Intrathecal drug delivery for chronic non-malignant pain: pharmacological complications, cost effectiveness and long-term outcomes

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Intrathecal drug delivery for chronic non-malignant pain: pharmacological complications, cost effectiveness and long-term outcomes

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Abstract

Background and aims
Intrathecal drug delivery (IDD) is a last resort treatment for the management of severe chronic pain due to its invasive nature, high initial cost, concerns about long-term opioid use and possible complications related to the procedure. Although it has been available since 1981 some of the possible complications of this treatment have only recently been observed and are not fully understood. Additionally the current available literature exploring the long-term effectiveness and cost effectiveness of IDD is limited. The aims of this study were to explore some of the least investigated complications, long-term effectiveness and cost effectiveness of IDD.

Methods
The methodology used included both retrospective and prospective data collection to investigate intrathecal morphine dose escalation, granuloma formation, hormonal effects, bone mineral density (BMD), long-term effectiveness and cost effectiveness of IDD.

Results
A model was developed that allows the prediction of the intrathecal opioid dose at year six of therapy based on year two dose and the duration of pain prior to initiation of intrathecal therapy. An association between opioid concentration and formation of intrathecal granulomas was confirmed for the first time in humans and a tool to assist recognition of asymptomatic granulomas was identified. It was observed that hypogonadism is prevalent in this population and free testosterone is a more reliable method to diagnose this condition. An association between low BMD and hypogonadism as a result of IDD was reported for the first time. Effectiveness of IDD was verified following a mean of 13.5 years of therapy. A new concept with implications for cost analyses was identified.

Conclusion
This study presents a thorough analysis of IDD therapy. Despite potential side effects, this therapy can be effective over periods longer than 10 years in appropriately selected patients. The cost effectiveness of IDD systems was confirmed based on real patients’ data. Most side effects can be prevented with attentive follow-ups.
Aos meus pais
por todo o vosso apoio...
Acknowledgements

I owe my deepest gratitude to Professor Jon Raphael and Professor Robert Ashford who believed in my capabilities and gave me this opportunity. Their expertise, guidance, and unfailing support have been essential to the completion of this project. I could not have asked for better supervisors.

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My time at Birmingham City University was more enjoyable thanks to my colleagues at the Graduate School. The memorable ski trip and Bala weekend will always be fond memories.

A special thanks to Ellie the cat who closely oversaw most of this thesis. Her timely biting and scratching always ensured that I would not get distracted from my work.

I am forever indebted to my family, and especially my amazing parents who have always encouraged me to pursue my goals even if it meant that I would have to move to another country. My special thanks to my friends in Portugal who always find the time to see me when I go back and also my friends in the United Kingdom who have welcomed me and helped me to feel at home.

Finally, to Elizabeth Sparkes, my wife to be and best friend, my sincere thanks for all her love, encouragement and patience...
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<th>Definition</th>
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<tbody>
<tr>
<td>AAN</td>
<td>American Academy of Neurology</td>
</tr>
<tr>
<td>AHRQ</td>
<td>Agency for Health Care Research and Quality</td>
</tr>
<tr>
<td>AT</td>
<td>Albumin-bound testosterone</td>
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<tr>
<td>BMD</td>
<td>Bone mineral density</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>BPI</td>
<td>Brief Pain Inventory</td>
</tr>
<tr>
<td>BT</td>
<td>Bioavailable testosterone</td>
</tr>
<tr>
<td>CG</td>
<td>Control group</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CRPS</td>
<td>Complex regional pain syndrome</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual energy X-ray absorptiometry</td>
</tr>
<tr>
<td>DoH</td>
<td>Declaration of Helsinki</td>
</tr>
<tr>
<td>FAI</td>
<td>Free androgen index</td>
</tr>
<tr>
<td>FBSS</td>
<td>Failed back surgery syndrome</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>FT</td>
<td>Free testosterone</td>
</tr>
<tr>
<td>GCT</td>
<td>Gate control theory</td>
</tr>
<tr>
<td>GG</td>
<td>Granuloma group</td>
</tr>
<tr>
<td>GnRH</td>
<td>Gonadotropin releasing hormone</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>GPCR</td>
<td>G protein-coupled receptor</td>
</tr>
<tr>
<td>HPG</td>
<td>Hypothalamic-pituitary-gonadal axis</td>
</tr>
<tr>
<td>HRG</td>
<td>Health Resource Group</td>
</tr>
<tr>
<td>IASP</td>
<td>International Association for the Study of Pain</td>
</tr>
<tr>
<td>IDD</td>
<td>Intrathecal drug delivery</td>
</tr>
<tr>
<td>IDDS</td>
<td>Intrathecal drug delivery systems</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
</tr>
<tr>
<td>MPQ</td>
<td>McGill Pain Questionnaire</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger ribonucleic acid</td>
</tr>
</tbody>
</table>
NICE  National Institute for Health and Clinical Excellence  
NHS  National Health Service  
NK1  Neurokinin 1  
NMDA  N-methyl-D-aspartate  
NRS  Numeric rating scale  
ORL1  Opioid-receptor-like 1  
PCT  Primary Care Trust  
PKC  Protein kinase C  
PNS  Peripheral nervous system  
QALY  Quality adjusted life year  
RCT  Randomised controlled trial  
REC  Research Ethics Committee  
RHH  Russells Hall Hospital  
SCS  Spinal cord stimulation  
SD  Standard deviation  
SEM  Standard error of mean  
SG  Substantia gelatinosa  
SHBG  Sex hormone binding globulin  
SPSS  Statistical Package for the Social Sciences  
STIR  Short Tau Inversion Recovery  
TT  Total testosterone  
USPSTF  United States Preventive Services Task Force  
VAS  Visual analogue scale  
WDR  Wide dynamic range  
WHO  World Health Organization  

**Scientific measures**

- g/cm²  Gram per square centimetre  
- IU/L  International units per litre  
- mL/day  Millilitres per day  
- mg/day  Milligrams per day  
- mg/mL  Milligrams per millilitre  
- nmol/L  Nanomoles per litre  
- pmol/L  Picomoles per litre
Publications, presentations and grants related to research presented within this thesis

Journal publications:
Duarte RV, Raphael JH, Southall JL, Baker C, Ashford RL. Intrathecal granuloma formation as result of opioid delivery: systematic literature review of case reports and analysis against a control group. Submitted for publication.


Published abstracts:


*International conference presentations:*


Duarte RV, Raphael JH, Labib M, Southall JL, Ashford RL. Importance of the sex hormone-binding globulin for the diagnosis of hypogonadism in patients undertaking intrathecal opioid administration. Poster presentation at the 30th Annual European Society of Regional Anaesthesia Congress. Dresden, Germany, 7-10 September 2011.

Other conference presentations:
Duarte RV. Intrathecal inflammatory masses: preliminary results of a case report literature review and comparison with a control group. Oral presentation at the Faculty of Health Research Students' Presentation Day, Birmingham City University, Birmingham, UK, 16th June 2010.


Grants:
Patrick Wall Bursary for travel to the 30th Annual European Society of Regional Anaesthesia Congress. Dresden, Germany, 7-10 September 2011. Awarded by the British Pain Society, £1,029.41.

Patrick Wall Bursary for travel to the 5th World Congress of the World Institute of Pain, New York, USA, 13-16 March 2009. Awarded by the British Pain Society, £800.
Chapter 1

Introduction

Section 1
Background to the study

Section 2
Pain: an introduction

Section 3
Intrathecal drug delivery for chronic non-malignant pain: a review

Section 4
Pilot study of intrathecal drug delivery complications/side effects
SECTION 1. Background to the study

Pain is one of the most universal sensations in the sense that, with the rare exception of individuals with congenital insensitivity to pain, at some point every person will experience some type of physical pain during the course of their lives. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (International Association for the Study of Pain 1979). This definition is regarded as the most approximate to the experience of pain since it takes into account both emotional and sensory dimensions.

The widespread use of morphine and over-the-counter availability of opium and alcohol based compounds that people used to self-medicate in the 1870s led to concerns by the physicians about the morphine habit (Meldrum 2003). The conflict between the physician's desire to relieve the patient’s pain and fear of inducing addiction still persists nowadays and can influence the selection of therapies that include opioids.

One of the possible modes of opioid administration is through intrathecal drug delivery (IDD). An IDD system consists of an implanted pump which delivers medication directly into the cerebrospinal fluid through a catheter. Patients that may benefit from this therapy include cancer pain patients and patients with intractable chronic non-malignant pain. Patients with chronic non-cancer pain have the potential for long-term survival and therefore adequate pain control is paramount to this population.

This thesis explores different outcomes of intrathecal drug delivery for the management of chronic non-malignant pain. Potential pharmacological complications derived from this therapy are explored. Investigations of long-term outcomes and cost effectiveness of this treatment are also undertaken. This will contribute to the understanding of this treatment in the context of chronic non-malignant pain for which many patients require pain management throughout the rest of their lives.

1.1.1 Structure of the thesis
This thesis is divided into five different chapters (Figure 1.1.1). Chapter 1 provides the background to the thesis. Besides the current structure of the thesis, section 1 presents the
aim and objectives of this research. Moreover, the collaboration established, ethical considerations and approval for the studies performed are clarified. Section 2 includes a brief history of pain with a focus on events/concepts/authors that contributed to the current understanding of pain. The physiology and different types of pain are described as well as the basic mechanisms of opioids. Section 2 also comprises the prevalence of chronic pain in Europe and the United Kingdom to provide an idea of the magnitude of the chronic pain problem. Furthermore, treatments usually undertaken for chronic pain are described with a focus on intrathecal drug delivery. Chapter 1, section 3 provides a literature review of IDD systems for chronic non-malignant pain, focusing on the possible complications/side effects and effectiveness of this therapy. Following the literature review (I), Chapter 1, section 4 presents the results of a pilot study that helped to determine which complications/side effects would be of interest to include in this thesis based on its occurrence, literature available and feasibility (II).

The subsequent chapters consist of the research undertaken to investigate the different complications/side effects identified in the pilot study. These were divided into increase in opioid dose (Chapter 2, section 1), granuloma formation (Chapter 2, section 2) and hormonal effects (Chapter 2, section 4). The study of the intrathecal opioid dose increase over a period of six years assumes particular importance as the escalation level can impact on subsequent side effects/complications resultant from this therapy. Similar to most medications, a high intrathecal opioid dose is synonymous with an increase in the probability of a side effect to occur such as the formation of intrathecal inflammatory masses (III). This possibility was investigated in Chapter 2, section 2 where the association between yearly opioid dose increases with the development of granulomas was examined. The formation of granulomas is one of the most perilous complications of IDD. When not detected and treated appropriately it can cause functional paraplegia. An additional study of granuloma development was performed to try to further the understanding of this side effect (IV). Endocrine complications such as hypogonadotropic hypogonadism are a risk factor for decreased bone mineral density with potential to cause osteoporosis. Therefore, the prevalence of low bone mineral density was also investigated in this population (V).

The occurrence of side effects/complications can influence both effectiveness and cost effectiveness of a treatment (VI). Chronic pain patients require effective long-term treatments to manage their pain. In Chapter 3, a prospective, longitudinal study with a mean
follow-up of 13 years is presented. In this study, benefits of IDD, despite potential complications are explored to evaluate if chronic non-malignant pain patients benefit from long-term pain relief when undertaking IDD therapy.

The long-term effectiveness and complications can affect the cost effectiveness of a therapy. IDD therapy is initially very expensive; therefore a cost effectiveness study was also carried out (VII). Currently, the cost effectiveness of a treatment is always taken into consideration when deciding which therapy to administer. In an UK national audit of centres where IDD was presented, the respondents indicated that they would perform more implants if funding were available (Williams and Grady 2008). Chapter 4 refers to a study investigating the cost effectiveness of IDD and the identification of a concept which may also
influence cost effectiveness evaluations of other therapies where there is a waiting time between the decision and commencement of treatment. Moreover the literature review also revealed the paucity of IDD studies concerning the long-term effectiveness and cost effectiveness of this therapy (VIII). Finally, Chapter 5 highlights the main findings resultant from this work (IX), clinical implications and possible directions for future studies.

1.1.2 Aim of the study
The aim of this study was to assess intrathecal drug delivery when employed in the management of chronic non-malignant pain patients.

1.1.3 Objectives of the study
The primary objectives of this study were to investigate the cost effectiveness and the long-term effects of intrathecal drug delivery systems (IDDS).

The secondary purposes were to explore the development of opioid tolerance, potential consequences of hormonal side effects and possible motives for the formation of granulomatous masses.

1.1.4 Collaboration
This research was a collaborative project between the Faculty of Health, Birmingham City University, Birmingham and the Pain Management Department, Russells Hall Hospital (RHH), Dudley. The subjects who took part in this study were recruited from the Pain Management Department at Russells Hall Hospital.

1.1.5 Ethical approval
Research ethics committees were first established in 1964 at the 18th World Medical Assembly, thereafter known as the Declaration of Helsinki (DoH). The initial purpose of the DoH was to avoid atrocities like the ones verified during World War II, when prisoners of the Nazis were used for experimentation, as well as to prevent pharmaceutical companies and research organizations from exploitation of poor populations by using them for testing new
treatments from which they would never benefit (Christie 2000; Giordano 2010). Since its inception, the DoH became the most widely accepted guidance on medical research involving human participants (Christie 2000). Six amendments to the DoH have been made in the intervening years to maintain relevance to contemporary medical practice with the latest adopted during the 59th World Medical Assembly in Seoul, South Korea in 2008 (World Medical Association 2008). The main objective of the DoH is to provide an ethical framework to safeguard those voluntarily participating in medical research.

The DoH is a document in constant evolution and under continuous scrutiny. It has recently been claimed that some of the DoH statements are of dubious interpretation (Giordano 2010). To avoid erroneous interpretation and to ensure that clinical research investigations are carried out in accordance with the DoH, Research Ethics Committees (REC) were created to ethically review every potential research project involving human participants.

Informed consent and ethical approval was not required for the majority of chapters included in this thesis according to the Russells Hall Hospital institutional guidelines and the National Research Ethics Service (2006) (Table 1.1.1).

The data included in Chapter 2 sections 1, 2 and 3 was collected retrospectively. A prospective design was used to carry out Chapter 2, sections 4 and 5. The data comprised blood tests and dual energy X-ray absorptiometry (DEXA) scans. Ethical approval was not required to perform this piece of research as it is routine practice at RHH to collect blood samples periodically from IDD patients. After analyzing the blood samples results only the patients diagnosed with hypogonadism were requested to have a DEXA scan. The diagnosis of hypogonadism is one of the indications to carry out a DEXA scan, thus the reason not to pursue ethical approval for this examination.

The data collected for the cost effectiveness analysis (Chapter 4) was retrospective in nature. However, the general practitioner (GP) notes were thought to be relevant for inclusion in the study. For that reason, informed consent was obtained from all participants to examine their GP notes in addition to the hospital records throughout the study period. Data collected from GP notes was not included in the study. Rationale for this decision is included in Chapter 4.
Ethical approval was sought to accomplish Chapter 3. Taking into account the DoH (World Medical Association 2008), a research protocol (appendix 1), patient information sheet (appendix 2) and patient consent form (appendix 3) were developed to apply for University sponsorship (appendix 4) and REC approval (appendix 5) prior to the commencement of recruitment.

<table>
<thead>
<tr>
<th>Research</th>
<th>Clinical audit</th>
</tr>
</thead>
<tbody>
<tr>
<td>The attempt to derive generalisable new knowledge including studies that aim to generate hypotheses as well as studies that aim to test them.</td>
<td>Designed and conducted to produce information to inform delivery of best care.</td>
</tr>
<tr>
<td>Quantitative research: designed to test a hypothesis.</td>
<td>Designed to answer the question: Does this service reach a predetermined standard?</td>
</tr>
<tr>
<td>Qualitative research: identifies/explores themes following established methodology.</td>
<td></td>
</tr>
<tr>
<td>Addresses clearly defined questions, aims and objectives.</td>
<td>Measures against a standard.</td>
</tr>
<tr>
<td>Quantitative research - may involve evaluating or comparing interventions, particularly new ones.</td>
<td>Involves an intervention in use ONLY. (The choice of treatment is that of the clinician and patient according to guidance, professional standards and/or patient preference.)</td>
</tr>
<tr>
<td>Qualitative research – usually involves studying how interventions and relationships are experienced.</td>
<td></td>
</tr>
<tr>
<td>Usually involves collecting data that are additional to those for routine care but may include data collected routinely. May involve treatments, samples or investigations additional to routine care.</td>
<td>Usually involves analysis of existing data but may include administration of simple interview or questionnaire.</td>
</tr>
<tr>
<td>Quantitative research - study design may involve allocating patients to intervention groups.</td>
<td>No allocation to intervention groups: the health care professional and patient have chosen intervention before clinical audit.</td>
</tr>
<tr>
<td>Qualitative research uses a clearly defined sampling framework underpinned by conceptual or theoretical justifications.</td>
<td></td>
</tr>
<tr>
<td>May involve randomisation.</td>
<td>No randomisation.</td>
</tr>
<tr>
<td>Although any of these may raise ethical issues, under current guidance:</td>
<td></td>
</tr>
<tr>
<td><strong>Research requires REC review</strong></td>
<td><strong>Audit does not require REC review</strong></td>
</tr>
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The UK ethical approval submission form is quite broad and detailed, however, it does take into consideration the majority of issues that can arise when conducting a patient based research and is therefore a useful and informative exercise. RECs were created primarily to protect patients from hazardous research, but they encompass a secondary responsibility to foster superior research (Masterton and Shah 2007).
The research ethics committee attended consisted of a combination of clinicians and academics from a range of specialties as well as lay members. Several questions regarding study design, recruitment process, protection of participants, patient information sheets and consent form were made during the meeting by different members of the board. After deliberation by the committee, the research project received a favourable opinion on the condition that a few adjustments were made. Following a review of the alterations the study was approved. Ethical approval was granted by Birmingham, East, North and Solihull Research Ethics Committee (REC reference: 08/H1206/184; appendix 5) and informed consent was obtained from all participants.
1.2.1 History of pain

The term “pain” derives from the Latin word *poena* meaning a penalty or punishment. Despite being experienced by almost everyone, the concept of pain has undergone several modifications throughout the ages and still today has not the same status in every society (Rey 1998). Ancient cultures believed that pain was related to evil, magic or to a punishment from the Gods. In Greek mythology Poine (or Poena) was the goddess of punishment. Pain has been attributed philosophical, political and religious meanings; these defined the suffering of individuals for much of human history and often complicated its treatment (Meldrum 2003). The Christians inherited many ideas from the Greeks and Jews, for whom disease and pain were punishment, inflicted for breaking divine law (Caton 1985). It is likely that Christ's Incarnation and His sufferings on the cross may have been responsible for other connotations, and the perception among Christians of pain as a form of divine retribution or a sign of having been chosen, which could have encouraged an attitude of stoic indifference towards pain (Caton 1985; Rey 1998). For many centuries in most of Western culture, people would try to hide their pain and, when unbearable, they would seek priests and the church to try to find some comfort. The dogma of pain as a test of faith was the predominant belief throughout the Middle Ages hence not much progress in the treatment of pain was made throughout this period. It was considered inevitable that men, women and children would suffer physical pain; what mattered to the good life was the meaning rather than the fact of pain (Meldrum 2003). However, pain during surgery was perceived differently even throughout this period and attempts were made to supply the most relief possible throughout surgical procedures. Plant derivatives such as alcohol, cannabis, mandrake and opium have been used for surgical analgesia for around 2500 years (Hamilton and Baskett 2000).

While the church dominated Western thought, medicine continued to develop in the Arabic world through the Middle Ages (Jaros 1991). This development was influenced by the translations of classical Greek and Roman works brought by Greek scholars who had fled to Persia when the Greek Academy was brought to an end because its teachings were considered pagan by an increasingly Christian world (Jaros 1991). An elaborate theory of pain was created by Avicenna, an Arabic physician, who believed that the body consisted of four temperaments (heat, cold, dryness and moistness) and each organ or limb had an ideal
balance for that organ (Jaros 1991). According to the same physician, there were 15 different types of pain (throb, tension, tearing, stabbing, relaxing, pricking, itching, irritant, incisive, heavy, fatigue, dull, corrosive, compressing and boring) and the type of pain would be the result of specific changes in the combination of temperaments.

A significant change of mood in Europe was observed during the 1600s, with a movement from the Age of Faith to the Age of Reason and people seeking to control the environment leaving their pessimism and passivity behind (Caton 1985). In 1664 René Descartes described a pain pathway (Descartes 1664). According to his example of fire as painful stimulus, if the fire is close to the foot, small particles of that fire (A) can activate a section of the skin (B) connected by a thread to the brain (F). This would work as a warning system, described as pulling a string attached to a bell at the other end, leading to a movement of the head and eyes towards where the stimulus was being received and moving the foot away from the fire (Figure 1.2.1). In other words, a fixed and dedicated pain pathway links the site were a peripheral noxious stimulus occurs to the brain, where the perception of pain takes place (Costigan and Woolf 2002).

Figure 1.2.1 Descartes’ pain pathway (Adapted from Descartes 1664)
Despite several criticisms, Descartes’ stimulus-response model, now known as specificity theory, was predominant for approximately three centuries until Ronald Melzack and Patrick Wall proposed the concept of the gate control theory (GCT) of pain (Melzack and Wall 1965).

In the early 19th century a gradual change of attitude regarding pain relief started to take place. This was due to the emphasis of utilitarian philosophy on reducing pain for the greatest number of people combined with the new philosophy of individual rights and the Romantic poets’ rethinking of pain and resolve in the importance of the individual experience (Morris 1998). Several factors contributed to this change of attitude and the implementation of this school of thought such as the American, French and German Revolutions, the Napoleonic wars, major new developments in physics, geology, biology and chemistry, the Western migration and Queen Victoria’s coronation in 1837 (Caton 1985). The progress verified during this era lead to an increase in prosperity as well as facilitation of migrations, travelling, and debate of ideas and concepts which created an atmosphere favourable to the advance in several scientific disciplines. This cultural change was required for the development of anaesthesia (Calatayud and González 2003). During this period, modern medicine as well as anaesthesia was born. This era is also noticeable for the discovery of morphine and its analgesic properties. In 1805, Friedrich Sertürner isolated morphine from opium, which made parenteral administration possible; after the development of the hypodermic needle and syringe in the 1850s, morphine started to be administered subcutaneously as an analgesic and its use became widespread (Hamilton and Baskett 2000). The development of a syringe with a hollow needle in 1855 by Alexander Wood made frequent subcutaneous administration so convenient that it might have inadvertently contributed to the overuse of morphine (Howard-Jones 1947).

The relief of physical pain started to be seen as a positive good and a few experimenters recognised the possibilities of sedative gases, especially ether (Meldrum 2003). On October 16, 1846, William T. G. Morton publicly demonstrated the anaesthetic properties of ether, with news of his work promptly spreading and ether starting to be used as an anaesthetic in most of the world within five months (Caton 1985). After Morton’s’ demonstration, several others claimed to have used ether for the same purpose, therefore, credit for the discovery of anaesthesia has been given to various individuals including William T. G. Morton, Horace Wells, Charles A. Jackson, Gardner Q. Colton and Crawford Long (Stoelting and Miller...
The introduction of surgical anaesthesia was one of the greatest breakthroughs of modern medicine and although considered a blessing by most of the patients, not all physicians were immediately enthusiastic about this concept due to ethical debates about operating on an unconscious patient, the possibility of retarding the healing process and religious writers considering anaesthesia a violation of God’s law (Meldrum 2003).

Spinal anaesthesia for surgery was first introduced on August 16\textsuperscript{th}, 1898. When faced with a patient who had suffered severe adverse effects from previous general anaesthesia, August Bier decided to try spinal anaesthesia by “cocainization of the spinal cord”, using 15 mg of cocaine injected intrathecally before performing a resection of a tuberculous ankle joint (Wulf 1998). To test the efficacy of the analgesia, Bier and his assistant also attempted spinal injections of cocaine on each other, developing severe headaches, a number of cuts, bruises and burns (Hamilton and Baskett 2000). Prior to this date, only local anaesthetic procedures such as topical anaesthesia of the eye and infiltration anaesthesia had been employed; spinal anaesthesia was the first major regional anaesthetic technique to be introduced into broad clinical practice (Wulf 1998).

The observation of severe side effects after administration of cocaine derivatives in combination with the introduction of general anaesthesia caused a restriction of spinal anaesthesia to only those who could not withstand general anaesthesia (Brock, Bell and Davison 1936). The status of the spinal anaesthesia technique suffered an additional setback on October 13, 1947, when Albert Woolley and Cecil Roe became paraplegic on the same day after receiving spinal anaesthesia for minor surgery at the same hospital, administered by the same anaesthetist, Dr Malcolm Graham (Maltby, Hutter and Clayton 2000). The patients sued their anaesthetist for alleged negligence. Initially it was thought that the origin of the paralyses was related to cracks in the ampoules which were invisible to the eye but which had caused a leak of phenol, a sterilizing agent and therefore the plaintiffs’ claims against both the hospital and Dr Graham failed (Cope 1954). The case was reassessed after new information was obtained which indicated that the most likely source of contamination was the water in which the syringes and needles were boiled, and the contaminating agent was an acid used to descale the water-boiling sterilizer (Hutter 1990). Despite the fact that there were other reports of neurological complications, the Woolley and Roe case made spinal anaesthesia unpopular, especially in the UK (Hutter 1990). Due to the uncertainty over the cause of the paralyses and fear of producing permanent
neurological damage, the practice of spinal anaesthesia in the UK was deterred for 20-25 years (Morgan 1995). The discovery, in 1973, of opioid receptors in the brain (Pert and Snyder 1973) and in 1977 in the spinal cord (Snyder 1977) led to the reintroduction of spinal opioid injections for clinical use.

In 1946 following on from observations made by George J. Guthrie and Guillaume Dupuytren, Harry K. Beecher challenged the belief, common at the time of a direct relation between the extent of the wound and the severity of pain reported. While working as a doctor during World War II, Beecher asked severely wounded soldiers (penetrating cerebral wounds, penetrating wounds of the thorax, extensive soft-tissue injury, compound fractures of long bone, penetrating abdominal wounds) who were able to speak if they were in pain, the severity of pain (slight pain, moderate pain, or bad pain) and if they wanted something to relieve the pain; to his surprise, only 23.7% reported their pain as bad and 73% of the soldiers said no to narcotics for pain relief (Beecher 1946). After returning to the Massachusetts General Hospital and asking the same questions to civilians with surgical wounds, 83% said yes to narcotics for pain relief (Beecher 1956). One of the possible explanations Beecher advanced for these findings was the association made by the participants with the pain they were suffering. For the soldiers, the injury meant the war was over for them and they would soon return home, while for the civilians, the surgery could be seen as the beginning of an undesired event. The same author described pain as an experience subject to modification by many factors, and these factors served to be more important than the extent or degree of the wound. Beecher questioned the use of morphine without inquiring the patient about the need for it and also noted that many times the morphine doses given did not correspond adequately to the severity of pain (Beecher 1946). A holistic approach for the management of pain which focused on the individual patient was proposed by Cicely Saunders, who also portrayed “total pain” as a clinical phenomenon that compounded physical and mental distress with social, spiritual and emotional concerns (Meldrum 2003). This approach is still in line with today’s understanding of pain.

In 1955, after analyzing the therapeutic effectiveness of placebos in treating subjective responses, Beecher recognised the importance of placebos and its potential application in research studies (Beecher 1955). The same author describes the importance of a control group, the double-blind technique as well as the value of randomisation. Following this
article randomised double-blinded control studies were recognised as one of the most valuable methodologies when investigating the effects of a medicine or treatment.

Ensuing on the work of Willem Noordenbos, William Livingston, Ivan Pavlov as well as the authors previously mentioned, Ronald Melzack and Patrick Wall wrote a paper focusing on somesthesia (sensory systems in the skin) and discussed the limitations of the specificity theory, presenting some of the concepts of what was to become the gate control theory of pain, such as physiological specialization (Melzack and Wall 1962). This article evoked some interest but had little impact among the scientific community. Melzack and Wall used the concepts from that article as the basis for a theory focusing specifically on pain mechanisms. The gate control theory was published in 1965 and since then has become a seminal work (Melzack and Wall 1965). Contrary to the direct stimulus-response relationship model described by Descartes, the gate control theory describes pain as a complex interaction of sensory and cognitive processes (Figure 1.2.2). These processes include past experience, attention, expectation and the situation in which the injury occurs (Melzack and Wall 1965). This explains why pain can be perceived differently in similar injuries.

![Figure 1.2.2 Schematic diagram of the GCT (Adapted from Melzack and Wall 1965)](image)

The pain experience as described by the GCT is the result of an interaction between three spinal cord systems after transmission of nerve impulses induced by stimulation of the skin: the substantia gelatinosa (SG) cells in the dorsal horn, the dorsal-column fibres that project
towards the brain, and the first central transmission (T) cells in each dorsal horn (Melzack and Wall 1965). The authors proposed that the SG (consists of small, densely packed cells extending the length of the spinal cord) functions as the gate control system, which is modulated by activity from the large (L) and small (S) fibres that influence the activation by the T cells of neural mechanisms comprising the action system responsible for response and perception. The action system is activated when the output of the spinal cord transmission (T) cells exceeds a critical level (Melzack 1996). An increase in activity in L fibres will inhibit the transmission of stimulus (closes the gate); S fibres activity facilitates the transmission (opens the gate) (Melzack 1996). The positive and negative effects of the large and small fibre inputs tend to counteract each other but if stimulation is prolonged the large fibres begin to adapt, causing an increase in small fibre activity, which results in the gate opening further and the output of the T cells to rise; however, if the large fibre activity is raised by vibration or scratching (which can overcome the tendency of the large fibres to adapt), the output of the cells decreases (Melzack and Wall 1965). The gate control system is also influenced by descending efferent fibres from the brain. The gate can also be closed or opened according to the information descending from the central nervous system. Pain response and perception are influenced by psychological factors such as prior experiences, attention and emotions which can open or close the gate. The presence or absence of pain is therefore determined by the balance between the sensory and central inputs to the gate control system (Melzack and Wall 1965).

The GCT theory had a huge scientific and clinical impact, causing an explosion in research on the physiology and pharmacology of the dorsal horns and descending control systems; psychological factors, previously regarded as reactions to pain, started to be seen as an integral part of pain processing; cutting nerves and pathways were gradually replaced by modulation techniques while electrical stimulation of the large afferent fibres started to be used for treating several painful conditions (Bonica 1991; Melzack 1996).

Painful conditions where sensory inputs are absent do not fit with the GCT, such as pain in paraplegics and phantom limb pain. Although peripheral and spinal processes are an important part of pain, the data on phantom pain indicated a need to go beyond the foramen magnum and into the brain (Melzack 1996). After analyzing the phantom limb phenomena, Melzack developed a new conceptual model, the neuromatrix (Melzack 1999). According to this theory, the body is felt as a unity and the brain mechanism that underlies the experience
comprises a unified system acting as a whole and producing a neurosignature pattern of the whole body (Melzack 1999). This model proposes that the neurosignature for pain experience is determined by the synaptic architecture of the neuromatrix, which is produced by genetic and sensory influences; moreover, the neurosignature pattern is also modulated by sensory inputs and cognitive events such as psychological stress (Melzack 1999). The same author suggests that the development of chronic pain syndromes may be determined or predisposed by genetic influences on synaptic architecture. Besides detecting and analyzing inputs, the brain generates perceptual experience even when no external inputs occur (Melzack 1996). Functional imaging studies during a noxious stimulus demonstrated the involvement of different regions of the brain assumed to process the affective, sensory, cognitive, motor, inhibitory and autonomic responses, confirming the existence of a neuromatrix (Derbyshire 2000). The output of the neuromatrix can be adjusted by different treatments to change the inputs and influences on the neuromatrix (Loeser and Melzack 1999).

The neuromatrix theory of pain does not invalidate the GCT but complements it. While the GCT clarifies why physical, acute pain can be perceived differently, the neuromatrix reveals an additional role of the brain in our pain perception and helps to explain phantom limb pain as well as chronic pain. The gate control theory of pain assumes particular importance for the development of the therapy explored in this thesis. The GCT lead to a rapid increase in research, more importantly to this work, into the physiology and pharmacology of the dorsal horns which resulted in the discovery of opioid receptors in the brain (Pert and Snyder 1973) and in the spinal cord (Snyder 1977). Ultimately, this path culminated in 1981 with the first morphine reservoir implanted in a human (Onofrio, Yaksh and Arnold 1981).

Alongside the theories of pain, the creation and foundation by John Bonica of the International Association for the Study of Pain (IASP) in 1973 and the journal Pain in 1975 had a significant impact on pain research, therapy and its dissemination.

To complement the described pain models, the following segment of this thesis provides a description of the physiology of pain.
1.2.2 Physiology of pain

The main purpose of pain is to alert the body to potential damage (nociception). When injury occurs, peripheral nociceptors are activated and the signal is conducted via afferent nerve fibres to the dorsal horn and the brain. The process of perception and response to pain can be divided into four different stages: transduction, transmission, modulation, and perception (Hawthorn and Redmond 1998; Cepeda, Cousins and Carr 2007) (Figure 1.2.3).

Transduction

Transduction consists of the conversion of a stimuli (mechanical, thermal or chemical) with the potential to cause damage into nerve impulses by nociceptors (unspecialised, unmyelinated, free nerve endings), also known as first order neurons. The nociceptors are located in any external (e.g. skin) or internal (e.g. muscle) area of the body with potential to...
sense pain. The nerve cell bodies are localized either in the trigeminal ganglia (specific for the trigeminal nerve in the face) or in the dorsal root ganglia (rest of the body) (Woolf and Ma 2007). The nociceptors transmit the stimuli information via sensory/afferent/nerve fibres to the central nervous system (CNS). There are two types of nerve fibres responsible for the transmission of noxious stimuli to the CNS: C fibres which are unmyelinated, with small diameter (0.25 to 1.5 µm) and conduct the information slowly (1 to 2.5 m/s rate); and A-delta (Aδ) fibres with larger diameter (1 to 5 µm), myelinated nerves that conduct the information faster (6 to 30 m/s) (Melzack and Wall 1988). Approximately 60 to 70% of all the sensory afferents are C fibres (Melzack and Wall 1988). The C fibres respond to mechanical, thermal and chemical stimuli, while the Aδ fibres respond to mechanical and thermal stimuli (Patel 2010). The fast-conducting Aδ fibres are responsible for a sensation of sharp, fast pain, while the slower C fibres produce the sensation of delayed, dull pain (Patel 2010). The pain from the Aδ fibres (first pain) lasts only for the length of the acute painful stimulus and the threshold for this pain is uniform from person to person; pain from C fibres (second pain) is more diffuse and persistent, lasting beyond the termination of an acute painful stimulus (Cross 1994). Tolerance to this second pain is variable from person to person because it is associated with the affective-motivational aspects of pain (Cross 1994).

The nociceptors are activated when stimulation occurs beyond a certain individual threshold. The thermal receptors respond to extremes of temperatures (heat or cold); mechanical receptors respond to pressure such as squeezing, crushing or as a consequence of tissue inflammation or oedema; chemical receptors can be stimulated by both external (sting of a wasp or nettle) and internal chemicals (Hawthorn and Redmond 1998). When the tissue is cut or burned, or a cell ruptured by excessive pressure, chemicals such as 5-hydroxytryptamine (5-HT or serotonin), histamine, potassium ions (K⁺) or acetylcholine are released; damage can also lead to synthetisation of other inflammatory mediators, such as bradykinin or cytokines (Hawthorn and Redmond 1998).

Transmission

Following transduction, the stimuli information is conducted by the afferent nerves to the dorsal root ganglia and enters the spinal cord through the dorsal horn (Hawthorn and Redmond 1998). Once in the spinal cord, these fibres ascend one or two segments in the
The dorsolateral tract of Lissauer, before entering the grey matter and terminating in laminae I, II or V (Cross 1994; Hawthorn and Redmond 1998) (Figure 1.2.4).

![Dorsal surface of the spinal cord with labels for different laminae and structures](image)

**Figure 1.2.4 Cross-section of the spinal cord (Adapted from Hawthorn and Redmond 1998)**

Lamina I receives inputs mainly from the skin and muscle nociceptors through both Aδ and some C fibres; lamina II, also known as substantia gelatinosa contains neurones that make local connections; and lamina V receives inputs from Aδ and C fibres, but also from interneurones in laminae I and II. C fibres innervate mainly the cells in the substantia gelatinosa layer of the spinal cord (Patel 2010). In the dorsal horn laminae, the afferent fibres synapse with second order neurons. The nociceptors release the excitatory neurotransmitters substance P and glutamate which bind respectively to neurokinin 1 (NK1) and N-methyl-D-aspartate (NMDA) receptors, causing an influx of calcium and activation of the calcium-dependent enzyme protein kinase C (PKC) in the second order neurons (Cepeda, Cousins and Carr 2007). These neurons have their cell bodies in the dorsal horn and their axon terminations in the thalamus (Cross 1994). They ascend from the spinal cord to the thalamus via the anterolateral spinothalamic pathway. There are two different types of second order neurons: those that respond to both nociceptive and non-nociceptive A-beta (Aβ) afferents are termed wide dynamic range (WDR) neurons; and those that respond exclusively to noxious stimuli are termed nociceptive-specific neurons (Besson and Chaouch...
WDR neurons are involved in the affective-motivational component of pain, while the nociceptive-specific neurons are involved in the sensory-discriminative aspects of pain (Cross 1994). Although the WDR neurons respond to both nociceptive and non-nociceptive inputs, they usually do not signal pain in response to stimulus at a non-nociceptive level. It is at this moment (transmission) that influences can be exerted and the message modified by other information, a process known as modulation.

**Modulation**

The GCT theory, also known as segmental modulation and described in the section 1.2.1 of this thesis, explains one of the mechanisms that can modify pain transmission (Melzack and Wall 1965). Although many advances have been verified, the GCT theory remains valid in its essence (Patel 2010).

Information can be transmitted from supraspinal levels (brain) to the spinal cord and these descending inhibitory nerves can control (modulate) the ascent of nociceptive information to the brain. As the nociceptive afferents enter the spinal cord via the dorsal horn, they form synapses with other nerve endings. Some of these nerve endings are from neurons whose cell bodies are in the brain and whose axons form a descending pathway (Hawthorn and Redmond 1998). These descending pathways have the potential to modify functions at the spinal level and can originate in the cortex, the thalamus and the brain stem (Cross 1994). The descending pathways carry signals from the aforementioned higher brain centres through the periaqueductal grey matter and the brain stem back to the dorsal horn (Hawthorn and Redmond 1998). The main transmitters of the descending inhibitory system are serotonin, noradrenaline and endogenous opioids (Cepeda, Cousins and Carr 2007; Patel 2010). The release of these transmitters inhibits the nociceptors that produce excitatory mediators such as substance P and glutamate, therefore preventing them from binding respectively to the NK1 and NMDA receptors in the dorsal horn (Cepeda, Cousins and Carr 2007).

