic arthr.-hand | hand |
| 205. | N0105 | Pyogenic arthr.-pelvic/thigh | pelvis/thi |
| 206. | N0106 | Pyogenic arthr.-lower leg | lower leg |
| 207. | N0107 | Pyogenic arthr.-ankle/foot | ankle/foot |
| 208. | N0108 | Staphylococc arthrit/polyarthr | unspecifie |
| 209. | N0109 | Pneumococc arthrit & polyarthr | unspecifie |
| 210. | N010A | Arthritis in Lyme disease | unspecifie |
| 211. | N010x | Pyogenic arthr.-multiple sites | unspecifie |
| 212. | N010y | Pyogenic arthr.-other specif. | unspecifie |
| 213. | N010z | Pyogenic arthr.-NOS | unspecifie |
| 214. | N011 | Sex acquired reactive arthrop | unspecifie |
| 215. | N0110 | Sex acqd reac arthrop-unspec | unspecifie |

Table A.3: Snapshot of 50 Read Codes under Chapter R

| | Read_C~e | Read_Term | Region |
|---|---|---|---|
| 3101. | R00z2 | [D]General aches and pains | unspecifie |
| 3102. | R00z2 | [D]Pain generalized | unspecifie |
| 3103. | R01 | [D]Musculoskeletal symptoms | unspecifie |
| 3104. | R01 | [D]Nerv/musculoskeletal sympt. | unspecifie |
| 3105. | R01z | [D]Nerv/musculoskel.symp.other | unspecifie |
| 3106. | R01z1 | [D]Growing pains - limbs | limb |
| 3107. | R01z2 | [D]Musculoskeletal pain | unspecifie |
| 3108. | R01zz | [D]Nerv/musculoskel.sympt.NOS | unspecifie |
| 3109. | R0224 | [D]Loc swellmass/lumpup limb | upper limb |
| 3110. | R0225 | [D]Loc swelmass/lumplow limb | lower limb |
| 3111. | R0229 | [D]Foot lump | foot |
| 3112. | R022A | [D]Shoulder lump | shoulder |
| 3113. | R022B | [D]Lump on hand | hand |
| 3114. | R022C | [D]Lump on knee | knee |
| 3115. | R022D | [D]Lump on leg | lower limb |
| 3116. | R022F | [D]Lump on thigh | thigh |
| 3117. | R022G | [D]Finger lump | hand |
| 3118. | R022H | [D]Wrist lump | wrist |
| 3119. | R022K | [D]Buttock swelling | buttock |
| 3120. | R027 | [D]Spontaneous bruising | unspecifie |
| 3121. | R027 | [D]Spontaneous ecchymoses | unspecifie |
| 3122. | R04 | [D]Head and neck symptoms | head/neck |
| 3123. | R0400 | [D]Facial pain | head |
| 3124. | R040z | [D]Pain in head NOS | head |
| 3125. | R040z | [D]Jaw pain | head |
| 3126. | R042 | [D]Neck swelling/mass/lump | neck |
| 3127. | R042 | [D]Swell.masslump head/neck | head/neck |
| 3128. | R0420 | [D]Swelling face | head |
| 3129. | R0420 | [D]Swelling in head or neck | head/neck |
| 3130. | R0422 | [D]Lump in head or neck | head/neck |
| 3131. | R04z | [D]Lesion face | head |
| 3132. | R04z | [D]Head and neck other sympt. | head/neck |
| 3133. | R04zz | [D]Head and neck symptoms NOS | head/neck |
| 3134. | R065 | [D]Chest pain | chest |
| 3135. | R0650 | [D] Retrosternal chest pain | chest |
| 3136. | R0650 | [D]Chest pain unspecified | chest |
| 3137. | R0652 | [D]Anterior chest wall pain | chest |
| 3138. | R0659 | [D]Parasternal chest pain | chest |
| 3139. | R065A | [D]Musculoskeletal chest pain | chest |
| 3140. | R065B | [D]Non-cardiac chest pain | chest |
| 3141. | R065B | [D]Non cardiac chest pain | chest |
| 3142. | R065C | [D]Retrosternal chest pain | chest |
| 3143. | R065D | [D]Central chest pain | chest |
| 3144. | R065z | [D]Chest pain NOS | chest |
| 3145. | R066 | [D]Swelling mass lump chest | chest |
| 3146. | R0661 | [D]Chest lump | chest |
| 3147. | R090B | [D]Groin pain | pelvis |
| 3148. | R090C | [D]Loin pain | pelvis |
| 3149. | R090G | [D]Pelvic and perineal pain | pelvis |
| 3150. | R090G | [D] Pelvic pain | pelvis |
| 3151. | R090G | [D] Perineal pain | pelvis |

# Appendix B

### Kaplan Meier curves of survival estimates for the baseline variables

The appendix contains Kaplan Meier curves illustrating differences in survival rates between the categories of selected baseline variables for chapter 6, 7 and 8. Figure B.6.1 to B.6.9 illustrate the survival estimates for switching to any analgesia for chapter 6 analysis.

