The transition from acute to chronic post-surgical pain – A prospective cohort study

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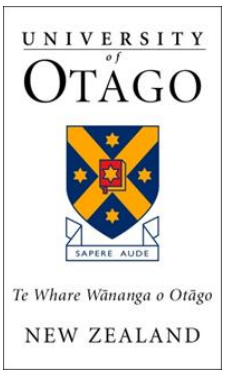

Submitted in fulfilment of the requirements for the degree of Bachelor of Medical Science with Honours

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Abstract

Background:

Chronic pain is pain which persists beyond the normal physiological healing timeframe. It affects up to 20% of the Australian and New Zealand populations. Chronic pain is also costly, not only in terms of healthcare costs, but also in lost work days and decreased productivity. Surgery is one of the leading causes of chronic pain, highlighting the need to understand and prevent the transition from acute to chronic post-surgical pain. This study has documented the onset and development of subacute pain and the development of chronic pain. The undertaking of this study may have added to the arsenal of tools used to predict which patients will go on to develop chronic pain. By predicting chronic pain development in advance, interventions may be developed to prevent the development of persistent post-surgical neuropathic pain. Considering the rising costs of healthcare, and the growing socioeconomic burden of chronic pain, strategies to prevent chronic post-surgical pain need to be carefully considered.

Hypothesis:

That one or more of the proposed factors measured perioperatively will predict continued pain at six weeks and three months after gynaecological surgery.

Aims:

1) To determine the prevalence of acute persistent pain at 6 weeks following surgery
2) To determine the prevalence of chronic pain at 3 months following surgery
3) To determine the extent to which (if at all) the perioperative factors measured predict continued pain at six weeks and three months.

Methods:

Patients were assessed at the Christchurch Women's Hospital Pre-Admission clinic and approached for written informed consent. Those agreeing to participate were given validated questionnaires to complete in order to document their physical, emotional and functional state pre-surgery. In addition a cold pressor test was carried out to determine pain threshold and tolerance. The cold pressor test involves placing a hand in cold water

containing ice. The pain slowly builds until the participant can bear it no longer, at which point it is voluntarily removed from the stimulus.

Intraoperative factors (anaesthetic techniques, surgical techniques, and analgesic use) were measured, as well as patient-controlled analgesia (PCA) use, and medications prescribed on discharge.

At 6 weeks, participants were telephoned, and validated questionnaires completed. At 3 months, all participants were again telephoned, and validated questionnaires were completed.

Results and conclusions:

Of the 54 participants 15.7% were deemed to be experiencing significant pain at 6 weeks post-operatively; 8.2% of participants were deemed to be experiencing significant pain at 3 months postoperatively. The psychometric questionnaires used often found differences between those experiencing pain and those not experiencing pain at given observation points, but only the Brief Illness Perception Questionnaire (BIPQ) appears to be predictive of developing prolonged postoperative pain. The mean difference (7.4 on a 0-50) scale may even be enough to see it used clinically alongside other predictive measures. Many of the demographic factors correlated with the experience of pain at a given time point(s), but none were predictive of the development of prolonged pain to significant levels.

The cold pressor test did not show any significant differences between those in pain at baseline, and those that are not in pain at baseline. However, pain threshold as measured by this test was shown to predict prolonged pain outcomes. Pain tolerance and pain endurance followed the same trend, but were not statistically significant.

No surgical approach or group was significantly more likely to develop a prolonged pain state than the others. However, it did seem as though laparotomy may be associated with poorer pain outcomes, which is supported by the literature. Intraoperatively, those who would later develop prolonged pain states were less likely to receive opioids, but possibly likely to receive greater doses if they did. Perhaps worryingly, those who would later develop prolonged pain states were significantly more likely to receive tramadol intraoperatively. There were no statistically significant trends in postoperative inpatient or

discharge prescribing, however non-significant trends were noted across both in terms of prescription of specific non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids.

Introduction to this thesis:

Chapters One, Two, and Four of this thesis review the relevant literature for the following: the pathophysiology and epidemiology of pain (Chapter One); the tools currently available for the management of pain (Chapter Two); the tools used in this study to measure pain; and the tools used in this study to measure pain related behaviour (Chapter Four). Chapter Three gives a brief overview of the relevant aspects of the gynaecological surgical types used in this study. Chapter Five of this thesis outlines how the protocol for this study was designed and tested, while Chapter Six outlines the hypothesis, specific aims, and methods used in data collection and analysis. Chapter Seven details the results discovered using the aforementioned methods. Chapter Eight discusses the results found in Chapter Seven, the limitations and strengths of the present study, and draws conclusions based on these. From this, Chapter Eight makes appropriate recommendations for future research and notes potential influences on clinical practice.

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Tables and Figures

Figures

Tables

List of abbreviations

ADHD – Attention-Deficit Hyperactivity Disorder

AFRM – Australasian Faculty of Rehabilitation Medicine

AIDS – Acquired Immune Deficiency Syndrome

AMPA – α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

ANZCA – Australia and New Zealand College of Anaesthetists

BIPQ – Brief Illness Perception Questionnaire

BSO – Bilateral Salpingo-oophorectomy

CDHB – Canterbury District Health Board

CGRP – Calcitonin-Gene-Regulated Peptide

COX-1/2 – Cyclooxygenase enzymes 1 and 2

CPSP – Chronic Post-Surgical Pain

CWH – Christchurch Women's Hospital

DASS-21 – Short form of the Depression Anxiety Stress Scale

DNA – Deoxyribonucleic Acid

FPM – ANZCA Faculty of Pain Medicine

GA – General Anaesthesia

GABA – Gamma-Amino Butyric Acid

HTM – High-Threshold Mechanoreceptors

IASP – International Association for the Study of Pain

IP – The group in pain at the baseline assessment (n=28)

IP3 – The group in pain at the 3 month assessment (n=4)

IP6 – The group in pain at the 6 week assessment (n=8)

MDD – Major Depressive Disorder

NDRI – Norepinephrine-Dopamine Reuptake Inhibitor

NICE – National Institute for Health and Care Excellence

NMDA receptor – N-Methyl-D-Aspartate receptor

NP – The group not in pain at the baseline assessment (n=26)

NP3 – The group not in pain at the 3 month assessment (n=45)

NP6 – The group not in pain at the 6 week assessment (n=43)

NSAIDs – Non-Steroidal Anti-Inflammatory Drugs

NZE – New Zealand European

NZM – New Zealand Māori

PACU – Post-Anaesthetic Care Unit

PAG – Periaqueductal Grey

PASS-20 – Short form of the Pain Anxiety Symptoms Scale

PCA – Patient-Controlled Analgesia

PCS – Pain Catastrophizing Scale

PDI – Pain Disability Index

PMN – Polymodal Nociceptors

PSEQ – Pain Self-Efficacy Questionnaire

PTSS – Pain Treatment Satisfaction Scale

RACP – Royal Australasian College of Physicians

RACS – Royal Australasian College of Surgeons

RANZCP – Royal Australia and New Zealand College of Psychiatrists

SCH – Southern Cross Hospital

SD – Standard Deviation

SF-MPQ – Short-Form McGill Pain Questionnaire

SNRI – Serotonin-Norepinephrine Reuptake Inhibitor

S/O – Salpingo-Oophoerectomy

SSRI – Selective Serotonin Reuptake Inhibitor

TCA – Tricyclic Antidepressant

TN – Trigeminal Neuralgia

TSK – Tampa Scale of Kinesiophobia – 13

UOC – University of Otago, Christchurch

VAS – Visual Analogue Scale

VRS – Verbal Rating Scale

95% CI – 95% Confidence Interval

Chapter One – Pain

1.1 Introduction to post-surgical pain

The International Association for the Study of Pain (IASP) defines pain as: 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' [1]. Pain is a subjective, multidimensional sensation with strong affective overlays [2]. As stated, it is a result of potential or real tissue injury, and is considered the normal physiological end-point of this [3]. Pain can arise in the absence of tissue injury. This is indicative and demonstrative of strong psychological links in pain [4]. The unconditioned response to pain is affectively negative. However, with conditioning an individual can become indifferent to, or even enjoy certain painful stimuli, such as different sexual behaviours, or the pain of physical exercise [2]. The unconditioned negative response to pain serves a protective function [5], as the result is avoidance of painful (and, by proxy, injury-inducing) stimuli. This is best exemplified by sufferers with congenital or acquired insensitivity to pain, conditions in which serious tissue injury and/or death result from the sufferer's lack of protective responses to injurious stimuli [5].

Soft tissue injury and/or inflammation, such as that caused by surgery, is the archetypical cause of acute pain [2]. In most cases, acute pain following surgery will decline in the days following surgery. Within weeks patients are free of pain, and able to go about their daily lives as they did prior to their surgery [6]. However, around one in ten [7] [8] patients do not recover as uneventfully. Their pain persists beyond the accepted 'normal' duration, becoming chronic, and in many cases intense and disabling [9]. Pain persisting after the surgical wound has healed is normally the result of nerve irritation. These sources of irritation can be exogenous to the nerve (such as inflammation), or endogenous to the nerve (such as nerve damage from the surgery) [7] [6]

Psychological factors such as depression and stress correlate with chronic pain following surgical procedures [10]. It is not yet known whether this relationship represents a cause or an effect, or simply a statistical association [11]. However, the evidence for a correlation between Chronic Post-Surgical Pain (CPSP) and psychological and demographic (e.g. age, gender) factors is strengthening [12].

Genetic factors can play a large role in the differences between individuals in terms of pain perception, duration, and response to treatment [6] [13] [14]**.** Changes in both the peripheral and central nervous systems alter an individual's responses to both painful stimuli and non-painful stimuli. Non-painful stimuli such as touch can be perceived as painful, a process known as allodynia. Painful stimuli are amplified and perceived as very painful, a process known as hyperalgesia. Internal factors (psychological, genetic, and neurochemical), and external environmental factors (such as social expectations) influence the severity and duration of an individual's experience of pain [15]. These advances in understanding of pain have caused the accepted view of pain to shift. Chronic pain can have the properties of a disease process in its own right, and not merely a symptom of an underlying problem [15].

1.2 Acute Pain

Acute pain is often thought of as a normal, predictable, protective response to noxious stimuli, such as chemical, mechanical, and thermal insults [3]. Pain exists to ensure withdrawal from dangerous situations and to condition the individual to avoid future encounters with painful stimuli. This description over-simplifies the complex mechanisms by which pain is detected and interpreted, as each individual interprets diverse painful stimuli differently [2]. This suggests that 'pain' as a negative response to a given stimulus is not fixed in terms of perception or intensity between individuals, or even in the same individual in different situations. Inter-individual physiological and psychological factors largely influence the perception of pain. Intra-individual differences in pain perception in various situations have strong psychological overlays as well [1].

1.2.1 Physiology

There are three commonly accepted 'types' of acute pain. They are as follows; nociceptive (or 'somatic'), visceral, and neuropathic [2] [16].

Nociceptive or somatic pain involves the activation of the receptors of sensory nerve fibres known as nociceptors. There are two classes of nociceptors. The first class consists of the high-threshold mechanoreceptors (HTMs) which are thinly-myelinated nociceptors with free nerve endings that are activated in response to mechanical insults [17]. The second class of nociceptors are the polymodal nociceptors (PMN), which form a heterogeneous group responding to a variety of thermal, chemical, and mechanical stimuli [18].

The afferent nerve fibres which carry the pain impulses from their nociceptive endings to the brain are also split into two categories. There are the myelinated (A delta) fibres (known as 'fast' fibres), that carry the HTM nociceptors, and the unmyelinated (C) fibres (known as 'slow' fibres), that carry the PMN nociceptors [2]. The pseudo-unipolar neurones to which these fibres belong have cell bodies residing in the dorsal root ganglia (or the trigeminal ganglion), and their fibres terminate in the dorsal horn of the spinal cord [17]. From here, the pain signals travel centrally via the neospinothalamic tract (for 'fast' pain), and the paleospinothalamic tract (for 'slow' pain). These axons terminate in the thalamus. From here are distributed widely throughout the brain, in particular to the cerebral cortex and limbic system [17].

'Physiological' pain is caused by a high-intensity, transient, noxious stimulus causing activation of local nociceptors [19]. 'Pathological' pain, however, occurs following damage to tissues (by ischaemia, or physical trauma), causing the release of inflammatory chemical mediators. As a result, regional nociceptors become sensitised to further noxious stimuli [19], resulting in peripheral hyperalgesia [20].

Visceral pain is pain arising from an internal organ. These signals are mostly carried by C fibre axons [2]. Visceral pain tends to be poorly localised for two reasons. Firstly, because the density of visceral nociceptors is lower than that found somatically. Secondly, it is poorly localised due to the highly diffuse central distribution of visceral nociceptive signals [16]. As a result, pain arising from the viscera is often 'confused' with somatic pain along the spinal dermatomes [16]. An example of this is the fact that pain is often experienced along the left lower cervical and upper thoracic dermatomes following a myocardial infarction.

Visceral pain differs from somatic pain in terms of its subjective qualities [16]. The pain sensations from visceral organs range from almost none (lung, liver), to pain in organs that are particularly sensitive to certain stimuli (such as myocardial ischaemia, and mesenteric tension) [21].

The recent IASP Taxonomy working group has redefined neuropathic pain as 'pain caused by a lesion or disease of the somatosensory nervous system' [22]. Neuropathic pain occurs as a result of abnormal functioning of a specific region of a part of the nervous system [2]. In peripheral neuropathic pain, this malfunctioning usually occurs as the result of an external insult, such as mechanical trauma or severe temperature. This results in a negative shift in the balance of factors regulating excitatory and inhibitory signals. In partial injuries, this gives rise to increased excitatory activity that can lead to hyperalgesia due to the lowered threshold for nociceptive excitatory transmission [16]. Central neuropathic pain occurs after damage (such as ischaemic injury) to regions of the central nervous system involved with somatosensory processing, leading to sensitisation of those neurones [2]. For example, central neuropathic pain can develop from damage to the spinothalamic tract [23].

Of course, no discussion of pain is complete without considering the psychological influences on the course of pain. Psychological factors influence not only the development and maintenance of pain, but the ability to cope with it. Pain, particularly when chronic, is associated with psychiatric disorders, such as depression and anxiety [24]. Likewise, somatoform disorders can cause the experience of pain with little or no identifiable organic causes [24]. As the IASP definition states, pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, *or described in terms of such damage*". This describes the intertwined nature of the sensory and emotional aspects of the pain experience.

1.2.2 Epidemiology

As is to be expected after the physiological insult sustained when one's body is sliced open, acute post-operative pain is very common among surgical patients. The severity and duration of this pain is dependent on the type of surgery and type of anaesthesia given [7], the adequacy of pain relief [25], and the patient's inherent psychological and physiological make-up [26] [27].

1.3 Subacute Pain

1.3.1 Physiology and pathology

'Persistent pain' is a concept poorly defined in the literature, with some articles using the term almost synonymously with chronic pain [7], while others appear to use it as a stage occurring between acute pain and chronic pain [28]. For the purposes of this study, the term 'subacute pain' is viewed as a pain state in between acute pain and chronic pain that will be measured at six weeks postoperatively. This is to construct a reference point between 'acute postoperative pain', and 'chronic pain at three months postoperatively'. This provides a more valuable insight than the 'acute versus chronic' dichotomy.

Because this pain state is loosely defined, the exact pathophysiological and psychopathological processes involved in the development of this pain state have not been studied per se. However, if subacute pain is viewed as a half-way point on a continuum from acute pain to chronic pain, it can be reasonably concluded that the pathological processes would resemble the process involved in the development of chronic pain.

Chanda et al 2011 [29] describe the differing characteristics between a group (n=40) suffering 'subacute' back pain (defined as 6-16 weeks duration), and a group (n=37) suffering 'chronic' back pain (defined as >1 year duration). Three statistically significant differences were found. The authors noted that other factors were close to significant levels, but not detected due to lack of power.

The three statistically significant findings were as follows: Firstly, and most relevant to this study, pain intensity. Interestingly, participants in the 'chronic' group scored significantly higher than the 'subacute' group on the Visual Analogue Scale (VAS). This is a 100mm line with zero being 'No pain' and ten being 'Worst pain ever'. This indicates that pain intensity is higher among those with longer duration. It remains unclear whether this is because their pain worsens over time, or simply that those with greater pain intensity are more likely to progress to chronic pain. Similar results have been replicated in other studies [30] [31].

The other two findings were specific to back pain (pain location, temporal dynamics of spontaneous pain), and were not comparable to any outcomes from the current investigation.

Most importantly, these findings suggest that subacute pain may not simply be an extension of acute or chronic pain; it may in fact form a distinct pain state. This thesis aims to further explore this idea, by repeating psychometric and pain score analyses at 6 weeks ('subacute') and at 3 months ('chronic') postoperatively, albeit limited by the timeframe available.

1.3.2 Epidemiology

Subacute pain is a relatively new and under-studied topic, making exact estimations of its prevalence difficult. However, if it is a pain state somewhere between acute pain and chronic pain, then the numbers experiencing subacute pain should be in between. The risk factors for developing chronic pain, such as surgical type, anaesthetic/analgesic technique, genetics, and socioeconomic factors [28] could logically be applied to subacute pain. For example, a patient undergoing a limb amputation, with all of the nerve damage and psychological factors involved, would likely have a longer recovery (in terms of pain as well as functionality) than a patient undergoing a laparoscopic hernia repair.

It follows that the 'risk' of developing subacute pain should be higher than that of chronic pain, as by definition one must experience pain through the subacute period and beyond to be classified as being in chronic pain.

The aspect of subacute pain that seems of the most practical importance is its transition to chronic pain. If more is learned about the differences between subacute and chronic pain, then perhaps controllable factors can be identified, and needless suffering prevented. In viewing pain as a three (or even more) step transition, rather than the 'acute versus chronic' dichotomy, perhaps more subtle insights can be gleaned.

1.4 Chronic Pain

Chronic pain, for all the research being carried out on it, is not overly well defined [2]. The general consensus appears to be that it is pathological pain that continues beyond the 'normal healing period' [32]. What constitutes the 'normal healing period' remains a point of ongoing debate, with most cut-off points between three and six months [29] [33], with these time points being rather arbitrary. Regardless of its exact definition, chronic pain has become a significant problem, both in terms of individual suffering [34] [35], and in terms of its economic impact [36] [37]. The postoperative estimates of chronic pain can vary from 5-60% [7]

[8] [28] [36]. Its incidence is higher in more invasive procedures such as thoracotomies, limb amputations, and mastectomies [28] [38].

Chronic pain can result from many causes, not just surgery. In Australia, 17% of Australian males and 20% of Australian females report chronic pain, as do 16.9% of New Zealanders [39] [40]. Chronic pain is costly, costing the Australian economy $34.4 billion per annum ($10,847 per sufferer) [41]. Large contributing factors are the cost of healthcare itself, absent workdays due to chronic pain, and reduced-effectiveness workdays. Chronic pain places the third-largest financial burden on Australia's healthcare system, behind only cardiovascular diseases and musculoskeletal conditions. The latter is also associated with chronic pain, so some of the costs ascribed to musculoskeletal conditions are likely at least partially due to chronic pain. Surgery was found to be the second most common cause of chronic pain in the United Kingdom [42]. This highlights the importance of identifying those most at risk, and the need to develop some preventative strategies.

1.4.1 Pathophysiology

The transition from acute to chronic pain is a complex process, an understanding of which is still in its infancy [34]. Understanding of the pathophysiological processes behind this transition is crucial, as targets can be uncovered that can be used to halt the transition [43].

Surgery, being a rather physiologically traumatic process, causes the release of a host of inflammatory mediators that sensitise peripheral nociceptors in the surrounding area [28]. A series of reactive changes then occurs within the central nervous system, resulting in central sensitisation [34]. These processes are likely protective, as increased pain sensations will naturally result in behaviour which reduces the risk of further damage, and allows healing. It has been suggested that chronic postoperative pain could be a failure of this system to 'reset', resulting in ongoing (and possibly even compounding) hyperalgesia, driven particularly at central level [34]. CPSP tends to closely resemble the characteristics of neuropathic pain. The surgical procedures with the highest risk of chronic pain tend to carry a high risk of major nerve involvement. Surgical injury to nerves contributes a significant proportion of chronic post-surgical pain [7].

Peripherally, as with any tissue injury, surgical procedures invoke an inflammatory response. The damaged tissues release pro-inflammatory substances (cytokines, prostaglandins, and histamine), triggering a localised inflammatory response. This sensitises local nociceptors and decreases the level of stimulus required to trigger them. The result is localised hyperalgesia [43]. This is known as peripheral sensitisation [44]. Peripheral nerve damage during surgery plays a major role in peripheral sensitisation, by creating hyperalgesia (excessive response to painful stimuli), and allodynia (a painful response to non-painful stimuli) [7]. Damaged neurones can exhibit altered sodium ion channel expression, resulting in spontaneous activity, and altered sensation [34]. In addition, within hours of the surgical trauma, afferent neurones exhibit (reversible) altered gene expression which results in an increase in excitatory neurotransmitters, and a decrease in inhibitory transmitters [45] [46].

Of course, inflammatory responses can be (and usually are) transient, and dissipate once the injury has healed. Major damage to a large peripheral nerve, however, is unlikely to ever fully return to its previous level of functioning. Nerve damage is far more likely to progress to chronic pain than inflammatory damage alone, although usually the peripheral component of chronic post-surgical pain would initially involve a combination of the two.

At the interface of peripheral and central sensory systems lies the dorsal horn of the spinal cord. Peripheral nociceptive neurones synapse here, and their signals can be altered by several mechanisms, particularly involving the N-methyl-D-aspartate (NMDA) receptor [34], calcitonin-gene-regulated peptide (CGRP) and Substance P [44]. Through these and other mechanisms, numerous intracellular alterations within the nociceptive afferents within the spinal cord, and result in increased sensitivity [28]. This is partially responsible for the phenomenon known as ‘wind up’ (temporary summation) seen in central sensitisation.

Peripheral sensitisation results in a large increase in the frequency and intensity of pain signals reaching the central nervous system from the periphery. The central nervous system correctly interprets this to mean that the body has been injured, and that protective measures need to be taken. Through diverse intracellular pathways resulting in ion channel and external receptor phosphorylation, these neurones become more excitable with a lower threshold for activation [7]. Using similar mechanisms as in peripheral neurones, central neurones are sensitised by the inflammatory markers released by the damaged tissue [45].

The brain becomes more responsive to potentially harmful stimuli, and protective measures (such as rest, and guarding of the injured area) are adopted by the affected individual. If these responses become excessive or longstanding, neurones can become so sensitive that non-noxious stimuli are sufficient to trigger a nociceptive response [46]. This gives rise to allodynia and secondary hyperalgesia (where uninjured areas become hypersensitive to painful stimuli) [28].

1.4.2 Epidemiology and public health implications

There are many factors known to influence the likelihood of developing chronic post-surgical pain. Factors known to decrease the risk include: increased age [47], female gender [48], pre-operative pain [49], severe acute post-operative pain [50], genetics [51], certain psychological factors [13], the anaesthetic technique used [13], and surgical factors (such as duration, likelihood of nerve damage) [52].

As previously stated, chronic pain develops in 5-60% of surgical patients. Not only the pain itself, but its flow-on effects, such as deleterious effects on mobility and cognition [53] [54], can have severe impacts on psychosocial [55] and workplace [53] functioning. In Germany, chronic pain (including that caused by surgery) costs an estimated 38 billion euro per year, in healthcare costs and in decreased work productivity [56]. Despite this, the basic medical degree in most Australasian (and American) [57] medical schools is lacking in detailed training in the management of pain in painful conditions, and these conditions are seen as outside of the scope of general practitioners [53]. As such, there is an increasing demand for practitioners who are trained in the management of complex pain, with Pain Medicine being recognised as a vocational specialty in its own right by the Medical Council of New Zealand in December 2012 [8]. In New Zealand, the specialty is overseen by the Australia and New Zealand Faculty of Pain Medicine (FPM), which grew within the Australia and New Zealand College of Anaesthetists (ANZCA), but its development has had inputs from other colleges, such as the Royal Australasian College of Surgeons (RACS), the Royal Australian and New Zealand College of Psychiatrists (RANZCP), the Royal Australasian College of Physicians (RACP), and the Australasian Faculty of Rehabilitation Medicine (AFRM). The accreditation of Pain Medicine as a specialty in New Zealand has generated expectations for improved care from both within the profession [8], and within the media [58] [59].

Chapter Two – Management of Pain

2.1 The clinical components of pain

In order to effectively manage pain, an understanding should be gained of more than just physical nociception. Naturally the treatment of pain usually requires the selection of an appropriate analgesic agent. This selection would be assisted by knowledge of the nociceptive insult in question. However, pain is a multifactorial experience, and thus pain management must target more than just the physical nociceptive aspect.

There are four accepted 'clinical components of pain' [(2)], namely, nociception, pain itself, suffering, and pain behaviour.

2.2 Issues surrounding adequate peri-operative pain management

The right to access effective pain management has been deemed a 'basic human right' [(60)]. As pain could arguably be described as the most unpleasant physical and emotional aspect of the human experience, the vast majority of sufferers desire to decrease both the frequency and severity of their pain experience. Considering the powerful emotional responses involved in pain, it seems reasonable to expect others to empathise with the pain experiences of sufferers, and feel compelled to assist in alleviating their pain. It is likely that this has created our ethical views around pain management.

Unfortunately opioids such as morphine and fentanyl that are the mainstays of inpatient treatment of acute pain [(61)] are potentially addictive, tolerance-forming, and subject to abuse. They are therefore tightly regulated [(60)]. These factors accompanied by misconceptions of opioid administration from physicians and patients alike (such as 'some pain is inevitable', and 'chronic opioid administration will certainly decrease quality of life') [(60)] result in up to 50% of surgical patients receiving inadequate analgesia [(62)] [(57)].

Inadequate management of acute postoperative pain increases the risk of adverse cardiovascular events [(63)], and enhances the risk of going on to develop chronic pain syndromes [(60)]. Chronic pain is accompanied by an increased risk of depression, anxiety, and other psychosocial impairments [(64)] [(65)]. The financial impact of chronic post-surgical pain

adds to sufferers' impaired capacity for productivity [66]. This highlights the need for effective peri-operative pain management.

2.3 Pharmacological management of pain

There is an ever-growing list of pharmacological agents available, with varying levels of evidence, used in the relief of pain. The choice of agent depends on the intensity and duration of the pain, and its aetiology. The major classes of pharmacological agents used for analgesic purposes are discussed below.

2.3.1 Opioid analgesics

No discussion of opioids in the literature appears complete without the famous quote

'*Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.'*

(Thomas Sydenham, circa 1680)

Opioids, in the form of the opium poppy *Papaver somniferum* have been used for analgesic purposes for thousands of years [67]. The 'archetypal' opioid, to which others (natural, semi-synthetic, and synthetic) are usually compared, is morphine [67].

As with most drugs, opioids as a class mimic existing endogenous compounds [68]. These endogenous compounds are referred to as 'endorphins', a term derived from the words 'endogenous' and 'morphine' [69]. There is a heterogeneous array of both the endorphins themselves and their receptors (the 'main' three being mu, kappa, and delta), produced largely in the pituitary gland [70]. These substances are known to modulate pain and stress in the brain. They have several peripheral functions, and are involved in the regulation of blood pressure and of gastrointestinal motility [70] [68].

All three opioid receptors are G-protein coupled. Their activation results in any of a number of intracellular cascades that largely lead to decreased neuronal excitability, and the resulting decreases in neurotransmission and neurotransmitter release [71] [72]. Paradoxically excitatory actions at the mu-receptor can occur [73].

The mu-opioid receptor, the main pharmacological target of morphine (by which it is named), and has both desirable effects (analgesia), and undesirable effects. Undesirable effects include physical dependence, respiratory depression, urinary retention, pruritus, and bradycardia. Other effects that could be classed as either desirable or undesirable depending on the circumstances of their use include euphoria (anti-depression), and constipation (anti-diarrhoeal) [71]. The mu-opioid receptor is distributed widely throughout the brain, particularly in areas involved in the higher processing of perceiving, integrating, and forming emotional responses, such as the cerebral cortex and limbic system [72]. It is also thought to decrease gamma-amino butyric acid (GABA) transmission in the periaqueductal grey (PAG). GABA is the major inhibitory neurotransmitter in the brain [74]. The PAG plays a role in regulating the descending inhibitory pain pathway [75] [67]. The decrease of GABA-ergic transmission results in increases in descending inhibitory signals in the PAG. These inhibitory signals sent down the descending inhibitory pain pathways decrease the perception of pain.

