Taking a Systems Neuroscience Approach to Persistent Postsurgical Pain:

Mechanisms, Prediction Tools and Preventive Strategies

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Acknowledgments and Statement of Originality

All the work presented in this thesis is my own but I am incredibly grateful to the following people for their generous support throughout my studies:

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Statement of Originality (as per the University of London guidance)

I, Sibtain Anwar, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged above and my contribution indicated. Previously published material is also acknowledged below.

I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

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I would also like to acknowledge and thank the European Association of Cardiothoracic Anaesthesiologists (EACTA) for their generous financial support in the form of the annual research grant, awarded in 2012.

Abstract

Background: Persistent postsurgical pain (PPP) is an increasingly recognised complication of surgery. Various putative risk factors have been identified over the last ten years. However the prevention of this phenomenon has proven difficult. I studied PPP following cardiac surgery to identify both means of prediction and prevention.

Methods: With ethics committee approval, I followed up 312 patients undergoing cardiac surgery over a six-month period in our hospitals. This established pilot data and allowed power calculation for the following prospective studies:

1. Randomised controlled trial (RCT) of pregabalin alone (P) or pregabalin combined with ketamine (PK), as compared to usual care (UC) for the prevention of PPP.

2. Quantitative Sensory testing before and after surgery, to identify central nervous system changes predictive of PPP, as well as any protective effect of P and PK in the active arms. Patients were risk stratified into vulnerable and resilient phenotypes, with the use of dynamic pain assessments of Conditioned Pain Modulation (CPM), Temporal Summation (TS) and Zone of Hyperalgesia (ZoH.)

Results: In the observational pilot cohort, 39.7% of patients described PPP following elective first-time cardiac surgery. The age of the patient, duration of surgery and acute pain during the recovery period all seemed to act as strong predictors for the development of PPP in this cohort study.

In the prospective RCT, pregabalin was protective for future PPP. The study demonstrated a significant improvement in PPP; OR= 0.11 and 0.046, for groups P and PK respectively at three months, as compared to the UC group. The addition of ketamine to pregabalin, as part of a multimodal regimen, had no significant effect on PPP outcomes in this trial.

Tolerability of both drugs on the first day of treatment was an issue. As an example, NNH (Number Needed to Harm) for diplopia was equal to 6.3 and 4.5, in P and PK respectively. This failed to impact on recovery, however, with improvements in median length of stay of 1 and 1.5 days respectively (p=0.023 and 0.002.)

The powerful and protective effects of pregabalin in the perioperative period are demonstrated by:

1. Increases in pressure pain threshold (PPT) at a site *remote* to the incision
2. Prevention of the development of new TS
3. Reduction in the zone of peri-incisional hyperalgesia

The likelihood of developing PPP in any cardiac surgical patient may be predicted by a combination of the following perioperative risk factors:

1. Perioperative QST markers of new TS and increased ZoH, at the site of surgical incision, as well as decreased PPT remote to the incision.
2. Inefficiency of CPM
3. Poor preoperative quality of life, measured with EQ-5D
4. Increased levels of state anxiety and catastrophising
5. Young age
6. Surgical risk factors of increased duration of surgery and poorly managed acute pain - but not surgical technique and extent of dissection.

<u>Conclusion:</u> This study suggests a potential to risk-stratify cardiac surgery patients and allow targeted preventive intervention for PPP.

Lay Abstract (Press Release at the ASA Annual Scientific Meeting 2013)

Also available at http://www.asahq.org/painaftercardiacsurgery

Persistent pain following cardiac surgery can be predicted and reduced

10.13.13

The incidence of chronic pain following cardiac surgery can be reduced in patients when the drug pregabalin is used before surgery and for 14 days post-surgery, according to a study presented at the ANESTHESIOLOGY™ 2013 annual meeting. The study also found that patients at risk of developing long-term post-operative persistent pain could be predicted by conducting pain sensitivity tests at the time of surgery.

“Heart disease can be painful and disabling; however, heart surgery to treat the disease often leaves patients with a new persistent pain around the incision site, which can be equally disabling and burdensome,” said Sibtain Anwar, M.B., M.A., F.R.C.A., research fellow at Barts and the London School of Medicine and Dentistry, England. “In the study we discovered a way to identify patients at risk for developing persistent postsurgical pain, as well as to prevent it with a regimen of pregabalin.”

In this double-blind, randomized and controlled study, 150 patients scheduled for elective cardiac surgery were divided into three groups. The first group received pregabalin preoperatively and for 14 days following surgery. The second group received the same regimen of pregabalin as the first group, plus an infusion of ketamine for 48 hours after surgery. The third group received an entirely placebo-based regimen. All other surgical and anesthetic care was unchanged and included patient controlled morphine following surgery.

Before and after surgery, quantitative sensory testing of the patients' nervous systems was performed. This was based on the idea that the nervous system response to the experimental pain in the laboratory may give insight into how it will respond to subsequent surgical pain. One technique involved inducing pain by applying measured pressure at four points on the chest, followed by a second "distracting" pain in the arm with the use of a very tight blood pressure cuff. Measuring a person's change in pain sensitivity before and after the distracting arm pain, as well as before and after surgery, predicted whether they would develop pain that persisted many months later, the study found.

The study also found that using pregabalin reduced the incidence of persistent postsurgical pain to 10 percent and 8 percent of the patients at three and six months, respectively. The incidence of pain in the placebo group was 50 percent at three months and 46 percent at six months. The addition of ketamine for the second group did not significantly affect pain after surgery, the study found.

This study demonstrated that an individual's psychology is also important. "Interestingly, a patient's anxiety and worry about the procedure in the days leading up to the surgery had a direct and independent effect on his or her acute and persistent postsurgical pain. Positive thoughts and attitude about pain in general improved long-term pain outcomes," explained Dr. Anwar. This observation has the potential to help doctors identify vulnerable individuals prior to surgery and to allow informed consent and discussion regarding risk of chronic pain.

Chronic pain following cardiac surgery is a serious side effect of the curative surgery. The prevalence of chronic pain after cardiac surgery ranges from 11 to 56 percent. More than 500,000 heart surgeries are performed in the United States each year, according to the National Heart, Lung and Blood Institute.

Prizes and Awards Related to This Thesis

- Australian Pain Society Annual Scientific Meeting Free Paper Award 2012

- European Association of Cardiothoracic Anesthesiologists (EACTA) Annual Research Grant 2012

- Invited oral presentation to the EACTA Annual Scientific Meeting 2013

- American Pain Society Young Investigator Award 2013

- Rising Star in Anaesthesia, Critical Care and Pain Medicine: Invited oral presentation at the National Institute of Academic Anaesthesia and the Royal College of Anaesthetists Jubilee Symposium 2013

- Association of Cardiothoracic Anaesthetists Annual Research Prize 2014

- International Association for the Study of Pain Travel Award for three research presentations at the World Congress on Pain Buenos Aires 2014

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List of Abbreviations

%	Percentage
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ASA	American Society of Anesthesiologists
B	Logistic regression derived coefficient
BD	Twice daily
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CNS	Central Nervous System
CPB	Cardio-Pulmonary Bypass
CPM	Conditioned Pain Modulation
CPEX	Cardiopulmonary exercise testing
CS	Central Sensitisation
DFNS	German Research Network on Neuropathic Pain
DNIC	Diffuse Noxious Inhibitory Control
EACTA	European Association of Cardiothoracic Anaesthesiologists
eGFR	estimated Glomerular Filtration Rate
EQ-5D	EuroQol score with 5 Dimensions
IASP	International Association for the Study of Pain
IBM	International Business Machines
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ITT	Intention to Treat
KPa	Kilo Pascal
LIMA	Left Internal Mammary Artery
LOS	Length of Stay
MHRA	Medicines and Healthcare products Regulatory Agency
NIH	Nociception Induced Hyperalgesia
NMDA	N-methyl- D- aspartate receptor
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NRS	Numerical Rating Scale
OIH	Opioid Induced Hyperalgesia
OR	Odds ratio
P	Pregabalin (arm of clinical trial)
PAG	Periaqueductal grey
PAN	Primary Afferent Neuron
PCA	Patient Controlled Analgesia
PCS	Pain Catastrophising Scale
PK	Pregabalin and ketamine combined (arm of clinical trial)
PNS	Peripheral nervous System
PPP	Persistent Postsurgical Pain
PPT	Pressure Pain Threshold

PVB	Paravertebral block
QST	Quantitative Sensory Testing
RA	Regional Anaesthesia
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RVM	Rostral Ventromedial Medulla
S-LANSS	Self report Leeds Assessment of Neuropathic Symptoms and Signs
SD	Standard Deviation
SAP	Statistical Analysis Plan
SPSS	Statistical Package for the Social Sciences
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEA	Thoracic Epidural Analgesia
TKR	Total Knee Replacement
TPT	Tactile Pain Threshold
TRPV	Transient Receptor Potential channel for Vanilloid
TS	Temporal Summation
UC	Usual Care (arm of clinical trial)
UK	United Kingdom
VAS	Visual Analogue Scale
VATS	Video Assisted Thoracoscopic Surgery
VFH	Von Frey Hair
WDR	Wide Dynamic Range
WUR	Wind Up Ratio

Chapter 1 Introduction

1.1 Overview and opening remarks

Pain after surgery is common and expected. Patients may undergo surgery to treat pre-existing pain or present pain-free to the hospital, and experience it postoperatively. In both cases, pain pathways are activated leading to acute pain. Patients expect this discomfort or pain to be short lasting (1). The management of acute pain is important, not only for comfort during recovery, but also to facilitate early rehabilitation (2, 3).

In the majority of cases, acute postsurgical pain is treated well and does not return. In some cases this recovery is not seen and pain persists beyond the expected duration of tissue healing. This duration to allow a diagnosis of persistence of pain is not clear in the literature, and can vary from two to three months, or even to six months and beyond.

Persistent pain could represent a worse tissue injury at the time of surgery leading to difficulty in managing pain in the immediate postoperative period and with changes persisting beyond the expected duration of tissue healing. Historically, this has been attributed to surgical technique and inadvertent intraoperative nerve damage but evidence is gathering that nerve-sparing technique may not make a significant difference to long-term pain outcomes (4).

The evidence suggests a smaller incision and less invasive techniques may improve analgesia in the recovery period. However the translation of this improved analgesia into lower prevalence of persistent postsurgical pain (PPP) is only seen in some procedures and certainly not all types of surgery (5, 6).

Patient related factors are also important. Age plays a significant role in the risk of developing PPP (7), whereas other factors such as gender and patient psychology are less clear, in terms of their contribution to the risk of developing persistent pain. Acute pain following surgery is the most consistent predictor of subsequent PPP (8)

Past experiences of pain may predispose an individual to PPP. The pain experience is shaped by the effects of pre-existing pain - from local disease or other remote sites - as well as psychological attitude to the potential threat of new injury (9). These factors may explain the link between acute and chronic pain, with some of the same risk factors potentially predisposing to both (10).

In this thesis, I will explore the transition from acute to chronic pain state using the PPP model, and specifically sternotomy (for cardiac surgery.) In addition to studying the mechanisms of transition, I will aim to intervene in this process, in the form of an efficacy study of analgesics to prevent this transition.

1.2 Cardiac surgery: the ideal surgical model?

Cardiac surgery today is common in the UK with over 30000 sternotomy cases carried out per year. Effective analgesia in the recovery from cardiac surgery is particularly important to prevent cardiovascular responses of tachycardia and hypertension as well as to ensure optimal respiratory mechanics. Analgesia facilitating recovery of lung function minimises pulmonary hypertension and resulting ventricular dysfunction secondary to heart-lung interaction, as well as ventricular interdependence (11).

Pain relief techniques following sternotomy vary from intravenous infusions, to nurse-led regular administration, to patient controlled analgesia (PCA) devices delivering opioids- typically morphine- on patient request. There is however considerable evidence that inadequate analgesia remains a problem (3). There is also good evidence that typically between a third and over half of all patients undergoing first-time cardiac surgery develop PPP (12) although this may be as high as 88%(13).

However, compared to other examples of major surgery cited in this chapter, PPP following cardiac surgery remains understudied. Most studies are retrospective, whereas prospective studies tend to include small numbers of patients and examine certain aspects of the transition to persistent pain, rather than a comprehensive assessment of the whole process. This is likely a result of

the high-risk nature of patients undergoing surgery and relative reluctance to include them in detailed clinical studies.

1.3 Study structure and rationale

Persistent postsurgical pain is a common problem but yet is severely lacking in evidence for its prediction as well as prevention (12, 14).

Previous study of PPP has tended to involve either identification of risk factors or effectiveness studies of various preventive analgesic regimens. Even in the study of potential risk factors, very few investigations have prospectively assessed the whole surgical pathway of preoperative pain, perioperative neuroplastic changes and postoperative recovery with an adequate duration of preventive analgesia.

The recent challenge put forward by Kehlet and Rathmell in Anesthesiology is to include all potential risk factors before, during and after surgery (14). This editorial also calls for procedure-specific study rather than comparing across all surgical procedures, operative techniques and underlying pathologies.

I also set out to challenge the notions that providing adequate perioperative analgesia alone is sufficient to block or reduction the nociceptive input to the Central Nervous System and this in turn can reduce the likelihood of developing

persistent pain. My aim was to demonstrate that an additional antihyperalgesic effect of an intervention is important in preventing sensitisation and the neuroplastic changes, which can subsequently be difficult to reverse. In order to achieve this, it was important to test hyperalgesia and sensitisation before, as well as following, surgery. This could also provide a mechanistic explanation for the link between acute and persistent postsurgical pain (15).

It was also important to learn lessons from the shortcomings of previous studies, as described above, in particular as regards control groups with minimal confounders as well as searching for a large enough effect to power the studies against i.e. *clinically* significant (rather than *statistically* significant) differences.

Therefore I set out to design the a series of studies to incorporate as many facets of the above suggested ideal study as possible and in a surgical model with moderate to severe acute pain, as well as sufficient prevalence of PPP to allow a decrease to be feasible in a reasonably sized intervention trial.

I originally considered thoracotomy as a model to study but the efficacy and assessment of the regional block again remained difficult to ascertain, even with surgically placed and directly viewed paravertebral catheters (16). It seemed potentially difficult to eradicate variability in quality of block simply by randomisation – without studying very large numbers. The role of the intensity

and efficacy of afferent blockade has not been fully reported and appreciated in previous studies (17). The other important variable in the case of surgery for cancer is the recurrence of tumour contributing to long-term pain, as well as treatment effects of radiotherapy and potentially chemotherapy (18).

Although cardiac patients may well be sensitised before surgery, by repeated episodes of ischaemic chest pain, they are free of continuous background tumour pain - as compared to other surgical models such as thoracotomy. There are also no treatment effects from radiotherapy and chemotherapy and, although symptoms can persist or remain untreated and refractory following surgery, persistence of pain as a result of tumour recurrence is not a confounder.

I considered the alternative of studying thoracotomy for benign disease such as recurrent pneumothorax, but this would seriously limit recruitment rates due to the relative infrequency of such cases.

I decided to study sternotomy (for elective cardiac surgery), as there are also several additional factors in favour of this particular surgical model.

Sternotomy involves a standardised incision in the absence (in most institutions, including our own) of a regional anaesthesia blockade of the subarachnoid, epidural or paravertebral spaces.

Post cardiac surgery analgesia is usually protocoled to include patient controlled analgesia (PCA) in the form of morphine, with adjunctive paracetamol only in the first instance. Soon after the removal of chest drains at approximately 36 hours, following uncomplicated surgery and recovery, the PCA is also removed and replaced with codeine and paracetamol. It is therefore possible to ensure adherence to this standard by developing a standardised anaesthetic and surgical protocol, agreed to by all teams responsible for the care of patients recruited to such studies.

In addition, cardiac surgical patients remain in hospital for a minimum of five days and with a median length of stay, in the NHS for elective cardiac surgery, of 9 days (http://www.drfoster.com) and therefore adherence to an analgesic drug trial can be monitored accurately during this period. Such interventions, especially drug trials, can be difficult to ensure compliance otherwise as demonstrated by diary-card measures in outpatient RCTs, for example (19).

The use of anxiolytic premedication for cardiac surgery in the form of benzodiazepines is in common place. Therefore this offered a unique opportunity to add to, rather than institute a new practice of, premedication. This is particularly attractive as pregabalin is also an anxiolytic and ranked first in terms of tolerability in a recent meta-analysis (20).

1.4 Justification for a retroactive modelling study

Prior to embarking on the prospective randomised controlled study, it was important to identify prevalence and confirm the need for further investigation in this particular group of patients, and in our particular institution and catchment area. In addition, this was an opportunity to model risk factors to be tested and confirmed with subsequent prospective study. There is also some evidence of increased risk of PPP following dissection and harvesting of chest arteries for coronary artery grafting (21) and therefore there was an opportunity to examine any differences in LIMA harvesting, as compared to sternotomy without this additional dissection.

I therefore set out initially to convenience sample all patients within a six-month cohort at our principal site of St Bartholomew's Hospital. Retrospective study of this nature is typically limited by under-reporting, as patients in pain are less likely to respond to a posted questionnaire (22). Healthy, pain-free patients are potentially more able to comply with such query and study. My intention was to attempt to reduce this somewhat by 'retroactively' recruiting patients to this study by means of direct conversation and query during a phone interview, with patient consent and ethics committee approval, as opposed to postal approach with paper questionnaire.

1.5 Hypotheses and study plan

The hypothesis of this work is that PPP is both **predictable** and **preventable**.

The thesis chapters address the following specific aims:

CHAPTER ONE: Introduce the concept of PPP and set out the study plan.

CHAPTER TWO: Review the current body of literature regarding mechanisms and risk factors for the development of PPP, as well as potential for its prevention.

CHAPTER THREE: Identify the scale of the problem in our population and model risk factors for the development of PPP.

CHAPTER FOUR: Trial potential preventive strategies in a prospective, randomised, clinical trial.

CHAPTER FIVE: Study the mechanisms of transition from acute to persistent pain with the use of QST.

CHAPTER SIX: Identify risk factors for the development of PPP and phenotype individuals based on preoperative and early postoperative assessment.

CHAPTER SEVEN: Summarise and discuss findings.

Chapter 2 A review of the literature

Surgery remains a most common and predictable source of pain (23). In addition, long term, persistent postsurgical pain is the most common complication following surgery, and yet the problem been only been recognised within the last fifteen years (24). In the case of inguinal hernia repair, for example, it is not only the most common complication but also the most serious (25).

Fortunately, most patients do recover from surgery within weeks and return to normal life. However, a strikingly large proportion of the surgical population continue to describe persisting pain at post operative periods of two to six months after surgery and beyond.

As set out in Table 1.1 prevalence of this phenomenon has been estimated to be as high as 40-70%, following surgery involving a high risk of nerve injury (e.g. breast surgery, thoracic surgery, limb amputation.) Rates of 10–30% are reported following other forms of surgery (e.g. joint replacement or bowel surgery) (12).

Procedure	Prevalence of overall PPP	Prevalence of severe PPP (NRS = 7-10)
Amputation	30 – 50%	5 -10%
Thoracotomy	30-40%	10%
Cardiac surgery	30 – 50%	5 – 10%
Inguinal hernia repair	10%	2-4%
Caesarian section	10%	4%

Table 2.1 Procedure specific prevalence, overall and for severe pain, as a percentage of total patients undergoing surgery
(Adapted from Kehlet et al 2006 (12))

Improving cancer and trauma surgery survival (26) is resulting in an increasing cohort of patients liable to develop PPP, which negatively impacts on the functioning and quality of life. With breast cancer surgery, the pain issues last for at least five years and affect half of all patients (18).

Cardiac surgery is no different, in this sense, although it has not been as extensively studied as other types of surgery. The incidence of persistent pain is not as high as thoracotomy or breast surgery but is nevertheless significant, ranging from 30-56% (27). One recent study, however, reports a much higher prevalence of PPP at three months of 88.3% in those undergoing LIMA harvesting and 75.5% in valve surgery patients (13).

Historically, acute and chronic forms of pain were viewed as separate disease processes. The study of PPP, in particular, has contributed to the view that these disease entities are more likely to represent a continuum, with a transition from one to the other over time. It is also important to consider that all chronic pain was once acute. Therefore the unique feature of PPP as a pain model, where the onset is fixed and can be identified in advance, allows controlled and detailed study of this transition. In addition, there is a potential for controlled assessment of possible preventive strategies.

2.1 Defining the phenomenon

The working definition of PPP is that set out by the Aberdeen Pain Clinic, which first described the epidemiology of this phenomenon in 1998(28). They defined PPP as a *new* pain developing after surgery and persisting for at least *two* months, where other causes for the pain have been excluded (29).

This arbitrary duration of two months contradicts the IASP (International Association for the Study of Pain) definition of chronic pain in general, which is defined as persisting for at least three months (30). An alternative, increasingly used definition includes duration beyond expected tissue healing. However, the lack of a clear and unanimously accepted definition for the duration of persistence of pain does hamper comparison across the literature. Consensus is gathering for an assessment of PPP at a sufficient time period following surgery

to allow tissue healing and recovery from acute pain – there is considerable debate whether this is at three months or six months, but considerable agreement that pain at two months is still likely to be a continuation of the perioperative period of acute pain (14, 31). I have therefore chosen to consider the three and six-month time points as the most relevant and important in my studies.

In addition to the debate regarding duration of PPP, there is no clear threshold for **intensity** of pain. Some studies include any patient with pain, while others include only moderate pain (32) - a score of either 3 or 4 on the VAS, depending on the study - or severe pain (usually 7 and above on the VAS.) The impact on quality of life and function is rarely included as a defining feature, unlike other forms of chronic pain (33, 34).

Incidences of PPP vary between different surgical procedures. However reports about the same procedure can also vary hugely in terms of outcomes. This may be due to different surgical technique or extent of disease.

Study design is also likely to have an influence. This has been hampered by continuing reliance on retrospective analyses, small sample sizes (Figure 2.1) and poor questionnaire response rates leading, in turn, to selection and response biases. Although retrospective studies are useful for initial inquiry and

hypothesis generation, suitably powered prospective studies are necessary to provide unbiased data, and in order to draw firm conclusions (14).

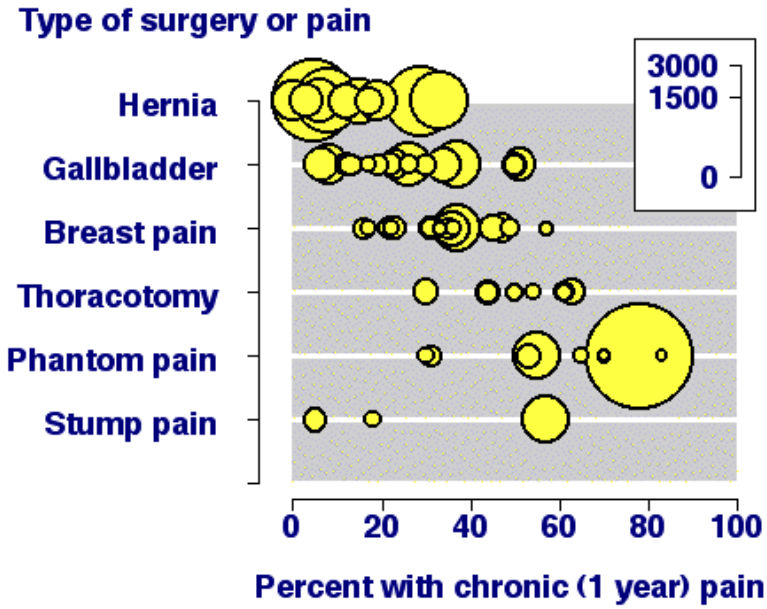

Figure 2.1 Procedure specific prevalence for PPP depending on sample size
Prevalence of PPP represented on x-axis and the total number of patients included in each study is represented by the size of the yellow circle (Available at: http://www.medicine.ox.ac.uk/bandolier/band103/b103-4.html Accessed on 10/12/14)

These limitations have contributed to the uncertainty regarding incidence and prevalence within populations, as well as the wide prevalence ranges quoted for a specific procedure. There is however little doubt that, even taking the most conservative values, this pain syndrome causes significant morbidity, with at least 40,000 cases per year in the UK (28). Considering the increasing numbers of surgical cases performed per year, the socio-economic impact is significant

and also rising. There is therefore clear consensus throughout the literature for prospective and procedure specific study of this important phenomenon (14).

2.2 Mechanisms of transition from acute to persistent pain states

It is important to consider mechanisms of transition in general before examining properties unique to PPP.

Acute nociceptor activity is transmitted to the dorsal horn of the spinal cord, where peptide and amino acid transmitters activate second order neurons to the brain. These nociceptive signals are processed in higher centres, utilising sensory-discriminative, motivational-affective and "top-down" modulatory pathways, in order to produce the emergent, subjective experience of pain.

However, a persistent, severe barrage of nociceptive input up-regulates both cyclooxygenase and interleukin 1β in the periphery, eventually sensitising second order neurons via the NMDA receptor. It is this sensitisation, in both the peripheral and central nervous systems, which leads to spontaneous as well as evoked pain, in and around the incision site.

Features of evoked pain, following sensitisation, include allodynia and hyperalgesia (35):

Allodynia: Pain in response to a *non*-nociceptive stimulus e.g. light brush stroke to skin

Hyperalgesia: Increased sensitivity to a nociceptive stimulus. This can include both a decrease in pain detection threshold or an increase in suprathreshold response (e.g. pain score.) Hyperalgesia can also be described in terms of:

Primary hyperalgesia: occurs in the periphery as a result of incision or surgical injury, in and around the wound. Release of local mediators sensitises a multitude of nocioceptors in the primary afferent neuron (figure 2.2.) This results not only from inflammation but also secondary to tissue ischaemia and acidosis. As one example, low pH activates several receptors and ion channels responsible for transducing nociception e.g. potassium channels, vanilloid (TRPV1, etc.) and purinergic receptors.