Figure B.6.1: Survival estimate curves by age group

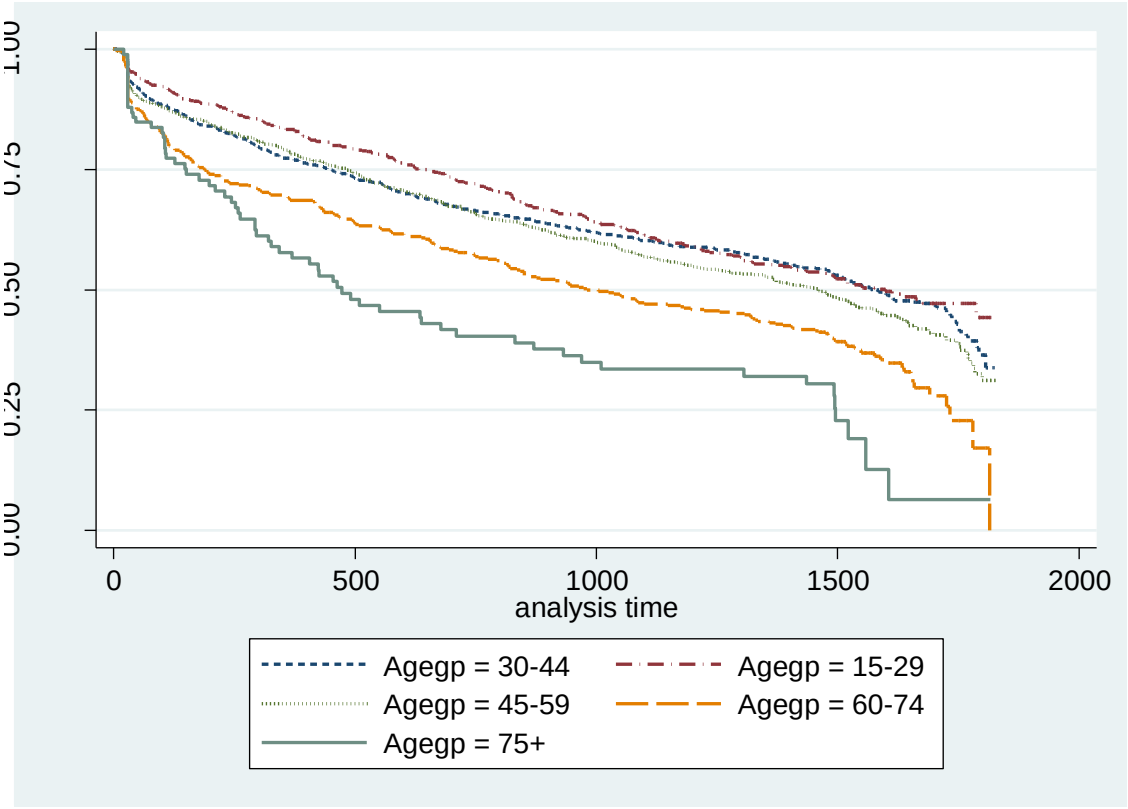

Figure B.6.2: Survival estimate curves by gender

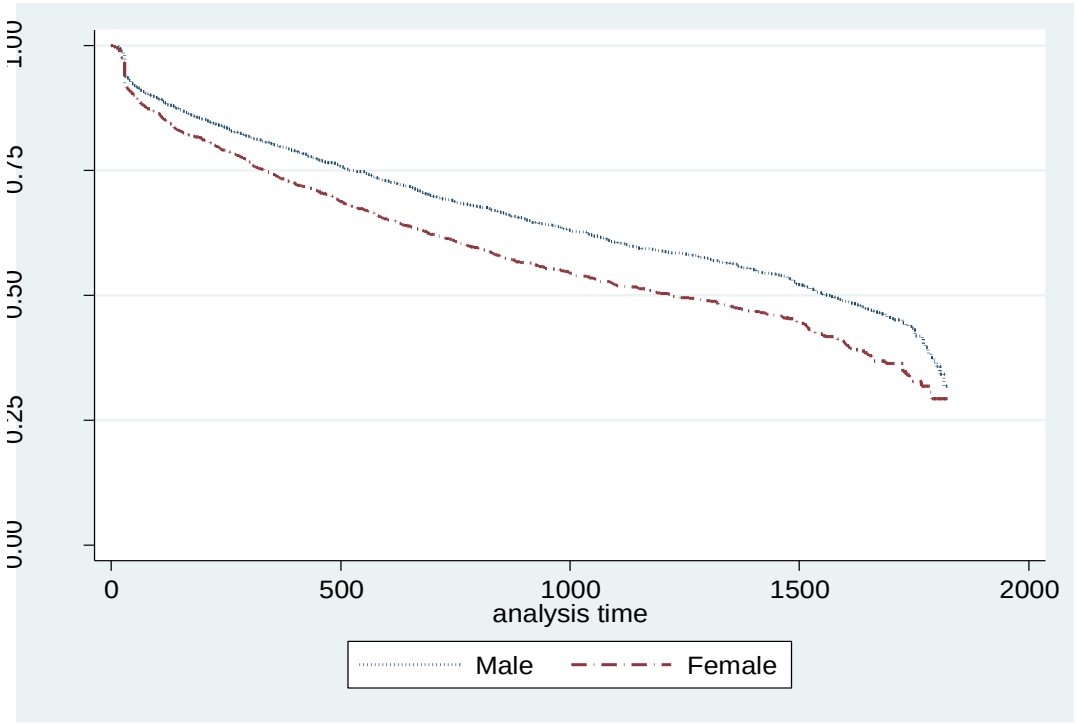


Figure B.6.3: Survival estimate curves by presence of comorbidity

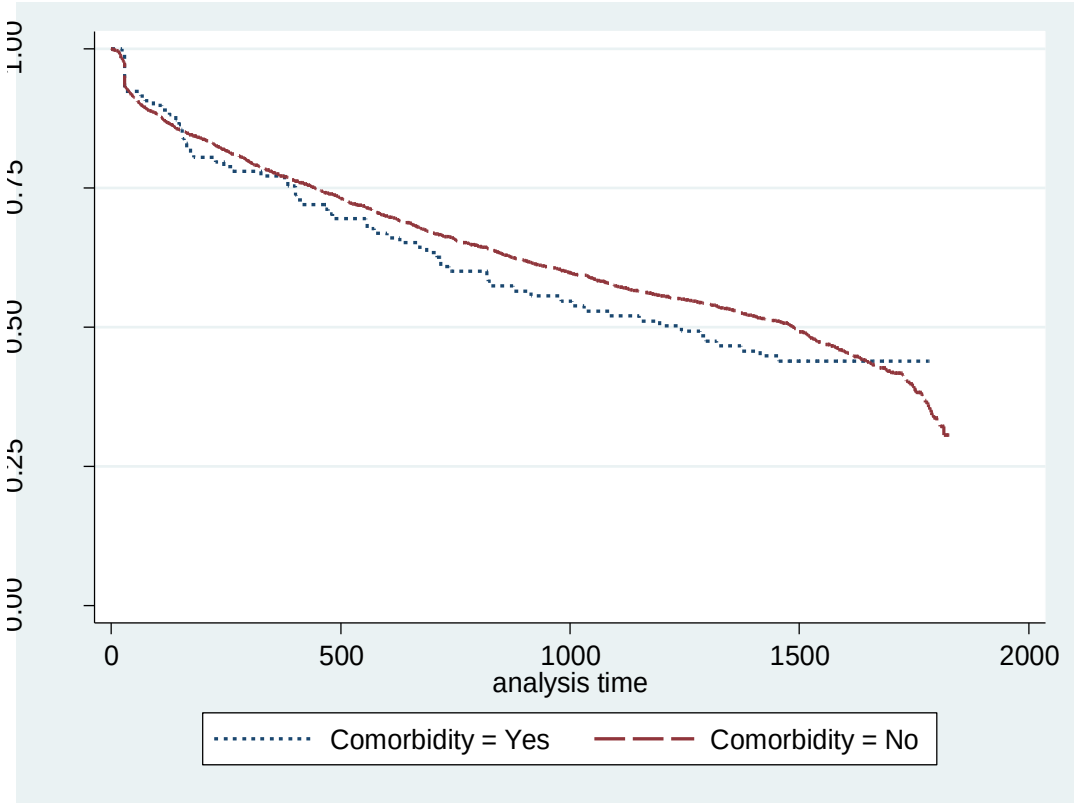

Figure B.6.4: Survival estimate curves by level of deprivation

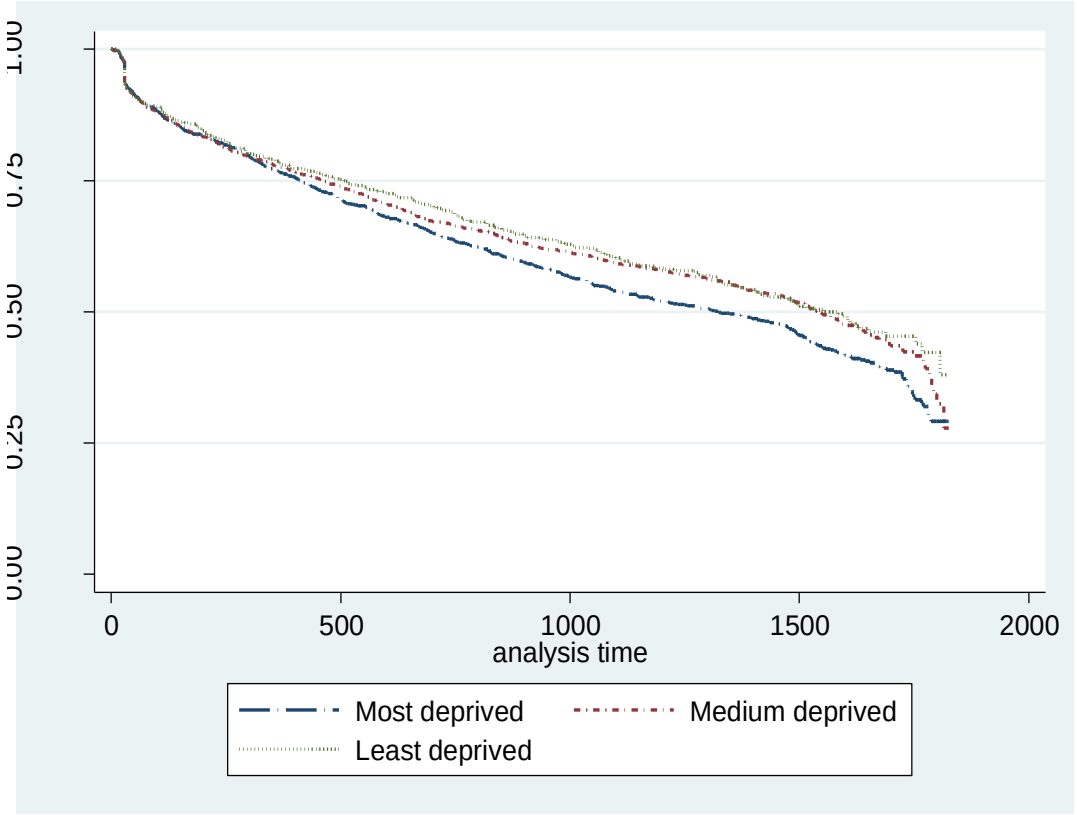


Figure B.6.5: Survival estimate curves by pain location

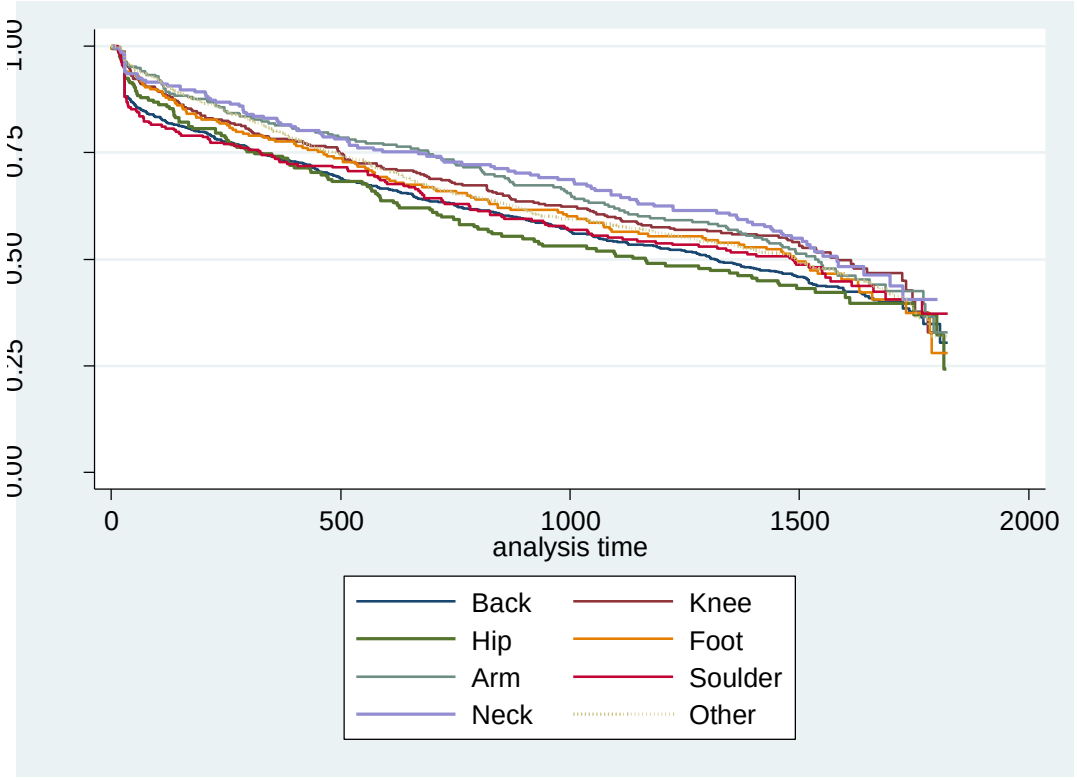

Figure B.6.6: Survival estimate curves by registered general practice