Due to the importance of serotonin and noradrenaline in pain modulation, selective serotonin reuptake inhibitors such as fluoxetine hydrochloride (Prozac) and tricyclic antidepressants such as amitriptyline were found to have analgesic properties and started to be used for the treatment of chronic pain (McQuay and Moore 1997).
Opioid receptors were first discovered in the brain (Pert and Snyder 1973) and afterwards in the spinal cord (Snyder 1977). Within the spinal cord, opiate receptors are localized in an area corresponding to the substantia gelatinosa, which is a first site for the integration of sensory information in the CNS (Snyder 1977). Since the discovery of opioid receptors in the brain, the existence of endogenous opioids was hypothesized and started to be investigated. Two enkephalin peptides were the first endogenous opioids to be isolated from the brain (Hughes et al., 1975). There are three groups of opioid peptides (enkephalins, endorphins, and dynorphins) that bind to the opioid receptors and are referred to as endogenous opioids (Atcheson and Lambert 1994). Exogenous opioids mimic the action of endogenous opioids. The mechanism of action of opioids is described in segment 4 of this section.

_Perception_

In the ascending pain pathway, once the WDR or the nociceptive-specific neurons reach the thalamus (where they terminate), they activate third order neurons. These originate in the thalamus and project to the cortex (Cross 1994). Neurons from the lateral thalamic nuclei project to the somatosensory cortex and allow the conscious localisation and characterisation of painful stimuli; neurons from the intralaminar and medial nuclear areas project to the anterior cingulate gyrus and are thought to be involved in the perception of suffering and the emotional reaction to pain (Cross 1994).

Another stage that could be included in this description of pain is interpretation. As the IASP definition states, pain is a sensory and emotional experience, and therefore, individual and personal. Even if evoked by identical forms of tissue damage, pain may differ significantly because of variations in factors such as social background and personal experience, including individual memories, beliefs and emotional state (Morris 1998).

1.2.3 Classification of pain

The classification of pain may take into consideration aspects such as duration, aetiology, intensity or type of injured tissue. Pain associated with tissue damage, inflammation, or a disease process expected to resolve with time, regardless of the pain intensity, is referred to as acute pain (Turk and Melzack 2001). Acute pain is characterized by a short duration, typically after an injury, surgery or disease and usually disappears during the healing
Acute pain can be regarded as a transitional period between coping with the injury and preparing for recovery (Melzack and Wall 1988). A few types of acute pain, such as post-herpetic neuralgia (nerve damage caused by herpes zoster) can frequently give rise to chronic pain (Merskey 2007).

The chronic pain syndrome is the consequence of a variety of pathological and psychological mechanisms that at any stage may have included tissue or nerve damage, in which symptoms have failed to resolve with healing or repair (Grady and Severn 1997). It is not the duration of pain that distinguishes acute from chronic, but the incapacity of the body to restore its physiological functions to normal homeostatic levels (Loeser and Melzack 1999). Chronic pain persists long after pain can serve any useful function and is no longer a simple symptom of injury or disease but a medical problem in its own right that requires urgent attention (Melzack and Wall 1988). The injury may exceed the capacity of the body to heal for several reasons, such as the loss of the body part, the extensiveness of the trauma and subsequent scarring, or the involvement of the nervous system in the injury as it can be damaged in such a way as to be unable to restore itself to a normal state (Loeser and Melzack 1999). When chronic pain is not treated effectively it is likely that stress, environmental and affective factors may be superimposed on the original injury and contribute to the intensity and persistence of the pain (Loeser and Melzack 1999).

Besides duration, pain can also be characterised according to diagnosis. A correct diagnosis is seen as the avenue to suitable treatment (Merskey 2007). Pain can be described as nociceptive, neuropathic or mixed.

Nociceptive pain is the result of tissue damage and can be either somatic or visceral. It results from the activation of the nociceptors by noxious mechanical, thermal or chemical stimuli (Costigan, Scholz and Woolf 2009) (Figure 1.2.5). Somatic pain refers to stimuli received in parts of the body such as skin, bones, or muscle while visceral pain is caused by the activation of nociceptors in the internal organs (viscera). Somatic pain sensations in the skin (superficial somatic) are sharp and well localised. Somatic pain in deeper areas such as muscle (deep somatic) can be harder to localise because it is frequently diffuse or spread over a large area. Visceral pain is caused by distension, spasm or contraction, twisting, ischemia, chemical irritation or inflammation (Hawthorn and Redmond 1998). It can be extremely difficult to pinpoint and can also be referred pain (the sensation of pain is
perceived in one part of the body and the pathology is in a different area). Examples of visceral pain include bladder pain, endometriosis pain or irritable bowel syndrome pain.

Neuropathic pain has been defined as pain arising as a direct consequence of a lesion or a disease affecting the somatosensory system (Treede et al., 2008). Neuropathic pain results from lesions to the peripheral (PNS) or central nervous system (Costigan, Scholz and Woolf 2009) (Figure 1.2.6). Peripheral neuropathic pain can be caused by mechanical trauma, metabolic diseases, neurotoxic chemicals, infection or tumour invasion involving numerous physiological changes within both the PNS and CNS (Dworkin et al., 2003; Woolf and Mannion 1999). Central neuropathic pain is generally the result of spinal cord injury or multiple sclerosis (Ducreux et al., 2006).

Disruptions of the normal sensory mechanisms may lead to different phenomena such as the occurrence of pain without a clear stimulus or in the presence of a non-nociceptive stimulus, also known as sensitisation (Woolf 1991). An example of sensitisation is allodynia where a non-noxious stimulus activates nociceptive pathways producing pain. In the presence of allodynia, when the non-nociceptive Aβ fibres synapse at the dorsal horn they
can cause the neurone to respond as if they were nociceptive fibres, and pain would be perceived even in response to light touch or other non-nociceptive stimuli (Hawthorn and Redmond 1998). Another disruption of the sensory mechanism is related with the continuous stimulation of C fibres which can lead to a “wind-up” reaction where the second order WDR neurons response increases progressively leading to an enhancement of the pain. This concept is important because, if a painful stimulus is present for a long time, it will become increasingly more painful and may cause changes to the nociceptive pathway and potentially leading to hyperalgesia (Hawthorn and Redmond 1998).

Pain can also have a mixed aetiology. Failed back surgery syndrome (FBSS) pain is a mixed type of pain (nociceptive and neuropathic). Patients with this condition experience constant pain following unsuccessful back or spine surgery. The nociceptive pain in FBSS can result from disc or bone injury, reaction to hardware or graft harvesting, or reactive spasm; the neuropathic pain in this condition can be due to nerve injury prior to or during surgery, chronic compression, scar tissue formation or arachnoiditis (inflammation of the arachnoid membrane that surrounds and protects the nerves of the CNS) (Prager 2002).

Figure 1.2.6 Neuropathic pain (Adapted from Costigan, Scholz and Woolf 2009)
1.2.4 Basic mechanisms of opioids

Opioids are a type of drug with the potential to provide pain relief by binding to and blocking receptors found in the brain and spinal cord. Opioids exert their effect by attachment to opioid receptors, a group of G protein-coupled receptors (GPCRs), which are the largest family of cell-surface molecules involved in signal transmission and more than 50% of the current available pharmacological agents target these receptors (Marinissen and Gutkind 2001).

There are three major opioid receptors subtypes: mu (µ), delta (δ) and kappa (κ) (Dickenson and Kieffer 2006); and the endogenous opioids act as agonists at these receptors. Endorphins and enkephalins have affinity with the µ receptor, enkephalins bind to the δ receptor and dynorphins bind to the κ receptor (Dickenson and Kieffer 2006; Lambert 1995). More recently, a receptor with similar structure to opioid receptors has been discovered and termed opioid-receptor-like 1 (ORL1) (Mollereau et al., 1994). These receptors are located in the dorsal horn of the spinal cord and midbrain and brain stem sites, and bind to the endogenous peptide nociceptin/orphanin FQ and not to conventional opioids. The effects of the ORL1 receptor agonists on pain modulation are still controversial and not fully understood as it seems to have differential functions based on spinal or supraspinal activity. When administered in supraspinal sites, nociceptin produces hyperalgesia, whereas spinal administration has an inhibitory effect and produces analgesia (Darland, Heinricher and Grandy 1998; Dickenson and Kieffer 2006; Taylor and Dickenson 1998).

The understanding of opioid pharmacology has advanced considerably since the µ, δ and κ receptors were cloned and sequenced successfully (Chen et al., 1993; Evans et al., 1992; Kieffer et al., 1992; Yasuda et al., 1993). The main mechanism of both endogenous and exogenous opioids seems to be related to the coupling of opioid receptors to calcium (Ca\(^{2+}\)) and potassium (K\(^{+}\)) channels. Opioid receptor activation opens the K\(^{+}\) channels or closes the Ca\(^{2+}\) channels, leading to a decrease of neuronal excitability and therefore producing analgesia (Dickenson and Kieffer 2006).

Throughout the spinal cord, the distribution and contribution of µ, δ and κ receptors to the total opioid binding is estimated at 70%, 24% and 6% respectively (Besse et al., 1990; Dickenson 1991), mostly (>70%) at a presynaptic location on the central terminals of both C and Aδ fibres (Dickenson and Kieffer 2006). This suggests that the main mechanism of
spinal opioid analgesia of both endogenous and exogenous opioids is via activation of presynaptic opioid receptors, which act to selectively decrease transmitter release from nociceptive afferents and therefore nociceptive transmission (Ossipov et al., 1995). The activation of postsynaptic opioid receptors has a similar effect on the second-order neurons. The postsynaptic opioid receptors activation causes a reduction in the response to the inputs from the first-order nociceptive neurons.

The different types of receptors have been suggested to regulate distinct pain stimuli (Dickenson and Kieffer 2006). Investigations with knockout mice reported that µ receptors influenced responses to mechanical, chemical and supraspinal thermal nociception; κ receptors modified spinally mediated nociception and chemical visceral pain; δ receptors influenced mechanical nociception and inflammatory pain (Martin et al., 2003). The same study suggested that although the specific contribution of each opioid receptor was subtle, the opioid system as a whole produces a significant inhibitory effect on physiological pain.

Morphine mimics the action of the β-Endorphin endogenous opioid and has a high affinity with the µ opioid receptor. The µ ligands are the most potent opioids, possibly because µ opioid receptors are present in larger number in the spinal cord (Dickenson and Kieffer 2006). Morphine acts via the µ receptor to activate potassium channels and to block calcium currents, reducing membrane excitability and transmitter release (Pasternak 2001). This was confirmed in µ knockout mice (mice with deoxyribonucleic acid sequence engineered to lack the µ opioid receptor) in which morphine did not produce analgesia (Matthes et al., 1996). There are however, several processes that can follow agonist-induced receptor activation such as phosphorylation or downregulation of the opioid receptor with potential to cause tolerance, dependence or withdrawal (these processes are explained in more detail in Chapter 2, section 1). With the exception of constipation, tolerance to opioid related side effects such as respiratory depression, nausea and sedation may also occur, however, this tolerance is favourable because it contributes to the effective use of the drugs and allows dose titration (Portenoy and Savage 1997).

Animal studies have demonstrated that intrathecal morphine administration was more effective than systemic administration in producing inhibitions of electrical, mechanical and chemical stimuli of spinal nerve ligated rats (Suzuki, Chapman and Dickenson 1999). The
same study also reported marked side effects, such as respiratory depression in the systemic route of delivery.

Because intrathecal drug administration delivers the medication directly into the intrathecal space it bypasses the blood brain barrier. Opioid analgesics applied closer to their sites of action should provide better analgesic efficacy without the adverse effects that accompany systemic administration of these composites (Figure 1.2.7). Spinally applied opioids act on the substantia gelatinosa of the dorsal horn causing both pre-synaptic and post-synaptic inhibition of primary afferent transmission (Cousins and Mather 1984). The analgesic effect of morphine when administered at the spinal level was first demonstrated in 1976 in animal studies (Yaksh and Rudy 1976). Prior to this investigation it was believed that narcotic analgesia was mediated by the action of a drug on a supraspinal level. The clinical application of these discoveries was demonstrated when spinally administered opioids were used to manage cancer pain successfully (Wang, Nauss and Thomas 1979).

Figure 1.2.7 Difference between systemic and intrathecal opioid administration to obtain the same level of analgesia (Adapted from Grady and Raphael 2008)

1.2.5 Prevalence of chronic pain in Europe and United Kingdom
Chronic pain is a highly prevalent condition, with an impact on an individual’s health, healthcare services, society and one for which successful treatment outcomes are difficult to achieve (Smith, Macfarlane and Torrance 2007). A systematic review of the prevalence of chronic pain in the general population reported a range of 10.1% to 55.2% after evaluation
of 13 articles (Harstall and Ospina 2003). In Europe, one in five adults (19%) suffer from chronic pain and more than a third of European households have at least one pain sufferer (chronic or acute) (Breivik et al., 2006). For this survey of 15 European countries and Israel, chronic pain was defined as pain lasting more than six months, experiencing pain during the last month, several times during the last week, and the reported last experience of pain having an intensity of five or more on a numeric rating scale (NRS) ranging from one (no pain) to 10 (worst pain imaginable). Prevalence of chronic pain in the United Kingdom corresponded to 13% which accounts for approximately 3.8 million of the UK population, with a third of these people suffering chronic pain constantly and 32% of these participants reporting severe pain (eight to 10 on the NRS) (Breivik et al., 2006). There were differences between the European countries studied with chronic pain incidence ranging from 12% (Spain) to 30% (Norway) and severe pain ranging from 18% (Netherlands) to 50% (Israel). Possible reasons advanced for this variance include differences in the perception of pain and pain treatment, age stratification of the population and lifestyle (Breivik et al., 2006). As the lifespan rises, it is likely that chronic pain will have a higher impact upon quality of life as increases in persistent pain have been observed in the elderly (Elliott et al., 1999). Chronic pain among adults of advanced age is a common problem which affects 50% of the elderly living in a community setting (Helme and Gibson 2001) and more than 80% of nursing home residents (Ferrell 1995).

Despite the differences among European countries (e.g. health care systems, treatment approach and development and technology), the UK Chief Medical Officer, Sir Liam Donaldson, has documented that chronic pain is a major health care problem in Europe that needs to be taken more seriously and action to alleviate this condition undertaken (Donaldson 2009).

### 1.2.6 Chronic pain treatments

Intrathecal drug delivery systems are a last resort treatment to treat severe chronic non-malignant pain due to their invasive nature, high initial cost, concerns about long-term opioid use, and the possible complications related to the procedure. It is considered that the use of IDD should only be considered at the end of a long treatment continuum after all possible alternative therapies have been tried and failed due to inadequate pain relief or intolerable adverse effects (Chambers and MacSullivan 1994; Krames 1996; Krames and Olson 1997).
There are also reports in the literature of situations where the patients requested pump removal because their primary care physicians refused to continue treatment with what they considered addictive drugs (Winkelmüller and Winkelmüller 1996). A treatment continuum for the management of chronic non-cancer pain has been suggested (Table 1.2.1).

Treatment strategies for the management of chronic pain start with the lowest risk, least invasive and less costly intervention and then progress if a treatment is not effective. The first attempts to manage chronic pain consist of conservative treatment options. These include exercise programs, relaxation, over-the-counter medications (e.g. ibuprofen), adjunctive medications (e.g. anti-depressants), physical rehabilitation and cognitive behavioural therapies. Cognitive and behavioural treatments can be used to change the effect of the pain on an individual’s life. If these treatments do not provide sufficient pain relief, more aggressive therapies such as nerve blocks (injection of a local anaesthetic or steroid applied directly to the nerve causing the pain) and oral opioids are attempted.

### Table 1.2.1 Pain treatment continuum (Adapted from Krames 1996; Krames and Olson 1997)

<table>
<thead>
<tr>
<th>Treatment Options</th>
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<tr>
<td>Exercise programs</td>
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<td>Meditation and relaxation</td>
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<td>Over-the-counter medications</td>
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<td>Adjunctive medications</td>
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<tr>
<td>Physical rehabilitation</td>
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<td>Cognitive and behavioural therapies</td>
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<tr>
<td>Somatic and sympathetic nerve blocking</td>
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<tr>
<td>Oral opioid medications</td>
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<td>Spinal cord stimulation</td>
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<tr>
<td>Intrathecal analgesia</td>
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<td>Neurodestructive procedures</td>
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</table>

**Oral opioids**

Following good treatment results observed in cancer patients, oral opioid therapies started to be prescribed to patients with chronic non-malignant pain if the cause of the pain could not be treated and/or when other treatment methods did not produce satisfactory results (Portenoy and Foley 1986; Zenz, Strumpf and Tryba 1992). Opioid treatment should be considered for both nociceptive and neuropathic pain conditions (Breivik 2005). No evidence exists to support the suggestion that non-malignant pain or different types of pain such as neuropathic pain are inherently unresponsive to opioid medication (Portenoy 1996). The
long-term use of opioids in chronic non-malignant pain is only justified if other drugs and methods with less risk of side effects have been tried and failed; the pain relief obtained with the opioid is significant and sustained; and the improvement in quality of life is sufficient to tolerate side effects and the risks of long-term adverse events of opioid therapy (Breivik 2005).

The World Health Organization (WHO) (1996) recommends a three step approach for the use of analgesics to provide pain relief (Figure 1.2.8). Non-opioids should be the administered for mild pain (step 1), followed by mild opioids if the pain continues or is moderate (step 2), and if the pain persists or is severe, strong opioids should be provided and the dose adjusted until pain relief is observed (step 3). Although commonly used, the systemic adverse effects of the medication administered via intravenous and oral routes often limit their use. Oral opioid therapy side effects may result in deterioration of the overall functional capabilities of the patients (Portenoy and Foley 1986).

![Figure 1.2.8 WHO three-step analgesic ladder (Adapted from World Health Organization 1996)](image)

*Intrathecal Drug Delivery Systems*

An intrathecal drug delivery system consists of a pump (Figure 1.2.9) implanted into an abdominal subcutaneous pocket which delivers medication directly into the cerebrospinal fluid through a catheter inserted into the intrathecal space of the spine and tunnelled under
Intrathecal spinal analgesia has become a recognized treatment for chronic non-malignant pain since the first reservoir was implanted in 1981 (Onofrio, Yaksh and Arnold 1981). Fully implantable devices have a lower infection rate when compared with external drug pumps (Sjöberg et al., 1992).

Oral administration was previously considered the optimal method of chronic opioid administration, however, emerging evidence demonstrates that intrathecal opioid delivery has a therapeutic advantage when comparing to alternative modalities (Mueller-Schwefe, Hassenbusch and Reig 1999). The use of opioids via IDD allows for a selective concentration to reach an important site of pain transmission, the spinal cord dorsal horn (Grady and Raphael 2008). Opioid administration into the intrathecal space achieves its effects at lower doses than using the oral or epidural route (North et al., 1991). The oral opioid dose conversion to an intrathecal dose is approximately 300:1 (Lamer 1994; Levy 1997), while the conversion ratio between epidural and intrathecal has been suggested to be 24:1 (Nordberg et al., 1984). The drug is highly localized, so its analgesic efficacy is maximized at lower doses (Coombs et al., 1983); and therefore, only a small amount of the drug reaches the circulatory system and is systemically absorbed (Winkelmüller and Winkelmüller 1996). Generally this leads to a decrease in the side effects, which also facilitates the provision of greater analgesia (Prager 2002).

![Diagram of a Synchromed programmable pump](image-url)
The cerebrospinal fluid has limited capacity to distribute intrathecally administered morphine away from the catheter tip (Bernards 2006; Flack, Anderson and Bernards 2011). This results in a greater delivery of the medication into the spinal cord. Besides having implications to the efficacy of the intrathecal therapy, this also means that only very small amounts of the medication would reach the supraspinal regions (Figure 1.2.10). Both brain and spinal cord are important sites of analgesia but they have a differing spectrum of non-analgesic effects with more derived from the brain (Grady and Raphael 2008).

![Figure 1.2.10 Central nervous system distribution of systemic and spinal analgesics](Adapted from Grady and Raphael 2008)

An intrathecal pump can have a programmable or constant flow rate and there are also variations concerning the volume of the reservoir. The selection will depend on what is considered to be more advantageous to the patients’ pain relief. With fixed rate pumps, changes in the delivery dose are only possible with a different concentration of the medication (Wallace and Yaksh 2000). Programmable pumps allow greater flexibility for
dosing changes and also allow for changes in the timing of medication delivery. This feature is particularly relevant for patients whose pain changes during the course of a day. Programmable pumps are also implanted when dose titration and regulation is anticipated (Prager 2002). The pump is refilled periodically via subcutaneous port injections. The frequency of refills depends on the flow rate of medication delivery that the patient requires. Patients with higher doses require more frequent refills.

The intrathecal medication administered to a chronic non-malignant patient is often low and drug delivery can be monitored with precision, therefore decreasing the risk of addiction.

_IDDS Procedure_
Due to the invasive nature, high initial cost, concerns about long-term opioid use and the possible complications derived from the procedure, IDD is only considered after more conventional treatments have failed. Generally, patient selection criteria for IDD includes inadequate pain relief with more conservative therapies, absence of surgically correctable lesions, pain responsive to oral, epidural or intrathecal opioids, 50% or greater pain relief during IDD trial, and no significant psychological / behavioural contraindications (Doleys et al., 1998).

At RHH Pain Management Department, a multidisciplinary assessment involving a pain consultant, a psychologist and a physiotherapist is undertaken to assess the different facets of pain and to determine patient suitability for IDDS. A biopsychosocial history is performed where factors such as pain topography, duration of pain, pain intensity, coping strategies, social support, history of anxiety and/or depression, previous treatments, and drug and/or alcohol abuse are taken into consideration. Before proceeding to surgery, a temporary inpatient trial of intrathecal medication takes place, lasting between two to five days to determine if the patient would obtain pain relief via intrathecal drug delivery. The trial consists of a single blinded placebo controlled administration of morphine. Patients are given different doses of morphine or saline, which they would be unaware of because they would not be informed and their drug chart would not be accessible to them. Placebo administration is randomly administered according to the preference of the physician in one or two of the days during the trial period. NRS pain intensity measurements are taken throughout duration of the trial, ranging from zero (no pain) to 10 (worst pain possible).
As recommended, if at least 50% pain reduction is achieved without intolerable side effects to medication and dose used during the trial, the patient should be considered a suitable candidate for IDD (Anderson and Burchiel 1999; Deer et al., 1999). In some countries, the implantation of the IDD system occurs immediately following a successful trial. In the United Kingdom, if the procedure is performed in a National Health Service (NHS) hospital, usually there is a waiting time between trial and full implantation because of the time required to obtain funding from the patient’s Primary Care Trust (PCT).

After implantation of the IDD device, the patients attend the hospital to refill the pump. At this time, adjustments are made to the medication if needed. The time between pump refills depends on the intrathecal dose the patient is being administered and can range from one month (patients receiving high intrathecal doses) to three or four months (patients on low intrathecal doses). Between follow-ups, a helpline managed by pain management nurses is available for urgent situations. The patient can also request an appointment if the pain is not under control or if there are suspicions of malfunctions.

The following section presents a review of the literature focusing on complications and effectiveness of intrathecal drug delivery.
1.3.1 Introduction

Prior to the start of the literature review, the author of this thesis was aware of the lack of randomised controlled trials (RCTs) investigating the efficacy of intrathecal drug delivery therapy for the management of chronic non-malignant pain. In contrast, several systematic literature reviews on this topic are currently available (Williams, Louw and Towlerton 2000; Turner, Sears and Loeser 2007; Patel et al., 2009; Noble et al., 2010; Hayek et al., 2011) (Table 1.3.1). A systematic review of multiple well-designed RCTs is considered the highest level of evidence for the efficacy of a pain treatment, followed by a well-designed RCT of adequate size as the next best level of evidence (McQuay et al., 1997). The best available long-term evidence for IDD is currently from open-label, uncontrolled, time-series studies (Noble et al., 2010).

Systematic reviews of observational studies, by assembling the results and assessing the methodological quality of the articles included in a review, represent as well a high level of clinical evidence. Different criteria can be employed to analyse the quality of evidence and grade of recommendation when performing a systematic review. The quality assessment tools employed in the reviewed systematic reviews are described. Some of the reviews evaluated both cancer and non-cancer studies but for the purpose of this thesis the results presented refer to non-cancer pain studies only.
<table>
<thead>
<tr>
<th>Author &amp; year</th>
<th>Bibliographic resources / search period &amp; language restrictions</th>
<th>Inclusion criteria</th>
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<th>Number of studies / patients</th>
<th>Outcome measures</th>
<th>Outcomes</th>
<th>Complications</th>
<th>Conclusions</th>
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<tr>
<td>Williams, Louw and Towlerton (2000)</td>
<td>MEDLINE, EMBASE, CancerCD, PubMed and reference lists. Search period and language restrictions not described.</td>
<td>Cancer and chronic non-cancer pain patients based in a hospital, hospice or community setting; different types of intrathecal pump systems for giving opioids in chronic pain control; different types of intrathecally administered drugs given by pump systems; comparisons of intrathecal delivery systems with other routes of analgesia delivery; case series and case reports were included in this review.</td>
<td>Acute pain studies were excluded (e.g. labour, postoperative and trauma pain); review articles with no original information; studies assessing the effectiveness of epidural therapy only; Case series reports that did not provide sufficient information on effects and side-effects.</td>
<td>49 studies / N = 2571 11 non-cancer studies / N = 666</td>
<td>Efficacy measures: visual analogue scale (VAS); Verbal Rating Score, McGill Pain Questionnaire (MPQ), Brief Pain Inventory, range of movement, and ability to return to work. Side-effects: pharmacological side-effects and complications. Costs: (a) costs of intrathecal pump systems, including initial costs, maintenance, number of outpatient visits, hospital admissions and use of health care resources; (b) financial benefits of the pump systems, such as reduction in drug costs, reduction in bed days, quicker return to work, reduction in the use of health service resources (GP visits, outpatient visits).</td>
<td>Mean VAS scores decreased from 7.6 pretherapy to 3.0 post-therapy. A further 27 studies showed some evidence of improvement after the use of intrathecal pumps. Decrease in supplemental analgesia ranged from 15% to 50%; good to excellent improvement in daily activities ranged from 22.3% to 82.5%; 6% to 8% improvement in ability to return to work; some improvement in sleep pattern; and 77% to 92% improvement in patient satisfaction. Information from cost-modelling projections may indicate some cost-benefit at varying times after initiation of therapy, depending on individual patient circumstances.</td>
<td>Pharmacological side-effects: nausea and vomiting (25%), sedation (17%), urinary retention (19%), pruritus (17%), myoclonic activity (18%), respiratory depression (3%). Less common pharmacological side-effects included amenorrhea, altered libido, constipation, oedema, opioid overdose, polyarthralgia, provocation of asthma, parental abuse of opioids, sweating, and incontinence. Mechanical related complications: included catheter dislodgement (between 5% and 18%); catheter obstruction/occlusion or disconnection (7.6%); pump failure (20%); CSF leakage (10%); haematoma/seroma (6.7%).</td>
<td>The use of intrathecal therapy in patients with chronic pain seems to be beneficial. Clearer and more standardised information is required before definite conclusions can be drawn regarding its effectiveness compared with alternative treatments.</td>
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<td>Turner, Sears and Loeser (2007)</td>
<td>MEDLINE, Science Citation Index Expanded, Cochrane Central Register of Controlled Trials, EMBASE, Current Contents Connect, Global Health, and International Pharmaceutical Abstracts. Hand search of reference lists was also performed. From starting date of the bibliographic databases until October 10, 2005 English language studies only.</td>
<td>Study addressed pain treatment with opioid or ziconotide delivered intrathecal via non-programmable pumps; patient pain diagnoses not limited to spinal stenosis or specific disease; study contained original data on pain, functioning or complications in humans; the only pump studied was non-programmable or data were presented separately for patients with programmable pumps; the first medication delivered intrathecally to all study participants was an opioid (with or without adjuvant medications) or ziconotide.</td>
<td>Non-programmable pumps studies; conference abstracts or case reports; more than 10% of the sample were being treated for spasticity or pain associated with a specific disease and data on pain, functioning or complications were not presented separately for patients without those conditions; and study focused only on patients who did not respond to the first intrathecal drug they were given, unless the study was of ziconotide.</td>
<td>10 studies / N = 342</td>
<td>Follow-up ranged from 6 to 60 months. Improvements in pain were observed in all the studies included in the effectiveness review. Mean ratings on 0-100 scales were 82.3 pre-IDD (3 studies), 45.2 at 6 months (3 studies), and 43.8 at 12 months (2 studies).</td>
<td>The mean follow-up was 27 months (range 7-60). Nonpharmacologic biologic complications: wound infection (12%), meningitis (2%), and pump malfunction (17%). Pharmacologic biologic complications: nausea/vomiting (33%), urinary retention (24%), pruritus (26%), and sexual dysfunction (25%). Hardware complications: catheter-related (18%), catheter migration or dislodgement (12%), catheter obstruction or occlusion (19%), and mechanical failure of pump or battery excluding normal battery replacement (5%). On average, 5% (range across 7 studies of 0% to 27%) had their IDD permanently removed by the time of follow-up (mean 32 months). Pain seems to improve but increases in opioid dose are often required to maintain pain relief levels. Long-term effects on pain remain unclear given the paucity of data from follow-ups longer than 1 year. Drug side-effects and other complications are common.</td>
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<td>Patel et al. (2009)</td>
<td>MEDLINE, EMBASE, Cochrane Library, systematic and narrative reviews, National Institutes of Health Clinical Trials Registry. Hand search of bibliographic references was also performed. From 1966 until December 2008 English language studies only.</td>
<td>Study clearly states the use of implantable intrathecal infusion system (programmable or fixed infusion rate) for non-cancer pain for long-term use; study must have a specific indication for intrathecal infusion and the drug injected; a minimum of 12 months follow-up was available; clear documentation of patient outcomes and complications were provided; and number of patients evaluated was at least 25.</td>
<td>Lack of clear documentation of infusion systems or mixed delivery methods; externalized infusion systems for short-term use; study for non-cancer pain with less than 12 months follow-up; and lack of clear documentation of the indications and patient population being studied.</td>
<td>4 studies / N = 386</td>
<td>Primary outcome: &gt; 50% pain relief. Secondary outcomes: Improvement of function, reduction in the amount of oral medication, decrease in side-effects from systemic drugs, and improvement in quality of life.</td>
<td>Satisfaction with treatment levels ranged from 60% to 92%. Pain reduction was observed ranging from 67.4% at 6 months to 58.1% at last follow-up. Improvements in levels of activity, quality of life and mood were observed. No change in work status was seen. One of the studies included in the review evaluated the use of Bupivacaine in combination with opioids considering this adjuvant medication as a safe and helpful method of treatment for patients who have not responded to intrathecal opioids alone.</td>
<td>One of the studies reported 14 pumps replaced, 25 pumps removed (28.9% considered treatment failures); in another study 40% required at least one surgical procedure to correct a technical problem; sweating, weight gain, nausea/vomiting, peripheral edema, pruritus, reduced libido were other side-effects observed.</td>
<td>Positive results for short and long-term relief were reported by 2 studies; results were not available for 1 study and were negative for 1 study. Level of evidence was considered either Level II-3 or Level III based on USPSTF criteria. Recommendation for intrathecal drug delivery is 1C/strong based on Guyatt et al. (2000) criteria.</td>
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<td>Author &amp; Year</td>
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<td>Noble et al. (2010)</td>
<td>Studies collected data on patients after at least 6 months from admission to hospital, excluding patients who had had chronic pain defined as lasting at least 3 months.</td>
<td>Did not include patients who had been diagnosed with cancer. Did not include patients who had been diagnosed with chronic obstructive pulmonary disease.</td>
<td>10 studies / N = 228</td>
<td>Adverse events (side-effects) and outcomes from study due to adverse events.</td>
<td>Adverse events unique to opioid inclusion pump (45%) included pump disconnections, misalignments, and pump complications. Surgical complications and post-operative infection were also observed. The percentage of patients who required readmission due to chronic pain was 4.5% (CI: 2.7% to 6.3%).</td>
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<td>Author &amp; year</td>
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<td>Hayek et al. (2011)</td>
<td>PubMed, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, hand search of reference lists. From 1966 until October 30, 2010. English language studies only.</td>
<td>Studies using intrathecal infusion device/system (programmable or fixed infusion rate) implanted for chronic pain for long term use. Specific indication for intrathecal infusion and the drug injected. A minimum of 3 months of follow-up was available for studies on cancer pain patients. A minimum of 12 months of follow-up was available for studies on non-cancer pain or studies involving both cancer and non-cancer pain patients. Clear documentation of patient outcomes and complications should have been provided. Number of patients evaluated must have been at least 24.</td>
<td>Lack of clear documentation of infusion systems or mixed delivery methods. Exclusion systems for short-term use. Studies for chronic non-cancer pain with less than 12 months follow-up and studies of cancer related pain with less than 3-month follow-up. Case reports, technical reports, surveys, animal studies, in-vitro pump evaluations.</td>
<td>20 studies / N = 1865</td>
<td>Quality assessment score of all studies was 61.3 ± 1.5 (50-78).</td>
<td>All cancer and non-cancer pain studies reported improvements following implantation of IDD system. The mean pain relief ranged from 31% to 66%, and 65% to 87% of the patients rated the IDD treatment as good or excellent. Decreases in systemic opioids were observed as well as an increase in intrathecal opioid dose throughout duration of therapy. Improvements in quality of life, mobility, mood and work status were observed in some studies. No evidence of tolerance was observed over 12 months in intrathecal ziconotide therapy.</td>
<td>Significant pain relief defined as a minimum of 2-point drop on an 11-point numerical pain scale or a decrease of baseline pain intensity by 30%.</td>
<td>The most common complications reported were device related malfunctions or procedure related complications including catheter malfunction, wound or pocket infections, catheter migration or fracture. Miscalculation of pump refill dates leading to severe pain was reported for 5 patients as well as a case of human error causing leak of medication from reservoir septum. 2 granulomas were observed, there were no mentions of hormonal side-effects. In a study with ziconotide, side effects occurred in 147 of 155 patients, most commonly confusion (43%).</td>
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</table>
1.3.2 Results

*Williams, Louw and Towlerton (2000)*

This review aimed to investigate the effectiveness, side effects and cost effectiveness of intrathecal pump systems for patients with chronic pain. The databases searched included MEDLINE and PubMed, however, PubMed contains all the MEDLINE citations, and therefore it is not clear why the authors mentioned the use of both databases and not only PubMed. The initial literature search resulted in 5764 studies that mentioned the use of opioids. Further reading revealed that 49 studies assessed efficacy of IDD for chronic pain; 11 of these were non-cancer pain studies. Although included in the review, the Anderson and Burchiel (1999) study was considered by the authors to be a cancer pain study when in fact all the patients had chronic non-cancer pain. The number of patients enrolled in these studies was 656. Quality assessment was performed using a modified version of the York model (Table 1.3.2), but no studies were excluded from the review based on this assessment tool score. Included in the seven studies that scored the highest (14 points out of 16 possible) were four non-cancer pain studies (Anderson and Burchiel 1999; Hassenbusch et al., 1995; Tutak and Doleys 1997; Winkelmüller and Winkelmüller 1996).

<table>
<thead>
<tr>
<th>Table 1.3.2 Assessing the rigour of longitudinal surveys or case series: modified York model (Adapted from Williams, Louw and Towlerton 2000)</th>
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</thead>
<tbody>
<tr>
<td>• Was the study based on an appropriate sample selected from a suitable sampling frame?</td>
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<td>• Was there a statement to suggest that only patients with intractable pain were included?</td>
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<td>• Did the article explain in detail what the selection criteria were?</td>
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<td>• Was follow-up long enough for important events to occur?</td>
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<td>• Were dose escalation details supplied?</td>
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<td>• Were outcomes assessed using a VAS or similar objective measure?</td>
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<td>• Were pre- and post-intervention VAS scores given?</td>
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<td>• Was another objective outcome measure given?</td>
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<td>• Was the same objective outcome measure given pre- and post-intervention?</td>
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<td>• Was an additional one or more outcome measures given?</td>
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<td>• Was the same additional outcome measure(s) given pre- and post-intervention?</td>
</tr>
<tr>
<td>• Was all the information on side-effects given?</td>
</tr>
<tr>
<td>• Were all the relevant complications shown in sufficient detail?</td>
</tr>
<tr>
<td>• Was there a trial of either epidural or intrathecal opioids prior to implantation?</td>
</tr>
<tr>
<td>• Was the trial blinded?</td>
</tr>
<tr>
<td>• Have the patients been incorporated into a clinical trial?</td>
</tr>
</tbody>
</table>
Morphine dose escalation was observed. For the studies that provided accurate initial and final dose information, the average dose increase per week ranged from 0.9% to 7% for non-cancer pain patients and from 11% to 160% for cancer pain patients.

This was the only review that also aimed to assess the cost-effectiveness of intrathecal pumps. The author’s conclusion regarding this outcome was that there was little evidence on the comparative costs of intrathecal pump systems with conventional therapies. Based on cost-modelling studies, it was suggested that intrathecal drug delivery may be cost-effective at varying times after initiation of therapy, depending on individual patient circumstances.

The authors concluded that the main risks associated with intrathecal pumps are pharmacological side effects of the drugs used and mechanical complications associated with the system used. Regarding effectiveness, it was concluded that the use of intrathecal therapy seems beneficial but definite conclusions can only be drawn with the emergence of clearer and more standardised information.