The kappa-opioid receptor has analgesic properties as well. Unlike the euphoria produced by the mu-receptor, kappa-receptor activation results in dysphoria [72]. Its side-effect profile largely limits the use of kappa-agonists. Its activation does not produce respiratory depression, but it is sedating and dissociating resulting in undesirable effects on cognition [72]. This means that specific kappa-agonists are of limited clinical value. Once actions of each specific subtype can be elicited and their respective target genes can be identified, more specific pharmaceutical agents will likely be developed.

The delta-opioid receptor has some analgesic properties, but can cause respiratory depression, potential convulsions, and physical dependence [71]. Because its analgesic effects are not as pronounced as those of the mu-receptors [76], research is currently being focussed around its potential use as a pharmacological target for novel antidepressants [76] [77] [78] [79].

The deduction of the chemical composition of morphine allowed the production of semi-synthetic opioids such as oxycodone and heroin (diacetylmorphine), and later fully synthetic opioids, such as fentanyl and methadone [67]. This was initially an attempt to retain morphine's analgesic properties, but not its addictive ones [80]. This remains a work in progress to date. The closest agent created thus far (in widespread use) is tramadol, which

acts as a serotonin-noradrenaline reuptake inhibitor as well as being a weak mu-receptor agonist [81]. Tapentadol is a newer, more potent mu-receptor agonist than tramadol. It is a noradrenaline reuptake inhibitor, but its serotonin reuptake inhibition is relatively weak [82].

The need for opioids with lower dependence/misuse liability cannot be overstated. For example, in 2008 in the United States, it was estimated that roughly 4.8% of the population over twelve years of age had used prescription opioids for non-medical purposes [83]. As well as directly searching for agents with inherently lower abuse/dependence liability, modifications to the methods of formulation are being developed. These include crush-resistant or tamper-proof formulations rendering the drug unable to be insufflated or taken intravenously [84].

Apart from the abuse/dependence potential, other adverse effects of opioids include respiratory depression, nausea and vomiting, pruritus and constipation. Acute opioid overdose is typically treated by administration of an opioid antagonist, such as naloxone or naltrexone [85]. Naloxone acts as an 'antidote' to opioid agonist overdose by competing with the agonist for the mu-opioid binding site (it acts on kappa- and delta-receptors as well), without activating the receptor itself [71].

In the management of acute pain, opioids are generally considered to be the gold standard and most effective agents in managing acute pain, particularly in the hospital setting [3]. Their role in chronic pain becomes much more contentious [86] [87] [88]. Even a Cochrane Collaboration review was unable to arrive at firm conclusions [89]. There is a need for further investigations into their long-term analgesic efficacy, the adverse effects of opioids, and the impact of opioids on quality of life and functionality. Unfortunately, as noted by the Cochrane Review [89], the follow-up period required renders the use of randomised controlled trials to be deemed impractical. This area will likely continue to rely on observational studies. In the meantime, the judgement of the individual clinician continues to dictate which patients will or will not receive opioids in chronic malignant or non-malignant pain.

2.3.2 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and steroids – The link between inflammation and pain

The 'Non-Steroidal Anti-Inflammatory Drugs' (NSAIDs) are the most heavily-prescribed drug class on the planet [(90)]. Brand names such as 'Neurofen®' (ibuprofen) and 'Voltaren®' (diclofenac) are likely to be the first pain reliever of choice for a consumer when confronted with mild to moderate pain. Unlike the opioids (of which only low-dose codeine, mixed with paracetamol is available over-the-counter in pharmacies in New Zealand) [(91)], many NSAIDs are readily available over-the-counter. As such, use of these medications is higher than that predicted by the prescription rate.

It is presumed that the NSAIDs' apparent analgesic qualities are largely due to their effects on inflammation. They do this by inhibiting the cyclooxygenase enzymes (COX-1 and COX-2), which in turn results in a decrease in prostaglandin synthesis, as the prostaglandins are involved in inflammation and pain signalling [(92)].

The NSAIDS are broadly grouped into two classes, namely, those that 'non-selectively' inhibit both COX-1 and COX-2 (although naturally the extent to which each is inhibited depends on the individual agent), and those which are selective for COX-2 (celecoxib, etoricoxib, and paracoxib) [(92)]. 'Non-selective' NSAIDs include ibuprofen, naproxen, diclofenac [(93)], and aspirin, although aspirin's most common clinical use is as an anti-platelet agent to reduce the risk of cardiovascular incidents [(92)]. The only COX-2 selective NSAID currently funded in New Zealand is meloxicam, although it shows COX-1 inhibition with increasing dose [(94)].

The clinical profiles of these agents are largely dependent on which of the two COX enzymes the individual agent targets the most. COX-1 (along with the prostaglandins it produces) is found in endothelial tissue, platelets, in parts of the upper gastrointestinal tract, and in the kidney [(95)]. As such it exerts control over platelet aggregation, renal blood flow, and mucous secretion in the upper gastrointestinal tract [(95)]. From this, some of the actions, both positive and negative, of non-selective NSAIDS can be deduced. For example, aspirin's anti-platelet effect is due to COX-1 inhibition in platelets. Likewise the negative gastrointestinal effects of NSAIDs can be explained by COX-1 inhibition in the stomach resulting in decreased

protective mucous secretions, exposing the gastric mucosa to the low pH acidic fluid in the stomach.

COX-2 is the enzymatic target by which NSAIDs largely have their desired clinical analgesic effects [92]. COX-2 is found in white blood cells (macrophages, leukocytes), connective tissues, and joints [95]. It is involved in inflammatory processes and in pain signalling, as well as in the inhibition of platelet aggregation [92]. So while selective COX-2 inhibiting agents may some of the gastrointestinal effects associated with non-selective agents, they come with an increased risk of serious cardiovascular incidents, such as myocardial infarction [96].

Paracetamol (acetaminophen) is one of the most commonly used analgesic and anti-pyretic agents worldwide [97]. The mechanism of action is complex, combining peripheral and central COX inhibition, and inhibition of other important central pathways such as the descending serotonergic pathway, and perhaps even the cannabinoid system, among others [98]. Although the precise mechanism of action remains unclear it becomes increasingly obvious that it is a central one [99]. Paracetamol is generally considered to have a superior side-effect profile to the NSAIDs [94] [92] [97], with few or no adverse effects on the gastrointestinal tract [100], and no discernable effects on platelet function or on cardiovascular events [101]. However, overdose of paracetamol is both more common, and more toxic than the NSAIDs [102]. It has become the most common cause of acute liver failure in the United States [103]. Nonetheless, it is recommended in New Zealand as a first-line analgesic, with or without codeine or an NSAID, depending on the circumstances [94].

Corticosteroids such as dexamethasone are often used as adjuvant analgesics [104], particularly in palliative care and in cancer management [104] [105]. In peri-operative pain management a single preoperative 0.1 mg/kg dose of dexamethasone is anti-emetic and provides enhanced analgesia [106]. Corticosteroids, like opioids, can mimic endogenous substances [107]. Steroids are involved in the modulation of neuronal development and plasticity, which is of interest in terms of pain management [107]. They are potent anti-inflammatory agents by directly binding to Deoxyribonucleic Acid DNA (as a steroid-receptor complex) and by directly exerting effects on target genes, such as decreasing the synthesis of inflammatory prostaglandins [108]. Unfortunately, chronic dosing with these agents

creates a potent immunosuppressant effect limiting their use in the peri-operative situation [109].

2.3.3 Adjuvant, novel, and secondary analgesics

Secondary analgesics are described by Shipton in 1997, as "those agents having a pain-relieving property as a secondary nature of their clinical activity. They can, however, be used as sole analgesic agents to treat various types of pain states" [110]. As such, this definition essentially covers a variety of pharmacological agents not primarily used for their analgesic effects. It encompasses a diverse range of drug classes and individual agents. The aforementioned paper classes these agents by mode of action. As there are many different classes and agents, only the more commonly-used secondary analgesics will be discussed.

-Antidepressants

The tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) have all found their way into the management of pain [110] [111] [112] [113]. Not only do they have pharmacological actions with direct analgesic effects [112], it seems logical that given the strong psychological factors at play in pain, their anti-depressant effects would most likely indirectly decrease the pain perceived [111] [110]. However, the efficacy of antidepressants in pain is limited, and restricted to certain pain syndromes. Only one of every three or four patients will experience a clinically significant reduction (50%) in pain [114] [115].

The tricyclic antidepressants (TCAs) have several pharmacological actions that contribute to their clinical effects. They inhibit the presynaptic reuptake of serotonin and noradrenaline, as well as acting as antagonists at several serotonin receptors (5-HT_2 in particular) [116], at α_1-adrenergic receptors [116], at H_1-and H_2-histaminergic receptors [117], and at muscarinic receptors [110] [111]. Two of the more commonly used agents, nortriptyline and amitriptyline, have slightly different effects. Amitriptyline causes a reasonably even reuptake inhibition of noradrenaline and serotonin, while nortriptyline favours noradrenergic reuptake inhibition [111]. In addition, it is becoming increasingly evident that these agents function as neuronal sodium channel blockers, decreasing pain signal transmission [118] [119]. These agents are most typically used in the treatment of neuropathic pain [111].

Selective Serotonin Reuptake Inhibitors (SSRIs), as their name suggests, inhibit the synaptic reuptake of serotonin (5-hydroxytryptamine, 5-HT), resulting in an effective increase in central nervous system serotonin levels. It is by this mechanism and its downstream effects that the SSRIs are presumed to exert their anti-depressant effects [120]. Their supposedly relatively benign side-effect profile is likely what led to interest in their use in pain [121] [114]. Despite this, it appears that the analgesic effects of SSRIs are less consistent and much less efficacious than those of the TCAs [121] [114]. This is perhaps somewhat surprising, given that knockout-mice studies have implicated 5-HT in inhibitory descending pain pathways [122] [123]. As such it would seem that SSRIs should be reserved for those who cannot tolerate the TCAs. Speculation is that perioperative dosing with an SSRI might potentiate the analgesic effects of opioids and even decrease certain opioid side effects [124].

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), like the SSRIs, inhibit the synaptic reuptake of serotonin. However, they also act to inhibit the reuptake of noradrenaline [114]. By not binding to histamine, acetylcholine, or α_1-adrenergic receptors, these agents have the potential to 'side-step' some of the common side-effects that can render TCAs intolerable to some patients [125]. Venlafaxine, the most commonly-used SNRI, has been reported to be efficacious in case reports [125], and a review of the literature by Grothe et al [126] seems cautiously optimistic.

Venlafaxine has been associated with a reduced incidence of chronic pain following mastectomy [127]. There is reasonable evidence to support duloxetine's efficacy in the treatment of painful diabetic peripheral neuropathy [128]. It is likely that the SNRIs are more efficacious in the treatment of pain than the SSRIs due to their noradrenaline reuptake inhibition, as noradrenaline reuptake inhibition is considered to be the main mechanism by which TCAs and SNRIs relieve pain [115] [114].

Bupropion is a 'novel' antidepressant, with a mechanism of action unlike TCAs, SSRIs, or the SNRIs. It is a noradrenaline-dopamine reuptake inhibitor (NDRI) [111]. It appears to have some analgesic effects. Only a few trials have been conducted to date [129] [130]. Only one double-blind randomised controlled trial (conducted by Semenchuck et al) with a cross-over design showed promising results. Of the forty one participants, thirty (73%) described their neuropathic pain as 'improved' or 'much improved' following the bupropion treatment

phases. The changes in pain score were significantly greater following bupropion treatment. The authors described it as 'well tolerated' at the doses used. More research is needed, although promising early results and tolerability make it an option for those unable to tolerate other antidepressant treatments.

-N-methyl-D-aspartate (NMDA) antagonists

Glutamate is the main excitatory neurotransmitter in the human central nervous system [131] [132]. As such, it seems reasonable to pursue ways of dampening certain glutamatergic systems to reduce pain signal transmission. There are an array of pharmacological agents known to antagonise the NMDA glutamate receptor, such as magnesium and ketamine [131]. The NMDA receptor has been implicated in the neuronal changes in 'wind-up' and central sensitisation (133). It contributes to the development of opioid tolerance [134] [135], which potentially give NMDA antagonists a clinical role in the prevention of opioid tolerance.

Ketamine is a non-competitive antagonist at the NMDA receptor, giving it analgesic and sedative effects through reduction of NMDA-mediated central sensitisation [136] [131]. Ketamine also has the potential to produce psychomimetic effects (as a dissociative hallucinogen). A systematic review conducted by Subramanian et al [137] concluded that these effects were unlikely to occur at analgesic doses. Despite this conclusion, central nervous system adverse effects (such as dizziness, diplopia, dysphoria, dreams, hallucinations, disorientation, strange sensations, light headedness, sleep difficulties, and confusion [137]) occurred at a rate of 0.7%-18% in ketamine-treated patients, depending on route of administration. Another systematic review, conducted by McCartney et al [138] found that in the 20 of 24 studies examined, 12 studies documented no adverse effects. Seven studies showed adverse effects, but none were statistically significant between patients treated with ketamine, and controls. The review states that the remaining study reported psychomimetic effects, but that there were no incidences of hallucinations [139]. As such, it seems likely that ketamine does not produce overt psychomimetic effects at doses required for analgesia. Those treated with ketamine for analgesia do not appear to show central nervous system symptoms at a higher rate than those treated with opioids alone.

In the aforementioned review by McCartney et al [138], they reported that 58% of the studies (14 of 24) showed ketamine to be efficacious in preventative analgesia (given to prevent

pain after surgery). In a meta-analysis conducted by Ong et al [140] of preventative analgesia in the management of acute postoperative pain, seven studies met the inclusion criteria of being randomised, double-blind studies. This study grouped ketamine with another NMDA antagonist, dextromethorphan. Only two of the seven identified studies displayed a statistically significant positive effect on postoperative pain intensity. However, when the study results were combined the authors felt that NMDA receptor antagonists showed no analgesic benefits, and that their efficacy remained 'equivocal'.

So while ketamine's role in preventative analgesia appears contentious, its use as an adjuvant to opioids appears promising. A systematic review conducted by Subramanian et al [137] identified thirty seven relevant double-blind, randomised controlled trials. The addition of ketamine to morphine patient-controlled analgesia (PCA) pumps did not improve analgesia [141]. However, a single-bolus or perioperative continuous infusion appeared to reduce morphine requirements. The authors proposed that the relatively high number of studies showing no statistically significant results could be explained by the surgical procedures in question. They hypothesised that in surgery requiring relatively small to moderate doses of opioids to provide analgesia, existing pain relief strategies are sufficient, and that the addition of an adjuvant was unnecessary. In more major surgeries, requiring large opioid doses, the addition of ketamine should create more benefit.

Much attention recently has been focussed on ketamine's possible role as a rapid-acting anti-depressant [142] [143] [144] [145] [146]. Given the links between depression and pain, particularly chronic pain, this raises the question of whether the use of ketamine in depressed chronic-pain patients could 'kill two birds with one stone'. Its anti-depressant effects could decrease pain, or at least modulate an individual's emotional response to it, and its analgesic effects could improve mood by the reduction or removal of the pain [147].

Dextromethorphan is an NMDA receptor antagonist largely used as an over-the-counter cough syrup [131]. It has fewer psychomimetic properties than ketamine, due to ketamine's stronger binding affinity at the NMDA receptor [148]. It is considered to be reasonably safe (with an over-the-counter status). In terms of efficacy, the McCartney et al review on preventative analgesics [138] reported dextromethorphan to be effective in a greater proportion of studies evaluated than ketamine (67% of dextromethorphan studies showed

statistically significant positive results, compared with 58% of ketamine studies). They suggested that dextromethorphan exerted its effects in two ways. Firstly, it exerted its effects by reducing acute opioid tolerance, a notion supported by experimental evidence [149]. Secondly, one study [150] reviewed showed statistically significant analgesic effects when dextromethorphan was administered alone as a premedication prior to surgery. This lent support to the notion that NMDA receptor antagonists directly reduced pain by decreasing central sensitisation.

Magnesium as an ion functions as an NMDA receptor antagonist [131]. However, it is debateable whether or not magnesium crosses the blood-brain barrier in sufficient quantities to produce NMDA receptor-mediated analgesic effects [151]. Whilst it seems likely that magnesium potentiates opioids to a clinically-useful level [152] [153], the McCartney el al review [138] concluded that none of the four studies showed any preventative analgesic effects of magnesium.

-Anticonvulsants

Anticonvulsants are a group of medications, with varying pharmacological modes of action, which were developed primarily for the treatment of epilepsy. They have subsequently been clinically applied in bipolar disorder [154] [155], and in pain management [156] [157]. These disorders all theoretically share similar neurophysiological pathologies, namely neuronal hyper-excitability [133] [158] [159], explaining the interest in expanding the use of anticonvulsants in these other disorders. In terms of pain management, application of these agents has been widely researched. They are used in the treatment of chronic pain [131] [156] [160]. More recently interest has grown in their use in postoperative pain [131] [161].

Carbamazepine acts on voltage-gated sodium channels, slowing their 'recovery' by slowing the rate of neuronal firing [162]. Carbamazepine is chemically similar to the TCA's [157] that may partially account for some of its actions. It is considered effective in trigeminal neuralgia (TN) with a suggestion by McQuay et al [156] that roughly seventy percent of patients could expect clinically significant benefits. Carbamazepine has some effects (although relatively weak) in diabetic neuropathy, but with less efficacy than in trigeminal neuralgia [158]. There is weak evidence, largely from case reports, that carbamazepine may have some efficacy in the treatment of the central pain syndromes [160]. Its adverse effects

resulted in withdrawal in up to eleven percent of study participants, and tolerable adverse effects were reported in roughly half of those treated [157]. Adverse effects included somnolence, changes in gait, dizziness, blurred vision, nausea, vomiting, and haematopoietic changes [133] [157] [158] [160].

Phenytoin was the first anticonvulsant studied and used in neuropathic pain for its antinociceptive properties [157]. Like carbamazepine, it acts on sodium channels. It might decrease synaptic glutamate by inhibiting its release [157] as well. Its efficacy appears to be more contentious, as shown in several recent guidelines in the American Journal of Medicine [163], in the Mayo Clinic Proceedings [164] , and in the National Institute for Health and Care Excellence (NICE) [165].

Lamotrigine, valproic acid, and topiramate are three other popular anticonvulsants that have been studied to varying extents in the treatment of pain, but at present do not have particularly strong evidence bases [157] [158]. Lamotrigine most likely acts by slowing neuronal sodium channels, and decreasing synaptic glutamate [158]. It has shown promise as an add-on therapy in TN [166], and as a stand-alone therapy in central neuropathic pain [167] and in diabetic neuropathy [168]. However its lengthy titration period, necessitated by the risk of the potentially life-threatening dermatological condition Stevens- Johnson syndrome [169] [170] [171], appeared to be correlated with high drop-out from studies [158], which may limit its clinical use. Valproic acid acts to increase overall GABA levels in the brain, by increasing its production and decreasing its degradation [157]. It also acts on sodium channels to prolong the 'recovery' phase [158], thus decreasing the rate of neuronal firing. There does not appear to be conclusive clinical evidence for analgesic or antinociceptive properties of valproic acid [172] [157] [158], despite promising pre-clinical findings in mouse studies [173] [174]. Topiramate acts as a sodium channel blocker, up-regulates GABA release, and inhibits the α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainite glutamate receptors [157] [158]. The research at present is inconclusive, with a study in central pain finding no positive effects in any subjects [175]. Another study did not find significant benefit in chronic lumbar radicular pain (although some secondary outcome measures were significant) [176]. Conversely, other studies in TN in multiple sclerosis patients [177], chronic low back pain [178], and diabetic neuropathy [179] have shown promising results. All three of these agents are likely to require further study before they can be recommended for widespread use.

Gabapentin is structurally a GABA analogue. However, it has no discernable activity at the GABA receptors, or apparent effects on GABA uptake or breakdown [180] [181]. It appears that gabapentin increases GABA production and/or release, resulting in an increase in brain GABA [181]. Gabapentin modulates calcium channels in the brain, and peripheral nerves by interacting with the $\alpha_2\delta$-subunit of voltage-gated calcium channels [157] [158] [180] [181], that in turn may modulate downstream neurotransmitter pathways [181]. It has a favourable side-effect profile. This is usually limited to temporary sedation, dizziness, and pedal oedema [157] [158]. It is excreted by the kidneys as the unchanged parent compound. It does not bind to plasma proteins, and does not affect hepatic enzymes [181] [182]. These characteristics all decrease the likelihood of drug-drug interactions [183]. So with a mechanism of action hypothetically capable of exerting analgesic and/or antinociceptive effects and a favourable side-effect profile, gabapentin could be of great clinical use.

There is strong evidence for gabapentin's role in the treatment of painful diabetic neuropathy [184] and in post-herpetic neuralgia [185] [186]. It has also been shown to provide synergistic analgesic effects when given in combination with nortriptyline [187]. A 2012 meta-analysis by Clarke et al [188] suggests it is effective in the prevention of chronic post-surgical pain. It is results like these, along with its favourable side-effect profile, that have made gabapentin a first-line choice in treating many forms of neuropathic pain [133] [157] [158] [187].

Pregabalin is, like gabapentin, is a structural analogue of GABA [157]. Its mechanisms of action appear very similar to those of gabapentin, its main target being the α2δ-subunit of voltage-gated calcium channels [189]. However, its binding affinity at this target is six times greater. As a result the required dose of pregabalin for pain is much lower than that of gabapentin [189]. With its major reported side-effects being sedation and dizziness, and its renal excretion [189], its similarities to gabapentin are fairly obvious. A 2009 Cochrane Collaboration systematic review [190] found no evidence for pregabalin in the treatment of acute postoperative, or chronic nociceptive pain. However, it was deemed effective in neuropathic pain states, such as post-herpetic neuralgia, as well as fibromyalgia. Another systematic review found it to be effective in the prevention of chronic post-surgical pain [188]. It is unsurprising that a drug that so resembles gabapentin, is effective in most if not all of the same indications.

Benzodiazepines are a group of anxiolytic, sedative-hypnotic agents which act at the $GABA_A$-receptor, up-regulating its response to GABA [191]. It is not known whether the benzodiazepines possess any analgesic effects unrelated to their effects on anxiety and mood, either alone or as adjunct therapies [192]. The only benzodiazepine which has been subjected to randomised controlled trial conditions is lorazepam [157] that was shown to be inferior to amitriptyline in post-herpetic neuralgia [193]. Given the high abuse and dependence risk associated with benzodiazepine treatment [192], the lack of evidence of efficacy [192] [157], and indeed the evidence that benzodiazepines may actively antagonise opioid analgesia [194], there is no evidence strong enough in favour the use of benzodiazepines as analgesics in any pain condition. However, in pain caused muscle spasm, benzodiazepines and other 'muscle relaxants' may relieve the pain by reducing the spasm [110] [195].

-α_2 adrenergic agonists

The α_2 adrenergic system modulates pain both peripherally and centrally [110] [196]. Their main site of action is the spinal cord that contains descending noradrenergic pain pathways [110]. Thus α_2 receptor–mediated inhibition of these pathways can produce powerful analgesia comparable to that mediated by opioids [197] They are usually limited to a role as adjunctive analgesics, as the systemic effects caused by α_2 adrenergic antagonism include sedation, cardiovascular depression (bradycardia, hypotension), and hypothermia, as well as the desired analgesia and anxiolysis [108] [110].

Clonidine is a α_2 adrenergic receptor antagonist, which was initially developed for its cardiovascular actions, namely, for the control of heart rate and blood pressure [108] [131]. As well as its adrenergic actions, evidence suggests it also acts as an imidazoline receptor agonist in the ventrolateral medulla that accounts for some of its hypotensive effects [198]. In anaesthesia and pain medicine, clonidine is used for the following: sedation and anxiolysis pre-operatively [198]; to decrease anaesthetic requirements intra-operatively [199]; and as an analgesic [108] [131] [198]. Clonidine is an effective analgesic and antinociceptive agent in its own right [198] [200] [201] by inhibiting the descending noradrenergic pain pathways [198]. It is also likely to have some use as an adjunct analgesic, having been shown to decrease morphine requirements following caesarean section [202]. It is particularly efficacious when delivered

epidurally and intrathecally, demonstrating analgesic effects on its own postoperatively [203] in an experimental setting [204]. When delivered by these routes, it also acts to potentiate and increase the duration of opioid analgesia in the post-operative setting [205] [206] [207].

Dexmedetomidine is a more potent α_2 adrenergic receptor antagonist than clonidine [208]. Its uses largely mirror those of clonidine, being used for pre-operative sedation and anxiolysis [198], intra-operatively to reduce anaesthetic requirements [209] and post-operative analgesic requirements [210]. Postoperatively it is used to reduce analgesic requirements [211] [212], however more research is required before it can be recommended in the treatment of chronic pain [213].

-Experimental and theoretical agents

There are many other pharmacological agents used in the treatment of pain. These are largely dependent on the source, duration, and specifics pertaining to the individual patient. Many of the adjuvant treatments, as outlined above, are clinically effective in less than half of those who take them. As such, the search for more reliable treatments continues.

Psychostimulants such as the attention-deficit hyperactivity disorder (ADHD) treatments dextro-amphetamine and methylphenidate, act as noradrenaline-dopamine reuptake inhibitors [214]. When combined with opioids, psychostimulants have been found to decrease opioid requirements, decrease somnolence and respiratory depression, and improve cognition, mood, and quality of life [214] [215] [216]. However, their clear potential for abuse and dependence has resulted in their use in pain management being restricted almost exclusively to end-of-life treatment such as cancer and Acquired Immune Deficiency Syndrome (AIDS) [110] [214] [215]. Caffeine, a much less potent psychostimulant that acts as an adenosine receptor antagonist [217], is a first-line treatment for acute migraine headaches when combined with paracetamol [218]. Even alone, it has been shown to have an analgesic effect on headaches [219].

Opioid antagonists such as naloxone and naltrexone appear to be effective in central post-stroke pain that occurs in 5-10% of stroke patients, and likely to be due to CNS vascular effects [110]. *Neuroleptics,* also known as ‘anti-psychotics’ or ‘major tranquilizers’, may have analgesic properties due to downstream effects of their antagonism of certain serotonin

and dopamine receptors [220] [221]. *Acetylcholine esterase inhibitors,* such as neostigmine, increase pain thresholds by increasing the action of cholinergic neurones in the dorsal horn of the spinal cord [108]. These have produced inconclusive results in humans thus far, with various mixtures and routes of administration providing different results [222] [223].

2.3.4 Anaesthesia

Pain management is a specialty that largely grew out of anaesthesia [8]. Anaesthetic techniques can have a dramatic impact on perioperative pain [224]. Anaesthesia is commonly thought of as simply a loss of consciousness or feeling. However, dependent on the surgical/procedural circumstances, there is often a need to combine unconsciousness with amnesia, analgesia, and muscle relaxation. This usually requires the use of multiple pharmacological agents, and often specialised equipment such as that used for respiratory support and monitoring [225]. Anaesthesia is typically divided into general anaesthesia that induces a loss of consciousness in the recipient, and local or regional anaesthesia that reduces or removes sensation from a specific area [225].

-General anaesthesia

General anaesthesia (GA) is a state of unconsciousness induced in order to facilitate surgical procedures [226]. The anaesthetist aims to monitor and maintain homeostasis across all major organ systems (renal, cardiovascular, respiratory, and neurological) in the process [225]. Other goals of GA are amnesia, analgesia, and muscle relaxation. Amnesia, specifically anterograde amnesia [226], during the surgical procedure, is achieved in GA by the patient's loss of consciousness. Only between 0.0068 and 0.9% of patients undergoing GA have been reported recall of the procedure [227]. Despite the patient's lack of consciousness, intra-operative analgesia (with opioids, local anaesthetics) is an important part of GA, as it can decrease postoperative pain and recovery times [228]. Muscle relaxation, also known as 'neuromuscular blockade', produces immobility, which is naturally desirable during surgical procedures.

There are three main 'stages' of GA. Induction, maintenance, and emergence. Induction is typically achieved using short-acting intravenous agents, classically barbiturates (thiopental) or opioids, but more recently propofol [229]). Ketamine, in combination with benzodiazepines,

is often used if propofol is contraindicated [230]. Maintenance of GA begins once the patient has lost consciousness, and typically requires a combination of agents. Typically, a volatile inhalational anaesthetic agent (such as sevoflurane), an intravenous induction agent (such as propofol), and an intravenous analgesic (such as fentanyl) are combined to provide 'balanced anaesthesia' [225] [229]. Intra-operative local anaesthesia, neuraxial blockade (epidural, spinal), and regional neural blockade are all useful tools in the pre-emptive reduction of postoperative pain [231]. The emergence phase, as the name suggests, is the period during which the patient is re-awakened. During this phase, both physical and mental reactions can occur. Mentally, patients can be confused and disorientated, which can lead to problematic behaviour such as thrashing that risks complications such as suture rupture [232]. Physically, there is a risk of 'autonomic hyper-responsiveness', where sympathetic excess results in hypertension and tachycardia [225]. However, postoperative pain is almost certainly the most common clinical challenge encountered after awakening. This is usually combatted both preventively (in theatre) and once the patient is awake [233].