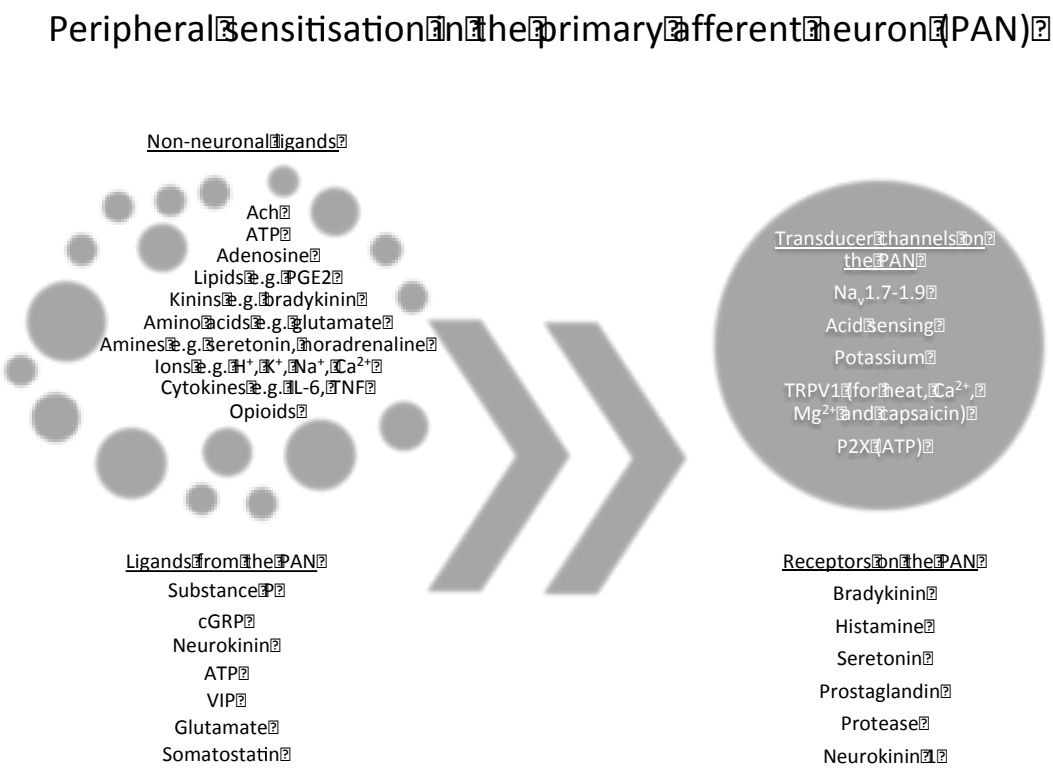

Figure 2.2 Peripheral sensitisation: ligands and sites of action
(PGE2= prostaglandin E2, Ach= acetylcholine, ATP= adenosine-5-triphosphate, IL-6= interleukin-6, TNF= tissue necrosis factor, TRPV-1 = transient receptor potential V1, P2X = purinergic receptor subtype P2X)

Secondary hyperalgesia: is observed in adjacent uninjured tissue as a result of changes within the dorsal horn (figure 2.3.) Prolonged firing of nociceptors in the periphery leads to the release of glutamate, the major excitatory neurotransmitter, in the central nervous system (35). Multiple receptors exist on the pre and post-synaptic membrane for glutamate: G-protein coupled,

metabotropic (mGluR) receptors, AMPA receptors – particularly for brief stimuli – and the NMDA receptor for persistent, high frequency c-fibre stimulation. The latter is blocked by magnesium ion at rest but this block is removed by, in particular, substance P and CGRP released from the c-fibre. The combined effect of this stimulation is to shift the dose response curve to the left leading to an enhanced sensitivity of dorsal horn neurons to peripheral inputs.

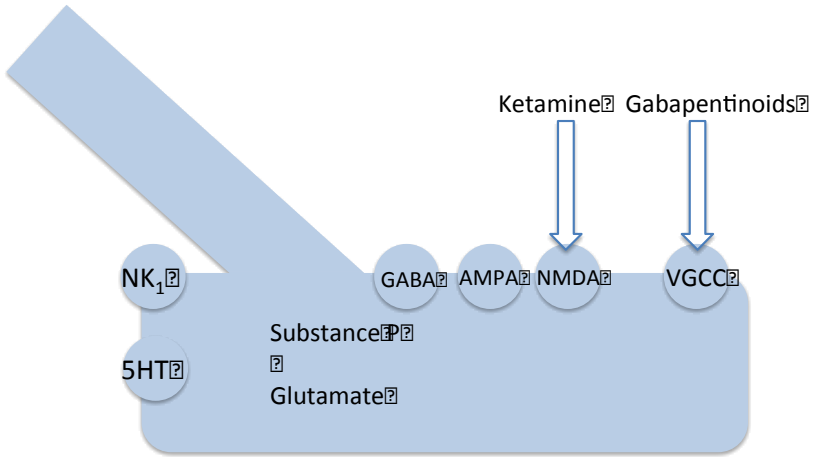

Figure 2.3: Mechanisms of central sensitisation at the dorsal horn and two potential targets for prevention
NK1= Neurokinin 1 receptor, 5-hydroxytryptamine receptor, GABA= gabba aminobutyric acid, NMDA=N-methyl-D-aspartate acid receptor, VGCC= voltage gated calcium channel,

This increased sensitivity or amplification may be seen in response to changes in both the magnitude and frequency of stimulus, with the latter observed **wind-up**

in the electrophysiological setting, with its in vivo correlate of **temporal summation**, as observed clinically in response to repetitive stimulation.

These changes spread segmentally around the primary site before involving supraspinal pathways, via effects on descending facilitation, in particular. This leads to increased sensitivity at the incision site or entirely remotely – eventually, becoming independent of the peripheral pain input, with non-painful stimuli eliciting pain (allodynia.) These changes are termed 'spreading' or **central sensitisation,** as illustrated in figure 2.4 (36). Activated microglia further maintain this state of excitation (35, 37, 38) by further up-regulating COX-2 to produce PGE2, as well as to release further neuromodulating agents such as IL-1, IL-6 and TNF α.

The complex interplay between peripheral and central sensitisation is difficult to study in isolation and requires a systems-based or integrative approach – utilising tools, which are able to measure the overall phenotype and behavioral response. This 'systems neuroscience' approach to studying complex neural networks, interactions and responses to environmental stimuli makes it possible to understand the mechanisms underpinning PPP and therefore aim to predict and, in turn, prevent the early changes.

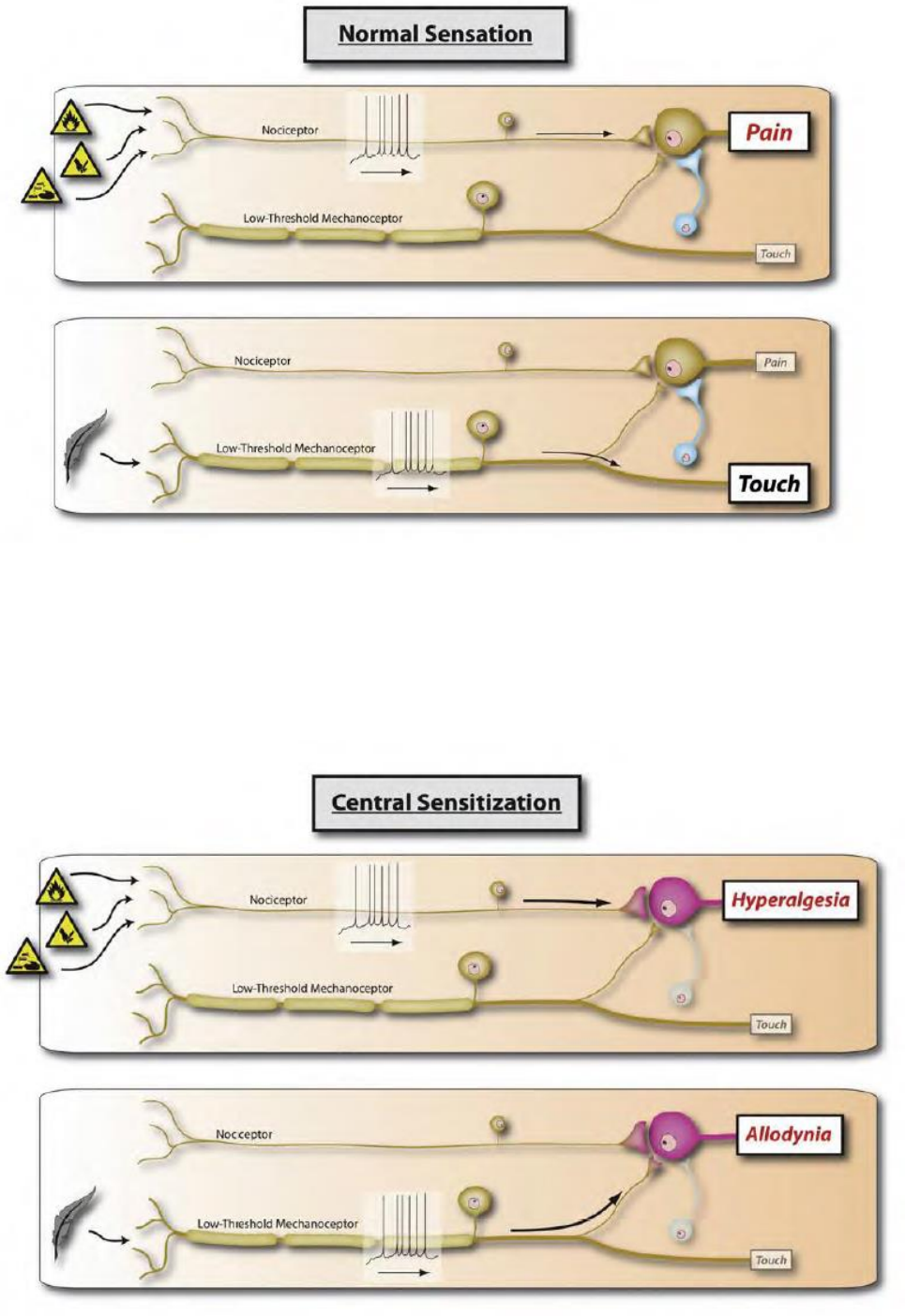

Figure 2.4 Mechanisms of sensitisation
Schematic representation of pathways for hyperalgesia and allodynia (36)

This neurophysiological phenomenon of central sensitisation can be clinically assessed using the surrogate measure of **secondary** hyperalgesia and it is hypothesised that this may play a role in the development of persistent pain states. This may be assessed in the clinical setting by the measurement of a zone of hyperalgesia around the surgical incision, for example (39). Interestingly, there seems to be very little correlation between this zone of secondary hyperalgesia and acute pain scores or analgesic requirement (17). In addition, most conventional treatments for acute postoperative pain have only minimal effects on this secondary hyperalgesia and therefore may be ineffective in treating this potentially relevant component in the development of pain persistence (40). In summary, the mechanisms of secondary hyperalgesia and central sensitisation are distinct from **primary** incisional sensitivity, hyperalgesia and pain.

These descriptions of evoked pain are in addition to the features of spontaneous pain e.g. burning, lancinating pain, dysaesthesia, hypoaesthesia or paraesthesia (41) These are also useful descriptors of changes, perhaps suggestive of the development of (acute as well as chronic) neuropathic pain, but difficult to measure objectively.

As well as considering the differences between spontaneous and evoked pains, it is also important to separately evaluate pain at rest and movement evoked pain. Importantly, the latter may interfere with the patient's rehabilitation, delaying

restoration of function and mobility, and is a highly relevant measure in studies as well as increasing their sensitivity and specificity (14, 42).

2.3 "Increasing the gain in pain"

Clifford Woolf and Michael Salter first used the above phrase in the context of amplification within nociceptive pathways in their seminal paper published in Science (43). The paper describes plasticity, which is *activity dependent*, and over time, sensitises the nervous system by the following processes:

Activation of nociceptors: Activity dependent and therefore rapidly reversible physiological process, which augments transmission and transduction.

Modulation: slow reversible changes but also early manifestations of functional pathology. These includes changes such as phosphorylation of receptors (Na and TRPV in the periphery and, centrally, AMPA and NMDA receptors as well as ion channels (Ca2+ in particular.)

Modification: structural changes e.g. cell connectivity, cell death and cytoarchitecture changes. Remodelling of the neuronal cytoarchitecture, in particular by glial cells, also occurs early in the presence of persistent severe acute pain. This example of neuroplasticity may be crucial in the transition from acute to chronic pain (35).

Therefore, the plastic nervous system is able to amplify or "increase the gain" either as an appropriate response to injury, or pathologically, in the presence of

a persisting painful stimulus, both manifesting as hyperalgesia.

2.4 Why study the surgical model?

Transition from acute to chronic pain has been studied in the nonsurgical population. A prospective investigation of the development of chronic temporomandibular join pain in 202 healthy female subjects led to 15 emergent cases over a three year period and allowed identification of patient-related risk factors (44). However no clear causative triggers were identified during this period. The relatively low likelihood of individuals developing spontaneous pain during the observation period makes study very difficult.

In comparison, surgery allows investigation and identification of predictive risk factors in initially pain free patients, in a timely manner, prior to initiation of a likely causative trigger. The likelihood of developing pain is also high, for example in surgery with a higher risk of nerve injury. Choosing a surgical setting, in which a high rate of developing chronic post-surgical pain is to be expected, provides a setting in which recruitment is feasible to achieve sufficient statistical power in a prospective study. (17).

2.5 Mechanisms for the development of PPP

The notion of a flexible plastic nervous system, incorporating hyperalgesia and subsequent sensitisation, has challenged the classic view of nociceptor activity

driving pain in a linear manner (31). However, following surgical incision, hyperalgesia results not only from this nociceptor activity (Nociception-Induced Hyperalgesia; NIH) but also in response to treatment of the surgical pain.

The mainstay of conventional treatment of moderate to severe acute postsurgical pain is the use of opioids titrated as necessary, with breakthrough pain in the recovery period. A paradoxical and undesirable effect of potent opioids is hyperalgesia (45) termed 'Opioid Induced Hyperalgesia' (OIH.)

Although OIH has been claimed to result from opioid tolerance (46) (i.e. loss of efficacy) it is instead a pronociceptive process, resulting in increased pain sensitivity. This may well explain the failure of certain preemptive analgesic trials where opioids formed the mainstay of preventive therapy (47).

Further evidence of the potential for OIH to affect opioid titration is seen in the quantal dose response relationship seen during treatment for acute postoperative pain. A linear relationship is observed for experimental pain if no hyperalgesic component is present (48).

In addition, the preventive effect of antihyperalgesics (on either NIH or OIH) may be potentiated by their opioid sparing effect, as this further reduces opioid induced hyperalgesia (17). The effect is mediated mainly via the NMDA receptor but the role of mu opioid receptors in descending modulatory centres, such as the Periaqueductal Grey (PAG) and eventually the Rostral Ventromedial Medulla (RVM), have also been implicated in this protective effect (49, 50).

The accurate and reliable diagnosis of hyperalgesia is impossible when based on clinical measures of pain and analgesic requirement. Standardised objective measures of pain thresholds and zones of hyperalgesia, using quantitative sensory testing (QST), therefore become essential, as I outline later in this chapter. Furthermore, any study of protective or "preventive" analgesics, targetting the process of hyperalgesia, requires QST alongside drug efficacy components of the trial (14, 51).

2.6 Patient related risk factors - identifying risk as a means to predicting pain outcomes

Identifying those at risk of PPP encompasses pre-surgical individual risk factors as well as the specific surgical insult (14). Potential risk factors include age and gender as well as the presence of pre-existing pain, in the prospective surgical site or elsewhere. Elicited features such as pain thresholds under experimental conditions are also considered as patient related factors, and are discussed later.

The following section sets out the current understanding of patient specific risk factors, including demographics, as well as pre-existing pain. Subsequent sections of this chapter will cover patient risk in terms of psychological contributors and "somatic" or surgery related risk - in the form of operative technique but also pain score in the immediate postoperative period. Acute postoperative pain could also be considered a patient related factor, if the same characteristics contributing to chronic pain are also believed to play a role in

acute pain. It may be an oversimplification to simply attribute acute pain to surgery related effects alone (10).

2.6.1 Demographics

There is strong correlation between decreasing age and increasing postsurgical pain, both acute as well as persistent (31) (1). The cancer literature attributes some of this relationship to larger tumour size and worse histological grading at diagnosis, and in breast cancer, as an effect of hormonal levels or negative oestrogen receptor status (52, 53). However the same age correlation has also been shown with joint replacements and hysterectomies for non-cancer indication, and therefore needs to be examined further (54).

Gender has not been shown to be a risk factor. The evidence is equivocal in terms of both acute and persistent pain after surgery, as well as treatment response to analgesics (55, 56) This is in contrast to the general pain literature, where there is a higher preponderance for pain amongst females (57).

2.6.2 Pre-existing pain

Pre-existing pain, at the site of operation or elsewhere in the body, predisposes individuals to PPP (58) (12). Non-surgical models also corroborate this finding.

The likelihood of postherpetic neuralgia, for example, can be predicted by the severity of acute Herpes Zoster pain (59).

Surgical examples are equally convincing, with phantom limb sensation and pain (60), PPP following hernia repair (5) and following thoracotomy (61) all demonstrating independent association with preoperative levels of pain in and around the incision site.

It can be conceptually difficult to tease this effect apart from other putative predisposing risk factors, such as psychology, or difficult to manage acute pain after surgery, resulting from this preexisting sensitisation- as well as any pre-existing opioid induced hyperalgesia.

2.7 Psychological risk factors: resilience versus vulnerability

2.7.1 Current literature

The psychology literature for acute pain following surgery is well developed with preoperative anxiety and depression long understood to influence postoperative pain (9). More recently, there has been increased interest in the effects of

neuroticism, preoperative fear, and vigilance and, in particular, catastrophising on surgical outcomes, including pain (62, 63).

Pain catastrophising describes dwelling on the worst possible outcome to pain, or more formally: a negative cognitive–affective response to anticipated or actual pain (64). There is some evidence of a correlation between scores on the Pain Catastrophising Scale (PCS, Appendix three) and pain in the acute recovery period specifically (65). This particular scale also demonstrates adequate internal consistency and construct validity (66).

The literature is not as clear regarding psychological risk factors and PPP. Conflicting data has included one series that demonstrated a lower incidence of PPP in those catastrophising or lacking optimism (67).

A prospective study of 625 patients examined psychological as well as somatic risk factors. In this work, Peters et al (67), demonstrated that catastrophising and low optimism were not predictive of PPP and, surprisingly, acute preoperative pain was protective. However their results were biased by the exclusion of patients admitted to the intensive care unit. Similar observation biases exist in retrospective collection of data by postal questionnaire, whereby the sickest patients are most unable to comply with study.

Two recent systematic reviews argue in favour overall of the role of catastrophising and to some extent anxiety in the development of PPP (9, 68). Hinrichs-Rocker and colleagues describe the concept of psychological vulnerability but lack the data to conclude confidently about the effects of perioperative anxiety or catastrophising (68). The paucity of data is cited as a limitation of this work and therefore prevents meta-analysis.

However the addition of more recent studies in a meta-analysis three years later by a different group concludes that catastrophising is indeed associated with PPP. They also conclude that anxiety, especially in musculoskeletal surgery, also seems to be associated, if not casual (9). There seems to be less certainty for other forms of surgery and therefore procedure specific study is once again suggested.

Another commonly studied risk factor for PPP, along with PCS, is anxiety, typically measured using the Hospital Anxiety and Depression scale (HAD) or the Spielberger State and Trait anxiety scales (69-71).

The literature is inconsistent however in the choice of other assessments for psychological risk, especially across differing surgical procedures (14). Reference is often made to overall psychological phenotype e.g. vulnerability,

resilience, flexibility (72) but this makes it difficult to make comparisons across different cohorts, either in individual studies or in a pooled manner.

There appears to be more agreement regarding fear (of surgery and the recovery period) specifically (67). Despite the lack of correlation with PCS and anxiety described at the beginning of this section, the same group also used a fear questionnaire and found that this correlated well with pain at six months. This is relevant to my work as one study of cardiac surgical patients provides qualitative evidence of fear and anxiety behaviour, in hospital prior to surgery but also at home while awaiting surgery (63).

2.7.2 Surgery specific study of psychological risk

Recent surgery-specific study confirms evidence for psychological risk of developing PPP. Studies in cohorts, undergoing hysterectomy for benign disease (54)and total knee replacement (TKR) (73), confirm the effects of catastrophising and preoperative anxiety, in particular.

The same group, based in Montreal, reported two series of persistent pain patients in the same year, one postsurgical (TKR) (74) and the other nonsurgical (75), confirming the similarities in psychological influence This interesting comparison implies that the mechanism of transition from acute of chronic following surgery are likely to share common principles with other forms of

pain, in particular catastrophising and fear of disability.

There are other psychosocial factors to consider. The spinal surgery model, in particular, has been used to study positive and negative affect and pain outcomes. Interestingly, preoperative affect was not significant in a 141 patient cohort but measurement at 6 weeks after surgery did significantly predict subsequent pain at 3 months. If corroborated, this could justify surveillance and potential intervention at 6 weeks after all spinal surgery (76).

It is however difficult to separate the interplay between psychological state before surgery and other risk factors such as preceding pain. In a large series of 464 patients, Aasvang and Kehlet's group were unable to find an effect of psychology above those of preceding pain, postoperative acute pain and QST measures. Psychology may play a role in these other risk factors but may not be solely responsible (5).

Once again, disparate study designs prevent meaningful comparison across studies. However it is interesting that there seems to be a consistent pattern of negative psychological factors impacting on long-term pain outcomes after surgical intervention (62, 65, 77).

2.7.3 The importance of psychological risk

The biopsychosocial model therefore seems to be important in the development,

maintenance and treatment of PPP (78) and this lead me to hypothesise that identifying risk factors may be useful in assessing their role in the development and transition form acute to persistent pain states during my thesis studies.

2.8 Surgery related risk: does technique matter?

It is important to consider the duration, extent and type of operation as potential risk factors for PPP. Intraoperative complications, in particular nerve damage, may also play a role. These are often described as 'somatic' risk factors to contrast them with the psychological risk described above. In addition, the perioperative period includes potentially modifiable risk factors such as acute pain as well as treatment effects of analgesics such as opioids. Each of these will be discussed in further detail:

2.8.1 Duration and invasiveness of surgery

Evidence has shown that duration and complexity of the surgical procedure may play a role. Peters et al, mentioned in the psychology section above, reported the association between the duration of surgery and the development of PPP (67).

In addition to duration of exposure and extent of surgery, surgical technique may also play a role. Laparoscopic approaches result in lower reports of chronic pain as compared to open cholecystectomy and hernia repair (5). It is difficult to attribute this to extent of incision, exposure and dissection or specifically reduced likelihood of nerve injury. In the case of lung surgery, however, the data

is conflicting as regards open versus video assisted thoracoscopic (VATS) approach to the lung. Earlier retrospective data implied equal incidences between the two techniques (79) (80). Prospective study and subsequent systematic review confirmed this equivocal finding, with only one large retrospective study demonstrating improved PPP outcomes with VATS (6). In the case of hernia surgery, for example, there is more agreement that less invasive surgery (namely laparoscopic incisions) may reduce the subsequent prevalence of PPP (81). This disparity between different surgical procedures gives extra weight to the argument for procedure specific study of PPP.

Additionally, in hernia repair, repeat surgery (in patients free of PPP) has been shown to have a higher incidence of moderate to severe pain at 12 months as compared to first time surgery. Similarly, repeated surgery in the case of breast cancer also independently increases the likelihood of developing PPP (32). This suggests sensitisation from each surgical procedure, which despite the lack of clinically identifiable pain on presentation for repeat surgery, can increase the likelihood of developing subsequent PPP. The identification of subclinical signs (e.g. temporal summation or hyperalgesia) may therefore identify these at-risk patients (36, 82).

2.8.2 Nerve injury as a cause

There is considerable debate in the literature regarding the importance of nerve damage in the development of persistent pain (83, 84). The issue is confused by the fact that not all PPP is neuropathic in nature. Conversely, not all patients with nerve damage develop PPP (85). Apparent pain-free recovery from surgery involving an original occult nerve injury also does not protect from subsequent chronicity (86), although this may also be an example of sensitisation rather than nerve injury per se.

The argument for the necessity of nerve damage to allow PPP is based on the higher incidences in procedures associated with a high likelihood of nerve damage. Over half of patients undergoing thoracotomy, mastectomy and limb amputation report pain at 6 months and beyond (12).

However, PPP may not always be neuropathic. Taking the example of thoracotomy, there is no association between intercostal nerve damage at the time of thoracotomy by nerve conduction study and subsequent PPP (4). Likewise, the mandibular osteotomy model demonstrates almost universal (90%) likelihood of nerve dysfunction but only 5% of these inferior alveolar nerve injuries resulted in neuropathic pain (10, 87) This disconcordance

suggests a more complex interaction between early nerve injury and persistence of pain symptoms.

Similarly in the case of mastectomy, confirmed injury to the intercostobrachial nerve (observed as postoperative numbness) does not result in neuropathic pain in many patients (88). There is more objective evidence for thoracotomy, with the use of validated questionnaires demonstrating that a significant portion of PPP patients do not exhibit neuropathic signs or symptoms (89) (90). There is also a significant incidence of PPP in procedures where very little postoperative sensory loss is seen e.g. laparotomy, hysterectomy. (91, 92).

Even in the case of thoracotomy, only half of patients with confirmed PPP demonstrate a neuropathic nature to their pain (89). It is important to bear in mind that this is only evidence from a single surgical procedure and therefore comparison across all types of PPP is difficult.

Although it is tempting to associate PPP to neuropathy and specifically to nerve injury during a long and difficult procedure, is this really the case or is the extent of other tissue exposure and damage, resulting in sensitisation in a vulnerable individual, more relevant?

Macrae also uses the analogy of an adverse drug reaction as an accepted iatrogenic complication and consequence of medical treatment with a general reluctance to blame the administering health practitioner (29). He compares this to the PPP situation where the operating surgeon is often blamed and potentially stigmatised for causing the complication. This could potentially lead to a difficulty with open discussion of the phenomenon and could explain the current reluctance to accept this common complication in the surgical literature, as well as the reluctance to discuss it during informed consent for elective surgery (93).

2.8.3 Acute pain as an independent risk factor

The effect of acute postsurgical pain on the development of PPP was first reported by Katz et al in 1996 in a follow up study of thirty patients previously recruited to a preemptive analgesia study for thoracotomy (94). They found that pain at rest and on movement at 24 hours following surgery correlated with pain scores at 18 months.

The easiest explanation for the association between acute postoperative pain and subsequent PPP is to assume causality (12). Likewise the approach to preventing PPP since the 1990's has centred on attempts to preemptively institute pain relief, especially regional anaesthesia and opioids, to perioperatively block noxious perioperative impulses from reaching the CNS.

However, if the relationship between acute postoperative pain and PPP is merely associative, and both are caused by one or more factors that are related, no degree of pain reduction in the acute period will prevent the development of PPP. This argument is supported by data from patients who develop PPP, on serial follow up, having been free of symptoms in both the acute period and at a previous assessment for PPP (86). Could this be an example of subclinical sensitisation in the first instance, which does not result in acute pain, but goes on to develop into PPP? Targetting acute pain alone may not help these patients.

2.9 Quantitative sensory testing: experimental pain response as a biomarker

As early as the nineteenth century, German experimental psychology laboratories were using the principle of psychophysics to test different sensory modalities, including pain (95). Psychophysics is the study of sensory stimuli and the psychological impression they create. The quantification and assessment of the relationship between physical stimuli and the sensory experience and perception they produce is known as Quantitative Sensory Testing (QST.)

Most clinical trials of analgesics measure subjective pain experience in terms of pain scores only, or indirectly using analgesic consumption. However the objective sensory changes resulting from injury are rarely recorded. Only QST allows the measurement of post-incisional neuroplasticity and its potential modulation by drugs (96).

Pain is a combined sensory, psychological and social experience and therefore psychophysical testing using QST is superior to the neurophysiological assessment of nociceptor field or range of activity alone. The latter is not sufficient to study pain mechanisms. It is necessary to integrate higher centre function and psychological perception of pain as much as possible with peripheral nociceptor activation. This approach of integrative or **Systems Neuroscience** is in its infancy in the field of pain research (97). It may go some way towards explaining why some patients transition from the ubiquitous

experience of pain, onto worse acute pain following surgery, and subsequently to persistent pain states, such as PPP.

An example of this integrated or systems neuroscience approach to the assessment and study of pain mechanisms is the increased attention, over the last decade, to mechanisms of diffuse noxious inhibitory control (DNIC.) DNIC is an individual's ability to engage endogenous analgesic pathways to inhibit painful transmission to the central nervous system and has been linked to decreased levels of postoperative pain. Intuitively this makes sense as it is akin to using regional anaesthesia perioperatively to prevent the transmission of sensory afferent barrage from reaching the nervous system. Failure of either of these systems could conceivably lead to pain.

This endogenous analgesic mechanism of DNIC, as an example of "top down control of pain, is separate from other descending inhibitory (and facilitatory) pathways, such as those from the ON and OFF cells of the Rostral Ventromedial medulla, as described in the next section (98). These mechanisms of modulation (in either direction) are important for the full range of biological function, from protection and rest of injured tissue (facilitatory) to survival by escape from threat, in an evolutionary "fight or flight" type manner (inhibitory) (99).