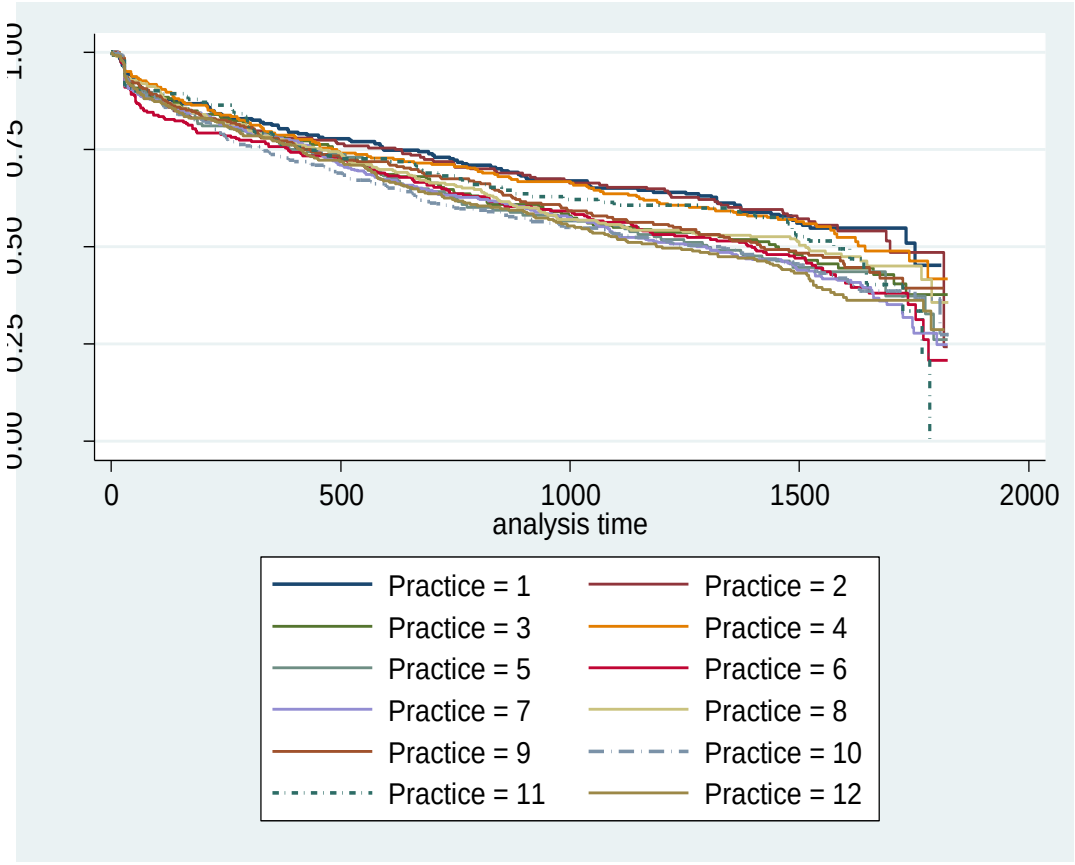


Figure B.6.7: Survival estimate curves by member of staff consulted

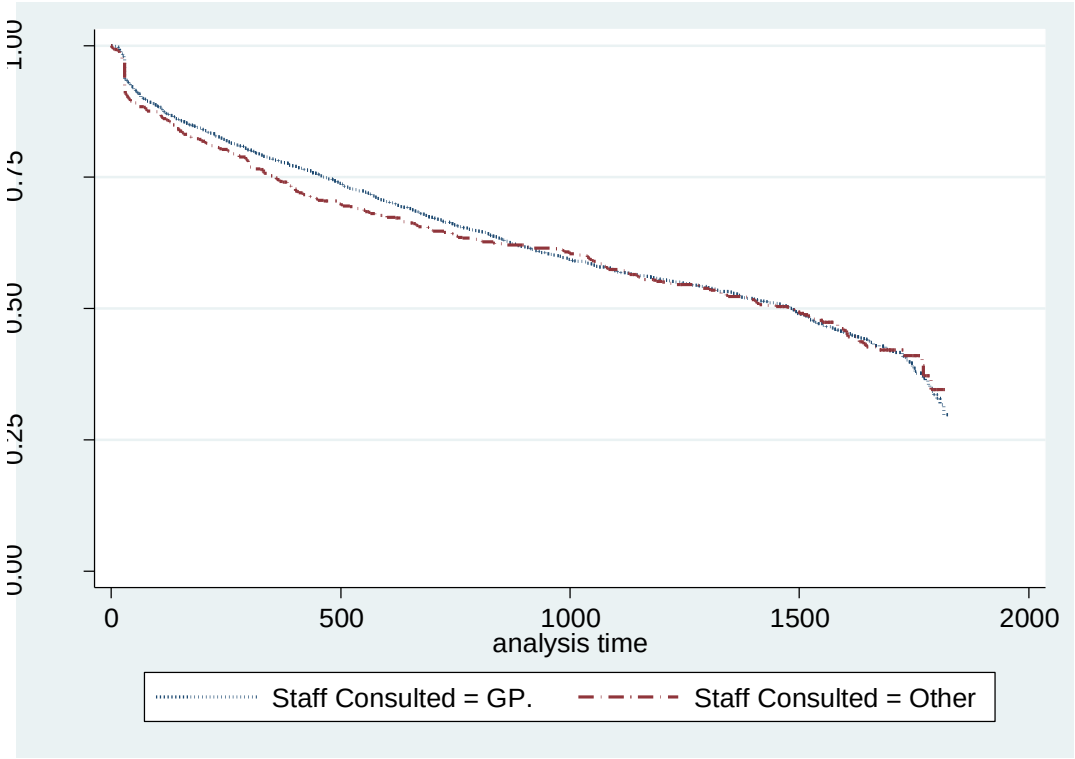

Figure B.6.8: Survival estimate curves by previous prescribed analgesia

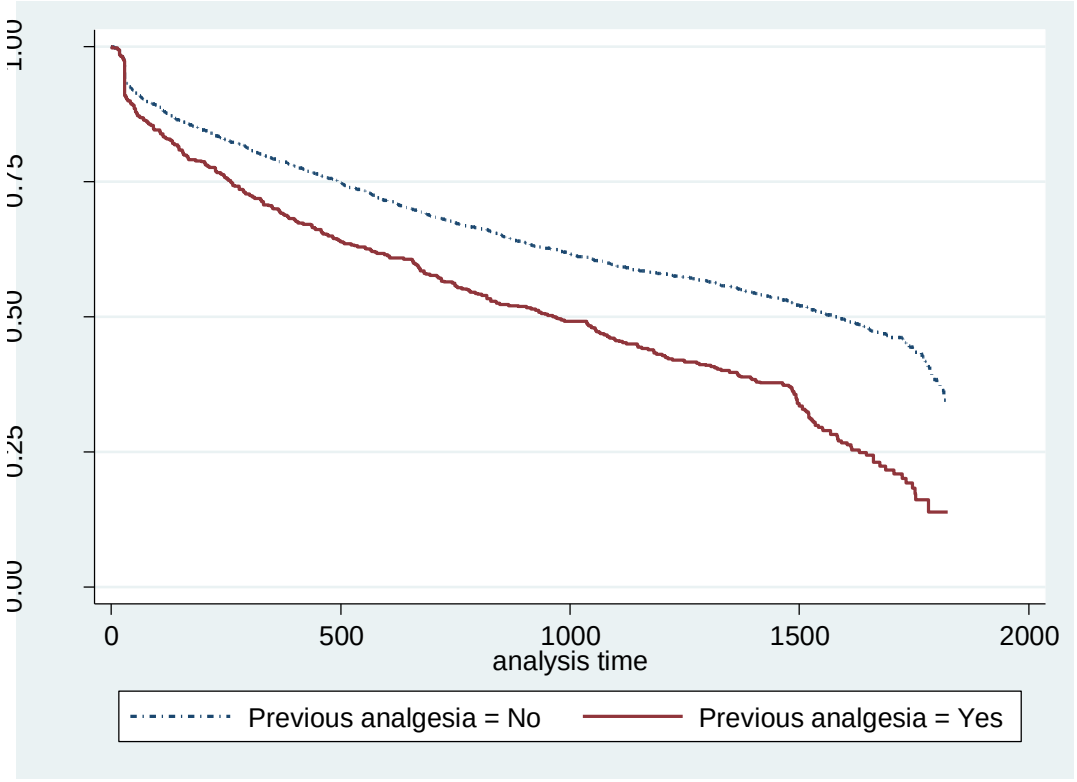


Figure B.6.9: Survival estimate curves by previous musculoskeletal consultation

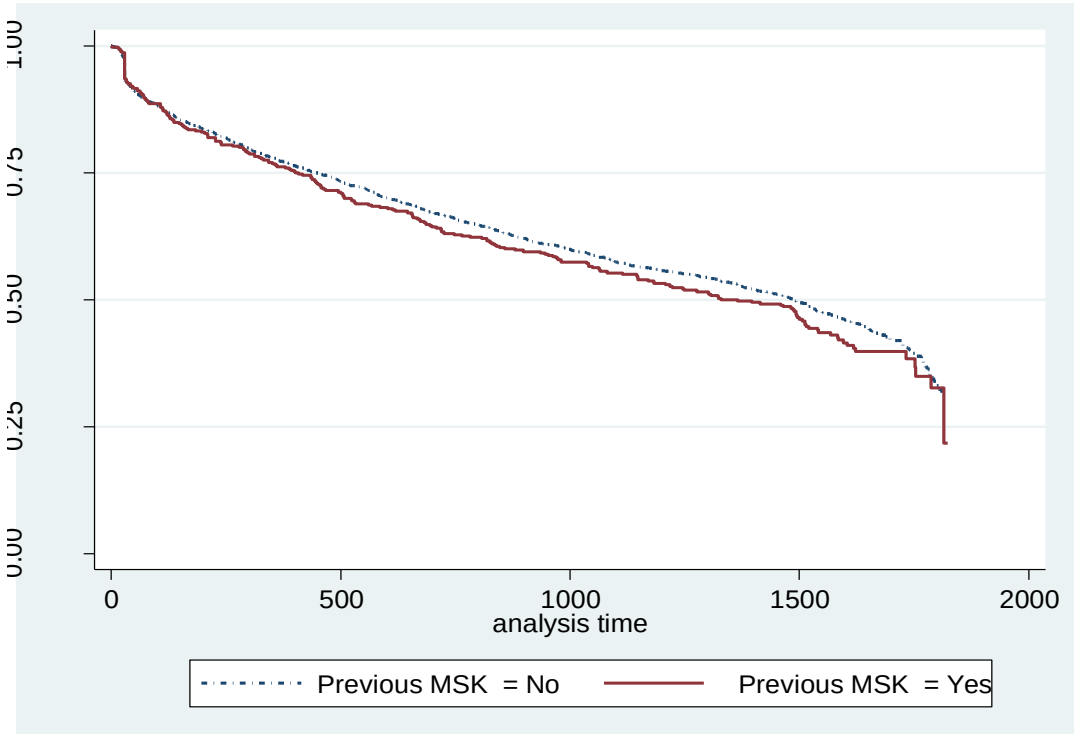

Figure B.7.1 to B.7.8 illustrate the survival estimates for switching from low potency analgesia (no medication, basic and weak analgesia) to stronger analgesia (moderate and strong analgesia) for chapter 7 analysis.