In terms of adverse outcomes from GA, there are two main kinds, namely, the effects of the pharmacological agents used, and incidents that occur while performing anaesthetic-related procedures (such as intubation). Adverse events occur in approximately 5% of patients undergoing GA, the majority of which are cardiovascular (hypertension, tachycardia) and/or respiratory (respiratory failure, bronchospasm) [234]. In terms of procedural adverse outcomes, some of the more common adverse outcomes include inadequate ventilation, and oesophageal intubation that can (rarely) lead to brain damage or death [235]. The volatile anaesthetic agents, like any pharmacological agent, can have unwanted adverse effects. These are, however, considered rare [236]. For example, rarely halothane has produced cases of hepatotoxicity [236]. Volatile anaesthetic agents along with succinylcholine (a depolarising skeletal muscle relaxant) have been implicated in a life-threatening condition known as malignant hyperthermia [237]. Between 1:5,000 and 1:100,000 patients undergoing GA will experience this condition. The increased bodily heat production is largely caused by muscle contractions [237]. This is akin to how 'shivering' in response to cold will increase body temperature. The use of opioids during GA can result in typical opioid adverse effects, such as respiratory depression [238]. As previously mentioned, very rarely GA-mediated amnesia

will partially fail, and a patient will have some memory of the surgical procedure [227]. This is known as 'accidental awareness'.

The importance of the perioperative period in the development of chronic pain has recently come to light [34] [44]. A multimodal analgesic approach, both during and following a surgical procedure may reduce the risk of chronic pain development in certain surgical groups [224] [239]. Ketamine appears useful in acute postoperative pain, but at subacute (measured at six weeks postoperatively) and chronic (measured at four months postoperatively) follow-up points ketamine does not appear to have any preventative effects [240].

-Local anaesthesia

Local anaesthetics are agents which cause a reversible loss of sensation in the area in which they are administered [241]. They act by reversibly inhibiting ion channels and effectively prohibiting action potential propagation. This prevents peripheral signals (pain in particular) from reaching the CNS [242]. Their main mechanism of action is through sodium channel blockade [242]. While many chemical compounds (e.g. certain antidepressants) may have local anaesthetic properties, those used clinically tend to be aromatic compounds that contain either an ester or amide bonds [243]. They are classed by these bonds, lignocaine being an example of an amide, and benzocaine an example of an ester local anaesthetic [244].

Local anaesthetics can be administered using a variety of techniques:

- Topical application tends to be reserved for more minor procedures/conditions (such as intravenous catheter insertion) [245]. Newer evidence suggests topical lignocaine may have a place in the treatment of neuropathic pain conditions (such as post-herpetic neuralgia) [246].

-Infiltration anaesthesia, whereby the local anaesthetic agent is delivered into the subcutaneous or intradermal layers of the skin. This is useful in the likes of minor skin surgery and for lumbar puncture [247] [248]. Theoretically, any local anaesthetic agent could be used in this manner. Lignocaine is particularly popular as it is short-acting [249]. The acidity of local anaesthetics can cause pain on administration, so sodium bicarbonate can be added to the solution to reduce this [250]. Adding adrenaline to the solution will increase the duration of anaesthetic effect [249].

-Intravenous regional anaesthesia such as the Bier's block carries a somewhat higher risk of systemic toxicity than other methods of administration [251,252]. Here, the local anaesthetic is delivered directly into the venous system of the body part in question, with a tourniquet (such as a tightly-inflated blood pressure cuff) proximal to the injection site. For obvious practical reasons, this procedure is largely limited to use in the limbs, in particular the upper limbs [249]. Despite the risk of systemic toxicity due to tourniquet leakage, this technique remains popular, being seen as a more efficient alternative to GA for minor upper limb procedures [251].

-Peripheral neural blockade involves selectively anaesthetising individual peripheral nerves (e.g. ulnar nerve block) and/or groups of nerves or a neural plexus (e.g. brachial plexus block) [249]. 'Central neural blockade' is an extension of this, with the agents being delivered centrally, typically in the epidural or intrathecal spaces. This provides more widespread anaesthesia/analgesia [249]. These blocks can be used in place of GA in certain patients, such as those at high risk of GA-related complications (e.g. the very elderly) [253]. They can be administered either as a single injection, or as a continuous infusion [254]. In order to block a peripheral nerve or neural plexus without causing neural injury, it should be accurately located. The larger peripheral nerves or neural plexuses are commonly in close proximity to large vessels. The consequences for inadvertently puncturing an artery or delivering local anaesthetics intravenously could potentially be disastrous. As such, these blocks are now commonly performed with guidance from the use of nerve stimulators and by ultrasound [255] [256]. In nerve stimulation electrical impulses are sent to determine the location of the desired nerve. Stimulating the motor function component of a nerve will cause the innervated muscles to contract. The use of intra-operative epidural opioids (dependent on lipophilicity) and intrathecal opioids significantly decreases postoperative opioid requirements [257]. A combination of intrathecal local anaesthetic and opioid has been successful in reducing both intra-operative and postoperative pain in caesarean section [258]. Peripheral neural blockade remains popular and successfully used in the diagnosis and management of chronic pain [259,260,261,262,263].

Adverse effects of local anaesthetics are uncommon if appropriate doses are given and administration protocols are followed [249]. However, there is still potential for adverse outcomes. Local anaesthetics account for 5-10% of all anaesthetic-agent adverse reactions

[264]. True 'allergies' to local anaesthetics are over-estimated, with other events often being incorrectly attributed to allergy [249] [264]. Local tissue toxicity occurs when the local anaesthetic agent fails to dilute into surrounding tissue, resulting in a high intra-neural concentration that may result in prolonged or permanent neurological damage [249].

Systemic toxicity from local anaesthetics occurs when the agent enters the circulation in sufficient concentration. The CNS is the most sensitive area to local anaesthetic toxicity [249]. Early signs of toxicity are largely neurological. The inhibitory pathways of the CNS are more susceptible to local anaesthetic inhibition than the excitatory pathways [264].The first signs of local anaesthetic toxicity are often agitation and sensory disturbances, followed by generalised tonic-clonic convulsions [249]. In severe overdose, CNS depression (particularly respiratory depression) soon follows [249]. Management includes the immediate cessation of local anaesthetic administration, seizure control (with benzodiazepines such as midazolam), airway management, and intravenous lipid emulsion therapy and fluid administration [249].

The cardiovascular system is subject to toxic effects from local anaesthetic agents as well. Local anaesthetics function as negative ionotropes, depressing cardiac contraction [265] and as peripheral vasodilators on vascular smooth muscle [266]. Appropriate clinical management choices depend on the local anaesthetic in question, whether it was mixed with adrenaline (a vasoconstrictor), and other factors. Lipid emulsion therapy (intralipid®) appears to be highly cardioprotective in this setting [267].

2.4 Non-pharmacological management of pain

As chronic pain is increasingly being recognised as a multi-dimensional illness, non-pharmacological management measures can be used alongside medication. Foremost among these are psychological interventions, and physical therapies [268]. These combination approaches have been shown to be more effective than medical management alone [269].

2.4.1 Psychological management of pain

The focus of psycho-social interventions is based on the recognition of the subjective experience and chronicity of chronic pain [270]. Psychological techniques focus on modifying behavioural and cognitive responses to pain, and dealing with emotional consequences of

the pain, rather than eliminating the pain itself [271]. There are several main types of psychological intervention, each with its own focus:

- *Psychophysiological techniques* attempt to bridge the gap between the psychological and physical aspects of chronic pain. For example, 'biofeedback' involves a patient learning to voluntarily control certain physiological processes, through understanding the results of physiological testing [272]. For instance, methods of voluntarily exerting control over one's blood pressure could be learnt. Relaxation techniques (such as diaphragmatic breathing and progressive muscle relaxation) show promise as well [268] [273].

- *Cognitive Behavioural approaches* to pain management focus on identifying and challenging behaviours and emotions contributing to continued disability [268] [273]. The aim is to modify the way patients view their pain and how they respond to it. The end goal is to increase a patient's self-efficacy [274]. Acceptance-based approaches such as 'Acceptance Commitment Therapy' are a form of this. This encourages patients to work through their pain experience and accept and embrace it, rather than modifying thought processes around it [275].

- *Operant Conditioning* approaches, such as graded activation, are based around the basic principles of operant conditioning (positive/negative reinforcement and positive/negative punishment) [276]. Here, positive behaviours are re-enforced and negative behaviours ignored. Following operant conditioning reasoning, maladaptive pain behaviours become conditioned over time. For example, if frequent verbal complaints of pain result in nurturing behaviours from others (positive reinforcement), the patient becomes conditioned to complain of pain in order to obtain nurturance. The reverse is true, in that therapies could be developed to condition patients into maintaining greater activity levels and less fear of pain, through graded exposure to each [268] [277].

Highly prevalent emotional/psychological comorbidities, such as depression [278], can complicate the treatment of chronic pain. Such patients are often labelled 'difficult'. The anger, sadness, and disappointment they often experience can worsen this perception [268]. Patient expectations often exceed the realities of treatment, which if not properly addressed can compound their problems [268].

2.4.2 Physiotherapy approaches to chronic pain

Physiotherapy is widespread in the management of chronic pain [279]. In back pain in particular, physiotherapy appears to improve quality of life [280]. The use of physiotherapy in rehabilitation could provide significant savings to the health system [281]. Physiotherapy is often administered alongside cognitive behavioural therapy, to help challenge maladaptive cognitive patterns such as fear-avoidance [282]. Self-management of pain is of great importance in chronic pain [283]. Exercises and techniques taught by physiotherapists assist with this. However, different clinicians appear to favour different approaches [284], without strong evidence to support one technique over another [279] [285]. A systematic review suggests that 'individually designed' approaches might confer greater benefits. However, this systematic review acknowledges that it is sorely limited by the quality of available studies [286]. Transcutaneous Electrical Nerve Stimulation (TENS) is an intervention whereby an electrical device on the skin delivers electrical pulse stimulation to the affected nerve(s). This appears to confer significant benefit to some patients [287].

Chapter Three – Gynaecological surgical types

The reasons for surgery, surgical groups, and surgical techniques used on participants in this study are briefly discussed.

3.1 Hysterectomy

3.1.1 Background

A hysterectomy is the removal of the uterus. The three main routes of surgical excision are laparoscopic, abdominal (laparotomy), and vaginal. Of the 'major' gynaecological surgeries, hysterectomy is the most frequently performed [(288)]. In the United States, the abdominal route is the most common accounting for two-thirds of hysterectomies performed. The second highest is the vaginal route (21%), with laparoscopic route (12%) being the third. Of these, 0.9 percent were performed robotically, and the remaining 1.2% comprised 'radical' hysterectomies [(289)]. Rates vary widely between countries [(290)]. In New Zealand, nearly a quarter of women will have undergone hysterectomy by the age of 60 [(291)].

3.1.2 Indications for hysterectomy

About 70% of hysterectomies in New Zealand were performed to improve quality of life [(291)], freeing sufferers from symptoms of chronic illnesses such as endometriosis [(292)]. The remaining procedures were performed to remove malignancies [(292)].

3.1.3 Surgical approach

Less invasive procedures typically result in fewer complications, and faster recovery times [(293)]. The vaginal approach to hysterectomy, whereby the uterus is removed via the vagina without the need for abdominal incision, is considered the 'ideal' approach. However, this is not suitable for all patients [(293)]. Laparoscopic surgery involves several small incisions, with a camera inserted through one so that the surgeon can visualise the internal organs. In the case of hysterectomy, it can be performed either to assist a vaginal hysterectomy [(294)], or as a stand-alone procedure [(295)]. There is some contention as to the efficiency of laparoscopic hysterectomy, with concerns about extended surgical duration, leading one trial labelling it

a “waste of time” [296]. Conversely, a meta-analysis found no significant difference between the two methods used [295]. One randomised controlled trial found significantly lowered postoperative pain in the laparoscopic group [297]. Abdominal hysterectomy is the most invasive of the hysterectomy techniques. It requires a large abdominal incision. It results in a higher rate of postoperative pain, and an extended recovery period, making it less preferable to laparoscopic and vaginal approaches [298].

Following a hysterectomy, 4.7-31.9% of patients can be expected to develop chronic pain [299]. Of note is that between 14.7% of the underlying female population in the United Kingdom and 24.0% of the underlying female population in the United States experience chronic pelvic pain [299]. It is possible that hysterectomy cures the pain experienced by some, but it can create ongoing pain for others. Higher acute pain scores [300], any pre-operative pain [300], and a previous caesarean section [301] are associated with the development of chronic post-hysterectomy pain. Surprisingly, the actual surgical approach has not previously been detected as a risk factor for the development of chronic post-hysterectomy pain [301]. Considering the differences in tissue insult, acute pain, and healing period, this requires further study. Interestingly, gabapentin has shown promise in the *prevention* of chronic post-hysterectomy pain [302].

3.2 Salpingo- and oophorectomy

3.2.1 Background

Oophorectomy is the surgical removal of the ovaries, while salpingectomy is the surgical removal of the fallopian tubes. In the United States, 26-68% of women undergoing hysterectomy undergo oophorectomy as well, particularly those close to or past menopause [303] [304] [305]. Bilateral salpingectomy (BSO) is common during hysterectomy where the ovaries are conserved [306].

3.2.2 Indications for salpingectomy and oophorectomy

Salpingo- and/or oophorectomy (S/O) can be performed either in isolation, or during hysterectomy. Both primary ovarian and secondary metastatic neoplasms may require oophorectomy [307]. Ovarian torsion [308], endometriosis [309], and pelvic adhesions [310] remain common indications for salpingectomy and oophorectomy.

3.2.3 Surgical approach

Salpingectomies and oophorectomies are performed laparoscopically or by laparotomy. When compared with laparotomy, laparoscopy offers fewer complications, shorter recovery time, and shorter hospital stays [311]. In the acute postoperative period, laparoscopy results in significantly lower Visual Analogue Scale (VAS) pain scores, and a greater chance of being pain-free [312]. This, along with the markedly smaller incision sites involved, makes laparoscopy the preferred approach. There does not appear to be any published literature outlining the incidence of chronic post-salpingectomy or post oophorectomy pain.

3.3 Surgical management of endometriosis

Endometriosis is a disorder characterised by the existence of ectopic endometrial tissue, generally found in the pelvis. It carries a large pain burden, with approximately 11% of pre-menopausal women have evidence of endometriosis, and 71-87% of women suffering chronic pelvic pain as a result [313] [314]. For those patients for whom medical management fails or is inappropriate or intolerable, surgical management becomes necessary [315,316]. In the majority of cases, when the woman is still of child-bearing age, minimally-invasive, fertility-protecting approaches are used in laparoscopic ablation or excision [315,317]. If both medical and minimally-invasive surgical techniques fail, hysterectomy with or without bilateral oophorectomy is usually indicated providing the woman does not plan on having future children [317]. If the ovaries are conserved, there is a higher risk of continued pain that might require future surgery [318,319]. The evidence behind the choice of surgical approach (laparoscopic versus laparotomy) is similar to that given for hysterectomy and salpingo-oophorectomy, with laparoscopy remaining the preferred approach [320].

3.4 Surgical repair of pelvic organ prolapse and pelvic floor defects

Pelvic organ prolapse (largely vaginal vault prolapse, and pelvic floor defects in the present study) occur in 11-19% of women by the age of 80 [321]. Of these 29% will require subsequent surgical repair [321]. The greatest risk factors are parity and previous hysterectomy [322,323]. For this indication, the abdominal approach is commonly performed, as it has a lower rate of prolapse recurrence [324]. However, the price of the abdominal approach is the increased risk of complications, and longer recovery times [324]. Laparoscopic surgery that is gaining popularity may provide an alternative. It allows the benefits of optimal access, without

many of the complications associated with abdominal surgery [325]. Little published data exists on the incidence of chronic pain following these procedures. It has been suggested that some vaginal meshes are associated with chronic pain development in as many as 30% of patients in which they are used [326].

Chapter Four – Measurement of pain

4.1 Introduction to the measurement of pain

The obvious primary goal of any tool designed to measure an individual's pain, or responses to pain, is to assist in diagnosis. It should potentially improve the clinical management of pain for that individual, leading to better pain outcomes and improved functionality. These tools also have implications for the scientific understanding of pain [(327)]. Given the large psychological overlay in pain, psychometric questionnaires play a sizeable role in the assessment of pain. Other methods include physical testing of existing pain (such as moving a potentially painful limb on physical examination), or inducing pain to determine the limits of an individual's pain threshold and tolerance by making use of electrical stimulation, or the cold pressor test.

4.2 Psychometric Questionnaires

4.2.1 Short form of the Depression Anxiety Stress Scale (DASS-21)

The link between lengthy pain experiences and negative psychological states (such as depression and anxiety) is well established [(328)] [(329)].

The DASS-21 (Short form of the Depression Anxiety Stress Scale) was designed [(330)] to determine the extent to which the participant was experiencing the core symptoms of anxiety and depression, as well as stress [(329).] It is the short form of the forty two-item DASS questionnaire that contains three sections of fourteen questions, one for each psychological measure [(330)]. The DASS-21 contains three sections of seven items, one for each psychological measure, as per its longer counterpart [(330)]. Both the DASS and the DASS-21 are self-report questionnaires [(331)]. Each item of the DASS-21 is scored from '0' (Did not apply to me at all) to '3' (Applied very much, or most of the time), giving a total score out of sixty three, and scores out of twenty one for each of the three components. These scores are often doubled for the sake of comparison to the full-length DASS.

The component of the DASS-21 labelled 'depression' assesses several of the core features of depressive affect. These include anhedonia, lack of motivation, hopelessness, and self-

deprecation. The ‘anxiety’ component likewise assesses the core symptoms of anxiety, including physiological anxiety (such as autonomic arousal, and muscle tension), and psychological anxiety. The ‘stress’ component assesses a group of symptoms distinct from those measured by the depression and anxiety components. These include tension, irritability, and being easily distressed by stimuli considered minor stressors, or even stimuli not normally considered as stressors [332].

The DASS and DASS-21 have been extensively validated in clinical [329] [332] and non-clinical [331] samples, and as such was included in this study as a potential predictor of pain outcomes.

4.2.2 Short form of the Pain Anxiety Symptoms Scale (PASS-20)

There is a relationship between the fear and resulting avoidance of pain, and the level of disability experienced in chronic pain [333]. The PASS-20 (Short form of the Pain Anxiety Symptoms Scale) is designed [333] to measure pain-related anxiety. It assesses four of the key symptoms of pain-related anxiety. These are: cognitive anxiety, physiological anxiety, fear of pain, and escape/avoidance of pain and activities that may induce or worsen pain [334]. It is the short-form of the forty-item PASS questionnaire, itself a twenty-item self-report assessing (like its longer predecessor) the aforementioned four key symptoms of pain-related anxiety. Each item of the PASS-20 is scored from ‘0’ (Never) to ‘5’ (Always), giving section scores out of twenty five to each of the four key symptoms, and a total score out of one hundred.

The ‘cognitive anxiety’ measure assesses an individual’s mental concerns, worrying, and other psychological symptoms (such as reduction in ability to concentrate). The component labelled ‘physiological anxiety’ is designed to measure the respondent’s somatic response to pain (or anticipation of pain). This largely involves symptoms relating to activation of the sympathetic nervous system, such as increased heart rate, sweating, and increased ventilation. The ‘Fear’ measure assesses fearful thoughts related to pain, to the potential of pain, and to possible consequences of painful activities. Finally, the ‘escape/avoidance’ component assesses a person’s actions to avoid or minimise pain [334].

Like the DASS-21, the PASS-20 has been validated in both non-clinical [334] [335] and clinical [333] [336] [337] samples as a useful tool in the assessment of pain. This is the reason for its inclusion in this study.

4.2.3 Short-form McGill Pain Questionnaire (SF-MPQ)

The Short-Form McGill Pain Questionnaire (SF-MPQ) is a measurement of perception of pain in adults suffering from chronic pain [338]. It was developed [338] largely because its predecessor, the McGill Pain Questionnaire (MPQ) takes up to twenty minutes to complete [339], making it difficult to administer in clinical and research scenarios that often run on narrow timeframes. The SF-MPQ attempts to view pain in more depth than traditional pain intensity scales. It contains a total of 17 items. Eleven describe the sensory aspects of pain, 4 relate to the affective aspects, there is a Visual Analogue Scale and a Present Pain Intensity Scale as well. The SF-MPQ lacks the 'evaluative' items contained within the full MPQ. It is roughly one fifth of the size of the full 70-item MPQ. Despite this, SF-MPQ scores have been shown to correlate well with MPQ scores [340].

The eleven-item sensory dimension of the SF-MPQ includes adjectives such as 'gnawing', 'aching', and 'throbbing' that describes the physical sensation experienced. The four-item affective dimension includes the adjectives 'exhausting', 'sickening', 'fearful', and 'cruel-punishing'; these document the emotional aspect of a person's pain. Each of these items is scored from 'None' (0), to 'Mild', 'Moderate', and 'Severe' (4). The next item is the Visual Analogue Scale, which is a ten centimetre line with the left end marked 'No pain', and the right marked 'Worst pain possible', along which the participant is asked to tick where they would rate their current pain. The final item is the Present Pain Intensity Scale, which asks participants to rate their pain out of the following: 'No pain' (0), 'Mild', 'Discomforting', 'Distressing', 'Horrible', and 'Excruciating' (6) [338]. The fifteen adjective items are scored from zero to four, as discussed above. This gives a score out of forty four for the sensory dimension, and a score out of sixteen for the affective dimension, with a total descriptor score of sixty. The Present Pain Intensity can be scored out of six, and the visual analogue scale can be scored out of one hundred (millimetres) by measuring the distance along the line, taking 'No pain' as the zero point.

The SF-MPQ has been widely used and validated [341] [342] [340] [339] questionnaire when used in patients suffering from chronic pain, leading to its inclusion in this study.

4.2.4 Pain Catastrophizing Scale (PCS)

Catastrophizing (excessive negative cognition surrounding pain) has been strongly implicated in the development of chronic pain states [277] [343] [344]. The Pain Catastrophizing Scale (PCS) [345] measures an individual's tendency to catastrophize in response to pain, or in response to the potential for pain.

The Pain Catastrophizing Scale (PCS) [345] The PCS measures 'catastrophizing' across three categories. These are tendencies: to focus strongly on thoughts about pain ('rumination'); to view oneself as helpless in dealing with pain-inducing situations ('helplessness'); and to over-estimate the potential threat of stimuli which induce pain ('magnification') [345].

The PCS is a 13-item self-report questionnaire. For each item the participant is asked to score how much that item applies to them, on a scale from zero ('not at all') to four ('all the time').

The component 'rumination' has four items relevant to it, and as such is scored out of a possible sixteen. The component 'magnification' has three items relevant to it, and is scored out of a possible twelve. The remaining six items are relevant to the 'helplessness' component, giving a possible total of twenty four. The total PCS score is derived by the summation of the three individual component scores, and is scored out of a possible total of fifty two [346]. The Pain Catastrophizing Scale has been widely used and validated [345] [344] [347], and as such has been considered to be a useful inclusion in this study.

4.2.5 Pain Disability Index (PDI)

The Pain Disability Index (PDI) [348] is a simple questionnaire for measuring the impact of pain on a person's ability to undertake tasks and activities essential to their daily living. It is used clinically to determine patients' disability due to pain over time, and to assist in evaluating the effectiveness of pain management therapies, particularly in chronic settings.

The PDI measures the effect of pain on seven areas of an individual's functioning, namely, occupational, home/family, recreational, social, sexual, activities of daily living, and life

support. There is one item for each area of functioning, and each item is ranked from zero ('no disability') to ten ('total disability'). This gives an overall disability score out of a possible seventy [349].

The PDI has been used in this study to assess the functional levels of participants post-operatively, particularly as some of their number progress into chronic pain, a use for which it has been validated in peer-reviewed literature [348] [349] [350] [351].

4.2.6 Brief Illness Perception Questionnaire (BIPQ)

The Brief Illness Perception Questionnaire (BIPQ) [352] is a self-report scale designed to assess the respondent's views on five dimensions of their illness. It is a shortened version of the Revised Illness Perception Questionnaire (IPQ-R), which is an eighty-item questionnaire, its length making it somewhat prohibitive in most clinical settings. As such, the nine-item BIPQ was developed as a more time-efficient alternative [352].
Five of the nine items of the BIPQ aim to assess the five accepted core components of illness perception. These are 'identity', 'cause', 'consequences', 'timeline', and 'cure/control'. 'Identity' is the label assigned to the illness by the sufferer, and what they see as being a part of it. 'Cause' describes the factors attributed as the cause of their illness. 'Consequences' are what the participant believes the outcome/s of their illness will be. The 'timeline' is how long the participant expects to suffer their present illness. 'Cure/Control' describes how strongly a participant believes they will be cured of their illness, or the extent to which symptoms can be managed.

Two of the items assess emotional considerations, under the headings 'emotions' and 'concern', with another representing the degree to which the participant comprehends their illness. The final item of the BIPQ is the item examining 'cause' (as described above). It is open-ended, and asks the participant to list, in order of significance, what they believe to be the three main factors that have caused their illness [352]. The first eight items featured in this questionnaire are scored on a zero to ten scale, with zero being the negative response (e.g.: 'No symptoms at all'), and ten being the affirmative (e.g.: 'Many severe symptoms'). The BIPQ has been validated in asthma [352], diabetes [352], migraine [353], and allergic rhinitis [354]. It has also been described in the literature as substantially easier to use than its

predecessor [352] [353]. It has predictive value for self-efficacy [355]. This questionnaire has been chosen to investigate its usefulness in pain management, its correlation with self-efficacy, and to discover how illness beliefs change as levels and duration of pain change.

4.2.7 Pain Self-Efficacy Questionnaire (PSEQ)

The Pain Self-Efficacy Questionnaire (PSEQ) [356] is a self-report scale administered to sufferers of chronic pain which assesses their beliefs about their own self-efficacy.

There are ten items ranked from zero to six, where 0 = ‘‘not at all confident’’ and 6 = ‘‘completely confident’’. The total score is calculated by adding the scores for each question, yielding a maximum possible score of 60. A higher score indicates a stronger belief in their own self-efficacy.

The PSEQ, like the PDI, is a well-validated [357] [356] [358], and has been shown to be a likely link in the relationships between chronic pain, depression, and disability [359]. We have used it to investigate correlations between chronic pain, perceived self-efficacy, and more objective disability.

4.2.8 Tampa Scale of Kinesiophobia – 13 (TSK-13)

The Tampa Scale of Kinesiophobia - 13 (TSK-13, referred to hereafter as the TSK) [360] is a thirteen item self-report questionnaire assessing a patient’s fear of movement and/or reinjury, leading to what is known as pain avoidance behaviour. It is a shortened version of the seventeen-item TSK, with the four reverse-scoring questions removed.

The TSK-13 items are all scored from one to four, where 1 = ‘Strongly disagree’ and 4 = ‘Strongly agree’. The total score is calculated from the sum of all questions, giving a maximum possible total of 52. The higher the score, the greater the levels of kinesiophobia.

The TSK has been shown to have excellent internal consistency and construct validity, and has been validated in several different chronic pain groups from low back pain (344), neck pain [361], shoulder pain [362] to temporomandibular disorders [363]. It has been selected for use in this study because of the growing evidence base suggesting a possible causative link between pain avoidance behaviour and the development (and continuation) of chronic pain

[363]. We believe that a combination of the TSK, measuring kinesiophobia (which logically leads to avoidance behaviour in an effort to minimise risk of pain/reinjury), and the PSEQ, should provide valuable insight into the relationship between patient functionality and chronic pain

4.2.9 Pain Treatment Satisfaction Scale (PTSS)

The Pain Treatment Satisfaction Scale (PTSS) [364] is a sixty nine item self-report questionnaire assessing an individual's level of satisfaction with their pain management. However, the length of this questionnaire, combined with the number of other questionnaires being used in this study, prohibited the use of the full questionnaire. As such, the version of the questionnaire used at the Burwood Pain Management Centre has been adopted that asks the questions most pertinent to the aims of this study. The version of the questionnaire used is comprised of 7 items, 5 of which are on a 0 to 10 scale, and 2 are 'yes' or 'no' questions. For example: "Was the treatment you received in line with what you expected at the beginning of treatment? Would you recommend this treatment to someone you know who has a similar problem?"