DNIC is assessed in the pain laboratory setting by comparing response to experimental pain stimulus before and after another, remote, conditioning stimulus. An effective or efficient system is one that is able to reduce the pain response to the initial stimulus. This simulated laboratory assessment of DNIC, termed Conditioned Pain Modulation (CPM) or the "DNIC-like" effect, is therefore assessing more than simple nociception (100).

CPM assessments of this DNIC-like effect are only one example of QST. This paradigm consists of a battery of very different, standardised stimuli ranging from single fibres, known as Von Frey hairs, to computerised applications of pressure (algometry) and temperature. Therefore perioperative QST allows standardised, structured and objective experimental pain assessment of an individual's *basal* pain perception and modulation, prior to new additional pain from the surgical insult.

2.10 Static versus dynamic assessments of pain

QST typically measures the three *static* thresholds of sensation, pain detection and tolerance. In addition a magnitude estimation by the subject of a *fixed* level of painful stimulus ("suprathreshold" – above the pain detection threshold but importantly below tolerance to allow testing), has also been shown to predict the postoperative pain experience more reliably than the pain detection threshold alone (101). It is also worth considering that tolerance can vary simply as a

result of the motivation of the subject and therefore may not be appropriate in the case of anxious clinical patients recruited to studies around the time of their surgery (102).

Static single assessments of sensory or pain threshold to pressure, for example, are practically easier to perform than repeated measures around dynamic changes in pain stimulus. There is also good evidence for their reliability in predicting pain outcomes. Brandborg demonstrated the reliability of pressure pain thresholds taken before gynaecological surgery in predicting acute postoperative pain, in particular, but also in predicting pain at 4 months following surgery. However these patients presented with pain and therefore may have implications for sensitivity to pain (15).

In a large prospective study of over 400 herniotomy patients, Aasvang and colleague demonstrated that suprathreshold measurements, in their case to heat at a temperature of 47 degrees Celsius for five seconds, were able to predict PPP. This corroborated the earlier findings of Granot and colleagues in caesarian section, albeit only predicting acute postoperative pain in the latter case (5, 101).

The measurement of zones of secondary hyperalgesia as predictors of subsequent pain began in the mid 1990's with Stubhaug's work demonstrating the effect of NMDA antagonism with ketamine (39). Lavand' Homme and

colleagues, in particular, have continued this work by assessing the protective effects of regional anaesthesia, as well as ketamine, as set out in the next section (103, 104). This is an important finding mechanistically, as it confirms the importance of hyperalgesia as a prelude to central sensitisation and the development of PPP.

However there has been a recent vanguard away from these static measures and towards dynamic assessments. These are designed to engage pain modulatory system and assess responses to an additional pain challenge, in an analogous manner to clinical pain (such as postsurgical pain.)

CPM assessments, as mentioned earlier, demonstrate that some individuals can inhibit their response to painful stimulus whereas others are unable to - and in fact summate (105, 106).

Likewise, in the case of chronic pain sufferers in general, some individuals are not able to efficiently inhibit pain but may in fact summate or even, at one end of the biological spectrum, be *pronociceptive*. Whether this pronociceptive state of pain modulation is a cause or effect of persistent pain is not so clear.

In the case of PPP specifically, only one study has examined the predictability of the development of pain using preoperative CPM assessments. Yarnitsky and

colleagues demonstrated in a series of 62 patients that impaired CPM response prior to thoracotomy was predictive of pain at six months following surgery: odds ratio of 0.52 (95% CI 0.33 – 0.77 and p = 0.0024) (107).

In addition, the concept of temporal summation, akin to wind-up in spinal wide dynamic range (WDR) neurons and demonstrated to be enhanced in idiopathic pain syndromes, has been shown to predict acute pain outcomes following thoracotomy with linear regression coefficients from 84 patients of r2 = 0.225 (p = 0.008)(82).

Wind-up is an electrophysiological phenomenon. It is observed in nociceptive neurons in response to repetitive stimulation of primary afferent C-fibers. Repetitive stimulation of these fibres leads to an increased discharge rate of the postsynaptic neurons, temporarily, before reaching a plateau or declining. This normal coding property of dorsal horn neurons is not a mechanism of hyperalgesia *per se*. However lowering of the threshold frequency or increasing the response rate is believed to indicate signal amplification. Therefore it may useful in predicting increased responsiveness of the neurons of the dorsal horn.

The principle of temporal summation is to simulate wind-up, in the in vivo environment, by repeatedly stimulating the same dorsal horn neurons to elicit a frequency-dependent response over time (108). There is some evidence from the acute pain literature of the utility of temporal summation in predicting pain

scores and analgesic requirement (82) but very little assessing the relationship with PPP.

2.11 Why not carry out more extensive testing and profiling?

In 2006, a protocol was proposed by the German Research Network on Neuropathic Pain (DFNS) details included an extensive battery range of mainly static assessments with the addition of summation. Developed in 180 healthy subjects and validated in 1236 patients, this extensive protocol is setting a gold standard of assessment for research as well as clinic-based diagnosis of neuropathy and is appropriate in the laboratory setting, as well as the neurology clinic (108).

However my assessments centred on the dynamic assessment of pain modulatory pathways which are not an integral part of the DFNS protocol and were also designed to be carried out in the clinical bedside setting, without access to the full range of equipment stipulated by the DFNS. Therefore for pragmatic reasons of limited experimental time and patient fatigue, especially in the anxious (63) preoperative cardiac surgical patient or postoperative intensive care patient, I used a modified QST schedule. In addition, my aim in this series of studies was to develop bedside/ 'point of care' screening and assessment tools, specific to sternotomy, as opposed to screening tools for neuropathic pain, as per the DFNS.

2.12 Preventive analgesia – is it more than just effective analgesia?

Preventive analgesia aims to reduce sensitisation from persistent afferent neural barrage and therefore achieve protection from the mechanisms described at the beginning of this chapter. The effects of this approach outlast the expected pharmacokinetic effect of the drug, usually described as 5.5 times the half-life (t1/2 x 5) (109).

This is different from preemptive analgesia, which times the analgesic intervention prior to incision in the hope of achieving superior analgesia and neuroprotection- as compared to delivering analgesia once pain is established.

Preemptive analgesics have not stood the test of controlled prospective study in the acute or PPP setting (110).

Common examples of *preventive* analgesics with their respective evidence of efficacy are set later in this chapter. These include neuraxial blockade (spinal anaesthesia or epidural), NMDA antagonists (ketamine) and the gabapentinoids (gabapentin and pregabalin) with their sites of action described in figure 2.3.

However it is important to acknowledge the potential effects of the following:

Local anaesthetic in and around the incision site (111).

Nitrous oxide as a NMDA antagonist (112) may prevent the development of PPP (113) as well as protecting from OIH e.g. from remifentanil infusion intraoperatively.

Future potential targets include Glial Derived Nerve Factor, Neurokinin and Purinergic receptor blockade and Sodium channel blockade (114).

Returning to the topic of opioid induced hyperalgesia (OIH), these agents all provide analgesia and spare the use of perioperative opioids but may also, as a result, be beneficial by reducing OIH. The antihyperalgesic role of all the candidate agents either directly or by sparing opioid use must be considered and specifically studied. A study of epidural ketamine failed to find a difference compared to saline in preventing PPP after limb amputation but surprisingly found a reduced prevalence of stump pain in both arms of 21% and 33% as compared to 70-80% reported in the literature (22). One explanation for this is the absence of opioids throughout the postoperative period as part of this particular protocol of local anaesthetic and ketamine only. Therefore opioid

sparing may be more important than simply allowing earlier mobilisation and rehabilitation.

Complete avoidance of opioids may of course be as inappropriate as the complete dependence on opioids, especially in surgery where the regional blockade of an extremity is not sufficient e.g. surgery on the chest or abdomen. The judicious multimodal use of antihyperalgesic agents along with careful dosing of opioids, with the aim of providing analgesia and sparing the need for opioids, is the alternative approach, utilising the relative advantages of both in moderation (115).

2.13 The importance (and limitations) of animal models

Most of the evidence for neuroprotection using preventive analgesics comes from the preclinical setting. However this has not proven easy to translate to human beings. The following reasons are cited for particular success in animal models:

- Animals are healthy and pain free before surgery
- Lack of polypharmacy or co morbidities
- Easier to control for confounders and to ensure homogenous population tested.

- Small sample size not an issue
- Surgical insult is typically to a limb/ extremity with segmental somatic innervation only and therefore easier to ensure continuous sensory blockade
- Surgery is short lived
- Different pain pathophysiology and neuropharmacology with differences in neuronal hyperexcitability and sensitisation with rats, in particular (more susceptible and induced to this state and therefore more readily blocked?)

Therefore their exists a huge disparity between the convincing animal data and the conflicting human studies of preventive analgesics.

2.14 Examples of successful translation to humans

I found a large body of literature examining different modalities and classes of preventive analgesics but with mixed results. There are three main categories to consider. In each case, I will consider the evidence for acute analgesic effect prior to discussing the prevention of PPP. The largest approach studied is the use of regional anaesthesia.

2.14.1 Regional anaesthesia

Most of the original work was based on the preemptive analgesia principle and sought to establish the importance of the *timing* of regional blockade on subsequent pain- namely whether the administration of analgesia prior to incision affected pain outcomes differently from delivery at the end of surgery. Multiple studies have contributed to this, with an overall impression that time at which the block is instituted has no overall effect (110)

I examined these studies further though as they give useful information regarding clinically meaningful - as compared to statistically significant - differences in pain studies. Some early studies of single doses of analgesic, via the epidural route, found statistically significant difference in postoperative VAS scores but only at certain time points, and not throughout the entire postoperative period (116). Furthermore, another study demonstrated reduction in VAS score of only 20mm (117). The remainder of the studies of single bolus, from the late 1990's and collated in a recent systematic review, all concluded non significant differences (110).

A similar pattern is seen with the continuous infusion literature. Likewise though, early reports of positive studies are plagued by VAS differences less than 20 mm (118, 119) and in some cases as low as 8mm (120). Later studies refute

these differences and overall systematic review, in 2002, again concludes equivalence in terms of timing of analgesia (110).

Only one of these studies examined the effect of regional analgesia on subsequent PPP. In a double blind manner, Obata and colleagues randomised 70 patients to mepivicaine, either before or following thoracotomy (119). This small study does demonstrate a reduction in the numbers of patients describing pain at three months and six months after surgery as a result of preincisional analgesia. This study is limited by small numbers and further compounded by the exclusion of twelve patients for postoperative epidural failure (2 patients), loss to follow up (5 patients), death before six month assessment (3 patients) or recurrence of malignancy within a year (2 patients) – all reasons to include and analyse data (on an intention to treat basis) rather than to exclude patients. It is possible to speculate however that the additional blockade of hyperalgesia during the early perioperative period, may have contributed to improved PPP outcomes- while not translating into improved pain scores in the acute period, for the reasons given earlier (17, 39).

Despite this paucity of data, the practice of preoperative (and not necessarily *preemptive*) insertion continues, mainly for logistic reasons. This approach allows the perioperative physician to establish and test the anaesthetic block in readiness for emergence from anaesthesia at the end of surgery.

Having refuted the role of timing the 'preemptive analgesic' regimen and established the importance of measuring clinically significant changes, it is now necessary to consider the effect of regional anaesthesia (RA) on preventing acute pain as well as PPP.

The analgesic benefit in the acute setting is clear from two recent systematic reviews (121, 122). Both these studies conclude in favour of RA, in terms of reducing pain scores and analgesic consumption.

PPP prevention is not as clear. Most of the evidence comes from early studies in thoracotomy and often involves comparison between paravertebral block (PVB) and thoracic epidural analgesia (TEA), with similar outcomes. This was therefore followed by enthusiasm for the use of PVB as an alternative to the neuraxial insertion of TEA, especially as epidurals may cause more complication (123). This approach followed study of PVB in the acute setting but also to prevent PPP, with evidence from intercostal nerve somatosensory evoked potentials from the chronic pain setting, demonstrating reduced firing and therefore afferent blockade (124, 125).

Comparison between either of these techniques and opioids alone favours the regional anaesthetic block (126). Study design is however an issue with only a few studies and only of small numbers of patients. This is compounded in

particular by post hoc analysis of long-term outcomes in studies designed with the intention of assessing acute pain only (127). Although these provide a useful signal for hypothesis generation, caution is suggested, as these are not a priori examination of the data.

A very recent Cochrane review reiterates this caution despite a positive conclusion in favour of PVB and TEA in preventing PPP following lung and breast surgery (128). Small numbers and examination centred on these two surgical groups specifically makes it difficult to generalise and extrapolate to other surgical procedures.

2.14.2 Ketamine

The next most commonly studied preventive agent is the NMDA receptor antagonist ketamine. The role of the NMDA receptor in central sensitisation was described at the beginning of this chapter.

Systematic review of ketamine supports its use in the acute pain setting, via the intravenous or epidural routes (129). However this study evaluates the addition of ketamine to opioids only. The PPP literature for ketamine is particularly confused though due to variability in duration and dose of ketamine used, as well

potentially due to the variable – and often underreported - efficacy of superimposed RA.

Outdated and *qualitative* systematic review by McCartney in 2004 (109) described poor quality studies but found in favour of ketamine overall for preventing PPP. Since then, study has continued with mixed results.

Suzuki and colleagues carried out a more recent confirmatory study, administering three days of ketamine infusion, but at only 0.05mg/kg/hr. Despite the small dose – as compared to routine clinical doses of 0.1-0.5 mg/kg/hr - they achieved a reduction in PPP at three months, but not at six months following thoracotomy (130).

Dualé and colleagues have refuted these Suzuki results, with a negative trial following the use of twice the dose of ketamine infusion per hour, as well as 1mg/kg bolus administered before surgery and then repeated during the procedure (131). The key limitation however with this study was the postoperative infusion was continued for only 24 hours and hyperalgesia would be expected to continue beyond that duration. In addition, neither of these studies reported epidural failure rates or block success e.g. in terms of levels of dermatomal block achieved.

The confusion arises when studies are designed to test the addition of agents such as ketamine and the gabapentinoids to RA. The variation in block success and duration of efficacy is difficult to control and is rarely reported. This is particularly important in studies of small numbers of patients where randomisation may not account for this variability of block. This may be contributing to the conflicting conclusions. This is indeed pragmatic, real world study of the effectiveness of these drugs in thoracotomy, where RA is standard practice and can fail postoperatively. However these conditions are not ideal for efficacy studies of additional ketamine or the gabapentinoids.

This is also a discussion on the power of a study, as both agents may be contributing to the same prevention of PPP and therefore to assess additional benefit, it is necessary to study larger numbers. As an example, a study of the effects of preoperative gabapentin as an analgesic following thyroidectomy concluded no effect in the acute setting of coexisting local anaesthetic block of the neck (superior cervical plexus block) (132). Despite the lack of difference at 24 hours, neuropathic pain at six months after surgery was reduced in the gabapentin arms suggesting either single dose preoperative gabapentin was protective or that there may have been sufficient variation in the efficacy of cervical plexus block in 24 patients analysed per group. In addition, if study numbers were much larger, randomisation would remove some of the effects of this variability in block success amongst groups. Failing that, it is important to report in detail the quality of RA achieved throughout the postoperative period.

Nevertheless there is sufficient overall and good quality evidence, from individual studies as well as systematic review, to include ketamine in further study of the prevention of PPP.

2.14.3 Gabapentinoids

The gabapentinoids, comprising gabapentin and pregabalin, have received the most recent attention in the study of preventive analgesia. Both gabapentin and pregabalin bind to the $\alpha_2\delta$ (alpha-2-delta) subunit of the voltage-gated channel and lead to a decrease in the release of neurotransmitters such as glutamate, norepinephrine and substance P - thereby targeting the putative role of these transmitters in central sensitisation. Both agents are established in the treatment of neuropathic pain. This neuromodulatory effect is not only used to treat neuropathic pain but also other centrally driven processes such as the suppression of the sensitised cough reflex observed in refractory cough (133)

As with the other techniques discussed so far, there is good evidence of acute pain reduction with both gabapentin and pregabalin. Historically, most studies investigated gabapentin but with recent interest in pregabalin. The gabapentin studies typically used varying doses and duration. Efficacy is seen in acute pain reduction with doses above 400mg (134) or duration beyond one postoperative day (111, 135). Likewise, pregabalin also shows efficacy, even at a single time

point, as long as it given at a high dose of 300mg (136). Systematic review and meta-regression confirms (137) good evidence for both these gabapentinoids in terms of analgesia, opioid sparing properties and tolerability (with Number Needed to Harm (NNH) for sedation of 35 and dizziness of 12.)

In terms of prevention of PPP, most studies again investigated gabapentin, with only three controlled trials of pregabalin. The effects of both on PPP is less clear due to short duration of regimen, but particularly so for gabapentin. When the issue of adequate duration has been addressed, promising studies have provided a strong signal of efficacy.

In a group of 240 patients undergoing total knee replacement Buvanendran and colleagues tested a prolonged regimen of oral pregabalin against a placebo in a randomised controlled trial. The active arm received 300mg pregabalin before surgery and then continued postoperatively at 150 mg twice daily for ten days before weaning doses for a further four days (138). This 14-day regimen reduced the incidence of neuropathic pain at 6 months from 5.2% to 0% (6/113 to 0/115 patients, no CI description but with a $p = 0.014$). They observed a significantly increased rate of sedation and confusion in the first day after surgery, which settled with continued use and therefore led to an overall recommendation of lower doses of pregabalin, with the hope of to reduced side effects and to allow physiotherapy and intensive rehabilitation.

These preventive findings were also confirmed in same year by a lumbar discectomy study but in patients with established neuropathic pain, therefore assessing a treatment effect in addition to surgery. This study demonstrated the effect of high dose (300mg) pregabalin given before and one day following surgery on reducing persistent pain at three months. The preexisting neuropathic pain is difficult to separate from PPP and there is an argument to be made that this is an assessment of pregabalin for treating neuropathic back pain rather than preventing PPP. In addition, the high doses used led to visual disturbances in the active study arm (139).

2.15 Important findings worth studying further?

Based on the paper by Buvanendran et al, I also chose to study the preventive effects of pregabalin 150mg BD, in the same regimen and duration postoperatively. I did consider reducing the dose to improve tolerability but this would have been at risk of losing efficacy. As an alternative, I chose to study surgical procedures with increased pain and analgesic requirement. The argument in favour of this approach is that opioid sparing in a procedure with relatively large use of morphine, for example, could perhaps lead to benefits in terms of reduced sedation, nausea and vomiting, to offset some of the pregabalin side effects described by Buvanendran et al.

Therefore instead of designing a dose finding or "duration finding" study in knee replacement or similarly painful surgery, my aim was to conduct a "side effect reducing study". As the literature set out above demonstrates repeatedly, sufficient dose and duration of administration of preventive analgesia is important to ensure efficacy.

The Buvanendran et al study in knee replacement was the only true study of preventive pregabalin published at the time of inception of my study. It felt appropriate to also study other surgical groups to establish reproducibility of this effect. My work also focuses on a group of patients staying in a monitored high dependency area for longer and with less need for early mobilisation and intensive ambulatory rehabilitation, and therefore may lead to improved patient tolerability of the preventive regimen.

2.16 Update of the literature since my studies began

Subsequently, and therefore not impacting on my decision to study pregabalin at this dose and regimen, Pesonen and colleagues investigated half the dose: 150mg before surgery followed by 75mg twice daily and only for 5 days duration in 70 patients. The study was designed and powered to detect a reduction in acute opioid use only following cardiac surgery, which it achieved. The secondary outcomes of pain at rest and during movement at 1 and 3 months were all non-significant except pain on movement at three months. It is tempting to speculate

if the pregabalin had been given longer than 5 days or at doses higher than 75mg BD, they may have found significant differences at one month and at rest and on movement at one month. However this study was designed to show safety in the elderly population as well as efficacy in the acute period primarily – both achieved with no difference in side effects between the two groups (despite including only patients aged above 75 years old) and a reduction in oxycodone use in the active arm. With only 35 patients in each group, it is likely that this study was underpowered for persistent pain outcomes.

This latter study did lead to a systematic review last year including all gabapentin and pregabalin preventive analgesia studies, which concluded that both agents are indeed effective overall (140) In terms of pregabalin, the authors go as far to comment that the improvements in pain outcomes (OR 0.09, 95% CI 0.02 to 0.79, p=0.007) is "clinically implausible" and, especially given the small number of studies , justifies further study in different surgical groups. They do however also caution against these impressive results by pointing out the potential publication bias resulting from omission of any negative studies (140).

2.17 How much reduction is enough?

There is an important distinction to be made between statistically significant differences in studies and clinically meaningful, relevant or important differences to patients. This is particularly important when preventive

approaches carry risk of adverse events. There is also the consideration of the ideal primary outcome measure: reduction in VAS or number of patients with pain in each group.

Clinical trials of analgesics report outcomes in terms of number of patients with pain at a fixed time point, functional ability of individuals or reduction in either pain score or analgesic requirement. The reduction in pain score is considered a success if there is a reduction of 30% and impressive if above 50% (141). However, patients expect even larger differences in outcomes to consider an intervention a success (34).

One way to overcome this is by looking for larger reductions, either in pain scores or in the number of patients remaining pain free. Both the positive studies of preventive pregabalin, described above, found large differences in PPP outcomes. There is a risk with powering against such large differences of a Beta error (i.e. a false negative.) However this may be deemed appropriate if a positive outcome at a level below this cut off would not be considered clinically meaningful. In addition the tougher the outcome measured, the lower the placebo effect observed (34).

There is also a debate developing over the role of preventive analgesia as simply additional robust multimodal analgesia delivered well or additional preventive

effect (56, 142). This argument is strengthened by the observed preventive effects of additional analgesics such as nitrous oxide to a multimodal regimen (113). Therefore there is perhaps an even stronger argument to demonstrate large treatment effects, which are clinically meaningful, as an example of a separate and discernable preventive or antihyperalgesic effect?

2.18 Study of mechanisms for preventive analgesia

Very few studies have examined preventive analgesic effects of drugs using QST. This approach offers an opportunity to study the mechanisms of preexisting sensitisation, summation and modulatory systems, as well the changes taking place as a result of surgery and, in turn, the protection offered by preventive analgesia. This integrated approach to studying the whole system in vivo, and as a functioning network, allows a systems-based explanation of mechanisms as well as pathology.

In addition, these tests (temporal summation, in particular) give an objective assessment of preoperative sensitisation, superior to patient report of preexisting pain (e.g. resulting from ischaemic chest pain related visceral hypersensitivity.) Postoperative repetition of these assessments allows comparison and evaluation for additional incisional sensitisation.

No studies of this manner had been published when I designed my studies. Other models have however been examined since. Wilder-Smith's team published a study in chronic pancreatitis patients demonstrating that the efficacy of pregabalin could be predicted by the CPM paradigm testing before treatment (143), in a manner similar to my hypothesis below.

A recent study demonstrated that a single dose of 300mg pregabalin reduced the area of secondary hyperalgesia following nephrectomy but had no effect on static measurement of pressure pain threshold (136). Unfortunately, this small group of 26 patients was not followed up to assess PPP. However this study is useful for hypothesis generation in terms of the effects of pregabalin on secondary hyperalgesia.

2.19 Summary

There is increasing agreement in the literature regarding the prevalence of PPP for different surgical interventions. However study design remains a limiting factor. The study of putative risk factors and likely triggers is still in its infancy and prevention remains the holy grail (144).

Chapter 3 Identifying the scale of the problem in our population and modelling risk factors – towards cohort development

3.1 Background and rationale

Figure 3.1 The risk of surgical incision
(Image available at http://www.medicaldaily.com/history-stroke-may-increase-risk-adverse-surgical-complications-even-non-cardiac-procedures-293190 Accessed 10/12/14)

All surgery leads to tissue damage but the technique deployed and extent of surgical exploration may affect the degree of damage. There is evidence for improved recovery and shorter need for hospital stay following the use of less invasive techniques such as video assisted thoracoscopic surgery (VATS.) However this improved recovery profile fails to translate well into reduced incidences of PPP (79, 80).

Both inflammation and direct nerve damage are capable of activating the nociceptive system but their relative contribution following surgery is not well understood. Not all patients with postoperative sensory dysfunction go onto develop PPP (87)and conversely, preserved nerve function in the postoperative period does not necessarily ensure the avoidance of persistent pain – as some patients free of pain at six months following breast surgery subsequently develop PPP many years later (86). These finding suggest that other factors, either affecting nerve injury or acting independently, may play an important role in the transition from acute to chronic pain.

Nerve identification and preservation has been suggested as a means to reduce the risk of PPP. Where it may be difficult to avoid damage, it has even been suggested that elective transection is preferable to inadvertent partial injury (83).

The role of surgical technique or extent of dissection during cardiac surgery specifically is less well understood. Harvesting of the internal mammary artery during cardiac surgery, with associated dissection of the anterior chest under retraction, is believed to be associated with transection or contusion of nerves. The intercostal nerves are particularly susceptible to damage during this process. This intraoperative injury may contribute to the development of neuropathic pain (145). However this has yet to be studied, alongside other putative risk factors, in order to assess the relative contributions of each.

Higher acute postoperative pain score has been cited as being associated with the development of PPP, while harvesting of the Left Internal Mammary Artery (LIMA) and prolonged surgery have also both been suggested as potential causes (particularly of neuropathic pain) (27).

3.2 Aims of Investigation

The aim of this chapter is to describe the prevalence of PPP following cardiac surgery in our institution. The literature reports a wide range of figures with varying methods of data collection, prospective as well as retrospective (the latter usually carried out postal questionnaire query, with variable response rates.) The measurement of prevalence in our population will also inform power calculations for a prospective study.

In addition, a secondary aim is to examine the relative contribution of potential surgical risk factors to the development of PPP.

3.3 Methods

With REC (research ethics committee) approval, I convenience-sampled (146) the medical records of a cohort of patients undergoing cardiac surgery in our institution over a six-month period. This time period was chosen for this pilot study to allow sufficient numbers to be assessed, given the rate of approximately

600 cardiac surgical cases performed per year at St. Bartholomew's Hospital. As this was an exploratory pilot study, I was unable to carry out a power calculation.

3.3.1 Risk factors

Patient charts were reviewed for the following potential risk factors:

Patient related

Gender

Age

Treatment related

Duration of sternotomy

Dissection and harvesting of the left internal mammary artery (LIMA)

Acute pain score at 24 hours following surgery

Patients were contacted by telephone at six months following surgery and verbal consent was taken to allow interviews regarding current pain experience. Current pain as an 'average for the week, in and around the sternotomy site' was assessed using a Numerical Rating Scale (with anchors of zero= no pain, 1= mildest pain possible and 10= maximum imaginable) and the self-report form of the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS). The latter is a validated tool – with 78% sensitivity demonstrating internal consistency and congruent validity - for clinical research, including postal and telephone query (147). The script used to interview patients is as per the published, validated form and is set out in Appendix Four.

Leg pain resulting from saphenous vein harvesting was also assessed in a similar manner, where applicable. In addition, quality of life assessments were made at the six-month time period using the validated UK data set of the EQ-5D tool (see Appendix One.) I also enquired about any sleep disturbance as a result of PPP as well as the use of current analgesia for its management.

3.3.2 Statistical analysis

Comparisons of PPP are made for surgical technique: sternotomy alone (for valve surgery) as compared to the additional harvesting of the internal mammary artery (for coronary artery bypass grafting.) This tests the hypothesis that mammary artery harvesting increases the likelihood of subsequent chronic

sternotomy pain.