Figure B.7.1: Survival estimate curves by age groups

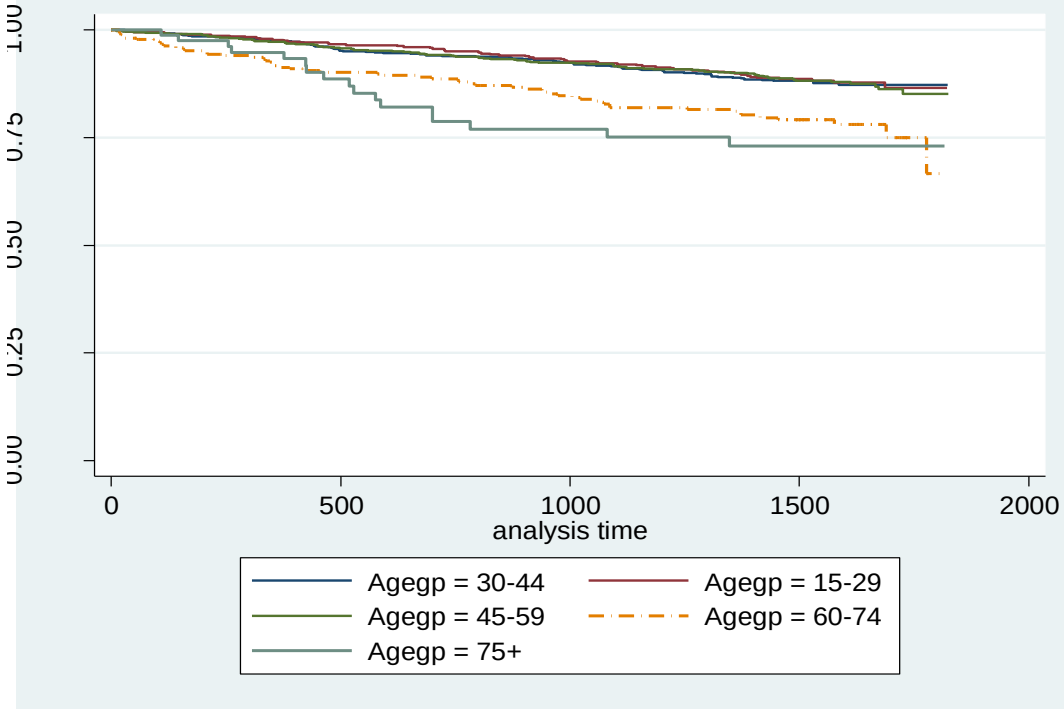


Figure B.7.2: Survival estimate curves by gender

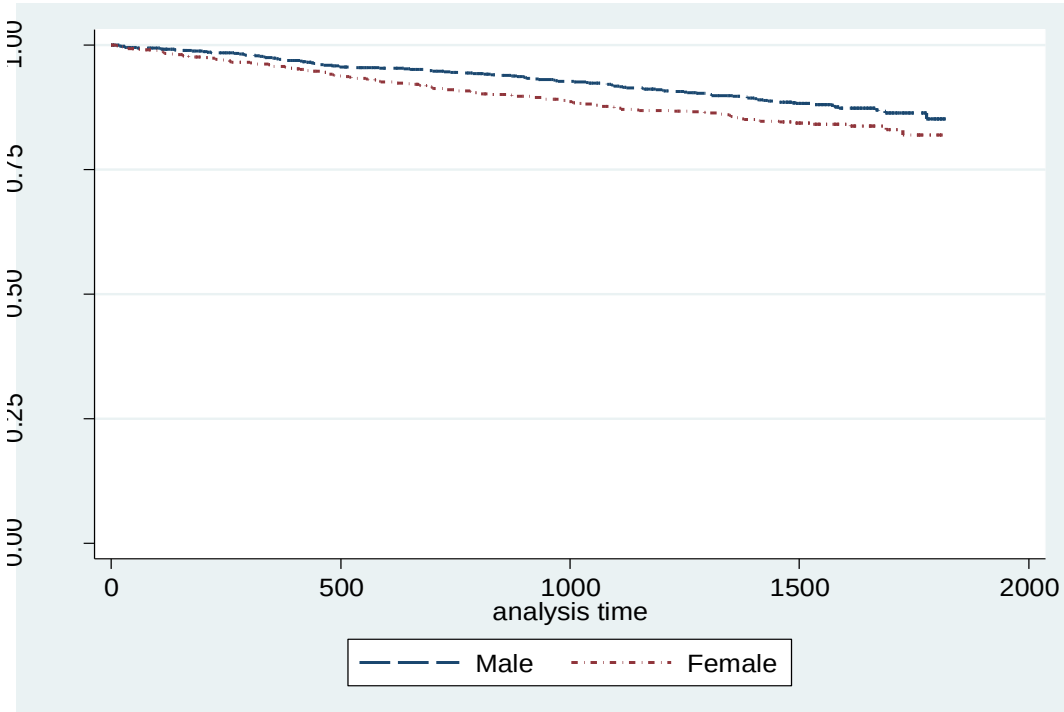

Figure B.7.3: Survival estimate curves by the presence of comorbidity

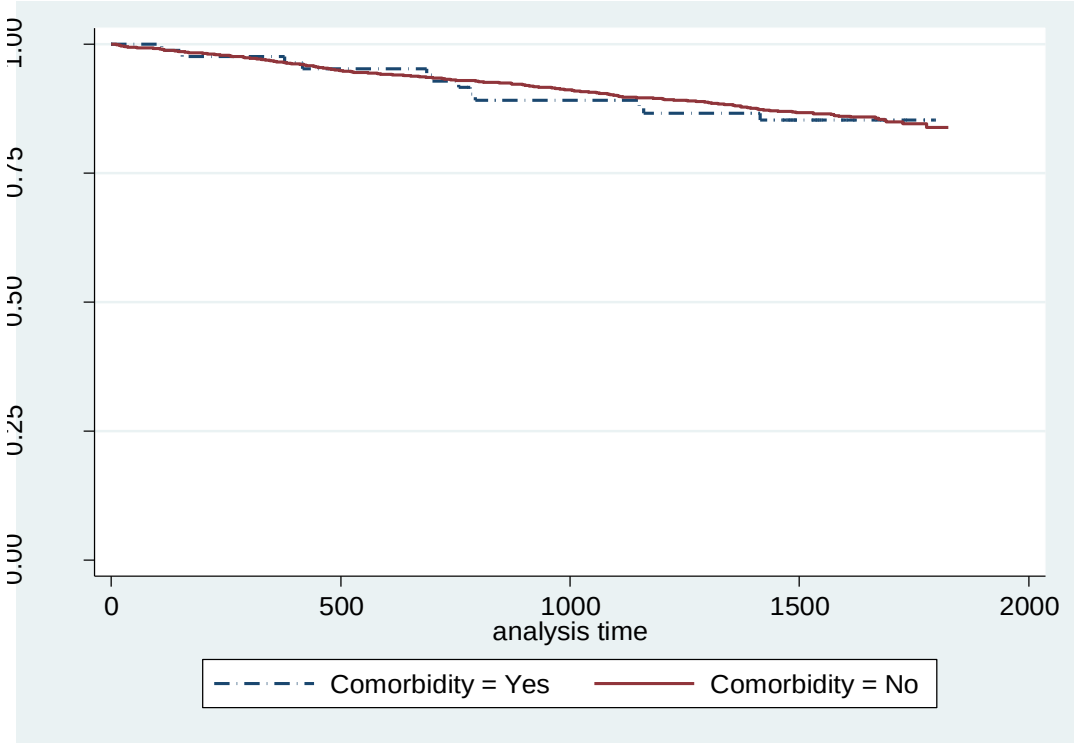


Figure B.7.4: Survival estimate curves by levels of deprivation

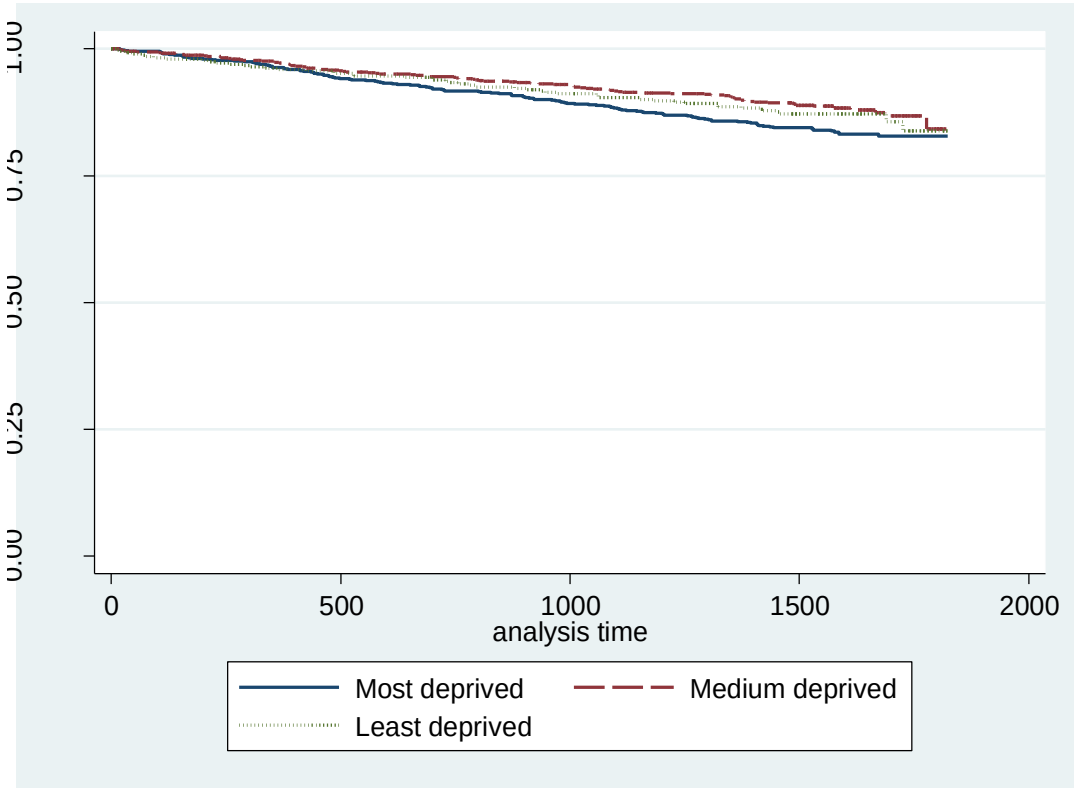

Figure B.7.5: Survival estimate curves by pain location

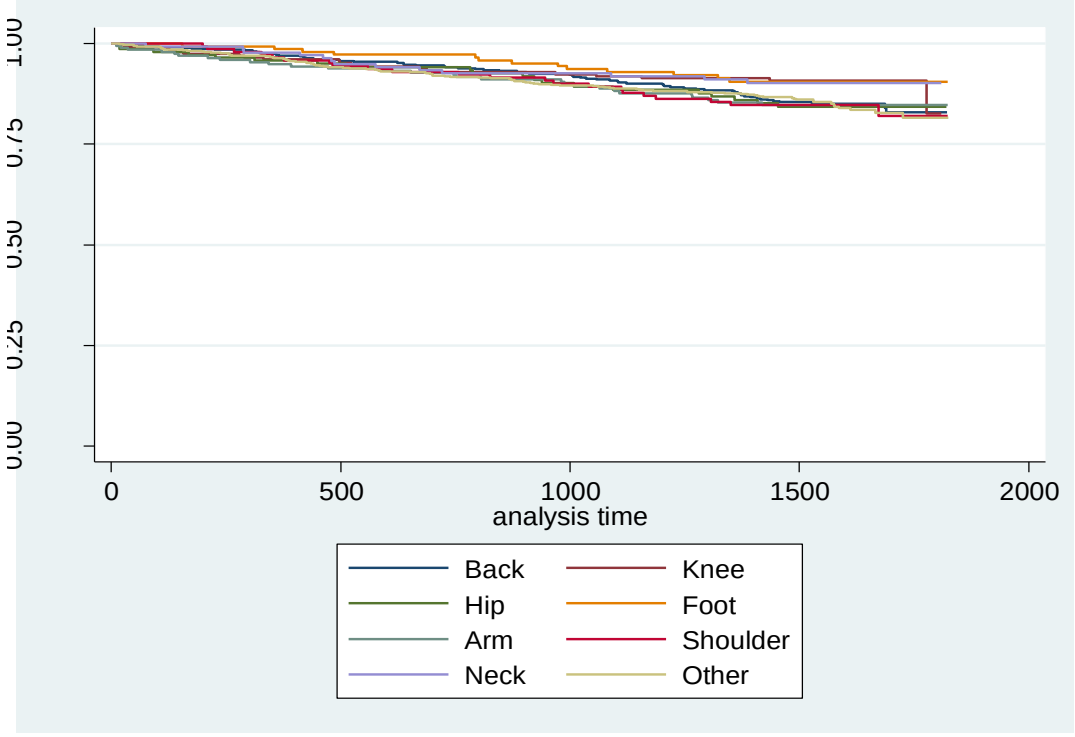


Figure B.7.6: Survival estimate curves by member of staff consulted

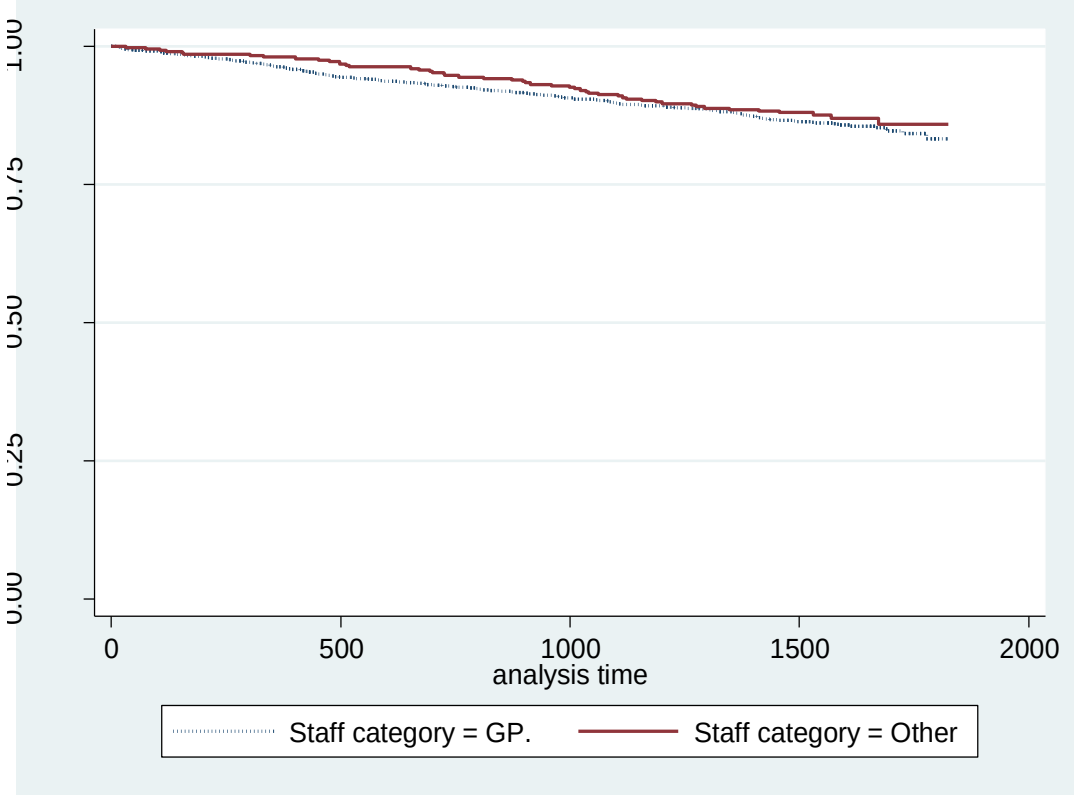

Figure B.7.7: Survival estimate curves by previous prescribed analgesia

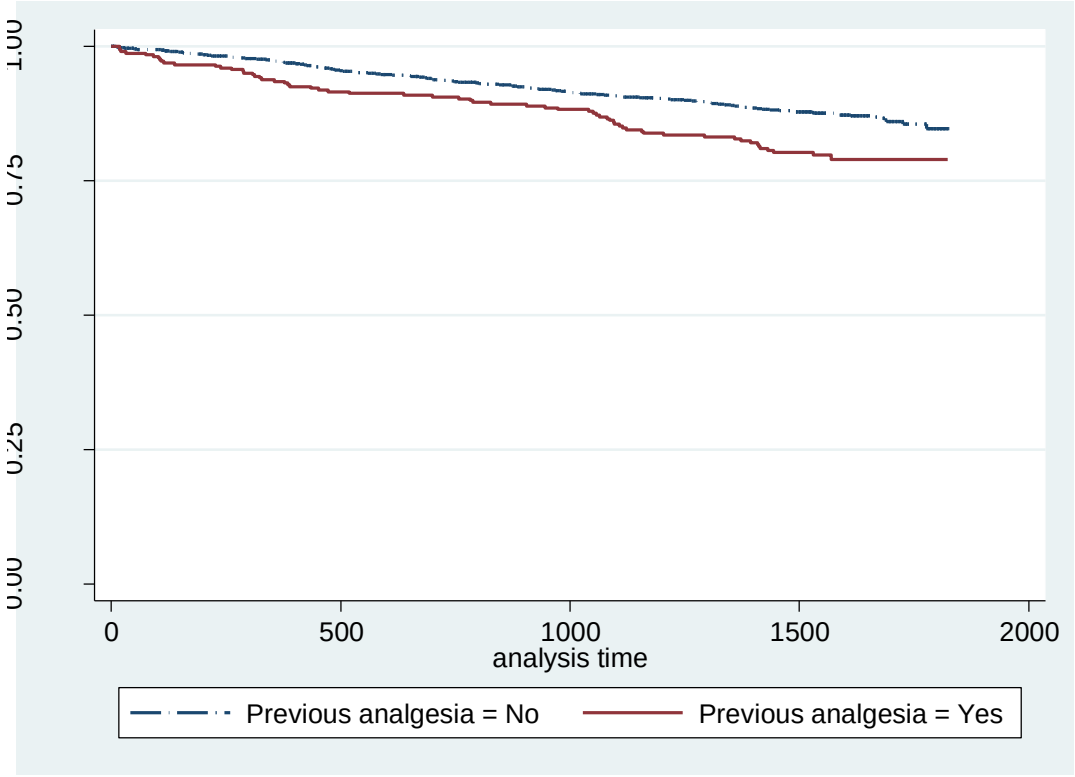


Figure B.7.8: Survival estimate curves by previous MSK consultation

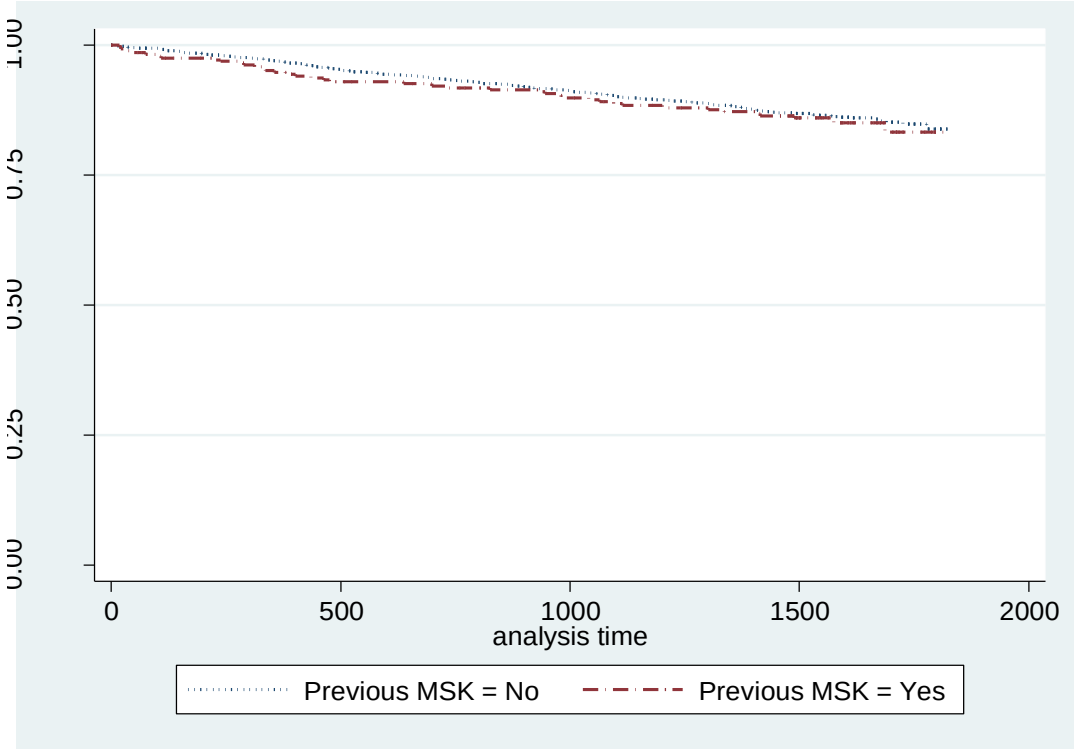

Figure B.8.1 to B.8.13 illustrate the survival estimates for switching from low potency analgesia (no medication, basic and weak