4.3 The Cold Pressor Test

The cold pressor test involves the participant placing their hand into a bucket of cold water (at 4 degrees centigrade), and removing it when they cannot bear it any more. The apparatus itself consisted of an 8-litre bucket, half-filled with ice, with a metal mesh over the ice to prevent ice burns. Cold water was then poured over the ice until it filled up above the mesh at a level deep enough for the participant's hand. Once the participant's hand was in the water, the participant informed the observer when the pain was first felt (the 'pain threshold') [365], and when the pain was unbearable (the 'pain tolerance') [365], at which point the limb was voluntarily removed. Pain endurance was the time difference between first feeling of pain (pain threshold) and the point at which the pain is no longer bearable (pain tolerance) [365]. Perceived control over anxiety-inducing stimuli such as the cold pressor test increases pain tolerance and endurance [366]. Given that the participant had total control over the cold pressor test, it is likely that pain tolerance and endurance in this test inflated the measured values. Perceived control had no influence on pain threshold or intensity [366].

As this perceived control over the cold pressor test existed in the same manner for all participants, it is unlikely that this produced any bias or confounders in the results.

To the researchers' knowledge, this test has not previously been carried out in comparable clinical research in New Zealand. However, the test is extensively documented in the literature (365), [366], [367], [368]. This test was based on such studies.

Chapter Five – Protocol Development

5.1 Pilot study

In order to best design and plan the main study detailed in this thesis, a pilot study was undertaken as part of the summer studentship program at the University of Otago, Christchurch. Ethical approval was obtained from the University of Otago Human Ethics Committee (Health) prior to commencing the study. This pilot study was designed under the assumption that the main study would comprise of a randomised controlled trial embedded into a cohort study. For clinical reasons beyond the control of the researcher, the randomised controlled trial element had to be discontinued, and the surgical population used altered.

5.1.1 Aims and methods of the pilot study

The aim of this pilot study was to design and partially pilot the proposed main cohort study of patients before and after surgery. Specifically, the aims were as follows:

1) To pilot the use of the cold pressor test, and the questionnaires that were to be used in the main study.
2) To determine the logistics of the main study, in terms of recruiting patients and performing the initial assessment at the pre-admission clinic at Christchurch Hospital.
3) To determine the sample size available, and get an indication of the proportion of patients willing to participate in the main trial.

Methods

Inclusion Criteria:	**Exclusion Criteria:**
Aged 17 years or over	Aged under 17 years
Those undergoing elective surgery for limb amputation, thoracotomy, and mastectomy surgery at Christchurch public hospital	Informed consent withheld
	Those with obvious cognitive impairments
	Those on secondary analgesics (such as tricyclic antidepressants and the α2δ-sub-unit voltage-dependent calcium channel blockers)[1]

Table 1 Inclusion and exclusion criteria of the pilot study

The rationale behind the inclusion and exclusion criteria chosen is outlined in chapter three of this thesis.

There were 13 patients that met the study criteria, and gave their informed consent to participate. Another participant was identified but excluded due to receiving the secondary analgesic venlafaxine. Consenting participants were then taken to a private room in the pre-admission clinic for assessment. The assessment piloted in this study was largely the same as that which was to be used as an initial assessment of participants in the main trial. It consisted of the following:

Demographic data: Ethnicity, gender, level of education, and current work status were recorded for each participant.

Validated questionnaires: The questionnaires[2] used in this pilot study had all been extensively validated. These were the: Short Form McGill Pain Questionnaire (369) (370); Pain Disability Index (349); the Pain Self-Efficacy Questionnaire (371); the Depression and Anxiety Stress Scales-21 (372); and the Pain Anxiety Symptoms Scale-20 (336).

[1] This exclusion criterion was put in place because the proposed main study involved a randomised control trial of two secondary analgesics. For logistical purposes, this component of the main study was dropped.
[2] The details of the questionnaires used in both the pilot, and main studies, are outlined in chapter four of this thesis.

Cold pressor test: The cold pressor test involved the participant placing their hand into a bucket of cold (at 4 degrees centigrade) water, and removing it when not being able to bear it any more. The apparatus itself was an 8-litre bucket, half-filled with ice and water, with a metal mesh over the ice to prevent ice burns.

Explanation of main trial: The research student gave a detailed explanation of the proposed main trial (inclusive of the randomised controlled trial) to each participant. Participants were then asked to indicate whether or not they would, if eligible to participate in said trial, have given their informed consent.

5.1.2 Relevant findings of the pilot study

No participants recruited for this study were deemed to be in significant pain at the time of, or in the week prior to, assessment at pre-admission clinic. This meant that only the demographic information and the DASS-21 were completed by all participants. Only one participant indicated that they would not have participated in the main study if eligible to participate.

Twelve participants in this study were undergoing mastectomy surgery; the one thoracotomy patient identified was undergoing an oesophagogastrectomy. No patients undergoing limb amputation were identified during the 10 weeks of the study.

5.1.3 Using the pilot study to assist in designing the main study

Over the 10-week course of this pilot study, 12 patients undergoing mastectomy, 0 patients undergoing limb amputations, and 1 patient undergoing a thoracotomy were identified at Christchurch Hospital Pre-admission clinic. This rate of patients acquired per week in the pilot study was substantially lower than that required for the main study. This led to a change in recruitment location from Christchurch Hospital Pre-admission Clinic to the Burwood Hospital Department of Orthopaedics, and then to the Christchurch Women's Hospital Pre-admission clinic. Discussions with staff suggested that approximately 5 patients per week could be recruited from Christchurch Women's Hospital Pre-admission clinic, substantially more than the 13 patients recruited in the 10 weeks of this pilot study.

Only 1 patient in an eligible surgical group was excluded from this pilot study, due to receiving the secondary analgesic venlafaxine [373]. This was removed as an exclusion criterion for the main study, since it was no longer relevant once the randomised controlled trial aspect had been removed. No eligible participants failed the person-place-time orientation test. None were considered sufficiently cognitively impaired as to be incompetent to give informed consent. No eligible patients declined to participate in this pilot study, and only 1 of the participants of this pilot indicated that they would not have participated in the main study if eligible to do so. This boded well for participation rates once the study had been shifted to a department with greater numbers of potential participants.

The design of the cold pressor test was not dramatically altered between the pilot study and main study, as it proved portable and functional. The way the study was introduced to potential participants was improved, and familiarity with the psychometric questionnaires was gained.

Chapter Six – Detailed Methods

6.1 Hypothesis and aims

6.1.1 Hypothesis

As laid out in the literature review, all of the measures taken in this study have experimental or at least hypothetical evidence to suggest a relationship with prolonged pain states. It was hypothesised that one or more of the measures taken (psychometric questionnaires, cold pressor test, clinical records, surgical and anaesthetic approaches) would predict pain at six weeks and three months postoperatively.

6.1.2 Specific Aims

1) The prevalence of acute persistent pain at 6 weeks postoperatively
2) The prevalence of chronic pain at 3 months postoperatively
3) The predictive value of the secondary measures collected, relating to each of the first two aims

6.2 Review of literature

Existing literature on the physiology, pathophysiology, and management of both acute and chronic pain was reviewed. Articles, reviews, and meta-analyses in peer-reviewed journals and textbooks were accessed, and the relevant information extracted. The search engines 'PubMed' and 'Google Scholar' were used to extract relevant articles. Physical copies of textbooks were accessed at the University of Otago, Christchurch (UOC) medical library, and the University of Otago Christchurch's Department of Anaesthesia.

6.3 Ethical approval

Ethical approval for the project required an extension of an existing proposal. This extension was granted by the University of Otago Research Human Ethics Committee (Health) on 8th May 2014 (reference number HE13/07). Locality authorisation for the project to be undertaken at Christchurch Women's Hospital was granted by the Canterbury District Health Board (CDHB) Research Office (Research Office allocated number 14082). Consultation with the University of Otago Christchurch's Māori Research Advisor was

undertaken. It was suggested that ethnicity data should be collected - that was already the case. In addition that those Māori participants are explicitly made aware that consent given for this research project was for the purposes of this study only. This was done not only with Māori participants, but extended to all other participants as well.

6.4 Study design

The study design was piloted in the summer before the main study took place. The methodology and results of the pilot study can be found in chapter five.

A prospective cohort study was undertaken in the Preadmission Clinic at Christchurch Women's Hospital (CWH). From here, patients who were undergoing gynaecological surgery and requiring at least an overnight stay at either CWH or Southern Cross Hospital (SCH) (under CDHB contract) were approached. Once informed consent had been obtained, participants were subjected to the cold pressor test, and filled in the baseline questionnaires. At six weeks, and three months following their surgery, participants were contacted by telephone, were asked about their pain (if any), and completed further questionnaires.

Following an individual's surgery, every effort was made to access the relevant records relating to their surgery.

Sample size

The planned sample size for the original iteration of the study was 140 participants. This was the number judged realistic from a logistical standpoint. As calculated by GPower 3.1[3], an a_2 = 0.05, and power of 80% , it would allow detection of correlations of 0.21 between baseline measurements and pain levels at follow-up The original design was a randomised controlled trial of gabapentin and nortriptyline for the prevention of CPSP, embedded within a prospective cohort study. The detectable Cohen's d for this study was 0.85. Ethical approval from the Ministry of Health's Health and Disability Ethics Committee was obtained, as was locality authorisation from the Canterbury District Health Board, and permission was granted by the Head of Department for the Department of Orthopaedics at Burwood Hospital. However, before the first participant could be recruited, several senior clinicians in

[3] http://www.gpower.hhu.de/en.html

the Department of Orthopaedics actively resisted having their patients involved in any research study. Their wishes were respected, and the study was moved to the specialty with the second highest number of potentially eligible patients: gynaecology. The resulting time delay in repeating the required approvals and the limited timeframe of the B.Med.Sc. (Hons) meant that the randomised controlled trial component unfortunately had to be removed, and fewer participants were able to be recruited. With the 3 month follow-up period of this study taken into consideration, approximately 10 weeks only could be allocated to recruitment. Based on the figures given by the Department of Gynaecology, it was decided that it could be reasonably expected that approximately 5 participants could be recruited per week. As a result, a target of 50 participants was set. This would allow detection of correlations of 0.34 between baseline measurements and pain levels at follow-up. Four extra participants were recruited in the 11th week to account for loss to follow-up.

6.5 Recruitment and consent

Selection

Patients were approached at Christchurch Women's Hospital pre-admission clinic by the research student or nursing staff. They were given a brief outline of study, and asked if they were interested in hearing more. If they expressed interest, they were taken to one of the rooms in pre-admission clinic once pre-admission had been completed.

Written informed consent

The trial and the requirements of participation were fully explained. Participants were given an information sheet to take away with them. They were encouraged to ask any further questions. The investigators' contact details were supplied (on the participant information sheet) should any questions occur at a later stage. They were reminded them that they retained the right to withdraw from the project at any stage without any disadvantage to them. Informed consent was obtained by the signing of the consent form.

The participants consented to the following: 1) Pre-operative assessment; 2) Access to their (relevant) clinical records; and 3) Consent to being contacted at 6 weeks and 3 months post-operatively to repeat the questionnaires.

6.6 Inclusion and exclusion criteria

Inclusion Criteria

All of the following criteria had to be met in order to enter the study, providing no exclusion criteria existed. They were:

1) To undergo gynaecological surgery requiring at least an overnight stay at Christchurch Women's Hospital or Southern Cross Hospital (under CDHB contract)

2) 16 years of age or older

3) To grant informed consent

Exclusion Criteria

Any potential participant would be ineligible to enter the study if one or more of the following criteria existed:

1) <16 years of age

2) Cognitively impaired

3) Withholding informed consent

4) Any person whose proficiency in English was such that they would require an interpreter to fully understand the study

Inclusion criteria (as listed above) were that patients were aged 16 years or older, and would be undergoing gynaecological surgery at Christchurch Women's Hospital. The age limit was placed in order that patients could give their own informed consent. The surgical groups were chosen because the gynaecological surgical group were a large surgical group carrying a large overall pain burden. There were 54 participants recruited.

Exclusion criteria (as listed above) were the following: patients aged less than 16 years (reasoning as above); those who withheld informed consent; those with obvious cognitive impairments that might render them incompetent to give informed consent; and any person whose proficiency in English was such to require an interpreter to fully understand the study. Obvious cognitive impairments would be measured by determining person, location

and time orientation. The questions used to determine this were as follows: 1) ‘Can you please tell me your full name? 2) ‘Can you please tell me where we are at present? 3) ‘Can you please tell me what year it is, and what day of the week it is?’. As the follow-up assessments were conducted over the telephone, it was not practical to include anyone whose English proficiency was not sufficient to complete the questionnaires without an interpreter.

6.7 Baseline assessment

The baseline assessment was carried out in pre-admission clinic. It comprised three parts, namely: the collection of demographic data; the administration of validated questionnaires to determine the participant’s pre-operative psychological state; and the cold pressor test to determine the participant’s pain threshold, tolerance, and endurance.

6.7.1 Demographic information, and validated questionnaires

The questionnaires aimed to potentially identify which (if any) psychological states (as measured by these questionnaires) would predict pain outcomes postoperatively. Multiple measures were taken, as a single questionnaire could not globally assess a person’s psychological state. The characteristics measured by these questionnaires were as follows:

DASS-21: Depression, anxiety, and stress, which are known to correlate with chronic pain states.

BIPQ: Participant perceptions and beliefs surrounding illness and pain.

SF-McGill: The severity and character of pain.

PTSS: How well a participant believed their pain was being managed.

PSEQ, TSK, PDI: Level of functioning, and how the pain is affected their daily lives.

The questionnaires used in the initial assessment for the main study were largely the same as those undertaken in the pilot study. All had been extensively validated. They were administered as follows:

Participants were asked to indicate if they were in any pain that was distressing or functionally impairing (3/10 or above on the verbal analogue scale) at any time in the week immediately preceding the assessment, and was related to the reason for their surgery.

In pain	DASS-21	BIPQ	Demographic information	PCS	PASS-20	PDI	SF-McGill
Not in pain	DASS-21	BIPQ	Demographic information				

Figure 1 Data collected at baseline for each group

Demographic data: Ethnicity, age, gender, level of education, and current work status were recorded for each participant. These factors are known to be related to depression, anxiety, illness perception, and the experience of pain. Participants were asked to indicate their smoking status, and alcohol and recreational drug use, as these are known be related to the progression of pain.

All participants were asked to indicate the appropriate day and time of day for follow-up telephone calls, and whether or not they would like to receive a copy of the results. Home phone, cell phone, email, other contact details were collected as well.

6.7.2 The cold pressor test

Pain threshold (time taken to feel pain) and pain tolerance (total time hand is submerged) were recorded. From these, pain endurance (pain tolerance minus pain threshold) was calculated. The water temperature in the tank was set at 4 degrees Centigrade. No distractions were allowed during the test, as these are proven to enhance pain tolerance [374,375].

The cold pressor test was carried out before the participant completed the questionnaires, in order that the observer could not subconsciously influence the subject's performance based on their pain versus no pain status, or on their psychological measures.

Participants were aware that a test limit existed for their safety. However, they were blinded to the actual said limit. For safety reasons, the test was terminated after 4 minutes if the participant had not already removed their hand. The test limit of 4 minutes was chosen to limit the risk of tissue injury, a limit supported by the literature [376,377,378].

6.8 Perioperative assessments

Complete perioperative data proved difficult to obtain for many participants due to incomplete files, and due to files being held by other District Health Boards. The following were searched for:

6.8.1 Surgical and anaesthetic techniques

Surgical approach (laparoscopic, laparotomy, per-vaginal); type of surgical procedure; the type and amount of all medications used; duration of surgery; and any perioperative surgical or anaesthetic complications.

6.8.2 Recovery room assessment

Analgesia given was recorded. Any complications occurring were recorded.

6.8.3 Postoperatively

The following were recorded:

- The amount of morphine/fentanyl used every 24 hours (obtained from Patient Controlled Analgesic pumps), and the weak opioid/NSAID/steroid use.

- The appearance of postoperative red flags (infection, bleeding, rupture of sutures)

- The analgesic medications on discharge from the hospital

The following were searched for on the clinical records database: history of chronic pain; any chronic medical condition; any chronic psychiatric condition; and the number of previous admissions/referrals to tertiary health centres.

6.9 6-weeks postoperatively

Participants were contacted by telephone at an appropriate time to respond to the questionnaires. If participants did not answer within 48 days of their surgery, they were considered lost to follow-up, and were not contacted at 3 months.

Participants were asked to indicate if they were in pain at any time of the week immediately preceding the assessment that was related to their surgery.

In pain*	Verbal scale of pain intensity	DASS-21	PTSS	PDI	PASS-20	SF-MPQ	Functional measures (TSK, PSEQ)
Not in pain	Asked to indicate when pain stopped	DASS-21	PTSS				

Figure 2 Data collected at 6 weeks for each group

*: 'In pain' – any pain which, in the participant's eyes, has caused distress or functional impairment over the preceding week. The pain must be the direct result of their surgery, and must be greater than or equal to 3/10 on the Verbal Rating Scale (VRS).

For all participants:

1) They were then informed that the researcher would contact them in another 6 weeks, and asked to indicate an appropriate time.

2) Information about late complications from their surgery (e.g. wound opening, after discharge infections, re-hospitalisation, etc.) were recorded.

6.10 3-months postoperatively

Participants were contacted by telephone at an appropriate time to complete the questionnaires. If participants did not answer within 48 days of their surgery, they were considered lost to follow-up.

Questionnaires:

1) For those with pain at 6 weeks (n=1)

For the patient still in pain, the same questionnaires as at week 6 were administered.

For those patients not in pain (n=7), the following was recorded: the date the pain stopped; and the reasons it stopped (if they had reasons). The DASS-21 questionnaire was administered.

2) Those with no pain at 6 weeks (n=43) were asked if, since the last contact by telephone, they had experienced any pain that they attributed to their surgery

-3 participants identified that they had developed pain in the time since the 6 week assessment. Two experienced intermittent pain only (one for < 5 minutes per day, another

only during menstruation). They were asked to complete the DASS-21, and SF-McGill questionnaires, and a verbal scale of pain intensity. The remaining participant, who had experienced 'sub-threshold' pain at 6 weeks (2/10 verbal scale of pain intensity), now experienced pain ranging from 3-7/10 on the verbal scale of pain intensity. She was asked to complete the DASS-21, PASS-20, PDI, PTSS questionnaires, the verbal scale of pain intensity, and the functional measures (TSK, PSEQ).

- For the rest with no pain at 6 weeks (n=40), only the DASS-21 questionnaire was administered.

Participants were informed that they would not be contacted again; they were reminded that they could request a copy of the results, or contact the research team if they had any questions. Participants were then thanked for their participation.

All efforts were made to ensure all participants received adequate care. At the cessation of the study, it was planned that any participant experiencing debilitating chronic pain would be referred to the Burwood Pain Management Centre for treatment. However, fortunately none of our participants experiencing continued pain were considered appropriate for referral, and were followed-up by their own General Practitioner.

6.11 Analysis of data

As previously noted, the sample size was limited by the following: the timeframe of the B.Med.Sc. (Hons) course[4]; several setbacks that resulted in a delayed start; the number of eligible patients seen at Christchurch Women's Hospital, and the number of eligible patients the research student was able to recruit. This rather small sample size resulted in limited statistical power to detect some of the less common outcomes and smaller associations.

Initially it was planned to calculate correlations between baseline measures and pain scores at 6 weeks and 3 months postoperatively. However, the change from orthopaedic to gynaecological patients meant that far fewer of the patients were in pain at baseline, and fewer still at follow-up, than expected. This meant that it was inappropriate to use correlations, as too many participants had pain scores of zero. Instead those patients in pain

[4] It is of note that this is not the first B.Med.Sc (Hons) thesis to cite course duration as a limiting factor (403,404)

were compared with those patients not in pain at each observation point. Baseline characteristics of those who progressed into prolonged pain states were compared with those who did not.

Data was entered into *Microsoft Excel* spreadsheets, and then into *OpenEpi* (Dean, A.G. et al, Open Source Epidemiologic Statistics for Public Health) for quantitative analysis. Any participants not completing follow-up point(s) were excluded from analyses relating to those point(s). There were 95% Confidence intervals (95% CI) calculated using the Score (Wilson) method. T-tests (dependent and independent) were used for comparisons of means and two-tailed p-values were used throughout. Chi-squared tests were used for comparisons of proportions. Linear regression was attempted to impute pain endurance on the cold pressor test in patients who reached the time limit of 240 seconds. Significance was reported when $p < 0.05$.

Chapter Seven – Results

Participants were recruited from pre-admission clinic at Christchurch Women's Hospital from 5th May 2014 until 31st July 2014. They were then followed up by telephone for their 6-week and 3-month assessments that ended on the 29th October 2014.

7.1 Participant flow

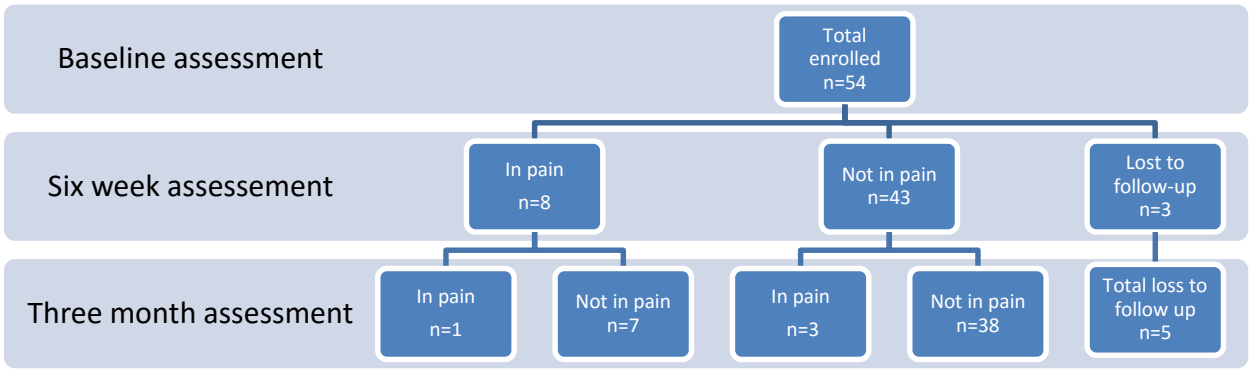

Figure 3 Participant flow. Note: All three participants lost to follow-up at 6 weeks had been in pain at baseline. Both participants lost to follow-up at 3 months had been pain-free at 6 weeks.

Ideally, data would have been collected about those who chose not to participate or were rendered ineligible by the exclusion criteria. Due to the clinical responsibilities of the nursing staff, a large number of patients were 'vetted' before the research student was even made aware of these patients. The research student was therefore unable to gather accurate data about non-participants. Conversations with the nursing staff revealed three main reasons why the staff would choose not to pass a patient on to the research student:

1) The nursing staff considered the patient too vulnerable or scared (for example those with significant comorbidities or malignancies or the very anxious).
2) The patient flagrantly failed an inclusion criterion, such as being very cognitively impaired, or unable to speak English.
3) Those patients who indicated they would not provide informed consent.

Due to the busy clinical environment, the nurses were often too busy to provide this information. The research student did not know how the study was introduced to patients in his absence. This might have made affected the uptake rates. As such, it is difficult to

make any accurate conclusions about the number of non-participants. Of the 61 patients personally approached by the student, 54 consented without meeting any of the exclusion criteria. Of the remaining 7 patients, 4 patients initially indicated interest, but either forgot or changed their minds, and left after their pre-admission was complete. Two patients refused to take part, and 1 patient was deemed too cognitively impaired. A number of patients under the age of 16 came through the pre-admission clinic. None of these were approached. This might have impacted the data as explained later.

7.2 Baseline characteristics

7.2.1 Demographic information and relevant history

For all participants, the following were recorded: ethnicity; age (date of birth); gender; level of education; and current work status. Participants were also asked to circle any given conditions they had suffered. Their smoking status and use of alcohol and recreational drugs was collected as well.

	Not in pain at baseline (n=26)	In pain at baseline (n=28)	Total (n=54)
Ethnicity			
NZ Māori	3 (11.1%)	2 (6.9%)	5 (9.3%)
NZ European	21 (77.8%)	23 (79.3%)	44 (81.5%)
Other	3 (11.1%)	4 (13.8%)	7 (13.0%)
Mean age (years)	48.4 (SD 12.9)	36.3 (SD 10.7)	42.1
History of:			
Chronic pain	8 (30.8%)	19 (67.9%)	27 (50%)
Mental illness	4 (15.4%)	9 (32.1%)	13 (24.1%)
Surgery	20 (76.9%)	17 (60.7%)	37 (68.5%)
Smoking			
Present (mean pack years)	7 (26.9%) (16.9 pack years, SD 9.7)	4 (14.3%) (5.3 pack years, SD 3.1)	11 (20.4%) (10.8 pack years) (95% CI 4.3, 17.3)
Former (mean pack years)	6 (23.1%) (20.3 pack years, SD 12.7)	5 (17.6%) (8.9 pack years, SD 6.9)	11 (20.4%) (14.4 pack years) (95% CI 6.4, 22.4)
Never	13 (50%)	19 (67.9%)	32 (59.3%)
Consume alcohol	14 (53.8%)	21 (75%)	35 (64.8%)
Yes (standard drinks per week)	3.7	3.4	3.6
Currently working	22 (84.6%)	22 (78.6%)	44 (81.5%)
Level of education			
University	5 (19.2%)	8 (28.6%)	13 (24.1%)
Other post-secondary	9 (34.6%)	12 (42.8%)	21 (38.9%)
Secondary school	7 (26.9%)	6 (21.4%)	13 (24.1%)
Unanswered	5 (19.2%)	2 (7.1%)	7 (12.9%)

*Table 2 Demographic and relevant medical information at baseline. *Two participants identified themselves with two ethnicities, and so for the purposes of ethnicity, percentages shown are percentage reporting each ethnicity, and sum to more than 100%.*

Age and ethnicity

All 54 participants in this study were biologically female, and all identified themselves as such. The 'Not in pain' (NP) group were a mean of 12.1 (95% CI 5.7, 18.6) years older than the 'In pain' (IP) group, which was a significant difference ($p < 0.001$). In the NP group, the youngest participant was 25 years of age, while the oldest was 73. By comparison, the youngest participant in the IP group was 20 years of age, and the oldest 67.

Table 2 shows that it is clear that both groups had similar distribution of ethnicities, with the predominant self-identified ethnicity being New Zealand European (81.5%). Two

participants selected multiple ethnicities, and in accordance with New Zealand Census reporting [379], each ethnicity stated was recorded, producing a total of over 100%. In the NP group, 'Other' ethnicities recorded were Latino-American, British, and Filipino origin. In the IP group, 'Other' ethnicities recorded were Irish, Dutch, Spanish, and unspecified European origin. The 2013 New Zealand Census [379] recorded 8.1% of the Canterbury region as NZ Māori, 86.9% as NZ European, and 14.1% as other ethnicities. This compares with the 7.4% (NZM), 80.6% (NZE), and 12% (Other) in this study, suggesting a representative spread of ethnicities within the study.

Relevant history

There were 27 participants (50%) that reported a history of chronic pain, defined as 'pain lasting longer than three months'. Those in the IP group were significantly more likely than those in the NP group to have had a history of chronic pain (p= 0.01). This is unsurprising, as many of the IP group would be undergoing surgery to relieve longstanding pain. The prevalence of chronic pain in the underlying New Zealand population is 16.9% [39].

A history of mental illness seems likely to go under-reported on a simple self-reporting questionnaire, due to embarrassment or inaccurate recall. It is possible that some participants thought the question was only relevant to current disorders, and did not report past issues. There were 13 participants (24.1%) that reported a prior or current mental illness; this was higher in the IP group than in the NP group, but not significantly (p= 0.15). Both groups individually as well as in total, are all lower than the lifetime prevalence for 'Any disorder' (39.5%) found in Te Rau Hinengaro: The New Zealand Mental Health Survey [380]. This survey asked specifically about symptoms of many disorders, and so was more sensitive than the question in this this study about a history of mental illness.

With the category of 'surgery' being broad, it has been difficult to find lifetime risk reports in the literature, particularly for New Zealand. One study from the United States reports a risk of intra-abdominal surgery by the age of 60 of 43.8% [381], while two others report female lifetime risks of prolapse and/or urinary stress incontinence surgery of 19% [382] and 20% [383], respectively. Naturally, with a mean age of only 41.5 years, the women in this study are not representative of a 'lifetime' risk. However, with an overall record of 37 participants (68.5%) with surgical histories, it seems that previous surgery is associated with risk of

further surgery. Interestingly, participants in the IP group were non-significantly more likely than those in the NP group to have previously undergone surgery (p = 0.20). If this is a true association, it could be at least in part due to the 12.1 year mean age gap between the two groups.