Logistic regression modelling compares differences for binary outcomes (e.g. presence or absence of PPP, neuropathic pain, medication requirement, sleep disturbance, etc.) whereas continuous data (e.g. pain scores on the NRS) are analysed with linear regression models.

Potential risk factors are analysed in a similar manner. Risk factors with significant interactions on univariate analysis are then combined in multivariate models to test relative contribution. Likewise hierarchical regression models are used to test the additional effects of individual risk factors to describe the strength of any relationship and potential for predicting long term morbidity.

3.4 Results

A total of 312 patients underwent cardiac surgery at St Bartholomew's from January to June 2010. Full data sets for procedure, pain score and recovery profile were only available for 210 patients, of whom 174 were interviewed. The 36 omissions were due to inability to contact (23), patient death (7) and unwillingness to participate (6).

Of the 174 patients studied, 132 (76%) were male and 42 (24%) female. 129 (74%) of patients underwent LIMA dissection for CABG.

3.4.1 Sternotomy pain

In total, 69 patients (39.7%) described persisting pain at six months post sternotomy, of whom 55.0% satisfied the screening criteria for a diagnosis of neuropathic pain according to the S-LANSS tool.

The severity of the reported PPP can be further categorised as follows:

38/69 = 55% as mild [NRS 1-3]

23/69 = 33% as moderate [NRS 4-6]

8/69 = 12% as severe [NRS 7-10]

Some authors advocate the reporting of only moderate to severe pain in studies (34)and this would therefore reduce the percentage of patients with PPP from 39.7% to 18% of the 174 patients studied, in total.

Logistic regression analysis of the binary outcomes of presence or absence of sternotomy pain at six months revealed age, duration of surgery and acute pain score to be potential predictive factors (Table 3.1)

PREDICTOR	B (95% CI)	p value
Age (years)	B=0.896 [O.862 – 0.931]	p<0.001**
Sex	B=1.644 [O.785 –3.444]	p=0.188
LIMA harvesting	B=1.264 [O.625 – 2.555]	p=0.514
Duration of surgery (minutes)	B=1.018 [1.010-1.025]	p<0.001**
Acute pain score (NRS)	B=3.665 [2.344-5.731]	p<0.001**

Table 3.1 Logistic regression analysis for the risk of developing PPP

Multivariate regression analysis of these variables further revealed theatre time, acute pain score and decreasing age to be most strongly associated with PPP of a neuropathic nature (all p<0.001).

Hierarchical linear regression identified the best predictive model for NRS pain score in the chest, given the independent variables available, to comprise patient age, theatre time and acute pain score. Using this model, with acute pain included as the first step, the NRS score is increased by one further point for every 90-minute increase in theatre time and every 13-year decrease in patient age.

3.4.1.1 Analysis for neuropathic pain specifically

Although LIMA harvesting was not predictive of the likelihood of developing overall PPP, it did predict neuropathic pain specifically. Logistic regression modelling for a S-LANSS score above 12 gives an odds ratio of 2.750 (95%CI 1.001 to 7.553) and a p value of 0.050. Although this just fails to achieve statistical significance, it does suggest a possible association of LIMA dissection with subsequent *neuropathic* pain.

Multivariate linear regression analysis of these variables revealed theatre time, acute pain score and decreasing age to be most strongly associated with PPP of a neuropathic nature (all $p<0.001$). However, LIMA grafting alone ceased to be significantly associated with subsequent neuropathic pain when the other factors, especially longer theatre time, were taken into account ($p=0.07$).

Hierarchical linear regression identified the best predictive model for S-LANSS score, given the independent variables available, to comprise patient age, theatre time and acute pain score. Using this model, the S-LANSS score is increased by one point for every 20-minute increase in theatre time and every 5-year decrease in patient age.

3.4.2 Leg pain

Leg pain was present in 62 out of 124 (50%) of those patients undergoing saphenous vein harvesting. Unsurprisingly, it is not predicted by LIMA dissection or theatre time – as additional time in the longer duration cases is usually spent operating on the chest (retraction time for LIMA harvesting, in particular.)

Acute pain is again strongly predictive: B=2.500 (95% CI 1.552 to 4.026) $p<0.001$

Age of the patient is also predictive with B=0.963 (95%CI 0.930 to 0.996) and p = 0.031. However when both these risk factors are combined in a multivariate model, age is no longer predictive with B =0.977 (95%CI 0.941 to 1.013) p=0.211. This could potentially be explained in one of the follow three ways:

1. Younger patients were less likely to require CABG and therefore undergo leg incision for saphenous vein harvesting. This would therefore skew the study population towards elderly patients undergoing leg surgery.
2. Increased psychological stress of undergoing sternotomy as compared to a leg incision and therefore less predictive powered for the PPP following the latter.

3. Underpowering as less patients underwent leg incision (124), as compared to sternotomy (174.)

3.4.3 QOL Assessments

The quality of life scores vary significantly between patients in pain and those who area pain free, even when potential confounders are included in an adjusted model of linear regression:

	Present	Absent	Mean difference	Adjusted mean difference*
Sternotomy site PPP	0.435 (0.370)	0.736 (0.277)	-0.279 (-0.373 to -0.185) p<0.001	-0.161 (-0.283 to -0.039) p=0.010
Leg PPP	0.499 (0.303)	0.739 (0.348)	-0.240 (-0.355 to -0.125) p<0.001	-0.159 (-0.280 to -0.038) p=0.010
Neuropathic PPP	0.315 (0.362)	0.749 (0.258)	-0.434 (-0.537 to -0. 332) p<0.001	-0.369 (-0.490 to -0.247) p<0.001

Table 3.2 Linear regression analysis for EQ-5D quality of life scores
***adjusted for age sex acute pain score theatre time and LIMA harvesting**

3.5 Discussion

These results demonstrate the significant long-term pain burden of undergoing cardiac surgery. The overall prevalence is similar to other centres in the literature (12).

Patient sex is important in most chronic pain conditions but is not necessarily the case following surgery (56, 57) In the current study, however, there is a potential for bias as males outnumbered females by 3 to 1. This may therefore have hidden any potential effect of, especially female, sex.

There seems an incredibly powerful predictive power of age, pain score and duration of surgery on future PPP. Of these, only pain score is modifiable but perhaps there is a role for aggressive pain management in young patients, especially in the immediate postoperative period.

Although two or three months are quoted as the minimum post-surgical intervals quoted in published definitions for PPP, the patients in this study were assessed at six months(28). Therefore when comparing this finding of 12% incidence of severe PPP to results from other studies, it should be borne in mind that the rate may be higher at these earlier time points post-surgery. Similarly, the figures for 'more than mild pain', of 45% of all patients reporting PPP, and

18% of all patients studied, may also have been found to be higher at two or three months following surgery. Interestingly, Kehlet and colleagues report a similar incidence of PPP following breast surgery at different time points, but with some patients improving while others reporting new PPP in and around the original incision site (86). Enquiry at a single time point, as in this study, obviously precludes such longitudinal, temporal comparisons.

The low EQ-5D scores observed in patients with pain are comparable to the UK National Pain Audit (http://www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2013-14/Pain-Audit-Report-2013.pdf) especially in those with persistent neuropathic pain and demonstrate significant long-term morbidity and disability.

3.5.1 Limitations

Retrospective study is limited by the lack of baseline values for pain (including medication requirement and sleep disturbance.) Objective and quantitative assessment of pain around the incision site is also not possible e.g. visceral hypersensitivity at the sternotomy site, as one example. Likewise, quality of life assessments before surgery are not possible to assess any changes – either improvement or deterioration following surgery.

In terms of data capture, this study was limited by the lack of complete medical notes in the case of over 100 patients. It is not possible to comment on whether these cases were random or skewed towards those with worse (or indeed better) pain outcomes.

Similarly, of the 23 patients who we were unable to contact, it is possible to speculate that may have resulted from increased pain compared to the remainder of the group.

Six patients refused to participate and although, a small number, this may have reflected dissatisfaction with outcomes. Only one patient was prepared to give a reason: although pain free, he described a poor experience with hospital follow-up, especially by medical teams.

3.6 Conclusions

Albeit retroactive and using the approach of convenience sampling, this study corroborates the reported prevalence range of PPP after sternotomy. It is interesting however that only half of the cases satisfied the screening criteria for neuropathic pain.

This study also confirms duration of surgery and the intensity of pain in the initial acute setting, as potential predictors of PPP. The increased prevalence of symptoms and signs in younger patients may justify more aggressive methods of prevention and management of their early postoperative pain.

Regression modeling reveals the potentially powerful predictive value of the following risk factors: age, acute pain and theatre time. This analysis supports the need for prospective study in order to develop and validate predictive tools for PPP.

Although one declared aim was to identify the role of surgical technique in the development of subsequent PPP, this is not clearly the case as regards LIMA dissection and harvesting. Other factors related to tissue injury and exposure may be relevant but these findings corroborate other study where similar PPP outcomes were reported when comparing open and video-assisted thoracic

surgery. In both examples, current analgesic regimens (centred on opioid analgesics) seem ineffective in managing the substantial risk for the development of PPP.

It is likely that patient related factors and early pain experience following surgery are more important in shaping the prevalence and experience of PPP, than surgical technique specifically.

Further investigation of patient related factors is therefore warranted as well as alternatives to opioids as a means of reducing acute postoperative pain, and perhaps PPP.

Chapter 4 Randomised controlled trial of preventive analgesia

The aim of the wise is not to secure pleasure, but to avoid pain.

Aristotle 384-322 BC

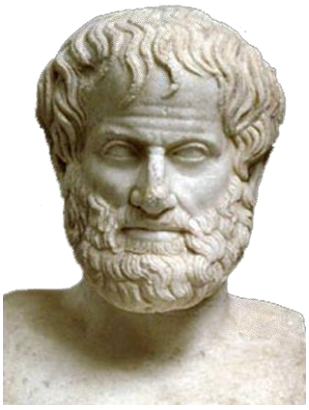

Figure 4.1Bust of Aristotle; Free Will and Antiquity
(Available at http://en.wikipedia.org/wiki/Free_will_in_antiquity Accessed on 10/12/14)

4.1 Introduction

Persistent pain following surgery is surprisingly common and difficult to treat once established. The identification of preventive measures therefore holds great promise (128, 140).

Study of various surgical procedures has however led to contradicting results with some of these differences attributed to poor study design (148).

There may also be differences in the mechanisms of persistence between different surgical groups, which may in turn be reflected in the varying efficacy of preventive analgesia (14). Very little data exists for cardiac surgery and therefore I took the opportunity to study this group of patients specifically.

I chose to test the ability of the antihyperalgesic drugs pregabalin and ketamine in terms of preventing this phenomenon. Both these agents have shown particular promise in systematic review of the literature to date (140, 148). Similarly in the case of cardiac surgery, although the data is limited in terms of prospective study, there is some signal for both these agents, in particular for the prevention of acute pain (7, 149, 150).

Ketamine has been studied more extensively than the gabapentinoids, including during cardiac surgery. However the preventive analgesia data, to date, is most compelling for the gabapentinoids, in particular pregabalin - with a recent systematic review reporting an odds ratio of 0.09 in terms of the reduction of the portion of patients with PPP following perioperative use. I also chose to test the combined multimodal effect of ketamine along with pregabalin to test the combined effect of these two anti neuropathic agents.

This important effect of combining analgesic therapy is well established in the management of acute pain following surgery (151, 152). Surprisingly few studies however have taken this approach with chronic pain, even in established neuropathic pain, although the exceptions have stood out for their efficacy (153, 154)

4.2 Hypothesis

The aim of this chapter is to test the hypothesis that the development of persistent pain after cardiac surgery can be prevented by the use of antihyperalgesic agents at the time of surgery, either alone or in a multimodal regimen.

4.3 Methods

The trial was conducted as per the protocol approved by the East London and The City Research Ethics Committee (REC) and the Medicines and Healthcare Products Regulatory authority (MHRA.)

The clinical trial (Heart PPPAIN – Heart surgery and Persistent Postsurgical PAIN trial) was registered on clinicaltrials.gov (NCT01480765) and recruitment began in December 2011 with data collection ending in March 2013.

4.3.1 Study design

Study design for clinical trials can be described in the form of

Patients, **Intervention**, **Comparator** and **Outcomes** (PICO.)

PATIENTS

For this parallel arm, randomised, double blind, placebo-controlled trial, I screened all patients satisfying the following inclusion criteria:

INCLUSION CRITERIA:

- Age 18 -80 years
- Undergoing cardiac surgery via first-time sternotomy

EXCLUSION CRITERIA:

- History of chronic pain, other than angina
- Regular use of pain medication, other than paracetamol and non-steroidal anti-inflammatory drugs.
- Concurrent use of any drugs for neuropathic pain e.g. antiepileptics, antidepressants
- Concurrent use of oxycodone, lorazepam or ethanol - as these drugs interact with pregabalin.
- Previous sternotomy
- Emergency surgery- decision to operate taken on the day of surgery
- Preoperative renal failure defined as eGFR <60 ml/min- as pregabalin is renally excreted
- Allergy to pregabalin, gabapentin or ketamine
- Pregnancy
- Limited understanding of numerical scoring scales
- Previous participation in other trials investigating analgesic agents, or any other IMP in previous three months

Patients undergoing valve surgery were included along with coronary artery bypass graft (CABG) cases. This gave the opportunity to examine the potential effect of LIMA dissection from the chest wall during CABG– usually with

extended diathermy for up to an hour – on subsequent PPP. Only in rare circumstances in our institution is CABG carried out without LIMA harvesting and therefore insufficient numbers were expected to make this comparison within this single surgical procedure.

When combining ischaemic heart disease patients with those with valve disease, is an important consideration to be made for the role of pre-existing central sensitisation in the chest from, for example, long standing ischaemic visceral pain. Therefore as set out in the following chapters, all patients were also examined for preoperative preexisting sensitisation (in the form of temporal summation, for example), to allow for consideration of this potential confounder.

As set out in the CONSORT diagram (figure 4.2), 150 patients were consented and block randomised to one of three treatment groups using a concealed computer-generated allocation sequence, created and managed in a blinded manner by the Barts Trials Pharmacy. This blinding was maintained until the full six-month follow-up data set was complete and submitted to the pharmacy trials manager.

INTERVENTION and COMPARATOR

The patients were randomised to the following three groups:

COMPARATOR = Usual Care (UC): Control group with placebo capsules and placebo ketamine (saline) infusion.

INTERVENTION #1 = Pregabalin (P): Received active pregabalin capsules with placebo ketamine (saline) infusion.

INTERVENTION #2 = Pregabalin and ketamine group (PK): Received active pregabalin capsules and active ketamine infusion.

All patients, medical and nursing teams, as well as research staff, were masked to treatment allocation.

Nursing staff administered an identical, blinded study capsule (containing either 150mg pregabalin or matched placebo lactose) to all patients two hours prior to surgery. These were supplied free of charge by Pfizer following a successful application to their IIR (Investigator Initiated Research) funding programme, with no other contribution to the design, conduct or publication of this trial.

Following surgery, these study capsules were continued twice daily for ten continuous days, followed by a dose reduction to 75mg for day 11 and 12 and 50 mg for days 13 and 14.

If patients were discharged from hospital prior to completion of the 14-day capsule regimen, pharmacy dispensed the remaining doses for the patient to complete the course at home. Any unused capsules were returned to the trial pharmacy and recorded along with any missed doses during the inpatient stay. Details of any missed doses during in patient stay or early withdrawal from either drug were also recorded.

The infusion of intravenous ketamine or matched placebo (saline) was started at the end of cardiac surgery once spontaneous circulation had returned and continued for 48 hours. The 50 ml syringe was prepared in a blinded manner by the Chemotherapy Trials Unit of the Barts Trial Pharmacy as either 10mg/ml of ketamine or matching placebo (0.9% sodium chloride.) This was infused at a rate of 0.01ml/kg/hour and therefore, in the case of the active arm, this amounted to 0.1mg/kg/hour of ketamine.

OUTCOMES

All outcomes were collected on case report forms, as set out in Appendix Five.

PRIMARY**:** Proportion of patients with pain at three and six months on the NRS

SECONDARY**:**

Acute pain scores, on the NRS, at the sternotomy site and (where applicable) the saphenectomy site.

Morphine consumption in the first 24 hours

Sedation and nausea scores

Prevalence of diplopia

Respiratory rate and blood carbon dioxide levels

Adverse and Serious Adverse Events (as per the event log, set out in Appendix Six.) These were managed by the data monitoring committee and reported as per the organogram set out in the Appendix Seven.

Extubation time

Length of stay on ICU and in the hospital

Quality of life at three and six months (EQ-5D VAS and index)

Prevalence of neuropathic pain at three and six months

Requirement for analgesics at three and six months

Sleep disturbance by pain at three and six months

4.3.2 Renal failure algorithm

In the case of renal failure during the postoperative period, the following protocol was followed:

Pregabalin clearance is directly proportional to creatinine clearance and therefore we will use eGFR measurements throughout the dosing period for pregabalin (or placebo) to decide on delay of drug. As the drug is not nephrotoxic but simply accumulates with renal failure, all patients will receive a dose 12 hours after the preoperative dose. Subsequent dosing will be guided by eGFR results:-

eGFR above 60ml/min will lead to continuing dosing.

eGFR of 45-60 will also lead to a dose being given but with vigilance and measurement of eGFR before the next dose, to observe the trend in renal function. If the eGFR remains in the range of 45-60, each dose will be preceded by repeat measurements and in the case of a trend of falling eGFR, as judged by investigation or hospital medical team, the patient will be withdrawn from the study.

eGFR of 30 – 45 will lead to an omission of IMP and again repeat measurement before the next dose in 12 hours time. Two successive missed doses will lead to premature withdrawal of the patient from the study. A single omission with a subsequent return to normal renal function will continue the protocol and this will be reported in the published results.

eGFR readings below 30ml/min at any point or the use of renal replacement therapy will lead to premature withdrawal of the patient from the study.

4.3.3 Clinical management

The patients were anaesthetised according to a standardised and agreed protocol. All patients received 20mg oral temazepam two hours prior to transfer to theatre along with the study capsule (pregabalin or placebo). Induction of anaesthesia took place with 2-3mcg/kg of fentanyl and 1-2mg/kg propofol bolus. Intraoperative opioid use was restricted to fentanyl in a range of 7.5 – 20 mcg/kg with documentation of any requirements above this dose. Anaesthesia was maintained with Isoflurane, prior to cardiopulmonary bypass (CPB), and converted to intravenous infusion of propofol for the remainder of the perioperative period.

Surgery was performed via median sternotomy and CPB was established on all patients to allow coronary artery bypass grafting, valve replacement or combined surgery. This was conducted using moderate hypothermia (30– 34 degrees Celsius), a membrane oxygenator and a roller pump. Myocardial protection was achieved using cold blood-crystalloid cardioplegia solution.

All patients remained sedated and ventilated for transfer to the intensive care unit following surgery and extubation took place according to institution protocol.

In addition to the trial regimen, all patients received usual care of patient

controlled analgesia (PCA) in the form of morphine 1mg bolus, with a lockout period of five minutes. All patients also received regular paracetamol (1g four times per day). Both these analgesics were continued until chest drains were removed at approximately 36 hours following surgery. Once the PCA was removed, regular codeine (30mg four times per day) was added to the paracetamol, with breakthrough pain of NRS>4 managed by administration of tramadol 50–100 mg, up to a maximum of three times per day.

4.3.4 Measurement of outcomes

The proportion of patients with sternotomy pain was assessed at three months following surgery using the NRS during a phone call and formed the primary outcome. This was assessed by phone call query using the NRS scale along with secondary outcomes of evoked pain on the NRS (with 3 maximal coughs) as well as leg pain, both at rest and on walking. During the same phone call, I also enquired about secondary outcomes of neuropathic pain (on the S-LANSS scale) as well as use of medication and sleep disturbance by pain. Identical questioning took place at six months following surgery.

The remainder of the secondary outcomes were measured during the postoperative period. Sternotomy pain scores at rest and following three maximal coughs were measured on the numerical rating scale at 24 hours following surgery as well as leg incision pain scores for those undergoing

saphenous vein harvesting. A movement evoked pain assessment for leg pain was not possible, as patients remained on bed rest in this early stage of recovery.

At the same time, side effects were recorded in terms of sedation and nausea on a 0-3 scale (nil, mild, moderate and severe) as well as any inpatient episodes of diplopia and dizziness.

The PCA device memory display provided the cumulative total dose of morphine consumed at the 24-hour postoperative time point.

Two-pass verification (or 'double data entry') was used to transfer all data from paper report forms to Excel (Microsoft Corp, USA) and SPSS (IBM Corp, New York, USA) for analysis.

4.3.5 Statistical analysis

This study was powered to detect a two-thirds reduction (34) in the prevalence of PPP. Pilot data (Chapter three) revealed a PPP prevalence of 39.7% in 312 consecutive patients undergoing elective sternotomy in our centre over a six-month period. Based on an alpha of 5% and power of 80%, we therefore calculated a sample size per group of 43 patients. To allow for attrition such as loss to follow up, we recruited 50 patients per group.

Results were analysed on an intention to treat (ITT) basis with imputation of missing data on the basis of average values for the group, as per the Statistical Analysis Plan set out in Appendix Eight. Alternative imputation methods exist (e.g. last value carried forward, worst or best possible scenarios) but average for the group most closely resembles the intention to treat principle, as protocol deviations (leading to missing data, for example) are treated as closely as possible to subjects adhering to protocol (155).

The primary outcome of proportion of patients experiencing PPP at three months is presented by treatment arm and compared using *logistic* regression modelling on SPSS. Results are presented as odds ratios (OR) with 95% confidence intervals. Similar analyses is performed for the other binary variables (neuropathic pain, sleep disturbance, long-term analgesic requirement.)

The continuous outcomes (NRS score, etc) are summarised by treatment group using appropriate descriptive statistics and 95% confidence intervals. These include numbers and percentages for categorical data, mean and standard deviation for normally distributed, continuous data or median and interquartile range for skewed data. Baseline characteristics between the treatment groups are also presented to assess similarity across randomisation groups.

Linear regression models are used to compare *continuous* variables across

treatment groups, including ANCOVA (analyses of covariance), employed to adjust for baseline characteristics where there is good clinical belief that they may be predictive of outcome e.g. age, pre operative quality of life or sensory state.

Similar regression models are used in chapters five and six, for subgroup analysis, to identify predictive risk factors. Given the relatively low power for testing interactions, these results should be considered exploratory only.

4.4 Results

Three and six month assessments were only possible on 148 patients (figure 4.2.) Two patients were lost to follow up: due to death on day seven following surgery and emigration following hospital discharge. Data was imputed for these two patients on an 'average for the group' basis.

4.4.1 Missing data

Inpatient data was missing on five patients, who were unable to provide responses or scores: in three cases of prolonged pulmonary ventilation and two patients requiring early re-intubation of the trachea. Therefore, early outcome data was not available, but three and six month follow up assessments were

possible for these patients. The remaining withdrawn patients, as set out in the CONSORT diagram (Fig 4.2), all agreed to follow up assessments while in hospital and at three and six months following surgery.

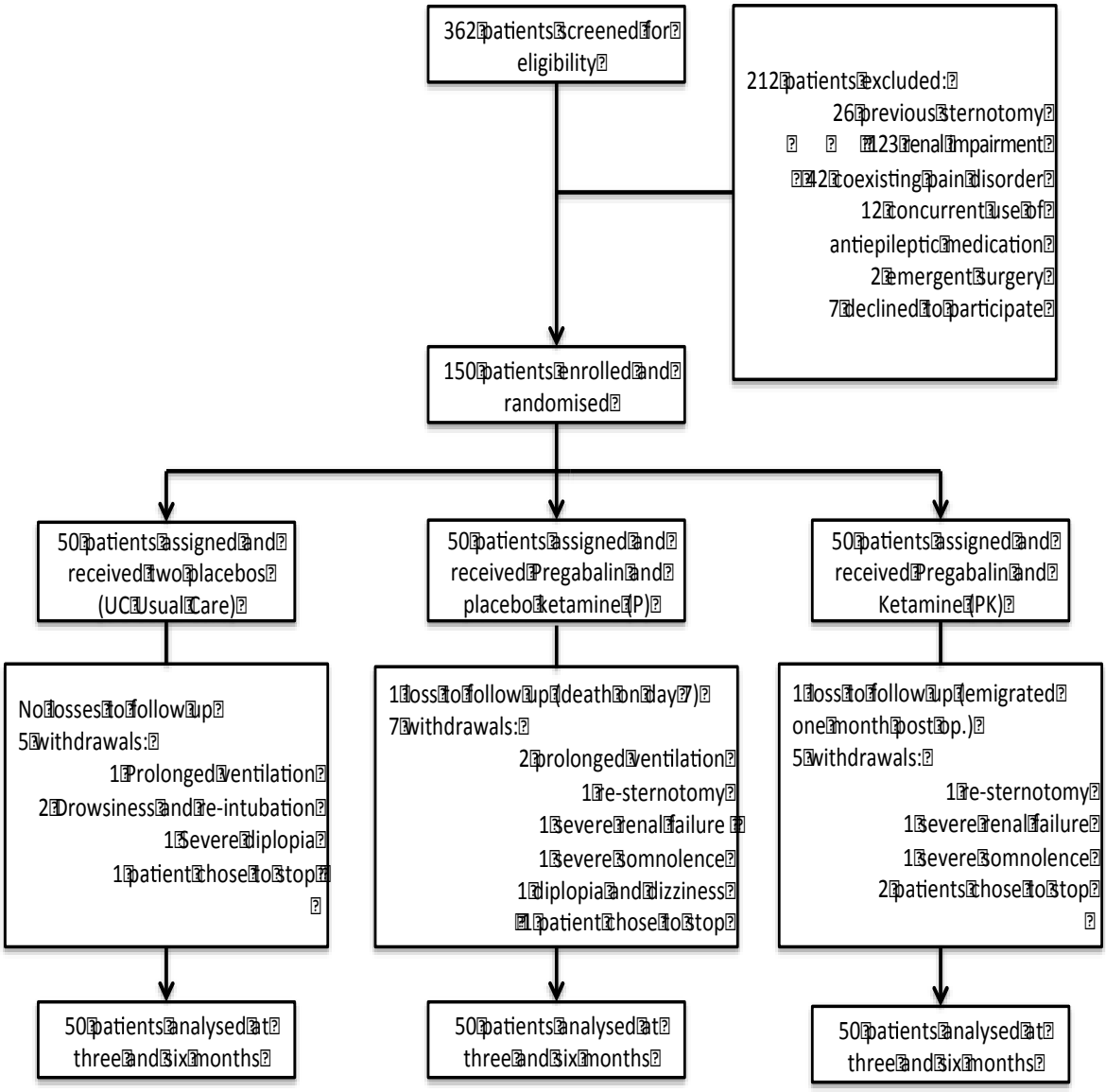

Figure 4.2 CONSORT diagram of patient flow through the RCT

4.4.2 Baseline characteristics

Baseline values were similar among the three groups (table 4.1) including quantitative sensory testing (PPT= Pain Pressure Threshold and CPM= Conditioned Pain Modulation) as well as psychological measures - see subsequent chapters.