Turner, Sears and Loeser (2007)
The authors performed a systematic literature review of IDD effectiveness and complications. This review was limited to programmable pumps because the authors considered that at the time the search was performed, the majority of implanted intrathecal pumps for chronic non-malignant pain were programmable. Literature search strategies were provided for all the bibliographic databases used (PubMed, Science Citation Index Expanded, Cochrane Central Register of Controlled Trials, EMBASE, Current Contents Connect, Global Health, and International Pharmaceutical Abstracts). Search sensitivity was verified by ensuring that almost all articles identified via hand search of reference lists were identified via one or more of the structured database searches. Hand search of reference lists was also carried out. Quality assessment was carried out with the American Academy of Neurology (AAN) evidence classification (Moxley et al., 2005) (Table 1.3.3). The same group also developed a system for translation of the evidence into recommendations (Table 1.3.4), however, it was not clear if the authors used this tool.
Besides the inclusion criteria specified in Table 1.3.1, there were specific methodological characteristics the papers should have. Additional inclusion criteria for the effectiveness review was that the study should be Class I to III or a Class IV study with independent observer-completed or patient-completed standardised measures of pain or functioning obtained both before IDD implantation (or ziconotide initiation) and at planned, regular follow-ups; data from patient baseline descriptive and outcome measures reported for all study participants who underwent IDD implantation (or ziconotide initiation) during the study period; and original data reported on pain or functioning before IDD implantation and for ≥ 75% of implanted patients at a follow-up ≥ 6 months. Articles that failed the inclusion criteria for the effectiveness review could still be used for the complications review if the article reported original data on complications for ≥ 6 months after pump implantation for ≥ 80% of patients that received a pump during the study period. The rationale for minimum proportions of patients and duration of therapy were not clarified. Two authors used a structured form to screen each article for the inclusion and exclusion criteria and

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
</table>
| I     | Evidence provided by a prospective, randomised, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:  
  a) primary outcome(s) is/are clearly defined  
  b) exclusion/inclusion criteria are clearly defined  
  c) adequate accounting for drop-outs and crossovers with numbers sufficiently low to have minimal potential for bias  
  d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences |
| II    | Evidence provided by a prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a randomised control trial in a representative population that lacks one criteria a–d |
| III   | All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment |
| IV    | Evidence from uncontrolled studies, case series, case reports, or expert opinion |

| Table 1.3.3 AAN quality of evidence classification for a therapeutic article (Adapted from Moxley et al., 2005) |
discrepancies were resolved by discussion; however, it was not clarified if there were any discrepancies. Following screening of abstracts, 78 articles were reviewed for possible inclusion in either the effectiveness or complications review. Fifty-two of the articles were excluded from both reviews with 26 remaining. For the effectiveness review, 20 more articles were excluded from the review; 14 for not meeting the study methodology criteria and 6 because they did not report pre-IDD data on pain or functioning; six articles were included. For the complications review, 16 articles were excluded because they did not report original data on complications for ≥ 6 months after pump implantation for ≥ 80% of the study participants who received a pump; 10 articles met the inclusion criteria.

Table 1.3.4 AAN system for translation of evidence to recommendations (Adapted from Moxley et al., 2005)

<table>
<thead>
<tr>
<th>Translation of evidence to recommendations</th>
<th>Rating of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A Rating requires at least one convincing class I study or at least two consistent, convincing class II studies</td>
<td>A = Established as effective, ineffective or harmful for the given condition in the specified population</td>
</tr>
<tr>
<td>Level B Rating requires at least one convincing class II study or at least three consistent class III studies</td>
<td>B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population</td>
</tr>
<tr>
<td>Level C Rating requires at least two convincing and consistent class III studies</td>
<td>C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population</td>
</tr>
<tr>
<td></td>
<td>U = Data inadequate or conflicting; given current knowledge, treatment is unproven</td>
</tr>
</tbody>
</table>

Improvements in pain intensity were observed in all six studies included in the effectiveness review. There was, however, a high attrition rate in the two studies reporting pain intensity ratings at a follow-up time longer than six months. Patients reporting ≥ 50% reduction in pain ranged from 38% to 56% at six months and 30% at 24 months or 44% at last follow-up with a mean of 29 ± 12 months. All the studies included in the effectiveness review were Class IV observational according to AAN levels of evidence (Moxley et al., 2005). Besides the pharmacological side effects in Table 1.3.1, other side effects mentioned, but for which no
prevalence were reported, included asthma, insomnia, dry mouth, nightmares, myoclonic jerk/spasm, dizziness, loss of appetite, diarrhoea, and headache.

Although the authors indicated the use of the AAN levels of evidence, no reference is made to what their recommendation regarding IDD therapy would be based on the results of their systematic review and quality appraisal of the available evidence.

*Patel et al. (2009)*

The aim of this study was to determine the efficacy, safety, and complications associated with the use of intrathecal drug delivery systems for long-term management of chronic non-cancer pain.

Some of the search terminology was described but the search strategy used was not included in the review. The studies were evaluated for the inclusion and exclusion criteria by two physicians and disagreements resolved by a third physician. The same method was employed for quality assessment of the studies. If a conflict of interest was present (e.g. an author reviewing his own study), the involved authors did not assess the study. There was no indication in the review if disagreements or conflict of interests occurred during the review process.

Quality assessment of the articles was performed using the levels of evidence from the United States Preventive Services Task Force (USPSTF), supported by the Agency for Health Care Research and Quality (AHRQ) criteria for observational studies that translates into quality of evidence levels (Harris et al., 2001) (Table 1.3.5), the Cochrane Musculoskeletal Review Group criteria for randomised trials as described by Koes et al. (1995) (Table 1.3.6) and recommendation for therapy based on Guyatt et al. (2006) grading of recommendations and quality of evidence (Table 1.3.7). The reason why the authors mentioned the Cochrane criteria for randomised controlled trials is unclear because no RCTs met the inclusion criteria and, therefore, no RCTs were assessed for methodological quality. Only the studies scoring at least 50 out of 100 on weighted scoring criteria were included in the analysis.
Table 1.3.5 Quality of evidence by research design (Adapted from Harris et al., 2001)

<table>
<thead>
<tr>
<th></th>
<th>Evidence obtained from at least one properly randomized controlled trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-1</td>
<td>Evidence obtained from well-designed controlled trials without randomization.</td>
</tr>
<tr>
<td>II-2</td>
<td>Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.</td>
</tr>
<tr>
<td>II-3</td>
<td>Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.</td>
</tr>
<tr>
<td>III</td>
<td>Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.</td>
</tr>
</tbody>
</table>

Table 1.3.6 Quality assessment criteria for Randomised Controlled Trials (Adapted from Koes et al., 1995)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study population:</strong></td>
<td></td>
</tr>
<tr>
<td>A Homogeneity</td>
<td>2</td>
</tr>
<tr>
<td>B Comparability of relevant baseline characteristics</td>
<td>5</td>
</tr>
<tr>
<td>C Randomization procedure adequate</td>
<td>4</td>
</tr>
<tr>
<td>D Drop-outs described for each study group separately</td>
<td>3</td>
</tr>
<tr>
<td>E &lt; 20% loss to follow-up</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 10% loss to follow-up</td>
<td>2</td>
</tr>
<tr>
<td>F &gt; 50 subjects in the smallest group</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 100 subjects in the smallest group</td>
<td>9</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>25</td>
</tr>
<tr>
<td>G Interventions included in protocol and described</td>
<td>10</td>
</tr>
<tr>
<td>H Pragmatic study</td>
<td>5</td>
</tr>
<tr>
<td>I Co-interventions avoided</td>
<td>5</td>
</tr>
<tr>
<td>J Placebo-controlled</td>
<td>5</td>
</tr>
<tr>
<td><strong>Effect</strong></td>
<td>30</td>
</tr>
<tr>
<td>K Patients blinded</td>
<td>5</td>
</tr>
<tr>
<td>L Outcome measures relevant</td>
<td>10</td>
</tr>
<tr>
<td>M Blinded outcome assessments</td>
<td>10</td>
</tr>
<tr>
<td>N Follow-up period adequate</td>
<td>5</td>
</tr>
<tr>
<td><strong>Data-presentation and analysis</strong></td>
<td>10</td>
</tr>
<tr>
<td>O Intention-to-treat analysis</td>
<td>5</td>
</tr>
<tr>
<td>P Frequencies of most important outcomes presented for each treatment group</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>100</td>
</tr>
<tr>
<td>Grade of recommendation / description</td>
<td>Benefit vs risk and burdens</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1A/strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
</tr>
<tr>
<td>1B/strong recommendation, moderate quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
</tr>
<tr>
<td>1C/strong recommendation, low-quality or very-low quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
</tr>
<tr>
<td>2A/weak recommendation, high quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
</tr>
<tr>
<td>2B/weak recommendation, moderate-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
</tr>
<tr>
<td>2C/weak recommendation, low-quality or very low-quality evidence</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
</tr>
</tbody>
</table>
Following review of titles, abstracts and manuscripts based on inclusion and exclusion criteria, 15 observational studies were considered for inclusion in the review. However, two manuscripts that were not reviewed because according to the authors, the full manuscripts were not available. After methodological quality assessment only four studies were included in the review. There were three studies for which no reason was provided to exclude from the review.

This systematic review concluded that intrathecal infusion systems used for management of chronic intractable pain provide positive long-term outcomes. The grade of recommendation was 1C/strong based on Guyatt et al. (2006) grading recommendations.

Noble et al. (2010)
The aim of this systematic review was to summarize the evidence pertaining to the safety and efficacy of long-term opioid therapy for chronic non-malignant pain. This review also included studies where the opioids administered were oral or transdermal but the results were presented separately. This Cochrane review is also an update and the full report of a previous opioid therapy systematic review (Noble et al., 2008) by the same group. The authors declare that the differences in the studies that met the inclusion criteria did not impact significantly on the conclusions of the previous review.

This was the only systematic review without language restrictions. Hand search of reference lists and review of grey literature was carried out. The authors mention that although grey literature was reviewed, only outcomes data from published, peer-reviewed literature was analysed.

Two independent reviewers screened abstracts against the inclusion criteria and assessed the quality of the possible relevant studies using a 10-item methodological quality assessment instrument developed by the ECRI Institute (Table 1.3.8). Discrepancies were resolved by consensus, although it was not mentioned if this occurred with any of the studies.
<table>
<thead>
<tr>
<th>Number</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>For the outcome of interest, was the performance among patients at baseline similar among patients who entered the study as compared to patients who completed the study to the timepoint of interest? (For the same study, answer may vary by outcome. If attrition is less than 15% for this outcome, we answer 'yes' even if characteristics were not compared).</td>
</tr>
<tr>
<td>2.</td>
<td>For all other important factors, were the characteristics of patients at baseline similar among patients who entered the study as compared to patients who competed the study to the timepoint of interest? (If attrition was less than 15% for the entire study, we answer 'yes' even if characteristics were not compared).</td>
</tr>
<tr>
<td>3.</td>
<td>Did the study enroll all, a consecutive series of, or a randomized sample of suitable patients within a time period?</td>
</tr>
<tr>
<td>4.</td>
<td>Was the study prospectively planned? (Although redundant with inclusion criteria, this factor remains important for the assessment of bias and influences the internal validity category).</td>
</tr>
<tr>
<td>5.</td>
<td>Did 5% or less of patients receive ancillary treatment(s).</td>
</tr>
<tr>
<td>6.</td>
<td>Was compliance with treatment at least 85%?</td>
</tr>
<tr>
<td>7.</td>
<td>Was the outcome measure of interest objective and was it objectively measured? (For the same study, answer may vary by outcome).</td>
</tr>
<tr>
<td>8.</td>
<td>Was a standard instrument used to measure the outcome? (For the same study, answer may vary by outcome. Although redundant with inclusion criteria, this factor remains important for the assessment of bias and influences the internal validity category).</td>
</tr>
<tr>
<td>9.</td>
<td>Did at least 85% of patients contribute data to this outcome? (For the same study, answer may vary by outcome and timepoint).</td>
</tr>
<tr>
<td>10.</td>
<td>Was the funding for this study derived from a source that would not benefit financially from particular results?</td>
</tr>
</tbody>
</table>
This was also the only systematic review to perform a meta-analysis when at least two studies of the same mode of administration addressed an outcome of interest. Ten intrathecal therapy studies met the inclusion criteria. All of these were open-label, single-arm time series. For two of these studies, it was unclear whether they were prospectively designed. The quality of evidence was considered low primarily due to failure to describe patient recruitment methods; failure to compare the characteristics of patients who completed the study with patients who did not in studies with attrition; high prevalence of use of adjuvant therapies and use of a funding source with a potential conflict of interest in the outcome. All the patients enrolled in intrathecal therapy studies reported severe pain at baseline due to nociceptive, neuropathic, or mixed pain. Only one intrathecal opioid patient appeared to present an opioid abuse and/or addiction behaviour in the form of drug-seeking behaviour, indicating a rate of 0.43% (1/228).

The most common reasons for withdrawal of a study were adverse events and insufficient pain relief. For each mode of administration, the studies reported that adverse events/effects diminished over time and the majority of these were minor. The withdrawal rates due to adverse events at follow-up means of 20 and 29 months were lower in intrathecal studies with a proportion of 8.9% (95% CI: 4.0% to 18.6%) when compared with the other modes of administration. For oral administration, the overall (weak and strong opioids) withdrawal rates for a follow-up range of six to 24 months were 22.9% (95% CI: 15.3% to 32.8%). For transdermal opioids the withdrawal rates for a follow-up range of six to 48 months were 12.1% (95% CI: 4.9% to 27%).

The withdrawal rates due to insufficient pain relief at a follow-up range of seven to 24 months for oral opioids were 10.3% (95% CI: 7.6% to 13.9%); for transdermal opioids at a follow-up range of 12 to 48 months were 5.8% (95% CI: 4.2% to 7.9%); and for intrathecal opioids at a follow-up range of six to 29 months were 7.6% (95% CI: 3.7% to 14.8%).

The proportion of patients who had at least 50% pain reduction using oral opioids was 44.3% (95% CI: 33.3% to 55.9%); for transdermal opioids was 38.2% (95% CI: 33.1% to 43.5%), however, this was the result of a single study. Under the protocol developed, the results of a single study cannot be used to form-evidence based conclusions. The proportion of patients undertaking intrathecal opioids that achieved at least 50% pain reduction was 44.5% (95% CI: 27.2% to 63.2%).
No conclusions could be drawn regarding the effects on quality of life and function for intrathecal patients due to inconsistent or inconclusive findings. No studies were identified for the function outcome for oral or transdermal opioids and for the quality of life outcomes they were inconclusive for both oral and transdermal opioids.

The authors concluded that the evidence regarding the effectiveness of long-term opioid therapy is currently too sparse to draw firm conclusions.

Hayek et al. (2011)

The aim of this systematic review was to evaluate and update the available evidence for the efficacy and safety of intrathecal infusions used in long-term management (> 6 months) of cancer and non-cancer pain. The inclusion and exclusion criteria states that non-cancer pain studies with less than 12 months follow-up and cancer pain studies with less than three months follow-up would not be included in the review. The search was carried out by two unblinded reviewers. Quality assessment was carried out using the same tools as in the Patel et al. (2009) systematic review.

Discrepancies in the analysis were evaluated by a third reviewer who, working with the other reviewers, reached a consensus. Studies scoring below 50 of 100 in the quality assessment were excluded from the review. The search was limited to English language studies. The keywords used for the search were provided. The authors also indicated that the reviewers did not evaluate their own articles (conflict of interests) but there is no clarification as to how this situation was resolved.

The search resulted in the inclusion of 20 studies. The majority (15) involved non-cancer pain patients’ observational studies and from the five cancer studies, four were observational studies and one was a randomised controlled trial involving only cancer pain patients. With the exception of three non-cancer studies, complications derived from the therapy were reported. All of the studies included reported positive outcomes including pain relief measured with a VAS or NRS.

This systematic review used both USPSTF and Guyatt et al. (2006) quality of evidence criteria. Based on Guyatt et al. (2006) criteria the authors suggest moderate
recommendation of IDD for both cancer and non-cancer pain management. However, this level of recommendation is absent from Guyatt et al. (2006) grade of recommendation / description.

1.3.3 Conclusion
All of the evaluated systematic literature reviews aimed to investigate the effectiveness of IDD for the management of chronic pain. It is interesting to notice that no study was included in all the reviews (Table 1.3.9). This occurred most likely due to the inclusion and exclusion criteria chosen as well as the assessment tool used to measure the methodological quality of the studies. However, both the Patel et al. (2009) and the Hayek et al. (2011) reviews had similar inclusion and exclusion criteria, the same quality assessment tools, methodology and two of the authors participated in both reviews. Seven additional studies published until the end of 2007 were included in the Hayek et al. (2011) review but not in the Patel et al. (2009) review. One difference in the inclusion criteria was the minimum number of participants included, 25 for the Patel et al. (2009) review and 24 for the Hayek et al. (2011) review. There was only one study with 24 participants and therefore meeting the exclusion criteria for the Patel et al. (2009) review. The Patel et al. (2009) review used an additional bibliographic database (National Institutes of Health Clinical Trials Registry) that was not used in the Hayek et al. (2011) review. Therefore, the reasons for the discrepancy in the number of included articles in these reviews are not clear.

The conclusions for the effectiveness of intrathecal drug delivery for the management of chronic non-malignant pain were similar for all the systematic reviews assessed. None of the systematic reviews identified randomised controlled trials for non-cancer pain. All of the reviews recognize the paucity of good quality long-term effectiveness papers for IDD therapy, especially non-cancer pain. Overall, the use of IDD for chronic non-malignant pain patients seems beneficial, but the current available literature is too sparse to draw definite conclusions regarding its effectiveness.

Following the review of intrathecal drug delivery for chronic non-malignant pain, a pilot study is presented. The side effects/complications of this therapy were investigated. The pilot study was carried out at Russells Hall Hospital Pain Management Department.
<table>
<thead>
<tr>
<th>Table 1.3.9 Non-cancer pain studies included in the systematic reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hassenbusch et al. (1995)</td>
</tr>
<tr>
<td>Borg and Krijnen (1996)</td>
</tr>
<tr>
<td>Maeyaert and Kupers (1996)</td>
</tr>
<tr>
<td>Paice, Penn and Shott (1996)</td>
</tr>
<tr>
<td>Yoshida et al. (1996)</td>
</tr>
<tr>
<td>Nitescu et al. (1996)</td>
</tr>
<tr>
<td>Willis and Doleys (1999)</td>
</tr>
<tr>
<td>Kumar, Kelly and Piriot (2001)</td>
</tr>
<tr>
<td>Roberts et al. (2001)</td>
</tr>
<tr>
<td>Dominguez et al. (2002)</td>
</tr>
<tr>
<td>Kumar, Hunter and Dementia (2002)</td>
</tr>
<tr>
<td>Shaladi et al. (2007)</td>
</tr>
<tr>
<td>Staats et al. (2007)</td>
</tr>
<tr>
<td>Ellis et al. (2008)</td>
</tr>
<tr>
<td>Ilia et al. (2008)</td>
</tr>
<tr>
<td>Duso, Davia and White (2009)</td>
</tr>
<tr>
<td>Aff et al. (2010)</td>
</tr>
</tbody>
</table>

Search period not mentioned

Search period from starting date of the bibliographic databases until October 10, 2005

Search period from starting date of the bibliographic databases until December 2008

Search period from starting date of the bibliographic databases until May 19, 2009

Search period from starting date of the bibliographic databases until October 30, 2010
SECTION 4. Pilot study of intrathecal drug delivery complications/side effects

This section was published as three separate abstracts in Regional Anesthesia and Pain Medicine 2008;33(5):e20/e201/e202 (Appendix 6, 7, 8). Appendix 8 was also selected for oral presentation at the Neuromodulation Society of United Kingdom and Ireland Joint Scientific Meeting with British Stereotactic and Functional Neurosurgery Group 2007. Appendix 6 was selected for oral presentation at the 27th Annual European Society of Regional Anaesthesia Congress 2008. These publications have been reformatted to fit with the overall PhD thesis.

1.4.1 Background
In order to determine which complications would be of interest to study, a pilot study was performed at Russells Hall Hospital, Pain Management Department to investigate which complications/side effects are more prevalent at this centre. This department is one of the largest UK centres for intrathecal drug therapies. IDD systems were introduced at this centre as a treatment for chronic pain in the late 1980s, and since then, its staff have acquired a vast knowledge and experience regarding this therapy.

Opioid dose increase and hormonal effects were investigated alongside the investigation of complications/side effects as they can be underreported. Opioid dose increase can be regarded as a normal consequence of long-term therapy and sexual dysfunction as a result of hormonal imbalance not always is reported by the patient to the consultant.

1.4.2 Methods
Complications/side effects
A longitudinal retrospective case notes review of 62 consecutive patients receiving continuous intrathecal analgesics by implanted reservoir administration was carried out. Patients’ case notes were screened from date of implant to August 2008. Data collected included duration of pain prior to implant, age at the time of IDD system implantation and duration of IDD therapy. Complications reported were recorded and categorized for the purpose of analysis.
**Opioid dose increase**

A longitudinal retrospective review of the doses of 47 patients receiving intrathecal morphine or diamorphine was performed through examination of the patients’ case notes from date of implant to August 2008. The intrathecal dose since implant date was computed for consecutive years. The data presented comprises the intrathecal opioid doses up to year 10. Less than 10 patients included in the study had been undertaking IDD therapy for longer than 10 years.

**Hormonal effects**

The hormone levels of seven males who had been receiving long-term (> 4 years) and low-dose (< 2.5 mg/day) intrathecal morphine therapy were reviewed. The hormones investigated included testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and sex hormone binding globulin (SHBG). The reference levels used for these hormones were: testosterone (male 20 to 49 years: 9.1 - 55.2 nmol/L; > 49 years: 6.3 - 26.6 nmol/L); LH (2.2 – 13.3 IU/L); FSH (1 - 7 IU/L) and SHBG (13 - 71 nmol/L). Morphine dose and duration of IDD therapy were also recorded.

**Data analysis**

The mean and standard deviation were calculated for the variables age, duration of pain prior to implant, duration of therapy, intrathecal dose and hormones studied. Proportions were calculated to examine the prevalence of the complications identified. Events per patient year were calculated using the formula: (number of events ÷ number of patients) ÷ average follow up). Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 12.0, SPSS Inc., Chicago, IL, USA).

**1.4.3 Results**

**Complications/side effects**

The mean age of the patients investigated was 59 ± 9 years (range: 38-77). The average duration of IDD therapy was 6.7 ± 4 years (range: 1-16). Prior to implantation of an intrathecal pump, the mean duration of painful symptoms was 14 ± 10 years (range: 2-38).
At the moment of this retrospective analysis, 53.3% of the patients had not reported any symptomatic complications/side effects. More than one adverse event was identified for 13 patients (20.9%) while 16 individuals (25.8%) had one single complication throughout the course of IDD treatment. Table 1.4.1 details the number of patients who had an adverse event during the course of IDD therapy.

**Table 1.4.1 Proportion of patients with reported complications**

<table>
<thead>
<tr>
<th>Patients (n=62)</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with complication</td>
<td>29</td>
</tr>
<tr>
<td>Patients with single complication</td>
<td>16</td>
</tr>
<tr>
<td>Patients with multiple complications</td>
<td>13</td>
</tr>
</tbody>
</table>

With the exception of life threatening overdose which is more likely to occur due to leakage or human error during pump refill, the other pharmacological side effects observed are common in long-term intrathecal therapy (Chaney 1995) (Table 1.4.2).

**Table 1.4.2 Complications identified and events per patient year**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Events (n)</th>
<th>Proportion (%)</th>
<th>Events / patient year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological</td>
<td>13</td>
<td>28.9</td>
<td>0.031</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>8.9</td>
<td>0.010</td>
</tr>
<tr>
<td>Life threatening overdose</td>
<td>3</td>
<td>6.7</td>
<td>0.007</td>
</tr>
<tr>
<td>Intrathecal granuloma</td>
<td>3</td>
<td>6.7</td>
<td>0.007</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2</td>
<td>4.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Itching</td>
<td>1</td>
<td>2.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Medical</td>
<td>9</td>
<td>20.0</td>
<td>0.022</td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
<td>13.3</td>
<td>0.014</td>
</tr>
<tr>
<td>Mild / superficial infections</td>
<td>4</td>
<td>8.9</td>
<td>0.010</td>
</tr>
<tr>
<td>Severe / deep infection*</td>
<td>2</td>
<td>4.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Psychological</td>
<td>1</td>
<td>2.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>4.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Technical / Equipment</td>
<td>23</td>
<td>51.1</td>
<td>0.055</td>
</tr>
<tr>
<td>Pump related **</td>
<td>11</td>
<td>24.4</td>
<td>0.026</td>
</tr>
<tr>
<td>Catheter related ***</td>
<td>10</td>
<td>22.2</td>
<td>0.024</td>
</tr>
<tr>
<td>Programming errors</td>
<td>2</td>
<td>4.4</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*requiring explantation

** malfunction, failure, pocket pain, difficult refill

*** kinking, migration, fracture
Infections usually occurred subsequent to implant, revision surgery or replacement of the pump. Three patients were diagnosed with intrathecal catheter tip granulomas, corresponding to 0.007 events per patient year. Complications related to the equipment or technical difficulties were the commonest adverse events identified with an occurrence rate of 0.055 events per patient year. Adverse events requiring discontinuation of IDD device, revision surgery or explantation of the IDD system accounted for 27.4% of the situations.

**Opioid dose increase**

The mean age of the patients was 60 ± 9 years (range 38-77) with an average duration of treatment of 6 ± 3 years (range 1-10). The mean opioid dose of these patients throughout the years was 2.66 ± 2.39 mg/day (range 0.3-14.2). There was a gradual increase in opioid dose with time to reach 5.23 mg/day (range 0.75-14.2) at 10 years (Fig. 1.4.1).

![Intrathecal morphine dose increase from beginning of treatment until year 10](image)
The graph illustrates that opioid dose increases with time, however, the increase is modest. Some patients did not demonstrate any tolerance and only one patient (#19 in the graph) very rapidly showed dose escalation, reaching an intrathecal opioid dose > 10 mg/day within four years of IDD therapy.

**Hormonal effects**

The mean age of the patients evaluated was 55 ± 7 years (range 45-66). The mean morphine dose was 1.5 ± 0.7 mg/day (range 0.35-2.3) and the mean duration of treatment was 7.2 years (range 4-15). Serum testosterone concentrations were below the lower limit of the reference range for age in three patients and borderline low in three other patients. Serum LH levels were low (< 2.2 IU/L) in five patients and FSH levels were within the reference range (1-7 IU/L) in all seven patients (Table 1.4.3).

<table>
<thead>
<tr>
<th>Table 1.4.3 Hormonal levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
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<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

* years; **IU/L; *** nmol/L

Based on serum testosterone and LH levels, five of the seven patients were considered to have hypogonadotropic hypogonadism.

**1.4.4 Limitations**

This pilot study allowed determination of the prevalence of complications/side effects at this centre. However, possible causes of the identified complications/side effects were not explored.

The opioid dose increase study was based on a single dose per patient per year. A more robust investigation could be performed with the dose per year based on the average of all
the refills throughout each year. Moreover, a complete data set would allow further analyses which were not possible with this sample.

The aim of the hormonal effects investigation was to verify if hypogonadotropic hypogonadism, also known as secondary hypogonadism could occur even at small doses. This study included a limited number of participants and did not investigate if the occurrence of hypogonadotropic hypogonadism could have more repercussions in the patients other than the potential loss of libido.

1.4.5 Need for this study
The pilot study enabled identification of which complications are more prevalent at this centre for IDD therapy administration. Taking into consideration the incidence and magnitude of the adverse events categorized, research feasibility and available literature; it was considered that an investigation of intrathecal opioid dose increase, intrathecal granuloma formation, and hormonal effects could potentially provide new knowledge in this area.

Intrathecal opioid dose increase was investigated because the possibility of tolerance development is a commonly used reason to withhold the use of opioid treatment until an undeniable need (Portenoy 1994). The opioid dose increase observed in the pilot study was modest; therefore it was considered that a more robust analysis as described above could shed some light into the dose escalation problematic.

The majority of possible pharmacological side effects resolve with time, often without the need of additional medication (e.g. nausea, urinary retention). Intrathecal granulomas have the potential to cause paralysis if not identified in its early development. Moreover, the conservative method to manage this adverse event, involves the decrease, change or cessation of the opioid administration impacting on a patients’ pain relief. Therefore, and since the current available literature on this topic is limited, an investigation of this IDD side effect would be of value.

The possible effect of IDD on the endocrine system is one of the least noted and investigated IDD side effects and consequently undertreated (Doleys et al., 1998; Reddy et
al., 2010). This usually occurs because the patients may attribute the signs and symptoms of hypogonadism to the chronic pain and its related conditions. Moreover, hormonal imbalance can cause further complications not directly related with the IDD therapy.

Additionally, due to the potential dimension of some of these adverse events and possible implications to the treatment and condition of the patients undertaking this therapy, the long-term benefits and the cost effectiveness of IDD were also considered to be of interest to investigate. The long-term effectiveness and cost effectiveness of IDD therapy have also been considered by the described systematic reviews as areas where current knowledge is limited.

The following chapters will focus on the mentioned pharmacological complications as a result of intrathecal drug delivery therapy.
Chapter 2

Pharmacological complications

Section 1
Intrathecal opioid dose increase throughout the years

Section 2
Yearly opioid dose increase as an early indicator of granuloma formation

Section 3
Systematic review of intrathecal granulomas case reports and comparison with a control group

Section 4
Hormonal effects as consequence of intrathecal drug delivery

Section 5
Osteopaenia and osteoporosis as a secondary side effect of intrathecal drug delivery
SECTION 1. Intrathecal opioid dose increase throughout the years

2.1.1 Abstract

Background and aims

The fear of the development of dependence, tolerance or addiction as a consequence of opioid medication contributes regularly to the stigmatisation and withholding of intrathecal opioid delivery therapy for chronic pain of non-malignant origin. Tolerance is defined as a phenomenon in which exposure to a drug results in a decrease of an effect or the requirement of a higher dose to maintain an effect. However, often the need of opioid dose escalation is the result of deterioration of a patient’s condition. The aim of this study was to describe the intrathecal opioid dose throughout the years in chronic non-malignant pain patients and to develop an intrathecal opioid dose predictive model.

Methods

A longitudinal retrospective assessment of medical records was performed and pump refill notes were screened from date of implant to November 2010 for 31 patients undertaking continuous intrathecal opioid delivery for the management of chronic non-malignant pain. All the participants included had a minimum of six years of IDD therapy when the data was collected. Changes in opioid dose were investigated and controlled for gender, age, duration of pain prior to IDDS, topography of pain, type of pain, IDD system replacements and administration of intrathecal adjuvant medication.

Results

Significant increases in the intrathecal morphine dose were verified between follow-up at one year and all subsequent observations, $F(2.075, 62.238) = 13.858, p < 0.001$. From year three onwards, no significant differences were observed with the following assessments, $F(3, 90) = 2.516, p = 0.63$, indicating stability of the morphine dose. A model that accounts for 76% of the variability of morphine doses at year six based on year two assessment was developed.

Conclusion

A model accounting for 76% of the variability of the opioid dose at year six based on the dose of year two combined with duration of pain prior to initiation of intrathecal therapy was developed. This model has the potential to assist the physician in the identification of a need.
for an alternative treatment strategy. Since many of the pump replacements are performed prior to year six, it can also assist in the informed decision of the benefits and risks of the maintenance of this therapy.

2.1.2 Introduction

Nomenclature of concepts

The concepts of addiction and dependence are often associated with tolerance. Therefore, it is important to clarify the differences between these terminologies. To describe a physically dependent patient as an addict may lead to stigmatization and potentially cause distress and risk of under-treatment (Portenoy 1991).

Dependence can be divided into physical and psychological. An individual is physically dependent on a substance when an abstinence syndrome or withdrawal occurs after sudden dose reduction, cessation of therapy or administration of an antagonist drug (Jaffe 1985). The phenomenology of physical dependence has been widely researched and described in animals (Gellert and Holtzman 1978; Martin et al., 1974; Redmond and Krystal 1984) and humans (Heishman et al., 1989a; Heishman et al., 1989b; Judson, Himmelberger and Goldstein 1980). Physical dependence is likely to commence with the initial administration of an opioid drug and its development should be assumed if the opioids are administered on a regular basis for pain relief (Collett 1998; Portenoy and Savage 1997). When there is a need to cease the opioid therapy, the current practice for pain management patients, is to reduce the opioid dose slowly, therefore reducing the likelihood of withdrawal symptoms. An abrupt stop of opioids or the administration of opioid antagonists is very likely to cause withdrawal (Kanner and Foley 1981).

Psychological dependence can be considered as a component of the addiction concept because it implies the craving of a substance for its psychological effects (Portenoy 1994). Addiction is characterized by the compulsive use of a substance (despite harm), drug seeking behaviours and a high tendency to relapse following withdrawal (Jaffe 1985; Rinaldi et al., 1988). In the clinical setting, addiction is also associated with noncompliance with suggested opioid changes (Raphael et al., 2010). Fear that opioid treatment may lead to addiction or abuse is one of the great medical concerns and at the same time a potential barrier to administration of this therapy (Noble et al., 2008). However, opioid addiction is
more common outside a pain clinical setting. In a recent systematic review, the observed signs of opioid addiction in pain management patients corresponded to seven cases in 4,884 participants, indicating a low rate of opioid addiction development (0.14%) (Noble et al., 2010). The same author considers that the low rates of addiction should only be generalized to patients without a history of addictive/abusive behaviours. Despite situations where extremely high doses of intrathecal opioids were administered, only one IDDS study has reported a possible development of opioid addiction in the form of drug seeking behaviour (Anderson and Burchiel 1999).

Tolerance refers to a phenomenon in which exposure to a drug results in a decrease of an effect or the requirement of a higher dose to maintain an effect (Jaffe 1985). Tolerance to opioids is characterized by a shortened duration and decreased intensity of the effects caused by depression of the central nervous system such as analgesia, euphoria or sedation (Jaffe 1985). The type of tolerance can be divided into innate or acquired (O’Brien 1995). Innate tolerance is genetically determined and refers to sensitivity or lack of sensitivity to a drug which can be observed during the first administration. Acquired tolerance can be divided into pharmacokinetic, pharmacodynamic and learned tolerance. Pharmacokinetic tolerance refers to modifications in the metabolism or distribution of the drug following repeated drug administrations which result in reduced concentrations in the blood and at the sites of drug action. Pharmacodynamic tolerance refers to adaptive changes which take place within the systems affected by the drug, such as changes ensuing drug administration in receptor density or receptor sensitivity, so that response to a given concentration of the drug is reduced. Learned or associative tolerance refers to a reduction of the effects of a drug as a result of learned compensatory mechanisms, for example through operant conditioning.

*Physiological mechanisms and potential contributors to opioid tolerance*

G protein-coupled receptors (GPCRs) are the largest family of cell-surface molecules involved in signal transmission and more than 50% of the current available pharmacological agents target these receptors (Marinissen and Gutkind 2001). Opioids exert their effect by attachment to a group of GPCRs (Figure 2.1.1). The GPCRs encompass seven transmembrane helices. These receptors are activated by extracellular stimulus which is then decoded into intracellular signals causing an activation of a guanine nucleotide-binding
protein (G protein). The G proteins are signal transducers that communicate signals from a diverse selection of sensory and chemical stimuli, such as light, odour, taste hormones, neurotransmitters, chemokines, autocrine and paracrine factors (Ferguson 2001; Neves, Ram and Iyengar 2002). The effect of the G protein is dependent on the type of binding agonist. The GPCRs respond to a multiplicity of extracellular stimuli, and activate a variety of intracellular signalling pathways (Kroeze, Sheffler and Roth 2003). After the agonist binds to the receptor, a structural arrangement in the receptor occurs. The signalling pathways that are activated will depend on the type of G protein to which the receptor is attached (Marinissen and Gutkind 2001; Neves, Ram and Iyengar 2002). The functional activity of GPCRs extends beyond the traditional model of receptor → G protein → effector (Ferguson 2001). Most biological responses that are mediated by GPCRs are not dependent on a single biochemical route, but result from the integration of the functional activity of an intricate network of intracellular signalling pathways (Marinissen and Gutkind 2001).

GPCRs can be grouped into five different families: glutamate, rhodopsin, adhesion, frizzled/taste 2 and secretin (Fredriksson et al., 2003). The glutamate family has a physiological role in a variety of central nervous system functions including pain modulation and also interacts with the opioid system (Fundytus 2001). Glutamate receptors have been found to be present in the brain, spinal cord and periphery in animals and humans (Fundytus 2001).

![Figure 2.1.1 G protein-coupled receptors](image)

The activity of GPCRs is characterized by a coordinated balance between molecular mechanisms controlling receptor signalling, desensitisation and resensitisation (Ferguson
2001). Receptor desensitisation (or tolerance) indicates the decline of GPCRs responsiveness to an agonist with time and it is an important physiological “feedback” mechanism that protects against both acute and chronic receptor overstimulation (Ferguson 2001). Nevertheless, receptor desensitisation can also significantly limit the therapeutic benefits of many receptor agonists (Ferguson 2001).

A combination of events contributes to the desensitisation of GPCRs: the uncoupling of the receptor from its G protein as a result of receptor phosphorylation, the internalisation (sequestration) of plasma membrane associated receptors, and the downregulation of the total cellular complement of receptors as a consequence of reduced messenger ribonucleic acid (mRNA) and protein synthesis (Ferguson et al., 1996). Second messenger-dependent protein kinases, G protein-coupled receptors kinases and arrestins are the three families of regulatory molecules known to contribute to the GPCR desensitization process (Ferguson 2001). Receptor phosphorylation is the fastest way of GPCR desensitisation, achieved within seconds to minutes of agonist stimulation by second messenger activated protein kinases (cAMP-dependent protein kinase (PKA) and protein kinase C (PKC)) and G protein-coupled receptors kinases (GRKs) that specifically phosphorylate agonist-activated GPCRs (Ferguson et al., 1996; Premont, Inglese and Lefkowitz 1995). Although receptor internalisation potentially contributes to desensitisation as a result of loss of plasma membrane associated receptors, it is thought to be primarily associated with receptor resensitisation (Ferguson et al., 1996).

One of the main contributors to the development of tolerance in both spinal and supraspinal systems appears to be the β-arrestin-2 mediated mechanism of desensitisation (Bohn, Lefkowitz and Caron 2002). The β-arrestin-2 is a G protein-coupled receptor-regulating protein which regulates the μ opioid receptors. Mice lacking β-arrestin-2 did not develop tolerance to acute or chronic morphine administration, but still developed morphine dependence (Bohn et al., 2000). In the absence of the β-arrestin-2 mechanism, the contributions of a PKC dependent regulatory system become apparent (Bohn, Lefkowitz and Caron 2002). These authors suggested that the spinal antinociceptive actions of morphine are regulated by β-arrestin-2 and PKC-dependent pathways, and within the spinal system both of these regulatory mechanisms contribute to the μ opioid receptors regulation.
N-methyl-D-aspartate (NMDA) is an agonist that mimics the action of glutamate at the NMDA receptor. Glutamates are the neurotransmitters that usually bind to the NMDA receptors. Dorsal horn neurons that process pain information have both µ-opioid and NMDA receptors (Price et al., 2000). These neurons are at the origin of ascending pain pathways. NMDA receptors consist of four transmembrane helices that are linked to an ion channel permeable to calcium ($\text{Ca}^{2+}$), sodium ($\text{Na}^{+}$) and potassium ($\text{K}^{+}$) (Fundytus 2001; MacDermott et al., 1986; Mayer et al., 1987). The mechanism related to morphine tolerance has been suggested to involve the NMDA receptor (Bilsky et al., 1996; Mayer, Mao and Price 1995). NMDA receptors mediate slow excitatory postsynaptic potentials, and activation of these receptors stimulates PKC activation (Fundytus 2001; Mao, Price and Mayer 1995). There is evidence indicating a role for PKC in pain; the inhibition of this protein reduces hyperalgesia and allodynia associated with nerve injury (Mao et al., 1992; Mayer, Mao and Price 1995) and mechanical hyperalgesia associated with thermal injury (Yashpal et al., 1995). PKC has been shown to be involved in several types of acute and chronic pain as well as tolerance and dependence, particularly through phosphorylation of the NMDA receptor or the G protein coupled to opioid receptors, therefore desensitising these receptors leading to a reduction of the efficacy of opioid agonist analgesics (Fundytus 2001). The effects on opioid receptors assume particular importance for certain types of intractable chronic pain where opioid therapy can be less effective, such as neuropathic pain (Fundytus 2001).