The comparison of self-reported mental illness, chronic pain, and surgical history with mental illness recorded in medical files will be discussed later.

Smoking

Despite appearing higher in the NP group, a Chi-squared at a significance level of 0.05 did not find a significant difference in the number of 'current smokers' (p = 0.25), or 'former smokers' (p = 0.63) between the two groups. However, a two-tailed independent t-test found that those currently smoking in the NP group had a significantly longer pack-year history. The same could not be said for the 'former smokers', with the 20.3 years vs. 8.9 years difference being not significant at 95% confidence interval (p = 0.10). The longer pack-year history in the NP group might at least be partially explained by the 12.1 year mean age gap between the two groups.

Recall bias likely affected reporting of the duration of smoking history for some participants. It is not known how this would affect the overall results. The prevalence of current smokers in New Zealand adults is 19.9% (18.8% of current smokers are adult females) [(384)]. Of the female population, 18.6% were regarded as 'ex-smokers' in 2006/2007 [(385)]. It is worth noting that the prevalence of New Zealand female smokers in the 30-39 age bracket (in which the IP mean falls) is 21.5%; it is 22.3% in the 40-49 age bracket, (in which the NP mean falls) [(386)].

Illicit drugs

Only one participant (1.85%) admitted to recreational drug use other than alcohol, compared to 23.8% of the adult New Zealand population [(387)]. It is likely that illicit drug use was under-reported in this study. This could possibly be due to fear that, despite assurances to the contrary, divulging the information could negatively affect some aspects of their health care, or result in legal issues. On the other hand this sample might simply have a

much lower rate of illicit drug use. In absence of a plausible explanation it seems likely that this is either a case of under-reporting, or a statistical anomaly.

Alcohol use

Of the 54 total participants, 35 (64.8%) consumed alcohol at least once per week. Those in the IP group were more likely than those in the NP group to report that they consume alcohol at least once per week, but not significantly (p= 0.10). The New Zealand average for females, as measured by the 2007/2008 New Zealand Alcohol and Drug Use Survey [388] is 43.2%. Using the Statistics New Zealand population indicators [389] there were 2,271,800 females in the New Zealand population as of 31st December 2013. Using these data, a Chi-Squared test for population proportions found that the 54 participants in this study were significantly more likely to consume alcohol at least once per week than the average New Zealand female ($p < 0.001$).

This study asked participants to record the number of standard drinks they consumed per week (NP 3.7, IP 3.4, total 3.6). The 2007/2008 New Zealand Alcohol and Drug Use Survey [388] did not ask about this, but rather focussed on whether or not people were likely to drink to excess in a single sitting. New Zealand population data on standard drinks consumed per week is not available in a form comparable to the data collected in this study.

Employment and education

A total of 44 participants (81.5%) were employed in either part- or full-time work. There was no statistically significant difference between the two groups in terms of the proportions employed in each group ($p = 0.57$). The 'Labour force participation rate' reported by Statistics New Zealand for the June 2014 quarter is 68.5% [390].

In terms of highest level of education, 13 (24.1%) participants had received tertiary education, 21 (38.9%) participants that had undertaken other post-secondary study, and 13 (24.1%) others that had at least one secondary school qualification. Five participants (19.2%) in the NP group, and 2 participants (7.1%) in the IP group did not answer the education question.

There were no significant differences in education between those in pain and those not in pain on a Chi-squared test, namely: tertiary qualification, p = 0.42; other post-secondary qualification, p = 0.54; and secondary qualification, p = 0.64. In 2013, 76.2% of the adult population (aged 25-64 years) had at least one secondary school qualification, with 26.1% holding a Bachelor's degree or higher [391]. In 2007, 41% of all adults (aged 25-64 years) had received tertiary education (included all post-secondary education) [392].

In this study, 63.0% of participants (28.6% tertiary education, and 38.9% 'other post-secondary' education) had completed post-secondary education (even when assuming that all 7 non-respondents had not). The lower confidence limit was found to be greater than the number given by the New Zealand government (49.6% versus. 41%), indicating that the participants in this study were significantly more likely than the underlying population to have completed a post-secondary qualification.

7.2.2 Validated questionnaires and pain score means (standard deviations)

	Not in pain at baseline (n=26)	In pain at baseline (n=28)	Total (n=54)	Possible range
DASS-21				
Depression	1.5 (1.8)	3.9 (3.5)	2.7 (3.5)	0-21
Anxiety	1.8 (3.0)	3.9 (4.2)	2.9 (3.4)	0-21
Stress	3.6 (3.2)	7.5 (5.4)	5.6 (4.8)	0-21
Total	6.9 (6.5)	15.3 (18.9)	11.2 (10.5)	0-63
BIPQ*	33.4 (10.2)	41.1 (7.6) (n=27)	37.3 (9.7)	0-50
'In pain' questionnaires:				
SF-McGill		(n=27)	**(95% CI)**	
Sensory	-	5.5 (5.3)	(3.4, 7.6)	0-44
Affective	-	1.6 (2.4)	(0.7, 2.5)	0-16
PPI	-	1.8 (1.2)	(1.3, 2.3)	0-6
Total	-	8.9 (8.0)	(5.7, 12.1)	0-66
VAS	-	2.1 (2.0)	(1.3, 2.9)	0-10
PCS		(n=25)		
Rumination	-	7.2 (4.4)	(5.4, 9.0)	0-16
Magnification	-	3.5 (2.6)	(2.4, 4.6)	0-12
Helplessness	-	8.5 (4.4)	(6.7, 10.3)	0-24
Total	-	19.2 (10.1)	(15.0, 23.4)	0-52
PDI	-	26.7 (14.5) (n=26)	(20.8, 32.6)	0-70
PASS-20		(n=27)		
Cognitive	-	13.0 (5.2)	(10.9, 15.1)	0-25
Escape	-	11.0 (5.9)	(10.7, 15.3)	0-25
Fearfulness	-	5.0 (4.5)	(3.2, 6.8)	0-25
Physiological arousal	-	8.2 (5.2)	(6.1, 10.3)	0-25
Total	-	37.2 (17.0)	(30.5, 43.9)	0-100
VAS Scores				
Pain high	-	7.3 (2.9) (n=26)	(6.1, 8.5)	0-10
Pain low	-	2.1 (1.7) (n=27)	(1.4, 2.8)	0-10
Usual pain	-	3.5 (2.0) (n=26)	(2.7, 4.3)	0-10

*Table 3 Validated questionnaires at baseline. *The 'Causal categories' section of the BIPQ is not included in this table. When one or more participant has not answered a given questionnaire, the number of respondents is given in the table as (n=X).*

DASS-21

Each section of the DASS-21 has 7 items (0-3 scale), with a maximum possible score in each section of 21, and maximum total score of 63. All DASS-21 section scores were significantly higher in the 'In Pain' (IP) group:

Using a two-tailed t-test for independent group means depression scores were significantly higher in the IP group than in the than the NP group [mean difference 2.4 (95% CI 0.9, 3.9) (p= 0.01)]. The normative data (norm) from 1,724 United Kingdom adults [372] for the depression subscale was 2.8 (SD 3.9). The 95% confidence interval for the IP group is (CI 2.5, 5.3), and the difference between the IP group and the published norm is not significant on a two-tailed independent t-test (p = 0.11).

Anxiety scores were significantly higher in the IP group than in the NP group [mean difference 2.1 (95% CI 0.1, 4.1) (p=0.02)]. The norm [372] for the anxiety subscale is 1.9 (SD 3.0), so the difference between the IP group and the published norm is significant (p = 0.02).

Stress scores were significantly higher (p = 0.002) in the IP group than the 'NP group [mean difference 3.9 (95% CI 1.5, 6.4) (p= 0.002). The norm [372] for the stress subscale is 4.7 (SD 4.2), so the difference between the IP group and the published norm is significant (p = 0.01).

Total DASS-21 scores were significantly higher in the IP group than in the NP group [mean difference 8.4 (95% CI 0.6, 16.2) (p= 0.002)]. The norm [372] for the DASS-21 is 9.4 (SD 9.7), so the difference between the IP group and the published norm is significant (p= 0.002).

BIPQ

The BIPQ contains 8 items (0-10 scale), with a maximum possible score of 80. The mean BIPQ score in the IP group (41.1) was significantly higher (p = 0.003) than the NP group (33.4) on a two-tailed t-test for independent means, with a mean difference of 7.7 (95% CI 2.8, 12.7). This indicates a more threatening view of illness in the IP group that seems logical given their higher anxiety and stress scores. Some examples of published norms are as follows: common colds 36.6; 'pre-diagnosis' chest pain 42; asthma 45.8; myocardial infarction 49.3; and diabetes mellitus 52.4 [352]. In terms of threats to their health, this would see the cohort as a whole (mean 37.3) viewing their illnesses as somewhere between the common cold, and undiagnosed chest pain The BIPQ also asked participants to rank-order the 3 most important factors they believe caused their illness. Participants filled in anywhere from 0 to 3 factors, with a total of 61 answers recorded. For the sake of analysis, these answers were grouped into categories. Twelve participants (19.7%) believed their gender or genetics caused their illness; there were 12 participants (19.7%) that answered,

but stated they had 'no idea' of the cause of their illness; 10 participants (16.4%) blamed their lifestyle or other self-controlled factors; 9 participants (14.8%) blamed childbirth; 9 participants (14.8%) blamed other assorted biological factors; 6 participants (9.8%) believed their age had a role to play; there were 3 4.9% that believed their illness was caused by chance or poor luck. Ten (18.5%) of the 54 participants did not answer this section of the BIPQ. 'Norms' for this section of the BIPQ do not appear to have been published for gynaecological patients.

SF-McGill, PCS, PDI, and PASS-20 scores

The means, standard deviations, and 95% confidence intervals for the SF-McGill, PCS, PDI, and PASS-20 scores are shown in Table 3. Naturally no comparisons can be made at baseline given that only patients in pain at baseline completed them.

The SF-McGill has an 11-item 'sensory' sub-scale, and a 4-item 'affective' sub-scale. Each item is scored out of 4, giving a maximum possible score of 44 for the 'sensory' sub-scale, and 16 for the 'affective' sub-scale. It has a 'present pain indicator' (PPI) which is scored out of 6, bringing the maximum possible total score to 66. The PCS is scored out of a total of 52, with 13 items (0-4 scale). The 'Rumination' 'Magnification' and 'Helplessness' sub-scales comprises of 4, 3, and 6 items respectively, with a resulting maximum possible scores of 16, 12, and 24. The PDI is a 7-item questionnaire, with its items scored on a 0-10 scale, giving a maximum total score of 70. The PASS-20 is a 20-item questionnaire, each of its items being scored from 0-5. Each of its 4 sub-scales (cognitive anxiety, escape/avoidance, fearfulness, and physiological arousal) has maximum scores of 25, with the overall maximum score being 100.

SF-McGill

The norms for the sensory and affective scales of the SF-McGill in patients with chronic back pain (n=188) are 11.9 (SD 0.9) and 3.0 (SD 0.6)[5], respectively [339]. These are both higher than the 5.5 ($p < 0.001$, two-tailed independent t-test) and 1.6 ($p < 0.001$). The PPI and VAS

[5] These standard deviations are calculated from the individual item standard deviations given in the paper.

scores naturally differ vastly between clinical circumstances, and a valid published comparison (for pre-operative or gynaecological patients) could not be found.

PCS

Women are reported to have significantly higher levels of pain catastrophizing (as measured by the PCS) than men both overall, and in the rumination and helplessness sub-scales [345]. As such, normative data for women (n=302) was used for comparison with this all-female cohort. The following calculations are two-tailed independent t-tests, using the norms[6] published by Sullivan et al [345]. This cohort only significantly differed from the norms in the helplessness sub-scale [helplessness 8.5 (SD 4.4) versus 7.2 (SD 3.0) ($p = 0.046$)]. The other sub-scales and the overall scores did not significantly differ. The cohort means are given first, namely: rumination 7.2 (SD 4.4) versus 8.8 (SD 3.6) ($p = 0.09$); magnification 3.5 (SD 2.6) versus 3.6 (SD 2.1) ($p = 0.85$); and total 19.2 (SD 10.1) versus total 19.5 (SD 8.5) ($p = 0.89$). These norms are for a pain-free cohort of psychology students, who were asked to recall a recent painful experience while completing the questionnaire.

PDI

Tait et al [349] report results from 401 chronic pain patients that were separated into 'low' and 'high' disability, based on which side of the median (46) they fell. The means for the 'low' and 'high' groups were 34.5 (SD 9.3) and 55.9 (SD 5.8), respectively. The mean for this study's 'In Pain' cohort was 26.7 (SD 14.5). For the sake of comparison, a 95% confidence interval was calculated using a two-tailed independent t-test for the 204 'low disability' participants in the Tait et al study, and was based on the mean of 34.5 and a standard deviation of 9.3. This study's 'In Pain' cohort was shown to significantly differ from the published norm for 'low disability' chronic pain patients: mean difference 7.4 (95% CI 3.7, 11.9) ($p < 0.001$). However, this study noted that women reported significantly less disability than men, but did not state the extent to which this occurred. Given how close the upper arm of the 'In Pain' group's CI comes to the lower arm of the Tait group (32.6 versus 33.2), it is likely that this is due to either the gender differences, or the fact that this compares patients from a chronic pain unit to pre-surgical patients likely to be suffering lower levels of

[6] In the paper by Sullivan et al, the section norms are given as item norms. For comparison these have been multiplied to give section norms and their standard deviations.

pain. It is quite possible to be a real difference, as people actually specifically undergoing treatment for chronic pain would likely be more disabled by it than those who are not.

PASS-20

The norms for each of the sub-scales of the PASS-20 are as follows: 12.3 (SD 6.7) for cognitive anxiety; 12.8 (SD 6.1) for escape/avoidance; 7.4 (SD 6.4) for fearfulness; 6.2 (SD 5.7) for physiological arousal; and a total of 38.6 (SD 20.4) for a cohort of n=282 [(333)]. With the exception of fearfulness, where our cohort scored significantly lower, these do not differ significantly from our cohort on two-tailed independent t-tests. These results are as follows: cognitive anxiety mean difference 0.2 ($p = 0.85$); escape/avoidance mean difference 2 ($p = 0.07$); fearfulness mean difference 2.4 ($p = 0.02$); physiological arousal mean difference 2 ($p = 0.07$); and total mean difference 0.4 ($p = 0.91$).

In the 'In Pain' group, 1 participant did not fill in the BIPQ (so n=27); 1 participant who did left two questions blank. In the 'Not in Pain' group, 1 participant had left three questions blank. One participant did not complete the SF-McGill (so n=27), 3 did not complete the PCS (so n=25), 2 did not complete the PDI (so n=26), and 1 did not complete the PASS-20 (so n=27). These scales have been analysed by the number who completed them (for example, the SF-McGill was analysed with n=27, not n=28). One person who filled out the PDI left the 'sexual' question blank. After discussion with a Consultant Biostatistician, it was decided that the sample size in this study, and the likely effect of the missing data points, was not great enough to warrant logistical regression.

Of the 'In Pain' group, the mean VAS scores were out of 10, where 10 indicates the worst pain possible. The VAS scores were as follows: highest pain 7.3 (SD 2.9); lowest pain 2.1 (SD 1.7); and usual pain 3.5 (SD 2.0). Twenty-seven of the 28 participants gave 'lowest pain' scores, and 26 participants gave scores for 'highest pain' and 'usual pain'.

7.2.3 Cold pressor test results (means, in seconds)

	Not in pain at baseline (n=26) (SD)	In pain at baseline (n=28) (SD)	Mean difference (95% CI)
Threshold	57.0 (59.4)	50.8 (47.1)	6.2 (-23.0, 33.4)
Tolerance	119.6 (73.4)	112.43 (88.0)	7.15 (-37.3, 51.6)
Endurance	87.5 (84.9)	77.9 (100.1)	9.6 (-60.2, 41.0)
Number who hit the test limit (240 sec)	5 (19.2%)	7 (25%)	Total: 12/54 (22.2%)

Table 4 Cold pressor test results (means, in seconds). Maximums of 240 seconds are included

Table 4 shows the mean scores and standard deviations in scores from the cold pressor test at baseline. The mean differences between the two groups and confidence intervals for each difference are displayed as well.

The NP group scored non-significantly higher on average in all three measures, but a greater percentage of the IP group reached the 240 sec limit of the test (25% vs. 19.2%).

None of these results were statistically significant. The confidence intervals for mean difference in threshold (-23.0, 33.4), tolerance (-37.3, 51.6) and endurance (-60.2, 41.0) all included zero. All p-values were shown by a two-tailed t-test for independent means to be > 0.05 (threshold p-value 0.67; tolerance p-value 0.75; endurance p-value 0.71). It would seem likely that those already in pain at the time of a pain-inducing test react differently to those who were not. It is conceivable that a true difference exists, but that it is smaller than this study was powered to detect.

It is worth noting that the 240 second time limit of the test is a ceiling which artificially lowered the tolerance and endurance scores for 7 participants (25%) in the IP group, and 5 participants (19.2%) in the NP group. It is impossible to know how much this will have lowered the 'true' tolerance and endurance for each group. Given the comparable rates in each group, it seems likely that this could have caused similar underestimations in both groups. A linear regression was undertaken to in an attempt to more accurately compare the pain endurance scores between the groups. Unfortunately, those who reached the 240 second time limit did not have threshold scores different to those who did not, so the imputed data was nonsensical. The imputed tolerance data points were all lower than 240 seconds, while clearly these individuals' tolerances were all at least 240 seconds. As such, the analysis is severely limited, as scores could not be extrapolated beyond the 240 second

time limit. These individuals were not excluded from the analysis, as this would have further underestimated the scores.

Those with a threshold and/or tolerance of 240 seconds were given an endurance of 240 seconds. This is because many had artificially-small endurances, for example, if a participant had a pain threshold of 230 seconds and then their pain tolerance reaches the 240 second limit, their observed pain endurance is 10 seconds.

Two participants in the NP group demonstrated pain thresholds greater than 240 seconds, compared to no (0) participants in the IP group. As there was no way of estimating the 'true' pain thresholds of these participants, their pain thresholds have been left unadjusted, and analysed as 240 sec. There were also 4 other participants in the IP group and 2 participants in the NP group with identical pain thresholds and tolerances (i.e. they removed their hand at the same moment as their first indication of pain). It seems unlikely that many of these people are completely incapable of enduring pain, although given the full participant-control of the cold pressor test it is possible they simply did not want to endure any pain, or more likely that they simply misunderstood the test.

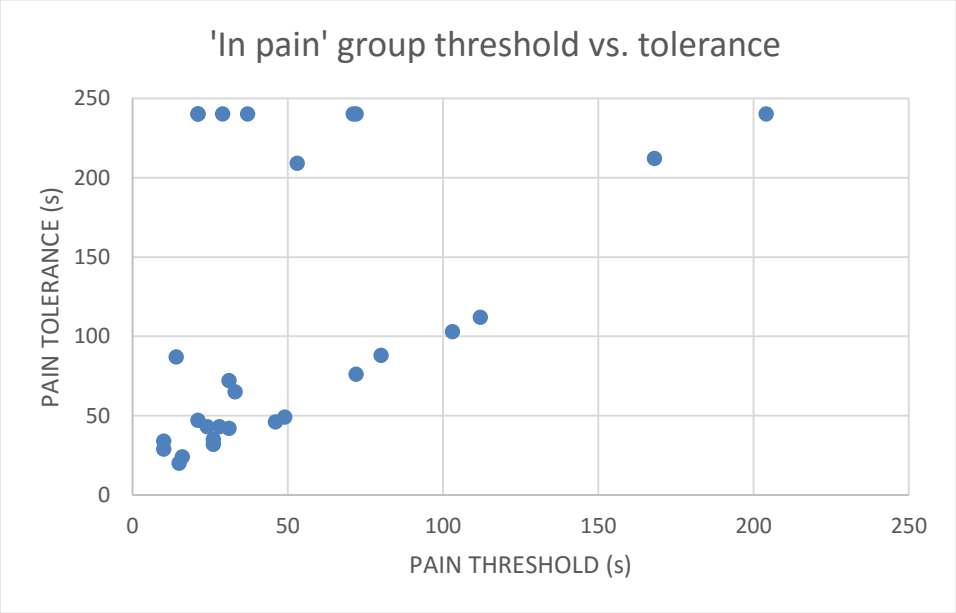

Figure 4 Pain threshold vs. pain tolerance – 'In pain'

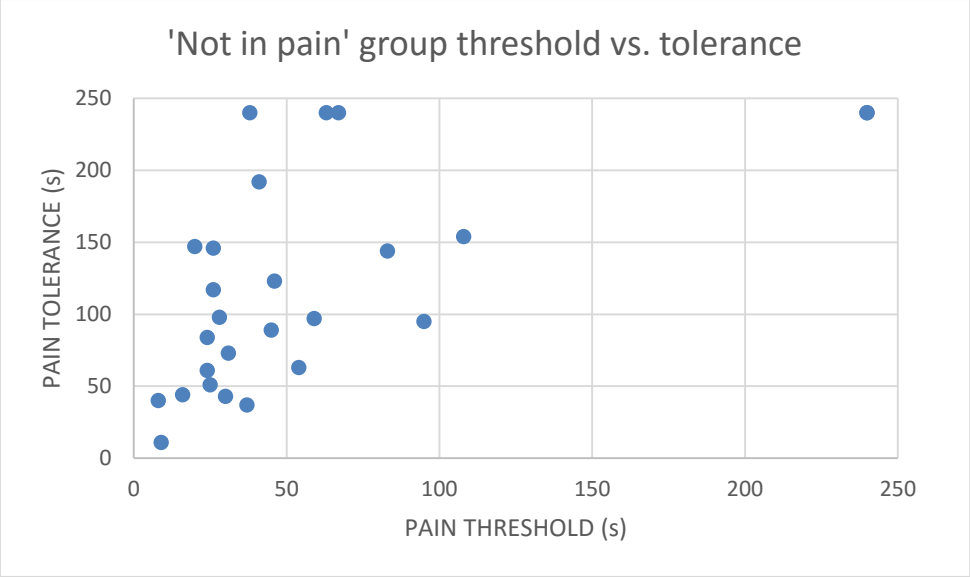

Figure 5 Pain threshold vs. pain tolerance – 'Not in pain'

Figures 4 and 5 show the relationship between pain tolerance and pain threshold. It used the relationship between the pain thresholds and pain tolerances of those who did not reach the 240 second limit to predict the pain tolerances of those who did reach the 240 second limit, based on their pain threshold.

7.3 Surgical records

Patient surgical records were obtained, with informed consent, for all patients. However, many of the records were found to be incomplete, with factors such as anaesthetic and Post-Anaesthetic Care Unit (PACU) data unable to be located for 7 of the participants.

From these records, several factors were extracted. The main factors examined were as follows: the surgical method; the duration of surgery; the complications during or following the surgery; and the pre-operative, intra-operative, and postoperative pharmacological management (including the anaesthetic technique). Also noted was the location of the surgery (either Southern Cross Hospital or Christchurch Women's Hospital), as well as the past medical history, and the medications being used to manage any current conditions.

7.3.1 Surgical data

	Not in pain at baseline (n=26) (%)	In pain at baseline (n=28) (%)	Total (n=54) (%) (95% CI)
Surgical route			
Laparoscopy	12 (46.2%)	24 (85.7%)	**36** (66.7%) (53.4%, 77.8%)
Laparotomy/abdominal	5 (19.2%)	2 (7.1%)	**7** (13.0%) (6.4%, 24.4%)
Vaginal	9 (34.6%)	2 (7.1%)	**11** (20.4%) (11.8%, 32.9%)
Primary surgical groups			
Hysterectomy	7 (26.9%)	3 (10.7%)	**10** (18.5%) (10.4%, 30.8%)
Hysterectomy + salpingo-oophorectomy	6 (23.1%)	7 (25.0%)	**13** (24.1%) (14.6%, 37.0%)
Salpingo- and/or oophorectomy	4 (15.4%)	2 (7.1%)	**6** (11.1%) (5.2%, 22.2%)
Excision of endometriosis	2 (7.7%)	9 (32.1%)	**11** (20.4%) (11.8%, 32.9%)
Pelvic floor/vaginal vault repair	10 (38.5%)	0	**10** (18.5%) (10.4%, 30.8%)
Other	2 (7.7%)	6 (21.4%)	**8** (14.8%) (7.7%, 26.6%)
Surgical duration (minutes)	94.8 (SD 43.9) (n=20)	78.6 (SD 27.3) (n=22)	**86.3** (SD 36.6) (95% CI 74.9, 97.7)
Hospital	(n=21)	(n=25)	
Christchurch Women's	15 (71.4%)	18 (72.0%)	**33** (71.7%) (57.5%, 82.7%)
Southern Cross	6 (28.6%)	7 (28.0%)	**13** (28.3%) (17.3%, 42.6%)

Table 5 Surgical factors identified from participants' patient records.

For the 'In Pain' group, 3 participants undergoing hysterectomy and/or oophorectomy (theoretically curative for endometriosis) underwent excision of endometriosis at the same time. They were categorised by their 'primary' indication or underlying/causative pathology. One participant undergoing hysterectomy underwent pelvic floor repair as well. Where a certain factor has not been identified for one or more participants, the number identified is shown as (n=X).

Those in pain at baseline were significantly more likely to undergo laparoscopic surgery, with the limits of each 95% confidence interval non-overlapping (in pain 68.5%, 94.3% versus not in pain 28.8%, 64.5%, p = 0.002). Neither group was significantly more or less likely to undergo laparotomy [95% confidence intervals of 2.0%, 22.6% (IP) versus 8.5%, 37.9% (NP), and p = 0.187]. For vaginal surgery, a Chi-squared test showed a p value of 0.012, indicating statistical significance. However, when 95% confidence intervals are calculated for each group using the Score (Wilson) method, the 'Not in Pain' group's lower limit (19.4%) crossed the upper limit of the 'In Pain' group (22.6%), suggestive of a lack of statistical significance.

There were little differences between the two baseline groups in terms of the surgical groups to which they belonged. The 95% confidence intervals for the two groups overlapped for hysterectomy [3.7%, 27.2% (IP) versus 13.7%, 46.1% (NP), p=0.13], hysterectomy with salpingo- and/or oophorectomy [12.7%, 43.4% (IP) versus 11.0%, 42.1% (NP), p=0.87], and salpingectomy and/or oophorectomy [2.0%, 22.6% (IP) versus 6.2%, 33.5% (NP), p=0.34]. The IP group was more slightly more likely to undergo excision of endometriosis; although the 95% confidence intervals for the groups overlapped, a significant p-value was found on a Chi-squared test [17.9%, 50.7% (IP) versus 2.1%, 24.1% (NP), p=0.03]. No IP participants underwent pelvic floor/vaginal vault repair, while 10 (38.5%) of the NP participants did. This result is statistically significant, with no overlap of 95% confidence intervals [0%, 12.1% (IP), 22.4%, 57.5% (NP)] and p < 0.001. Six participants (21.4%) in the IP group underwent 'other' types of surgery; four of these participants underwent ovarian cystectomy, 1 underwent a diagnostic laparoscopy, and 1 underwent an adhesiolysis. Two participants (7.7%) in the NP group underwent 'other' surgical type surgery, 1 a tubal ligation, and the other a diagnostic laparoscopy.

In terms of surgical duration, the mean difference between the two groups was 19.8 minutes [95% CI -2.8, 42.4 (p= 0.083) two-tailed independent t-test] that was not statistically significant.

The past medical histories recorded in the patients' files were compared to those given at the baseline assessment. This comparison revealed that 14 participants (compared to 13 recorded on the baseline data sheets) had experienced mental illness, and 46 participants

(compared with 37 self-reported) had a record of previous surgery. Recall bias is likely to have played a large role in this, especially for surgeries undertaken a long time ago. Only 14 participants (compared with 27 self-reported) were found to have documented chronic pain. This indicates that much of the chronic pain these people experience is either not detected by the medical system, or is dealt with at a primary health care level.