	Trial groupings		
	Usual care (UC)	Pregabalin (P)	Pregabalin & ketamine (P+K)
Male sex (%)	36/50 (72%)	41/50 (82%)	40/50 (80%)
Age (years)	63.4 (11.4)	64.9 (12.8)	61.8 (12.4)
Weight (Kilograms)	80.1 (15.9)	77.9 (14.1)	78.2 (15.1)
Pre op EQ-5D index	0.597 (0.310)	0.563 (0.301)	0.538 (0.322)
Anxiety: Spielberger score	39.3 (12.5)	38.2 (8.8)	41.2 (11.8)
Catastrophising: Pain Catastrophising Scale score	16.4 (12.3)	16.2 (12.3)	17.7 (12.9)
Percent change in PPT with CPM	37.0 (49.0)	29.7 (25.9)	29.5 (40.9)

Presence of preoperative temporal summation at the sternotomy site	17/50 (34%)	15/50 (30%)	14/50 (28%)
Presence of remote temporal summation (forearm)	10/50 (20%)	9/50 (18%)	9/50 (18%)
Duration of surgery (minutes)	278 (60)	296 (93)	305 (95)
LIMA dissection	35/50 (70%)	39/50 (78%)	37/50 (74%)

Table 4.1 Baseline characteristics of patients as per randomisation group
Data is presented as portion (percentages) or mean (standard deviation) PPT= pressure pain threshold, CPM= conditioned pain modulation, LIMA= left internal mammary

4.4.3 Primary outcome

Both active arms demonstrated a significant decrease in the prevalence of pain at three and six months when compared to the control group, either unadjusted or adjusted for covariates in a mixed model (table 4.2) All these results are significant at the $p < 0.001$ level. The factors included in the mixed models are those with potential to influence the outcome, namely: age, gender, weight, preoperative EQ-5D index, state anxiety, pain catastrophising, % PPT change to CPM, Temporal summation (sternotomy site and remotely), duration and type of

surgery (involving dissection of chest arteries.) The QST measurements of PPT and CPM are set out in detail in subsequent chapters.

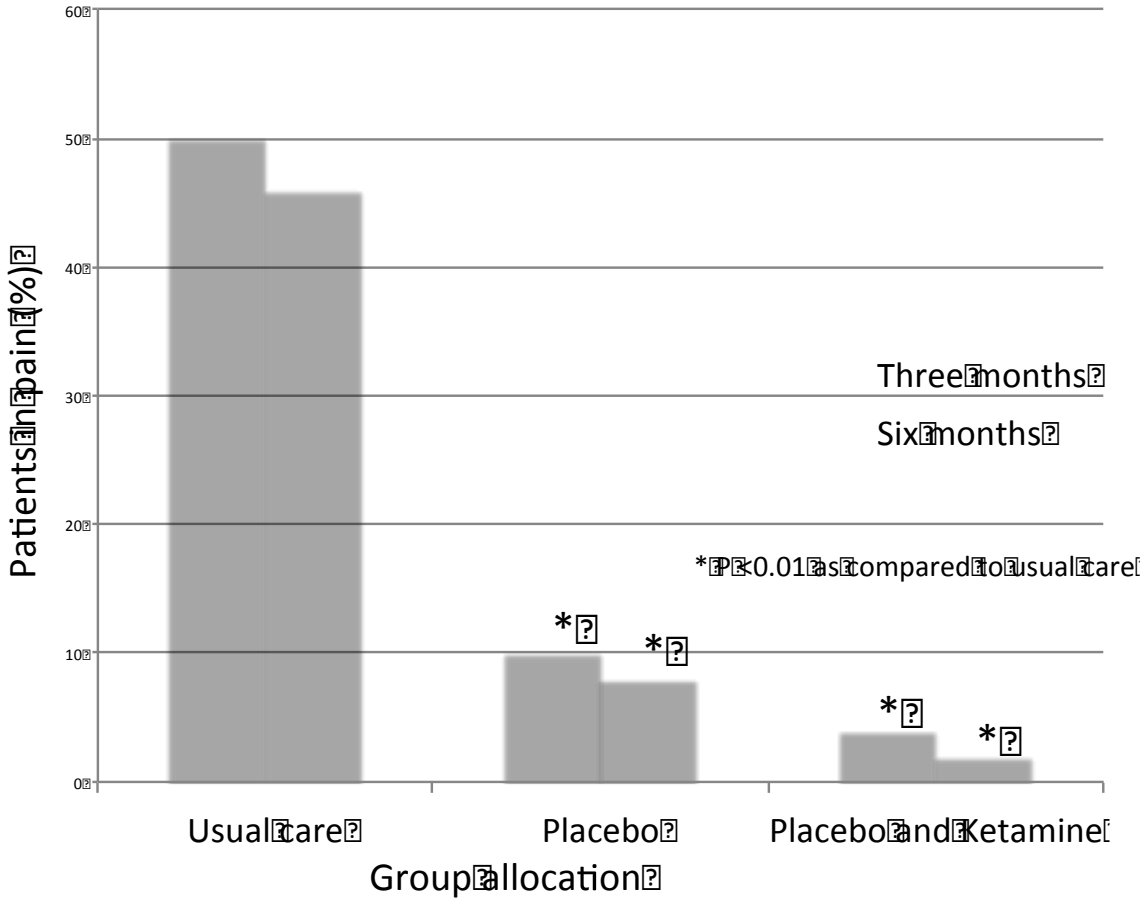

Figure 4.3 Primary outcomes
Proportion of patients with pain, at 3 and 6 months, based on the NRS. Logistic regression across treatment arms revealing p values < 0.01 as compared to usual care. Non-significant differences found between the two active arms.

Comparisons between the two active arms for the primary outcome reveal no difference in efficacy (OR=0.99, 95% CI: -3.00 to 5.00, P=0.62.) No further

comparison is therefore made between the active arms, as this study is not powered to detect such changes.

4.4.4 Secondary outcomes:

Both active arms reported significant decrease in acute pain scores when compared to the control arm (3.04 on the NRS for group P unadjusted and 2.823 adjusted; 2.98 for group PK and 3.058 adjusted for the other variables.) These differences are significant at a level of $p<0.001$ (table 4.2).

In terms of the potential sedating effects of the pregabalin and ketamine in active arms, there were no significant differences in time to extubation or length of stay on the intensive care unit (figure 4.4). Statistically significant increases in sedation scores were observed in the active arms but are unlikely to be of clinically meaningful difference. Details of all adverse events are logged in Appendix Six with the reporting organogram for SUSARs set out in Appendix Seven. Despite increased sedation in both active arms, Morphine requirement was significantly reduced, as compared to the control group (Table 4.2):

	Group allocation			Between group differences (95% CI.) Unadjusted comparison		Between group differences (95% CI.) Adjusted comparison*	
	Placebo = Usual care (UC)	Pregabalin (P)	Pregabalin & ketamine (P+K)	UC vs. P	UC vs. P+K	UC vs. P	UC vs. P+K
PRIMARY OUTCOMES:							
Prevalence of PPP at 3 months following surgery	25/50 (50%)	5/50 (10%)	2/50 (4%)	Odds ratio: 0.111 (0.038 to 0.326) P<0.001	Odds ratio: 0.042 (0.009 to 0.190) P<0.001	Odds ratio: 0.046 (0.011 to 0.200) P<0.001	Odds ratio: 0.002 (0.000 to 0.046) P<0.001
Prevalence of PPP at 6 months following surgery	23/50 (46%)	4/50 (8%)	1/50 (2%)	Odds ratio: 0.130 (0.044 to 0.383) p<0.001	Odds ratio: 0.024 (0.003 to 0.187) p<0.001	Odds ratio: 0.038 (0.007 to 0.207) p<0.001	Odds ratio: 0.001 (0.000 to 0.031) p<0.001

SECONDARY OUTCOMES:							
Acute pain score - at rest: Sternotomy (NRS)	4.10 (3.13)	1.06 (1.36)	1.12 (1.80)	-3.04 (-4.00 to -2.08) p<0.001	-2.98(-3.99 to -1.97) p<0.001	-2.82 (-3.79 to -1.85) p<0.001	-3.06 (-4.05 to -2.06) p<0.001
Acute pain score - cough: Sternotomy (NRS)	4.10 (3.13)	1.06 (1.36)	1.50 (2.12)	-2.56 (-3.77 to -1.35) p<0.001	-3.08 (-4.35 to -1.81) p<0.001	-2.45(-3.67 to -1.23) p<0.001	-3.23 (-4.60 to -2.00) p<0.001
Acute pain score - at rest: Saphenectomy (NRS)	3.72 (3.11)	0.92 (1.50)	0.12 (0.77)	-2.80 (-3.94 to -1.67) p<0.001	-2.22 (-3.45 to -1.00) p=0.003	-2.32 (-3.57 to -1.07) p<0.001	-2.01 (-3.24 to -0.78) p=0.002
Morphine consumption at 24hrs (mg)	57.86 (27.63)	27.86 (14.46)	25.24 (16.74)	-30.00 (-38.75 to -21.24) p< 0.001	-32.62 (-41.68 to -23.55) p< 0.001	-28.05 (-36.94 to -19.16) p< 0.001	-32.59 (-41.76 to -23.41) p< 0.001

Side effect analysis: Extubation time (minutes)	407 (196)	424 (231)	441 (266)	17 (-68 to 102) p = 0.689	34 (-59 to 127) p = 0.467	27 (-63 to 117) p = 0.556	11 (-82 to 103) p = 0.824
ICU stay (hours)	20.6 (12.07)	16.9 (8.75)	17.9 (11.14)	-3.71 (-7.90 to 0.48) p=0.082	-2.72 (-7.33 to 0.109) p=0.245	-3.20 (-7.61 to 1.22) p= 0.154	-2.97 (-7.58 to 1.63) p= 0.202
Sedation score	Median= 2 (IQR=0)	Median= 2 (IQR=1)	Median= 2 (IQR=1)	Mann Whitney p=0.044	Mann Whitney p=0.035	N/A	N/A
Nausea score	Median= 2 IQR 2	Median= 0 IQR 0	Median= 0 IQR 1	Difference = -2 P=0.003	Difference= -2 p=0.005	N/A	N/A

Prevalence of diplopia	4/50 (8%)	12/50 (24%)	15/50 (30%)	Hazard ratio= 3.63 (1.08 to 12.2) p=0.037 NNH=6.25	Hazard ratio= 4.93 (1.50 to 16.2) P=0.008 NNH=4.54	Hazard ratio= 4.03 (0.045 to 15.6) P=0.043	Hazard ratio= 6.81 (1.68 to 27.5) P=0.007
Respiratory rate at 24 hours (breaths/min)	12.4 (4.54)	14.9 (3.68)	14.9 (3.40)	2.56 (0.918 to 4.20) p= 0.003	2.50 (0.906 to 4.09) p=0.002	2.01 (0.50 to 3.68) p=0.011	2.22 (0.67 to 3.78) p=0.006
pCO2 = blood carbon dioxide tension (KPa)	5.73 (0.88)	5.14 (0.58)	5.22 (0.76)	-0.580 (-0.884 to -0.292) p<0.001	-0.51 (-0.838 to -0.183) p=0.003	-0.524 (-0.82 to -0.23) p=0.001	-0.525 (-0.854 to -0.195) p=0.002
Recovery: Extubation time (minutes)	407 (196)	424 (231)	441 (266)	17 (-68 to 102) p = 0.689	34 (-59 to 127) p = 0.467	27 (-63 to 117) p = 0.55	11 (-82 to 103) p = 0.82

ICU stay (hours)	20.6 (12.07)	16.9 (8.75)	17.9 (11.14)	-3.71 (-0.790 to 4.75) p=0.082	-2.72 (-7.33to 1.89) p=0.245	-3.196 (-7.61 to 1.22) p= 0.154	-2.97 (-7.58 to 1.63) p= 0.202
Length of stay in hospital (days)	Median = 7.5 (IQR =9)	Median = 6.5 (IQR=4)	Median = 6 (IQR= 3)	1 day Mann Whitney P= 0.023	1.5 days P= 0.002	N/A	N/A
Quality of life: EQ-5D Index	0.323 (0.302)	0.619 (0.267)	0.661 (0.156)	0.296 (0.183 to 0.409) p<0.001	0.338 (0.242 to 0.4330) p<0.001	0.309 (0.197 to 0.420) p<0.001	0.369 (0.277 to 0.4610) p<0.001
EQ-5D VAS	48.2 (22.1)	68.6 (21.1)	71.2 (12.8)	20.4 (12.0 to28.0) p<0.001	23.0 (15.8 to 28.2) p<0.001	22.7 (14.5 to 30.9) p<0.001	26.3 (19.5 to 33.2) p<0.001

Prevalence of neuropathic pain at sternotomy site	16/50 (32%)	3/50 (6%)	0/50 (0%)	Odds ratio 0.185 (0.057 to 0.603) P= 0.005	N/A (zero event)	Odds ratio 0.126 (0.028 to 0.560) P=0.007	N/A (zero event)
Prevalence of neuropathic pain at saphenectomy	8/38 (21%)	1/42 (2%)	0/41 (0%)	Odds ratio 0.183 (0.036 to 0.924) P=.0040	N/A (zero event)	Odds ratio 0.149 (0.008 to 2.762) p=0.201	N/A (zero event)
Analgesics required for sternotomy site or leg pain	22/50 (44%)	7/50 (14%)	1/50 (2%)	Odds ratio 0.176 (0.067 to 0.466) p<0.001	Odds ratio 0.022 (0.003 to 0.173) p<0.001	Odds ratio 0.115 (0.036 to 0.370) p<0.001	Odds ratio 0.001 (zero to 0.45) p<0.001
Sleep disturbed as a result of sternotomy site or leg pain	19/50 (38%)	5/50 (10%)	1/50 (2%)	Odds ratio =0.167 (0.056 to 0.492) p=0.001	Odds ratio 0.031 (0.004 to 0.240) p=0.001	Odds ratio 0.108 (0.029 to 0.403) p=0.001	Odds ratio 0.006 (zero to 0.092) p<0.001

Table 4.2 Primary and secondary outcomes

Data is presented as proportion, mean (standard deviation) or median (interquartile range.) Comparisons are presented as odds ratios, mean differences (95% confidence interval) or Mann Whitney test result. *Comparison adjusted for age, gender, weight, preoperative EQ-5D index, state anxiety, pain catastrophising, % PPT change to CPM, Temporal summation (sternotomy site and remotely), duration and type of surgery

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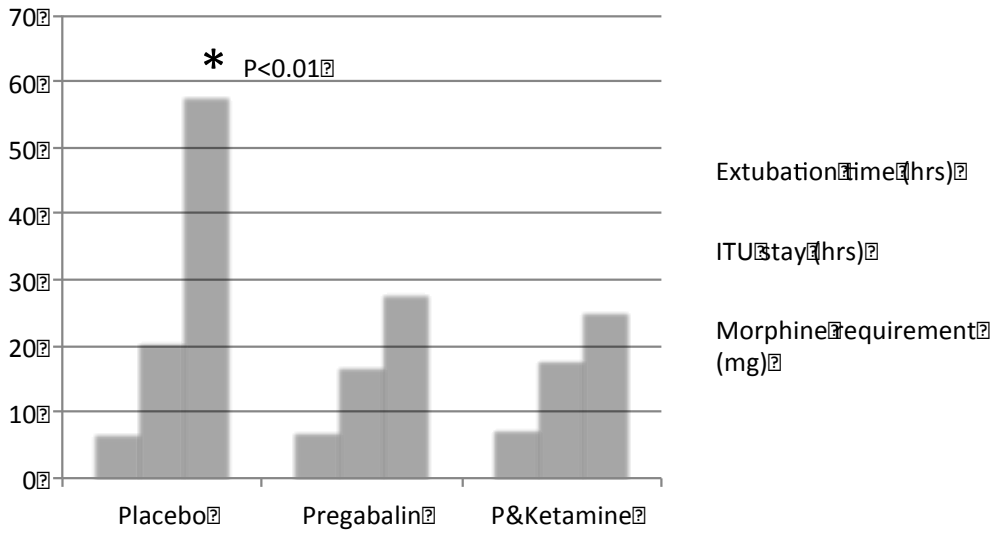

Figure 4.4 Secondary outcomes of recovery, as per randomisation group.
Linear regression of y-axis values of hours for extubation time/ ITU stay and milligrams for morphine requirement. Statistical significance is only achieved for morphine requirement in both arms as compared to placebo/ usual care.

Length of stay was significantly different between control group and each of the active arms (Median difference =1 day for group P and 1.5 day for group PK.)

Comparison between both active arms however leads to a non-significant difference of 0.5 days (p=0.678).

Both active arms lead to significant differences in quality of life as measured by EQ-5D. This is translated into lower use of analgesics, as well as reduced prevalence of sleep disturbance.

Only one patient died during the conduct of the study and therefore mortality comparison across groups was not carried out.

4.5 Discussion

This data suggests a large effect of pregabalin on both acute and chronic pain outcomes following cardiac surgery, which in this study translated into improved quality of life and function at three months. These differences are sustained at six months following surgery.

The size of these differences in this study is surprising and may in part be explained by study design. Unlike most other studies of preventive analgesia, our study was devoid of confounders of other potential preventive analgesia e.g. regional anaesthesia. The aim was also to study a group of surgical patients who would be free of preoperative (e.g. cancer) pain but would subsequently

experience significant postoperative pain, with a high incidence of PPP (26, 156). The additional benefit of this particular surgical model is the inpatient stay covers a sufficient period of time to ensure compliance with at least the initial trial regimen.

The currently employed analgesic regimen for cardiac surgery may be considered insufficient and out of date, being largely reliant on intravenous opioids, with little use of adjunct analgesics (3, 157, 158). This is likely to contrast with usual care for other surgical procedures where enhanced recovery and short stay (or day case) care is established and practiced e.g. knee surgery .

It is also possible that there is a unique feature of cardiac surgical patients, which may make this particular group of surgical patients more susceptible to the preventive effects of pregabalin. In particular, TS may be pronounced in this group (secondary to visceral hypersensitivity from ischaemic pain, in particular) and this may be more responsive to pregabalin than other surgical models e.g. thoracotomy. This is a hypothesis based on personal communication with Professor David Yarnitsky at the IASP (International Association for the Study of Pain) World Congress on Pain in 2014 and therefore requires further investigation.

There seems to be little difference between the two active interventions, i.e. the additional benefit of ketamine appears to be discernable as a small trend but not statistically significant at the level of powering in this study, which was not designed or powered to detect differences between the two active arms.

The relative contribution of opioid induced hyperalgesia is discussed in following chapters on mechanistics but is likely to have played a role in both acute and chronic pain scores. Opioid sparing may be leading to - and not just an effect of - improved pain, by reductions in OIH. In addition to reduced OIH, opioid sparing may also facilitate recovery from major surgery, with earlier of return of normal bowel function as well as engagement with rehabilitative strategies, such as physiotherapy (159). This causality, or 'chicken or egg ' question, is difficult to examine without randomising patients to differing opioid regimens – beyond the scope of this study.

Assessments of pain with movement are recognised as sensitive discriminators of post-surgical pain (149, 160) However the effect of pregabalin seems so large in this study as to limit the additional benefit of this assessment, leading to similar scores as those at rest.

Interestingly, only a minimal placebo effect is seen in the control arm. This is very different to the significant placebo seen in analgesic studies (161, 162) and

is difficult to explain. It is possible to speculate that this is related to the complex and prolonged nature of the surgery and recovery, with perhaps reduced ability of participants to remember and attribute preventive analgesic effect to the placebo. It is also possible that postoperative cognitive dysfunction which is a recognised and common effect of cardiac surgery may have impacted on this reduced effect (163, 164) of recall and therefore placebo.

A nocebo effect is however observed in the control arm with patient reporting of diplopia as well as withdrawals due to intolerability to drug (161).

There is a statistically significant improvement in blood levels of carbon dioxide as well as recorded respiratory rate in the active arms, possibly due to the opioid sparing effect of the agents. However these differences are too small to be clinically meaningful.

Tolerability is an issue in this study. The drug specific effects of diplopia and dizziness were significantly increased in both active arms leading to 'Number Need to Harm' (NNH) of 6.25 and 4.54 for group P and PK respectively. This therefore may justify a dose-finding (or even a 'duration-finding') study, to improve tolerability of the regimen.

4.5.1 Study limitations

There is an argument to be made for the use of continuous scales such as the Visual Analogue Scale (VAS) to increase accuracy, as compared to the 11-point NRS. However the use of NRS is proposed by the National Institutes of Health 'Toolbox' for acute pain and analgesic efficacy studies (165). The overall consensus in the current literature suggests the appropriate use of NRS in unidimensional settings of pain intensity, such as this trial (166).

Face to face assessment of patients at three and six months was logistically impossible given the large geographical catchment area of our hospitals, extending throughout South East England and as far as South Wales. It is however acknowledged that phone call interviews may lead to reporting bias. This was minimised by the use the S-LANSS tool, which is validated for use with phone interviews(147), as well as structured, script-based assessments of PPP as set out in Appendix Four and Five.

This study is underpowered for comparisons between the active arms, as this would likely have involved many hundreds of patients with associated costs and timelines, which were deemed not feasible.

A fixed dose regimen was used on all patients regardless of weight. In addition, there was no scope within this study to titrate dose to individual response or tolerability. A more complex design may have made this possible, but in fact may not be a practical solution for the routine clinical setting. Further studies at fixed lower doses or for shorter periods of administration may be useful to find the best risk-benefit ratio and most effective solution.

The powerful effect of the active arms on acute pain and opioid use may have led to unblinding of patients and care givers. Some of this may have been offset by the use of active placebo (e.g. benzodiazepines.) An alternative approach is to formally assess the extent of blinding with questionnaires. In any future work, I would interview patients and investigators to assess the degree of blinding maintained throughout the study.

4.5.2 Conclusions

This clinical trial suggests a large effect of pregabalin on both acute and chronic pain outcomes following cardiac surgery, which translates into long term improved quality of life and function. While impacting on tolerability, in terms of diplopia, the large reduction in opioid use may be leading to overall improved recovery and shortened length of stay in hospital.

Having demonstrated proof-of-concept as regards the preventive properties of pregabalin in the cardiac surgical population, this justifies a multi-centre pragmatic randomised-controlled trial to definitively assess whether this intervention can demonstrate effectiveness in the 'real world'.

Chapter 5 Quantitative Sensory Testing of perioperative pain pathways

5.1 Introduction

Pain is a complex and multifaceted sensory, as well as emotional, experience. A complete description of the pain experience is therefore unlikely to ever be possible.

Certain aspects of nociceptive processing in humans can however be studied to give some insight into the overall pain experience.

Historically, clinicians took the view of a linear, hard-wired system with a 'Descartian' flow of pain information from the periphery to the central nervous system, in order to allow processing and interpretation (Figure 5.1).

Fig. 1

Figure 5.1 Descarte and the History of Pain Theory
(http://en.wikipedia.org/wiki/History_of_pain_theory Accessed 10/12/14)

However this 'Cartesian' linear explanation of pain transmission is unable to explain the variability in response between individuals to a standard stimulus. It is also unable to account for modulation of pain in different circumstances and over longer periods of time (167).

In recent times, work led by Melzack and Wall transformed the understanding of the modulation of pain processing pathways. This, in turn, has led to the understanding of descending mechanisms, inhibitory or facilitatory, which result in reduction or amplification of pain signals, respectively (168).

Quantitative Sensory Testing (QST) is one method to assess these pronociceptive (or facilitatory) mechanisms, in tandem with opposing antinociceptive (or inhibitory) pathways, in order to establish their relative roles in the overall perception of pain (169). This approach to pain testing allows quantitative assessment of evoked responses to standardised activation of the nociceptive system but with the advantage that, unlike clinical pain, experimental stimulus intensity, duration and modality are controlled and fixed over time. Only the response is patient-dependent and variable.

QST can also act as a more objective measure of the efficacy of an analgesic, as compared to subjective assessment based on pain scores, or secondary effects such as analgesic requirement in the setting of a painful condition (170).

I reviewed the QST literature to establish the modes and assessment most suited to the perioperative setting, as set out in detail in Chapter Two.

5.1.1 Pain thresholds

Response to experimental pain can be described at one of three levels:

1. Pain threshold: stimulus required to elicit baseline pain (i.e. level of first perceiving an increasing stimulus to be painful)

2. Suprathreshold: fixed stimulus causing pain but with measurement of an individual's response (e.g. pain score)

3. Pain tolerance: maximum tolerable stimulus, in terms of pain

These static surrogate measures of the pain experience provide a single snapshot of perceived pain.

An alternative is to dynamically challenge the nervous system, in order to engage any modulatory mechanisms, either inhibitory (antinociceptive/analgesic) or facilitatory (pronociceptive). These modulatory neuroplastic mechanisms are difficult to measure with static assessments of pain threshold, as they (by definition) require comparisons over time or space. If included though, they do however potentially allow an assessment of the whole range of the persistent pain experience (figure 5.2):

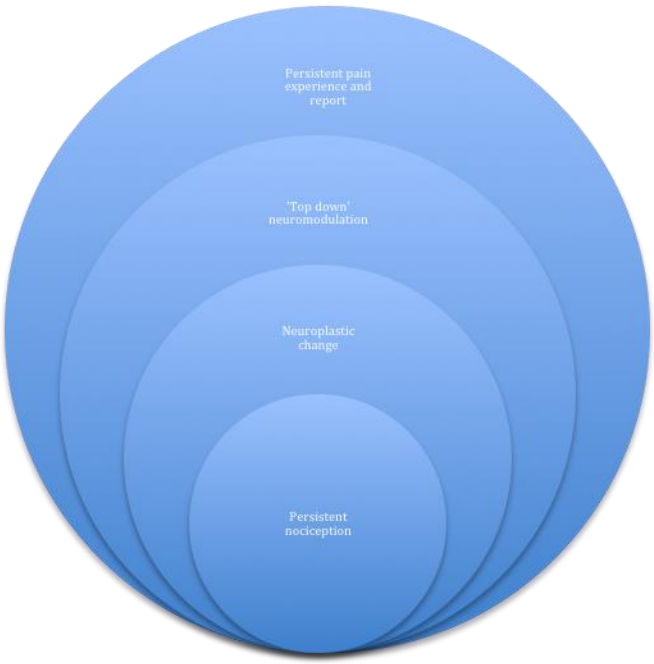

Figure 5.2 Hierarchy of pain processing leading to the pain experience

This dynamic testing, or 'challenge' to the nervous system, has led to a shift away from symptom-based pain description and towards a mechanism-based approach to diagnosing, profiling and potentially treating persistent pain (96).

The perioperative setting is distinct from widespread pain conditions as the source of pain is specific and localised. Likewise the effects of systemic analgesia in widespread pain conditions can be tested at any point on the body but, in the case of PPP, require peri-incisional testing. This has implications in terms of feasibility of testing around, for example, recently closed and dressed incisions.

However these peri-incisional measurements can be compared to more remote sites, in order to make the distinction between local (peripheral) and distant (central) changes - such as sensitisation.

5.1.2 Hyperalgesia and Central Sensitisation

Summation, as one example of the facilitation of pain, can be tested by repetitive stimulation. This provides a clinical (or in vivo) means of testing the in vitro phenomenon of wind-up, both of which act as indirect indicators for central or spreading sensitisation.

An alternative method for assessing sensitisation away from the site of tissue injury is to repeat the threshold-level stimulus - but at some distance from the incision. By approaching the incisional site and recording the point at which pain is first elicited, this allows another measure of hyperalgesia termed the 'zone of hyperalgesia.' Again this is relevant only when pain is localised (e.g. incisional) as opposed to widespread pain e.g. fibromyalgia.

Static measurements can also be useful when compared over time. A fall in pain threshold before and after surgery, for example, constitutes hyperalgesia and therefore adds a dynamic, temporal component to the assessment.

As well as establishing baseline values for comparison postoperatively, these pre-operative assessments also provide information for exploring risk factors for PPP. This is described further in the following chapter, in terms of attempts to phenotype patients before surgery, and to stratify the risk of developing PPP

These assessments of central sensitisation and hyperalgesia are by no means exhaustive, but instead provide a pragmatic battery of portable tests suitable to the testing of high-risk patients in the clinical setting.

An established and validated protocol exists for performing QST, specifically to allow the phenotyping of neuropathic pain patients. This protocol developed by the German Research Network on Neuropathic Pain (DFNS) has made the translation from a research tool to a clinically applicable measure, albeit requiring considerable time and resource in the pain QST laboratory with the patient.

My aim however was to develop a portable and reproducible ('at the bedside' or 'point of care') protocol to allow real-world, pragmatic, clinical assessment in

less than hour. I therefore modified the DFNS protocol to suit the perioperative pain environment and in particular to incorporate dynamic pain challenges, simulating the additional surgical insult which takes place on the background setting of a functional (generally pain-free) nervous system.

This tailored approach is designed to quantify the effects of analgesics on acute pain, as well as PPP, and to once again assess the effects of preventive analgesics in a prospective randomised controlled study. In this chapter, I present the findings from pre and postoperative QST assessments of the patients in the RCT described in the last chapter with the aim of studying the mechanisms of effect of the preventive analgesic regimens.

In terms of pain assessments following cardiac surgery, this is the first mechanistic (QST) study of preventive analgesia following this type of surgery. Extrapolation to other types of chest surgery (e.g. thoracotomy or major breast surgery) needs to be treated with caution but this work has potential to assist in hypothesis generation for these similar surgical procedures and trajectories of PPP (14).

5.2 Methods

As described in the previous chapter, I was granted ethics approval by the East London and the City Research Ethics Committee to study patients undergoing elective cardiac surgery. As part of the approved protocol, all patients underwent QST assessments on the day before surgery as well as postoperatively while recovering from surgery. These tests were performed around the site of sternotomy as well as remotely on the forearm.

The postoperative time period of four days was chosen to ensure that all patients were captured before discharge from hospital – given the minimum stay of five days in our hospitals. However this was also late enough to ensure a steady and sustained effect of pregabalin, as well as the cessation of the ketamine infusion.

All testing took place in a quiet environment with the patient in a comfortable semi-reclined (45 degree angle) position. Patients were asked to close both eyes for the duration of testing.

5.2.1 Baseline measurements

These were measured at four standard points on the chest around the planned site of surgery (midline sternotomy) at the level of the second and third rib

bilaterally and at 5 cm from the midline (marked as **X** on figure 5.3.) Remote measurements were taken on the right forearm at the mid point between the wrist and the elbow.

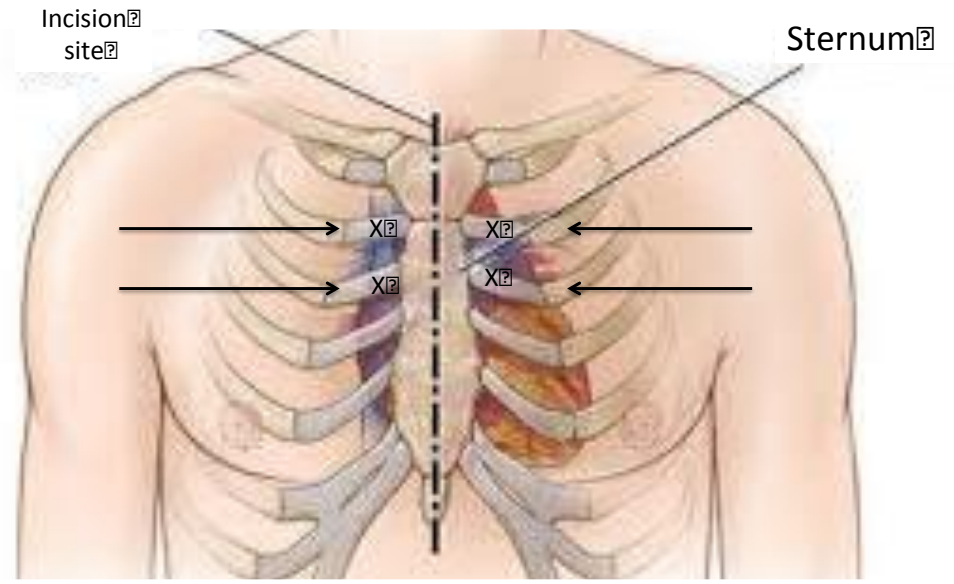

Figure 5.3 QST testing sites
X marks four testing sites at 5cm from the midline on the second and third rib bilaterally. Arrows indicate lateral starting points for zone of hyperalgesia testing, travelling at 1cm incremental steps, towards the X point.

5.2.1.1 Mechanical pain detection thresholds

Seventeen, progressively rigid, monofilament, von Frey fibres allowed the measurement of tactile pain detection thresholds (TPT) at the four standardised

points on the chest. These measurements were repeated on the right forearm to determine remote TPT.

The filaments represent stimuli from 0.039 – 4386mN. The TPT is defined as the least force that elicits a sensation of pain. The exact threshold is found by repetitive testing of ascending fibre sizes, until the same von Frey fibre elicits two similar responses in succession.

These ascending von Frey filaments were applied perpendicular to the skin for one second and to the point of deformation of the fibre until the patient described pain.

5.2.1.2 Central sensitisation assessments

Temporal summation to mechanical stimulation, again as an indicator of central sensitisation, is performed with a von Frey fibre *one reading below* the TPT. This stimulation is performed at a frequency of 2HZ for 60secs, at the four test points as well as a control measurement remotely on the forearm. NRS score increases of more than one point are reported as positive TS, as described in the literature (5, 82).

5.2.1.3 Measurement of pressure pain thresholds (PPT)

This test measures sensitivity of peripheral pain pathways to increasing mechanical pressure. A hand held pressure algometer (Figure 5.4). (Somedic AB, Stockholm, Sweden) was used to measure PPTs at the same four standardised testing points on the chest as well as the remote (right forearm) site

Figure 5.4 Pressure algometer (Somedic AB, Stockholm, Sweden)

The diameter of the contact tip is $1cm^2$. A standard pressure of 30 kPa/sec was applied perpendicular to the skin until the subject defined the pressure as pain. The mean of four, random-ordered, measurement points was used in analysis.

5.2.2 Postoperative assessment with QST

Assessments were repeated to assess changes in pressure algometry-derived thresholds. The percent change in values from baseline, following surgery, was calculated.

In addition, two dynamic assessments of central sensitisation were carried out:

Temporal summation at the site of surgery (peripheral sensitisation) in addition to remotely: on the forearm (central sensitisation.) The technique, described above, was repeated.

Zone of secondary hyperalgesia measured with the VFH used to elicit pain at the standard four points – but instead stimulating from the lateral chest towards- and perpendicular to- the midline sternotomy. The VFH was advanced in one-centimeter increments (towards the X point on figure 5.3) until the first sensation of pain was achieved. This distance from the midline sternotomy was measured using a paper tape measure. The sum of the four recording at each of the test points on the chest is used as a measure of secondary hyperalgesia and indicative of central sensitisation changes following surgery.

No further QST assessment took place. While pain assessments, in the form of structured questions, took place via phone call at three and six months, QST assessments were logistically impossible due to the large catchment areas and referral region of our hospitals – as far afield as South Wales.

5.2.3 Statistical analysis

As set out in chapter four, the study was powered against clinical outcomes of PPP and therefore there remains a potential for underpowering of the QST aspect of the study. No pilot QST data was however available for power calculations.

Data is described in term of frequencies or means for the group, with comparisons based on logistic and linear regression respectively.

5.3 Results

The original QST data per patient is set out in Appendix Nine. On analysis, the baseline values for the QST assessments were similar across all three randomisation groups, ensuring the groups are similar prior to treatment:

	Trial groupings			Intra group comparisons x3
	Usual care (UC)	**Pregabalin (P)**	**Pregabalin & ketamine (PK)**	
PPT Sternotomy site (KPa)	242 (111)	281 (102)	275 (123)	Non significant
PPT remote (KPa)	232 (114)	290 (124)	266 (140)	Non significant
Percent change in PPT with CPM	37.0 (49.0)	29.7 (25.9)	29.5 (40.9)	Non significant
Presence of preoperative temporal summation at sternotomy site	17/50 (34%)	15/50 (30%)	14/50 (28%)	Non significant
Presence of remote temporal summation (forearm)	10/50 (20%)	9/50 (18%)	9/50 (18%)	Non significant

Table 5.1 Baseline QST measurements
Data is presented as mean (SD) or proportions (%) PPT = pressure pain threshold, CPM = conditioned pain modulation

Both active arms demonstrate an increase in PPT when tested at a site remote to the incision (table 5.2). The control group however demonstrates a decrease in the PPT, indicating hyperalgesia (by definition.)

Similar testing at the site of sternotomy however reveals non-significant differences in hyperalgesia following surgery in the treatment arms. It is possible to speculate the additional nociceptive pain has balanced out any benefit of anti-neuropathic effect of the trial drugs, leaving no overall benefit.

	Trial groupings			**Between group differences (95% CI)** **Unadjusted comparison**		**Between group differences (95% CI)** **Adjusted comparison***	
	Placebo = Usual care (UC)	Pregabalin (P)	Pregabalin & ketamine (P+K)	UC vs. P	UC vs. P+K	UC vs. P	UC vs. P+K
% change in PPT sternotomy site from baseline	-11.9 (41.3)	-3.89 (36.2)	-10.3 (37.6)	7.99 (-7.42 to 23.4) p=0.306	1.57 (-14.1 to 17.2) p=0.843	-2.97 (-5.74 to 24.64 p=0.219	3.39 (-12.58 to 19.35 p=0.67
%change in PPT remote from baseline	-19.6 (31.8)	8.70 (32.9)	15.7 (45.9)	28.3 (11.7 to 44.8) p=0.001	35.3 (14.9 to 55.7) p=0.001	25.60 (10.26 to 40.95) p=0.02	37.766 (17.115 to 58.42) p=0.001
New TS at sternotomy site	17/50	3/50	2/50	0.136 (0.037 to 0.503) p=0.003	0.089 (0.019 to 0.411) p=0.002	0.012 (0.00 to 0.21 p=0.003	0.011 (0.00 to 0.21) p=0.003

New TS at remote site	16/50 (32%)	5/50 (10%)	3/50 (6%)	0.236 (0.079 to 0.708) p=0.010	0.136 (0.037 to 0.503) p=0.003	0.153 (0.041 to 0.569) p= 0.005	0.061 (0.012 to 0.318) p = 0.001
Loss of TS at sternotomy site	4/50 (8%)	4/50 (8%)	7/50 (14%)	1.00 (0.236 to 4.24) p=1.000	1.872 (0.512 to 6.85) p=0.343	1.23 (0.885 to 3.25) p=0.657	1.855 (0.415 to 5.44) p=0.564
Loss of TS at remote site	2/50 (4%)	6/50 (12%)	5/50 (10%)	3.27 (0.627 to 17.0) p=0.159	2.67 (0.492 to 14.4) p=0.255	3.98 (0.549 to 12.8) p=0.342	2.01 (0.593 to 12.9) p=0.337
Zone hyperalgesia	34.9 (19.0)	18.8 (15.2)	14.2 (12.1)	-16.14 (-22.97 to -9.31) p <0.001	-15.60 (-21.76 to -9.44) p <0.001	-20.73 (-27.04 to -14.42) p <0.001	-20.77 (-27.15 to -14.39) p <0.001

Table 5.2 QST changes dependent on treatment arm
Proportions with odds ratios or mean difference (95% CI) and p values

Although comparisons for PPP between the two active arms are limited due to underpowering- see Chapter Four- I nevertheless carried out an exploratory analysis for effect of additional ketamine on zone of hyperalgesia. This was performed as a post hoc analysis, as ketamine is believed to reduce hyperalgesia in a more effective manner than other agents, such as pregabalin.

This exploratory analysis reveals a mean reduction in the zone of 4.59 cm with the addition of ketamine (95%CI 10.0 to 0.866) giving a non-significant p value of 0.098. This is again likely to be due to underpowering, but provides a signal that ketamine may potentially have an effect on hyperalgesia, if tested in a larger study population. The effect of ketamine in isolation is difficult to assess adequately, however, as it was administered in a multimodal arm along with pregabalin.

A similar analysis for all other dynamic, as well as static QST measures, between the two active arms reveals non-significant differences. As an example: comparison of new TS at the chest reveals a B value of 0.653 (95% CI of 0.104 to 4.085) p =0.648 and, similarly, new TS remotely gives a B value of 0.574 (95%CI 0.130 to 2.55) and p= 0.465

5.4 Discussion

Both active arms demonstrated the potential to mitigate the development of the indirect markers of central sensitisation as shown by the results for TS and Zone

of Hyperalgesia. That pre-existing TS was not shown to subside significantly may be a reflection of the relatively short interval of four days between baseline and post-operative measurements, and/or continuing post-operative pain signals maintaining central sensitisation at this time.

Both drugs seem to increase PPT. This is surprising and contradicts previous work demonstrating the stability of PPT (171), even with analgesics. However this may reflect the anti-neuropathic effects of pregabalin or ketamine and therefore may give an indication of the mechanism of action of these drugs.

QST is used to assess small fibre sensory function and therefore is able to describe abnormalities in these fibres when associated with pain states. My results therefore add weight to the argument that the early development of PPP is unrelated to large fibres changes following nerve injury, transection or contusion. This therefore adds doubt to the hypothesis of inadvertent intraoperative nerve injury and the potential for protecting patients by early identification and elective transection of nerves (81). One way to reconcile these differences is to accept the fact that PPP demonstrates different features following different procedures – procedure specific study is the only way to confirm this.

5.4.1 Limitations

Pain pressure thresholds were measured instead of supra threshold measurements or pain tolerance. This may have limited the sensitivity of assessments (5, 101).

Published work from settings other than PPP, in particular pre clinical studies, use Wind Up Ratios as a means to comparing changes in pain as a result of the TS test. I chose to use the alternative TS technique of assessing any increase in pain as a positive test (5, 82). It is possible to speculate that the results may have varied with the WUR approach as well as providing continuous ratio data for analysis, increasing statistical power, for example, as compared to binary outcomes.

Certain QST assessments were underpowered. I may have considered powering against all secondary outcomes, including QST, rather than simply the primary outcome of PPP. This would however have necessitated a prospective pilot study of the RCT prior to the main recruitment.

QST was found to be impractical around a dressed saphenectomy leg wound and therefore this study is only able to comment on post-sternotomy changes. Ideally this could have been carried out a later stage e.g. follow-up outpatients clinic once all dressings had been removed.

5.4.2 Conclusions

Evidence is presented for an objective and mechanistic assessment of the efficacy of pregabalin in preventing PPP. This ability to measure the sensory changes present during surgical pain states hold great potential to allow further study of the transition to PPP as well efficacy studies of analgesics, acute as well as preventive.

Chapter 6 Making Predictions – Towards the identification of individuals at risk of developing PPP

6.1 Introduction

"Prediction is very difficult, especially if it's about the future."

Figure 6.1 Nils Bohr; Nobel Laureate in Physics
Available at http://micro.magnet.fsu.edu/optics/timeline/people/bohr.html Accessed on 10/12/14)

The prevalence of chronic pain in society is increasing, with new as well as established therapies not necessarily improving outcomes in patients with persistent pain (172). Neuropathic pain is particularly difficult to treat (173).

Likewise, established PPP (of any type) is often resistant to treatment (174). Prevention of PPP, in the form of pharmacotherapy, therefore holds great promise - but varying tolerability remains an issue due to drug side effects. The early identification of high-risk patients to allow targeted therapy is an attractive solution to this dilemma.

Phenotyping of patients based on their psychophysical and neurophysiological response to experimental pain is one such approach to risk profiling.

In the previous chapter, I discussed the use of QST as a method for measuring postsurgical pain as well as analgesic response. Differences in response to standardised stimuli were described when antihyperalgesic agents were applied to the perioperative setting. However three questions remain to be answered:

1. Do pre-operative pain challenges simulate surgical pain and therefore predict the nervous system response to subsequent surgical insult?
2. Do early QST changes following surgery predict long term outcome?
3. Can we predict PPP with methods other than QST?

6.1.1 QST as a means to phenotyping high risk patients

Quantitative sensory testing (QST) measures input–response relations within the nervous system, allowing detection and quantification of nociceptive neuroplasticity (96). This nervous system input-response relationship is very different though from the overall pain experience and its clinical assessment, in terms of pain score or secondary effects on analgesic consumption (175).

As an experience, pain is both subjective and ubiquitous and therefore its objective assessment at any given point in time poses challenge. Dynamic, repeated measurements over time can however increase the likelihood of capturing the real pain experience by engaging descending pathways, to give an integrated response.

Descending pain modulatory circuits exist to allow filtering of nociceptive transmission by the central nervous system, in order to inhibit or facilitate input - to varying degrees, under differing conditions. This so-called 'top down' control of pain is greatly influenced by emotional and cognitive factors as a result of connections in the brainstem centres of the medulla.

6.1.1.1 Conditioned Pain Modulation

HIPPOCRATES: "If two sufferings take place at the same time, but at different points, the stronger makes the weaker silent"

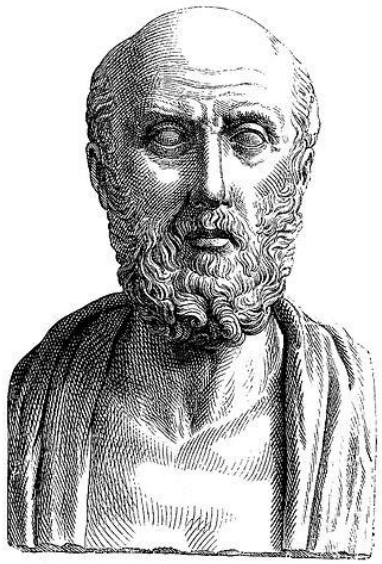

Figure 6.2 Hippocrates; Roman portrait bust
(Available at http://en.wikipedia.org/wiki/Hippocrates Accessed 10/12/14)

The ability of an organism to moderate and influence pain impulse from the periphery in a 'top-down' manner is termed "counter irritation" or diffuse noxious inhibitory control (DNIC.) This DNIC-like effect can be simulated in humans by applying a painful stimulus while measuring pain in a secondary site, using QST. This platform or protocol of testing in humans is termed Conditioned Pain Modulation (CPM) and its *inefficiency*, or limited ability to reduce the

intensity of pain experienced in the secondary site, is linked to idiopathic pain syndromes such as fibromyalgia and temporomandibular joint (TMJ) pain. This phenomenon has been described in terms of an 'endogenous analgesic system' (49, 106). There is some evidence for its inefficiency in persistent pain following injury - as well as return of efficiency following the removal of peripheral painful stimulus e.g. in the case of knee replacement for osteoarthritis (176).

This has led to a field of work investigating the physiological mechanisms underlying the ability of some individuals to modulate their response to painful stimulus via intact or *efficient* CPM (105), while others are inefficient – and, at the extreme end of the biological spectrum, may be pronociceptive and in fact summate (105, 177, 178).

In addition to this diffuse effect of CPM (mediated at the spino-bulbar-spinal level) there is also another important descending pain modulatory circuit contributing to the net stimulus reaching the central nervous system.

The RVM (rostral ventromedial medulla) communicates with the periaqueductal gray of the midbrain to generate pro or antinociceptive actions from ON or OFF cells, respectively. The balance shifts from predominantly ON in acute inflammation to a more even balance as healing takes place. However, in persistent pain states, an imbalance is maintained, whereby normally mild, innocuous stimuli continue to activate ON cells. Pain transmission therefore

remains disinhibited, leading to hyperalgesia and allodynia.

These facilitatory and inhibitory pathways can be examined in isolation in preclinical models. In human experimental models, however, the net effect is seen. For example, ischaemic arm pain in humans increases the pain threshold measured at the forehead or at the dental pulp (179). These changes are maintained with removal of the conditioning stimulus and therefore reflect more than distraction.

The relative contribution of the different descending modulatory systems is variable and dynamic. Therefore further understanding of their function and role before and after surgery in controlling transmission has potential to help understand an individual patient's risk of developing PPP.

Most of this work has been carried out in patients with established chronic pain, especially idiopathic disorders such as TMJ and fibromyalgia. One study investigating new PPP, in pain free patients, demonstrated the correlation between preoperative CPM and resulting thoracotomy pain at six months with OR of 0.52 (0.33–0.77 95% CI, $p = 0.0024$ in only 62 patients) (180).

6.1.1.2 Temporal summation

As described in the previous chapter, temporal summation is the in vivo equivalent of wind up demonstrated in spinal wide dynamic range (WDR) neurons and is enhanced in certain idiopathic pain syndromes. Although I demonstrated changes in this phenomenon with the use of antihyperalgesic agents at the time of surgery, there is potential to examine whether pre-existing TS, as well as early changes in TS following surgery, can predict the development of subsequent PPP. Only one study in the literature demonstrates predictability of acute pain with preoperative TS but the patients are not followed up for PPP (82).

When combining ischaemic heart disease patients with those with valve disease, there is an even greater consideration to be made for the role of pre-existing central sensitisation in the chest from, for example, long standing ischaemic visceral pain. Therefore, it was also necessary to examine all patients preoperatively for preexisting sensitisation (in the form of temporal summation, for example), in order to take into consideration this potential confounder.

6.1.2 Psychological vulnerability and resilience as a predictors of risk

No data is available, to the best of my knowledge, regarding the effects of preoperative anxiety or catastrophising on PPP following cardiac surgery.

In chapter two, I set out the PPP literature in terms of psychological comorbidity and, in particular, trait. There is good robust evidence for the role of anxiety trait in particular (including following cardiac surgery) but with conflicting evidence for state anxiety. The evidence base is also increasing as regards catastrophising but with little evidence to date in the cardiac surgical setting (67). The thoracic surgery literature is better developed (77). I therefore investigated the effect of state anxiety and catastrophising (using the tools set out in Appendices Two and Three) on PPP specifically in the cardiac surgical population.

6.1.3 Patient and surgical risk factors for PPP

Finally, the potential roles of patient demographics (age and gender), as well as surgical characteristics (of prolonged operation and poorly managed acute pain), are discussed in the analysis of a cohort of 174 patients in chapter three. This study allows corroboration of these findings.

6.2 Methods

To address the question of predictability, I analysed five potential predictors:

1. Perioperative QST changes, as described in the previous chapter
2. Baseline measurements of CPM
3. Psychology assessments of state anxiety and catastrophising
4. Patient demographics of age and gender
5. Surgical risk factors (duration of surgery, LIMA harvest and acute pain.)

6.2.1 Perioperative QST changes

As set in the previous chapter, QST changes were observed as a result of surgery and, in particular, the treatment allocated by randomisation. However it is possible to speculate that these early perioperative changes may give indication of the transition from acute pain to more persistent changes in pain processing leading eventually to PPP. This could apply to patients receiving usual care as well as those benefitting from preventive analgesia.

6.2.2 Conditioned Pain Modulation (CPM)

A key component of conditioned pain modulation is engagement of the endogenous analgesic system to reduce pain intensity or increase threshold to pain detection or tolerance. CPM was therefore calculated as the difference in algometer-derived PPT reading following the application of the conditioning remote noxious stimulus.

Figure 6.3 Pressure algometer (Somedic AB, Stockholm, Sweden)

Conditioning was chosen as ischaemic arm pain (figure 6.4). This is an accepted procedure in cardiac surgical patients as part of the remote ischaemic preconditioning (RIPC) platform for cardioprotection (181). Therefore the logistics – and indeed risks to the patient of preoperative severe pain increasing

risk of stress and ischaemia- were specifically addressed. It also lends itself to bedside testing, unlike a thermal testing protocol, for example, where high-risk cardiac surgical patients may need to leave the monitored, clinical setting to attend the pain QST laboratory.

The pain challenge component of CPM was achieved by inflating the right arm to 250mm Hg for 15 minutes - or to the point where a NRS of 5/10 in that arm. In the case that this was not achieved by the end of the 15 minutes of inflation, the cuff was further inflated in 10mm Hg increments to eventually achieve this pain score. Two patients remained refractory to this level of ischaemic pain and they were asked to clench their right fists in order to achieve adequate intensity of ischaemic pain. PPT measurements were repeated at this point (figure 6.3) to measure the CPM effect.

Figure 6.4 Ischaemic arm pain challenge

6.2.3 Psychology

All patients completed the Spielberger state anxiety and Pain Catastrophising Scale questionnaires following recruitment to the study (Appendix Two and Three respectively.)

The Spielberger state anxiety inventory (Appendix Two) is a widely used instrument for measuring transient and therefore preoperative levels of anxiety. The scale contains 20 items, with each question being scored on a four-point Likert scale. This instrument has been validated widely and exhibits excellent test-retest reliability (182).

Catastrophising is a well-known descriptor for baseline neuroticism and a likely contributor to persistent pain states (65). Most of the robust evidence, including meta-analysis of data, has taken place over the last three years and therefore since the start of this study. However the Pain Catastrophising Scale (Appendix Three) is a long-standing, validated tool for assessing pain-specific features - as set out in Chapter 2 - and each patient completed this following recruitment to the study.

6.2.4 Patient demographics and features of surgery

As described in chapter four, baseline features of age, gender, duration of surgery and dissection of the chest wall artery (LIMA) are similar across groups but this data allows comparison for the ability of these factors to predict subsequent PPP.

6.3 Results and Discussion

6.3.1 Perioperative QST changes

Analysis of QST data (presented in Appendix Nine) was initially carried out for all 150 patients and then repeated for the control group, to assess for any confounding effect of the active drugs and to allow objective assessment of the relationship between QST values (dependent on treatment allocation) and pain outcomes.

Assessments of PPT at the chest, before surgery and changes following surgery, in both the control arm and the full set of patients are not powerfully predictive of PPP (with the full set of patients only just reaching significance.)

	All 150 patients	Control arm only
Pre op PPT	0.997 (0.993 to 1.00) p=0.104	0.998 (0.993 to 1.00) p=0.430
Delta PPT (% change)	0.987 (0.974 to 0.999) p=0.041	0.990 (0.975 to 1.00) p=0.180

Table 6.1 Logistic regression analysis of the predictive power of perioperative QST changes at the surgical site
B values, with 95%CI, derived from logistic regression modelling (p value)

Different results are found at a site remote to the surgical incision (right forearm.) The baseline PPT values at the remote site remain non-predictive but changes following surgery are strongly predictive:

	All 150 patients	Control arm only
Pre op PPT	1.001 (0.997 to 1.00) p=0.735	1.004 (0.997 to 1.01) p=0.233
Delta PPT (% change)	0.936 (0.908 to 0.965) p=<0.001	0.921 (0.873 to 0.971) p=0.003

Table 6.2 Logistic regression analysis of the predictive power of perioperative changes at a remote site
B values, with 95%CI, derived from logistic regression modelling (p value)

6.3.1.1 Baseline TS measurements

These measurements were taken at the sternotomy site and remote testing points, as set out in table 6.4 below.

Pre operative recordings at the sternotomy site fail to significantly predict PPP (B=0.478 [0.213-1.073] p =0.074). Although statistically non significant, this could provide a useful signal of the contribution of ischaemia-driven visceral hypersensitivity, for example, as discussed in the conclusions section of this chapter.

Away from the chest, where there is potentially less contribution from visceral hypersensitivity of ischaemia, there is no such signal: B=0.993 [0.365-2.703]

p=0.989

6.3.1.2 Changes in TS measurement

Development of *new* TS following surgery is however powerfully predictive of subsequent PPP:

	All 150 patients	Control arm only
New TS Sternotomy site	12.3 (4.38 to 34.8) p=<0.001	7.944 (1.884 to 33.5) p=0.005
New TS remotely	13.75 (5.07 to 37.3) p=<0.001	14.6 (2.82 to 80.0) p=0.010

Table 6.3 Logistic regression analysis of the predictive power of new TS B values, with 95%CI, derived from logistic regression modelling

6.3.1.3 Measures of zone of hyperalgesia

As well as TS assessments of central sensitisation, the zone of hyperalgesia is also highly predictive, with control arm B values of 1.059 (1.02 to 1.10) p= 0.003 and grouped analysis of 150 patients revealing B= 1.071 (1.043 to 1.10) with p<0.001

6.3.2 Combined analysis of risk factors unrelated to treatment allocation

The differences in predictability between the control arms and across all randomisation groups could reflect a strong masking effect of the treatment arm. One way to examine to examine this is to analyse all 150 patients and repeat the analysis in the control arm alone:

Full 150 patient analysis:

PREDICTOR	B (95% CI)	P value
Randomisation group	B=0.162 [0.077 – 0.339]	p<0.001 **
Age	B=0.980 [O.950 – 1.010]	p=0.189
Sex	B=0.806 [O.323 –2.011]	p=0.645
Weight (kg)	B=1.018 [O.992 – 1.045]	p=0.171
Pre op Eq-5D index	B=0.343 [0.105-1.118]	p=0.076
Spielberger state anxiety	B=1.057 [1.019-1.097]	p=0.003**
Catastrophising	B=1.055 [1.021-1.089]	p=0.001**
PPT Change with CPM	B=0.987 [0.976-0.999]	p=0.033*
Preoperative presence of TS Sternotomy site	B=0.478 [0.213-1.073]	p=0.074
Preoperative presence of TS remote	B=0.993 [0.365-2.703]	p=0.989
Duration of surgery (minutes)	B=1.000 [0.995-1.004]	p=0.858
Surgical technique	B=0.594 [0.255-1.381]	p=0.226

Table 6.4 Predictive factors across all treatment arms
B values, with 95%CI, derived from logistic regression modelling (p value)

Control arm analysis (50 patients):

PREDICTOR	B (95% CI)	P value
Age	B=0.940 [O.890 – 0.992]	p=0.026*
Sex	B=1.000 [O.291 –3.437]	p=1.000
Weight (kg)	B=1.025 [O.988 – 1.064]	p=0.183
Pre op Eq-5D index	B=0.046 [0.004-0.556]	p=0.016*
Spielberger state anxiety	B=1.091 [1.026-1.159]	p=0.005**
Catastrophising	B=1.103 [1.038-1.172]	p=0.002**
PPT Change with CPM	B=0.984 [0.971-0.998]	p=0.026*
Preoperative presence of TS Sternotomy site	B=0.837 [0.259-2.700]	p=0.765
Preoperative presence of TS remote	B=1.658 [0.405-6.785]	p=0.482
Duration of surgery (minutes)	B=1.011 [1.000-1.021]	p=0.045*
Surgical technique	B=0.826 [0.246-2.776]	p=0.758

Table 6.5 Predictive factors for control arm only
B values are presented, with 95%CI, derived from logistic regression modelling (p value)
PPT =pressure pain threshold, CPM = conditioned pain modulation, TS =temporal summation

6.3.3 Treatment effect analysis

Another means to consider the potentially powerful effect of the intervention is to carry out analysis of 'treatment effect interaction' (183).

This analysis involves multivariate regression modeling of three separate factors:

- Any given potential predictor
- Randomisation group
- PRODUCT of the randomisation group and predictor (randomisation group*predictor)

This technique of analysis reveals products, which are non-significant for all the factors in table 4, with the exception of TS at the sternotomy site and duration of surgery (p=0.039 and p=0.026 respectively.) As these analyses are carried put post hoc and the p values are reasonably close to zero, these exploratory findings are not strong enough to draw any further conclusions.

6.3.4 Is the treatment able to protect vulnerable phenotypes?

Another established way to quantify the degree of protection provided by the intervention is to measure the degree of variance predicted by a particular tool across the randomisation groups (107). I chose the powerful predictability of CPM and analysed Pearson's correlations with PPP scores at three months:

All 150 patients r=-0.218 i.e. 21.8% of the variance in NRS at three months is predicted by CPM response (p=0.007).

Next I present a group-by-group analysis of the **degree of variance** of CPM:

- UC group -0.328 = 32.8% (p=0.020)
- P group -0.174 = 17.4% (p=0.231)
- PK group -0.089 = 8.9% (p=0.543)

This decrease in the contribution of CPM to subsequent PPP, in both active arms, again demonstrates a potential treatment effect interaction or protective effect and introduces the concept of 'protective' analgesia rather than simply 'preventive' analgesia (110).

6.3.5 Is QST able to predict drug efficacy?

It is difficult to test whether QST can predict drug efficacy, as the treatment arms were so effective. However comparing pain and pain free patients in the (pooled) active arms may suggest prognostic indicators, in terms of QST measures (table 6.6):

Potential QST predictor	PPP patients	Pain free patients	Between group differences
Pre op TS Sternotomy site	5/7	18/93	7.19 (1.31 to 39.5) p=0.023
Pre op TS remote	4/7	11/93	1.93 (0.343 to 10.8) p=0.457
New TS sternotomy site	1/7	4/93	3.71 (0.356 to 38.6) p=0.273
New TS remote	2/7	6/93	5.80 (0.924 to 36.4) p=0.061
% change with CPM	6.94 (12.8)	31.3 (39.0)	24.3 (-5.19 to 53.8) p=0.105
% change in postoperative PPT at sternotomy	-25.7 (53.2)	-5.69 (35.3)	20.0 (-8.53 to 48.6) p=0.167
% change in postoperative PPT at a remote site	-59.5 (31.2)	13.3 (38.8)	72.8 (-5.57 to 151) p=0.068
Zone of hyperalgesia	24.9 (17.9)	15.9 (13.4)	-9.00 (-19.8 to 1.62) p=0.095

Table 6.6 Potential predictors in patients receiving active drug
Proportions or means (SD); Between group differences are presented as odds ratios or mean differences (with 95% confidence interval.) Logistic regression for proportions and linear regression for continuous data. QST = quantitative sensory testing, PPT= pressure pain threshold, CPM = conditioned pain modulation, TS = temporal summation, %= per cent, PPP = persistent postsurgical pain.

6.4 Conclusions

My main finding from this study suggest that dynamic assessment of patients is the most useful preoperative assessment of a patients likelihood of developing PPP following cardiac surgery.

This could be considered analogous to the use of experimental exercise stress testing (CPEX – cardiopulmonary exercise testing) prior to major surgery as a lab-based simulation to the whole body stress of undergoing major surgery at a later date. Rather than statically testing individual organ systems (chest x-ray, echocardiogram, etc.) the predictability of risk and outcome is greatly increased by a dynamic challenge of the whole system, engaging adaptive and compensatory mechanisms (figure 6.5).

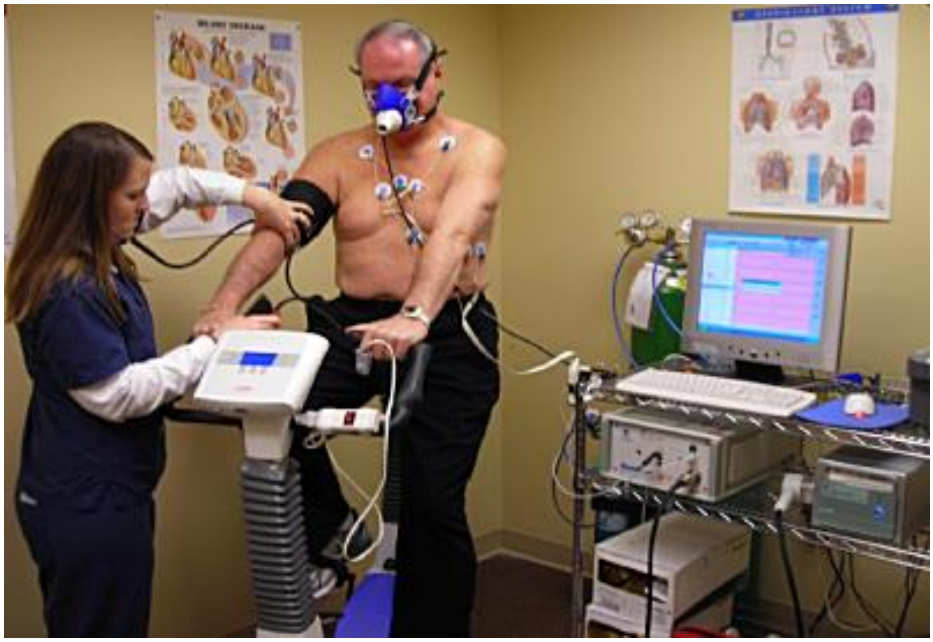

Figure 6.5 Cardiopulmonary exercise testing before surgery
(Available at http://www.wikidoc.org/index.php/Cardiopulmonary_exercise_testing Accessed on 10/12/14)

Static preoperative parameters are not predictive. It is possible to speculate that the use of suprathreshold rather than threshold measurements may have improved this component of the study (5).

However a decrease in PPT following surgery, essentially hyperalgesia, is predictive and could potentially be used as a tool for predicting outcomes. This contradicts a large study in hernia surgery with follow up assessments at three and six months revealing that temperature thresholds were not predictive (5) This is likely resulting from surgical site testing (groin) in this latter study of hernia surgery but, in my study, may be related to the use of pressure-based threshold measurements – this may be more applicable to musculoskeletal pain following chest closure.

CPM is able to predict PPP but not acute pain (according to the literature.) This is suggestive of different contributions towards pain persistence. Tissue damage in the immediate postoperative period is reflected in the amount of acute pain reported. It is therefore possible to speculate that a modulation system may not yet be able to impact on this new insult. Over time however, it may be able to adapt and therefore affect the amount of pain perceived by the individual i.e. PPP (107).

New TS is able to predict PPP whereas pre-existing summation was not significant in this study. This may reflect the fact that visceral hypersensitivity, for example, may already be engaging modulatory (mainly inhibitory) pathways, which have adapted to this need over time. Therefore they may not be flexible or responsive enough to account for additional new surgical insult. A more likely explanation is the fact that this study was underpowered to detect this effect of pre-existing TS. Alternatively, there may be a unique feature of ischaemic

hypersensitivity (and therefore preexisting summation in these patients), which may not be sensitive to the classic TS platform.

Preoperative quality of life (measured with the EQ-5D tool, as set out in Appendix One), state anxiety and catastrophising are all powerfully predictive, providing convenient and low resource methods for identifying patients at risk. I chose not to test anxiety trait as there exists a solid evidence base for trait but with conflicting evidence for the potential role of state anxiety (9) There was therefore a potential to overburden study participants with a further redundant questionnaire prior to extensive QST testing, both before and following complex surgery. However this could also be considered a limitation, as the opportunity to corroborate the predictive value of anxiety *trait* specifically, was not taken.

Surgical technique does not seem to be predictive. Patient age and duration of surgery could prove useful by increasing vigilance by care providers in the perioperative period, as well early and aggressive postoperative intervention, in younger patients or those having undergone prolonged surgery.

Caution must also be exercised regarding extrapolation findings from one to other surgical procedures to another and therefore these findings to be corroborated in other procedures.

6.4.1 Limitations

6.4.1.1 QST limitations

CPM measurements were performed before surgery and not repeated in the postoperative period- unlike TS assessments. This was based on the idea that TS, - as a surrogate of central sensitisation - may be manipulated by antihyperalgesic agents, such as pregabalin and ketamine, whereas the descending inhibitory pathways are chiefly noradrenaline-mediated and therefore less likely to change with the use of these agents. CPM may well change over time depending on pain load, or in tandem with the establishment of hyperalgesia and CS if they overwhelm this system. Duloxetine, for example, may be useful in modulating this noradrenaline based process and may have proved a more useful arm in this current study than the multimodal arm – in particular with repeated measures of CPM.

QST was not performed at three and six months due to reasons of logistics as described in the previous chapter. However it is possible to speculate that subsequent changes in descending inhibitory (or facilitatory) mechanisms may impact on the emergence of clinically reported PPP in patients with previously inhibited 'subclinical' hyperalgesia or CS.

6.4.1.2 Psychology testing and its limitations

Self-report questionnaires/ instruments such as the Spielberger and PCS instruments described are convenient tools for measuring personality traits but have their limitations. Most important of these are recall bias and social desirability. Recall bias is in turn affected by self-deception as well as social desirability. Social desirability is the tendency of the individuals to report what they think the experimenter wants to hear rather than an accurate self-report. This is particularly the case if the interviewer is a professional, especially a treating doctor. Structured interviews carried out by a third party may improve the accuracy of these measures but add to the complexity of the study, especially in the preoperative setting before major surgery. Therefore, it is important to bear these in mind when making intra-group comparisons. However intergroup assessments as part of the perioperative RCT are less prone to bias as randomisation removes some of this variability.

I have carried out grouped comparisons based on means or frequencies and not examined individual pain experiences or trajectories. Chapman and colleagues, in particular, call for an approach of following individual pain trajectories (184) rather than group or population study.

This also speaks to the idea of personalised medicine or individualised care where clinical and research activity aims to profile and identify responders or

"vulnerable" individuals e.g. for preventive RCTs. The findings of this study contribute to this notion of personalised medicine where there is potential in the future to provide individuals with bespoke risk data and manage this risk accordingly.

Chapter 7 Conclusions and future work

7.1 Overview

The overarching conclusion of this thesis is that PPP following cardiac surgery, while common, can also be predicted and potentially prevented.

The hope is that this would lead to further work allowing the identification of PPP risk in individual patients, informed consent and early intervention to prevent long term pain and suffering following elective cardiac surgery.

"It is easier to find men who will volunteer to die, than to find those who are willing to endure pain with patience."

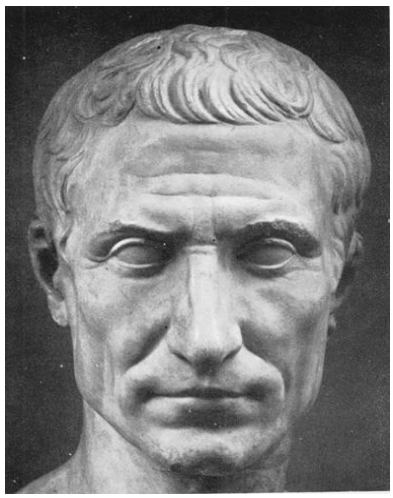

Figure 7.1 Julius Caesar
(Image available at http://en.wikipedia.org/wiki/Julius_Caesar Accessed on 10/12/14)

This is however the first ever study of the mechanisms of preventive analgesia in cardiac surgery and further study is therefore warranted to corroborate these findings and further explore dose and duration required to ensure both efficacy and tolerability.

7.2 Summaries of individual chapters

7.2.1 Study one (Chapter 3)

39.7% of patients undergoing first time sternotomy in our hospitals describe PPP following elective cardiac surgery. The age of the patient, duration of surgery and acute pain during the recovery period all seem to act as strong predictors for the development of PPP in his cohort study.

7.2.2 Study two (Chapter 4.)

The neuromodulatory effects of pregabalin on CS and hyperalgesia may be preventing the transition of acute postsurgical pain to PPP. In addition, the effects of improved analgesia in the perioperative period seems to translate into reduced opioid requirement and shorter length of stay in hospital.

7.2.3 Study three (Chapter 5.)

The effect of pregabalin in the perioperative period may be demonstrated by measures of:

4. Increase in PPT at a site *remote* to the incision
5. Prevention of the development of new TS
6. Reduction in the zone of peri-incisional hyperalgesia

7.2.4 Study four (Chapter 6.)

The likelihood of developing PPP may be predicted by a combination of the following perioperative risk factors:

1. Perioperative QST changes, namely in PPT (at a site remote to the incision), new TS and Zones of Hyperalgesia.
2. Efficiency of CPM
3. Preoperative quality of life (measured with EQ-5D)
4. Levels of state anxiety and catastrophising
5. Patient age
6. Surgical risk factors (duration of surgery and acute pain but not surgical technique i.e. extent of dissection.)

7.3 Strengths and weaknesses

This thesis demonstrates the significant morbidity and loss of quality-of-life associated with PPP following cardiac surgery. It also confirms the prevalence of this phenomenon in our patient population. Retroactive prevalence data is corroborated by prospective RCT outcomes.

The randomised controlled trial was carried out in a double- blind, placebo-matched manner and therefore represents the main strength of this thesis.

Blinding was ensured by the use of inert placebos, in the form of lactose-containing capsules and normal saline infusions. However this carries a risk of unblinding of patients, clinical staff and investigator when the active drugs have demonstrable sedating and psychoactive properties.

The use of active placebo with properties similar to the active drug may therefore have ensured blinding more thoroughly e.g. benzodiazepines, such as oral temazepam or intravenous midazolam.

However this may have proved unsafe in the cardiac surgical setting, where the premedication also included an additional 20mg oral temazepam. This therefore may have led to a significant risk of over sedation during the perioperative period in patients receiving placebo.

Furthermore, an appropriate active placebo for the psychoactive properties of ketamine may not exist. The absence of a ketamine-only arm in the RCT however makes this less important when discussing active placebo in this particular study.

The absence of a separate ketamine arm may be considered a limitation of this study. While the combination of pregabalin and ketamine, as a multimodal intervention, represents an important step, the clinical trial may have benefited with an additional 'ketamine only' arm – accepting that this however adds another factor of complexity to a clinical trial.

Similarly, it may have been useful to assess the effects of duloxetine - in a separate or multimodal manner- as a noradrenaline uptake inhibitor. This is particularly pertinent given the powerful effect of CPM efficiency on the subsequent development of PPP. It is tempting to speculate that duloxetine may rescue patients with inefficient baseline CPM.

Performing a prospective pilot study may have provided more robust data for the power calculation as well as providing pilot QST data for some of the underpowered components of the study, as described in chapters five and six.

It is also important to consider the practical and pragmatic ('real world') translation of this work. While these assessments are feasible in the research

setting, they may pose difficulties in terms of time, and therefore cost, in the clinical environment. The test protocol duration of sixty minutes may not be feasible for all patients in a pre assessment clinic or on the day of admission for surgery.

Given the relatively small number of patients investigated in each arm, these findings need to be corroborated in a large, fully powered, multi centre, phase-three clinical trial, likely requiring many hundreds of patients.

7.4 Potential for impact

This work further confirms the phenomenon of PPP as a clinically relevant and societally important one. Interestingly this relatively understudied complication of surgery remains largely ignored in the consent of patients (185). At the very least, this work should add to the growing body of procedure-specific literature on PPP to allow better-informed discussions with patients regarding the risks of elective surgery.

This study represents a phase two clinical trial of pregabalin, specifically for the prevention of PPP in cardiac surgery. The next stage for this research question is the development of a multi-centre, suitably powered, phase three clinical trial to establish clinical effectiveness.

Although the QST component of this thesis is labour intensive, this is also worth pursuing within a trial infrastructure. In particular, the assessments of PPP at three or six months following cardiac surgery remain unexplored in the current literature.

My studies also suggest a number of predictive tools, which may be useful in risk stratifying pain-free, pre-operative patients for the development of subsequent PPP.

This also has the potential to subsequently personalise the perioperative pain management of the 'at-risk' surgical patient in terms of:

1. Prehabilitation, or 'Prehab', including preventive analgesia but also optimising treatment of pre-existing pain conditions.

2. Psychological screening and treatment of anxiety and catastrophising states.

3. Education and vigilance regarding the expected course of recovery and options to seek further help in the case of persistent symptoms at defined time points.

In addition to profiling of risk in patients and personalising pain medicine before the initiation of surgical intervention, there is also scope to screen patients in the immediate to early postoperative period for signs of the development of PPP. This could take the form of hyperalgesia testing, for example, at the bed site as set out in chapter six.

7.5 Future work

While caution must be exercised in terms of extrapolating to other types of surgery (14), it is possible to hypothesise that similar features may be elicited from investigation of other surgical models. This in turn justifies further studies to define and identify surgical, procedure- specific cohorts of patients with PPP.

This work is underway to validate these finding in two specific surgical models, also involving surgery on the chest:

7.5.1 Breast surgery

Together with colleagues at the cancer hospitals of the Royal Marsden NHS Foundation Trust, I have started a clinical trial of a complex intervention to prevent PPP following breast surgery. This encompasses the following complex intervention, as compared with usual care, in the hospitals of this specialist cancer institution:

- Pre operative pain consultation
- QST assessments centred on CPM and PPT
- Education
- Psychological intervention
- Preventive pregabalin regimen
- Perioperative paravertebral blockade (initiated preoperatively and to continue for 48 hours following surgery.)
- Daily inpatient pain review
- Two week follow up call and clinic visits, as required

7.5.2 Thoracic surgery

We have assessed the effects of effective paravertebral block in the immediate postoperative period on pain scores, analgesic requirement and PPP following thoracotomy at the largest UK thoracic surgical unit at Guy's Hospital in London. A study investigating the timing of this block for video assisted thoracoscopic surgery (VATS) is also under way.

As regards the cardiac surgical model, it is perhaps necessary to undertake dose finding or 'duration finding' studies for pregabalin and/ or ketamine to ensure the translation of this study's findings into clinical practice. The diplopia effects of pregabalin at the doses given in this trial may act as a barrier to its adoption into routine practice.

As described above, the inefficient CPM susceptibility of some patients could also be targeted by the investigation of duloxetine and its ability to engage the noradrenergic reuptake pathway. This may also allow examination of changes in CPM over time and with the institution of preventive analgesia.

Looking further afield, non-surgical models may warrant investigation in a similar manner to better understand the mechanisms of transition from acute to persistent pain states as well as the potential to intervene with similar complex interventions e.g. refractory angina, non-cardiac chest pain, cancer pain, and opioid-induced hyperalgesia.

7.6 Concluding remarks

My work has confirmed the need for procedure specific study of PPP and has added to the relatively new body literature on risk factors and the potential to predict the onset of this phenomenon. Prevention, particularly with acceptable levels of side effect, remains the holy grail (144).

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Chapter 9 Appendices

Appendix One. Quality of life assessment: EQ-5D

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

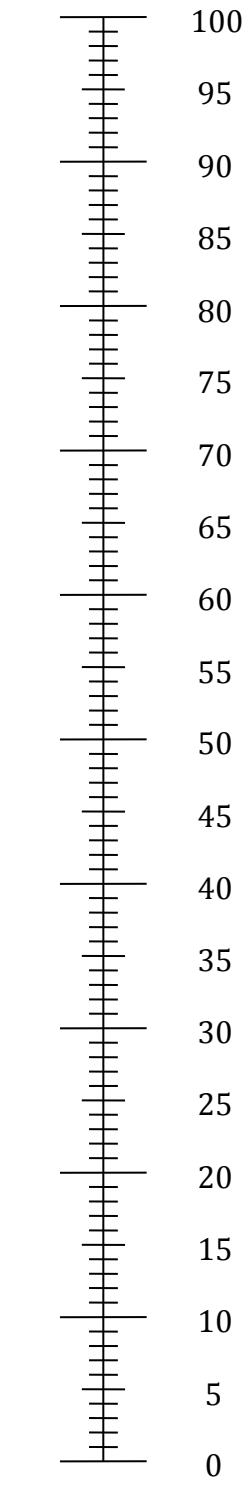
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix Two. State Anxiety Inventory

Read each statement and select the appropriate response to indicate how you feel right now, that is, at this very moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	1	2	3	4
	Not at all	**A little**	**Somewhat**	**Very Much So**
1.	I feel calm	1	2	3	4
2.	I feel secure	1	2	3	4
3.	I feel tense	1	2	3	4
4.	I feel strained	1	2	3	4
5.	I feel at ease	1	2	3	4
6.	I feel upset	1	2	3	4
7.	I am presently worrying over possible misfortunes	1	2	3	4
8.	I feel satisfied	1	2	3	4
9.	I feel frightened	1	2	3	4
10.	I feel uncomfortable	1	2	3	4
11.	I feel self confident	1	2	3	4
12.	I feel nervous	1	2	3	4
13.	I feel jittery	1	2	3	4
14.	I feel indecisive	1	2	3	4
15.	I am relaxed	1	2	3	4
16.	I feel content	1	2	3	4
17.	I am worried	1	2	3	4
18.	I feel confused	1	2	3	4
19.	I feel steady	1	2	3	4
20.	I feel pleasant	1	2	3	4

Appendix Three. Pain Catastrophising Scale

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feeling that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worry all the time about whether the pain will end	0	1	2	3	4
I feel I can't go on	0	1	2	3	4
It's terrible and I think it's never going to get any better	0	1	2	3	4
It's awful and I feel that it overwhelms me	0	1	2	3	4
I feel I can't stand it anymore	0	1	2	3	4
I become afraid that the pain will get worse	0	1	2	3	4
I keep thinking of other painful	0	1	2	3	4

events					
I anxiously want the pain to go away	0	1	2	3	4
I can’t seem to keep it out of my mind	0	1	2	3	4
I keep thinking about how much it hurts	0	1	2	3	4
I keep thinking about how badly I want the pain to stop	0	1	2	3	4
There’s nothing I can do to reduce the intensity of the pain	0	1	2	3	4
I wonder whether something serious may happen	0	1	2	3	4

Appendix Four. S-LANSS assessment tool for neuropathic pain

Study number:
Date of assessment:

On a scale of 1- 10, please indicate how bad your pain has been in the last week (‘0’ means no pain and ‘10’ means pain as severe as it could possibly be.)

_____ / 10

Medication taken for this specific pain:

· In the area where you have pain, do you also have ‘pins and needles’, tingling or pricking sensations?

Yes / No

2· Does the painful area change colour (e.g. look mottled or more red when the pain is particularly bad)?

Yes / No

3· Does your pain make the affected skin abnormally sensitive to touch? (e.g. unpleasant sensations or pain when lightly stroking the skin / wearing tight clothes)

Yes / No

4· Does your pain come on suddenly in bursts for no apparent reason when you are still? (e.g. like electric shocks, 'bursting' or 'jumping' sensations)

Yes / No

5· In the area where you have pain, does your skin feel unusually hot like a burning pain?

Yes / No

6· Gently rub the painful area with yourt index finger and then rub a non painful area (e.g an area of skin further away.) How does this rubbing feel in the painful area?

Same / Different

7· Gently press on the painful area with your finger tip and then gently press on a non painful area (e.g an area of skin further away.) How does this feel in the painful area? Same / Different

Appendix Five. Case Report Form

HEART PPPAIN STUDY

Patient study number:

ALL Inclusion criteria satisfied?

☐Informed Consent
☐First time sternotomy for cardiac surgery
☐Patient aged 18 - 80 years

Exclude patient if ANY of following:

☐Emergency surgery (decision to operate taken on the day of surgery)
☐Previous sternotomy
☐Preoperative renal failure (eGFR <60 ml/min)
☐History of chronic non-anginal pain
☐Chronic pain medication other than paracetamol and non-steroidal anti-inflammatory drugs
☐Concurrent use of oxycodone, lorazepam, or ethanol.
☐ Concurrent use of any drugs for neuropathic pain e.g. antiepileptics, antidepressants
☐Allergy to pregabalin, gabapentin or ketamine
☐Pregnancy
☐Limited understanding of numerical scoring scales
☐Previous participation in other trials investigating analgesic agents or any IMP in previous three months

Adverse event report:

Serious Adverse Event/ SUSAR report:

eGFR abnormalities/ Other reason for withdrawal:

QST EXAMINATION

PRE OP

TPT Sens + Pain +

PPT algometer + PPT post CPM +

PAIN DIFF WITH TS Chest + Arm: +

POST OP

TPT Sens + Pain +

PPT +

PAIN DIFFERENCE WITH TS Chest + Arm +

Zone of hyperalgesia (cms) +

Date _____ and duration of surgery _____ (mins)
Harvest site(s)
Total morphine consumption at 24 hours post surgery _____mg

VAS sternotomy at 24 hrs at rest _____ / 10
VAS sternotomy at 24hr following 3 maximal coughs _____ / 10
VAS leg incision at 24 hrs _____ / 10 N/A
Sedation score at 24 hrs _____ (Nil/ mild/ mod/ severe) pCO2 = _____
Nausea scores at 24 hrs _____ (Nil/ mild/ mod/ severe) RR = /min

Time to extubation _____ mins
Length of stay in ITU ____ hrs
Length of stay in hospital ____ days

Survival 28 days: YES ☐
NO☐

PHONE ASSESSMENT AT 3 MONTHS

Survival: YES ☐
NO☐

NRS at 3 months Sternotomy _____ / 10 Change with 3 coughs/ movement:

Leg pain _____/ 10 Change with movement:

Analgesics used for wound pain

Sleep disturbance by wound pain: YES☐
NO☐

PHONE ASSESSMENT AT 6 MONTHS

Survival: YES ☐
NO☐

NRS at 3 months Sternotomy _____ / 10 Change with 3 coughs/ movement:

Leg pain _____/ 10 Change with movement:

Analgesics used for wound pain

Sleep disturbance by wound pain: YES☐
NO☐

Appendix Six. Individual patient SAE (Serious Adverse Event) log

Study Title:

HEART PPPAIN

Investigator: Dr S Anwar

Patient number **3**

	Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved unknown / 2 = persisting / 3 = death / 4 =
	Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1	Renal failure onset date:___15 Dec 11	2	4	1	1	1 date if resolved: 16-Dec-11

Patient number **5**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Sedation onset date:__13 Dec 11	2	4	1	3	1= resolved 2 = persisting 3 = death 4 = unknown date if resolved: 13th dec 11
2 Diplopia onset date:___13 Dec 11	2	4	1	4	1 date if resolved: 13th dec 11

Patient number **6**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Somnolence 6th Jan 2012	2	4	1	3	1= resolved unknown date if resolved: 7th Jan 2012
2 Dizziness 6th Jan 2012	2	4	1	4	1 date if resolved: 7th Jan 2012

Patient number **7**

	Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
	Name of Event					
1	Diplopia onset date:__23 Dec 11	1	1	1	4	1 date if resolved: 24-Dec-11

Patient number **11**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event					
1 Sedation onset date:__7th Jan 2012	2	1	1	2	1 date if resolved: 7th Jan 2012
2 Diplopia onset date:__6th Jan 2012	1	1	1	3	1 date if resolved: 8th Jan 2012

Patient number **19**

	Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
	Name of Event					
1	Diplopia onset date:__17 Jan 2012	2	3	1	4	1 date if resolved: 19-Jan-12

Patient number **20**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved / 2 = persisting / 3 = death / 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Reintubation onset date:__19th jan 2012	3	4	1	1	date if resolved: 19th Jan 2012

Patient number **22**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved unknown / 2 = persisting / 3 = death / 4 =
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__21 Jan 12	2	3	1	4	1= resolved unknown / 2 = persisting / 3 = death / 4 = date if resolved: 21-Jan-12
2 Dizziness onset date:__21 Jan 12	2	3	1	4	1 date if resolved: 21-Jan-12

Patient number **23**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__22 Jan 12	2	1	1	4	1 date if resolved: 22nd Jan 2012

Patient number **26**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event					
1 Resternotomy onset date:__22 Jan 12	3	4	1	1	1 date if resolved: 22-Jan-12
2 Diplopia 22-Jan-12	2	4	1	3	4 date if resolved: 22-Jan-12

Patient number **27**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved unknown / 2 = persisting / 3 = death / 4 =
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__21 Jan 12	1	3	1	4	1 date if resolved: 22-Jan-12
2 Dizziness onset date:__21 Jan 12	1	3	1	4	1 date if resolved: 22-Jan-12

Patient number **30**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event					
1 Diplopia onset date:__29 Jan 12	2	3	1	4	1 date if resolved: 29th jan 2012

Patient number **35**

	Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
	Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1	Diplopia onset date:__31 Jan 12	1	3	1	4	1 date if resolved: 31st jan 2012

Patient number **36**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event					
1 Diplopia onset date:__2 Feb 13	2	3	1	4	1 date if resolved: 2nd feb 2012

Patient number **42**

	Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
	Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1	Resternotomy onset date:__02 Feb 12	3	4	2	1	1 date if resolved: 02-Feb-12
2	Pericardial tamponade onset date:__	3	4	2	1	3 date if resolved:

Patient number **46**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event					
1 Dizziness onset date:__8th Feb 2012	1	1	1	3	1 date if resolved: 8th Feb 2012

Patient number **49**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved / 2 = persisting / 3 = death / 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Dizziness onset date:__10 Feb 12	1	1	1	3	1 date if resolved: 10-Feb-12

Patient number **50**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved unknown / 2 = persisting / 3 = death / 4 =
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__10 Feb 12	2	3	1	4	1= resolved unknown date if resolved: 11-Feb-12
2 Dizziness onset date:__10 Feb 12	2	3	1	4	1 date if resolved: 11-Feb-12

Patient number **53**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved unknown / 2 = persisting / 3 = death / 4 =
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__16 Feb 12	2	3	1	4	1= resolved unknown date if resolved: 17-Feb-12
2 Dizziness onset date:__16 Feb 12	2	3	1	4	1 date if resolved: 17-Feb-12

Patient number **56**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__15 Feb 12	1	3	1	4	1 date if resolved: 16-Feb-12
2 Dizziness onset date:__15 Feb 12	1	3	1	4	1 date if resolved: 16-Feb-12

Patient number **63**

	Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved unknown / 2 = persisting / 3 = death / 4 =
	Name of Event		1 2 3 4	1 2	1 2 3 4 5	
2	Unresponsiveness onset date:__21 Feb 12	3	4	1	1	1 date if resolved: 21-Feb-12

Patient number **67**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__24 Feb 12	3	4	1	4	1 date if resolved: 26th Feb 2012
2 Drowsiness onset date:__24 Feb 12	3	4	1	4	1 date if resolved: 27Th Feb 2012

Patient number **69**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved unknown / 2 = persisting / 3 = death / 4 =
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__26 Feb 12	2	3	1	4	1 date if resolved: 26-Feb-12

Patient number **76**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved / 2 = persisting / 3 = death / 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Reintubation onset date:__02 Mar 12	3	4	1	1	1 date if resolved: 02-Mar-12

Patient number **78**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event					
1 Diplopia onset date:__03 Mar 12	2	3	1		1 date if resolved: 04-Mar-12

Patient number **84**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__18 Apr 12	1	1	1	4	1 date if resolved: 18-Apr-12

Patient number **91**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__04 May 12	2	1	1	4	1= resolved 2 = persisting 3 = death 4 = unknown date if resolved: 04-May-12

Patient number **94**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event					
1 Diplopia onset date:__07 May 12	2	3	1	4	1 date if resolved: 08-May-12

Patient number **101**

	Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
	Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1	Acute renal failure onset date:__19 May 12	2	4	1	1	1 date if resolved: 21st may 2012

Patient number **103**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event					
1 Diplopia onset date:__17 May 12	1	1	1	4	1 date if resolved: 17-May-12

Patient number **104**

	Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved / 2 = persisting / 3 = death / 4 = unknown
	Name of Event		1 2 3 4	1 2	1 2 3 4 5	
2	Ventricle fibrillation onset date:__16 May 12	3	4	1	1	1 date if resolved: 16-May-12

Patient number **110**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event					
1 Diplopia onset date:__20 May 12	1	1	1	3	1 date if resolved: 21-May-12
2 Drowsiness onset date:__20 May 12	2	1	1	3	1 date if resolved: 21-May-12

Patient number **126**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event					
1 Diplopia onset date:__15 Jun 12	2	3	1	4	1 date if resolved: 16-Jun-12

Patient number **127**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved unknown / 2 = persisting / 3 = death / 4 =
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__15 Jun 12	2	1	1	4	1 date if resolved: 15-Jun-12

Patient number **134**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication none / dose adjusted / temporary stop / permanent stop	Medicine taken for this AE? no / yes	Relation to trial med not related / doubtful / possible / probably / very likely	AE outcome 1= resolved / 2 = persisting / 3 = death / 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__13 Jul 12	2	4	1	3	1 date if resolved: 14-Jul-12
2 Dizziness onset date:__13 Jul 12	2	4	1	3	1 date if resolved: 14-Jul-12
3 Nausea	3	4	1	1	1 date if resolved:

Patient number **135**

	Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
	Name of Event					
1	Post-operative cardiac arrest onset date:__16 Jul 12	3	4	1	1	1 date if resolved: 16-Jul-12

Patient number **139**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event					
1 Diplopia onset date:__20 Jul 12	1	1	1		1 date if resolved: 20-Jul-12

Patient number **140**

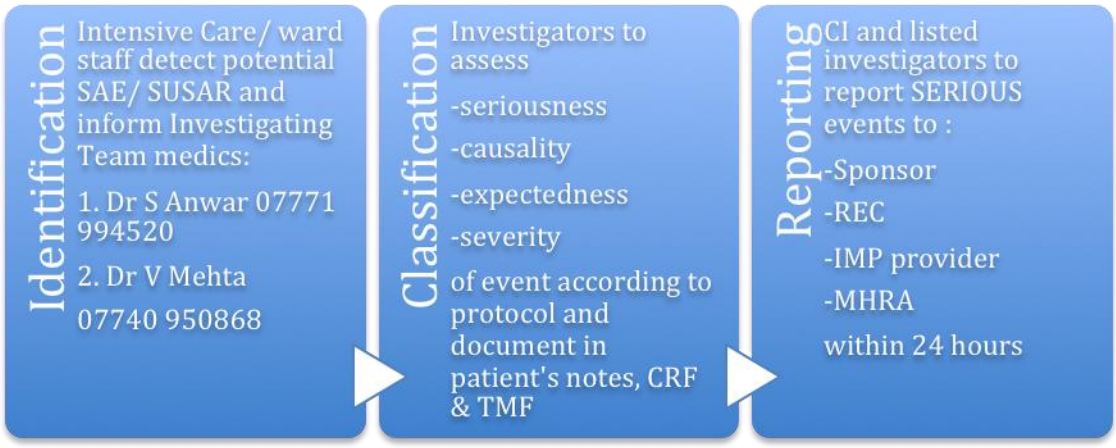
Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__24 Jul 12	1	4	1	1	1= resolved 2 = persisting 3 = death 4 = unknown date if resolved: 25-Jul-12

Patient number **144**

Adverse events Has the subject reported any adverse events? No ☐ Yes X	Severity 1 = Mild 2 = Moderate 3 = Severe	Action Taken with trial medication 1 none 2 dose adjusted 3 temporary stop 4 permanent stop	Medicine taken for this AE? 1 no 2 yes	Relation to trial med 1 not related 2 doubtful 3 possible 4 probably 5 very likely	AE outcome 1= resolved 2 = persisting 3 = death 4 = unknown
Name of Event		1 2 3 4	1 2	1 2 3 4 5	
1 Diplopia onset date:__28 Jul 12	2	1	1	4	1= resolved 2 = persisting 3 = death 4 = unknown date if resolved: 28-Jul-12

Appendix Seven. Reporting SUSAR/ SAE

Prospective, double-blinded, randomised, placebo controlled trial of pre-emptive analgesia to prevent pain following sternotomy for cardiac surgery.



This process was followed in the case of SUSAR (Suspected Unexpected Serious Adverse Reaction) or SAE (Serious Adverse Event.)
CRF (case report form), TMF (trial master file), CI (chief investigator), REC (research ethics committee), IMP (investigational medicinal product), MHRA (Medicines and Healthcare products Regulatory Agency.)

Appendix Eight. Statistical Analysis Plan

HEART PPPAIN study:
HEART surgery and Persistent Postsurgical PAIN

Introduction

This statistical analysis plan sets out the methods to be used to analyse the primary and secondary outcomes from the HEART PPPAIN study. This plan is based on the study protocol (Prospective, double-blinded, randomised, placebo controlled trial of pre-emptive analgesia to prevent pain following sternotomy for cardiac surgery. Version 6 14th Sept 2012).

Analyses are in accord with ICH-E9 statistical guidelines for clinical trials and updated CONSORT reporting checklist for clinical trials.

Research questions & hypotheses

The HEART PPPAIN study seeks to answer two associated questions:

1. What is the clinical efficacy of pregabalin, either alone or in combination with ketamine, in preventing the development of persistent postsurgical pain (PPP) following sternotomy for cardiac surgery?
2. What is the predictability of the development of PPP using experimental pain modalities at the time of surgery and is it possible to predict the preventive effect of pregabalin, as well as additional ketamine, on this phenomenon?

It is hypothesised that pregabalin combined with ketamine is superior to pregabalin alone, which in turn is superior to placebo, in preventing the transition from acute to chronic pain in and around the scar following cardiac surgery. It is also hypothesised that the individual's response to pain challenges before and immediately after surgery can predict their likelihood of developing PPP in the long term.

Description of Outcomes

- **Primary Objective** – assess whether the use of a preventive analgesia reduces the incidence of PPP at three and six months

- **Secondary Objective** – assess the effect of preventive analgesia on acute pain, recovery, length of hospital stay, quality of life and survival outcomes as well as the predictability of pain using quantitative sensory testing (QST)

Primary Endpoint –

- Presence of pain on the Numerical Rating Scale (NRS) at the sternotomy site at 3 and 6 months following surgery.

Secondary Endpoints –

- ACUTE:
- Total morphine consumption at 24 hours post surgery (continuous : ratio)
- NRS scores at 24 hrs post surgery, at rest and following 3 maximal coughs (ordinal)
- Sedation and nausea scores at 6 hours post surgery (ordinal)
- Carbon dioxide level in blood (continuous: ratio)
- Side effects present in the form of dizziness, confusion, blurred vision (categorical/binary)
- Time to extubation (continuous : ratio)
- Length of stay in intensive care and in hospital (continuous : ratio)
- 28-day mortality (categorical/binary)

FOLLOW UP AT 3 MONTHS:

- NRS pain score around leg incision site, if applicable (ordinal)
- Neuropathic pain assessment at 3 months post surgery (S-LANSS) (ordinal or continuous??)
- Quality of life and mood on EQ-5D (ordinal or continuous??)
- Analgesics taken and sleep disturbance (Categorical/ binary)
- Survival (categorical/binary)

FOLLOW UP AT 6 MONTHS:

- Numerical Rating Scale (NRS) pain scores at rest and following movement/ cough. (ordinal)
- Neuropathic pain assessment at 6 months post surgery (S-LANSS) (ordinal or continuous??)
- Quality of life and mood on EQ-5D (ordinal or continuous??)
- Analgesics taken and sleep disturbance (Categorical/ binary)
- Survival (categorical/binary)

Power Calculation

This study is powered to detect a two-thirds reduction in the percentage of patients with pain at 3 and 6 months. Pilot data revealed a PPP prevalence of 39.7% in 312 consecutive patients, undergoing elective sternotomy in our centre over a six-month period. Based on an alpha of 5% and power of 80%, we therefore calculated a sample size per group of 43 patients. To allow for drop off and loss to follow up, we will recruit 50 patients per group.

Inclusion Criteria:

- Informed Consent
- First time sternotomy for all cardiac surgery
- Patient aged 18 - 80 years

Exclusion criteria:

- Emergency surgery (decision to operate taken on the day of surgery)
- Previous sternotomy
- Preoperative renal failure (eGFR <60 ml/min)
- History of chronic non-anginal pain
- Chronic pain medication other than paracetamol and non-steroidal anti-inflammatory drugs
- Concurrent use of oxycodone, lorazepam, or ethanol.
- Concurrent use of any drugs for neuropathic pain e.g. antiepileptics, antidepressants
- Allergy to pregabalin, gabapentin or ketamine
- Pregnancy
- Limited understanding of numerical scoring scales
- Previous participation in other trials investigating analgesic agents or any IMP in previous three months

Statistical analysis

- All analyses will be undertaken using SPSS (version 21) by Dr. Sibtain Anwar

Descriptive analyses

Basic descriptive statistics will be carried out. This will include numbers and percentages for categorical data, mean and standard deviation for normally distributed, continuous data and median and interquartile range for skewed data. Baseline characteristics between the treatment groups will also be compared to assess the degree to which comparability of randomisation was achieved.

Inferential analyses

Regression ANCOVA (analyses of covariance) will be employed. These models adjust for baseline characteristics where there is good clinical belief that they may be predictive of outcome

Primary outcome: logistic regression +selected covariates depending on group differences

Secondary outcomes

1. Acute
- VAS 24 hr = linear regression adjusting for baseline VAS +selected covariates as outlined above
- Total morphine, time to extubation and LOS in hospital = linear regression +selected covariates
- Side effect episodes and mortality = binary (yes/no) and therefore logistic regression

2. 3 months
- S-LANSS = linear regression adjusting for baseline VAS +selected covariates as outlined above
- EQ-5D = linear regression adjusting for baseline VAS +selected covariates as outlined above
- Mortality = as above

3. 6 months
- S-LANSS = as above
- EQ-5D = as above
- Mortality = as above
- Primary outcome (NRS) = as above

Subgroup analysis:

Given the relatively low power for testing interactions, these results should be considered exploratory only.

Independent variables as risk factors for chronic pain at three and six months:

Age (continuous)

Sex (categorical)

Pre op EQ-5D (continuous : interval or ordinal?)

Strait anxiety Spielberger (continuous : interval or ordinal??)

Catastrophising score (continuous: ratio or ordinal??)
LIMA harvesting (categorical/ binary)
TS (temporal summation) at the sternotomy site prior to surgery (categorical/ binary)
TS (temporal summation) remotely prior to surgery (categorical/ binary)
Duration of surgery in minutes (continuous: ratio)
Percentage change in pressure pain thresholds following preoperative 'CPM' challenge (continuous: ratio)

Dependent variables as risk factors for chronic pain at three and six months:

Acute NRS pain score in first 24 hours (ordinal)
Percentage change in PPT after surgery (continuous: ratio)
Change in TDT (continuous: ratio)
Change in TPT (continuous: ratio)
Change in Remote TDT (continuous: ratio)
Change in Remote TPT (continuous: ratio)
Percentage change in remote PPT after surgery (continuous: ratio)
TS (temporal summation) at the sternotomy site after surgery (categorical/ binary)
TS (temporal summation) remotely after surgery (categorical/ binary)
Zone of hyperalgesia around the incision after surgery (continuous: ratio)

Protocol violations and missing data/ loss to follow up:

In a superiority trial, intention-to-treat (ITT) analysis is conventionally used as the most conservative approach to minimise the possibility of a type I error, i.e. falsely concluding that one treatment is superior to another. ITT includes data in the primary analysis from participants who drop out or violate the protocol to ensure differences between treatments under test are not falsely inflated and ensuring the most rigorous conditions apply before rejection of the null hypothesis (i.e. treatment A is not superior to treatment B). However, in non-equivalence trials the null hypothesis is the opposite, and states that the experimental treatment is inferior to the reference treatment. As this is a superiority testing study, ITT analysis will be carried without the need for per protocol processing of data.

For ITT analysis, missing data will be imputed based on mean or median values for the randomisation group of the individual patient, as appropriate for the distribution of data.

Appendix Nine. Original QST data

PPT preopS	PPT postCPM	PPT postopS	PPT preopR	PPT postopR	TS newsS?	TS newR?	ZoH	PPP?
376	423	588	557	841	0	0	12	0
208	361	216	359	353	1	0	14.75	0
204	216	114	301	252	0	0	35	1
350	385	218	415	257	0	0	8	1
282	433	231	389	198	0	0	8.5	0
182	140	160	255	360	0	0	10.5	0
164	179	276	437	420	1	0	25	0
193	335	109	405	511	0	0	9.5	0
304	443	219	175	140	0	0	23	0
292	638	265	384	361	0	0	14	0
232	317	155	255	355	0	0	9	0
182	216	128	567	562	1	0	10	0
139	157	103	329	277	0	0	60	1
271	415	211	538	606	0	0	6.5	0
275	357	228	447	485	0	0	14	0
187	441	108	387	429	0	0	54	1
168	161	164			0	1	12	1
119	141	106			0	1	45	0
192	200	114			0	0	32	0
303	299	388	399	340	0	0	63	0
216	238	231	412	418	0	1	44.75	1
100	84	65	385	335	0	0	66	1
136	141	160	279	344	0	0	22	0

214	197	408	412	380	0	1	42.5	1
201	456	191	515	570	0	0	7	0
301	413	220	388	431	0	0	32	0
226	242	301	410	428	0	0	49.5	0
136.75	143.25	151.75	297	256	0	0	36	0
129	161	87	370	290	0	0	20	0
222	216	143			0	0	34	0
330	337	223	362	408	0	0	11	0
241	338	281	512	665	0	0	19	0
255	377	510	444	407	1	0	15	0
376	571	273	398	475	0	0	9.5	0
205	213	163	411	394	0	0	0	1
267	265	97	351	289	0	0	33	1
201	391	183	498	560	0	0	7.5	0
215	197	147	309	391	0	0	12	0
177	319	102	411	466	1	0	48	1
694	815	279			0	0	24	0
318	555	336	523	653	0	0	20.5	0
438	525	437			0	0	0	0
533	603	425			0	0	0	0
262	383	94	532	485	1	1	46	1
105	247	174	480	527	0	0	7.5	0
233	279	503	298	228	0	0	34.5	1
425	607	266	482	375	0	0	14	0
213	410	446	349	404	0	0	14.5	0
298	558	267	392	361	0	0	38	0
153	168	131	291	341	0	0	7.5	0
260	572	186	488	362	0	1	13.5	0
300	460	148	472	456	0	0	22	0
205	203	168	312	349	1	0	35	3

243	301	235	212	195	0	0	7.5	0
174	193	171	285	275	0	0	12.5	0
436	425	109			0	0	0	0
185	246	103	312	230	1	1	44	1
141	144	103	295	234	1	0	45	1
294	452	177	377	459	1	1	31.5	1
306	461	257	412	440	0	0	20	0
282.5	324.75	201.25	412	394	0	1	36.5	0
185.25	415.75	415.75	204	132	0	1	50.5	1
399.25	390.5	193.5	297	178	1	1	39	1
160	190.5	101	205	93	0	1	48.5	1
248.75	513.75	190	253	311	0	0	9.5	0
398	568	274.75	452	461	0	0	12	0
189.5	182.25	119.5	180	94	1	0	37	1
292.5	494	240	295	324	0	0	46	0
363.25	530.25	216.25	436	565	0	0	15.5	0
337	275	284	235	292	0	0	9	0
359.25	438.25	257.25	396	173	0	0	32.5	1
445.75	432.25	262	387	401	0	0	20	0
217	209	328	146	178	0	0	12.5	0
224.25	220.25	237.25	224	139	1	1	56	1
212.24	414.5	181	251	189	0	0	32.5	0
234.25	473.25	239.5	220	241	0	0	11.5	0
412	597.5	338.5	383	391	0	0	11	0
268.75	466.75	305.25	304	301	0	0	6	0
417.875	389.625	277.125			0	0	36	0
255.125	234	151			1	1	26	0
385.125	368.625	339.875			0	0	26	0
418.5	437.5	166.5	545	221	0	0	12	1
227	480.75	300.25	297	306	0	0	22	0

495	706	377.75	493	511	0	0	10	0
293	238	346	301	350	0	0	0	0
368.5	379.75	353.5	324	411	0	0	10	0
314.5	262.25	205.5	300	121	0	1	8.5	0
190.25	310	92.75	189	141	0	0	58	0
359.5	389.5	311.5	397	409	0	0	4	0
245.75	494	302	249	418	0	0	6.5	0
297	421.75	356.25	352	314	0	0	11	0
305.5	274.75	211.25	397	314	0	0	37	0
370.75	590	314.75	352	341	0	0	15.5	0
155	132	267.25	193	304	0	0	0	0
87.5	120.25	86.5	194	86.5	0	0	29	0
144.5	392.5	199.25	211	232	0	0	11.5	0
144.25	187.5	200.5	193	243	0	0	4.5	0
410	609.25	422	500	498	0	0	5.5	0
175	181.5	212.25	184	91	1	0	36.5	0
500.5	560.5	526.25	499	511	0	0	30.5	0
188	185	285.5	185	219	0	0	5.5	0
492	493.5	345	481	222	0	1	54	1
220	206.5	294.25	214	334	0	0	2	0
175.25	313.75	212	183	255	0	0	9.5	0
203.5	159.5	212.25	215	197	0	0	31	0
274.5	307.5	135.25	297	124	0	1	65.5	1
267.25	446.25	227	290	312	0	0	11.5	0
387.5	559.75	146.75	294	195	0	0	11	0
84	108.75	75.25	130	159	0	0	6.5	0
132	168.5	258.5	113	212	0	0	6.5	0
128.5	317	121.25	188	203	0	0	10	0
256.5	452.5	232.5	175	88	1	1	35.5	0
263.25	255.75	205.5	296	356	0	0	10	0

371.5	555.5	292.25	414	456	0	0	12	0
589.625	765	592.25	589.625	765	0	0	0	0
502.25	702.75	403.75	412	382	0	0	9.5	0
368.75	638	229	312	315	0	0	14.5	0
241	363	269	350	425	0	0	16	0
198.25	219.25	261.25	274	311	0	0	7.5	0
390.75	333	185.25	376	254	0	0	39	1
234.125	234.5	232.875	121	188	0	1	77	0
283.75	276.75	125.5			0	0	0	0
264.25	328.875	266			0	0	77	0
354.75	324	435			0	0	12	0
742	871.75	240.75	814	152	0	0	5.5	0
216.5	377	161.75	282	312	0	0	18	0
179	463.5	234.75	241	305	0	0	13	0
373.25	378.75	256.25	347	357	0	0	6	0
209.75	264.5	189.75	281	225	0	0	0	0
111	97.5	195.5	148	388	0	0	49	0
128.25	163.5	181	185	299	0	0	4.5	0
287.75	479.5	194.25	392	481	0	0	11.5	0
340	695	348.25	311	355	0	0	16	0
204.25	349.25	232	244	232	0	0	0	0
277	328.75	205.75	182	219	0	0	12	0
189.5	218.25	178.75	147	233	0	0	20	0
100.25	107	110.75	323	109	1	1	42.5	1
211	337.5	172.5	242	194	0	1	44	0
139.5	150.5	49	250	421	0	0	44.5	0
243.25	219.25	202.25	123	149	0	0	9	0
210.5	196.5	132.75	176	132	1	0	51	1
158.125	148.625	83.125			1	1	45	1
145.5	103.5	117.75	145.5	103.5	1	1	44	1

265.8	298	185.75	265.8	298	0	0	36	0
192.5	184.25	204	176	189	0	0	12.5	0
268.25	193.75	303	362	388	0	0	18.5	0
193	178	104.5	194	121	0	0	41	0
253.75	205	239.5	176	388	0	0	14.5	0
245.75	314	186.75	296	259	0	0	12	0
318.25	497	85.5	314	102	1	1	5.5	1

QST data is presented on a sequential patient basis.
PPT = pressure pain threshold in kilo pascals, preopS = preoperatively at the sternotomy site, postCPM = following conditioned pain modulation, postopS = postoperatively at the sternotomy site, preopR = preoperatively at a remote site, postopR = postoperatively at a remote site, TS newS? = development of new temporal summation at the sternotomy site [0=No, 1= Yes], TS newR? = development of new temporal summation at a remote site [0=No, 1= Yes], ZoH = zone of hyperalgesia in centimeters, PPP?= presence of persistent postsurgical pain. [0=No, 1= Yes.]