analgesia) to stronger analgesia (moderate and strong analgesia) for chapter 8 analysis (NorStOP data).

Figure B.8.1: Survival estimate curves by age group

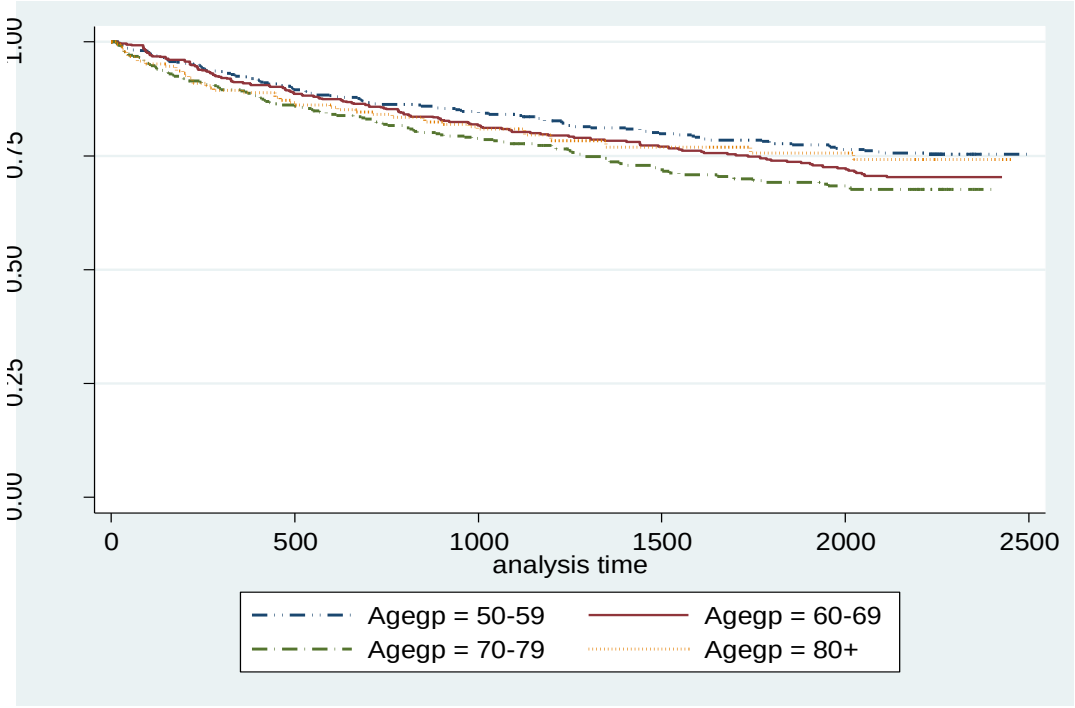


Figure B.8.2: Survival estimate curves by gender

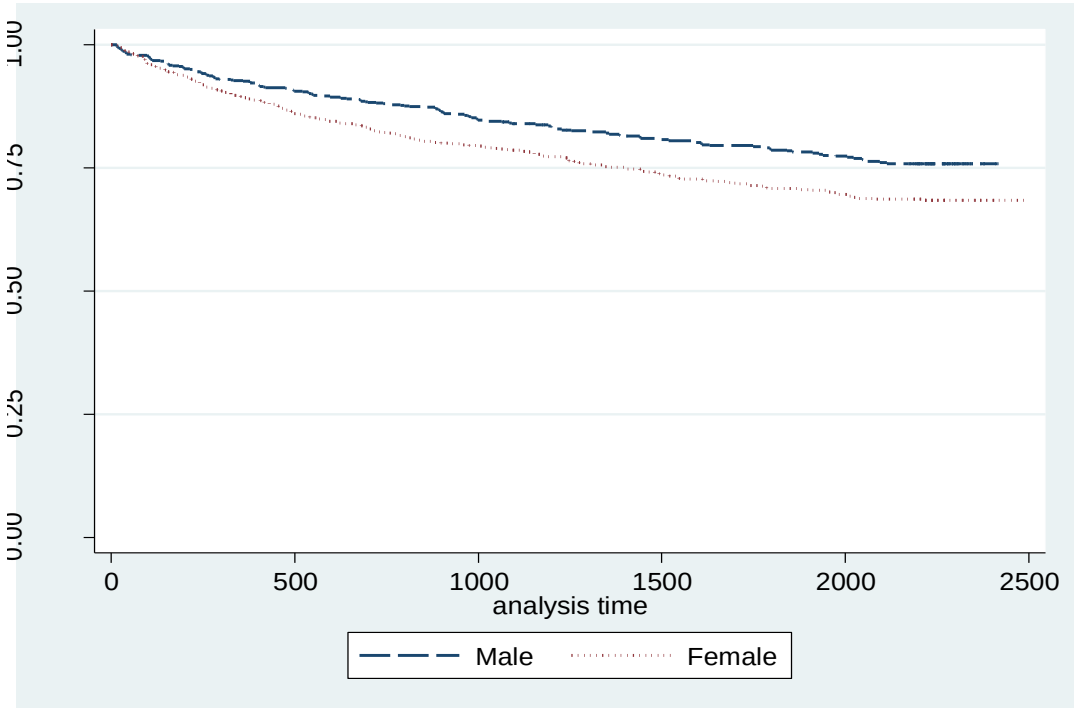

Figure B.8.3: Survival estimate curves by previous prescribed analgesia

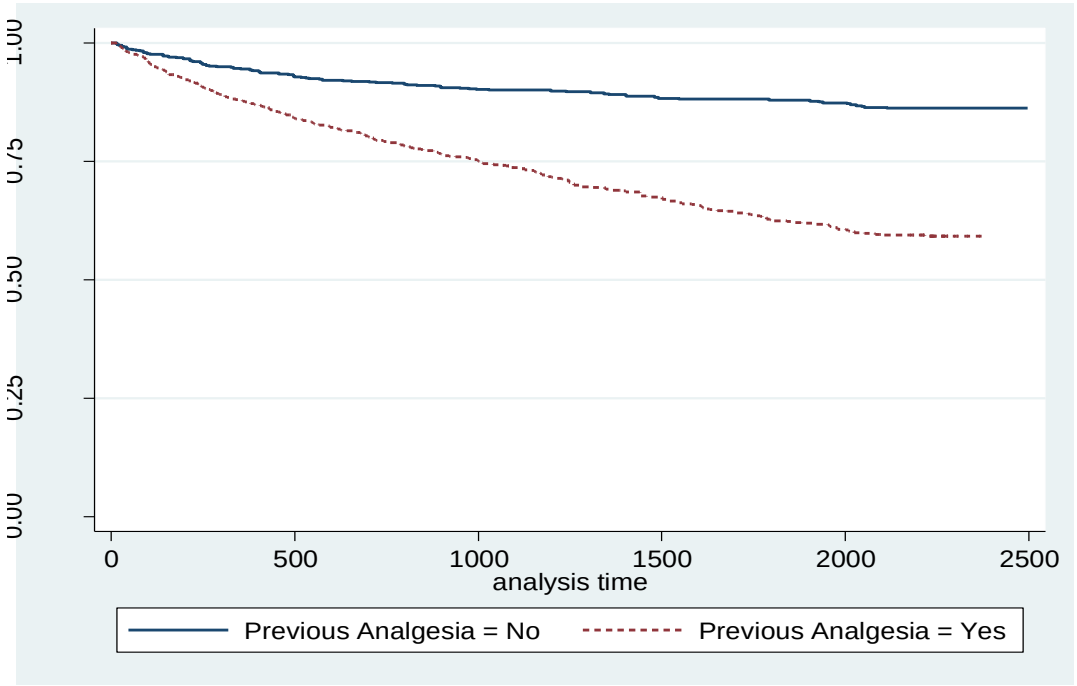


Figure B.8.4: Survival estimate curves by analgesia prescribed on initial consultation