7.3.2 Analgesic use

	Not in pain at baseline (n=26)	**In pain at baseline (n=28)**	**p-value**
Intra-operative analgesics:	**(n=23)**	**(n=24)**	
Opioids (any)	21 (91.3%)	23 (95.8%)	0.53
Opioid equivalents given (1 mg oral morphine)	67.2mg	71.8mg	See text
Clonidine	5 (21.7%)	7 (29.2%)	0.56
Paracetamol	13 (56.5%)	8 (33.3%)	0.11
Parecoxib	18 (78.3%)	15 (62.5%)	0.24
Lignocaine	2 (8.7%)	2 (8.3%)	0.97
Post-op analgesics:	**(n=23)**	**(n=24)**	
Opioid equivalents	22 (95.7%) (48.1mg) (n=22)*	23 (95.8%) (64.1mg) (n=22)*	0.98
Clonidine	3 (13%)	2 (8.3%)	0.60
Paracetamol	21 (91.3%)	22 (91.7%)	0.97
Ibuprofen	7 (30.4%)	11 (45.8%)	0.28
Diclofenac	5 (21.7%)	4 (16.7%)	0.66
Gabapentin	0	1 (4.2%)	0.32
Patient-Controlled Analgesia (opioid eq.)	5 (21.7%) (223.6mg)	5 (20.8%) (142mg (n=4))	0.94
Discharge analgesics:			
Codeine	13 (50%)	13 (46.4%)	0.80
Tramadol	9 (34.6%)	11 (39.3%)	0.72
Paracetamol	23 (88.5%)	25 (89.3%)	0.92
Ibuprofen	11 (42.3%)	15 (53.6%)	0.41
Diclofenac	8 (30.8%)	9 (32.1%)	0.91

*Table 6 Intra- and post-operative, and discharge analgesic use between baseline groups. *Several missing individual pieces of data, such as when 'fentanyl' is written in the notes, but the quantity is omitted*

Table 6 shows the use of intra-operative and postoperative analgesics as a comparison between the baseline groups (IP, NP). Opioid use has been standardised to units of '1 mg of oral morphine' using a Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists opioid equivalency chart that is yet to be released to its Fellows. Where a certain factor has not been identifiable for one or more participants, the number identified is shown as (n=X).

Inpatient (intra-operative and postoperative) medication charts could be found for 23 participants (88.5%) in the NP group, and 24 participants (85.7%) in the IP group. Discharge medication information could be found for all participants, as recorded from both their files and participants themselves (during the 6 week phone call). However, medication dosage and duration could not be reliably discovered for the majority of participants, and as such has been omitted from analysis.

As can be seen in Table 6, none of the medications were significantly more likely to be given to either group intra-operatively, postoperatively, or on discharge (all p-values > 0.05). It would appear that pre-operative pain does not greatly alter the pharmacological pain management intra-operatively, postoperatively, or upon discharge from hospital. Pain scores could not be reliably recovered from the records, so it is impossible to know whether this represented truly equal pain between the groups, or inadequate analgesia in the IP group (or, conversely, excessive analgesia in the NP group).

The mean doses of opioids charted have been shown. For many participants it was difficult to ascertain from the notes the doses given, and whether a drug was actually given or simply charted. The doses given have all been standardised to the equivalent of 1 milligram of morphine. This has been calculated from a range of different medications, and often the route of administration (e.g. intravenous, oral) is not stated in the notes. As such, much of the calculations behind the standardised opioid dosages given here have been deduced, and should be interpreted with caution. As there were only 5 participants per group who were identified as having a patient-controlled analgesia pump, and the fact that the dosage data for one of the participants in the IP group could not be found, emphasises cautious interpretation of these results.

7.4 6-week assessments

7.4.1 Prevalence of subacute pain

During the 6 week follow-up assessments, 3 patients could not be reached by telephone. After multiple attempts at making contact, they were considered lost to follow-up. All of these participants had been in pain at baseline. Of the remaining 51 participants, 8 participants (15.7%) (95% CI 8.2%, 28.0%) were deemed to be experiencing continued disruptive or distressing pain. A further 10 participants (19.6%) (95% CI 11.0, 32.5%) continued to experience pain, but only intermittently and of a low-grade (never exceeding 3/10 on the verbal analogue scale). Of the 8 participants categorised as 'In Pain' at the 6 week follow-up point, 6 of these participants (75%) had been classed as 'In Pain' at the baseline assessment.

7.4.2 Psychometric questionnaires and pain scores

Results of DASS-21 and PTSS questionnaires, means (standard deviations)

	Not in pain at 6 weeks (n=43)	In pain at 6 weeks (n=8)	Difference (95% CI, p)	Possible range
DASS-21 (6weeks)				
Depression	1.9 (3.2)	2.8 (2.8)	0.9 (-1.5, 3.3, p= 0.43)	0-21
Anxiety	2.1 (2.5)	3.1 (3.6)	1.0 (-2.1, 4.1, p= 0.47)	0-21
Stress	3.6 (4.2)	6.0 (4.4)	2.4 (-1.3, 6.1, p= 0.18)	0-21
Total	7.3 (8.8)	11.9 (10.0)	4.6 (-4.0, 13.2, p= 0.25)	0-63
DASS-21 (baseline)				
Depression	2.6 (3.5)	3.4 (3.5)	0.8 (-2.2, 3.8, p= 0.57)	0-21
Anxiety	2.6 (3.4)	4.4 (3.0)	1.8 (-0.8, 4.4, p= 0.16)	0-21
Stress	5.5 (5.0)	6.1 (4.2)	0.6 (-3.1, 4.3, p= 0.73)	0-21
Total	10.7 (10.6)	14.9 (9.2)	4.2 (-3.8, 12.2, p= 0.27)	0-63
PTSS (6 weeks)	44.9 (5.7)	42.3 (6.8)	2.6 (-3.2, 8.4, p = 0.34)	0-50

Table 7 Results of DASS-21 and PTSS psychometric questionnaires at 6 weeks

DASS-21

When the DASS-21 was re-administered at 6 weeks, those 'In pain' at the 6 week assessment (IP6) scored higher in every sub-scale of the DASS-21 than those 'Not in pain' at the 6 week assessment (NP6). However, none of these differences were significant. When the baseline DASS-21 scores of the IP6 group were compared to those of the NP6 group, the same non-significant trends were found.

The cohort's overall DASS-21 scores did not change significantly between baseline and 6 weeks on a two-tailed dependent t-test, from which the three participants lost to follow-up were excluded, the mean difference was 2.41 (95% CI -2.3, 6.3 t = 1.217, p = 0.229).

PTSS

Given that the version of the PTSS used in this study is a modified one (used by the Burwood Pain Management Centre), no normative data are available. The PTSS used is a 7-item questionnaire, 5 items being 0-10 scale questions (with a possible maximum of 50), with the other 2 items being 'yes or no' questions. Those not in pain at 6 weeks scored their surgical experience higher, but not significantly. Overall, 48 (94.1%) participants answered 'yes' to the question - 'Was the treatment you received in line with what you expected at the beginning of treatment' (there was 1 'no' from those in pain, and 2 from those not in pain). Forty –six participants (90.2%) answered 'yes' to the question - 'Would you recommend this treatment to someone you know who has a similar problem?' (2 answered 'no' from those in pain, and 3 answered 'no' from those not in pain). Our participants scored a mean of 43.8 (SD 8.5) for the PTSS. This would seem to be a high level of satisfaction with the pain management received in hospital.

Comparison of the 'In pain (baseline)' and 'In pain (6 weeks)' groups – psychometric questionnaires

	In pain (baseline) (n=28)	In pain (6 weeks) (n=8)	Possible range
TSK	-	13.8 (9.8)	0-52
PSEQ	-	36.4 (15.8)	0-60
SF-McGill	(n=27)		
Sensory	5.5 (5.3)	13.3 (2.3)	0-44
Affective	1.6 (2.4)	2.3 (1.9)	0-16
PPI	1.8 (1.2)	1.4 (1.1)	0-6
Total	8.9 (8.0)	16.9 (3.9)	0-66
VAS/VRS	2.1 (2.0)	2.1 (1.9)	0-10
PCS	(n=25)		
Rumination	7.2 (4.4)	5.6 (3.5)	0-16
Magnification	3.5 (2.6)	1.6 (1.6)	0-12
Helplessness	8.5 (4.4)	4.8 (3.2)	0-24
Total	19.2 (10.1)	12.0 (6.8)	0-52
PDI	26.7 (14.5) (n=26)	14.1 (9.1)	0-70
PASS-20	(n=27)		
Cognitive	13.0 (5.2)	10.6 (4.7)	0-25
Escape	11.0 (5.9)	8.6 (5.8)	0-25
Fearfulness	5.0 (4.5)	4.9 (2.8)	0-25
Physiological arousal	8.2 (5.2)	6.8 (3.4)	0-25
Total	37.2 (17.0)	30.9 (14.0)	0-100
VAS/VRS Scores			
Pain high	7.3 (2.9) (n=26)	5.4 (1.5)	0-10
Pain low	2.1 (1.7) (n=27)	2.6 (1.7)	0-10
Usual pain	3.5 (2.0) (n=26)	3.9 (1.3)	0-10

Table 8 Comparison of the baseline 'in pain' and 6 week 'in pain' groups - 'In pain' questionnaires

Table 8, and this section as a whole, shows the characteristics of patients in pain at each time point, rather than tracking individual patients over time. Due to the telephonic style of the 6 week follow up, the VAS used in the SF-McGill and baseline questioning had to be replaced with a Verbal Rating Scale (VRS). The VRS is scored from 0-10, and correlates well with the VAS [393]. The mean differences, 95% confidence intervals, and p-values were not

calculated, as the groups were not independent as required for an independent t-test. Not much would be gained from dependent t-tests, as only 6 participants would have met the requirements. The Table shows the difference between the scores of the two groups as wholes, not simply the change in the scores of those 6 who were in pain at both points. Of the 'In pain' group at 6 weeks (IP6), 25% were not in pain at baseline; only 21.4% (6 participants) of the 'in pain' group at baseline (IP) developed subacute pain, meaning the other 22 IP data points could not be matched to a 6 week equivalent.

On the SF-McGill, the IP6 group scored higher on the sensory and affective subscales, as well as on the total SF-McGill score. The reverse was true of the PPI, although insubstantially (mean difference 0.4). VAS/VRS scores did not differ between the groups. The identical VAS and VRS scores (2.1, 2.1) and very similar standard deviations (2.0, 1.9) between the groups supports the interchangeable use of scores from these two scales. This notion does not seem unreasonable given that they are the same scale, with the reporting method being the only difference. The published norms for the SF-McGill are 11.9 and 3.0 for the sensory and affective scales, respectively [339]. On two-tailed independent t-tests, the IP6 group scored significantly higher on the sensory sub-scale [mean difference 1.4 (95% CI 0.7, 2.1), $p < 0.001$], but significantly lower on the affective scale [mean difference 0.7 (95% CI 0.2, 1.2), $p= 0.01$] than these norms.

On the PCS the IP group scored higher than the IP6 group on all 3 subscales. Overall, the IP group scored higher than the IP6 group on the PCS (mean difference 7.2). The IP6 group scored significantly lower on the rumination (norm 8.8, SD 3.6, $p=0.04$) and magnification (norm 3.6, SD 2.1, $p= 0.01$) sub-scales than the published norms [345] on two-tailed independent t-tests. The differences between in scores on the helplessness (norm 7.2, SD 3.0, $p=0.07$) and total PCS score (norm 19.5, SD 8.5, $p= 0.40$) were not significant.

PDI scores in the IP group were higher than those of the IP6 group. The IP6 group scored significantly lower than the published norm [348] [mean difference 20.4 (95% CI 12.7, 28.1), $p < 0.001$] on a two-tailed independent t-test. The norm for the 'low disability' group is 34.5.

The means of every sub-scale, and the total PASS-20 score, were higher in the IP group than in the IP6 group; cognitive (mean difference 2.4); escape (mean difference 2.4); fearfulness (mean difference 0.1); physiological arousal (mean difference 1.4); and total (mean

difference 6.3. In two-tailed independent t-tests, the IP6 group scores did not significantly differ from the published norms [333] on any sub-scale; fearfulness (norm 7.8, SD 6.4, p= 0.27), cognitive anxiety (norm 12.3, SD 6.7, p=0.35); and the escape (norm 12.8, SD 6.1, p= 0.08) sub-scales. The IP6 group scores were higher than the published norms on the physiological arousal (norm 6.2, SD 5.7, p= 0.64) sub scale, but not significantly. For the total PASS-20 score, the IP6 group scored lower than the published norm, but not significantly (norm 38.6, SD 20.4, p=0.20).

In terms of VAS/VRS scores the IP group scores were greater than those of the IP6 group for 'highest pain' (mean difference 1.9). For 'lowest pain' (mean difference 0.5) and 'usual pain' (mean difference 0.4), the IP6 mean scores were higher.

7.5 3 month follow up

7.5.1 Prevalence of chronic pain

During the 3 month follow-up assessments, 2 participants could not be reached by telephone. One had been in pain at baseline, but neither of the two was in pain at 6 week follow-up. After multiple attempts at making contact, they were considered lost to follow-up. All participants had been in pain at baseline. Of the remaining 49 participants, 2 participants (4.1%) (95% CI 1.1%, 13.7%) were deemed to be experiencing continued disruptive or distressing pain on a daily basis. Both had been in pain at baseline, and one had been in pain at 6 weeks. Another 2 participants (4.1%) (95% CI 1.1%, 13.7%) described continuous intermittent moderate to severe pain (one upon micturition, the other during menstruation). Neither of these participants had been in pain at baseline measurement or at 6 weeks. The fact that only one of the four had been in pain at 6 weeks questions the pain of the other three was a late result of their surgery, or was unrelated. Therefore only the 2 participants experiencing daily disruptive or distressing pain were asked to complete the TSK, PSEQ, PCS, PDI, and PASS-20.

7.5.2. Psychometric questionnaires and pain scores

Results of 3-month questionnaires, means (standard deviations)

	Not in pain (n=45)	In pain (n=4)	Total (n=49)	Possible range
DASS-21*				
Depression	0.5 (1.1)	4.5 (3.1)	0.9 (1.7)	0-21
Anxiety	0.5 (1.2)	2.8 (2.5)	0.8 (1.6)	0-21
Stress	1 (1.5)	6.8 (1.3)	1.6 (2.4)	0-21
Total	2.1 (3.5)	16.5 (5.4)	3.3 (5.2)	0-63
TSK (n=2)	-	12 (scores: 12, 12)	-	0-52
PSEQ (n=2)	-	48 (scores: 46, 50)		0-60
SF-McGill				
Sensory	-	10.5 (4.7)	-	0-44
Affective	-	2.3 (0.5)	-	0-16
PPI	-	2.5 (1)	-	0-6
Total	-	15.3 (4.6)	-	0-66
VRS	-	2.3 (1.7)	-	0-10
PCS (n=2)				
Rumination	-	6 (scores: 5, 7)	-	0-16
Magnification	-	4 (scores: 4, 4)	-	0-12
Helplessness	-	6 (scores: 4, 8)	-	0-24
Total	-	16 (scores: 15, 17)	-	0-52
PDI (n=2)	-	14.5 (scores: 6, 23)	-	0-70
PASS-20 (n=2)				
Cognitive	-	5 (scores: 5, 5)	-	0-25
Escape	-	4 (scores: 4, 4)	-	0-25
Fearfulness	-	2.5 (scores: 2, 3)	-	0-25
Physiological arousal	-	5 (scores: 7, 3)	-	0-25
Total	-	16.5 (scores: 15, 18)	-	0-100
VRS Scores				
Pain high	-	6.3 (2.2)	-	0-10
Pain low	-	0.5 (0.6)	-	0-10
Usual pain (n=2)	-	4.5 (scores: 4, 5)	-	0-10

*Table 9 Results of 3-month questionnaires. *One participant excluded from analysis, as explained in the text*

DASS-21

For the purposes of reporting the DASS-21 results, all 4 participants experiencing continued pain have been included in Table 7 as 'In Pain'.

One person 'Not in Pain' was in a relapse of major depressive disorder (MDD) relapse at the time of follow-up and scored as follows: D = 12; A = 4; S = 13, with an overall DASS-21 score of 29 (10 times the 'Not in Pain' mean of 2.9). As such, they have been excluded from 3-month DASS-21 score analysis as an outlier. Two-tailed t-tests revealed significantly higher depression scores in the 'In Pain at 3 months' (IP3) group than the 'Not in Pain at 3 months' (NP3) group [mean difference 4 (95% CI 2.6, 5.4, $p < 0.001$)]. Likewise for anxiety [mean difference 2.3 (95% CI 0.9, 3.7, $p = 0.002$)]; for stress [mean difference 5.8 (95% CI 4.2, 7.4, $p < 0.001$)]; and the overall DASS-21 score [mean difference 14.4 (95% CI 5.6, 23.2, $p = 0.014$)].

As with the comparisons between the IP and IP6 groups in the section above, t-tests could not be carried out on much of this data, as the groups were not mutually exclusive.

For the depression sub-scale, the NP3 group scored lower than both the NP6 group (mean difference 1.4) and the NP group (mean difference 1.0). The IP3 group scored higher than both the IP6 group (mean difference 1.7) and IP group (mean difference 0.6). The very small (n=4) size of the IP3 group means that a large effect size would be needed to be reliably detected, and the influence of chance on samples this small cannot be understated.

For the anxiety sub-scale, the NP3 group again scored lower than both the NP6 group (mean difference 1.6) and the NP group (mean difference 1.3). The IP3 group scored lower than both the IP6 group (mean difference 0.3) and the IP group (mean difference 1.1).

For the stress sub-scale, the NP3 group again scored lower than both the NP6 group (mean difference 2.6) and the NP group (mean difference 2.6). The IP3 group scored higher than the IP6 (mean difference 0.8) but lower than the IP group (mean difference 0.7).

Overall, the NP3 group scored lower than both the NP6 group (mean difference 5.2) and the NP group (mean difference 4.8). The IP3 group scored higher than the IP6 group (mean difference 4.6), but lower than the IP group (mean difference 1.2).

SF-McGill

While all 4 participants that were deemed to be experiencing distressing or disruptive pain at 3 months were asked to complete the SF-McGill. This remains a very small sample size, and comparisons drawn between the IP3 and IP6 and the IP groups should be interpreted

with caution. On the sensory sub-scale, the IP3 group scored lower than the IP6 group (mean difference 2.8), but higher than the IP group (mean difference 5.0). On the affective sub-scale, the means of the IP3 and the IP6 groups were identical (2.3), both marginally higher than the IP group (mean difference 0.7). On the PPI, the IP3 group scored higher than both the IP6 group (mean difference 1.1) and the IP group (mean difference 0.7). Overall, the IP3 group scored lower than the IP6 group (mean difference 1.6), but higher than the IP group (mean difference 6.4). The VAS/VRS scores (and SD's) were nearly identical [IP 2.1 (SD 2.0), IP6 2.1 (SD 1.9), IP3 2.3 (SD 1.7)].

The VAS/VRS scores asked outside of the SF-McGill were as follows: In terms of 'highest pain', the IP group scored higher than the IP3 group (mean difference 1.0), who, in turn, scored higher than the IP6 group (mean difference 0.9). In terms of 'lowest pain', the IP6 group scored higher than the IP group (mean difference 0.5), who, in turn, scored higher than the IP3 group (mean difference 1.6). In terms of the 'usual pain', only 2 IP3 participants answered (as the other 2 had intermittent pain, giving a 'usual pain' of 0). Their scores were 4 and 5, respectively on the VRS, both marginally higher than the IP mean of 3.5 and the IP6 mean of 3.9.

Other questionnaires

Only 2 participants answered the TSK, PSEQ, PCS, PDI, and PASS-20 at the 3 month observation. Informal comparisons to the IP and IP6 groups can be cautiously explored. For the TSK, both IP3 participants scored 12, similar to the mean of 13.8 scored by the IP6 group. Both scored higher (46, 50) on the PSEQ than the IP6 group mean of 36.4. Yet the 95% confidence interval of 23.2, 49.6 for the IP6 group suggest it is possible that both IP3 group scores fit within a similar range as the IP6 scores. On the PDI, the IP3 scores of 6 and 23 are difficult to interpret, as so dissimilar. Both are lower than the IP group mean of 26.7; they fall either side of the IP6 group mean of 14.1.

For the PCS, IP3 scores could be compared with both the IP, and IP6 groups. On the rumination sub-scale, the IP3 scores (5, 7) were comparable to the IP mean (7.2) and the IP6 (5.6) mean. On the magnification subscale, the IP3 scores (4, 4) were comparable to the IP mean (3.5), but were above the upper limit of the 95% confidence interval for the IP6 group [mean 1.6 (95% CI 0.3, 2.9)]. This might represent a true difference, or simply be the result

of small sample sizes. On the helplessness subscale, the IP3 scores (4, 8) were comparable to, or slightly lower than the IP mean (8.5), but once more were slightly higher than the IP6 mean of 4.8. Overall for the PCS, the IP3 scores (15, 17) were slightly lower than the IP mean of 19.2, but slightly higher than the IP6 mean of 12.0.

Similar to the PCS, the PASS-20 scores could be compared across all three observation points. The IP3 pair appeared to score lower on every subscale (and overall). On the cognitive subscale, the IP3 scores of 5 and 5 were both lower than the IP mean of 13.0 and IP6 mean of 10.6. Similarly, on the escape subscale, the IP3 scores (4, 4) were lower than the IP mean of 11.0 and the IP6 mean of 8.6. On the fearfulness subscale, the IP3 scores of 2 and 3 were both lower than the IP mean of 5.0 and the IP6 mean of 4.9. On the physiological arousal sub-scale, the IP3 scores (7, 3) were again lower than the IP mean of 8.2, although the score of 7 was similar to the mean of 6.8 for the IP6 group. Overall, the IP3 scores of 15 and 18 were both roughly half of the IP mean of 37.2, and of the IP6 mean of 30.9.

7.6 Predictive value of secondary measures on prolonged post-surgical pain

Given the small number of participants experiencing pain at 6 weeks (n=8) and at 3 months (n=4), it was decided to include all of these n=11 (one was in pain at both points) into a 'prolonged pain' group. Seven (63.6%) (95% CI 35.4%, 84.8%) of these participants had been in pain at baseline, compared to 28 (51.9%) of the cohort at baseline.

7.6.1 Predictive value of baseline demographic data

In terms of ethnicity, 9 of the 'prolonged pain' group identified themselves as New Zealand European, and 2 identified themselves as 'Other' (Latino American, and British). None of those who experienced 'prolonged pain' self-identified as NZ Māori at baseline, although 5 (8.9%) of the baseline ethnicities stated they were NZ Māori, and 11 (20.4%) of the 54 total participants were deemed to be in 'prolonged pain' (20.4% of 5 being roughly one participant).

The mean age of those who experienced 'prolonged pain' was 43.8 (SD 11.5). When their ages are removed from the rest of the cohort (so that n=43), the cohort mean age is 41.7 (SD 13.5) that is not significantly different (p = 0.610, two-tailed independent t-test). Seven

(63.6%) of those experiencing 'prolonged pain' had a self-reported history of chronic pain, compared with 20 (43.5%) of the rest of the cohort that was not a significant difference (p = 0.313). Three (27.3%) of those experiencing 'prolonged pain' had a self-reported history of mental illness as compared to 10 (21.7%) of the rest of the cohort that again was a non-significant difference (p = 0.779). Of the prolonged pain group, 9 (81.8%) reported previous surgery, not significantly different from the 28 (65.1%) of the rest of the cohort (p = 0.289). Those experiencing 'prolonged pain' were not significantly: more or less likely to consume alcohol weekly (9 versus 26, p = 0.187); to have ever smoked (6 versus 16, p = 0.298); presently employed (8 versus 36, p = 0.401); have completed post-secondary education (5 versus 29, p = 0.177).

7.6.2 Predictive value of baseline psychometric questionnaires

The means for the baseline cohort (n=43) in the DASS-21 were as follows: depression 2.6 (SD 3.5); anxiety 2.5 (SD 3.4); stress 5.5 (SD 5.0); and total 10.3 (SD 10.8). Despite the 'prolonged pain' group scoring higher on all three subscales (and overall) at baseline, there was no significant difference as measured by two-tailed independent t-tests on the depression subscale 3.7 (SD 3.3) [mean difference 1.1 (95% CI -1.3, 3.5 p = 0.344)], the anxiety subscale 4.2 (SD 3.0) [mean difference 1.7 (95% CI -0.5, 3.9 p = 0.121)], the stress subscale 6.2 (SD 3.8) [mean difference 0.7 (95% CI -2.2, 3.6 p = 0.617)], or the total DASS-21 score 14.0 (9.1) [mean difference 3.7 (95% CI -3.0, 10.4 p = 0.263)].

Ten of the 11 participants in 'prolonged pain' answered the BIPQ. Their mean score was 43.3 (SD 9.8), compared with the mean score of the rest of the baseline cohort (n=43) of 35.9 (SD 9.3). This result was significant at 95% confidence [mean difference 7.4 (95% CI 0.01, 14.8, p = 0.049)], indicating a more threatening view of illness at baseline in those who would later go on to develop 'prolonged pain'. All but one of the 4 participants that experienced 'prolonged pain' who had not been in pain at baseline had scores higher than the mean of 32.4 (SD 9.6) for the rest of the 'Not in Pain at baseline' group (n=22) (21, 37, 43, 54). Similarly, all but 1 of the 6 participants (one participant did not answer the questionnaire) in 'prolonged pain' who had experienced pain at baseline had scores higher than the mean of 39.7 (SD 7.6) for the rest of the 'In Pain at baseline' group (n=21) (38, 42, 46, 48, 50, 54) (p = 0.041, two-tailed t-test).

Only 6 of the 7 participants in prolonged pain in pain at baseline completed the SF-McGill at baseline, with means of 3.7 (SD 2.1) and 0.8 (SD 1.3) for the sensory and affective subscales, respectively. By comparison, the means for the rest of the IP cohort were 6.0 (SD 5.8) and 1.9 (SD 2.5), respectively. The difference in sensory scores was not significant [mean difference 2.3 (95% CI -0.8, 5.3, p = 0.136)], neither was the difference in affective scores significant [mean difference 1.1 (95% CI -0.4, 2.6 p = 0.149)].

Baseline comparisons for other questionnaires: means (standard deviations)

	IP baseline, not prolonged (n=21)	**Prolonged pain (n=7)**	**Mean difference (95% CI, p)**	**Possible range**
PCS	(n=20)	(n=5)		
Rumination	7.0 (4.8)	8.4 (2.3)	1.4 (-1.8, 4.6 p = 0.362)	0-16
Magnification	3.5 (2.9)	3.6 (1.4)	0.1 (-1.8, 2.0 p = 0.913)	0-12
Helplessness	8.6 (4.9)	8.2 (1.3)	0.4 (-2.2, 3.0 p = 0.750)	0-24
Total	19.1 (11.2)	20.2 (3.6)	1.1 (-5.1, 7.3 p = 0.716)	0-52
PDI	28.2 (15.6)	20.2 (5.9) (n=5)	8 (-1.0, 17.0 p = 0.080)	0-70
PASS-20		(n=6)		
Cognitive	13.8 (4.8)	10.0 (5.6)	3.8 (-2.1, 9.7 p = 0.175)	0-25
Escape	12.1 (6.0)	7.3 (4.0)	4.8 (-9.4, -0.2 p = 0.041)	0-25
Fearfulness	5.7 (4.8)	3.2 (1.4)	2.5 (-5.0,-0.04 p = 0.046)	0-25
Physiological arousal	9.0 (5.1)	5.3 (4.5)	3.7 (-1.2, 8.6 p = 0.119)	0-25
Total	40.5 (16.5)	25.8 (13.6)	14.7 (-0.04, 9.4 p = 0.051)	0-100

Table 10 Comparisons of baseline scores between the prolonged pain group and the remainder of the IP group

Table 10 shows comparisons between the baseline questionnaire scores of those in prolonged pain who experienced pain at baseline and those for the remainder of the IP group. Mean differences, and the 95% confidence intervals and p-values around these were calculated using two-tailed independent t-tests. Where any participant had not completed a questionnaire, the resulting group size is recorded in the table as (n=X).

None of the differences between the two groups were significant at 95% confidence on the PCS or the PDI. However, on the PASS-20 all scores were lower for the 'prolonged pain' group, reaching significance on the escape (p = 0.041) and fearfulness (p = 0.046) subscales. The difference in total PASS-20 scores nearly reached significance (p = 0.051, upper arm of the 95% confidence interval around the mean difference 0.04).

In terms of VAS pain scores at baseline, there were no significant differences between those who went on to develop 'prolonged pain', and those who did not. Where any participant(s) from either group did not give a certain score, this is reflected by the (n=X). Lowest pain scores for those who developed 'prolonged pain' (n=7) were 2.0 (SD 1.0) versus 2.1 (SD 1.9) for those who did not (n=19) [mean difference -0.1 (95% CI -1.3, 1.1 p = 0.864)]. Highest pain scores for those who developed 'prolonged pain' (n=7) were 7.6 (SD 1.0) versus 6.8 (SD 2.6) for those who did not develop 'prolonged pain' (n=20) [mean difference 0.8 (95% CI -0.6, 2.2 p = 0.260)]. The usual pain scores for those who developed 'prolonged pain' (n=6) were 4 (SD 1.1) versus 3.3 (SD 2.2) for those who did not develop 'prolonged pain' (n=19) [(mean difference 0.7 (95% CI -0.7, 2.1 p = 0.314)]. Two-tailed independent t-tests were used for these analyses.