Morphine delivered into the intrathecal space of morphine-tolerant rats induced the release of glutamate and aspartate (an excitatory amino acid such as glutamate) in the spinal cord producing a loss of the morphine analgesic effect (Wen et al., 2004). The same effect was observed in the cerebral spinal fluid of terminal cancer pain patients undertaking long-term intrathecal morphine delivery for pain relief (Wong et al., 2002). The administration of an NMDA antagonist in combination with morphine in rats blocked the release of morphine induced excitatory amino acids and attenuated morphine tolerance development (Lin et al., 2005; Wen et al., 2004). The findings of these studies seem to indicate an association between the release of excitatory amino acids and the development of morphine tolerance. It has been suggested that the administration of amitriptyline as an adjuvant medication may help to prevent the development of morphine tolerance by reducing the release of morphine induced excitatory amino acids (Tai et al., 2006; Tai et al., 2007).
Animal studies have demonstrated opioid tolerance to be pharmacodynamic, time and dose dependent, receptor specific and reversible if the agonist is removed (Sosnowski and Yaksh 1990; Stevens and Yaksh 1992). A comparison of morphine self-administration in rats with adjuvant-induced arthritis and pain-free rats was performed to evaluate the development of tolerance in a model of chronic pain (Lyness et al., 1989). The morphine dose in the arthritic rats remained stable for 29 days, while an escalation in the dose of the pain-free rats was observed. The addition of an anti-inflammatory to the arthritic rats initially led to a reduction in the morphine intake, but with the reduction of the adjuvant-induced arthritis, these rats increased their opioid intake. The authors suggested that this may be related to the positive reinforcement properties of the opioid. The initial positive reinforcement for the arthritic rats was analgesia, hence the dose stability. As the pain disappears, the arthritic rats may look for other positive reinforcements such as euphoria, or to prevent withdrawal symptoms. The authors inferred that the presence of pain may have a significant influence on the development of tolerance in animals. The development of tolerance to antinociceptive opioid drug effects within a small time frame described in animal studies does not seem to occur in humans.

The predominant pharmacodynamic tolerance described in animal studies should not be considered as the cause for loss of analgesia in humans unless there is no evidence for pharmacokinetic or learned tolerance (Portenoy 1994). Unlike the animal models of tolerance, human pain is more complex and there are several factors that may lead to a decrease in the analgesic effect of a drug. Psychological processes such as anxiety, depression, mood and cognition influence pain perception and may lead to a worsening of pain (Berna et al., 2010; Portenoy 1994; Turk and Okifuji 2002; Vlaeyen and Linton 2000). A contributor for an increase in pain perception is also the progression of a condition or its associated factors, such as an increase of activity in central or peripheral nociceptive pathways (Portenoy 1994).

**Importance of this study**

Patients with chronic non-malignant pain have the potential for long-term survival and therefore adequate pain control is paramount to this population. The investigation of opioid dose escalation assumes particular importance because the possibility of tolerance development is a commonly used reason to withhold the use of opioid treatment until an
undeniable need (Portenoy 1994). The opioid dose via intrathecal route is often low when administered to a chronic non-malignant pain patient and drug delivery can be monitored with precision, therefore decreasing the risk of addiction. The oral opioid dose conversion to an intrathecal dose is approximately 300:1 (Lamer 1994; Levy 1997), while the conversion ratio between epidural and intrathecal has been suggested to be 24:1 (Nordberg et al., 1984).

The primary purpose of this study was to describe the results of a long-term, longitudinal assessment of the intrathecal opioid dose of a cohort of patients undertaking IDD therapy for the management of chronic pain of non-malignant origin. A secondary objective was the development of an intrathecal opioid dose predictive model.

2.1.3 Methods

Participants

Thirty one patients undertaking continuous intrathecal opioid delivery by implanted reservoir administration for chronic non-malignant pain at Russell's Hall Hospital Pain Management Department were included in the study. The sample consisted of 19 females (61.3%) and 12 males (38.7%) with an average age at the time of IDD system implantation of 48 ± 1.5 years (range: 30-63). The average duration of pain prior to IDD was 12 ± 1.4 years (range: 2-35). Participants who had undertaken IDD therapy for at least six years when the data was collected were included in this study.

The pain syndrome the majority of the participants (74.2%) experienced was nociceptive, and included degenerative spine disease, post spinal fractures or cervical dysplasia. Three patients (9.7%) had neuropathic pain as the result of complex regional pain syndrome type II and five patients (16.1%) suffered from mixed nociceptive-neuropathic pain including failed back surgery syndrome caused by multiple spinal operations. For the purpose of comparison, the pain topography was divided into low back and other. For most participants, the topography of pain was the lower back (48.4%), while in the other group the pain was localized in the abdominal area, knee or back pain radiating to one or both legs. In all cases, the catheter was inserted in the lumbar area and positioned in the thoracic area, most commonly T10.
Data collection

A longitudinal retrospective assessment of medical records was performed and pump refill notes were screened from date of implant to November 2010. Intrathecal drugs administered and intrathecal opioid dose (mg/day) were recorded (Table 2.1.1). To try to attain optimal pain relief, some patients had additional drugs besides morphine added to the intrathecal medication, such as bupivacaine (87.1%), clonidine (35.5%) and baclofen (19.4%). The type of pain of the patients (12.9%) that were not administered adjuvant intrathecal medication was nociceptive. Yearly opioid dose averages were computed for each patient from the time of implant until last refill between June and November 2010.

| Table 2.1.1 Mean morphine dose per patient over study period (mg/day) |
|-------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Patient | Baseline | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
| 1 | 0.495 | 2.504 | 3.152 | 3.830 | 4.196 | 4.618 | 5.048 |
| 2 | 0.495 | 1.437 | 3.374 | 4.063 | 4.151 | 4.662 | 5.168 |
| 3 | 0.495 | 1.697 | 7.339 | 10.689 | 12.754 | 12.989 | 12.072 |
| 4 | 0.495 | 0.749 | 1.776 | 2.098 | 2.398 | 2.697 | 2.897 |
| 6 | 0.550 | 1.552 | 1.502 | 2.028 | 2.313 | 2.087 | 1.998 |
| 9 | 0.990 | 1.579 | 2.572 | 2.498 | 2.498 | 2.708 | 2.897 |
| 10 | 0.495 | 1.040 | 1.359 | 1.452 | 1.863 | 2.031 | 2.109 |
| 13 | 1.125 | 1.395 | 1.950 | 2.316 | 2.250 | 2.230 | 2.830 |
| 15 | 0.495 | 2.549 | 3.741 | 3.741 | 4.151 | 4.464 | 4.530 |
| 16 | 0.495 | 0.605 | 0.864 | 1.045 | 1.122 | 1.205 | 1.425 |
| 21 | 0.495 | 2.410 | 3.974 | 4.398 | 4.765 | 4.931 | 5.265 |
| 22 | 0.495 | 1.485 | 1.975 | 2.421 | 2.287 | 2.864 | 3.252 |
| 23 | 0.495 | 2.262 | 4.040 | 4.762 | 5.796 | 6.214 | 6.248 |
| 24 | 0.495 | 1.507 | 1.575 | 2.183 | 3.882 | 5.081 | 4.863 |
| 25 | 0.990 | 3.783 | 6.245 | 8.504 | 10.505 | 4.179 | 8.492 |
| 27 | 0.750 | 1.063 | 1.432 | 1.887 | 2.065 | 2.109 | 2.065 |
| 29 | 0.449 | 0.675 | 3.042 | 2.700 | 2.480 | 2.656 | 2.800 |
| 30 | 0.750 | 3.221 | 3.904 | 4.318 | 4.440 | 2.025 | 2.100 |
| 31 | 1.998 | 2.548 | 2.997 | 2.997 | 2.575 | 3.041 | 3.141 |
| 32 | 1.000 | 1.394 | 2.050 | 1.799 | 1.749 | 3.115 | 3.499 |
| 35 | 0.349 | 0.679 | 0.646 | 0.866 | 1.379 | 1.785 | 2.291 |
| 36 | 0.250 | 0.400 | 0.622 | 0.688 | 0.677 | 0.799 | 0.849 |
| 41 | 0.500 | 1.450 | 1.750 | 1.750 | 2.008 | 3.626 | 4.915 |
| 43 | 0.200 | 0.967 | 2.424 | 4.000 | 5.366 | 4.095 | 1.517 |
| 47 | 1.554 | 1.776 | 2.087 | 2.398 | 2.775 | 2.864 | 3.075 |
| 51 | 1.000 | 1.165 | 1.601 | 1.554 | 1.621 | 0.368 | 1.770 |
| 52 | 0.715 | 0.814 | 1.034 | 1.221 | 1.320 | 1.551 | 1.499 |
| 53 | 1.250 | 2.610 | 3.000 | 3.000 | 3.000 | 3.000 | 2.832 |
| 55 | 0.500 | 0.879 | 1.177 | 1.304 | 1.590 | 1.667 | 1.617 |
**Data analysis**

Repeated-measures ANOVA were performed to investigate changes in opioid dose throughout the treatment period. Repeated-measures ANOVA examine all members of a sample measured at several time points. Assumption of sphericity was verified through Mauchly’s test. This test, through analysis of sphericity (homogeneity of the variances of the differences between data from the same participant) is used to validate the result of the repeated-measures ANOVA analysis of variance (Field 2005). If the assumption of sphericity were violated, the degrees of freedom associated with the analysis needed to be corrected. Degrees of freedom were corrected using Greenhouse-Geisser estimate of sphericity, when the variances of the differences between levels were significantly different. The Greenhouse-Geisser correction is an estimate of distance from sphericity and it is used to investigate if the data meets the assumption of sphericity (Field 2005). Opioid dose changes were controlled for gender, age, duration of pain prior to IDDS, topography of pain, type of pain, IDD system replacements and administration of intrathecal adjuvant medication. This allows verification if other variables have a significant impact in the variable of interest, which for this study is the opioid dose.

Stepwise multiple regression analyses were used to evaluate the significance of the variables above mentioned in a model predicting the intrathecal morphine dose at year six based on the dose at year two. Stepwise multiple regression evaluates whether variables entered in a model strengthen the model or should be removed, based on correlation with the outcome variable (Field 2005). Shapiro-Wilk test was carried out to investigate if the unstandardized residuals data was normally distributed, therefore examining the validity of the model derived from the multiple linear regression. The Shapiro-Wilk test verifies if the distribution of scores is significantly different from a normal distribution. In this situation, it was employed to investigate the distribution of the residuals, which represent the difference between the value a model predicts and the value observed in the data on which the model is based (Field 2005).

Since the variable type of pain was divided into three categories, the variable was recoded to create two dummy variables with two categories each in order to carry out the linear regression. A dummy variable is a way of recoding a categorical variable with more than two categories into several dichotomous variables (Field 2005).
Data is reported as mean ± standard error of mean (SEM). Statistical significance represented \( p < 0.05 \). Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 17.0, SPSS Inc., Chicago, IL, USA).

### 2.1.4 Results

Gender \( (F(1.812, 39.874) = 0.623, p = 0.526) \), age at time of implant \( (F(1.812, 39.874) = 0.185, p = 0.811) \) and duration of pain prior to IDDS implantation \( (F(1.812, 39.874) = 2.389, p = 0.109) \) did not have a significant effect in the intrathecal opioid dose. The addition of adjuvant intrathecal medication did not have a significant effect on dose throughout the years, \( F(1.812, 39.874) = 0.220, p = 0.782 \). The morphine dose was not influenced by the location of pain \( (F(1.812, 39.874) = 0.227, p = 0.776) \) or type of pain \( (F(4.074, 57.032) = 1.38, p = 0.252) \).

Although not statistically significant, it was observed that neuropathic pain patients required lower doses throughout duration of therapy (Table 2.1.2). At baseline the opioid doses were approximately the same between the different types of pain. At two year follow-up, differences start to be evident, remaining throughout the duration the study.

<table>
<thead>
<tr>
<th>Type of pain (n)</th>
<th>Baseline*</th>
<th>2 year follow-up*</th>
<th>4 year follow-up*</th>
<th>Last follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptive (23)</td>
<td>0.84 ± 0.17</td>
<td>2.43 ± 0.32</td>
<td>3.11 ± 0.52</td>
<td>3.5 ± 0.49</td>
</tr>
<tr>
<td>Neuropathic (3)</td>
<td>0.82 ± 0.23</td>
<td>1.63 ± 0.69</td>
<td>1.82 ± 0.59</td>
<td>1.82 ± 0.51</td>
</tr>
<tr>
<td>Mixed (5)</td>
<td>0.66 ± 0.17</td>
<td>3.55 ± 0.75</td>
<td>5.28 ± 1.40</td>
<td>4.51 ± 1.19</td>
</tr>
<tr>
<td>Total (31)</td>
<td>0.81 ± 0.13</td>
<td>2.53 ± 0.28</td>
<td>3.34 ± 0.47</td>
<td>3.51 ± 0.42</td>
</tr>
</tbody>
</table>

* Mean ± SEM

During the study period, 12 patients did not need a replacement of the IDDS. Pump replacements were performed at a mean follow-up period of 59 ± 3.72 months (range: 17-84). None of the patients required more than one IDDS replacement. The patients that required a replacement of the IDDS had a higher opioid dose throughout the study period (Figure 2.1.2).

The intrathecal opioid dose was not significantly affected by the need of an IDDS replacement \( F(1.812, 39.874) = 2.562, p = 0.095 \). In accordance with the average duration
of therapy until an IDD system replacement surgery was required, a reduction in the opioid dose can be observed in Figure 2.1.3 between years 4 and 5.

Significant increases in the intrathecal morphine dose were verified between follow-up at one year and all subsequent observations, \( F (2.075, 62.238) = 13.858, p < 0.001 \). From year three onwards, no significant differences were observed with the following assessments, \( F (3, 90) = 2.516, p = 0.63 \).

![Graph showing intrathecal morphine dose based on need for IDD replacement](image)

Multiple linear regressions were used to analyze the relationship between yearly morphine doses. The results of the regression analysis indicated that the morphine doses of year two together with duration of pain were significant predictors of the intrathecal opioid doses at year six (year six dose = -0.509 + [1.296 x (year two dose)] + [0.061 x (duration of pain)]). Although the duration of pain initially was found not to have a significant effect in the intrathecal opioid dose throughout the duration of the study, it was verified that it improved this model, albeit modestly. Gender \( (p = 0.419) \), age at time of implant \( (p = 0.2) \), topography of pain \( (p = 0.46) \), type of pain 1 \( (p = 0.406) \) and type of pain 2 \( (p = 0.544) \) were not
significant predictors for the model. This model accounted for 76% of the variability of morphine doses at year six based on year two assessment. The residuals follow normal distribution ($p = 0.809$), which indicates that the assumptions for regression were met and confirms the validity of the model.

### 2.1.5 Discussion

In this sample, a slow increase in opioid dose was observed. Statistically significant increases were observed on a yearly basis from baseline up to year three, but the intrathecal opioid dose increase ceased to be significant from the third year onwards indicating stability. The average intrathecal dose of 3.51 mg/day at last follow-up (year six) was lower than previously reported average doses of 7.42 mg/day at 29.14 months (Kumar, Kelly and Pirlot 2001); 9.6 mg/day at year one (Paise, Penn and Shott 1996), and 12.2 mg/day at year three (Atli et al., 2010). An approximate opioid dose of 4.7 mg/day has been reported, although at an average of 3.4 years (Winkelmüller and Winkelmüller 1996). This suggests differences in practice between departments administrating this therapy.
Nevertheless, previous surveys have reported modest morphine dose escalations in patients with chronic non-malignant pain (Paice, Penn and Shott 1996; Winkelmüller and Winkelmüller 1996).

There are several factors that may have contributed to the modest dose escalation throughout duration of therapy. To some extent, the small increase verified in the intrathecal opioid dose may be related with the fact that the majority of the patients (87.1%) were receiving intrathecal bupivacaine in addition to the intrathecal morphine. The addition of intrathecal bupivacaine has been effective in keeping a low intrathecal morphine dose in the treatment of cancer pain as well as preventing the potential side effects of high doses of intrathecal morphine (Sjöberg et al., 1994; van Dongen, Crul and De Bock 1993). Drugs that have the potential to reduce the addiction liability of opioids or enhance the analgesic efficacy of opioids, as well as having analgesic properties on their own, may be useful as adjuvant therapies in combination with opioids (Fundytus 2001). This supports the suggestion that the use of adjuvant analgesics appears to contribute to an opioid-sparing effect. Other factors could also be relevant, such as the continuous care by the same team, in the same context, allowing the establishment of a doctor/nurse-patient relationship in a safe environment for the patient.

Contrary to what was expected, the opioid dose administered to neuropathic pain patients was lower than the dose received by the nociceptive pain patients. In accordance with our results, previous literature has reported lower opioid dose administered to neuropathic pain patients when compared to the dose administered to patients with nociceptive pain (Kumar, Kelly and Pirlot 2001; Winkelmüller and Winkelmüller 1996). The lower dose in patients with this pathology may also be related with the administration of adjuvant medication. Neuropathic pain has shown to be responsive to intrathecal therapy but opioids alone may not always be sufficient to control it (Paice et al., 1997). The reduced sensitivity of neuropathic pain to opioids may be the result of a decreased expression of µ opioid receptors in dorsal root ganglia neurons as a consequence of nerve injury (Zhang et al., 1998).

There was no evidence of opioid addiction or abuse in the investigated patients. The screening and exclusion of patients with a history of addictive behaviours prior to intrathecal morphine trial could have contributed to this outcome. The cerebrospinal fluid has limited
capacity to distribute intrathecally administered morphine away from the catheter tip (Flack, Anderson and Bernards 2011). Besides having implications to the efficacy of the intrathecal therapy, this also means that only very small amounts of the medication would reach the supraspinal regions. It is known that the opioid regulation of pain involves μ opioid receptors in both spinal and supraspinal regions of the central nervous system (Bohn, Lefkowitz and Caron 2002). The amygdala, whose nuclei have no direct association with analgesia, has the greatest abundance of opioid receptors in the brain and the receptors in this area are likely to be associated with the influences of opioids on emotional behaviour (Snyder 1977). It seems plausible that the development of addictive behaviours as a consequence of intrathecal morphine therapy is even more remote than with the use of systemic opioid therapy because of the much lower dose and region of opioid receptor activity.

It is likely that the reason for the modest opioid escalation observed was due to progress/deterioration of the patients’ condition, rather than tolerance. Progression of a disease may result in an increase of nociceptive activity, development of sensitisation or changes in the pain modulation processes, leading to an increase in pain and consequently a requirement of dose escalation. Morphine doses may stabilize for long periods and when dose escalation occurs it is usually considered to be due to tolerance, progress of the disease (Bennett et al., 2000) or opioid induced hyperalgesia (Angst and Clark 2006; Chu, Angst and Clark 2008). In the clinical setting, true pharmacological tolerance to the analgesic effects of opioids is an uncommon cause for the need of opioid dose escalation to maintain analgesic effects (Portenoy 1994). The need for higher doses to maintain an effect as a result of the progression of pathology should not be considered as tolerance; the requirement of higher doses should only be perceived as tolerance when the prior administration of a drug is the reason for the change in dose (Portenoy 1994; Portenoy and Savage 1997).

It is important to note the limitations of this study. Pain ratings were not requested on a regular basis to verify if a change or deterioration in pain occurred. The study presented in Chapter 3 of this thesis demonstrates a small, non-significant increase in the pain ratings between assessments following IDDS implantation. This increase in pain could be due to progression of disease or decrease of therapy effectiveness (tolerance), leading to the small increases observed in the morphine dose.
Oral opioid medication was not collected from the notes. At this centre rescue oral opioid medication has been provided to the patients on an individual basis, for occasional flare-ups. The average duration of pain prior to IDDS was 12 years. Prior to implantation of IDDS, all these patients have tried and failed more conservative treatments, including oral opioid medication with little or no benefit or unbearable side effects. The effective rescue medication dose is a fraction of the effective intrathecal dose. Hence, systemic medication as well as other interventions that might have been undertaken during the study period would only be sporadic to cope with flare-ups and would therefore have limited impact in the results verified. Providing additional oral medication to patients may improve their psychological well being as well as an improvement in effective pain control. There is no evidence of a correlation between reduction in pain intensity and the intake of additional oral medication (Kumar, Kelly and Pirlot 2001; Winkelmüller and Winkelmüller 1996).

This model assumes particular importance because it can predict 76% of morphine dose variability at year six. Since the pump battery life usually ranges between 48 to 60 months (de Lissovoy et al., 1997; Kumar, Hunter and Demeria 2002) an informed decision can be made taking into account the risks and benefits of continuing intrathecal opioid therapy. The possibility of anticipation of the opioid dose could also lead to consideration by the physician of alternative bio-psycho-social treatment strategies. Examples of alternatives are the addition of adjuvant drugs to the intrathecal mixture and physical or behavioural approaches (Flor, Fydrich and Turk 1992; Guzmán et al., 2002). There is no intention to declare that the future treatment of a patient should be decided based on a mathematical model. This model should be seen as a supplementary tool assisting a physician’s work.

Intrathecal opioid therapy strategies differ across pain management centres. Therefore, the applicability of this model to other centres needs to be tested. A large, international, multicentre study could have the potential to develop a model applicable to the majority of centres where intrathecal drug delivery therapy is administered.

### 2.1.6 Conclusion

The opioid dose escalation observed was not a limiting factor for this therapy as the increase throughout the years was modest. Due to the duration of the study and small dose increase verified, it is likely that increased or altered pain contributed more than
pharmacological tolerance to the tolerance to the analgesic effects. Concerns about development of tolerance do not justify the delay or withholding of intrathecal opioid therapy for chronic non-malignant pain.

The evaluation of the intrathecal opioid dose throughout a six year period allowed the development of a model. This model accounts for 76% of the variability of the opioid dose at year six based on the dose of year two combined with duration of pain prior to initiation of intrathecal therapy. This has significant clinical implications. It can assist the physician to identify the need of an alternative treatment strategy. Moreover, since many of the pump replacements are performed prior to year six, it can assist in the informed decision of the benefits and risks of the maintenance of this therapy.

The following section of this thesis focuses on a potential early indicator of the formation of intrathecal inflammatory masses as a result of intrathecal opioid therapy.
SECTION 2. Yearly opioid dose increase as an early indicator of granuloma formation

This section has been published in Neuromodulation 2010;13(2):109-113 (appendix 9). It has been reformatted to fit with the overall PhD thesis.

2.2.1 Abstract

Objectives
The objective of this study was to investigate the association between intrathecal drug, flow rate, drug concentration and drug dose with the formation of intrathecal inflammatory masses.

Methods
A retrospective longitudinal study of 56 consecutive patients receiving long-term intrathecal analgesic administration was undertaken through screening of medical records. Data regarding drug flow rate, dose per day and concentration of drugs administered were recorded for morphine, diamorphine, bupivacaine, clonidine and baclofen and averages computed.

Results
The average follow-up time post-implant was 91 ± 55 months (range: 9–209). Four of the 56 patients were diagnosed with intrathecal granuloma indicating a rate of 7%, the equivalent to 0.009 events per patient year. Twenty-one of the patients had received morphine either alone or combined; 22 had received diamorphine either alone or mixed; and 13 crossed over from diamorphine to morphine. None of the patients with granuloma crossed over before diagnosis. A significant correlation was found between opioid dose (r = 0.275, p < 0.05), yearly increase of the opioid dose (r = 0.433, p < 0.05) and granuloma formation. Clonidine appeared to have a protective effect for the non-granuloma patients. No association was found with flow rate (r = 0.056) or opioid concentration (r = 0.214).

Conclusion
This is the first detailed study showing an association of diamorphine with granulomas. This study supports the previous finding of intrathecal opioid dose being a risk factor for intrathecal granulomas and clonidine being protective. In addition, it was found that the
yearly increase in opioid dose is a risk factor for the development of granulomas and could serve as an indicator for closer surveillance.

2.2.2 Introduction
One of the possible side effects of intrathecal opioid administration is the development of an intrathecal inflammatory mass, also known as granuloma, granulomata or granulomatous mass (Fig. 2.2.1). Although rare, the magnitude of this complication can be serious with potential for neurologic morbidity if not recognized and treated appropriately (Blount et al., 1996; Cabbell, Taren and Sagher 1998; Miele et al., 2006a). An intrathecal granuloma is a soft tissue mass resulting from an inflammatory reaction and usually located at the level of the catheter tip.

The formation of a spinal granuloma due to opioid administration using an implanted pump delivery system was first observed in the epidural space in 1985 (Rodan et al., 1985) and in the intrathecal space in 1991 (North et al., 1991).

Although this lesion develops very slowly, patient re-evaluation and vigilance is essential for an early diagnosis (Deer, Raso and Garten 2007). Failure to identify the occurrence of a granuloma can lead to a diagnosis of tolerance and an increase in the rate of infusion (Anderson et al., 2001; Bejjani, Karim and Tzortzidis 1997).

Granuloma detection
It is of extreme importance to detect a granulomatous mass in its early stages. The increase in size of a granuloma occurs with the maintenance of intrathecal drug administration while it remains undetected. The appearance of clinical symptoms can be sudden. The clinical presentation of these masses is usually marked by an increase in pain while receiving the scheduled medication, which previously controlled the painful symptoms, and small increases in the intrathecal medication dose only provide temporarily relief (Langsam 1999a). Typically, this increase is followed by slow progressive signs and indicators of neurological deterioration including incontinence, constipation, loss of balance, sensory loss and paraparesis with a potential to culminate in functional paraplegia (Deer et al., 2008a; North et al., 1991).
When attending for a refill at Russells Hall Hospital Pain Management Department, all patients are asked if since the last follow-up, the pain was controlled and if new symptoms had emerged, such as new pain, altered sensation or weakness of limb. In case of new symptomatology, a neurological examination (sensory and motor function) would take place. If a clear change was observed, a magnetic resonance imaging (MRI) scan would be performed. For this purpose, programmable pumps would be turned off, non-programmable pumps emptied, and the imaging would be carried out via a 1.5 Tesla MRI system through Short Tau Inversion Recovery (STIR) sequence. In the existence of doubts regarding the formation of intrathecal inflammatory masses, a second MRI would be completed with the contrast-enhancing agent Gadolinium.
Treatment

Several techniques to manage inflammatory masses have been reported in the literature. When detected early, the mass might recede using a conservative approach which consists of replacing the medication administered with preservative-free saline (Cabbell, Taren and Sagher 1998; Shields et al., 2005; Toombs et al., 2005) or with a different opioid (McMillan, Doud and Nugent 2003) thus avoiding surgery. The authors report near complete resolution of the granuloma after one or two months. Following confirmation of the mass recession, re-initiation of intrathecal therapy should be carefully monitored to avoid recurrence of the intrathecal inflammatory mass.

When surgery is elected, several alternatives are possible. Repositioning of the catheter at a distance of about 2 cm from its prior location can be effective in preventing the growth of the mass (Deer et al., 2008a). Surgery to remove the granuloma occurs in the presence of significant neurological symptoms (Blount et al., 1996; Cabbell, Taren and Sagher 1998). This intervention is often accompanied by the removal of the catheter and occasionally, the drug reservoir, along with the mass (Deer, Raso and Garten 2007; North et al., 1991).

Enduring neurological disabilities have been associated with delayed diagnosis and treatment (Coffey and Burchiel 2002). The same authors stated that situations where the mass filled the spinal canal and surgery was not performed promptly contributed to permanent neurological impairment.

Despite the severity of this complication, there are reports in the literature of patients requesting the resumption of the intrathecal opioid delivery regardless of the risk of recurrent granulomatous masses (Cabbell, Taren and Sagher 1998; McMillan, Doud and Nugent 2003).

Aetiology

Since the first report of an intrathecal granuloma as consequence of IDDS in 1991 (North et al., 1991), several hypotheses for its formation have been depicted. It has been hypothesized that the formation of these masses could be the result of an inflammatory reaction to the catheter (Anderson et al., 2001; Bejjani, Karim and Tzortzidis 1997),
morphine or other preservative used inadvertently, or a reaction to the trauma sustained during catheter implantation (Bejjani, Karim and Tzortzidis 1997).

Intrathecal administration maintains a relatively high drug concentration within and around the spinal cord, which may contribute to the phenomenon of catheter tip mass formation (Coffey and Burchiel 2002). Inflammatory masses have developed more commonly in result of IDDS therapy involving opioids such as morphine (North et al., 1991), hydromorphone (Fernandez, Madison-Michael and Feler 2003), diamorphine (Mutagi et al., 2007), fentanyl (Zacest et al., 2009), sufentanil (Gupta, Martindale and Christo 2010) or tramadol (De Andrés et al., 2010a). Less commonly, administration of intrathecal baclofen alone has also been related to this complication (Deer, Raso and Garten 2007; Murphy et al., 2006).

The association between opioid concentration and the development of catheter tip intrathecal granulomas has only been inferred from case reports and animal studies (Deer et al., 2008a). Animal studies revealed an apparent dose or concentration response in relation to the development of intrathecal masses in both dogs and sheep (Gradert et al., 2003; Yaksh et al., 2002; Yaksh et al., 2003). However, the formation of granulomas in humans is less predictable than in sheep and dog models (Deer et al., 2008a). Whether the absolute opioid dose, concentration, or both (or neither) influence a patient’s risk for development of a granulomatous mass remains unclear (Hassenbusch et al., 2002). The correlation of opioid dose with the formation of inflammatory masses in humans has only been demonstrated in a small sample size (seven patients) study (McMillan, Doud and Nugent 2003).

The aim of this study was to investigate the association between intrathecal drug, flow rate, drug concentration, and drug dose with the development of intrathecal inflammatory masses.

### 2.2.3 Methods

A single centre retrospective longitudinal study of 56 consecutive patients receiving continuous intrathecal analgesics by implanted reservoir administration was undertaken through assessment of medical records. All participants undertaking IDD at Russells Hall Hospital were included in the study. Pump refill notes from date of implant to June 2009 were screened for flow rate (mL/day), dose (mg/day) and concentration (mg/mL) of drugs
administered intrathecally. The drugs delivered were morphine, diamorphine, bupivacaine, clonidine, and baclofen. Yearly averages and yearly changes in concentration and dose were computed for each patient from the time of implant until last refill between April and June 2009. For patients diagnosed with granuloma, only the data until date of diagnosis was considered for analysis. Information regarding positioning of the catheter tip was recorded from the surgical notes.

**Data analysis**

The Kolmogorov-Smirnov test was carried out to test normality of numerical data followed by the appropriate statistical tests. Dichotomous data was compared using the Mann–Whitney U-test. Mann–Whitney U-test is a non-parametric test that investigates differences between two independent samples (Field 2005). Associations between variables were investigated through Spearman’s correlations. Spearman’s correlations analyses the strength of relationship between two non-parametric variables (Field 2005). Means are reported as mean ± standard deviation.

Statistical significance represented \( p < 0.05 \). Events per patient year were calculated using the formula \((\text{number of events } ÷ \text{ number of patients} ) ÷ \text{ average follow up}\). Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 12.0, SPSS Inc., Chicago, IL, USA).

**2.2.4 Results**

The sample comprised 33 women (58.9%) and 23 men (41.1%) with an average age at time of implant of 50 ± 10 years (range: 30–72). The mean duration of painful symptoms prior to date of implant was 14 ± 9 years (range: 2–36) and the average follow-up time post-implant was 91 ± 55 months (range: 9–209). Twenty-one of the patients had received morphine either alone or with one or other of bupivacaine, clonidine, and baclofen; 22 of the patients had received diamorphine either alone or with one or other of bupivacaine, clonidine, and baclofen; and 13 participants crossed over from diamorphine to morphine. None of the patients with granuloma crossed over before diagnosis.
Four of the 56 patients were diagnosed with intrathecal granuloma. The rate of this diagnosis was 7%, the equivalent to 0.009 events per patient year. Besides the patients with granulomatous masses, 16% of the remaining patients presented clear changes in their pain including new symptoms. Following an MRI scan, no intrathecal inflammatory masses were detected in these patients. Drugs administered at the time of granuloma diagnosis included morphine mixed with bupivacaine (N = 1), diamorphine alongside clonidine and bupivacaine (N = 2) and diamorphine combined with bupivacaine and baclofen (N = 1).

The mean time span until granuloma formation was 39.5 ± 13.5 months (range: 22–52). The mean time of treatment for the non-granuloma patients was 90 ± 57 months (range: 9–209). In this sample only one patient receiving morphine was diagnosed with granuloma. Until diagnosis, the mean intrathecal morphine concentration of this patient was 7.95 mg/mL and the mean morphine dose was 3.91 mg/day. The mean intrathecal morphine concentration for non-granuloma patients was 5.83 ± 3.01 mg/mL (range: 1.55–12) and the mean morphine dose was 2.21 ± 1.20 mg/day (range: 0.52–5.60). Both dose and concentration were inferior to the maximum recommended concentration and dose values to minimize not only the risk of granuloma formation but also the risk of all other possible side effects (Table 2.2.1).

At the time of diagnosis three of the patients were receiving diamorphine intrathecally. The average diamorphine concentration of these patients was 14.62 ± 5.74 mg/mL (range: 11.09–21.25) and the dose was 4.72 ± 1.79 mg/day (range: 3.61–6.80). The patients not diagnosed with granuloma had a mean diamorphine concentration of 12.23 ± 6.87 mg/mL (range: 1.23–30.36) and the average diamorphine dose was 3.78 ± 2.57 mg/day (range: 0.60–11.23).

The mean clonidine concentration received by the patients diagnosed with granuloma was 0.01 ± 0.006 mg/mL (range: 0.008–0.017) and the mean clonidine dose was 0.004 ± 0.002 mg/day (range: 0.003–0.005). For the non-granuloma patients, the mean clonidine concentration was 0.029 ± 0.04 mg/mL (range: 0.009–0.17) and the mean concentration dose was 0.01 ± 0.016 mg/day (range: 0.003–0.06).

Associations were attempted between the variables and granuloma formation (Table 2.2.1). No significant association between flow rate and granuloma was established (r = 0.056).
Additionally, the opioid concentration was not significantly associated with granulomatous masses ($r = 0.214$). A significant positive correlation was found between opioid dose and granuloma, $r = 0.275$, $p < 0.05$. The patients diagnosed with inflammatory masses had a significantly higher opioid dose ($Mdn = 3.96$) compared with those not diagnosed with granuloma (opioid dose median = 2.42, $U = 40.00$, $p < 0.05$, $r = -0.27$).

The yearly increase of the opioid dose was computed and a significant correlation was found with granuloma formation in this sample, $r = 0.433$, $p < 0.01$. The mean opioid dose increase per year was significantly higher in patients where a granuloma was identified ($Mdn = 0.83$) than those with no granuloma formation (opioid dose increase per year median = 0.21, $U = 6.00$, $p < 0.005$, $r = -0.43$) (Fig. 2.2.2).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Maximum recommended (Deer at al., 2008a)</th>
<th>Non-granula patients</th>
<th>Granuloma patients</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of treatment (months)</td>
<td>-</td>
<td>n = 52; 90 ± 57 (9-209)</td>
<td>n = 4; 39.5 ± 13.5 (22-52)</td>
<td>r = -0.236</td>
</tr>
<tr>
<td>Flow rate (mL/day)</td>
<td>-</td>
<td>n = 52; 0.36 ± 0.19 (0.15-1.5)</td>
<td>n = 4; 0.36 ± 0.08 (0.32-0.49)</td>
<td>r = 0.056</td>
</tr>
<tr>
<td>Opioid concentration (mg/mL)</td>
<td>-</td>
<td>n = 52; 9.28 ± 6.07 (1.23-30.36)</td>
<td>n = 4; 12.95 ± 5.75 (7.95-21.25)</td>
<td>r = 0.214</td>
</tr>
<tr>
<td>Opioid dose (mg/day)</td>
<td>-</td>
<td>n = 52; 3.01 ± 2.15 (0.64-11.57)</td>
<td>n = 4; 4.68 ± 1.55 (3.79-7.00)</td>
<td>r = 0.275*</td>
</tr>
<tr>
<td>Opioid yearly change (mg/day)</td>
<td>-</td>
<td>n = 48; 0.22 ± 0.19 (-0.08-0.97)</td>
<td>n = 4; 0.88 ± 0.43 (0.48-1.41)</td>
<td>r = 0.433**</td>
</tr>
<tr>
<td>Morphine concentration (mg/mL)</td>
<td>20 mg/mL</td>
<td>n = 32; 5.83 ± 3.01 (1.55-12)</td>
<td>n = 1; 7.95</td>
<td>r = 0.167</td>
</tr>
<tr>
<td>Morphine dose (mg/day)</td>
<td>15 mg/day</td>
<td>n = 32; 2.21 ± 1.21 (0.52-5.60)</td>
<td>n = 1; 3.91</td>
<td>r = 0.241</td>
</tr>
<tr>
<td>Morphine yearly change (mg/day)</td>
<td>-</td>
<td>n = 27; 0.38 ± 0.44 (-0.12-1.39)</td>
<td>n = 1; 1.55</td>
<td>r = 0.324</td>
</tr>
<tr>
<td>Diamorphine concentration (mg/mL)</td>
<td>-</td>
<td>n = 31; 12.23 ± 6.87 (1.23-30.36)</td>
<td>n = 3; 14.62 ± 5.74 (11.09-21.25)</td>
<td>r = 0.206</td>
</tr>
<tr>
<td>Diamorphine dose (mg/day)</td>
<td>-</td>
<td>n = 31; 3.78 ± 2.57 (0.60-11.23)</td>
<td>n = 3; 4.72 ± 1.80 (3.61-6.80)</td>
<td>r = 0.206</td>
</tr>
<tr>
<td>Diamorphine yearly change (mg/day)</td>
<td>-</td>
<td>n = 29; 0.23 ± 0.19 (-0.083-0.797)</td>
<td>n = 3; 0.86 ± 0.60 (0.42-1.54)</td>
<td>r = 0.447*</td>
</tr>
<tr>
<td>Bupivacaine concentration (mg/mL)</td>
<td>40 mg/mL</td>
<td>n = 32; 8.72 ± 1.53 (1.74-10)</td>
<td>n = 4; 8.92 ± 0.72 (7.95-9.69)</td>
<td>r = 0.000</td>
</tr>
<tr>
<td>Bupivacaine dose (mg/day)</td>
<td>30 mg/day</td>
<td>n = 32; 3.01 ± 2.26 (0.85-13.92)</td>
<td>n = 4; 3.22 ± 0.47 (2.89-3.91)</td>
<td>r = 0.255</td>
</tr>
<tr>
<td>Baclofen concentration (mg/mL)</td>
<td>-</td>
<td>n = 8; 0.21 ± 0.15 (0.016-0.50)</td>
<td>n = 1; 0.29</td>
<td>r = 0.274</td>
</tr>
<tr>
<td>Baclofen dose (mg/day)</td>
<td>-</td>
<td>n = 8; 0.058 ± 0.038 (0.014-0.11)</td>
<td>n = 1; 0.095</td>
<td>r = 0.411</td>
</tr>
<tr>
<td>Clonidine concentration (mg/mL)</td>
<td>2 mg/ml</td>
<td>n = 16; 0.029 ± 0.04 (0.009-0.17)</td>
<td>n = 2; 0.01 ± 0.006 (0.008-0.017)</td>
<td>r = -0.257</td>
</tr>
<tr>
<td>Clonidine dose (mg/day)</td>
<td>1 mg/day</td>
<td>n = 16; 0.011 ± 0.016 (0.003-0.06)</td>
<td>n = 2; 0.004 ± 0.002 (0.003-0.005)</td>
<td>r = -0.273</td>
</tr>
</tbody>
</table>

* P < 0.05; ** P < 0.01
The mean yearly increase of diamorphine dose was also found to be influential in the formation of these masses. This variable was significantly correlated with granuloma development, $r = 0.447$, $p < 0.05$. The mean diamorphine dose increase per year was significantly higher in patients diagnosed with granuloma ($Mdn = 0.62$) than in those where no development of masses occurred (diamorphine dose increase per year median = 0.19, $U = 5.00$, $p < 0.05$, $r=-0.44$) (Fig. 2.2.3).

Two out of three patients (66.66%) with the catheter tip positioned at T11 were diagnosed with granuloma compared with one out of 33 patients (2.94%) with the catheter tip at T10.

2.2.5 Discussion
The average duration of intrathecal administration in this study was 39.5 ± 13.5 months. Contrary to what was expected, an association between flow rate and granulomatous masses was not found. It has been recommended that ultra slow flow rates should be
avoided and the drug delivered into the dorsal CSF space at L1-L2 or at T7-T10 (Deer et al., 2008a). Most implanters position the catheter in the thoracic level which has the narrowest relative intrathecal space and slow CSF (Yaksh et al., 2002) even though granulomas have been known to form at all levels of the intrathecal space (Deer et al., 2008a).

In this sample, intrathecal granuloma formation was identified in patients receiving morphine and diamorphine. Diamorphine is considered to have several advantages over morphine. Because it is more soluble, diamorphine can be combined with larger quantities of other analgesics for intrathecal administration, thus achieving greater analgesic effects (Kleinberg et al., 1990). Theoretically the greater solubility might have been considered protective for the risk of granuloma; however, this was not verified. The development of granuloma when the treatment is carried out with intrathecal diamorphine may be a result of the diamorphine breaking down into morphine (Raphael et al., 2004).

Average opioid dosage and yearly increase were associated with the formation of intrathecal inflammatory masses. The yearly increase is a presumable risk because a high dose is a risk, but could be useful as an early indicator of development of granulomatous masses. When higher doses are required, patients should be properly informed of the association with granulomas and its risks and the physician should be alert for signs of spinal cord compression (Miele et al., 2006b). In a study with canines it was verified that the dogs with intrathecal masses had a considerably lower cisternal CSF/plasma morphine ratio than the dogs without masses (Yaksh et al., 2003). According to the same author, the lower cisternal levels could be due to a misdistribution resulting from the mass at the catheter tip, explaining the need for dose escalation. In this study, all patients diagnosed with granuloma had opioid doses <10 mg/day which indicates that this side effect may also occur with lower doses.

Concentration of all the drugs administered was also investigated but no significant association was found with granulomatous masses in this study group, although high concentration of all opioids may increase patient risk of granuloma formation (Coffey and Burchiel 2002; Deer et al., 2008a; Yaksh et al., 2002). One of the possible explanations for the association between average opioid dose and granuloma formation, although not between opioid concentration and granulomatous masses, is that it may be due to the more common clinical practice of altering the delivered dose rather than the drug concentration when responding to patients’ level of pain. The effect of this dose alteration yet maintenance
of drug concentration is to cause a compensatory flow rate change in the commonly used programmable pumps. Consequently, this pragmatic clinical sample may have been unable to detect an association between granuloma formation and flow rate.

Although significance was not found, clonidine appeared to have a protective effect in this sample confirming studies based on animal data (Yaksh et al., 2003). A report has suggested that clonidine may not have the same protective effect in humans (Toombs et al., 2005). Although not eliminating the risks, clonidine may help to reduce the incidence of granuloma formation. The patients diagnosed with inflammatory masses presented higher values both for concentration and dose for the majority of the intrathecal drugs, except for clonidine.

Further studies using human data are warranted as the formation of granulomatous masses in humans is less predictable than in animal models (Deer et al., 2008a). In addition, it is necessary to confirm if clonidine is significantly associated with the prevention of intrathecal inflammatory masses at the catheter tip of intrathecal drug delivery devices.

A limitation of this study is the low number of patients diagnosed with granulomas in this group. A larger sample may corroborate these findings and allow determination of a cut-off point for yearly opioid change as well as possibly confirming associations with other hypothesis such as opioid concentration, flow rate and catheter tip location and design.

2.2.6 Conclusion

This thorough evaluation of medical records has confirmed the association of opioid dose with the formation of granulomas. Intrathecal opioid dose is a risk factor but also the yearly opioid increase has proven to be influential in the formation of intrathecal inflammatory masses. In this group diamorphine has not prevented the occurrence of granulomas. Calculating the opioid dose increase per year throughout treatment can indicate a clinical change and, therefore, facilitate the early detection of asymptomatic intrathecal inflammatory masses, consequently decreasing the possible side effects of this complication for the patient. Calculating the yearly opioid change could give clinicians a useful and inexpensive method of early recognition of this side effect and, at the same time, gathering data that
could be valuable for future studies in this area. Confirming previous preclinical studies, in this study, clonidine appeared to have a protective effect.

The following section presents a study conducted with the aim of overcoming the most noteworthy limitation of the current section – the small number of patients diagnosed with an intrathecal granuloma. A systematic review of intrathecal granulomas case reports was performed and the data extracted was compared with a control group.
SECTION 3. Systematic review of intrathecal granulomas case reports and comparison with a control group

This section is under review by the journal Clinical Neurology and Neurosurgery. It has been reformatted to fit with the overall PhD thesis.

2.3.1 Abstract

Background and aims
Continuous intrathecal analgesia using opioids and other analgesics has become a recognized therapy for the management of severe and otherwise intractable chronic pain. Intrathecal granuloma is a potentially serious complication derived from this therapy. The cause of catheter tip granulomas remains speculative despite opioid dose and/or concentration being hypothesized as being related with this complication. The aim of this study was to investigate the existence of an association between formation of catheter tip intrathecal inflammatory masses with opioid dose and/or concentration.

Methods
A systematic review of catheter tip granulomas case reports and comparison with a control group was carried out. A Boolean search was conducted in the electronic databases MEDLINE and EMBASE using a combination of MESH/Thesaurus terms and free text. The patients' data extracted from the case reports was tested for homogeneity with a control group. Subsequent analysis investigating the association of opioid dose, concentration and flow rate with the formation of catheter tip granulomas was performed.

Results
Following screening of abstracts and hand search of reference lists, 32 articles were retrieved for review. Seventeen articles resulting in 24 patients with granulomata were included in the review. One patient in our department with a history of granuloma formation was added to this group. The control group comprised 31 patients with an average follow-up of 68.3 ± 9.7 months. The groups were homogeneous considering the variables age, gender and duration of pain prior to implant. Morphine dose (r=0.821, p<0.001) and concentration (r=0.650, p<0.001) were significantly correlated with the development of catheter tip intrathecal masses.
Conclusion
Opioid dose and concentration were significantly associated with the development of catheter tip granulomas. A correlation with opioid concentration was confirmed for the first time. The relative risk can be decreased by reducing dose and concentration from 15 mg/day and 20 mg/mL to 10 mg/day and 15 mg/mL respectively.

2.3.2 Background
The study presented in Chapter 2, Section 4 was well received by experts in the field (see comments in appendix 9), which included two of the authors of the consensus statement for management of intrathecal catheter-tip inflammatory masses (Deer et al., 2008a). Attempts at a more robust study aimed at exploring the results of the previous section were made. A multicentre study which would involve other UK pain management departments where this procedure is performed was considered but set aside due to differences in (not) recording intrathecal pump refills data. As an alternative, Medtronic, Inc. (one of the main manufacturers of IDDS) was contacted to investigate the possibility of accessing unpublished reports for data of intrathecal granulomata formation as previously accomplished by Coffey and Burchiel (2002). The process of obtaining the company’s approval to use this data would be bureaucratic, complex and consequently long with no guarantees of a successful outcome. The solution found for the continuation of the research on granuloma formation was to perform a systematic review of the case reports available in the literature and use the extracted data for comparison with a control group.

The objective of this study with an augmented group was to further examine the association between intrathecal opioid dose and granuloma development and to investigate the possible links between flow rate and drug concentration with the formation of intrathecal inflammatory masses.

2.3.3 Methods
Experimental design
A systematic literature review of case reports and subsequent analysis by comparison with a control group was performed. This design allows investigation of variables with potential to cause formation of granulomas by comparing a group of patients with this condition with a
group of patients undertaking the same therapy that did not develop this side effect. Because the majority of granuloma patients were derived from the literature, an investigation of homogeneity of the groups was carried out prior to analysis. To investigate if the groups were suitable for analysis, comparisons for the variables age, gender, duration of pain prior to implant and duration of therapy were performed. Moreover, to decrease the influence in the analysis of outliers not caused by sampling or data errors but due to the changes in practice of intrathecal medication delivery, a truncation method was used.

**Search strategy**

Information on duration of IDD therapy, dose and concentration of drugs administered at time of diagnosis was sought from granulomatous masses case reports using a Boolean search conducted in the electronic databases MEDLINE and EMBASE. A combination of MESH/Thesaurus terms and free text terms were employed according to the database (Figure 2.3.1). The year of publication was restricted to between 1991 (first intrathecal granuloma due to IDD reported (North et al., 1991)) and 25th August 2010. There were no language restrictions. Hand searches of reference lists of included studies, previous reviews and consensus statements were performed. Search sensitivity was checked by ensuring that all articles identified via hand search of reference lists were identified through the structured bibliographic database searches.

<table>
<thead>
<tr>
<th>MEDLINE</th>
<th>EMBASE</th>
</tr>
</thead>
<tbody>
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<td>1. “intrathecal granuloma*”.af</td>
<td>1. “intrathecal granuloma*”.af</td>
</tr>
<tr>
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<td>2. “catheter tip granuloma*”.af</td>
</tr>
<tr>
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<td>5. “catheter tip inflammatory mass*”.af</td>
</tr>
<tr>
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<td>7. #1 or #2 or #3 or #4 or #5 or #6</td>
</tr>
<tr>
<td>8. granuloma/</td>
<td>8. granuloma/</td>
</tr>
<tr>
<td>9. spinal cord compression/</td>
<td>9. spinal cord compression/</td>
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<td>10. spinal cord injuries/</td>
<td>10. spinal cord injury/</td>
</tr>
<tr>
<td>11. #8 or #9 or #10</td>
<td>11. #8 or #9 or #10</td>
</tr>
<tr>
<td>12. infusion pumps/</td>
<td>12. infusion pumps/</td>
</tr>
</tbody>
</table>
Inclusion and exclusion criteria

Papers were included in the review on the basis that they provided individual information related to dose or concentration of intrathecal opioids administered. Articles were excluded if any of the following was observed: the articles were reviews or guidance papers that did not present original work; morphine dose and/or concentration were presented as group averages instead of individual values; no intrathecal opioid medication had been delivered until granuloma development; the opioids administered are not currently in use at the department from which the control patient group were drawn; infection, tumour or trauma could not be ruled out as the cause of the granuloma reported. The author of this thesis selected the studies for inclusion in the review.
Data extraction
Data extraction was undertaken by the author of this thesis after the articles considered suitable were retrieved. The data extracted from the case reports consisted of gender and age of the patient, duration of pain prior to implant, duration of IDD therapy, drugs administered, morphine peak concentration (mg/mL) and morphine peak dose administered (mg/day). Detailed summaries of the studies selected for inclusion are presented (Table 2.3.1). The drug information most of the articles reported was peak dose and/or peak concentration, thus the reason to extract this information and not use mean doses or concentrations delivered throughout the duration of IDD therapy.

Control group
Fifty six patients receiving continuous intrathecal analgesics by implanted reservoir administration at Russells Hall Hospital, Dudley, one of the largest UK centres for intrathecal drug therapies. A longitudinal retrospective assessment of medical records was performed and pump refill notes were screened for dose (mg/day), concentration (mg/mL) and flow rate (mL/day) of morphine administered intrathecally. Twenty four patients were receiving diamorphine and were excluded from the analysis for purposes of comparison. Although diamorphine breaks down to mono-acetyl morphine which in turn breaks down to morphine (Raphael et al., 2004), concentrations and doses are different from morphine. One of the 32 patients receiving morphine had been diagnosed with granuloma formation and was added to the group generated from the systematic review of case reports (see Table 2.3.1, RHH).

Data analysis
The Kolmogorov-Smirnov test was performed to test normality of numerical data. Homogeneity of the group of patients diagnosed with granuloma and the control group was tested for the variables age, gender, years in pain prior to IDDS and duration of therapy. Gender differences between the groups were analyzed with Pearson’s Chi-Square test. The majority of the numerical data was not normally distributed; therefore differences between patients diagnosed with granuloma and those from the control group were investigated through Mann-Whitney tests. Age was the only variable normally distributed, however, to keep uniformity with the other variables, it was examined with a non-parametric test.
Associations between variables were investigated through Spearman’s correlations. Statistical significance represented $p < 0.05$. Means are reported as mean ± SEM.

While verifying the distribution of the data, several outliers were identified for the variables dose and concentration. In an effort to reduce the impact of these outliers, increasing the power of nonparametric tests, a truncation method was used (Osborne and Overbay 2004). This method was employed as the outliers observed were not caused by sampling or data errors but were due to the changes in practice of intrathecal medication dose delivery through awareness of possible complications related to high intrathecal dose and concentration. Using the recommended values derived from an expert panel (Deer et al., 2008a), the maximum values for morphine dose and concentration subsequent to truncation of the data were 15 mg/day and 20 mg/mL respectively.

Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 17.0, SPSS Inc., Chicago, IL, USA). Post hoc power analyses were performed using G*Power 3.1.2 software (Faul et al., 2007).

2.3.4 Results

Systematic literature review
The search resulted in a total of 771 abstracts after removal of duplicates. Following screening of abstracts and hand search of reference lists, 32 articles were retrieved for review (Figure 2.3.2).

Articles were excluded after reading the full text when information regarding dose or concentration administered was not provided (Bejjani, Karim and Tzortzidis 1997; Langsam 1999b; Leong, Laing and Saines 2010; Phillips et al., 2007); there were no opioids included in the intrathecal medication (Deer, Raso and Garten 2007; Kunkel, Sörensen and Matschke 2010; Murphy et al., 2006); the opioids were hydromorphone (Fernandez, Madison-Michael, and Feler 2003; Peng and Massicotte 2004; Phillips et al., 2007; Ramsey et al., 2008; Wadhwa, Shaya and Nanda 2006; Zacest et al., 2009), fentanyl (Zacest et al., 2009), tramadol (De Andrés et al., 2010a) or sufentanil (Gupta, Martindale and Christo 2010) which are currently not administered in the institution where the control group is followed; or the
granuloma could be the result of infection, tumour or trauma (Cabbell, Taren and Sagher 1998; Lehmberg et al., 2006; Perren et al., 2004; van Dongen, van Ee and Crul 1997).

Seventeen articles resulting in 24 patients with information regarding dose and/or concentration of intrathecally administered morphine were included in the analysis (Table 2.3.1). In reports where a reoccurrence of a granulomatous mass was observed (Cabbell, Taren and Sagher 1998; De Andrés et al., 2010b; Hoederath et al., 2010), only the morphine dose and/or concentration until the formation of the first mass were considered.

Eight of the studies reported a rapid increase in the morphine dose prior to diagnosis (Anderson et al., 2001; Blount et al., 1996; Cabbell, Taren and Sagher 1998; Hoederath et al., 2010; Miele et al., 2006b; North et al., 1991; Phillips et al., 2007; Toombs et al., 2005).
### Table 2.3.1 Articles and patients diagnosed with granulomata included in the review

<table>
<thead>
<tr>
<th>Author</th>
<th>Gender</th>
<th>Age</th>
<th>Duration of therapy (months)</th>
<th>Drug(s)</th>
<th>Opioid concentration (mg/ml)</th>
<th>Opioid dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North et al. (1991)</td>
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<td>14</td>
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<td></td>
<td>120</td>
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<td>11</td>
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<td>Morphine</td>
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<td>14</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
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<td>8</td>
<td>Morphine</td>
<td>45</td>
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<tr>
<td>Cabbell, Taren and Sagher (1998)</td>
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<td>8</td>
<td>Morphine</td>
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</tr>
<tr>
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<td>F</td>
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<td>48</td>
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<tr>
<td>Miele et al. (2006b)</td>
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</tr>
<tr>
<td></td>
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<td>Morphine</td>
<td>15</td>
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<td>Phillips et al. (2007)</td>
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<tr>
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<td>10</td>
<td>6.5</td>
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</table>
The subjects identified in the case reports, in addition to the patient from our department, comprised of 13 males (52%) and 12 females (48%) with an average age at the moment of diagnosis of 54 ± 1.9 years (range: 38-76). The average duration of treatment until intrathecal inflammatory mass formation was 36.6 ± 6.5 months (range: 3-108) and the mean peak dose and concentration were respectively 23.19 ± 4.9 mg/day (range: 3.5-120) and 37.29 ± 6.37 mg/mL (range: 10-75). Following truncation of data, the mean peak dose and concentration were respectively 13.06 ± 0.76 mg/day (range: 3.5-15) and 18.12 ± 1.11 mg/mL (range: 10-20).

**Control group (Table 2.3.2)**

The control group consisted of 11 males (35.5%) and 20 females (64.5%). The mean age in this group was 50.7 ± 1.9 years (range: 30-72) and the average follow-up period post implant was 68.3 ± 9.7 months (range: 9-203). The mean peak opioid dose was 2.89 ± 0.26 mg/day (range: 0.85-6.88) and the average peak concentration was 6.94 ± 0.64 mg/mL (range: 1.70-18). Eleven of these patients had crossed over from diamorphine to morphine during their treatment. In addition to the patients who developed a granuloma, 16% of the remaining patients presented clear changes in their pain including new symptoms. Following a magnetic resonance imaging scan, no masses were detected in these patients.
<table>
<thead>
<tr>
<th>Patient</th>
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<th>Opioid dose (mg/day)</th>
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<tr>
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<td>Male</td>
<td>57</td>
<td>5.00</td>
<td>3.13</td>
</tr>
<tr>
<td>45</td>
<td>Female</td>
<td>56</td>
<td>6.00</td>
<td>2.50</td>
</tr>
<tr>
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<td>Female</td>
<td>38</td>
<td>5.70</td>
<td>2.86</td>
</tr>
<tr>
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<td>45</td>
<td>1.70</td>
<td>0.86</td>
</tr>
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<td>1.50</td>
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<td>6.00</td>
<td>2.20</td>
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<td>3.00</td>
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<td>Male</td>
<td>54</td>
<td>9.00</td>
<td>4.50</td>
</tr>
<tr>
<td>55</td>
<td>Female</td>
<td>46</td>
<td>5.00</td>
<td>1.85</td>
</tr>
</tbody>
</table>
Homogeneity between groups

Demographic differences between patients diagnosed with granuloma (GG) and the control group (CG) were investigated prior to analysis, to confirm if these could be compared (Table 2.3.3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Granuloma diagnosis (N=25)</th>
<th>Control group (N=31)</th>
<th>Test statistic</th>
<th>p value</th>
<th>Statistical test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age *</td>
<td>54 ± 1.9 (38-76)</td>
<td>50.7 ± 1.9 (30-72)</td>
<td>-1.002</td>
<td>0.321</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>Gender</td>
<td>M (13); F (12)</td>
<td>M (11); F (20)</td>
<td>(X^2(1) = 1.542)</td>
<td>0.280</td>
<td>Chi-Square</td>
</tr>
<tr>
<td>Duration of pain prior to IDDS *</td>
<td>11.7 ± 1.7 (3-20)</td>
<td>14.3 ± 1.7 (2-36)</td>
<td>-0.384</td>
<td>0.711</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>Months with IDDS</td>
<td>36.6 ± 6.5 (3-108)</td>
<td>68.3 ± 9.7 (9-203)</td>
<td>-2.483</td>
<td>&lt; 0.05</td>
<td>Mann-Whitney</td>
</tr>
</tbody>
</table>

* years

No significant differences were observed for age, gender and duration of pain prior to IDDS between granulomata patients and the control group. The number of months with IDDS in the CG (\(Mdn = 49\)) was significantly longer than the duration of treatment of patients in the GG (\(Mdn = 24.5\)), \(U = 203.5\), \(p < 0.05\), \(r = -0.34\). This was not considered as an impediment for analysis as the risk of developing an inflammatory mass increases with the duration of intrathecal therapy. The incidence has been reported as 0.04% after one year, increasing to 1.15% after six years (Yaksh et al., 2002).

Associations with granuloma formation

Both morphine dose (\(r = 0.821\), \(p < 0.001\)) and concentration (\(r = 0.650\), \(p < 0.001\)) were significantly associated with the development of intrathecal masses.

The morphine concentration was significantly higher in the GG (\(Mdn = 20.0\)) than in the CG (\(Mdn = 6.0\)), \(U = 13\), \(p < 0.001\), \(r = -0.72\) (Fig. 2.3.3). The morphine dose in the GG (\(Mdn = 15\)) was significantly higher than in the CG (\(Mdn = 2.82\)), \(U = 13.5\), \(p < 0.001\), \(r = -0.82\) (Fig. 2.3.4). Post hoc power analyses were performed indicating a power of 81% for dose administered and a power of 52% for concentration.
Figure 2.3.3 Peak morphine concentration and granuloma formation

Figure 2.3.4 Peak morphine dose and granuloma formation
The relative risk of developing a granuloma increases with dose and concentration (Table 2.3.4 and 2.3.5). Although possible, the risk of granulomata is lessened with lower doses and concentrations.

**Table 2.3.4 Morphine dose and relative risk of granuloma formation**

<table>
<thead>
<tr>
<th>Morphine</th>
<th>Granuloma (N=23)</th>
<th>No Granuloma (N=31)</th>
<th>Total</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose &lt; 5 mg/day</td>
<td>2</td>
<td>28</td>
<td>30</td>
<td>0.066</td>
</tr>
<tr>
<td>Dose ≥ 5 mg/day</td>
<td>21</td>
<td>2</td>
<td>24</td>
<td>0.875</td>
</tr>
<tr>
<td>Dose &lt; 10 mg/day</td>
<td>3</td>
<td>31</td>
<td>34</td>
<td>0.088</td>
</tr>
<tr>
<td>Dose ≥ 10 mg/day</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Dose &lt; 15 mg/day</td>
<td>8</td>
<td>31</td>
<td>39</td>
<td>0.205</td>
</tr>
<tr>
<td>Dose ≥ 15 mg/day</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 2.3.5 Morphine concentration and relative risk of granuloma formation**

<table>
<thead>
<tr>
<th>Morphine</th>
<th>Granuloma (N=12)</th>
<th>No Granuloma (N=31)</th>
<th>Total</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration &lt; 10 mg/mL</td>
<td>0</td>
<td>25</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Concentration ≥ 10 mg/mL</td>
<td>12</td>
<td>6</td>
<td>18</td>
<td>0.666</td>
</tr>
<tr>
<td>Concentration &lt; 15 mg/mL</td>
<td>2</td>
<td>30</td>
<td>32</td>
<td>0.062</td>
</tr>
<tr>
<td>Concentration ≥ 15 mg/mL</td>
<td>10</td>
<td>1</td>
<td>11</td>
<td>0.909</td>
</tr>
<tr>
<td>Concentration &lt; 20 mg/mL</td>
<td>3</td>
<td>31</td>
<td>34</td>
<td>0.088</td>
</tr>
<tr>
<td>Concentration ≥ 20 mg/mL</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

Flow rate and catheter tip location were not found to be associated with the formation of intrathecal inflammatory masses ($p > 0.05$).

**2.3.5 Discussion**

Opioid dose and concentration were found to be associated with the development of catheter tip granulomas indicating that this link might be more causal than casual.

The mean peak morphine dose of 3 mg/day at an average follow up of 70 months in our patient group was lower than previously reported doses of 4.7 mg/day after an average of 3.4 years (Winkelmüller and Winkelmüller 1996); 7.42 at 29.14 months (Kumar, Kelly and Pirlot 2001); 9.6 mg/day at one year (Paice, Penn and Shott 1996); and 21 mg/day at 52 weeks (Yaksh and Onofrio 1987). However, it is important to state that with the exception of the Yaksh and Onofrio (1987) paper which was published before the first case report of an intrathecal granuloma, the opioid doses reported are significantly lower, even after
truncation of data, than those of the patients with granulomata and therefore significant differences would also be observed between these cohorts and the patients diagnosed with granuloma.

Opioid dose has previously been suggested to be associated with intrathecal inflammatory masses formation (Duarte et al., 2010; McMillan, Doud and Nugent 2003). Concentration rather than daily dose has been suggested to be the primary contributing factor in the development of these masses (Allen et al., 2006); however, a significant association had not yet been established in human data. In this study, significant differences between the groups were verified despite the effect size being more elevated for opioid dose. This may be due to the fact that it might be more usual to adjust the delivered dose than to alter the drug concentration when responding to patients’ level of pain to obtain a compensatory flow rate change in the commonly used programmable pumps. This would also explain why in the McMillan, Doud and Nugent (2003) and Duarte et al. (2010) studies an association with concentration was not established.

The influence of dose and concentration applies only to catheter tip granulomas. When the mass is a consequence of an infection or reaction to catheter material then sometimes the granuloma can be traced along the length of the catheter (Langsam 1999b).

Flow rate was not found to be significantly associated with the development of catheter tip granulomas, possibly due to the flow rate being computed with the peak concentration and peak dose values. Throughout the course of treatment the flow rate was likely to change when concentration, dose or both were altered. It is advisable to avoid ultra slow flow rates and the drugs should be delivered into the dorsal cerebrospinal fluid space at L1-L2 or T7-T10 to prevent the formation of intrathecal inflammatory masses (Deer et al., 2008a).

An association between catheter tip location and development of inflammatory masses was not established in this study. This can be related to the fact that most implanters position the catheter tip in the thoracic level (Yaksh et al., 2002), even though these masses have been known to form at all levels of the intrathecal space (Deer et al., 2008a).

The identification of this complication in its early stages is imperative and determinant to reduce the magnitude of the consequences. Forty per cent of the reports mentioned that a
rapid increase in the dose administered was observed prior to granuloma diagnosis. The development of a granuloma reduces the efficacy of the intrathecal medication (Bloomfield et al., 1995) and the failure to identify the occurrence of a granuloma can lead to a diagnosis of tolerance and an increase in the rate of infusion (Anderson et al., 2001; Bejjani, Karim and Tzortzidis 1997). Although this lesion develops very slowly, patient re-evaluation and vigilance are essential for an early diagnosis (Deer, Raso and Garten 2007).

MRI remains as the gold standard for diagnosing intrathecal inflammatory masses; however, routine imaging in all patients with intrathecal pumps is not cost-effective taking into consideration the low occurrence of granulomas and the elevated cost of an MRI (Deer 2004). Pump refills have been suggested as a good opportunity to examine patients’ lower extremity motor, sensory and reflex function (Aldrete et al., 1994). The yearly opioid dosage change can be used as an early indicator of the formation of granulomas (Duarte et al., 2010). If new pain symptoms are observed alongside clear changes in intrathecal medication requirements, an MRI or as an alternative a computed tomography myelogram should follow (Deer et al., 2008a).

Both dose and concentration should be kept as low as possible to reduce the relative risk of granulomata. The relative risk can be decreased by reducing dose and concentration from the currently recommended maxima of 15 mg/day and 20 mg/mL to 10 mg/day and 15mg/mL respectively. These doses are still higher than the average reported to achieve an optimal pain control (Kumar, Kelly and Pirlot 2001; Paice, Penn and Shott 1996; Winkelmüller and Winkelmüller 1996). Patients that require high doses should be adequately informed of the risk of granuloma formation and what signs and symptoms might occur (Miele et al., 2006b; Penn 2003). When the maximum recommended values for dose and concentration do not generate the desired pain relief, Ziconotide should be taken into consideration as an alternative intrathecal medication. To date there are no reports associating this drug with the occurrence of catheter tip granulomas and its use has been recommended in the 2007 polyanalgesic consensus conference algorithm for intrathecal drug selection (Deer et al., 2008b).

The findings, though significant, have to be considered against the background of the limits of the study. In our department, besides the morphine patient diagnosed with granuloma formation, 16% of the remaining patients had presented clear changes in their pain including
new symptoms but were not found to have developed an inflammatory mass following MRI screening. Despite not all the patients in the control group being screened for granulomata using an MRI scan, the rate of this diagnosis has been reported to be the equivalent to 0.009 events per patient year (Duarte et al., 2010), which means it would have little or no statistical impact in the analysis. The analysis is also limited by the exclusion of patients diagnosed with inflammatory masses not being administered morphine as the intrathecal medication. It was considered that for the purpose of comparison, it would be preferable to only include patients undertaking an identical intrathecal therapy. Therefore, it cannot be ascertained if the same results would be verified with other opioids not investigated in this study. One of the limitations of this study is the fact that the control group is based on a single centre cohort. A large multi-centre study is warranted not only to confirm these findings but also to investigate other hypotheses as to the aetiology of granulomas, including dose and concentration of other intrathecal agents, flow rate, catheter tip design and location. An analysis of the dose, concentration and flow rate throughout duration of treatment instead of peak values would shed more light on the role of intrathecal medication in the formation of granulomas.

2.3.6 Conclusion
This is the first review of case reports performed in a systematic method studying the influence of opioid dose and concentration in the development of catheter tip intrathecal inflammatory masses. The comparison with a control group allowed for the first time to statistically confirm a long-standing inference that concentration plays an important role in the formation of granulomas. Additionally, significant differences were observed for dose administered corroborating results of previous studies.

The relative risk can be decreased by reducing dose and concentration from the currently recommended maxima of 15mg/day and 20 mg/mL to 10mg/day and 15mg/mL respectively.

The following section of this thesis evaluates the prevalence of hypogonadism in a cohort of male patients undertaking intrathecal drug delivery for the management of chronic non-malignant pain.
SECTION 4. Hormonal effects as consequence of intrathecal drug delivery

This section was published as two separate abstracts in Regional Anesthesia and Pain Medicine; in press. One of these abstracts was selected for oral presentation at the 30th Annual European Society of Regional Anaesthesia Congress, 2011. These publications have been reformatted to fit with the overall PhD Thesis.

2.4.1 Abstract

Background and aims

Opioids are one of the factors that can modulate the functioning of the hypothalamic-pituitary-gonadal axis at the hypothalamic or pituitary level, with the potential to cause hypogonadism. The aim of this study was to investigate the effects of long-term opioid intrathecal drug delivery therapy on the hypothalamic-pituitary-gonadal axis of male chronic non-malignant pain patients and the possible occurrence of differences between hypogonadism diagnostic criteria.

Methods

Twenty consecutive male patients undertaking long-term IDD therapy for chronic non-malignant pain had the gonadal axis evaluated by assays of luteinising hormone (LH), follicle stimulating hormone (FSH), total testosterone (TT) and sex hormone binding globulin (SHBG). Free androgen index (FAI), free testosterone (FT) and bioavailable testosterone (BT) were calculated.

Results

The average age at the time of blood collection was 58 ± 1.47 years (range 47-69), the average time from implantation of IDD system to hormone assay was 92 ± 12.8 months (range 15-203) with a mean intrathecal opioid dose of 3.22 ± 0.64 mg/day (range 1-9.7). The mean LH was 2.69 ± 0.99 IU/L (0.2-19.9), FSH 7.98 ± 1.57 IU/L (0.3-23.9), SHBG 54.7 ± 6.76 nmol/L (17-123) and TT 7.18 ± 1.19 nmol/L (1.2-18.8). Testosterone levels were significantly below the cut-off mark of 12 nmol/L for borderline/low testosterone ($t = -4.043$, $p < 0.005$, $r = 0.68$). The mean FAI was 16.89 ± 3.63 (1.9-57.06), the average FT was 109.64 ± 20.68 (14-328) and the average BT was 2.57 ± 0.48 (0.33-7.7). Based on either TT or FT being low or borderline/low, 19 (95%) of the investigated patients, were biochemically...
hypogonadal. Significant differences were observed between diagnosis based on FT and FAI, $\chi^2(1) = 10.588, p < 0.01$.

Conclusions

Hypogonadism is common in patients undertaking intrathecal drug delivery. The diagnosis of hypogonadism in IDD patients, should take into consideration not only total testosterone but also free testosterone or bioavailable testosterone, LH and FSH levels.

2.4.2 Introduction

The hypothalamic-pituitary-gonadal (HPG) axis starts to function with the secretion by the hypothalamus of the gonadotropin releasing hormone (GnRH) which stimulates the pituitary gland to produce luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH and FSH are released into the systemic circulation, stimulating the gonads (testicles and ovaries) to produce the sex hormones testosterone (androgen) and estradiol (estrogen) respectively (Figure 2.4.1). These sex hormones control the secretion of GnRH, LH and FSH via a negative feedback on the hypothalamus and pituitary gland (Katz and Mazer 2009). Testosterone or estrogen levels affect sexual and reproductive development as well as behaviour and gender characteristics.

Opioids are one of the factors that can modulate the hypothalamic-pituitary-gonadal axis functioning at the hypothalamic or pituitary level, with the potential to cause central hypogonadism, also known as secondary hypogonadism or hypogonadotropic hypogonadism. Animal studies suggest that the opioid control of gonadotropin release occurs via the inhibition of the GnRH by β-endorphin (Schulz et al., 1981), most likely at µ-receptors (Pfeiffer et al., 1983). This inhibition secondarily reduces the release of LH and FSH by the pituitary gland and production of testosterone by the gonad, indicating hypogonadism. This condition is caused by disorders at the hypothalamic or pituitary level leading to decreased testosterone production with loss of libido (Figure 2.4.2). It is characterized by low or low-normal FSH levels, low or low-normal LH levels and low testosterone levels (Petak et al., 2002). The main site of action of both exogenous and endogenous opioids appears to be in the hypothalamus, but further modulating effects may occur at the pituitary level and at the end organs (Morley 1981).
The influence of exogenous opioids on reproductive capability was inferred based on the observation that many heroin addicts were amenorrhoeic or hypogonadal (Genazzani et al., 1993). This deduction was confirmed by studies which reported low testosterone levels in heroin addicts (Mendelson and Mello 1975; Mendelson, Mendelson and Patch 1975) and subjects on methadone maintenance programmes (Bliesener et al., 2005; Hallinan et al., 2008; Mendelson, Mendelson and Patch 1975).

Testosterone circulates in plasma non-specifically bound to albumin, specifically bound to the sex hormone binding globulin (SHBG) and only a small percentage of testosterone is unbound (Vermeulen, Verdonck and Kaufman 1999). SHBG also binds to estradiol which is the predominant female sex hormone. The free and the non-specifically bound testosterone represent a small percentage of the hormone available, however, there is good evidence that this fraction reflects more accurately the clinical situation than total testosterone in plasma (Vermeulen, Verdonck and Kaufman 1999). The unbound or free testosterone is able to link to and activate a receptor. SHBG bound to testosterone will inhibit this action.
The gold standard test for verification of the androgen status is an assay of free testosterone (FT) or bioavailable testosterone (BT) by equilibrium dialysis, however, this technique is not practical for routine evaluations since it is time consuming, requires sophisticated equipment, the use of freshly purified radioactive tracers, several hours of dialysis to achieve equilibrium and a long counting time for radioactivity (Raverot et al., 2010; Vermeulen 2005). This procedure examines the levels of total testosterone, SHBG and albumin, therefore allowing a precise analysis of FT and BT values.

An alternative to this method is the calculation of FT and BT through the Vermeulen equations (Vermeulen, Verdonck and Kaufman 1999). In the FT equation, $K_t$ is the association constant of SHBG for testosterone; $N = K_a C_a + 1$ where $K_a$ is the association constant of albumin for testosterone, and $C_a$ is the albumin concentration.

$$FT = \frac{T - (N \times FT)}{K_t \times [SHBG - T + (N \times FT)]}$$
BT is the sum of FT with the albumin-bound testosterone (AT). The calculated FT has been considered as a reliable index of unbound testosterone (Hackett et al., 2008; Rosner et al., 2007; Vermeulen, Verdonck and Kaufman 1999).

\[ BT = FT + AT \]

The free androgen index (FAI) is also often calculated to examine the presence of hypogonadism. This index takes into consideration testosterone and SHBG levels.

\[ FAI = \frac{100 \times T}{SHBG} \]

In this equation both testosterone and SHBG are expressed as nanomoles per liter (nmol/L) (Harman et al., 2001; Vermeulen, Verdonck and Kaufman 1999). The FAI is an index of free testosterone, it does not indicate the actual physical concentration of free testosterone (Miller et al., 2004). The validity of FAI as a reliable equivalent of free testosterone has been questioned with studies considering FAI a poor index of free testosterone (Kapoor, Luttrell and Williams 1993; Vermeulen, Verdonck and Kaufman 1999).

The possible effect of intrathecal drug delivery on the endocrine system is one of the least noted and investigated IDD side effects (Doleys et al., 1998). Currently, opioid induced hypogonadism is under-recognised and undertreated (Reddy et al., 2010). Some patients may attribute the signs and symptoms of hypogonadism such as decreased libido, tiredness, loss of muscle mass and strength, among others to the chronic pain and its related conditions, rather than the intraspinal medication (Doleys et al., 1998; Katz and Mazer 2009). Moreover, hypogonadism symptoms are often denied by the patient and ignored by the physician (Petak et al., 2002). The current limited clinical awareness of the opioid effects on the endocrine system, together with the lack of information on their long-term consequences, is likely to result in a lack of information provision to the patient when long-term opioid therapy is being considered (Vuong et al., 2010).

It is important to detect and refer these patients to appropriate care as chronic low levels of testosterone can lead to effects on sexual function and fertility (Roberts et al., 2002), as well
as to other complications such as muscle atrophy, anaemia, and cognitive impairment (Morales and Heaton 2001; Roberts et al., 2002; Zitzmann and Nieschlag 2000).

The aim of this study was to investigate the effects of long-term intrathecal opioid therapy on the hypothalamic-pituitary-gonadal axis of male chronic non-malignant pain patients and variations in the prevalence of this complication according to the diagnostic criteria employed.

### 2.4.3 Review of the literature

Six studies have been published on the effect of IDD in the endocrine system. The first study (Paice, Penn and Ryan 1994) investigated this side effect in six male patients undertaking intrathecal opioid delivery for FBSS (n=1), reflex sympathetic dystrophy (n=1), pain due to hemangioma of the spinal cord (n=1), visceral pain (n=1), postherpetic neuropathy (n=1) and back pain and arachnoiditis (n=1).

The next publication on this topic was by the same first two authors, a letter reporting the case of a woman that became amenorrheic following IDD therapy (Paice and Penn 1995).

A cross-sectional study investigated the testosterone levels of 15 consecutive male patients (Doleys et al., 1998). The only endocrine marker investigated was testosterone, therefore it would not be possible to distinguish between primary or secondary hypogonadism in this study. Low back pain was present in 86.7% of the sample, while the other 13.3% were diagnosed with cervical radiculopathy.

Abs et al. (2000) studied both male and female patients being administered intrathecal opioids and compared the results with a control group with analogous pain syndromes but not receiving opioid treatment. This study evaluating the endocrine consequences of intrathecal opioids involved the greatest number of participants (n=73). Diagnosis of the patients included FBSS (n=47); chronic pancreatitis; complex regional pain syndrome (CRPS) I and II; polyneuropathy; neurinome; spinal stenosis; phantom limb pain; and scoliosis and neck pain.
One month following the publication of the Abs et al. (2000) study, a case-control study comparing 30 IDD patients with a matched control group of chronic pain patients not taking any form of opioid drugs was published (Finch et al., 2000). The patients involved in this study presented with FBSS (n=15); spinal pain (n=5); CRPS I (n=6); benign spinal tumor (n=1); facial pain (n=1) and chronic pancreatitis or abdominal pain (n=2).

A prospective, short term (12 weeks) study evaluated the hypothalamic-pituitary-gonadal axis function in males during the first weeks of intrathecal opioid delivery (Roberts et al., 2002). The diagnosis were FBSS (n=4); CRPS I (n=3); cervical discogenic pain (n=1); post-thoracotomy pain syndrome (n=1) and central pain (n=1). The patients were evaluated before and after one, four and 12 weeks of intrathecal opioid delivery.

**Gonadal axis in males (Table 2.4.1)**

In the Paice, Penn and Ryan (1994) study, the route of opioid delivery was intrathecal in five of the six patients included in the study. The remaining patient was being administered opioids via epidural route. Four of the six patients were receiving an average additional oral opioid therapy of 71.8 ± 112.6 mg/day (0-280). Testosterone levels were significantly below the normal levels ($t= -3.11$, $p = 0.026$). Prolactin, LH and SHBG were within the normal limits. The FSH levels were above normal, although the difference was not statistically significant. Only one of the patients was within the normal testosterone level range.

The investigation of the testosterone levels of 15 consecutive male patients by Doleys et al. (1998) indicated that the average testosterone level was significantly below the cut-off mark for low testosterone ($t = -7.80$, $p < 0.0001$). The majority of patients (86.7%) were also taking oral opioids in addition to the intrathecal therapy. Criteria for inclusion in this study included at least six months of intrathecal morphine administration, however, the duration of IDD therapy reported ranged from 14 - 473 days. This inaccuracy did not seem to influence the results since the testosterone levels in all the patients were below the cut-off mark for low testosterone.

In the Abs et al. (2000) study, after initiation of IDD therapy, 23 out of 24 male participants (95.8%) noticed a decrease or even disappearance of libido and potency, whereas prior to treatment 25 of 26 males considered their libido as normal. Serum testosterone ($p < 0.001$) and FAI ($p < 0.001$) levels were significantly lower in the IDD group compared to the control
The majority of IDD patients (25/86.2%) and one control patient had a testosterone level below 9.0 nmol/L. The FAI level was lower than twenty in 18 of the 29 male IDD patients (62.1%) and in one control patient. The LH concentration was significantly lower in the opioid group ($p < 0.001$). No differences between the groups were identified for serum SHBG and FSH. This study measured bone mineral density (BMD) in 49 of the opioid patients which revealed a z-score of -0.19 ± 1.54 (range: -4.17 – 2.4) at the lumbar spine and -0.53 ± 1.46 (range: -5.91 – 2.87) at the femoral neck. There was no indication of the number of patients with osteoporosis or osteopaenia. No comparison was made with the control group because BMD was not measured in that group.

In the Finch et al. (2000) study, IDD male patients showed significantly lower testosterone ($p=0.0032$) and FAI levels ($p = 0.0126$) when compared with a group of chronic pain patients not taking any form of opioid drugs. One male patient was excluded in this study on the basis of a history of mumps orchitis prior to IDD therapy. Six male patients reported poor libido and four of these were impotent with the onset of symptoms corresponding to commencement of IDD therapy. FSH and LH levels, although lower in the IDD group were not significantly different when compared with the control group. SHBG and prolactin levels were within the normal range for both groups. After cessation of intrathecal opioid delivery in two men aged 37 and 64 years old, there was an increase in testosterone levels from 8.3 to 12 nmol/L and 1.3 to 9.9 nmol/L, respectively. Hypogonadotropic hypogonadism was present in all male IDD patients and absent in the control subjects.

The participants in the Roberts et al. (2002) study were administered oral opioids at an average of 211 ± 60 mg/day of morphine equivalents prior to IDD. The oral opioid dose decreased throughout IDD therapy to a median dose of 23.5 and 7.9 mg/day at four and 12 weeks assessment, respectively. The majority of the patients were already below the lower limit of the reference range of serum testosterone (10-35 nmol/L) prior to the start of intrathecal therapy. Nevertheless, significant decreases in testosterone and FSH levels were verified after one, four and 12 weeks of intrathecal opioid delivery ($p < 0.0001$).
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</tr>
</thead>
<tbody>
<tr>
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<td>6</td>
<td>Cross-sectional study</td>
<td>15</td>
<td>Case-control study</td>
</tr>
<tr>
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<td>39.8 ± 5.7 (34-50)*</td>
<td>42.7 ± 9.78 (25-59)*</td>
<td>48.4 ± 11 (23-66)*</td>
<td>46.5 ± 3.5**</td>
<td>6</td>
</tr>
<tr>
<td>Duration of pain</td>
<td>47.7 ± 33.4 months*</td>
<td>290.67 ± 156.97 days (14-473)*</td>
<td>26.6 ± 16.3 months (3-61)*</td>
<td>2.5 years median (0.02-8)</td>
<td>11.5 (0.8-24)</td>
</tr>
<tr>
<td>Duration of IDDS</td>
<td>18.65 ± 17.6*</td>
<td>5.07 ± 3.37 (0.8-12.3)*</td>
<td>4.8 ± 3.2 (0.6-15)*</td>
<td>Mean = 11.6 (0.5-40)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Morphine dose (mg/day)</td>
<td>6.86 ± 4.16 (0.9-12.73)*</td>
<td>5.03 ± 2.15 (1.11-7.88)*</td>
<td>6.9 ± 5.2 (1.4-25)*</td>
<td>4.9 ± 1.1**</td>
<td>2.6 ± 0.5 / 3.3 ± 0.6 / 5.3 ± 1.2¥</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>23.1 ± 20.7 (5-108)*</td>
<td>29.1 ± 11**</td>
<td>4.6 ± 0.5 / 2.5 ± 0.2 / 3.2 ± 0.3 / 3.8 ± 0.4†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAI</td>
<td>124.12 ± 64.14*</td>
<td>4.7 ± 2.6 (0.3-10.6)</td>
<td>Median = 3</td>
<td>3.3 ± 0.5 / 2.3 ± 0.7 / 1.8 ± 0.3 / 3.0 ± 0.6†</td>
<td></td>
</tr>
<tr>
<td>Free testosterone (pmol/L)</td>
<td>23.27 ± 19*</td>
<td>1.7 ± 1.4 (0.1-7.2)</td>
<td>Median = 2</td>
<td>256 ± 61 / 319 ± 43 / 274 ± 35 / 223 ± 39†</td>
<td></td>
</tr>
<tr>
<td>FSH (UI)</td>
<td>10.02 ± 6.55 (4.7-21)*</td>
<td>1.7 ± 1.4 (0.1-7.2)</td>
<td>2.8 ± 4.2 / 28.1 ± 5.0 / 24.9 ± 4.0 / 28.3 ± 4.2†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH (UI)</td>
<td>306 ± 228.6 (180-648)*</td>
<td>36.1 ± 20.9 (12-85)</td>
<td>4.6 ± 0.5 / 2.5 ± 0.2 / 3.2 ± 0.3 / 3.8 ± 0.4†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin (mUI)</td>
<td>35.77 ± 9.56 (27.95-47.52)*</td>
<td>36.1 ± 20.9 (12-85)</td>
<td>Testosterone (p &lt; 0.001), FAI (p &lt; 0.001) and LH (p &lt; 0.001) levels significantly lower in the opioid group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>35.77 ± 9.56 (27.95-47.52)*</td>
<td>36.1 ± 20.9 (12-85)</td>
<td>Significant differences between groups for testosterone and FAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Testosterone levels significantly below the normal levels (t = -3.11, p = 0.026)</td>
<td>Testosterone levels significantly below the cut-off mark for low testosterone (t = -7.8, p &lt; 0.0001)</td>
<td>Testosterone (p &lt; 0.001), FAI (p &lt; 0.001) and LH (p &lt; 0.001) levels significantly lower in the opioid group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Significant decreases observed for testosterone and FSH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± SD (range)

** Mean ± SEM

¥ Mean ± SEM at 1, 4, and 12 weeks respectively

† Mean ± SEM at baseline, 1, 4 and 12 weeks respectively
**Gonadal axis in females (Table 2.4.2)**

Paice and Penn (1995) published a letter reporting the case of a woman that became amenorrheic after IDD treatment. The patient ceased menstruating within one month following pump implantation. Endometrial biopsies, serum estradiol, FSH and LH levels were normal indicating that the patient was not menopausal.

In the Abs et al. (2000) study, following commencement of IDD therapy, 22 out of 32 women (68.8%) noticed a decrease or disappearance of libido, whereas prior to treatment 32 of 36 women considered their libido as normal. LH levels were inferior to 2 U/l in nine of 21 premenopausal women (42.9%) in the IDD group. FSH levels were less than 2 U/l in five of the 21 premenopausal women (23.8%). Serum LH, FSH, estradiol and progesterone concentrations were lower in the opioid group, although not statistically significant probably due to the small number of premenopausal patients in the control group (n=3). Fourteen of 21 premenopausal women became amenorrheic and seven developed an irregular menstrual cycle, with ovulation only in one woman.

The LH ($p < 0.001$) and FSH ($p = 0.012$) levels in postmenopausal women were significantly lower in the IDD group than in the six postmenopausal control women. No significant differences were observed between the groups for estradiol and progesterone concentrations. In this study, five female patients were excluded without being accounted for.

In the Finch et al. (2000) study, all the premenopausal women reported low libido since commencement of therapy. Five of the seven women reported amenorrhea; in two of these the amenorrhea predated the intrathecal therapy. Seven of the twelve postmenopausal women were on sex hormone replacement therapy which was ceased at least two weeks prior to hormone assay. These women reported low libido levels both before and after initiation of intrathecal opioid therapy. All estradiol levels were within the normal postmenopausal range. FSH (subjects, $24.5 \pm 10.8$ IU/L; controls $78.5 \pm 3.7$ IU/L; $p = 0.0037$) and LH (subjects, $12.3 \pm 7.2$ IU/L; controls $35.3 \pm 3.6$ IU/L; $p = 0.0024$) levels were significantly lower than those observed in the control group.
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Case report</td>
<td>Case-control study</td>
<td>Case-control study</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>1F</td>
<td>73 (44F)</td>
<td>30 (19F)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Premenopausal (21)</td>
<td>Premenopausal (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postmenopausal (18)</td>
<td>Postmenopausal (12)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>53</td>
<td>49.8 ± 12.3 (27-81)*</td>
<td>38.3 ± 1.5**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>64.8 ± 1.9**</td>
</tr>
<tr>
<td><strong>Duration of pain</strong></td>
<td>3 years</td>
<td>5 years</td>
<td>6 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26.6 ± 16.3 months (3-61)*</td>
<td>2.5 years median (0.02-8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.8 ± 3.2 (0.6-15)*</td>
<td>Mean = 11.6 (0.5-40)</td>
</tr>
<tr>
<td><strong>Morphine dose</strong></td>
<td>3 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Estradiol (pmol/L)</strong></td>
<td>Within normal levels</td>
<td>127 ± 124 (18-437)*</td>
<td>Median = 125</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100.2 ± 122.6 (18-125)*</td>
<td>Within normal range</td>
</tr>
<tr>
<td><strong>Progesterone (nmol/L)</strong></td>
<td>1.6 ± 2.6 (0.3-11.8)*</td>
<td>1.0 ± 0.6 (0.3-1.2)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.4 ± 5.6 (0.1-26)*</td>
<td>Median = 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.6 ± 17.6 (0.5-66.9)*</td>
<td>24.5 ± 10.8**</td>
</tr>
<tr>
<td><strong>FSH (mIU/mL)</strong></td>
<td>Within normal levels</td>
<td>2.7 ± 2.6 (0.1-9)*</td>
<td>Median = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.3 ± 3.3 (0.1-9.4)*</td>
<td>12.3 ± 7.2**</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Patient developed amenorrhea</td>
<td>LH, FSH, estradiol and progesterone concentrations lower in the opioid group</td>
<td>Three out of 7 women developed amenorrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LH ($p &lt; 0.001$) and FSH ($p = 0.012$) levels significantly lower in the ID group</td>
<td>FSH and LH significantly lower than in control group</td>
</tr>
</tbody>
</table>

* Mean ± SD (range)
** Mean ± SEM
2.4.4 Methods

Participants

Twenty consecutive male patients undertaking long-term IDD therapy at Russells Hall Hospital for the management of chronic non-malignant pain were included in the study. Patients who had received testosterone supplementation within the previous three months were not included (Roberts et al., 2002). The pain syndrome the majority of the participants (58.8%) experienced was nociceptive, while neuropathic pain was present in 5.8% of the patients and 35.3% suffered from mixed nociceptive-neuropathic pain. All the patients were receiving intrathecal opioids for the management of their pain. Intrathecal morphine was the only medication administered to 50% of the sample. In individual cases, other substances were added to the intrathecal medication, such as bupivacaine (50%), clonidine (25%) and baclofen (12.5%).

Assessment of Sex Hormones

The gonadal axis was evaluated by measurement of single serum concentrations for the indicative markers of endocrine glands functioning, such as LH, FSH, total testosterone (TT) and SHBG (Table 2.4.3). The validity of single serum concentrations assessment has been demonstrated in patients evaluated for testosterone replacement therapy (Vermeulen and Verdonck 1992). SHBG was measured by immunoradiometric assay (Oregon Diagnostica, Espoo, Finland) according to the manufacturer’s instructions with intra-assay coefficients of variation (CV) of two to 5%. All other assays were performed by automated chemiluminescence on the ACS:180 (Chiron Diagnostics, East Walpole, MA, U.S.A.) according to the manufacturer’s instructions with within-run CV of less than 5% for LH and FSH and less than 10% for testosterone. Calculations of the free androgen index (FAI), free testosterone (FT) and bioavailable testosterone (BT) were also carried out (Harman et al., 2001; Vermeulen, Verdonck and Kaufman 1999).

Normal reference ranges for LH represented a value between 2.2-13.3 IU/L, FSH 1-7 IU/L and SHBG 13-71 nmol/L. A TT level of < 8 nmol/L, FT < 180 picomoles per liter (pmol/L), BT < 3.8 nmol/L was considered as biochemical hypogonadism and TT levels of 8 – 12 nmol/L, FT 180-250 pmol/L, BT 3.8-6.1 nmol/L as borderline/low (Hackett et al., 2008). FAI levels < 15.3 were considered as hypogonadism (Harman et al., 2001).
During a seven month period (April to October 2010) 20 blood samples were obtained. The blood tests were collected between 8am and 11am. All blood assays were carried out by the Department of Clinical Biochemistry at Russells Hall Hospital, Dudley.

**Data analysis**

Results are expressed as mean ± SEM unless specified otherwise. The Kolmogorov-Smirnov test was performed to test distribution of numerical data, followed by the appropriate statistical tests. One-sample T test was performed to investigate differences between TT levels of the sample with normal endocrine values. Associations between variables were investigated by Spearman’s correlation coefficients. Analysis of categorical data was carried out through Pearson’s Chi-Square test. Results were considered statistically significant at $p \leq 0.05$. Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 17.0, SPSS Inc., Chicago, IL, USA).

<table>
<thead>
<tr>
<th>Patient</th>
<th>FSH</th>
<th>LH</th>
<th>TT</th>
<th>SHBG</th>
<th>FAI</th>
<th>BT</th>
<th>FT</th>
</tr>
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<tbody>
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<td>1</td>
<td>0.3</td>
<td>0.2</td>
<td>9.7</td>
<td>17</td>
<td>57.06</td>
<td>6.180</td>
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</tr>
<tr>
<td>2</td>
<td>9.4</td>
<td>1.9</td>
<td>4.4</td>
<td>39</td>
<td>11.28</td>
<td>1.730</td>
<td>73.80</td>
</tr>
<tr>
<td>3</td>
<td>6.6</td>
<td>2.4</td>
<td>3.6</td>
<td>26</td>
<td>13.85</td>
<td>1.780</td>
<td>75.70</td>
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<tr>
<td>4</td>
<td>5.2</td>
<td>1.5</td>
<td>10.1</td>
<td>65</td>
<td>15.54</td>
<td>2.920</td>
<td>125.00</td>
</tr>
<tr>
<td>5</td>
<td>5.2</td>
<td>2.0</td>
<td>10.3</td>
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<tr>
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<td>7</td>
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<td>2.5</td>
<td>4.9</td>
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<td>8</td>
<td>3.9</td>
<td>0.7</td>
<td>3.0</td>
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<td>7.14</td>
<td>1.110</td>
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<td>9</td>
<td>0.9</td>
<td>0.2</td>
<td>1.2</td>
<td>63</td>
<td>1.90</td>
<td>0.329</td>
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</tr>
<tr>
<td>10</td>
<td>5.4</td>
<td>1.6</td>
<td>2.0</td>
<td>21</td>
<td>9.52</td>
<td>1.080</td>
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<td>11</td>
<td>22.4</td>
<td>2.1</td>
<td>5.0</td>
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<td>5.68</td>
<td>1.090</td>
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<td>4.5</td>
<td>1.9</td>
<td>2.1</td>
<td>17</td>
<td>12.35</td>
<td>1.250</td>
<td>53.10</td>
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<tr>
<td>13</td>
<td>7.5</td>
<td>17.5</td>
<td>40</td>
<td>43.75</td>
<td>7.700</td>
<td>328.00</td>
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</tr>
<tr>
<td>14</td>
<td>10.1</td>
<td>3.7</td>
<td>18.8</td>
<td>79</td>
<td>23.80</td>
<td>5.000</td>
<td>213.00</td>
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<tr>
<td>15</td>
<td>4.3</td>
<td>4.1</td>
<td>15.2</td>
<td>109</td>
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<td>2.980</td>
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<tr>
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<td>0.2</td>
<td>10.6</td>
<td>20</td>
<td>53.00</td>
<td>6.360</td>
<td>271.00</td>
</tr>
<tr>
<td>17</td>
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<td>2.3</td>
<td>2.8</td>
<td>75</td>
<td>3.73</td>
<td>0.682</td>
<td>29.10</td>
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<tr>
<td>18</td>
<td>4.7</td>
<td>1.0</td>
<td>4.0</td>
<td>52</td>
<td>7.69</td>
<td>1.290</td>
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</tr>
<tr>
<td>19</td>
<td>2.8</td>
<td>0.7</td>
<td>2.4</td>
<td>50</td>
<td>4.80</td>
<td>0.784</td>
<td>33.50</td>
</tr>
<tr>
<td>20</td>
<td>13.0</td>
<td>19.9</td>
<td>10.0</td>
<td>123</td>
<td>8.13</td>
<td>1.700</td>
<td>72.60</td>
</tr>
</tbody>
</table>
2.4.5 Results

The sample consisted of 20 male IDDS patients with a mean age at the time of blood collection of 58 ± 1.47 years (range 47-69). The average time from implantation of the IDD system to hormone assay was 92.12 ± 12.81 months (range 15-203) with a mean intrathecal opioid dose of 3.22 ± 0.64 mg/day (range 1-9.7). The mean duration of pain prior to commencement of IDD was 13.9 ± 2.34 years (range 3-35) (Table 2.4.4).

The mean TT level was 7.18 ± 1.19 nmol/L (1.2-18.8), which was significantly lower than the cut-off mark of 12 nmol/L for borderline/low testosterone \( (t = -4.043, p < 0.005, r = 0.68) \).

The mean FT levels were significantly lower than the cut-off mark of 180 pmol/L for low FT \( (t = -3.403, p < 0.005, r = 0.61) \). The mean BT levels were significantly lower than the cut-off mark of 3.8 nmol/L for low BT \( (t = -2.533, p < 0.05, r = 0.50) \). No significant differences were observed between the mean FAI and the cut-off mark of 15.3 for hypogonadism \( (p = 0.665) \). LH, FSH and SHBG mean levels were within the normal reference range.

| Table 2.4.4 Sample characteristics |
|-----------------|-----------------|
| Nr. patients    | 20 (100%)       |
| Age (years)     | 58 ± 1.47 (47-69) |
| IDDS duration (months) | 92.12 ± 12.81 (15-203) |
| Opioid dose (mg/day) | 3.22 ± 0.64 (1-9.7) |
| LH (IU/L)       | 2.69 ± 0.99 (0.2-19.9) |
| FSH (IU/L)      | 7.98 ± 1.57 (0.3-23.9) |
| SHBG (nmol/L)   | 54.7 ± 6.76 (17-123) |
| FAI             | 16.89 ± 3.63 (1.9-57.06) |
| BT (nmol/L)     | 2.57 ± 0.48 (0.33-7.7) |
| FT (pmol/L)     | 109.64 ± 20.68 (14-328) |

Statistics are presented as mean ± SEM (range)

Based on TT, 17 (85%) of the patients were hypogonadal with 12 (60%) at less than 8 nmol/L and five (25%) between eight and 12 nmol/L (Figure 2.4.3). Based on FT calculations, 17 (85%) were hypogonadal with 15 (75%) at less than 180 pmol/L and two (10%) patients between 180 and 250 pmol/L. The same outcome was observed for the analysis of BT calculations, therefore FT was considered for further statistical comparisons as the result would be the same if carried out with either FT or BT. Based on hypogonadism defined as FAI < 15.3 in men, 14 (70%) patients were identified. Based on either TT or FT
being low or borderline/low, 19 (95%) of the investigated patients, were biochemically hypogonadal. In this sample FAI was highly correlated with FT ($r = 0.929$, $p < 0.01$) and BT ($r = 0.929$, $p < 0.01$) and less associated with testosterone ($r = 0.701$, $p < 0.01$). FT ($r = 0.866$, $p < 0.01$) and BT ($r = 0.866$, $p < 0.01$) were more strongly correlated with testosterone.

Significant differences were observed between diagnosis based on FT and FAI, $\chi^2(1) = 10.588$, $p < 0.01$. No significant differences were observed between diagnosis based on TT and FT ($p = 0.404$) or TT and FAI ($p = 0.14$).

![Figure 2.4.3 Hypogonadism according to diagnostic criteria](image)

### 2.4.6 Discussion

The gonadotropin levels of the patients in our sample were either low or low-normal, which suggests that testosterone suppression was caused at the hypothalamic-pituitary-gonadal axis through an inhibition of pituitary FSH and LH secretion. Direct suppression at a testicular level would result in primary hypogonadism, characterized by an increase in FSH
and LH levels. Smaller changes observed in FSH are likely to be due to its relatively long circulatory half-life (Grossman 1983). In a group of cancer survivors on opioids, 90% exhibited hypogonadism and median testosterone levels; LH levels but not FSH levels were found to be significantly lower when compared with cancer survivors not on opioid therapy (Rajagopal et al., 2004). The important role of endogenous opioids in the control of LH secretion has been demonstrated (Genazzani et al., 1993). Suppression of the hypothalamic-pituitary-gonadal axis by intrathecal opioids may be caused by a similar mechanism to that of endogenous opioids (Finch et al., 2000). Nevertheless, the suppression of LH levels may be less accentuated when the opioids are administered orally or transdermally rather than intrathecally (Vuong et al., 2010). Direct effects of opioids at the testicular level, including decreased secretion of testosterone have also been reported (Cicero et al., 1975).

Total testosterone levels were significantly below the cut-off mark of 12 nmol/L for borderline/low testosterone even after an average duration of IDD therapy equivalent to 92 ± 12.8 months (range 15-203). The reduction in testosterone levels is a secondary result of a primary suppression of the hypothalamic-pituitary-LH axis caused by opioids (Cicero 1980). Low testosterone levels in intraspinal opioid patients after an average duration of treatment of 47.7 months have been demonstrated (Paice, Penn and Ryan 1994).

Significant differences were observed in this study when the diagnoses of hypogonadism were compared based on calculated FT or BT and FAI. The prevalence of this complication based on diagnosis criteria ranged from 70% (14 patients) for FAI, to 85% (17 patients) based on TT or FT. When both TT and FT were considered 95% (19 patients) were diagnosed as biochemically hypogonadal. The incidence of this side effect although variable, is approximate across prior studies. The diagnostic criteria may account for much of this variation. The majority of studies investigating the effects of intrathecal opioids in the endocrine system have considered mainly TT, LH and FSH levels. To our knowledge, this is the first study with IDD patients that also used Vermeulens’ calculated free testosterone as a diagnostic tool. In studies where FAI was calculated, 25 of 29 intrathecal opioid patients (86.2%) had a testosterone level lower than 9.0 nmol/L but only 18 of the patients (62.1%) had a FAI lower than 20 (Abs et al., 2000). Another study reported that all the patients (n=10) had testosterone below the normal range of 10 to 35 nmol/L, however, the average FAI was 29.1 ± 11.0 (Finch et al., 2000). The prevalence of hypogonadism in male patients
undertaking oral opioids has been reported to range from 83% to 90% (Daniell 2002; Fraser et al., 2009; Rajagopal et al., 2003). These results indicate a high prevalence of opioid induced hypogonadism, regardless of the administration route. Even at clinically very low intrathecal opioid doses (1.5 ± 0.7 mg/day (range 0.35-2.3)) hypogonadism was present in five out of seven patients (Alam et al., 2008).

It is important to note the limitations of this study. A small number of patients was included without a control group and the gonadal status was not evaluated prior to commencement of IDD therapy. Women were not included in this study. Low libido and amenorrhea have been reported in female IDDS patients (Abs et al., 2000; Finch et al., 2000; Paice and Penn 1995), although the prevalence has been reported to be lower in women (Fraser et al., 2009).

The development of hypogonadism is multifactorial and in this specific population there are many other possible confounding factors. Psychological aspects such as depression, passive coping strategies and catastrophising are some of the factors hypothesized to influence the sexual function in chronic pain patients (Monga et al., 1998). However, chronic pain did not seem to be the cause of gonadal function reduction which was observed in patients undertaking intrathecal morphine therapy (Finch et al., 2000). Of the possible chronic illnesses identified in a longitudinal study with 890 male participants, only cancer (9%) was associated with a greater decrease in testosterone levels than the decrease that occurred with aging alone (Harman et al., 2001).

The hypothalamic-pituitary-gonadal axis should be routinely monitored in IDD patients and adequate treatment provided. Hypogonadism is a risk factor associated with several conditions. Low total testosterone, FT and SHBG are independent risk factors for later development of type 2 diabetes (Feldman et al., 1994; Haffner et al., 1996). Low testosterone levels may be associated with increased cardiovascular risk (Hackett 2009).

Opioid induced hypogonadism may be reversible. Clinically significant improvements in hypogonadal symptoms, sexual function and mood were observed in men with opioid induced androgen deficiency being treated with transdermal testosterone patches (Daniell, Lentz and Mazer 2006). Improvements in aspects of sexual activity and decrease in ratings of mood aspects such as depression, anger and fatigue were detected in previously
untreated hypogonadal men following testosterone injections (Burris et al., 1992). Recovery of serum testosterone levels following cessation of IDD therapy or significant improvements in libido following hormonal replacement therapy have been reported (Abs et al., 2000; Finch et al., 2000). After the opioid is stopped, testosterone levels generally recover within one month (Cicero et al., 1975; Mendelson and Mello 1975; Wang, Chan and Yeung 1978).

The increase of testosterone levels and consequently libido may have added importance to chronic pain patients. The results of animal studies have suggested that reduced libido may be linked with a lower pain threshold (Forman et al., 1989; Pednekar and Mulgaonker 1995). In humans, it has been observed that men with opioid-induced androgen deficiency required lower oral opioid doses during hormonal replacement therapy, suggesting that hypogonadism patients may have a lower pain threshold (Daniell 2002).

2.4.7 Conclusion

Hypogonadism is common in patients undertaking IDD therapy for the management of chronic non-malignant pain. The hypothalamic-pituitary-gonadal axis should be routinely monitored in patients undertaking intrathecal opioid administration from the start of therapy. This assessment should include evaluation of total testosterone, free testosterone or bioavailable testosterone, LH and FSH.

This section allowed confirmation that hypogonadism is a prevalent side effect of intrathecal drug delivery. Hypogonadism is a risk factor for decreased bone mineral density. The following section of this thesis evaluates the prevalence of low bone mass density in the hypogonadal patients identified in the current section.
SECTION 5. Osteopaenia and osteoporosis as a secondary side effect of intrathecal drug delivery

2.5.1 Abstract

Background and aims
Hypogonadism is common in patients undertaking intrathecal opioid therapy and a known risk factor for decreased bone mineral density (BMD). There is limited information available about BMD levels in intrathecal opioid patients. The aim of this study was to investigate BMD levels and the presence of osteopaenia and osteoporosis in the hypogonadal patients identified in the previous section of this thesis.

Methods
The patients diagnosed with hypogonadism based on free testosterone (FT) in the previous section were included in this study. BMD was evaluated via dual energy X-ray absorptiometry (DEXA) scans of the femur and lumbar spine or left forearm. Osteopaenia was defined as a T-score between -1.0 and -2.5 SD, and osteoporosis as a T-score at or below -2.5 SD.

Results
The average age was 59.1 ± 1.99 years (range 47 - 69) and the average duration of intrathecal drug delivery therapy was 99.8 ± 15.96 months (range 22 - 203) with a mean intrathecal opioid dose of 3.70 ± 0.90 mg/day (range 1 - 9.7). The mean duration of pain prior to IDD was 15.2 ± 2.89 years (range 4 - 35). Individual T-scores below -1.0 SD in at least one site were identified in 10 (71.4%) of the participants. Osteopaenia defined as a T-score between -1.0 and -2.5 SD was diagnosed in eight (57.1%) of the patients at femoral, neck (50%) or hip (28.6%), forearm (14.3%) or lumbar (14.3%) sites. Osteoporosis defined as a T-score at or below -2.5 SD was detected in three (21.4%) of the subjects at the femur site.

Conclusions
These findings show that hypogonadal intrathecal opioid patients have increased risk of developing low bone mass density. The assessment of BMD in hypogonadal intrathecal opioid delivery patients should be performed and adequate treatment provided to avoid the consequences of osteopaenia or osteoporosis.
2.5.2 Introduction
Osteoporosis has been defined by a consensus statement as a disease characterized by low bone mineral density which indicates an increased fragility of the bone and consequent increase of the risk of fracture (Consensus Development Conference 1991). Osteopaenia should not be mistaken with osteoporosis. Osteopaenia is an asymptomatic risk factor for osteoporosis characterized by a decrease in the bone mineral density whether in the presence or absence of osteoporosis (Kanis 1990). The prevalence of osteoporotic fractures is high with an estimated 9.0 million osteoporotic fractures occurring in the year 2000 of which 1.6 million were at the hip, 1.7 million at the forearm and 1.4 million were clinical vertebral fractures (Johnell and Kanis 2006). According to the same study, the greatest incidence of these fractures was in Europe (34.8%).

A DEXA scan is a reliable and commonly used technique to assess BMD (Cummings, Bates and Black 2002). This scan consists of two low dose X-ray beams with distinct energy peaks. The X-ray beams are absorbed by bone and soft tissue allowing the calculation of bone mineral content. The amount of mineral in the specific site scanned, divided by the area of bone measured, can derive a value for BMD (Kanis 2002). The presence of osteopaenia or osteoporosis can be established by the measurement of BMD (Figure 2.5.1). A comparison of an individual BMD measurement with the mean BMD value of a young healthy adults’ reference range provides a T-score. A Z-score is an age-matched score and compares an individual BMD with the mean for that age. The standard against which BMD reduction should be measured is a normal range derived from young healthy adults (Nordin 1987). The current recommendation of the World Health Organization and International Osteoporosis Foundation is to use the National Health and Nutrition Examination Survey reference database for women aged 20-29 years as reference range (Kanis and Glüer 2000).

The BMD concentration is normal if not more than one standard deviation (SD) below the young adult mean; a value that lies between one and 2.5 SD below the mean indicates low bone mass or osteopaenia (individuals who would benefit from prevention of bone loss); a score of 2.5 SD or more below the young adult mean value suggests osteoporosis; a value of 2.5 SD or more below the young adult mean alongside one or more fragility fractures is indicative of severe or established osteoporosis (Kanis et al., 1994; Kanis and Glüer 2000). The proportion of patients with osteoporosis increases exponentially with age, because
although BMD is normally distributed at all ages, it decreases progressively with age (Kanis et al., 1994) (Figure 2.5.2).

Diagnostic cut-off values for men are less well defined than for women (Kanis 2002), however a similar cut-off value for hip BMD that is used in women can be used for the diagnosis of osteoporosis in men (Kanis and Glüer 2000).

The risk of fracture is multifactorial and several independent risk factors, including hypogonadism, contribute to an increase in this risk above that reflected by BMD alone (Kanis 2002). Sex steroids are important for the maintenance of bone mass and may protect men against osteoporosis (Riggs, Khosla and Melton 2002; Vanderschueren et al., 2004). Hypogonadism, as demonstrated in the previous section of this thesis is common in patients undertaking intrathecal opioid therapy. To our knowledge, the assessment of BMD in patients undertaking intrathecal drug delivery is limited to the Abs et al. (2000) study. The
authors suggested a tendency towards decreased BMD in these patients. However, the prevalence of osteopaenia or osteoporosis was not reported.

The aim of this study was to investigate the presence of osteopaenia and osteoporosis in a sample of hypogonadal patients undertaking intrathecal opioid delivery for the management of chronic non-malignant pain.

2.5.3 Methods
The 17 male patients diagnosed as hypogonadal through calculated free testosterone (FT) or bioavailable testosterone (BT) on the previous section of this thesis were considered for inclusion in this study. Three patients were excluded. One patient was excluded on the basis
that the primary indication for IDD use was spinal osteoporosis; one patient had the intrathecal opioid therapy discontinued and one patient passed away.

Assessment of Bone Mineral Density

Bone mineral density was measured via DEXA scans of the femur (neck and hip) and lumbar spine or left forearm using the Lunar Prodigy DEXA (GE Lunar Corp., Madison, WI, USA). Lumbar spine scan was not carried out in patients who had previous spinal surgery. In those cases, assessment was performed at the left forearm site. Results are presented as BMD (g/cm$^2$), T-scores and Z-scores (Table 2.5.1). Osteopaenia was defined as a T-score between -1.0 and -2.5 SD, and osteoporosis as a T-score at or below -2.5 SD. Measurements of height, weight and body mass index (BMI) were also performed. BMI was calculated using the following metric formula:

$$\text{BMI} = \frac{\text{weight in kilograms}}{\text{height in meters}^2}$$

The BMI scores were categorised according to the World Health Organisation key cut-off points as < 18.5 (underweight), ≥ 18.5 and ≤ 24.9 (normal weight), ≥ 25 and ≤ 29.9 (overweight), and ≥ 30 (obese) (World Health Organization 2000). Bone densitometry DEXA scans were carried out by the Department of Radiology, at Corbett Hospital, Dudley.

Data analysis

Results are reported as mean ± SEM unless specified otherwise. The Kolmogorov-Smirnov test was performed to test distribution of numerical data, followed by the appropriate statistical tests. Comparisons between groups were carried out with the Mann-Whitney test. Results were considered statistically significant at $p \leq 0.05$. Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 17.0, SPSS Inc., Chicago, IL, USA).
<table>
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<th>Patient</th>
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<th>T-score neck</th>
<th>Z-score neck</th>
<th>BMD hip</th>
<th>T-score hip</th>
<th>Z-score hip</th>
<th>BMD forearm</th>
<th>T-score forearm</th>
<th>Z-score forearm</th>
<th>BMD lumbar</th>
<th>T-score lumbar</th>
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<td>0.876</td>
<td>-2.4</td>
</tr>
</tbody>
</table>
2.5.4 Results

The average age of this sample was 59.1 ± 1.99 years (47-69). The average duration of IDD therapy was 99.8 ± 15.96 months (22-203) with a mean intrathecal opioid dose of 3.70 ± 0.90 mg/day (1-9.7). The mean duration of pain prior to IDD was 15.2 ± 2.89 years (range 4-35). The mean BMI score was 28.83 ± 1.86 kg/m² (20.1 - 45.4). According to the BMI score, the majority of the patients (64.3%) were either overweight or obese and none of the patients were underweight.

Table 2.5.2 shows the results of the BMD assessment. Individual T-scores below -1.0 SD in at least one site were identified in 10 (71.4%) of the participants. Osteopaenia defined as a T-score between -1.0 and -2.5 SD was diagnosed in eight (57.1%) of the patients at femoral, either neck (50%) or hip (28.6%), forearm (14.3%) or lumbar (14.3%) sites. Osteoporosis defined as a T-score at or below -2.5 SD was detected in three (21.4%) of the subjects. One of the patients presented osteoporosis levels both at the hip and femoral neck site; another patient, besides osteoporosis levels at the hip and femoral neck sites, also presented a score below -2.5 at the forearm site. The other osteoporotic patient presented osteoporosis levels at the hip site and osteopaenia levels at the femoral neck and forearm sites. Two patients had osteopaenia levels both at hip and femoral neck locations. One patient presented osteopaenia levels at both femoral (neck and hip) and forearm sites; and one patient presented osteopaenia levels at both femoral (neck and hip) and lumbar sites.

No statistical differences were observed between the patients within normal reference range values and those with osteopaenia or osteoporosis for age (p = 0.760) or BMI (p = 0.374).

Several known risk factors for osteoporosis were present in this sample. All of the patients were hypogonadal. Half of the participants reported low levels of calcium intake, 43% were active smokers and 36% prior smokers. In addition, three of the patients reported high propensity to fall, indicating two to three falls in the last six to 12 months and one patient reported a recent rib fracture.
### Table 2.5.2 Bone Mineral Density measurements

<table>
<thead>
<tr>
<th>Site of measurement</th>
<th>BMD (g/cm²)</th>
<th>T-score</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck (n = 14)</td>
<td>0.922 ± 0.037 (0.734-1.176)</td>
<td>-1.14 ± 0.29 (-2.6-0.8)</td>
<td>-0.19 ± 0.29 (-1.9-2.0)</td>
</tr>
<tr>
<td>Total hip (n = 14)</td>
<td>0.962 ± 0.044 (0.686-1.222)</td>
<td>-0.99 ± 0.34 (-3.1-1.0)</td>
<td>-0.30 ± 0.34 (-2.6-1.9)</td>
</tr>
<tr>
<td>Forearm (n = 10)</td>
<td>0.745 ± 0.020 (0.665-0.845)</td>
<td>-0.45 ± 0.40 (-3.2-1.2)</td>
<td>0.00 ± 0.37 (-2.4-1.7)</td>
</tr>
<tr>
<td>Lumbar (n = 4)</td>
<td>1.183 ± 0.129 (0.876-1.487)</td>
<td>-0.30 ± 0.94 (-2.4-2.0)</td>
<td>0.10 ± 0.90 (-1.9-2.3)</td>
</tr>
</tbody>
</table>

Statistics are presented as mean ± SEM (range)
2.5.5 Discussion

Osteopaenia was present in 57.1% of the participants, while osteoporosis was detected in 21.4% of the subjects. One patient presented osteoporosis levels at the femur sites and forearm; another osteoporotic patient presented scores below -2.5 at both femur sites; and the other patient with osteoporosis also had osteopaenia levels in the forearm and femoral neck. There is limited available literature investigating the effects of opioids on BMD. This effect is likely to be secondary to opioid induced hypogonadism and not a direct effect of opioids. Hypogonadism is an important risk factor for development of osteoporosis in both sexes, but opioids have not been considered a risk factor and smoking and alcohol intake were considered weak risk factors (Kanis 2002). Tendency in intrathecal opioid patients towards decreased BMD has been noted previously (Abs et al., 2000), although the incidence of osteopaenia or osteoporosis was not reported. An association between oral opioid administration and reduced BMD was established (Kinjo et al., 2005) but this study failed to investigate the presence of hypogonadism in the investigated sample. In a cross-sectional study, osteopaenia was present in 50% of the male patients undertaking oral opioids (Fraser et al., 2009) although it is not clear if the six patients with osteopaenia were hypogonadal.

An association between oral opioid medication and an increase in fracture risk has been reported (Vestergaard, Rejnmark and Mosekilde 2006), however bone mineral density assessment was not performed. The authors suggested that this increase in fracture risk was possibly related to the risk of falls due to the central nervous system side effect of dizziness caused by oral opioids. Opioid induced dizziness is less likely to occur in IDD patients since only a fraction of the opioid delivered via intrathecal route reaches the brain. Low bone mass is an important component of the risk of fracture as well as non-skeletal factors such as propensity to fall (Center et al., 2000; Kanis 2002). Many fragility fractures occur in the absence of osteoporosis, although in the presence of this disease, the risk of fracture is higher (Kanis et al., 1994). Osteoporotic fractures are a significant cause of morbidity and mortality especially in the developed countries (Johnell and Kanis 2006), and are associated with increased mortality, particularly in men (Center et al., 1999).

The assumption that hypogonadism is a risk factor for decreased BMD is not always confirmed. No association between age-related hypogonadism (based on total testosterone) and decreased BMD was found in elderly men (Amin et al., 2000). In contrast, free
testosterone (calculated according to the Vermeulen equation (Vermeulen, Verdonck and Kaufman 1999)) was demonstrated to be an independent predictor of BMD and fractures in elderly men (Mellström et al., 2006) and a positive predictor of cortical bone size in young men at the age of peak bone mass (Lorentzon et al., 2005). These contradictory findings may have occurred because free testosterone is more important physiologically than testosterone. Sex hormone binding globulin levels, which generally are genetically determined, seem to play an important role in bone mass density, hence the reason for free testosterone to be a stronger predictor than total testosterone alone. Recently it has been demonstrated that SHBG levels in healthy adult men at the age of peak bone mass were positively associated with cortical bone size independently of sex-steroid levels (Vanbillemont et al., 2010). However, in middle aged and elderly men, SHBG elevation was significantly associated with the occurrence of osteoporotic fractures (Hoppé et al., 2010; Legrand et al., 2001; Lormeau et al., 2004). Although not yet confirmed, it has been suggested that the effect of SHBG on BMD may change with age and/or testosterone sufficiency or deficiency (Khosla 2006).

The limitations of this study need to be acknowledged. A small number of participants were included without a control group and bone mineral density assessment was not performed prior to commencement of intrathecal opioid therapy. Female patients were not included in the study. A large meta-analysis, which included approximately 39,000 men and women has concluded that the age-specific risk of hip fracture is similar in both men and women with the same BMD and age (Johnell et al., 2005). Despite these limitations, the high prevalence of decreased BMD suggests that the IDD population may have an increased risk for osteoporotic fractures.

It is important to provide adequate treatment to patients with low bone mass density. The presence of either osteopaenia or osteoporosis suggests that intervention is appropriate to avoid their consequences (Kanis 1990). BMD can be normalized and maintained within the normal range in men with either primary or secondary hypogonadism by continuous, long-term hormonal replacement therapy (Behre et al., 1997; Katznelson et al., 1996; Leifke et al., 1998). The full effect of testosterone replacement therapy on BMD has been reported to take up to 24 months (Snyder et al., 2000).
2.5.6 Conclusion
This study suggests an association between hypogonadism and low bone mass density in patients undertaking intrathecal opioid delivery for the management of chronic non-malignant pain. Early detection of hypogonadism followed by appropriate treatment may be paramount to reduce the risk of osteoporosis development and prevention of fractures in this population. Furthermore, surveillance of BMD levels in hypogonadal intrathecal opioid delivery patients should be performed.

The following chapters of this thesis focus on the long-term effectiveness and cost effectiveness of IDD. After an analysis of some of the possible pharmacological complications it is essential to verify if this therapy is cost effective and if long-term benefits are discernible despite the possible complications.
Chapter 3

Long-term effectiveness of intrathecal drug delivery

A 13 year follow-up cohort study of intrathecal drug delivery therapy
This chapter has been accepted for publication by the Journal of Neurosurgical Anesthesiology; in press. Aspects of this work have been selected for oral presentation at the 30th Annual European Society of Regional Anaesthesia Congress, 2011. It has been reformatted to fit with the overall PhD thesis.

3.1 Abstract

Background

Chronic pain of non-malignant origin requires effective long-term treatments, since for many patients, pain management will be necessary throughout the rest of their lives. Intrathecal drug delivery systems have become a recognised therapy for the management of severe and otherwise intractable chronic pain and their long-term outcome is particularly important. However, it is still not clear if this treatment can be effective for periods up to 10 years or longer given the paucity of long-term follow-ups.

Methods

Twenty patients participated in a longitudinal study with an average follow-up of 13.5 years (range: 10.4-17.9), equivalent to 271 patient years following IDD system implantation. Investigation was carried out through a questionnaire prior to IDD and after an average of four and 13 years of IDD therapy and assessment of pharmacological data and complications/side effects.

Results

Significant differences were identified between the three time points for the following sensory and psychosocial variables: pain intensity, pain relief, coping, self-efficacy, depression, quality of life, housework, mobility, sleep and social life (all $p < 0.001$). Beneficial changes were still visible following 13.5 years of IDDS therapy when compared with assessment prior to IDDS for all the variables mentioned ($p < 0.005$). No significant differences were detected between assessments at averages of four and 13.5 years.

Conclusion

This study, with one of the longest follow-up time spans reported in the IDDS literature, shows that IDDS has the potential to be a life-long solution in appropriately selected chronic non-malignant pain patients.
3.2 Introduction
The current non-cancer intrathecal drug delivery literature is limited by the absence of randomised controlled trials (RCTs). Recent systematic reviews were unable to find RCTs evaluating the effectiveness of long-term IDDS for the management of chronic non-malignant pain (Hayek et al., 2011; Noble et al., 2010; Patel et al., 2009). In appropriately selected patients, based on Level II-3 or Level III evidence, the recommendation for intrathecal infusion systems for long-term relief in chronic non-malignant pain is currently 1C/strong, which indicates that benefits clearly outweigh the risk and burdens (Patel et al., 2009). Although case series studies may be more prone to criticism than RCTs, they currently provide the best available evidence for this intervention (Noble et al., 2010).

IDDS therapy may have the potential to be a life-long pain management solution for chronic non-cancer patients. A favorable outcome has been reported at a three year follow-up (Atli et al., 2010). However, it remains to be seen whether this treatment can be effective at periods up to 10 years or even several decades (Hassenbusch et al., 1995). Long-term effects of IDDS remain unclear, given the paucity of data from follow-ups longer than one year (Noble et al., 2010; Turner, Sears and Loeser 2007). It has been considered that before firm conclusions regarding this therapy can be made, it may be necessary to examine the outcome of this therapy for five to 10 years (Wallace and Yaksh 2000). The aim of this study was to investigate through a prospective approach the long-term effectiveness of IDDS treatment.

3.3 Methods
A longitudinal study with an average follow-up of 13.5 years (range: 10.4-17.9), the equivalent to 271 patient years following IDDS implantation was performed. Assessment was retrospective regarding the patients condition prior to IDDS and prospective in the subsequent follow-ups at an average of four years and at an average of 13 years following IDDS implantation.

Participants
A cohort of 36 consecutive patients previously described was revisited (Raphael et al., 2002). Sixteen of the patients who completed the questionnaire in the previous study (44%)
were lost to follow-up. The majority (62.5%) due to death not directly related to a known pharmacological effect of the opioid. There is an awareness of the co-morbidities and pathologies that the patients suffered and developed. Recently, it has been reported that chronic pain patients have an increased 10 year mortality, either because of the high intensity of the pain and/or the associated disability irrespective of the cause of chronic pain (Torrance et al., 2010). The mortality rate following IDDS implantation was reported to be 3.89% within one year and superior to the 1.36% mortality rate after spinal cord stimulation (SCS) implantation over the same interval (Coffey et al., 2010). The main cause of mortality for IDDS patients was respiratory depression due to opioid or central nervous system depressant drugs as a primary or contributing factor. Nevertheless, from the nine index cases reported by Coffey et al. (2010), seven patients received an initial intrathecal opioid dose that exceeded the 0.2 - 1 mg/day dose mentioned on the drug manufacturer label; two of the patients had a history of prescription drug abuse or overuse, and the two patients with an initial intrathecal opioid dose within the suggested range were obese, which may contribute to decreased respiratory reserve (Coffey et al., 2010).

Two patients (12.5%) did not wish to participate in the study, however, these should not be considered as failures as IDDS therapy has not been discontinued. The remaining four patients (25%) continued their treatment at a different center. As this treatment cannot be accounted for, these patients could be regarded as treatment failures. The rate of discontinuation of intrathecal opioid therapy due to unsatisfactory pain relief or adverse side effects is lower (17%) when compared with the discontinuation rates of oral opioid (45%) or transdermal opioid therapy (25%) (Chapman et al., 2010).

Twenty patients receiving continuous intrathecal opioid analgesics by implanted reservoir administration for chronic non-malignant pain at Russells Hall Hospital Pain Management Department, Dudley were included in the study. The sample consisted of 10 women (50%) and 10 men (50%) with an average age at time of last assessment of 60 ± 1.98 years (range: 43-79). The average duration of pain prior to IDDS implant was 9.63 ± 1.39 years (range: 2-26). The mean follow-up period following pump implantation was 13.5 ± 0.66 years (range: 10.4-17.9). The pain syndrome was nociceptive in 40% of the patients and mixed nociceptive-neuropathic in the remaining 60%. The topography of pain for the majority of the patients (85%) was the low back, mostly following failed back surgery (60%).
topographies included the abdomen, spine and leg. Radiating pain from the low back to the legs was present in 65% of the participants.

A research protocol (appendix 1), patient information sheet (appendix 2) and patient consent form (appendix 3) were developed to submit an application for University sponsorship (appendix 4) and Research Ethics Committee (REC) approval (appendix 5) prior to the commencement of recruitment. Ethical approval was granted by Birmingham, East, North and Solihull Research Ethics Committee (REC reference: 08/H1206/184, appendix 5) and informed consent was obtained from all participants.

Patients who participated in the previous assessment were approached when attending for follow-up (pump refill) at the hospital. The study was explained at this time and patients received an information form, questionnaire and patient consent form. The questionnaires were given to the patients to complete at their convenience. Decision whether to participate or not in the study was communicated by the next follow-up (between one and three months). Questions/concerns the patients had regarding participation were fully addressed. The questionnaires were returned when the patient attended for the next pump refill. All participants enrolled in the study read and signed a written informed consent form outlining the relative advantages and disadvantages to participation in the study as well as the study objectives. Participation was voluntary and remuneration was not offered as the results were dependent upon the participants’ opinion and remuneration could bias their answers. All patients were entitled to withdraw from the study at any time without prejudice to future care.

Sensory and psychosocial measures
A questionnaire (appendix 10) was completed at three different time points: baseline, averages of four years and 13 years of IDDS therapy. The baseline data was collected retrospectively following an average of four years (range: 0.5-9) of IDDS treatment. For the other time points, the data was collected prospectively at an average of four years and at an average of 13 years following IDDS implantation. Although patient recall presents a potential source for bias and concern, there are reports in the literature on the accuracy of pain recall (Morley 1993; Salovey et al., 1993) and research that found fair to moderate agreement for recalled versus initial reports after a mean interval of 9.4 years (Dawson et al., 2002).
The questionnaire comprised of sensory, psychological and sociological dimensions and requested comments on satisfaction about treatment. The questionnaire followed the scale design of the Brief Pain Inventory (BPI) pain interference items (Cleeland and Ryan 1994). The patients were approached to participate in the study by a non-clinical researcher not involved in the treatment process and the questionnaire was given to the patients to complete at their convenience. The questionnaires were returned when the patient attended for the subsequent pump refill.

Pain intensity was measured through an eleven point NRS (where zero represents no pain and 10 represents worst possible pain) (Dworkin et al., 2005). Clinical changes were calculated from the NRS scores measured prior and after four years of IDDS therapy; and prior and after 13 years of treatment by the following method: \((\text{NRS baseline} – \text{NRS endpoint}) / \text{NRS baseline}\) x 100 (Farrar et al., 2001). Clinically important changes were classified in accordance with a consensus statement that established a 10 - 20% decrease as minimally important, ≥ 30% as moderately important and ≥ 50% as a substantial change (Dworkin et al., 2008).

Psychological aspects of pain were addressed by measurement of coping skills, dependency, depression and quality of life. Eleven point scales with zero representing no interference with coping ability, no dependency, no depression or no implication in quality of life due to pain and 10 representing maximum imaginable interference with coping ability, dependency, depression or quality of life due to pain. Sociological dimensions of pain were addressed by measurement of housework, mobility, sleep and social life. The same method was employed with zero representing no interference in activity due to pain and 10 representing the utmost interference possible in activity due to pain.

Five-point verbal rating scales were used to assess satisfaction about treatment (very unsatisfied, fairly unsatisfied, adequate, fairly satisfied or very satisfied) and perception of worthiness (not at all worthwhile, not very worthwhile, adequate, quite worthwhile or very worthwhile) (Gracely and Dubner 1987).

The questionnaire has not been validated for the measurement of psychosocial variables. For the purpose of comparison with the previous assessments the questionnaire needed to
remain the same, hence the motive why validated questionnaires were not used to assess the psychosocial dimensions studied.

Pharmacological data and complications

The patients’ case notes were screened from date of implant to November 2010. Intrathecal drugs administered and intrathecal opioid dose (mg/day) were recorded. Yearly opioid dose averages were computed for each patient from the time of implant until last refill between June and November 2010. The intrathecal opioids administered included morphine and diamorphine. All patients received either morphine or diamorphine since the beginning of therapy. Due to concerns regarding the stability of diamorphine in the intrathecal pump, which could result in corrosion of the mechanism and eventual malfunction, patients were scheduled to have diamorphine converted to morphine (Simpson 2004). At the time the study was carried out, 80% per cent of the patients had already had the diamorphine medication converted to morphine. In individual cases, other substances were added to the intrathecal medication, such as bupivacaine (95%), clonidine (75%) and baclofen (30%).

The intrathecal pumps used throughout duration of therapy were programmable (Medtronic SynchroMed) for 60% (12) of the patients and fixed rate (Medtronic Isomed or Codman) for 15% (three) of the participants. Four (20%) of the patients had the pump changed from programmable to fixed rate and one (5%) from fixed rate to programmable when undertaking a pump replacement.

Complications related with IDDS therapy identified from the case notes were recorded and categorized. Since initial assessment for IDDS therapy, all the patients included in the study attended this centre for pain management related therapies. Throughout the duration of treatment, when attending for a pump refill, the patients were asked if the pain was under control or if new symptomatology had emerged. Between follow-ups, a helpline managed by pain management nurses would be available for urgent situations. Information regarding complications, side effects or new symptoms would be recorded in the patients’ case notes.
Data analysis
Means are reported as mean ± SEM. The Kolmogorov-Smirnov test was performed to test normality of numerical data. The majority of the numerical data was not normally distributed and attempts to transform the data were unsuccessful. Sensitivity analyses were performed to compare the results for the variables studied with parametric, non-parametric and bootstrap tests and no differences were observed.

The results presented evaluate differences between the three periods using repeated measures ANOVA. To further investigate differences between the three time points, a Bonferroni correction was applied in order not to inflate Type I error probability and significance represented $p < 0.016$. A Bonferroni correction consists in dividing the significance level (0.05) by the number of tests conducted (Field 2005). Post-hoc tests were performed using bootstrapped paired-samples $t$ test based on 10,000 samples (Thompson and Barber 2000). The bootstrap technique creates samples based on the variance of the existing dataset to allow analysis with more robust parametric tests.

Differences between four years and 13 years follow-up involving categorical variables were investigated using Fishers’ exact test. Differences between four years and 13 years follow-up involving categorical grouping variables were investigated using bootstrapped independent-samples $t$ test based on 10,000 samples. Statistical significance represented $p < 0.05$ except when otherwise mentioned. Statistical tests were performed using the Predictive Analytics Software (PASW) (version 18.0, SPSS Inc., Chicago, IL, USA).

3.4 Results
Response to treatment
IDDs therapy was considered to be very worthwhile by 90% of the patients at the last assessment. The perception of worthiness by the patients was not significantly different when compared with the four-year follow-up ($p = 0.368$). All of the investigated patients indicated that they would recommend IDD as a pain management treatment. Significant differences were observed between the assessments for the variables included in the Table 3.1. Other variables presented non-significant differences between assessments, including ability to work ($p = 0.113$), sex life ($p = 0.070$), capacity to drive ($p = 0.132$) and occurrence of nightmares ($p = 0.337$).
To further investigate these results, analyses comparing the different time points (pre-treatment with four years post-treatment; pre-treatment with 13 years post treatment, and four years post-treatment with 13 years post-treatment) were carried out with significance representing $p < 0.016$ following a Bonferroni correction.

Beneficial changes were observed for sensory (pain intensity, pain relief), psychological (coping, dependence, depression, quality of life) and social aspects (housework, mobility, sleep, social life) when comparing the assessments at four years and 13 years with evaluation prior to treatment (Table 3.2). No statistically significant differences were observed for the variables studied between the prospective assessments at an average of four years and 13 years of IDDS therapy.

The average clinical change calculated from the NRS scores after four years of IDDS therapy was $43.40 \pm 5.46\%$ with 25% of the patients obtaining between $\geq 10\%$ and $< 30\%$ decrease, whereas 30% of the participants achieved between $\geq 30\%$ and $< 50\%$ decrease and 40% of the subjects attained $\geq 50\%$ decrease. Thirteen years following treatment the average clinical change relative to NRS scores prior to treatment was $37.91 \pm 5.44\%$ including 20% of the participants with $\geq 10\%$ and $< 30\%$ decrease, 20% obtaining $\geq 30\%$ and $< 50\%$ decrease and 55% achieving $\geq 50\%$ decrease. No statistically significant differences were observed between the clinical change after four years and the clinical change subsequent to 13 years of IDDS treatment ($p = 0.460$). Patient gender did not seem to contribute to clinical change obtained either at four years ($p = 0.225$) or 13 years of therapy, ($p = 0.693$).

Following an average of 13 years of IDDS therapy, 90% of the patients continued to be very satisfied with the treatment. No significant differences were observed for satisfaction between the prospective assessments ($p = 0.822$). No differences in the variables studied were observed between patients with nociceptive pain and those with mixed nociceptive-neuropathic pain ($p > 0.05$).
### Table 3.1 Changes in sensory and psychosocial variables throughout time and investigation of significant differences

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Variable (NRS)</th>
<th>Pre-treatment*</th>
<th>4 years post-treatment*</th>
<th>13 years post-treatment*</th>
<th>Test statistic</th>
<th>Test statistic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory</td>
<td>Pain intensity</td>
<td>8.65 ± 0.29</td>
<td>4.95 ± 0.53</td>
<td>5.30 ± 0.35</td>
<td>F(2, 38) = 34.061</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain relief</td>
<td>7.90 ± 0.48</td>
<td>4.00 ± 0.56</td>
<td>4.75 ± 0.49</td>
<td>F(2, 38) = 27.889</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Psychological</td>
<td>Coping</td>
<td>8.25 ± 0.35</td>
<td>4.25 ± 0.71</td>
<td>4.20 ± 0.50</td>
<td>F(2, 38) = 42.185</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dependence</td>
<td>7.80 ± 0.37</td>
<td>4.90 ± 0.70</td>
<td>4.65 ± 0.63</td>
<td>F(2, 38) = 15.669</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>7.10 ± 0.65</td>
<td>3.45 ± 0.73</td>
<td>2.90 ± 0.54</td>
<td>F(2, 38) = 26.361</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
<td>8.45 ± 0.49</td>
<td>4.95 ± 0.69</td>
<td>4.45 ± 0.48</td>
<td>F(2, 38) = 20.511</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Sociological</td>
<td>Housework</td>
<td>8.40 ± 0.47</td>
<td>5.85 ± 0.65</td>
<td>5.60 ± 0.53</td>
<td>F(2, 38) = 13.099</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mobility</td>
<td>9.05 ± 0.32</td>
<td>6.25 ± 0.61</td>
<td>6.15 ± 0.49</td>
<td>F(2, 38) = 14.614</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep</td>
<td>9.05 ± 0.25</td>
<td>5.80 ± 0.66</td>
<td>6.95 ± 0.34</td>
<td>F(1.524, 28.960) = 14.070</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Social life</td>
<td>9.15 ± 0.30</td>
<td>6.00 ± 0.62</td>
<td>6.50 ± 0.51</td>
<td>F(1.535, 29.174) = 14.079</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± SEM

### Table 3.2 Differences between assessments for sensory and psychosocial variables

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Variable (NRS)</th>
<th>Pre-treatment - 4 years post-treatment</th>
<th>Pre-treatment - 13 years post-treatment</th>
<th>4 years post-treatment - 13 years post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory</td>
<td>Pain intensity</td>
<td>t(19) = 8.156, p &lt; 0.001, r = 0.88</td>
<td>t(19) = 8.257, p &lt; 0.001, r = 0.88</td>
<td>t(19) = -0.58, p = 0.576, r = 0.13</td>
</tr>
<tr>
<td></td>
<td>Pain relief</td>
<td>t(19) = 7.535, p &lt; 0.001, r = 0.87</td>
<td>t(19) = 6.525, p &lt; 0.001, r = 0.83</td>
<td>t(19) = -1.157, p = 0.269, r = 0.26</td>
</tr>
<tr>
<td>Psychological</td>
<td>Coping</td>
<td>t(19) = 8.508, p &lt; 0.001, r = 0.89</td>
<td>t(19) = 7.781, p &lt; 0.001, r = 0.87</td>
<td>t(19) = 0.95, p = 0.930, r = 0.21</td>
</tr>
<tr>
<td></td>
<td>Self-efficacy</td>
<td>t(19) = 5.445, p &lt; 0.001, r = 0.78</td>
<td>t(19) = 4.730, p &lt; 0.005, r = 0.74</td>
<td>t(19) = 0.374, p = 0.717, r = 0.09</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>t(19) = 5.417, p &lt; 0.001, r = 0.78</td>
<td>t(19) = 6.294, p &lt; 0.001, r = 0.82</td>
<td>t(19) = 1.027, p = 0.325, r = 0.23</td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
<td>t(19) = 5.627, p &lt; 0.005, r = 0.79</td>
<td>t(19) = 6.016, p &lt; 0.001, r = 0.81</td>
<td>t(19) = 0.668, p = 0.511, r = 0.15</td>
</tr>
<tr>
<td>Sociological</td>
<td>Housework</td>
<td>t(19) = 4.899, p &lt; 0.001, r = 0.75</td>
<td>t(19) = 4.499, p &lt; 0.005, r = 0.72</td>
<td>t(19) = 0.376, p = 0.714, r = 0.09</td>
</tr>
<tr>
<td></td>
<td>Mobility</td>
<td>t(19) = 5.176, p &lt; 0.001, r = 0.76</td>
<td>t(19) = 4.924, p &lt; 0.001, r = 0.75</td>
<td>t(19) = 0.145, p = 0.891, r = 0.03</td>
</tr>
<tr>
<td></td>
<td>Sleep</td>
<td>t(19) = 4.779, p &lt; 0.005, r = 0.74</td>
<td>t(19) = 5.047, p &lt; 0.001, r = 0.76</td>
<td>t(19) = -1.591, p = 0.133, r = 0.34</td>
</tr>
<tr>
<td></td>
<td>Social life</td>
<td>t(19) = 5.507, p &lt; 0.001, r = 0.78</td>
<td>t(19) = 5.101, p &lt; 0.001, r = 0.76</td>
<td>t(19) = -0.630, p = 0.532, r = 0.14</td>
</tr>
</tbody>
</table>

A Bonferroni correction indicates p < 0.016 as significant
Pharmacological data

The mean opioid dose throughout duration of treatment was 3.93 ± 0.56 mg/day (range: 1.21 – 10.78) and ranged from 0.55 ± 0.06 mg/day (range: 0.2 – 1) at baseline, to 4.81 ± 0.78 mg/day (range: 1.23 – 12.02) at year 13 (Figure 3.1). An opioid dose greater than 10 mg/day was administered to only one patient.

The dose administered at baseline was not associated with the average dose at year one. From year one onwards, every yearly mean intrathecal opioid dose was significantly correlated with the following year. The weakest correlation verified occurred between year one and year two, $r = 0.648$, $p < 0.05$. Following that year, all correlations were significant at $p < 0.01$. From year three onwards the intrathecal opioid dose did not increase significantly when compared with the subsequent year ($p > 0.05$). This indicates some opioid dose stability following year three of therapy.

![Figure 3.1 Mean intrathecal opioid dose progression from initial dose to year 13](image)
No evidence of opioid addiction or abuse was observed in the investigated patients. No significant associations were identified between the percentage of clinical change and the intrathecal opioid dose ($p > 0.05$). No differences were observed when analyzing intrathecal opioid dose differences taking into consideration patients’ gender ($p > 0.05$) or type of pain ($p > 0.05$).

**Complications/side effects**

Complications were assessed retrospectively from the patients’ notes (Table 3.3). These included acute pharmacological side effects such as respiratory depression, nausea/vomiting, drowsiness, and a case of drug overdose secondary to catheter fracture. In all these situations, the side effects resolved either with time or medication. No intrathecal devices in this sample were discontinued due to the occurrence of pharmacological side effects. The most frequent complications were related with the equipment, either pump or catheter with a rate of events per patient year equivalent to 0.0592. Fracture or blockage of the catheter or pump failure was responsible for 53.32% of the complications identified.

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Number of occurrences</th>
<th>Proportion of occurrences (%)</th>
<th>Events / patient year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacological</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea / vomiting</td>
<td>5</td>
<td>16.68</td>
<td>0.0185</td>
</tr>
<tr>
<td>Overdose *</td>
<td>1</td>
<td>3.33</td>
<td>0.0037</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>1</td>
<td>3.33</td>
<td>0.0037</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3</td>
<td>10.00</td>
<td>0.0111</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>1</td>
<td>3.33</td>
<td>0.0037</td>
</tr>
<tr>
<td>Itching</td>
<td>1</td>
<td>3.33</td>
<td>0.0037</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection in pump pocket</td>
<td>2</td>
<td>6.68</td>
<td>0.0074</td>
</tr>
<tr>
<td><strong>Technical / Equipment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pump related **</td>
<td>8</td>
<td>26.66</td>
<td>0.0296</td>
</tr>
<tr>
<td>Catheter related ***</td>
<td>8</td>
<td>26.66</td>
<td>0.0296</td>
</tr>
</tbody>
</table>

* secondary to catheter fracture
** failure, difficult refill
*** kinking, fracture
Throughout the study period an average of 2.05 ± 0.18 pump replacements (range: 1-3) were performed at a mean follow-up period of 4.95 ± 0.39 years (range: 3-9) for the first replacement, 9.86 ± 0.67 years (range: 7-16) for the second replacement and 14.43 ± 0.89 years (range: 11-17) for a third replacement.

Although no intrathecal inflammatory masses were diagnosed in this sample, 25% of the patients presented clear changes in their pain, including new symptoms. Current recommendations suggest that if new pain symptoms are observed alongside clear changes in intrathecal medication requirements, a MRI or as an alternative a computed tomography myelogram should follow (Deer et al., 2008a). Following investigation through MRI scan, no intrathecal granulomas were detected.

3.5 Discussion
The clinical change suggested at least minimally important changes for 95% of the participants at both follow-ups. The absence of statistically significant differences regarding pain intensity reduction between pain syndromes is in agreement with previous studies (Winkelmüller and Winkelmüller 1996). Intrathecal opioids were effective in reducing pain intensity even after an average of 13 years following initiation of therapy. It is known that there is a reduction in pain relief with the passage of time (Kumar, Kelly and Pirlot 2001). Although a small increase in pain intensity was observed at the 13 year follow-up, when compared with assessment at four years, this was not statistically or clinically significant, suggesting stability of this therapy, which is one of the important findings of this study. Even after 13 years, the patients’ pain intensity was significantly lower when compared with the assessment prior to IDDS therapy.

Improvements in the psychosocial variables studied were observed between assessments at baseline and four years. Moreover, these improvements were maintained at the last follow-up since statistically significant differences were not observed for these variables between the four year follow-up and the last follow-up. A cure for pain in patients undertaking IDDS is unlikely, therefore, one of the most important outcomes for these patients is improvement in quality of life. Quality of life significantly improved after IDDS and did not change significantly when the four year follow-up and last follow-up were compared despite the long treatment duration in this sample. Significant improvements in activity
levels, depression and quality of life following implantation of IDDS are consistent with previous reports (Kumar, Kelly and Pirlot 2001; Paice, Penn and Shott 1996; Thimineur, Kravitz and Vodapally 2004; Winkelmüller and Winkelmüller 1996).

The rate of complications was equivalent to 0.111 events per patient year. The pharmacological side effects observed are consistent with available literature (Chaney 1995; Kumar, Kelly and Pirlot 2001; Ruan 2007; Winkelmüller and Winkelmüller 1996). Acute side effects such as nausea, vomiting, dizziness or itching are more common after commencement of the therapy and usually resolve with standard medical management during the initial three months (Anderson and Burchiel 1999). Decreased libido was reported by one male patient, although this side effect was probably underreported in this study. The possible effect of IDDS on the endocrine system is one of the least noted and investigated IDDS side effects (Doleys et al., 1998). This occurs, mainly because the signs and symptoms of hypogonadism such as decreased libido, tiredness, loss of muscle mass and strength, among others may be attributed to the chronic pain and its related conditions (Katz and Mazer 2009). An investigation of the endocrine consequences of long-term IDDS reported that the large majority of men and women involved in the study developed hypogonadotropic hypogonadism (Abs et al., 2000). None of the patients included in this study was diagnosed with intrathecal granulomas. However, the number of events per patient year at this centre has been reported to be 0.009 (Duarte et al., 2010).

Despite the side effects and complications identified, the majority of patients (90%) revealed satisfaction with the treatment and considered IDDS to be worthwhile. Similar results were obtained by Winkelmüller and Winkelmüller (1996) where 92% of the patients included in the study were satisfied with the therapy.

In this sample, a slow increase in opioid dose was needed to maintain adequate pain control. Statistically significant increases were observed on a yearly basis from baseline up to year three, but the intrathecal opioid dose increase ceased to be significant from the third year onwards. Adjuvant intrathecal medication was added to 95% of the patients, which in conjunction with responsible follow-up treatment may have contributed to the low dose of intrathecal opioids administered. The addition of intrathecal bupivacaine has been effective in keeping a low intrathecal morphine dose in the treatment of cancer pain, as well as preventing the potential side effects of high doses of intrathecal morphine (Sjöberg et al.,
The average intrathecal dose throughout the duration of therapy of 3.93 mg/day was lower than previous reports. The highest average intrathecal opioid dose of 4.81 mg/day was observed at year 13. The opioid doses in this centre were lower than previously reported average doses of 7.42 mg/day at 29.14 months (Kumar, Kelly and Pirlot 2001); 9.6 mg/day at year one (Paice, Penn and Shott 1996), and 12.2 mg/day at year three (Atli et al., 2010). An approximate opioid dose of 4.7 mg/day has been reported, although at an average of 3.4 years (Winkelmüller and Winkelmüller 1996). Morphine doses may stabilize for long periods and when dose escalation occurs is usually due to tolerance, progress of the disease (Bennett et al., 2000) or opioid induced hyperalgesia (Angst and Clark 2006; Chu, Angst and Clark 2008). A failure to identify the occurrence of a granuloma can also lead to a possible diagnosis of tolerance (Bejjani, Karim and Tzortzidis 1997).

No significant differences or correlations were observed for the level of opioid dose and type of pain, pain intensity or percentage of clinical change. This is in conformity with previous studies (Kumar, Kelly and Pirlot 2001; Winkelmüller and Winkelmüller 1996).

An average of two pump replacements was verified in this sample. An important addition to the selection of intrathecal pump devices available would be the development of a rechargeable programmable pump. This could have the potential to reduce the number of replacement surgeries, thus increasing cost-effectiveness and reducing interference with the treatment plan.

It is important to note the limitations of this study. The sample size was relatively small and a control group was not included. For a last option treatment for severe pain it is challenging to find a comparative group, especially for a long-term study. Oral opioid medication was not collected from the notes. At RHH Pain Management Department rescue oral opioid medication has been provided to the patients on an individual basis for occasional flare-ups. The average duration of pain prior to IDDS was 9.63 years. Prior to implantation of IDDS all of these patients have tried and failed more conservative treatments, including oral opioid medication, with little or no benefit or unbearable side effects. The effective rescue medication dose is a fraction of the effective intrathecal dose. Hence, systemic medication, as well as other interventions that might have been undertaken during the study period, would have been sporadically provided to cope with flare-ups and would, therefore, have
limited impact in the results verified. Providing additional oral medication to patients may improve their psychological well being as well as an improvement in effective pain control; however there is no evidence of a correlation between reduction in pain intensity and the intake of additional oral medication (Kumar, Kelly and Pirlot 2001; Winkelmüller and Winkelmüller 1996).

3.6 Conclusion
Improvements were observed in sensory, sociological and psychological outcomes. These multidimensional benefits remained stable after 13.5 years of IDDS therapy, substantiating the effectiveness of IDDS therapy. In appropriately selected chronic non-malignant pain patients, IDDS has the potential to be a life-long solution and should be considered, as the advantages of IDDS clearly outweigh the disadvantages. Patients being considered for an IDDS should be informed of the potential side effects and complications derived from this therapy. When other pain management treatment options have been considered and failed, the age of the patient should not be an obstacle to IDDS as the rate of complications, side effects and the increase of opioid dose may not be substantial when compared with the possible benefits of this therapy. Long-term benefits from this treatment are not necessarily related to exaggerated intrathecal opioid doses. To our knowledge, this study represents one of the longest follow-up time spans reported in the IDDS literature.

The following chapter of this thesis evaluates the cost effectiveness of intrathecal drug delivery systems based on real patient data and investigates the existence of a period with potential impact in QALY analysis.
Chapter 4

Cost effectiveness of intrathecal drug delivery

Influence of a latent period in the cost effectiveness of intrathecal drug delivery systems for chronic non-malignant pain
This chapter has been published in the British Journal of Neurosurgery 2011;25(3):401-406 (appendix 11). Aspects of this work have been published as two separate abstracts in the journals Pain Practice (Appendix 12) and Regional Anesthesia & Pain Medicine (Appendix 13). It has been reformatted to fit with the overall PhD thesis.

4.1 Abstract

Background

Previous studies have considered IDDS to be a cost effective pain management therapy for chronic non-malignant pain. The period of time between being placed on a waiting list for IDDS and the implant (latent period) has not been taken into consideration for cost effectiveness analysis. The aim of this study was to investigate the influence of a latent (waiting) period when assessing cost effectiveness of IDDS.

Design

A retrospective longitudinal analysis of all pain related costs for a period of not less than four years was undertaken by assessment of medical records. The total cost of patient care for two years before latent period, the latent period itself and two years after the implant of an IDDS was computed, according to the NHS tariff. An EQ-5D questionnaire was completed by all participants before and after IDDS implant. Total costs were converted to cost per day for comparison with latent period.

Results

The sample consisted of five males and seven females with a mean age at the time of implant of 54 ± 10.59 years. The average duration of the latent period was 263 ± 176 days. The cost of conventional treatments during the pre-implant phase, excluding the latent period, was significantly higher (\(M=£5,005.86, SE=£918.56\)) compared with the costs of the same phase including the latent period (\(M=£4,086.35, SE=£959.09, t(11) = 2.23, p = 0.05, r = 0.56\)). The cost per day changed significantly over the different periods (\(\chi^2(2) = 24.00, p<0.05\)).

Conclusion

The variability and significantly inferior costs of the latent period may influence cost effectiveness evaluations and consequently decision making if not considered. Further
studies analysing the influence of a latent period on the cost effectiveness of other treatments are warranted.

4.2 Introduction

There are several forms of economic evaluation and it is important to define each of the possible methods. All the types of economic evaluations include a measurement of costs in monetary units. The differences occur in the measurement of the effects of a treatment, how this is reported and if the costs of an intervention are compared with an alternative (Table 4.1). A full economic evaluation compares two or more health interventions and considers both costs and effects; partial economic evaluations consider either costs and/or effects but do not involve a comparison with an alternative intervention or do not relate costs with effects (Drummond et al., 2005).

In cost minimisation analysis there is a comparison of two or more alternatives where the effect of the interventions is assumed to be equal; therefore the least costly is the more efficient. This differs from cost effectiveness analysis since this method does not assume the intervention effects to be equal. Consequences of different interventions are measured using a single outcome such as cost per pain-free day. Cost utility analysis is similar to cost effectiveness analysis except that the outcome is measured in utility measures such as quality adjusted life years. Cost utility analysis is the approach required by the National Institute for Health and Clinical Excellence (NICE) to determine the relative cost effectiveness of health interventions (Phillips 2009a). In cost benefit analysis, the total expected costs are weighed against the total expected benefits of an intervention, including return to work. Since all the costs and consequences or benefits are expressed in monetary units, this implies the estimation of monetary values associated to direct health benefits, such as pain relief, and indirect benefits, such as productivity gains.

Cost analysis or cost comparison, albeit considered partial economic evaluations, also compares an intervention with an alternative but does not take into account the effects. This type of economic evaluation is similar to cost minimisation analysis where the effects are not measured, but assumed to be the same. Cost description consists of an examination of the costs of a single intervention. Cost outcome description considers both costs and consequences but no comparison is made with an alternative intervention.
<table>
<thead>
<tr>
<th>Type of economic evaluation</th>
<th>Comparison with alternative intervention</th>
<th>Measurement of costs</th>
<th>Measurement of effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full economic evaluation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost minimisation analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>No - effects of intervention assumed to be equal</td>
</tr>
<tr>
<td>Cost effectiveness analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes - in natural units (e.g. cost per pain-free day)</td>
</tr>
<tr>
<td>Cost benefit analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes - in monetary units</td>
</tr>
<tr>
<td>Cost utility analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes - in utility measures (e.g. life years gained (LYG), quality adjusted life years (QALYs))</td>
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<tr>
<td>Partial economic evaluation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cost analysis / cost comparison</td>
<td>Yes</td>
<td>Yes</td>
<td>No - effects not measured</td>
</tr>
<tr>
<td>Cost description</td>
<td>No</td>
<td>Yes</td>
<td>No - effects not measured</td>
</tr>
<tr>
<td>Cost outcome description</td>
<td>No</td>
<td>Yes</td>
<td>Yes - in natural units (e.g. cost per pain-free day)</td>
</tr>
</tbody>
</table>
The cost effectiveness of a treatment is an important factor in decision making in the United Kingdom. The UK National Institute for Health and Clinical Excellence considers as acceptable cost effectiveness a range of £20,000-£30,000 per Quality Adjusted Life Year (QALY) (National Institute for Health and Clinical Excellence 2008).

Excluding the management of critical/emergency situations, most health care treatments involve an uneven waiting time for the patient between decision and procedure. During this stage, which was named as the ‘latent’ period, health care interventions may be absent as the patient is awaiting a determined treatment. The latent period was identified while working on the cost effectiveness of IDDS treatment for the management of chronic non-malignant pain. It was noticed that after a patient had undergone all the possible conventional treatments short of IDDS for pain management and the decision to use IDDS had been taken, changes were evident. At the point of being told that an IDDS was going to be implanted, both the attitude of the patient and the treating clinician changed. The patient was on a holding phase, a latent period.

There are limited patient based studies investigating the cost effectiveness of IDDS compared with more conventional therapies (Anderson, Burchiel and Cooke 2003; Kumar, Hunter and Demeria 2002). These studies limited the time horizon of the assessment of cost and outcome to that of the study. An alternative to this method is to use a computer-generated cohort of patients based on best and worst case scenarios (de Lissovoy et al., 1997; Hassenbusch et al., 1997). These studies extrapolate the cost and outcome findings to the lifetime of the patient. All these studies have considered IDDS to be cost effective.

None of the mentioned studies took into consideration the above-mentioned latent period. The objective of this study was to evaluate whether the latent period has a significant influence on QALY calculations and therefore the cost effectiveness analyses of IDDS.

4.3 Review of the literature
A hand search of reference lists of relevant articles and systematic reviews was carried out. Studies where an economic evaluation of IDD for the management of chronic non-malignant pain was completed were included in the review (Table 4.2). The effects and cost outcomes of the included studies are presented in Table 4.3.
Studies were excluded if both cancer pain patients and non-cancer pain patients were investigated without costs being differentiated between these conditions (Bedder, Burchiel and Larson 1991); the article was a review and not an economic assessment (Nguyen and Hassenbusch 2004); the article was a review article including a computer-generated model but for cancer pain patients (Hassenbusch et al., 1997); the article was a review including the results of two unpublished economic evaluations but did not provide enough detail (Mueller-Schwefe, Hassenbusch and Reig 1999). The economic evaluations reported in the Mueller-Schwefe, Hassenbusch and Reig (1999) review were not included in Table 4.2 or 4.3 because of lack of detail provided. Nevertheless, a synthesis of the analysis is presented below.

**Mueller-Schwefe, Hassenbusch and Reig (1999)**

This review of IDD cost effectiveness included two different cost analyses. A cost analysis comparing the costs of intrathecal pumps with oral morphine therapy was performed. The report comprised 12 IDD patients followed over a period between 10 to 14 years. The daily cost of intrathecal morphine therapy including the costs of surgery, the implantable system, morphine, refill kit and treatment was significantly less than the costs of oral morphine therapy. However, the costs of oral therapy were based on estimations.

The other cost analysis presented within this review compared intrathecal morphine and clonidine with an equivalent dose of sustained-release oral morphine. The analysis was based on estimates for both therapies and concluded that after one year of therapy, the cost of IDD was approximately one third that of oral medication therapy.

**de Lissovoy et al. (1997)**

A computer-generated model deriving cost calculations based on expected resource use and published diagnostic and therapeutic protocols was developed. A large (n = 1000) simulated cohort was projected throughout the estimated time span of the pump battery life (36 to 60 months). This model focused on chronic pain as a result of failed back surgery syndrome.
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<tr>
<td>Type of economic analysis</td>
<td>Cost effectiveness</td>
<td>Cost effectiveness *</td>
<td>Cost analysis</td>
</tr>
<tr>
<td>Indication</td>
<td>FBSS</td>
<td>FBSS</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>1000</td>
<td>67</td>
<td>40</td>
</tr>
<tr>
<td>Comparator</td>
<td>Conservative pain therapies</td>
<td>Conservative pain therapies</td>
<td>Epidural infusion</td>
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<tr>
<td>Study design</td>
<td>Modelling (based on previous studies)</td>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td>Follow up post implant</td>
<td>3 to 5 years</td>
<td>5 years</td>
<td>Selection trial only</td>
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<tr>
<td>Setting</td>
<td>Multi center</td>
<td>Single center</td>
<td>Single center</td>
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</table>

* The authors however did not relate the costs with the effects
A model can only be as good as the information used to create it. Taking into consideration that the authors created a model for the duration of a pump battery life between 36 to 60 months, it is important to verify the follow-up period of the studies used to obtain effectiveness and complications information. The rates of adverse events were based on three studies with the following average follow-up periods: one month (Hassenbusch et al. 1990), $14.6 \pm 0.57$ months (range 8 – 94 months) (Paice, Penn and Shott 1996) and 27.8

<table>
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<tr>
<td>Effects outcome</td>
<td>Effects were calculated only for IDD patients. These were based on 2 previous studies. Proportion of patients expected to obtain good to excellent pain relief were 0.73 (base case), 0.81 (best case) or 0.65 (worst case).</td>
<td>IDD patients presented a 5 year average improvement of 27% in disability, compared to the 12% reported by the conventional pain therapies group. The average 5 year pain relief score for IDD patients was $61 \pm 5.2%$. The authors did not relate the costs with the effects.</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Cost outcome</td>
<td>The cost of intrathecal therapy was less expensive in a base ($82.893) and best case scenarios ($53.468) when compared to alternative therapies ($85.186). In a worst case scenario ($125.102), the cost of IDD would be superior to alternative pain therapies. Incremental cost effectiveness ratios were also calculated for the possible scenarios. The cumulative cost of IDD would be less than alternative therapies after 11 months (best case) or 22 months (base case). In a worst case scenario the cost of IDD would always be superior to alternative therapies.</td>
<td>Break-even points for IDD to become less expensive occur at 26 months (best case), 28 months (base case) or 30 months (worst case). The costs of IDD were in any of the possible scenarios less than alternative therapies after the mentioned period.</td>
<td>The cost of trial with intrathecal injection ($1.862 \pm 546$) was significantly less ($p &lt; 0.0001$) when compared to epidural infusion ($4.762 \pm 508$).</td>
</tr>
</tbody>
</table>
months (range 5 – 47) (Krames and Lanning 1993). It was also noticed that one of the studies (Hassenbusch et al., 1990) was examining epidural and not intrathecal administration.

The effectiveness of IDD was assessed through the percentage of patients reporting good or excellent pain relief in two different studies. In one of the studies, 81% reported good to excellent pain relief (Krames and Lanning 1993), while in the other study only 65% of the patients reported the same amount of pain relief (Auld, Maki-Jokela and Murdoch 1985). The intraspinal route of delivery was epidural and not intrathecal in the Auld, Maki-Jokela and Murdoch (1985) study. Incremental cost ratios were calculated regarding a base case (average pain relief of the two studies), best case (Krames and Lanning 1993) and worst case (Auld, Maki-Jokela and Murdoch 1985).

Although it was stated that the model was focused on chronic intractable pain attributed to failed back surgery syndrome, none of the studies used to structure the model were exclusively exploring this condition.

Charges for alternative pain management therapies were defined for a 60-month period based on a representative pattern of care. The authors acknowledged the non-existence of published reports describing the history of patients with intractable pain or their health expenditures over time.

According to the developed model, in the base case scenario, the cumulative cost of IDD may be less than alternative pain management after 22 months; in the best case after 11 months; and in the worst case scenario alternative therapy would always be less expensive than IDD.

Kumar, Hunter and Demeria (2002)
A comparison of IDD with more conventional therapies was carried out using real patients with actual cost data; in contrast with the de Lissovoy et al. (1997) study which used a computer-generated model. The study sample consisted of 88 patients with chronic low back pain as a result of failed back surgery syndrome who did not obtain adequate pain relief during a SCS trial. The patients were randomly assigned into either an IDD trial group.
or conventional pain therapies group. The groups were initially equally distributed and matched for age, gender and number of operations undertaken prior to initiation of the study. The randomisation process is not clearly described by the authors. From the patients assigned to the IDD trial group, 21 patients were excluded from the study and did not proceed to IDD implantation due to poor response (pain relief < 50%), undesirable side effects or unwillingness to accept the procedure.

The authors used the Oswestry Disability Index (Fairbank and Pynsent 2000) and the VAS (Jensen, Karoly and Braver 1986) to measure effects of the therapies. The patients in the IDD group reported a five-year average improvement of 27% in disability, compared to the 12% reported by the conventional pain therapies group. The average five-year pain relief score as measured by the VAS was 61 ± 5.2%. No pain relief scores were presented for the patients in the conventional pain therapies group. In the abstract and methods it is stated that the impact of IDD on quality of life would be analysed prior to implantation and for each year subsequent to beginning of therapy. However, the authors did not relate the costs with the effects.

There are also some statements that may lead the reader to question if the five-year costs are actual costs or estimations. An example is the following statement: “costs of pharmacotherapy for each patient were calculated according to the Saskatchewan Health Formulary, allowing a predetermined government-approved pharmacist mark-up schedule and a flat rate for dispensing according to pharmaceutical standards. From this we calculated a monthly and subsequently yearly cost, which was then extrapolated to a five-year period” (Kumar, Hunter and Demeria 2002). Pump replacement costs can also be questioned. It seems that all patients only required one inpatient day stay for replacement when the authors justification for the 6.24 days average as inpatient for implantation was: “the length of hospitalisation in this province is longer because of its socialised pattern of medicine, sparse population, obliging the patient to travel up to 1,000 miles for this type of treatment, and lack of supportive infrastructure” (Kumar, Hunter and Demeria 2002).

The authors also mention that based on their experience with IDD patients, an escalation of the intrathecal medication dose would result in an increase in maintenance costs of $120 per year. However, in table 5 of the manuscript (Figure 4.1), years two, three, and four of IDD therapy are all reported to have a cost of $1,055 indicating a plateau and not an
increase of $120 per year. The non inclusion of trial costs is another limitation of this study as well as the lack of rationale for placing all the complications in the costs of year one or the pump replacements in the costs of year five, even though the authors reported replacements at year four both in best and worst case scenarios.


This study proposed to compare in a randomised, prospective manner, the safety and cost of continuous epidural infusion with intrathecal injection when employed during trial for IDD patient selection. Moreover, the authors tried to identify the prognostic value of intrathecal and epidural trial defined in terms of the proportion of patients in each group who had at least 50% pain relief following six months of IDD therapy. From the initial 86 consecutive patients, only 37 patients were enrolled in the study. Eighteen patients were excluded because details of psychological evaluation were not available at the time of screening; the surgical team planned to conduct the trial with opioids other than morphine (n = 4); the patient decided to pursue treatment options other than IDD (n = 4); the planned management of infusion system would be performed at a remote clinic (n = 2); the patient declined randomisation (n = 18); or coverage was refused by the insurer (n = 3).

For the trial to be considered successful, at least 50% pain relief was required on two consecutive ratings using a 0-10 numerical analogue scale. Six patients had failed intrathecal injection trial and four patients failed epidural infusion trial, resulting in 27 patients that proceeded to IDD implantation. Three of these patients did not provide complete study data during the six months of study period.
Follow-up data was collected at three and six months after implantation of IDD and patients were asked to rate the extent of pain relief, present pain and perceived benefit on a scale of zero (worst) to five (best). Patients were asked to record the systemic medication use at each follow-up, quantify health care use and to rate the severity of common opioid related side effects on a scale of zero (none) to three (severe). There were no significant differences in outcome following implantation between the trial groups.

The economic evaluation of this study consisted of a comparison of the costs of intrathecal injection with epidural infusion. The costs of the trial with epidural infusion were significantly higher than that required for the intrathecal injection trial with no difference observed in the outcome at the six month follow-up.

4.4 Methods

Subjects
Twelve consecutive patients who filled the EQ-5D before and one year after having an IDDS fitted for chronic non-malignant pain relief at RHH. All patients were selected from the same pain management department. Informed consent was obtained from the patients to examine their hospital records and GP notes throughout the identified study period.

Data collection
Information previous to decision for IDDS surgery, latent period (which varied in length from patient to patient) and after IDDS implant was assembled, allowing for a study period of at least four years. GP notes were screened and taken into consideration to be included in the analysis; however, due to difficulties in identifying which treatments/medications prescribed were related to the pain pathology, these costs were excluded.

After identifying the implant date for each patient, the date they were informed of suitability for IDDS implant and placed on the waiting list (taken to be the same date and in most cases recorded as such) was verified. A two year period prior to the date they were informed of the implant was then established as well as a period of two years after the date of the implant. The period of time between being placed on the waiting list and the date of the
The actual implant was identified as the latent period. Cost effectiveness of IDDS was assessed using the period before implant both including and excluding the latent period. Within each period of study, for each patient, all operative and injection treatments, investigations, drugs and consultations related to pain management were identified. Drugs were costed in agreement with the British National Formulary (BNF) 57 (Joint Formulary Committee 2009). Treatments and appointments were checked against the RHH Finance Department records for accuracy and then costed according to the NHS tariff using Health Resource Group (HRG) codes for the year 2009. All prices were adjusted to their value in the year 2009 and estimated using British Pounds Sterling.

The total costs for each identified period were calculated. As the latent period varied from patient to patient, the costs were converted to an average daily cost for the purpose of comparison of the latent period with the pre and post IDDS implant periods.

**EQ-5D and QALY**

Each patient had filled in an EQ-5D questionnaire prior to the IDDS being implanted. The patients then repeated this exercise with a second EQ-5D questionnaire one year after the IDDS was fitted. This allowed for a comparison to be made regarding the patient's perceived health state before and after the implantation of the IDDS.

The EQ-5D questionnaire is a validated measure of the outcome of health care and is applicable to a wide range of health conditions (Rabin and de Charro 2001). It is designed to complement condition specific measures and allows the collection of data for comparative purposes. It provides both a compact, descriptive profile and a single index value which may be used in the calculation of clinical and economic health care. The EQ-5D allows a self-description of health related quality of life to be recorded (Rabin and de Charro 2001).

The QALY is an outcome measure that takes into account, both the quantity and quality of the extra life provided by a healthcare intervention. It is the numerical, arithmetic product of the life expectancy and also the quality of life for the remaining years. The quantity is fairly easy to calculate but the quality, which is much more difficult to assess, can be measured by quality of life questionnaires such as the EQ-5D. The cost per QALY allows for different treatments to be compared and measured in a common unit.
Data analysis
The Kolmogorov-Smirnov test was performed to test normality of numerical data. EQ-5D data was compared using Wilcoxon’s Signed Rank Test. The analysis of cost data should be carried out with either parametric (if the data is normally distributed) or bootstrapping methods (Thompson and Barber 2000). The mean costs of treatment pre-implant (including latent period) and pre-implant (excluding latent period) were compared by using Student’s \( t \) test and standard confidence intervals. As the data was not normally distributed, these results were analysed with a non-parametric bootstrap method (Thompson and Barber 2000). All confidence intervals were estimated at the 95% level with bias corrected and accelerated.

In order to allow comparison of pre-implant and post implant with the latent period, all values were converted to a cost per day and initially compared using Friedman’s ANOVA. A Bonferroni correction was used with \( p \leq 0.016 \) considered as significant for comparisons between the three different periods and Student’s \( t \) test with non-parametric bootstrap carried out. Statistical significance represented \( p \leq 0.05 \) except when otherwise mentioned. Statistical tests were performed using the Predictive Analytics Software (PASW) (version 18.0, SPSS Inc., Chicago, IL, USA).

4.5 Results
The sample was comprised of seven females (58.3%) and five males (41.7%) with a mean age at time of implant of 54 ± 10.59 years (range 41-71). The average duration of painful symptoms prior to implant was 14 ± 6.6 years (range 4-23). The mean duration of the latent period was 263 ± 176 days (range 3-489).

The mean EQ-5D value prior to IDDS was 0.3341 ± 0.1763 (range 0.1-0.7) and following implant was 0.6458 ± 0.1389 (range 0.4-0.8). EQ-5D levels were significantly higher subsequent to IDDS implant (Mdn = 0.675) than before implant (Mdn = 0.300), \( z=-2.907, p < 0.005, r = -0.59 \) (Figure 4.2).

The mean cost per year of conventional treatments prior to the latent period (pre-implant 1) with 95% confidence intervals was £5,005.86 (£3,384.04-£6,924.88); the mean cost per year of conventional treatments including the latent period (pre-implant 2) was £4,086.35.
(£2,331.51-£6,282.71); for the initial two years, the mean cost per year of IDDS, was £13,134.85 (£10,778.82-£15,726.56).

Table 4.4 shows that IDDS treatment, including implant, costs £8,128.99 more than conventional treatments but results in an extra 0.3117 QALYs, the equivalent to 114 days of perfect health.

Figure 4.2 Patients assessment of own health state prior and post IDD

<table>
<thead>
<tr>
<th></th>
<th>Pre-implant</th>
<th>Post-implant</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean costs of treatment (£)</td>
<td>£5,005.86</td>
<td>£13,134.85</td>
<td>£8,128.99</td>
</tr>
<tr>
<td>Mean QALY</td>
<td>0.3341</td>
<td>0.6458</td>
<td>0.3117</td>
</tr>
<tr>
<td>Average cost per QALY (£)</td>
<td>£14,983.11</td>
<td>£20,338.88</td>
<td></td>
</tr>
<tr>
<td>Incremental cost per QALY of conventional treatments versus IDD</td>
<td></td>
<td></td>
<td>£26,079.54</td>
</tr>
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</table>
The extra cost to gain one additional QALY, or in other words, the incremental cost per QALY for IDDS versus conventional treatments, not including the latent period, is £26,079.54.

Using the same process including the latent period, it is possible to observe that the average cost per QALY of conventional management of pain decreases, and as a result the difference and the incremental cost per QALY of IDDS versus more conservative treatments increases (Table 4.5).

| Table 4.5 Comparison of conventional treatments (including latent period) versus IDD |
|----------------------------------|-------------|-------------|-------------|
| Mean costs of treatment (£)      | Pre-implant 2 | Post-implant | Difference  |
| Mean QALY                         | 0.3341      | 0.6458      | 0.3117      |
| Average cost per QALY (£)         | £12,230.92  | £20,338.88  |             |
| Incremental cost per QALY of conventional treatments versus IDD |             |             | £29,029.52  |

On average, the cost of conventional treatments during the pre-implant phase excluding the latent period (pre-implant 1) was significantly higher \((M = £5,005.86, \ SE = £918.56)\) compared with the costs of the same phase including the latent period (pre-implant 2) \((M = £4,086.35, \ SE = £959.09, t (11) = 2.23, p = 0.05, r = 0.56)\).

The mean cost per day of conventional treatments (pre-implant 1) with 95% confidence intervals was £13.71 (£9.36-£18.77), for the plateau period was £1 (£0.42-£1.69) and for the post-implant was £35.99 (£29.26-£43.69).

The cost per day changed significantly over the different periods \((\chi^2(2) = 24.00, p < 0.05)\) (Figure 4.3).

Student’s \(t\) tests with non-parametric bootstrap were used to follow up this finding. A Bonferroni correction was applied, so all effects are reported at a 0.0167 level of significance (Table 4.6).
The cost per day changed significantly from pre-implant to latent period, from pre-implant to post-implant and from latent period to post implant.
4.6 Discussion

The cost effectiveness of IDDS was attested even when the latent period (where costs are significantly lessened) was not taken into consideration. However, if the duration of the latent period had been longer for some patients, the cost effectiveness range of £20,000-£30,000 per QALY considered by NICE as acceptable would have been surpassed.

Cost effectiveness was confirmed at a two year follow-up, including all the resultant costs of surgery and intrathecal pump. IDDS has shown to have inferior cumulative costs compared to conventional pain treatments for failed back syndrome during a five-year period (Kumar, Hunter and Demeria 2002). Following the high initial cost of equipment required for IDDS treatment, conservative treatments became more expensive during the follow-up period (Kumar, Hunter and Demeria 2002).

Although in this study the average cost per QALY was superior for IDDS treatment it did result in an extra 114 days of perfect health. The significant differences verified in the EQ-5D values demonstrate that the patients receiving IDDS perceive an improvement in their health state when compared to the period where more conventional treatments were administered. One of the most significant comparisons was that of the QALY cost with the latent period included for each patient against the QALY cost with the latent period removed, showing the effect of the latent period on any subsequent QALY calculations. QALYs provide an indication of the benefits gained from medical procedures, in terms of quality of life, however, suffers from a lack of sensitivity when comparing the efficacy of two similar drugs and in the treatment of less severe health problems (Phillips 2009b).

Long-term psychosocial benefits have been reported in the literature (Raphael et al., 2002; Winkelmüller and Winkelmüller 1996). Change in work status however, may not change. Retired individuals or patients who have been off work for more than three years prior to IDDS are unlikely to return to work regardless of pain relief (Anderson and Burchiel 1999; Kumar, Kelly and Pirlot 2001; Paice, Penn and Shott 1996).

The inclusion of GP costs would only increase the value of the costs prior to implant. After IDDS implantation all pain related treatments would be acknowledged in the hospital records, whose costs were all taken into account. Including GP costs in the analysis would increase the cost effectiveness of IDDS. The majority of medication used for pain
management purposes is relatively inexpensive. There are however some exceptions. Considering these exceptions, in the event that even half of the sample was undertaking expensive analgesic medication, this would have a significant impact on the costs pre-treatment, therefore further increasing the cost-effectiveness of IDDS.

The confirmation of statistically significant differences between the costs prior to implantation including and excluding the latent period, and the changes between pre-implant, latent and post-implant further corroborates the importance of taking this time span into consideration for cost-analysis purposes. One of the main reasons for extended latent periods is concerned with difficulties securing funding in the NHS. This situation can differ between Primary Care Trusts and thus pain clinic centres, according to budgetary restrictions.

The patient, following a successful intrathecal catheter trial, knows whether an effective pain relief mechanism has been found for them. This may be, and often is, the culmination of years of unsuccessful treatment, which at last has led to an effective pain relief. The patient now knows that effective pain relief is possible. They also know that it is just a matter of time before it is made available to them, their place being assured on a waiting list. The ability to cope with pain when the prospect is for a limited time only, instead of being the normal and unending situation, increases in the patient dramatically. The clinician has now to a certain extent ‘solved’ that particular patient’s problem by finding an effective method of pain relief and management for them. They can now move on to other problems, leaving the patient in a ‘holding phase’ or ‘latent period’ during which time the next most effective pain relief is provided, often in a higher dose and as a stop gap until the IDDS is implanted. When cost effectiveness is calculated, this latent period must be identified for each patient and dealt with if it is not to unduly influence the costs and resultant QALY calculations. In a recent randomised controlled trial (RCT) analysing the placebo effect where one of the arms consisted of patients on the waiting list, it was noticed that these showed improvement at three week follow-up (Kaptchuk et al., 2008).

This study was based on hospital records where all procedures taking place during the study period were documented, contrary to the de Lissovoy et al. (1997) hypothetical computer-generated cohorts of patients. This study also concluded that despite the initial cost of equipment, IDDS has long-term benefits. Computer-generated models are useful tools for
policy and decision making, however, these are only as good as the information inserted to generate the model.

A limitation of this study was the small single centre sample size and not being a RCT. In recent systematic reviews, no IDDS randomized trials met the authors' inclusion criteria, meaning there were no RCTs with IDDS or the quality of the available RCTs was poor (Hayek et al., 2011; Noble et al., 2010; Patel et al. 2009). One of the difficulties in performing RCTs with this therapy concerns the moral and ethical considerations that what a patient is submitted to is acceptable.

These results merit further investigation as they cannot be generalised since the period of time the patient can be held in a latent stage can be variable across different centres' nevertheless they should be taken into consideration if even slightly different per patient. Leaving a patient waiting for treatment does not confer any economic advantage, but can influence a cost-effectiveness analysis.

The use of the EQ-5D at some point in the latent period would allow verification of how patients perceive their health state during this waiting time.

4.7 Conclusion
This study allowed a comparison between two moments, prior to and following IDDS implant, of suitable candidates for IDDS who went through an analogous progression until IDDS treatment.

IDDS offers an economically feasible alternative solution for chronic non-malignant pain patients whose current treatment is inappropriate or ineffective. Assessments of the cost effectiveness of a health care treatment should take into consideration the existence of a latent period since this may influence not only cost efficacy evaluations but also decisions to go through with a treatment. The latent period can influence cost effectiveness analysis as analyses not considering this holding phase will make a treatment appear to be less cost effective. Since the latent stage would be included in a pre-therapy period and its costs per day are relatively low, this would overall decrease the pre-therapy total costs and the longer the duration the higher impact it would have. Further studies need to be carried out to
confirm whether differences between pre-implant and the latent period occur, particularly in other health care procedures where there is an asymmetrical waiting time between decision and treatment.
Chapter 5

Conclusion

Findings and clinical implications

Future research

Conclusions
This evaluation of intrathecal drug delivery for the management of chronic non-malignant pain is limited by the sample being derived from a single centre and the number of participants included in each of the studies. This process was invaluable to further the researcher’s knowledge and skills. An understanding of research methods, ethics in research, assessment of scientific articles and statistical approaches was acquired during the course of this PhD. Despite the findings and clinical implications of this thesis, the understanding gained during this process allows the researcher to acknowledge that this study could be have enhanced by the addition of more national or international centres providing this therapy. Besides the additional patients, this factor would allow some of the results to be more relevant to other pain management centres administrating intrathecal drug delivery for chronic non-malignant pain. The findings and clinical implications of this study, and recommendations for future research are further developed in this chapter.

5.1. Findings and clinical implications

The possibility of prediction of the opioid dose at year six.

The development of a model accounting for 76% of the variability of the opioid dose at year six based on the dose of year two combined with duration of pain prior to initiation of intrathecal therapy was developed. This has significant clinical implications. This model has the potential to assist the physician in the identification of a need for an alternative treatment strategy (Figure 5.1). Moreover, since many of the pump replacements are performed prior to year six, it can assist in the informed decision of the benefits and risks of the maintenance of this therapy prior to replacement surgery.

A novel tool to identify asymptomatic intrathecal granulomas.

Through calculation of the opioid dose increase per year throughout the duration of treatment, a clinical change may be detected. The formation of intrathecal inflammatory masses is one of the most hazardous adverse events of IDD because this can form a space-occupying lesion within the spinal canal causing spinal cord compression and neurological deficit. If asymptomatic and not recognised by the physician, the patient can perceive a decrease in pain relief which can be diagnosed as tolerance, leading to increases in opioid dose. The calculation of the yearly opioid change is a potentially useful and inexpensive method of early detection of clinical change and possibly identification of asymptomatic intrathecal granulomas.
An association between intrathecal granulomas and opioid concentration was established for the first time in humans.

This thesis presents the first systematic review of case reports describing the development of catheter tip intrathecal inflammatory masses. The comparison of the extracted data with a control group meant that it was possible, for the first time, to statistically confirm the association between concentration and the formation of granulomas in humans. This association had been inferred but never confirmed in human studies. Opioid dose and concentration are both associated with the formation of intrathecal inflammatory masses. The relative risk of occurrence of these masses can potentially be halved through a reduction of the opioid dose and concentration from the currently recommended maxima of 15mg/day and 20 mg/mL to 10mg/day and 15mg/mL respectively.

Prevalence of hypogonadism based on free testosterone assessment.

It was verified that hypogonadism is common in patients undertaking IDD therapy for the management of chronic non-malignant pain. The hypothalamic-pituitary-gonadal axis should be routinely monitored in patients undertaking intrathecal opioid administration from the start of therapy. This is the first study with IDD patients that also used Vermeulens’ calculated free testosterone as a diagnostic tool. The calculation of free testosterone seemed to be a more reliable measure than the free androgen index. Assessment of the hypothalamic-pituitary-gonadal axis should include evaluation of total testosterone, free testosterone or bioavailable testosterone, LH and FSH. Moreover, the early detection of hypogonadism, followed by appropriate treatment, may be paramount to reduce the risk of developing other complications such as muscle atrophy, anaemia, cognitive impairment, type two diabetes and cardiovascular risk.
5.1 IDD treatment diagram to help prevent some of the potential side effects explored in this study

* A cut-off increase was not possible to determine in this study but a rapid increase can be indicative of development of an intrathecal inflammatory mass

** Lifestyle advice includes exercise, daily calcium / vitamin D supplements, ensuring safe levels of alcohol consumption and not smoking
An association between hypogonadism and low bone mass density as a result of IDD delivery was reported for the first time.

An association between hypogonadism and low bone mass density in patients undertaking intrathecal opioid delivery for the management of chronic non-malignant pain was observed. This is the first study reporting the incidence of low bone mass density in hypogonadal IDD patients. Surveillance of BMD levels in hypogonadal intrathecal opioid delivery patients should be performed followed by appropriate treatment to reduce the risk of osteoporosis development and prevention of fractures in this population.

A study with the longest follow-up time span reported in the IDDS literature investigating the outcomes of this treatment was carried out.

The currently available literature investigating the long-term outcomes of IDD has a maximum average follow-up time of four years. This study represents the longest follow-up time span reported in the IDDS literature with an average follow-up of 13.5 years (range 10.4-17.9). This study is particularly pertinent as it is very common for chronic non-malignant pain patients to require pain management treatment for the remainder of their lives. This study demonstrates that IDD has the potential to be a life-long solution for the management of chronic non-malignant pain and that potential benefits can remain stable even during long-term administration.

A new important concept with influence on cost effectiveness analysis was identified.

The cost-effectiveness of IDDS for the management of chronic non-malignant pain based on real patients' data was confirmed. Moreover, this study allowed the identification of a latent stage, which may affect the cost effectiveness analyses when patient information is collected prior and post administration of a therapy. The variability and significantly inferior costs of the latent period may influence cost effectiveness evaluations, and consequently decision making, if not considered.

5.2 Future research

Prediction of opioid dose escalation

Since intrathecal opioid therapy strategies differ across pain management centres, the morphine dose model developed needs to be tested to confirm its applicability to other centres. A large, international, multicentre study could have the potential to develop a model.
applicable to the majority of centres where intrathecal drug delivery therapy is administered. Besides observation of opioid dose increase, the assembly of periodical pain ratings alongside additional oral medication could provide valuable information to the discussion of tolerance in humans undertaking long-term opioid therapy.

*Intrathecal granulomas*
A larger, multi centre data set has the potential to provide additional information regarding the formation of intrathecal inflammatory masses. A study with this design would facilitate investigation of other hypotheses as to the aetiology of granulomas, including dose and concentration of other intrathecal agents, flow rate, catheter tip design and location. It could also provide clarification of the potential preventive role of clonidine. When collecting the data regarding the dose, concentration and flow rate, mean values should be sought. This information would be more representative of the treatment period than peak values of dose, concentration and flow rate.

*Hormonal effects*
It would be of interest to investigate the impact of decreased sex hormones on pain levels. It has previously been suggested that reduced libido may be linked with a lower pain threshold. The confirmation of this link would mean that besides opioid induced hyperalgesia, pharmacological tolerance or deterioration of a patient’s condition, the hypothalamic-pituitary-gonadal axis could also play a role in the escalation of the opioid dose. Investigation of this axis should also be carried out in female IDD patients.

*Bone mineral density*
Longitudinal studies investigating the predictive value of hypogonadism for fracture risk in patients undertaking intrathecal drug delivery are required. The assessment of bone mineral density alongside evaluation of the hypothalamic-pituitary-gonadal axis prior to start of intrathecal opioid therapy and further assessments throughout therapy could indicate if low BMD can be a direct consequence of opioid delivery or a consequence of hypogonadism. Investigation of BMD should also be carried out in female IDD patients.

*Long-term effectiveness of IDDS*
A longitudinal study with prospective collection of data prior to implantation of IDDS could provide confirmation of the long-term effectiveness of intrathecal drug delivery. A
randomised controlled trial of IDDS has been carried out for cancer pain (Smith et al., 2002). This study reported improvement in pain scores, reduced toxicity scores and improved survival for those patients undertaking IDD. An adequately powered randomised controlled trial for chronic non-malignant patients would be of substantial value to the IDD therapy and literature.

Cost effectiveness
Studies analysing the cost effectiveness of health related treatments where a waiting period is frequent are warranted to confirm the presence of a latent stage. Investigation of patients' perception and quality of life during this period would also be of value.

5.3 Conclusions
In appropriately selected patients IDDS may have the potential to be a life-long solution for the management of chronic non-malignant pain. The advantages of this therapy clearly outweigh the disadvantages. The multidimensional benefits remained stable even following 13.5 years of IDDS therapy, substantiating the effectiveness of IDDS therapy.

Patients being considered for an IDDS should always be informed of the potential side effects and complications derived from this therapy. When other pain management treatment options have been considered and failed, age of the patient should not be an obstacle to IDDS as the rate of complications, side effects and the increase of opioid dose may not be substantial when compared with the possible benefits of this therapy.

The long-term benefits from this treatment are not necessarily related with exaggerated intrathecal opioid doses. The intrathecal opioid dose increase observed throughout the years was modest. Therapy strategies differ across treatment centres and can explain much of the variation in intrathecal opioid dose administered and escalation. Nevertheless, concerns about development of tolerance do not seem to justify the delay or withholding of intrathecal opioid therapy for chronic non-malignant pain.

It is extremely important to monitor dose escalation as it may be indicative of the formation of intrathecal inflammatory masses. Both dose and concentration of opioids contribute to the formation of granulomas. The calculation of the opioid dose increase per year throughout
treatment can indicate a clinical change and, therefore, facilitate the early detection of asymptomatic intrathecal inflammatory masses, consequently decreasing the possible side effects of this complication for the patient. The association between opioid concentration and formation of granulomas was confirmed for the first time in humans.

Hypogonadism is common in patients undertaking IDD therapy for the management of chronic non-malignant pain. For assessment of this complication, calculated free testosterone or bioavailable testosterone are more reliable than calculation of the free androgen index. Hypogonadism is also a risk factor for the decrease in bone mass density. A high prevalence of low bone mass density in hypogonadal patients undertaking intrathecal opioid delivery for the management of chronic non-malignant pain was observed.

Despite the high initial cost, which is frequently a reason for not providing this treatment, it was confirmed that IDDS is a cost effective therapy for the management of chronic non-malignant pain. IDDS offers an economically feasible alternative solution for chronic non-malignant pain patients whose current treatment is inappropriate or ineffective.

This thorough study of intrathecal drug delivery presents a wide evaluation of this therapy with its scope encompassing the long-term effectiveness, cost effectiveness and assessment of several adverse events of this treatment. This study demonstrates the long-term effectiveness and cost effectiveness of IDDS. Adequate and thoughtful follow-ups have the potential to prevent the development of the majority of complications derived from this therapy.

Intrathecal drug delivery for the management of chronic pain of non-malignant origin represents a treatment where numerous pre-conceived ideas still exist. These pre-conceptions subsist not only in the general population but also in medical staff and funding providers. Consequently, intrathecal drug delivery also represents a challenging area of study that merits further exploration and is one that can benefit from new knowledge.
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Appendices