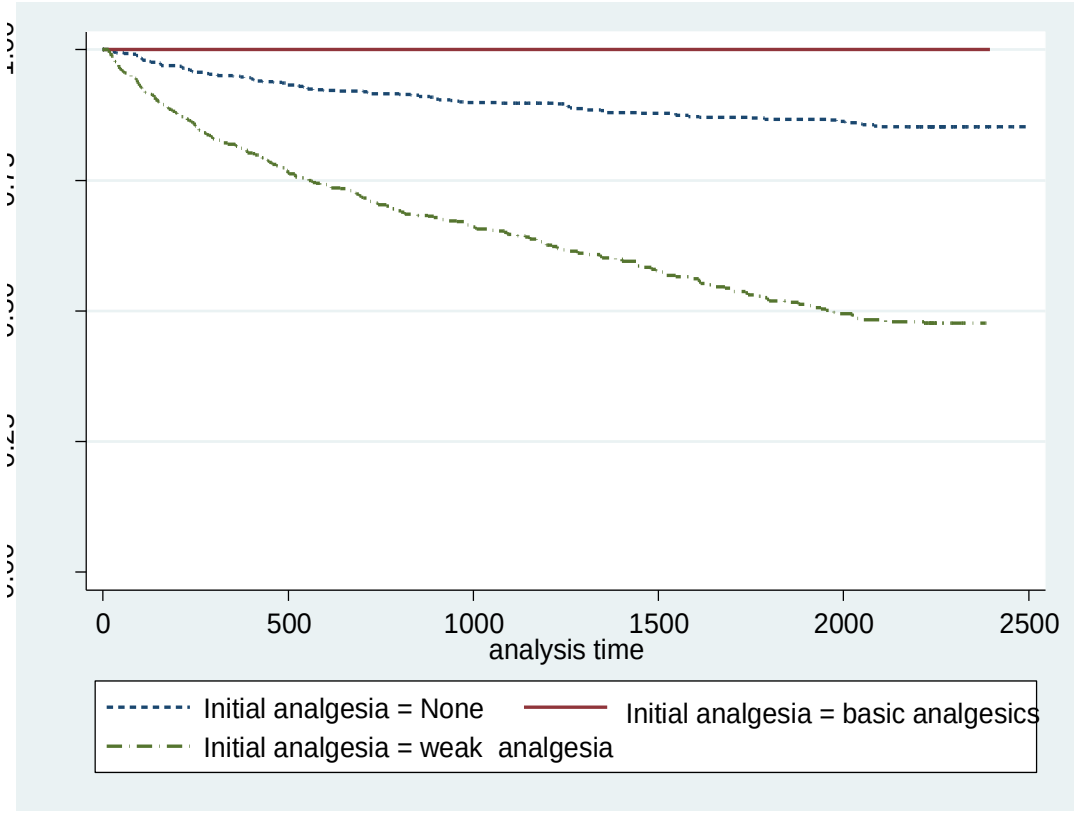

Figure B.8.5: Survival estimate curves by age group

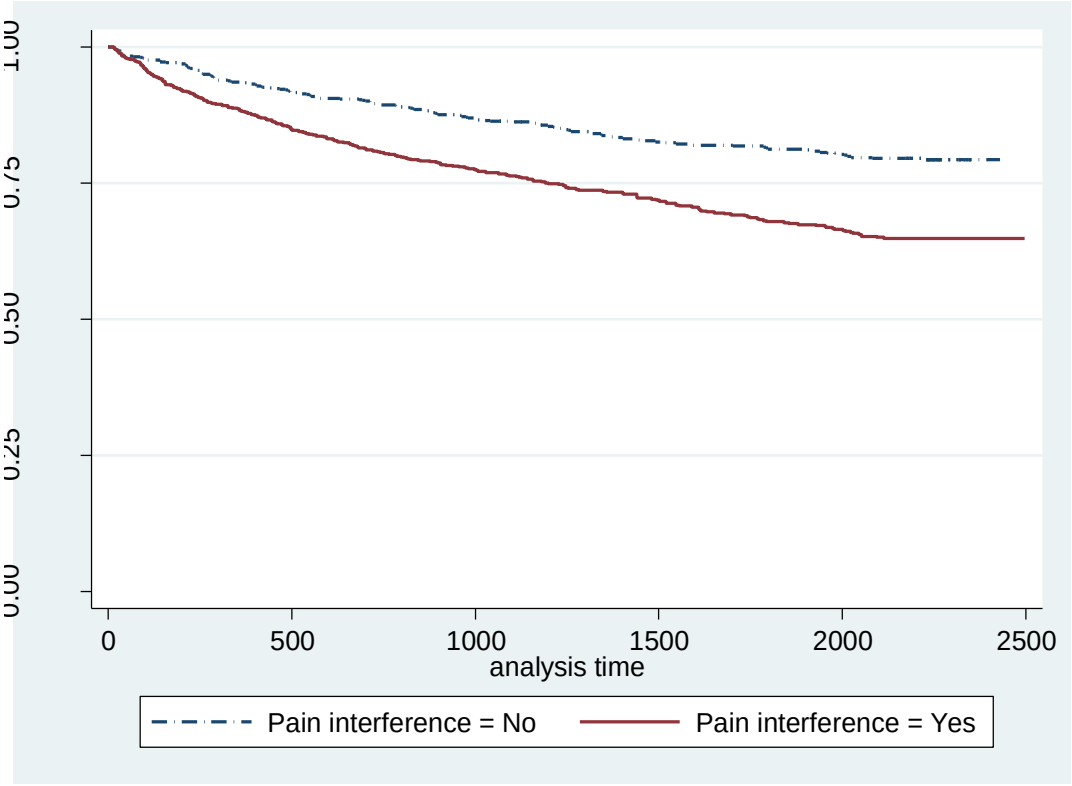


Figure B.8.6: Survival estimate curves by over the counter medication used

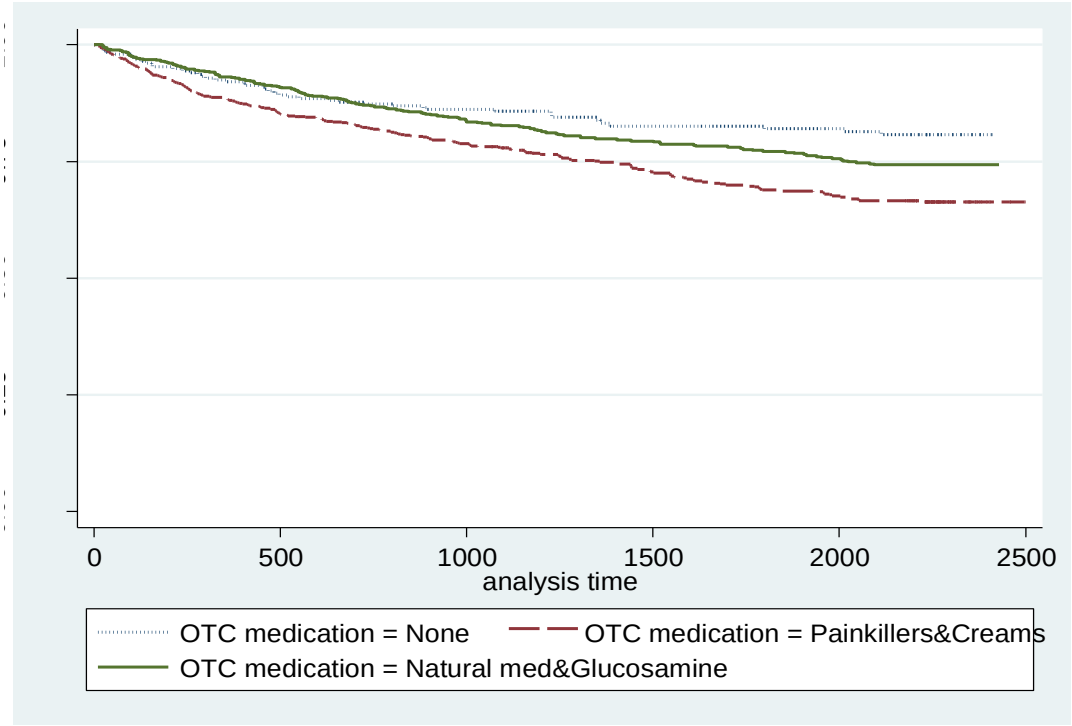

Figure B.8.7: Survival estimate curves by patient BMI

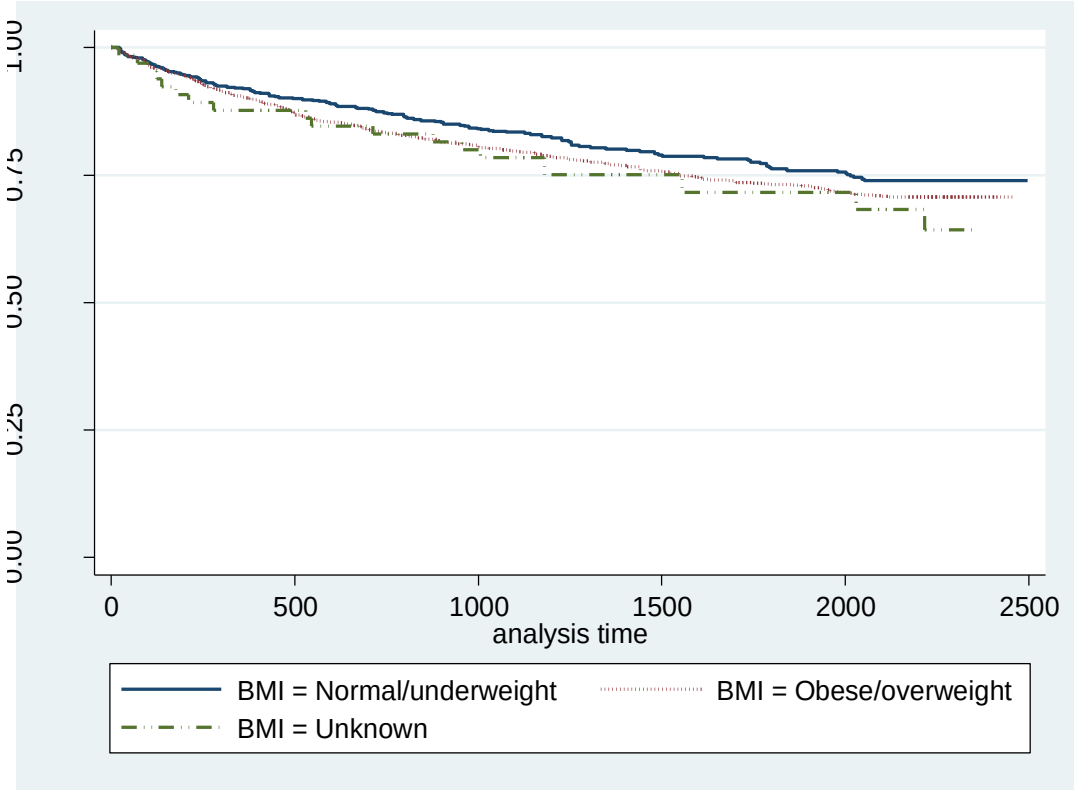


Figure B.8.8: Survival estimate curves by the presence of selected comorbidity

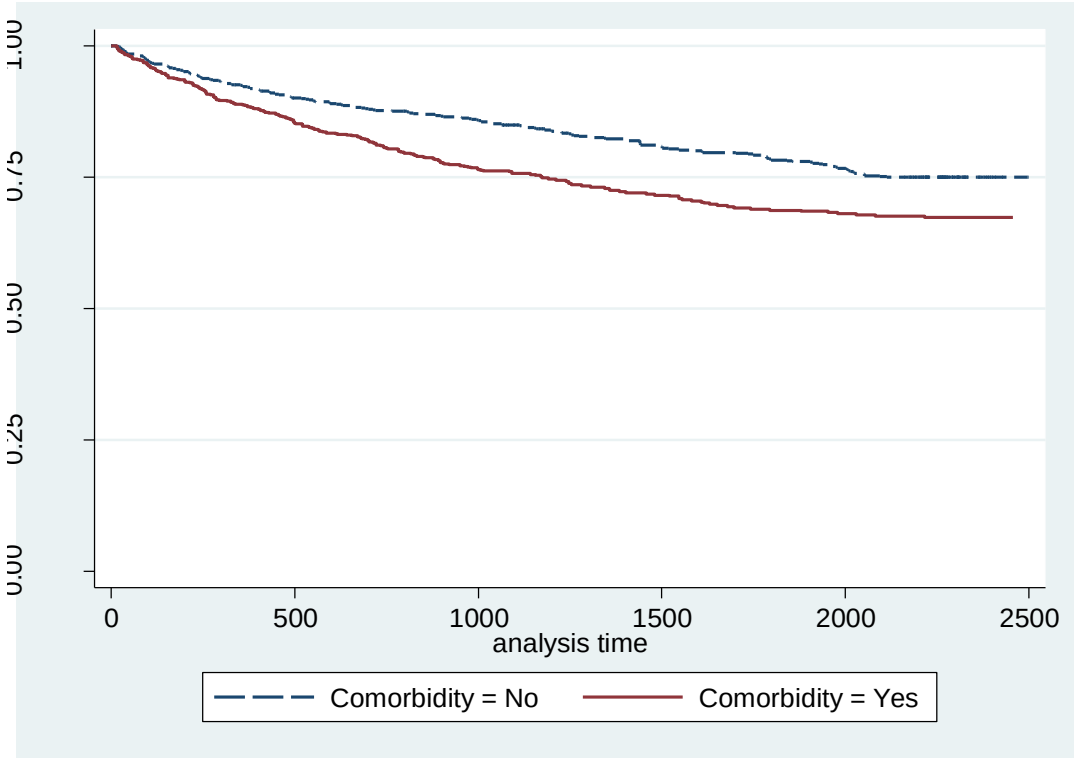

Figure B.8.9: Survival estimate curves by adequate access to GP

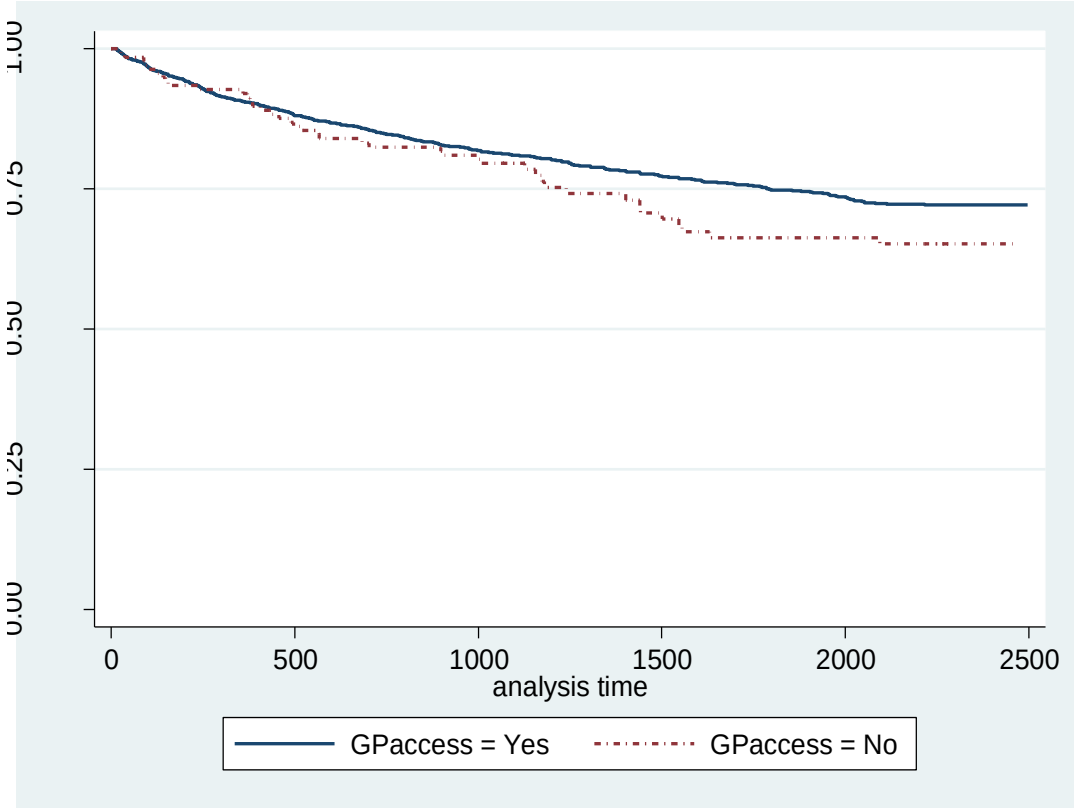


Figure B.8.10: Survival estimate curves by age group

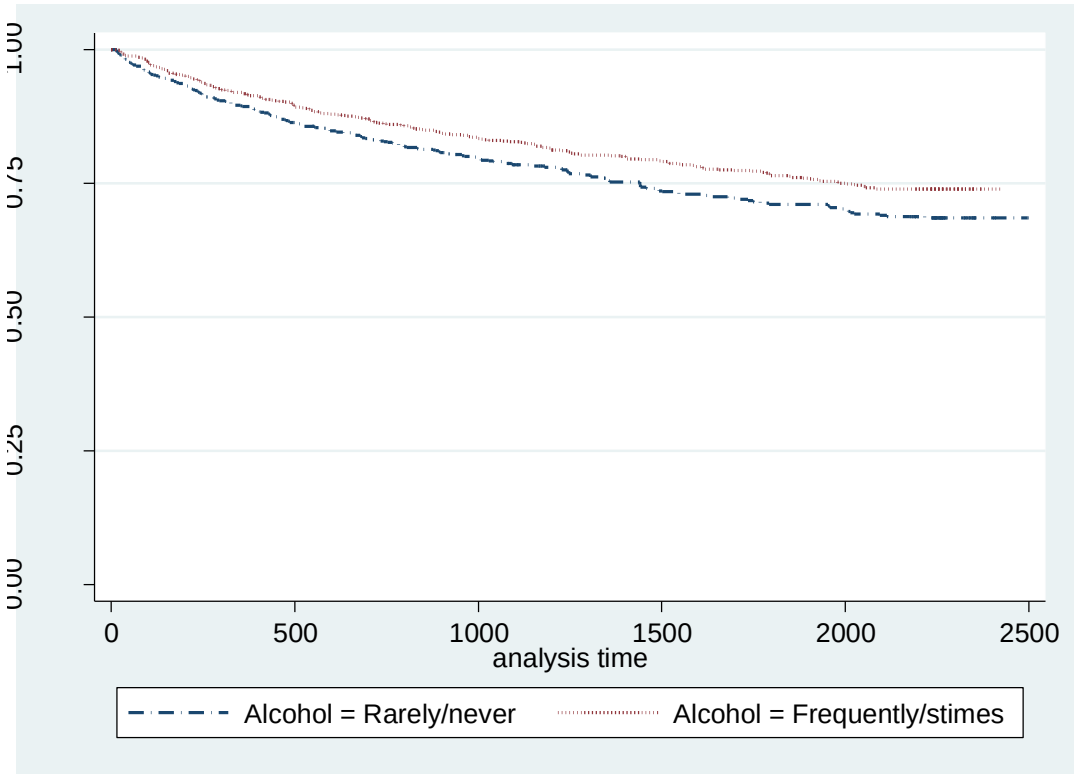

Figure B.8.11: Survival estimate curves by presence of widespread pain