7.6.3 Predictive value of the cold pressor test

The cold pressor test results between the prolonged pain group and the rest of the cohort were as follows: Tolerance: the rest of the cohort's (n=43) mean of 123.6 (SD 78.4) was higher than the 'prolonged pain' group's (n=11) mean of 86.5 (SD 85.0), but not significantly so [mean difference 37.1 sec (95% CI -23.3, 97.4) (p = 0.209)]. Threshold: the rest of the cohort's mean 61.4 (SD 56.3) was higher than the 'prolonged pain' group's mean of 24 (SD 17.7), this time significantly so [mean difference 37.4 sec (95% CI 17.1, 57.7) (p < 0.001)]. Endurance: the rest of the cohort's mean of 85.4 (SD 93.6) was higher, but not significantly, than the 'prolonged pain' group's mean of 70.9 (SD 90.4) [mean difference 14.5 sec (95% CI -50.7, 79.8 (p = 0.64)].

7.6.4 Predictive value of peri-operative data

Much of the surgical information could not be located for various individuals. Totals for each group are given as (n=X) where appropriate.

Three (27.3%) of the 11 participants experiencing ‘prolonged pain’ had a self-reported history of mental illness, as compared to 10 (22.7%) of the rest of the cohort (n=44). This result is not significant (p = 0.750). Seven (63.6%) of those in ‘prolonged pain’ reported previous experience(s) of chronic pain, as compared to 20 (45.5%) of those for the rest of the cohort who did not that is not significant (p = 0.280). Ten (90.9%) of those in ‘prolonged pain ‘reported previous surgery, as compared to 27 (61.4%) of those for the rest of the cohort. This result was did not reach significance, but was the closest of the three in its reach (p = 0.061).

Those who experienced ‘prolonged pain’ were so spread out across the surgical groups that formal statistical analysis essentially became impossible. Information on surgical group could only be found for 10 of the 11 participants. The surgical groups were as follows: hysterectomy (1); hysterectomy and salpingectomy and/or oophorectomy (3); salpingectomy and/or oophorectomy (1); excision of endometriosis (4); pelvic floor repair (1); and other surgery (1). Four participants in the ‘prolonged pain’ group, and 7 participants in the rest of the cohort underwent excision of endometriosis, a difference that was almost significant (p = 0.087). This difference is likely confounded by the fact that the 3 who underwent hysterectomy and excision of endometriosis simultaneously were classed as hysterectomies, and that none of these 3 experienced ‘prolonged pain’. If, for the sake of argument, they are included as ‘excision of endometriosis’, the difference is 4/10 versus 10/44, p = 0.258.

It was found that 63.6% of those who experienced ‘prolonged pain’ (n=11) underwent laparoscopic surgery, as did 29 (65.9%) of those who did not (p = 0.803). Three (27.3%) in the ‘prolonged pain’ group and 4 (9.1%) in the remainder of the cohort underwent laparotomy (p = 0.075). Two (18.2%) in the ‘prolonged pain’ group, and 9 (20.5%) in the rest of the cohort underwent per-vaginal surgery (p = 0.976).

The mean duration of surgery in the ‘prolonged pain’ group (n=10) was 88.5 minutes (SD 48.3), and 86.6 minutes (SD 33.1) in the rest of the cohort (n=32) that was not significant difference [mean difference 1.9 (95% CI -33.7, 37.5, p = 0.909)]. Eight (80%) of those in ‘prolonged pain’ for whom location of surgery could be discovered, had their surgery performed at CWH. This is not significantly different to the 25 (67.6%) in the rest of the

cohort (n=37) (p = 0.373). The remaining 2 (20%) of those in 'prolonged pain' and 11 (29.7%) in the rest of the cohort had their surgeries performed at SCH.

Analgesic use between the prolonged pain group and the rest of the cohort

	Rest of cohort (n=43)	**Prolonged pain (n=11)**	**p-value**
Intra-operative analgesics:	**(n=37)**	**(n=10)**	
Opioid equivalents (1 mg oral morphine)	36 (97.3%) (70.5 mg)	8 (80%) (93.9 mg)	0.047
Clonidine	8 (21.6%)	4 (36.4%)	0.238
Paracetamol	17 (45.9%)	4 (36.4%)	0.728
Parecoxib	26 (70.3%)	7 (63.6)	0.984
Lignocaine	4 (11.8%)	0	0.276
Post-op analgesics:	**(n=37)**	**(n=10)**	
Opioid equivalents	36 (97.3%) (43.7 mg)*	9 (90%) (106.7 mg)*	0.313
Clonidine	4 (11.8%)	1 (9%)	0.944
Paracetamol	34 (91.9%)	9 (%)	0.849
Ibuprofen	12 (32.4%)	6 (60%)	0.112
Diclofenac	9 (24.3%)	0	0.084
Gabapentin	1 (2.7%)	0	0.596
Patient-Controlled Analgesia (opioid eq.)	8 (21.6%) (mean** 177.4mg)	2 (18.2%) (28mg and 416mg)	0.912
Discharge analgesics:			
Codeine	23 (53.5%)	3 (27.3%)	0.121
Tramadol	11 (25.6%)	6 (54.5%)	0.064
Paracetamol	38 (88.4%)	10 (90.9%)	0.810
Ibuprofen	18 (41.9%)	8 (72.7%)	0.067
Diclofenac	16 (37.2%)	1 (9.1%)	0.073

*Table 11 Analgesic use between the prolonged pain group, and the rest of the cohort. *Several missing data points where opioids were given, but doses not noted. **1 patient's PCA records did not contain volumes, so n=7 for this mean*

Intra-operatively, the only statistically significant difference in analgesics between the groups was the number of participants in each group given opioids. It was found that 36 (97.3%) of the 37 'rest of the cohort' participants for whom intra-operative data could be found, received opioids intra-operatively. By comparison, 8 (80%) of the 10 'prolonged pain' participants whose data could be found received opioids (p = 0.047). However, participants

who would go on to develop' prolonged pain' received a mean difference of 23.4 mg more oral morphine equivalents in theatre. Due to the difficulties converting the various opioids into oral morphine equivalents, and the difficult data (some missing, some illegibly hand-written) it would be rash to attempt to draw significant conclusions from the differences in oral morphine equivalents between these groups. Interestingly, those given opioids in the 'prolonged pain' group (n=8) were significantly more likely (p = 0.014) to receive tramadol than those given opioids in the rest of the cohort group (n=36). This significance remained even when those who had not received opioids in theatre were factored in (p = 0.046, two-tailed t-test).

Postoperatively, there were no significant differences in the analgesics received by either group. As stated above, it is difficult to analyse the opioid doses between the groups. If anything, this data was even more poorly recorded. It was often difficult to tell which medications had simply been charted, and which had actually been given. However, the means of 106.7 mg ('prolonged pain' group) versus 43.7 mg ('rest of the cohort' group) appear strikingly different. Another interesting point postoperatively was the use of diclofenac. Although it did not reach levels of significance (p = 0.084), *none* of the people who went on to develop 'prolonged pain' received diclofenac postoperatively, as compared to 9 (24.3%) of those who did.

On discharge, none of the medications prescribed to one group significantly differed from the other group. With that said, the two weak opioids (codeine and tramadol) were prescribed almost inversely to each group. Codeine was prescribed on discharge to 53.5% of the 'rest of cohort' versus 27.3% to the 'prolonged pain' participants (p = 0.121). Tramadol was prescribed to 25.6% of the 'rest of cohort' group versus 54.5% of 'prolonged pain' participants (p = 0.064). The same trend held for the two of the most popular NSAIDs, ibuprofen and diclofenac. Ibuprofen was prescribed to 41.9% of the 'rest of cohort' participants versus 72.7% of the 'prolonged pain' participants (p = 0.067). Diclofenac was prescribed to 37.2% of the 'rest of cohort' participants versus 9.1% of 'prolonged pain' participants (p = 0.073).

Chapter Eight – Discussion and conclusion

The study which had been planned over four months, and gained approval from all necessary parties such as the national Health and Disabilities Ethics Committee (HDEC), the University of Otago, and the relevant departments, was never to recruit a single participant. This study had planned to use orthopaedic patients (namely hip and knee arthroplasties). It included a randomised controlled trial embedded within the cohort study, whereby half of the participants still experiencing significant pain six weeks postoperatively would be given a combination of gabapentin and nortriptyline. Unfortunately, several senior individual clinicians within the Department of Orthopaedics actively resisted the study due to concerns about the medications being trialled, and loss of control over the management of their patients enrolled in the study. While both of the proposed medications are widely regarded to be safe and efficacious, the concerns of these clinicians were respected, and another department had to be chosen.

The specialty then identified to have the second-highest number of potential participants, was Gynaecology. The head of department, and the individual staff, were all more than happy to facilitate the study. The protocol was adapted, and the large chain of paperwork (ethics, locality authorisations… etc.) started up again. Unfortunately, due to the twelve month time constraint, it was not considered plausible to recruit enough participants to conduct a statistically meaningful randomised control trial. The resultant study was essentially a fleshed-out, extended version of the pilot study outlined in Chapter Six of this thesis. It is strongly believed that a randomised controlled trial of these (or similar) medications in the prevention of chronic post-operative pain should be conducted in future.

8.1 Interpretation of results

The sample sizes, for reasons outlined previously, were not as large as originally planned. This limited interpretations of the formal statistical analyses, and can result in many type II errors (failure to correctly reject the null hypothesis). The calculations have been performed as meticulously as possible, and conclusions drawn only on the data obtained. However, the

small cohort (n=54), and resultant smaller individual groups, rendered it difficult to detect small to medium effect sizes, and are subject to bias and sampling error.

8.1.1 Prevalence of subacute and chronic pain

Of the 8 participants who were identified as experiencing clinically significant pain at 6 weeks following their surgery, 6 participants had been classified as 'in pain' at the baseline assessment. Their SF-McGill scores on the sensory scale, but not the affective scale, were significantly different ($p < 0.001$ and $p = 0.41$, respectively) to their baseline scores. These differences in the sensory scale suggest that the pain experienced by these participants was unlikely to have been simply a symptom of their underlying condition, as it was significantly different in nature. As such, it seems reasonable to assume this pain was largely a result of the surgery. However, the student researcher who conducted all interviews at all three points was not sufficiently experienced in gynaecology to make detailed judgements. The limited information gathered by the questionnaires and the nature of the follow up assessments (by telephone) could still limit such judgement.

Of the 4 participants who were identified as experiencing clinically significant pain at three months following their surgery, only one of these had been identified as in 'subacute' pain at the six week follow up point. However, 2 of the remaining 3 participants had reported sub-threshold pain at that time that was recorded, and 2 of these 4 participants had been in pain at the baseline assessment. On the sensory scale of the SF-McGill, the scores of these 2 participants had changed sufficiently between baseline (4, 6) and 3 months (10, 17) to consider them likely to be an effect of the surgery. As with those in pain at 6 weeks, their affective scores did not appear to differ from baseline to 3 months (0, 3 to 2, 2).

Given the small number in pain at the follow-up points, the decision was made to analyse them (n=11) as one 'prolonged pain' group. Seven participants (63.6%) in this group had been in pain at baseline, 1 (9.1%) was in pain at both 6 weeks and 3 months. It is worth noting that smaller (n < 300), single-centre studies have been shown to find lower CPSP rates [394] that may partially account for the low apparent prevalence.

8.1.2 Factors influencing the risk of developing subacute and chronic postoperative pain

Does the presence of pain pre-operatively predict postoperative pain states?

Over half of the participants, 28 of 54, were deemed to be in clinically significant pain at the baseline preoperative assessment. Participants who were in pain at baseline were slightly more likely than those who were not to experience pain at either follow-up point, but not significantly (6 weeks and/or 3 months) (7 of 11, or 63.6%, p= 0.48). This suggests that those experiencing preoperative pain are *possibly* more likely to develop postoperative pain persisting to the subacute and then chronic phases. At an individual level, however, this would not seem to be a strong predictive factor. As such, the results of this study cannot support the clinical use of this as a predictive factor in the absence of further evidence.

Does the presence of subacute pain predict the development of chronic pain?

Eight of participants were identified as experiencing subacute pain when followed-up six weeks postoperatively. Four of the participants were identified as experiencing chronic pain when followed up six weeks postoperatively. One participant experiencing subacute pain developed chronic pain, while 7 did not. By comparison, 3 participants who were not experiencing pain at 6 weeks developed chronic pain at 3 months, while 45 remained pain-free at 3 months. This is not necessarily the expected result, as it would seem logical that one would have to pass through the subacute stage to reach a chronic pain state. However, as mentioned earlier, 2 of the remaining 3 participants had reported sub-threshold pain at that time that was recorded. It is therefore possible that either sub-threshold pain is more important than previously thought, or the way sub-threshold pain was differentiated from 'above threshold' pain in this study was not entirely accurate. As previously stated, smaller ($n < 300$), single-centre studies have shown lower CPSP rates [(394)], so it is possible, indeed likely, that sample size has impacted on these results. It still seems logical to aggressively treat and follow up, those still experiencing pain 6 weeks postoperatively. Not only will they benefit from the pain management in the short-term, but it may prevent them going on to develop chronic pain. Further research is needed into subacute pain, and its relationship with peri-operative and chronic pain states.

Psychometric questionnaires

As discussed in the literature review, psychological and social factors such as depression, anxiety and gender [12,10] are known to influence (and be influenced by) pain (both acute and chronic). In this study, many psychosocial factors were analysed through the use of the psychometric questionnaires. These are described in Chapter Four, and can be found in Appendix One.

In the 'In Pain' group, baseline depression, anxiety, stress, and total DASS-21 scores were all higher than in the 'Not in Pain' group. This reinforces the association between pain and negative affect, even if no direction of causality can be directly established from this data. The effect of this higher level of psychological distress on perioperative clinical outcomes warrants further investigation. Of interest was the overall drop in the cohort's mean DASS-21 scores. The cohort at 3 months scored lower than it had at 6 weeks (mean difference 4.7) and at baseline (mean difference 7.9). This reflects the true shift in the proportion of the cohort who were in pain, and the resulting effect on affective scores. Also, the 'not in pain' group at 3 months scored lower on every sub-scale than either of the previous 'not in pain' groups. This would indicate the change in the proportion of the cohort who were in pain not to be the sole factor resulting in improved affective scores.

Depressive, anxiety, and stress symptom scores, as measured by the DASS-21, were associated with the pain state at all 3 follow-up points. DASS-21 scores in all subsections were higher in those who progressed into 'prolonged pain' states, but not significantly so. Depressive scores were the closest to reaching significance, but still had $p=0.34$. It is possible that the effect these scores can detect remains too small for the sample size (and therefore too small to use clinically on individual patients), or that another affective questionnaire might have greater predictive value. Taking into account this data and the data in the literature, it seems likely that depressive symptoms are associated with the postoperative development of lasting pain states. The early detection and management of these symptoms could beneficially affect pain outcomes, as well as distress levels. Even in the absence of pain, it seems logical that thorough detection and management of depressive symptoms would improve the quality of life.

It would appear from the BIPQ results that those who go on to develop prolonged pain after surgery have a more threatening view of their illness before their surgery than those who do not. This appears to conflict with the results of the PASS-20. Two of the PASS-20 subscales escape, and fearfulness were even scored significantly lower at baseline by those who developed 'prolonged pain' than those who did not. This would appear to indicate that patients who go on to develop prolonged pain states postoperatively identify their illness as particularly threatening, but are no more (if anything, they are less) emotionally distressed by their illness (and/or pain) than those who do not develop prolonged pain states. This seems to be backed up, although not to significant levels, by the sensory and affective scales of the SF-McGill; those who went on to develop prolonged pain states scored lower in these scales. Those who would develop prolonged pain also scored lower, almost at significant levels in the PDI, suggesting it is possible that these people are less disabled by their pain pre-operatively. PCS scores were so similar between the groups making it difficult to draw any conclusions from the available data.

Wildly extrapolating from the data from the psychological questionnaires could paint the clinical picture of the 'archetypal' person at higher risk of developing prolonged post-surgical pain. This person may be reasonably functional (PDI scores) with a slightly lowered affect (DASS-21 scores), who identifies their illness as particularly threatening to their health (BIPQ scores), but without appearing unduly concerned by it (PASS-20, PCS scores). VAS pain scores at baseline did not differ statistically significantly, nor were the raw means widely separated (the greatest being a mean difference of 0.8 for 'highest pain'). This makes it unlikely to be a clinically useful tool for predicting prolonged pain states. Of course, the sample sizes involved severely limit conclusions drawn from formal statistical analysis. Differences that do not truly exist may appear to, and ones that do exist may be missed.

The only factor that could realistically be interpreted from these data as a potential 'screening'-type tool for the risk of developing prolonged pain is the BIPQ. With a mean difference of 7.4 (95% CI 0.01, 14.8, $p = 0.049$) on a 0-50 scale, if this is a 'true' difference it would imply a mean of 14.9% higher scores in those at risk of developing prolonged pain. While this is not a great enough difference to predict accurately each individual who could develop prolonged pain, it could provide a 'piece of the puzzle' in guiding clinical practice. Future studies in this area should further investigate if the BIPQ has a role in preoperatively

predicting prolonged postoperative pain. More research is needed regarding predictive abilities of each of the other questionnaires. In order to claim that none existed on the basis of this small sample study could potentially throw the baby out with the bathwater.

Any correlation of the characteristics measured by these questionnaires with lasting pain states implies that these symptoms should be detected and managed early. Simple tools such as the questionnaires used in this study could be used to screen preoperative patients, to enable early detection and intervention, not only to influence pain outcomes, but psychosocial and functional outcomes as well. In patients identified as having 'at risk' factors preoperatively, follow up several weeks postoperatively could potentially prove useful in the secondary prevention of chronic pain, by intervening at the subacute (or acute persistent pain) phase. This should be investigated in future studies. This study simply may not have had the statistical power to show the associations between the likes of the SF-McGill or the DASS-21 on pain progression; else unknown biases and/or confounding factors might have influenced the outcomes. It is also possible, although unlikely, that there simply was no association between these questionnaires and the measured outcomes in this population. Perhaps the measures did not fit the methods. In a study of this size, it is likely to be a combination of these factors.

Demographic information

Overall, none of the demographic factors (age, ethnicity, education, work status, smoking status, and alcohol intake) or relevant histories (self-reported chronic pain, mental illness, or surgery) differed significantly between those who progressed into prolonged pain states, and those who did not. Given the relevant literature [12,11,28,2,6] surrounding this issue, it seems likely that this study was simply not sufficiently powered to detect the effects of these.

In terms of ethnicity, there were no significant differences between the groups at baseline, and the cohort appeared to be in line with the 2013 New Zealand Census data for Canterbury. None of those experiencing prolonged pain self-identified as New Zealand Māori. It seems likely this is due to sample size, or under-reporting of pain by the New Zealand Māori participants. At the very least, this suggests that there are likely no increased

rates of inferior prolonged pain outcomes among New Zealand Māori patients undergoing moderate to major gynaecological surgery at CWH (or at SCH under CDHB contract).

The literature suggests that younger [6] and female [28] patients are at increased risk of developing postoperative chronic pain. As this study was conducted on gynaecological patients, all of whom self-identified as 'Female' (from the options 'Male', 'Female', and 'Other'), it is not possible to draw comparisons between the genders from the results of this study alone. In terms of age, the mean age of participants in this study was 42.1 (SD 13.2). Age was not a significant factor in predicting who would develop prolonged pain, so these results can therefore neither support nor reject the hypothesis that age influences the development of chronic pain. However, it is possible that the relationship between age and likelihood of developing prolonged pain may not be linear. As this study was also undertaken using a group of patients who were largely over 30 years of age, it cannot be concluded from these results whether teenagers or younger adults are at increased risk of developing prolonged pain compared to other age groups and developmental periods. There is evidence that components of the brain do not complete development until the age of the mid-20's [395]. As the subjective experience of pain is almost entirely in the brain, it seems plausible that different developmental stages may influence pain experience and behaviour.

Participants who experienced 'prolonged pain' had increased rates of self-reported chronic pain, mental illness, weekly alcohol consumption and former or current smoking. Also, their rates of employment and completed secondary education were lower. However, none of these results were significant. As one could reasonably expect all of these trends [2,28] it appears likely that the small sample size has resulted in type II errors.

Perhaps unsurprisingly, given the long-term pain caused by conditions such as endometriosis, the preoperative cohort had a much higher likelihood of a history of chronic pain (50%) than would be expected in the underlying population (16-20%). Furthermore, a history of chronic pain may indicate a psychological and/or physiological predisposition towards developing prolonged pain states [6]. It seems reasonable to cautiously suggest that those who have previously experienced chronic pain would be more likely to repeat this experience in future, as supported by the trend observed in this study.

The preoperative cohort was less likely to report a history of mental illness than would be expected in the underlying population. This is most likely to be due to the simple wording of the question, when compared to the more detailed questions and broader range of questions asked in the likes of Te Rau Hinengaro [380]. Given the association between pain and certain mental illnesses [396], it seems likely that the non-significant trend of increased rate of mental illness observed in those at higher risk of developing prolonged pain, may be a true one.

The participants in this study were all, necessarily, undergoing surgery. A greater proportion of this cohort than would be expected from the admittedly limited evidence (68.5% vs. 19-43.8%) [381] [382] had undergone surgery in the past. Of particular note is that these sources stated lifetime risk, while the mean age of women in this study was only 41.5 years. This would point to previous gynaecological surgery being a risk for requiring further gynaecological surgery, whether through surgical failure or complications, recurrence of disease, or through chronic post-surgical pain. This study did not observe all relevant factors relating to the risk of requiring gynaecological surgery, so it is possible that there are other factors causing the observed association.

The increased proportion of smokers, and greater pack-year history seen amongst those 'not in pain' at baseline, is likely to be due to the higher mean age of more than a decade. This is more likely than smoking being protective against pain, as evidence [397] clearly suggests an association between chronic pain and smoking. This supports the observed trend of the increased likelihood of smoking in those who would go on to develop prolonged pain. This cohort was significantly more likely to consume alcohol at least once weekly than the average adult female in New Zealand (64.8% vs. 43.2%). For this too, the evidence [397] shows an association between chronic pain and alcohol, supporting the observed trend of increased frequency of alcohol consumption in those who would go on to develop prolonged pain.

This cohort was more likely to have completed secondary school (87.1% vs. 76.2%), and to have completed post-secondary education (58.7% vs. 41%) than the average New Zealand adult. The use of the term 'Labour force participation rate' by the Statistics New Zealand source [391] was ambiguous. However, it would seem that a greater proportion of this cohort

was employed in full- or part-time work than the average New Zealand adult population (81.5% vs. 68.5%). This may be due to the inclusion of younger adults in the Statistics New Zealand findings, while the cohort used was largely comprised of middle-aged and older adults. These comparisons may reflect some of the inequities of health distribution in New Zealand in that the better educated and the employed have greater opportunities to receive tertiary health care. Those who are employed and those with higher educational qualifications are less likely to experience chronic pain [398], lending weight to the trends observed here.

Predictive value of the cold pressor test

The cold pressor test was chosen for the study because of its ease of use, and relatively high reliability in predicting an individual's pain tolerance [399]. At baseline, 'those in pain' scored slightly lower (but not significantly so) than 'those not in pain' on all measures. However, for those who experienced prolonged pain (at 6 weeks and/or 3 months), the lower baseline cold pressor test scores appeared to predict the likelihood of experiencing prolonged pain across all 3 measures. The pain threshold was the only significant measure, with the mean difference for this measure being in excess of 30 seconds (37.4 seconds), a potential difference large enough for clinical use. Pain tolerance and pain endurance were not significantly predictive, and had mean differences of 35.6 and 14.5 seconds, respectively. Analysis of pain tolerance data and pain threshold data (in a few), but in particular pain endurance data was severely limited by the 240 second threshold, resulting in underestimations of unknown size. For threshold and endurance this simply results in a cut-off. However, because endurance is derived from these two scores (tolerance minus threshold), if an individual's threshold is high and their tolerance reaches the test time limit, their derived pain endurance would appear to be very low. It is of note that those who would not go on to develop prolonged pain had higher mean scores in all three areas. If a way can be found to neutralise the effect of the time limit, a preoperative cold pressor test could be a useful clinical tool in predicting prolonged pain experience following surgery. It would need to be combined with other known predictive factors and the patient's clinical picture. It is concluded that the cold pressor test could be a useful clinical tool in the prevention of chronic postoperative pain. By preoperatively identifying those most at risk, this allows their inpatient management and postoperative follow-up to be modified

accordingly. This could result in the secondary prevention of the development of chronic postoperative pain.

Perioperative factors

Intraoperative factors

Several aspects of the surgery itself were examined. Firstly, participants were grouped by surgical groups. These were as follows: excision of endometriosis, hysterectomy, hysterectomy and salpingectomy and/or oophorectomy, salpingectomy and/or oophorectomy, pelvic floor/vaginal wall repair, and other surgeries which were undergone by 8 patients (14.4%). Those in the 'prolonged pain' group were grouped too sparsely for formal statistical analysis, if anything this indicates that they were evenly spread across the groups. Surgical approach was also noted. There were 36 patients (66.7%) that underwent laparoscopic surgeries, 7 patients (13.0%) underwent laparotomies, and 11 patients (20.4%) that underwent per-vaginal surgeries. Laparotomy appeared to be most strongly correlated with adverse pain outcomes, with 27.3% of those in prolonged pain versus 9.1% of those not in prolonged pain, having undergone laparotomy. This difference was only just non-significant on a Chi-squared test (0.075). An argument could be made for the use of a one-tailed test when the existing literature [400] and clinical understanding points towards a higher risk of prolonged pain states following laparotomy. This would make a baseline assumption, and give a statistically significant p-value of 0.038. However, given the sample sizes involved, even a 'significant' result would have to be interpreted with caution, and as such the two-tailed test is likely to be more accurate. With a mean difference of 1.9 minutes ($p = 0.909$) between those who later developed prolonged pain and those who did not, duration of surgery appeared non-predictive of poorer pain outcomes. That is not to say that duration of surgery beyond a certain length of time could not prove to be a useful predictor, although the results of this study do not support this.

All of the surgeries were performed under general anaesthesia. Interestingly, a greater proportion of those who would not no go on to develop prolonged pain received intra-operative opioids ($p = 0.047$). Whether this is simply due to sample size, or whether use of opioids in theatre is protective against prolonged pain cannot be stated from this data. Conversely, those who would go on to develop prolonged pain states appeared to receive

greater doses of opioids intra-operatively; they received a mean of 23.4 mg of oral morphine equivalents more than the rest of the cohort did. Due to difficulties converting doses, and difficulties recovering data, the dosage data is difficult to draw conclusions from. However, it is possible that these increased doses are in fact a risk factor for prolonged pain, rather than the previous conclusion of 'receiving opioids at all' being protective. Further research is required into the relative merits and demerits of intra-operative opioids. Of note, those who would go on to develop prolonged pain were significantly more likely to have received tramadol intra-operatively ($p = 0.014$). This study was not geared towards examining the safety and efficacy of intra-operative tramadol. However in the absence of explanations to the contrary, this is a potentially disquieting result. More detailed study into the long-term effects of intra-operative tramadol should be undertaken to rule it out as a risk factor for prolonged pain states.

Postoperative factors

The Post-Anaesthetic Care Unit (PACU) data was briefly examined. In the clinical records, duration of PACU stay was not stated frequently enough to enable any conclusions to be drawn. Analgesic use was better recorded in PACU. The analgesic use in PACU was combined with analgesic use on the wards to give one set of 'inpatient, postoperative' values. While there were no statistically significant differences between the groups, it was interesting to see that ibuprofen was prescribed more often to those who would go on to develop prolonged pain (60% versus 32.4%), while the opposite was true of diclofenac (0 versus 24.3%). Discharge analgesics were largely limited to weak opioids such as codeine (26 patients) and tramadol (20 patients), paracetamol (48 patients), and NSAIDs such as ibuprofen (26 patients) and diclofenac (17 patients). There were 41 patients that were discharged on opioid medications (codeine and/or tramadol). None of the prescribing on discharge was significantly predictive of progression to prolonged pain states. However, there was a trend of more ibuprofen being prescribed to those who would go on to develop prolonged pain (72.7% versus 41.9%), and an opposite trend for diclofenac (9.1% versus 37.2%). Somewhat in keeping with the more frequent use of intra-operative tramadol in the 'prolonged pain' group, patients were more likely to be prescribed tramadol on discharge, although this result was not significant (54.5% vs. 25.6%). It seems plausible that this could be a true association, as the reverse was the case for codeine prescription on discharge

(27.3% versus 53.5%, p = 0.121), resulting in a similar proportion receiving a weak opioids. There appear to be a trend of prescribing in terms of both NSAIDs and weak opioids on discharge from hospital associated with the development of prolonged pain states. However, these results are not significant. Future work could focus on whether this is a true association with larger samples (and other surgical types) or not. Future work could also concentrate on discovering whether this potential association can be explained by other factors (e.g. a risk factor for prolonged pain could also be an indication for tramadol) or not.

Location of surgery could be identified for 47 of the participants. Thirteen of the surgeries were performed at Southern Cross Hospital, and 34 of the surgeries were performed at Christchurch Women's Hospital. The IP and NP groups were split evenly between the hospitals, with 7 (28%) of 'those in pain' at baseline, and 6 (28.6%) of 'those not in pain' at baseline having their surgery performed at Southern Cross Hospital.

Three participants were noted to have moderate to severe adverse postoperative outcomes: one presented to the Emergency Department 13 days postoperatively with a suspected postoperative infection; one presented to the Emergency Department several days postoperatively with vomiting and intense pain; one suffered an accidental uterine perforation intra-operatively and required an extra night in hospital as a result. The first of these 3 experienced subacute pain at 6 weeks, but was pain-free by 3 months. The second patient had no pain at either follow-up point, and the third patient was lost to follow-up at the 6 week assessment. It would seem likely that complications such as these increase the risk of developing prolonged pain issues.

8.2 Limitations of the study

As has been previously stated, this study faced many challenges from the outset. Time limitations and the wishes of individual senior clinicians meant that the planned randomised controlled trial of nortriptyline and gabapentin in those in pain at six weeks had to be excised from the study protocol. In itself, this meant that several aspects of study planning had to be compromised, and follow-on errors may have adversely affected the accuracy of the results. For example, the specialty with the second highest (the highest having been orthopaedics) number of eligible patients was gynaecology. While the staff in gynaecology were more than accommodating, and the patients willing to help, the surgeries undertaken

there tended to be more minor than those planned to be used (hip and knee arthroplasties) with resultant lower rates of postoperative chronic pain [299] [401]. So the time limitations caused by the several-month delay while the project was redesigned resulted in fewer than the optimal number of participants being recruited. This combined with a patient group with lower rates of prolonged postoperative pain meant that study power was somewhat compromised. As such, it seems likely that a (or several) type II error(s) exists in this study. Chronic pain is usually arbitrarily defined as pain lasting >3 or > 6 months [402], so time constraints forcing the time point at which pain was defined as 'chronic' to be 3 months had little effect. On the other hand, if chronic pain is defined as 'pain persisting beyond the accepted period of healing', three months is well beyond this point.

In terms of study methodology, as with essentially every study ever conducted, flaws occurred for the sake of practicality. As highlighted earlier, the structure of the pre-admission clinic necessitated assistance from the nursing staff for the purposes of recruitment. Of course, their clinical duty to the patient came before the study, and so some potentially eligible participants were 'shielded' by them. From conversations with the staff, it seems these patients were largely the very anxious, and/or those with significant medical comorbidities. This likely skewed the baseline characteristics of participants in favour of those having less psychological and physiological distress. Given the correlation between psychological state and the experience of pain [65], it is likely that any sampling bias related to psychological distress would have impacted the pain scores at baseline, and potentially at the later follow-up points.

Some of questionnaires used were designed and only validated for use in chronic pain patients, so their accuracy in those in acute pain has not yet been validated. However, the associations between the depression and anxiety scores and pain in this study points to the questionnaires having a wider scope than their current use. It was felt that questionnaires developed for pain would be more useful in a pain-based study than some of the more general screening questionnaires. The quality of answers to the questionnaires may have been compromised during the six week and three month follow up calls. This is mere conjecture, but a large number of participants answered 'straight zeros' to the DASS-21 by telephone, despite not doing so at their baseline assessment. It seems plausible that having

to answer sensitive/embarrassing questions to a 21 year-old male may have resulted in some participants answering ‘zero’ to all questions to avoid embarrassment.

The same observer recruited all patients, conducted all baseline assessments, and all patients at both follow-up points. It therefore stands to reason that any subconscious bias/biases that this observer possessed would have been distributed equally to each participant. In one sense, this is a good thing, because if said bias/biases can be identified, then the correction/s can be applied much more easily than for multiple potential biases from multiple observers. On the other hand, if said bias/biases cannot all be identified, which it is likely some have not been, then the results may be systematically skewed in a certain direction. In terms of follow-up, obviously every effort was made to contact all participants. This is evidenced by only three participants being lost to follow-up at the six week stage. At the three month stage, however, it is possible that ‘those in pain’ at six weeks were subconsciously deemed ‘more important’ to the study, and pursued more intensely. The single observer was not clinically experienced in the field of gynaecology. As a result, participants’ reports of pain may have been inaccurately attributed to their surgery, when it is possible that some participants’ pain was unrelated to the operation (such as a recurrence of their original condition). This was mitigated somewhat by comparing the subjective nature of the pain at each time point, using the information gathered by the SF-McGill. If the subjective nature of the pain was significantly different, it seems likely the cause of the pain was different as well.

Loss to follow-up was not a large problem, with only five of fifty four participants (9.3%) dropping out. All five dropouts were unreachable by telephone despite multiple attempts to contact them. Three were lost at the six week stage, with another two being unreachable during the three month assessments. It is of note that four of these participants (and all the three lost at six weeks) had been identified as being ‘in pain’ at the baseline assessment; the remaining one suffered from an unspecified mental illness. This raises suspicion that those lost to follow-up at this point were potentially more likely to develop lasting pain states. Only eight participants (14.8%) were identified as experiencing clinically significant pain at the six week follow-up point. Given the characteristics of those who were lost, it seems that this is an underestimate, and the true number would probably lie between 14.8-20.4%, which is not an insignificant change.

8.3 Generalisability and applicability

The underlying population from which this cohort was recruited was adult women being pre-admitted for gynaecological surgery at Christchurch Women's Hospital. The exclusion criteria were not particularly limiting. The largest limiting factor in terms of the generalisability of the results was likely the 'safety net' put in place by the nurses to protect patients they felt were vulnerable from the study. However, given that recruitment for this study was undertaken over an 11-week period, it stands to reason that roughly one fifth of the patients who met the study's criteria in 2014 were approached. In the absence of any explanation to the contrary, it seems likely that this cohort is representative of women undergoing moderate to major gynaecological surgery through the Christchurch Women's Hospital Pre-Admissions Clinic. The sample size, as has been mentioned, is likely to have affected the results, and the conclusions and generalisability as a result. The participants did not appear to significantly differ from the New Zealand Census data in any aspect, and as such it is likely that these results could be cautiously applied to many of New Zealand's gynaecological services.

8.4 Implications of the results, and recommendations for future research

The results of this study have raised more questions:

- A void in the literature seems to exist surrounding postoperative pain in gynaecological surgeries in New Zealand. For example, the rates of each route of performing a hysterectomy do not appear to have been published, nor has any data been published comparing the pain outcomes of the respective routes.
- Gabapentin has shown promise in prevention of post-hysterectomy chronic pain (302). It is strongly believed that a randomised controlled trial of gabapentin or similar medications in the prevention of chronic post-operative pain should be conducted in future.
- Further research is needed into subacute pain, and its relationship with peri-operative and chronic pain states dissected. At present it seems to be seen simply as an arbitrary half-way point between acute and chronic pain. However the biological and psychological changes that occur around this time have not yet been studied in-depth, and key pieces of this puzzle are still missing.
- Further research is required into the relative merits and demerits of intra-operative administration of opioids. Particularly alarming was the statistically significant pattern of intra-operative tramadol being prescribed to those who would later develop prolonged pain states. It is unclear from our results exactly what role opioids play in the development of these states, be it a protective factor or a risk factor, but it seems clear that an effect is present.

In terms of recommendations for carrying out future studies of this vein, the most prominent to have come out of this study is that:

- The required sample size for studies such as this is larger than typically expected. A greater number of researchers collecting data (the nature of a university thesis restricts this to simply the student investigator) in a multi-centre manner would allow for many more participants to be recruited within a similar time-frame.
- Record-keeping following surgery, particularly anaesthetic and PACU notes, is often not performed to the level required for high-quality research data. Although it would greatly increase the time requirements on individual researchers, the collection of this data in

real-time would be of much greater use. Perhaps recruiting individual anaesthetists and nurses as data collectors could assist with this.

- A follow-up period of 6-12 months would likely be optimal for a study such as this. Within the restraints of the B.Med.Sc (Hons) programme this was not feasible, as increasing the follow-up period to 6 months would have almost halved the already limited sample size.

8.5 Conclusion

At 6 weeks and 3 months postoperatively, 15.7% and 8.2% of participants, respectively were deemed to be experiencing significant pain. The psychometric questionnaires used frequently detected differences between those experiencing pain and those not experiencing pain at given observation points. Only the BIPQ, however, appeared predictive of developing prolonged postoperative pain. The mean difference (7.4 on a 0 to 50) scale is even enough to see it used clinically alongside other predictive measures.

The cold pressor test did not show any significant differences between 'those in pain' at baseline, and those 'not in pain' at baseline. However, pain threshold as measured by this test was shown to predict outcomes of persistent or prolonged pain. Pain tolerance and pain endurance followed the same trend, but were not statistically significant.

No surgical approach or group was significantly more likely to develop a persistent or prolonged pain state than others. However, laparotomy seemed to be associated with poorer pain outcomes. This is supported by the literature. Intraoperatively, those who would later develop persistent or prolonged pain states were less likely to receive opioids, or more likely to receive larger doses when they did. Perhaps worryingly, those who would later develop persistent or prolonged pain states were significantly more likely to receive tramadol intraoperatively. There were no statistically significant trends in postoperative inpatient or discharge prescribing. In terms of prescription of specific NSAIDs and weak opioids, non-significant trends were noted across both inpatient and discharge prescribing.

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Appendix one – Questionnaires

Section 1: Personal Information

Name:

Ethnicity/ethnicities: NZ Māori / NZ European / Other (please specify)

Date of birth:

Gender: M / F/ Other

Have you ever suffered from any of the following? (Please circle, and give details):

Pain persisting for three months or longer

Mental illness

Other major medical condition

Any condition requiring surgery

Are you a : Non-smoker

: Former smoker*

: Current smoker**

*** For how many years did you smoke?**
How many packs per day (on average) did you consume?

**** For how many years have you smoked?**
How many packs per day (on average) do you consume?

How many standard drinks of alcohol would you consume on an average week?

Do you use any recreational drugs?

Section 2: Pain Information

(a) How severe is your pain?

If zero (0) means 'no pain', and ten (10) means 'the worst pain you can imagine', what have been your levels of pain over the past week?

	No pain										Worst pain you can imagine
Lowest pain	0	1	2	3	4	5	6	7	8	9	10
Highest pain	0	1	2	3	4	5	6	7	8	9	10
Usual pain	0	1	2	3	4	5	6	7	8	9	10

Section 3: Healthcare and medications

(a) How many times *in the past 3 months* have you seen any of the following for your pain?

	Number of Times
General Practitioner / family doctor	
Medical specialists (e.g. Orthopaedic surgeon, Neurologist, Rheumatologist)	
Health professionals other than doctors (e.g. Nurse, Physiotherapist, Occupational Therapist, Psychologist)	

Alternative/Complementary health professionals (e.g. Homeopath, Massage Therapist, Acupuncturist)	
A hospital emergency department	
Admitted in hospital for more than one night because of your pain	

Section 4: Work and education status

(a) What is your current work status?
Please tick (☑) one box below to show your current work status:
(Work includes paid work, unpaid work, study and caring for others.)

☐ 1 I am working in paid or unpaid work, or studying
☐ 2 I am actively involved in the process of returning to paid or unpaid work
☐ 3 I plan to return to paid or unpaid work, but not right now
☐ 4 I am not planning on returning to paid or unpaid work

(b) On the line below, please indicate how ***important*** working is to you

Not at all important — Extremely important

0 1 2 3 4 5 6 7 8 9 10

(c) On the line below, please indicate how ***confident*** you are about your ability to work

Not at all confident — Extremely confident

0 1 2 3 4 5 6 7 8 9 10

If you are working, please answer the following questions:

How many hours do you work each week?
_____ **hours paid work (d)**
_____ **hours voluntary work (e)**
_____ **hours education (f)**

(g) Has this changed because of your pain? Yes ☐ No ☐

How many hours would you like to work each week?
_____ **hours paid work (d)**
_____ **hours voluntary work (e)**
_____ **hours education (f)**

(k) Are you currently receiving...

(Please tick the box the applies to you)

1☐ WINZ benefit
2☐ ACC Weekly Compensation
3☐ Superannuation
4☐ No financial assistance
5☐ Other

(l) What is your highest level of education?

(Please tick the box the applies to you)

1☐ Secondary school
2☐ Certificate
3☐ Diploma
4☐ Trade
5☐ University
6☐ Other

Short form McGill Pain Questionnaire (Ronald Melzack © 1984)

Please indicate with a tick [√] the boxes that describe how your pain feels now:

	NONE	MILD	MODERATE	SEVERE
THROBBING				
SHOOTING				
STABBING				
SHARP				
CRAMPING				
GNAWING				
HOT-BURNING				
ACHING				
HEAVY				
TENDER				
SPLITTING				
TIRING-EXHAUSTING				

SICKENING

FEARFUL

PUNISHING-
CRUEL

Please mark on the line below where you would rate your pain now

NO I----------I WORST

PAIN PAIN POSSIBLE

Please indicate with a tick [√] in the box that describes how strong your pain

intensity feels

NO PAIN MILD DISCOMFORTING DISTRESSING HORRIBLE EXCRUCIATING

Section 5: Questionnaires

DASS-21

Please read each statement and **circle a number 0, 1, 2 or 3** which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

	0 – Did not apply to me at all 1 - Applied to me to some degree, or some of the time 2 - Applied to me a considerable degree, or a good part of time 3 - Applied to me very much, or most of the time	Did not apply to me at all	Applied to me to some degree, or some of the time	Applied to me a considerable degree, or a good part of time	Applied to me very much, or most of the time
1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it hard to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg sense of heart rate increase, heart missing a beat)	0	1	2	3

20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3

PASS-20

Circle any number from 0 = "never" to 5 = "always" for each item.	Never					Always
1. During painful episodes it is difficult for me to think of anything besides the pain	0	1	2	3	4	5
2. I will stop any activity as soon as I sense pain coming on	0	1	2	3	4	5
3. I worry when I am in pain	0	1	2	3	4	5
4 Pain makes me nauseous.	0	1	2	3	4	5
5. I avoid important activities when I hurt	0	1	2	3	4	5
6. I can't think straight when in pain	0	1	2	3	4	5
7. Pain seems to cause my heart to pound or race	0	1	2	3	4	5
8. When I feel pain I think that I might be seriously ill	0	1	2	3	4	5
9. As soon as pain comes on, I take medication to reduce it	0	1	2	3	4	5
10 When I feel pain, I am afraid that something terrible will happen	0	1	2	3	4	5
11 I think that if my pain gets too severe, it will never decrease.	0	1	2	3	4	5
12 I find it difficult to calm my body down after periods of pain	0	1	2	3	4	5
13 When I hurt, I think about the pain constantly	0	1	2	3	4	5
14 When pain comes on strong, I think that I might become paralysed or more	0	1	2	3	4	5
15 Pain sensations are terrifying	0	1	2	3	4	5
16 I find it hard to concentrate when I hurt	0	1	2	3	4	5
17 I go immediately to bed when I feel severe pain.	0	1	2	3	4	5
18 I try to avoid activities that cause pain	0	1	2	3	4	5
19 I begin trembling when engaged in an activity that increases pain	0	1	2	3	4	5
20 When I sense pain, I feel dizzy or faint	0	1	2	3	4	5
Circle any number from 0 = "never" to 5 = "always" for each item.	Never Always					

PSEQ

Please note how confident you are that you can do the following things at present (**despite the pain**).

Remember, this questionnaire is not asking whether or not you have been doing these things, but rather how *confident* you are that you *can* do them at present *despite your pain*.

To answer**, please circle one of the numbers** on the scale beside each sentence, where 0 = not at all confident and 6 = completely confident.

	Circle any number from 0 = "Not at all confident" to 6 = "Completely confident" for each item.	Not at all confident						Completely confident
1	I can enjoy things, despite the pain.	0	1	2	3	4	5	6
2	I can do most of the household chores (e.g. tidying-up, washing dishes, etc) despite the pain.	0	1	2	3	4	5	6
3	I can socialise with my friends or family members as often as I used to do, despite the pain.	0	1	2	3	4	5	6
4	I can cope with my pain in most situations.	0	1	2	3	4	5	6
5	I can do some form of work, despite the pain. ('Work' includes housework, paid and unpaid work).	0	1	2	3	4	5	6
6	I can still do many of the things I enjoy doing, such as hobbies or leisure activity, despite the pain.	0	1	2	3	4	5	6
7	I can cope with my pain without medication.	0	1	2	3	4	5	6
8	I can still accomplish most of my goals in life, despite the pain.	0	1	2	3	4	5	6
9	I can live a normal lifestyle, despite the pain.	0	1	2	3	4	5	6
10	I can gradually become more active, despite the pain.	0	1	2	3	4	5	6

PDI

We would like to know how much your pain is preventing you from doing what you would normally do, or from doing it as well as you normally would. Please think of the *overall impact* of your pain in your life, not just when the pain is at its worst. A score of (0%) means no disability at all, and a score of (100%) signifies that **all of the activities** in which you would normally be involved have been **totally disrupted or prevented by your pain**. For each of the 7 categories of activity listed, **please circle the number** on the scale which describes your typical level of disability.

1. Family/home responsibilities

This category refers to activities related to the home or family. It includes chores or duties performed around the house (e.g. gardening) and errands or favours for other family members (e.g. driving the children to school).

0%	10	20	30	40	50%	60	70	80	90	100%
no disability			mild		moderate			severe		total disability

2. Recreation

This category includes hobbies, sports, and other similar leisure time activities.

0%	10	20	30	40	50%	60	70	80	90	100%
no disability			mild		moderate			severe		total disability

3. Social Activity

This category refers to activities which involve participation with friends and acquaintances other than family members. It includes parties, theatre, concerts, dining out, and other social functions.

0%	10	20	30	40	50%	60	70	80	90	100%
no disability			mild		moderate			severe		total disability

4. Occupation

This category refers to activities that are a part of or directly related to one's job. This includes non-paying jobs as well, such as household duties or volunteer work.

0%	10	20	30	40	50%	60	70	80	90	100%
no disability			mild		moderate			severe		total disability

5. Sexual Behaviour

This category refers to the frequency and quality of one's sex life.

0%	10	20	30	40	50%	60	70	80	90	100%
no disability			mild		moderate			severe		total disability

6. Self-care

This category includes activities which involve personal maintenance and independent daily living (e.g. taking a shower, driving, getting dressed etc.)

0%	10	20	30	40	50%	60	70	80	90	100%
no disability			mild		moderate			severe		total disability

7. Life-support activity

This category refers to basic life-supporting behaviours such as eating, sleeping, and breathing.

0%	10	20	30	40	50%	60	70	80	90	100%
no disability			mild		moderate			severe		total disability

PTSS

The following questions are designed to measure how satisfied you are with different aspects of your pain treatment. Please circle the number that best describes the degree of satisfaction you have with the pain treatment you have received.

1	How satisfied were you with the overall pain management you received whilst in hospital?	Not satisfied 0 1 2 3 4 5 6 7 8 9 10 Completely satisfied
2	How satisfied were you with staff warmth, respect, kindness and willingness to listen?	0 1 2 3 4 5 6 7 8 9 10
3	How satisfied were you with the competence of the staff?	0 1 2 3 4 5 6 7 8 9 10
4	How satisfied were you with the ease of getting to appointments, hours of treatment, etc?	0 1 2 3 4 5 6 7 8 9 10
5	Was the treatment you received in line with what you expected at the beginning of treatment?	Yes No
6	How useful have you found any written resources you've been given?	Not useful 0 1 2 3 4 5 N/A 6 7 8 9 10 Extremely useful
7	Would you recommend this treatment to someone you know who has a similar problem?	Yes No

BIPQ

For the following questions, please circle the number that best corresponds to your views:

How much does your illness affect your life?

0 1 2 3 4 5 6 7 8 9 10

no affect at all severely affects my life

How long do you think your illness will continue?

0 1 2 3 4 5 6 7 8 9 10

a very short time forever

How much control do you feel you have over your illness?

0 1 2 3 4 5 6 7 8 9 10

absolutely no control extreme amount of control

How much do you think your treatment can help your illness?

0 1 2 3 4 5 6 7 8 9 10

not at all extremely helpful

How much do you experience symptoms from your illness?

0 1 2 3 4 5 6 7 8 9 10

no symptoms at all many severe symptoms

How concerned are you about your illness?

0 1 2 3 4 5 6 7 8 9 10

not at all concerned extremely concerned

How well do you feel you understand your illness?

0 1 2 3 4 5 6 7 8 9 10

don't understand at all understand very clearly

How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)

0 1 2 3 4 5 6 7 8 9 10
not at all affected emotionally extremely affected emotionally

Please list in rank-order the three most important factors that you believe caused your illness.

The most important causes for me:-

1. _____

2. _____

3. _____

TSK

For the following questions, please circle the number that best corresponds to your views:

People aren't taking my medical condition seriously enough

0	1	2	3	4
Strongly disagree				Strongly agree

My body is telling me I have something dangerously wrong

0	1	2	3	4
Strongly disagree				Strongly agree

My illness has put my body at risk for the rest of my life

0	1	2	3	4
Strongly disagree				Strongly agree

I am afraid I might injure myself accidentally

0	1	2	3	4
Strongly disagree				Strongly agree

If I were to try to overcome it, my pain would increase

0	1	2	3	4
Strongly disagree				Strongly agree

Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening

0	1	2	3	4
Strongly disagree				Strongly agree

I wouldn't have this much pain if there weren't something potentially dangerous going on in my body

0 1 2 3 4

Strongly disagree Strongly agree

Pain always means I have injured my body

0 1 2 3 4

Strongly disagree Strongly agree

Pain lets me know when to stop exercising so that I don't injure myself

0 1 2 3 4

Strongly disagree Strongly agree

It's not really safe for a person with a condition like mine to be physically active

0 1 2 3 4

Strongly disagree Strongly agree

I'm afraid that I might injure myself if I exercise

0 1 2 3 4

Strongly disagree Strongly agree

I can't do all the things normal people do because it's too easy for me to get injured

0 1 2 3 4

Strongly disagree Strongly agree

No-one should have to exercise when he/she is in pain

0 1 2 3 4

Strongly disagree Strongly agree

Appendix two – Participant information sheet and consent form

Participant Information Sheet

Study title:	The transition from acute to chronic post-surgical pain – a prospective cohort study	
Principal investigator:	**Name** Professor Edward Shipton **Department** Anaesthesia **Position** Head of Department	Contact phone number: (03) 3641642

Introduction

Thank you for showing an interest in this project. Please read this information sheet carefully. Take time to consider and, if you wish, talk with relatives or friends, before deciding whether or not to participate.

If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you and we thank you for considering our request.

What is the aim of this research project?

This project is a study of patients before and after surgery to determine those with risk of developing, and to develop strategies to help managing and preventing, acute persistent and chronic pain.

Who is funding this project?

This project is receiving funding from the University of Otago, Christchurch

Why have you been asked to be a part of this study?

For this study we hope to recruit women undergoing elective gynaecological surgeries at Christchurch Women's Hospital. Some patients undergoing these types of surgery experience persistent pain after surgery, which can develop into chronic pain. To participate

in this study, you must be sixteen years of age or older, able to give informed consent, and able to understand the English language without an interpreter.

If you participate, what will you be asked to do?

At the pre-admission assessment clinic you will be asked to provide written informed consent to take part in this project. Before your surgery, you will be asked to complete a number of questionnaires which explore your previous and recent health, and the impact on your life of the condition for which you are having an operation. You will also be asked to undertake a 'cold pressor test' to determine your pain tolerance. This test involves placing your hand or forearm in cold water. This will become more and more uncomfortable and when it becomes unbearable you can withdraw your hand and forearm from the water. Completing the questionnaires and the cold pressor test should take no more than 30 minutes.

We will also ask for your consent to access your relevant medical records.

At six weeks after your surgery, and at three months after your surgery, you will be telephoned at a time convenient to you (we will ask for suitable times at your first interview), and the questionnaires will be repeated, in order to assess changes in your functioning, mood, and other factors since your surgery. These telephone interviews should take no longer than 20 minutes.

No aspect of your care will be affected by either refusal or agreement to participate. Participation is 100% voluntary.

Is there any risk of discomfort or harm from participation?

The validated questionnaires will explore you experiences of pain and your emotional and mental states. If the line of questioning develops in such a way that you feel hesitant or uncomfortable you may decline to answer any particular question(s).

The cold pressor test will induce mild to moderate discomfort, ending when you voluntarily remove your hand from the water. In the very unlikely scenario that you have any major adverse reaction to the test, a clinician will be called to ensure your safety.

What specimens, data or information will be collected, and how will they be used?

Information recorded will be your NHI number (for medical records access), your responses to the questionnaires, and the results of your cold pressor test. These results, along with relevant information from your medical records, will be used along with the information from others participating in this study, to give the final results.

You will be asked to indicate whether or not you would like to receive a copy of the results of this study on its completion. If so, this will be sent to you by post.

What about anonymity and confidentiality?

Every attempt will be made to preserve your anonymity. Only the researchers listed on this form will have access to the raw data collected in the course of this study. The data collected will be securely stored for at least 10 years in secure electronic servers, and locked physical cabinets, so that only those mentioned below will be able to gain access to it. Your data will have all factors which could potentially identify you removed before results are compiled, and published.

If you agree to participate, can you withdraw later?

You may withdraw from participation in the project at any time up until your de-identified data has been integrated into the study results, and without any disadvantage to yourself.

Any questions?

If you have any questions now or in the future, please feel free to contact either:

Name Professor Edward Shipton **Position** Head of Department **Department** Anaesthesia	Contact phone number: (03) 3641642
Name Associate Professor Peter Sykes **Position** Head of Department **Department** Obstetrics and Gynaecology	Contact phone number: (03) 3641642
Name Campbell MacLachlan **Position** Medical student **Department** Anaesthesia	Contact phone number: (03) 3641642

This study has been approved by the University of Otago Human Ethics Committee (Health). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (phone +64 3 479 8256 or email gary.witte@otago.ac.nz). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.

The transition from acute to chronic post-surgical pain – a prospective cohort study

Principal Investigator: Professor Edward Shipton (ted.shipton@otago.ac.nz (03) 3641642)

CONSENT FORM FOR PARTICIPANTS

Following signature and return to the research team this form will be stored in a secure place for ten years.

Name of participant:……..

1. I have read the Information Sheet concerning this study and understand the aims of this research project.
2. I have, if I so desired, had sufficient time to talk with other people of my choice about participating in the study.
3. I confirm that I meet the criteria for participation which are explained in the Information Sheet.
4. All my questions about the project have been answered to my satisfaction, and I understand that I am free to request further information at any stage.
5. I know that my participation in the project is entirely voluntary, and that I am free to withdraw from the project at any time without disadvantage.
6. I know that as a participant I will be expected to complete the validated questionnaires and the cold pressor test. I also give consent for the researchers listed on the information sheet to access my medical records as relevant to this study.
7. I appreciate that the cold pressor test that most likely will induce mild to moderate discomfort, ending when I remove my hand.
8. I know that the validated questionnaires will explore my experiences of pain and my emotional and mental states, and that if the line of questioning develops in such a way that I feel hesitant or uncomfortable I may decline to answer any

particular question(s) , and /or may withdraw from the project without disadvantage of any kind.

9. I understand the nature and size of the risks of discomfort or harm which are explained in the Information Sheet.
10. I know that when the project is completed all personal identifying information will be removed from the paper records and electronic files which represent the data from the project, and that these will be placed in secure storage and kept for at least ten years.
11. I understand that the results of the project may be published and be available in the University of Otago Library, but that any personal identifying information will remain confidential between myself and the researchers during the study, and will not appear in any spoken or written report of the study.
12. I know that there is no remuneration offered for this study, and that no commercial use will be made of the data.

Signature of participant:		**Date:**
Signature and name of witness:		Date: