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The Sensory Amplification of Pain: The Adrenaline Model of Headache Causation

**A thesis presented in fulfilment of the requirements for the degree of
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Abstract

Current models of headache causation including vasodilatation and myofascial models are inconsistent with many headache phenomena. In recent decades the pathophysiology of headache disorders has been thought to involve peripheral and central sensitisation but the cause of this sensitisation has been elusive. The significant aim of this thesis was to develop a model to explain headache disorders which has resulted in the development of the Adrenaline Model of Headache Causation, a model which explains the origin of both peripheral and central sensitisation and is consistent with the headache phenomena found in the literature.

This model proposes that activation of the stress pathways of the body, in particular the hypothalamic-pituitary-adrenal (HPA) pathway and sympathetic nervous system (SNS), results in the secretion of several neurotransmitters including histamine, serotonin, noradrenaline and adrenaline in the brain and the secretion of adrenaline and noradrenaline into the blood stream, all of which results in subsequent activation of second messenger cascades, opening of ion channels and lowering of action potential threshold in the pathways of nociception resulting in central and peripheral sensitisation. Furthermore an acute stress response from a headache trigger can create episodes of headache as the same neurotransmitters and hormones produce action potentials in the pathways of nociception in the presence of central and peripheral sensitisation.

The model proposes that a sustained elevation of SNS and HPA activity leads to sensitisation of central nervous system pathways (e.g. noradrenaline, adrenaline, serotonin, histamine) that lower the pain threshold by acting on the thalamus and dorsal horn. Adrenaline and noradrenaline released from the adrenal medulla may also bind to peripheral nociceptors reducing their threshold of firing. Triggers including psychological stress, poor sleep, hypoglycaemia and changes in temperature activate the HPA and SNS pathways increasing the likelihood of action potential generation in the pathways of nociception in people with sensitisation leading to episodes of headache. In people without sensitisation of the neuronal pathways of nociception these stimuli will not usually lead to headache symptoms as the threshold for generation of action potentials in the pathways of nociception is not normally reached. Essentially the

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threshold for transmission of action potentials in the pathways of nociception is set by the tone of the SNS and HPA pathways.

The Adrenaline Model of Headache Causation is consistent with the literature on chronic tension-type headache (CTTH) including headache medication effects, headache triggers, pathophysiological experiments and epidemiological findings. This model gives an insight into treatment strategies aimed at the causation of headache disorders including regular exercise, heat, relaxation therapies and improving sleep.

The Adrenaline Model of Headache Causation predicts that heat may be beneficial for headache disorders. The Wellington Education and Self Treatment (WEST) headache study, a single blind, randomised control trial was performed using heat in the form of sauna for people with CTTH. Thirty seven participants completed the study with 20 in the control group who performed soft tissue massage and 17 in the sauna group who also performed soft tissue massage and attended the sauna for 20 minutes three times a week. A baseline one month daily diary of headache intensity and duration was followed by a two month daily headache diary. Questionnaires were completed measuring depression, sleep disturbance and headache disability before and after the trial. The study showed a statistically significant improvement in the primary outcome of headache intensity of 44% in the intervention group. Seventy nine percent of participants in the sauna group had over 50% reduction of headache index. Heat in the form of sauna is a simple, cheap and self directed treatment that is effective and can be added to the arsenal of treatments available to health practitioners treating headache disorders.

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Chapter 1

INTRODUCTION, AIMS AND CHAPTER SUMMARY

Headache disorders including tension-type headache (TTH) and migraine are syndromes (symptoms with no known cause). The symptom of pain in the head seems to affect every aspect of a person's well being causing disability (Schwartz, Stewart, & Lipton, 1997) and is a major public health problem because it costs billions of dollars in treatment and lost productivity worldwide (Berg & Stovner, 2005; Mannix, 2001; Stovner & Hagen, 2006; Vinding, Zeeberg, Lyngberg, Nielsen, & Jensen, 2007).

The origin of headache disorders has been elusive despite significant research and the underlying mechanism of headache disorder has not progressed significantly in the past 20 years (Olesen, 2006a). People still suffer from headache disorders such as chronic tension-type headache (CTTH) or migraine for several years, if not decades. The exact steps that can be taken to prevent the onset and perpetuation of headache disorders are still not fully understood. A sound model to explain the causation of headache disorders would help to delineate the steps patients can take to prevent the onset and perpetuation of their symptoms.

Great strides have been made in some fields of headache research. These include describing the links between headache and associated phenomena such as sleep disturbance (Andrea, 2006; Jennum & Jensen, 2002), anxiety and depression (Breslau, et al., 2000; Zwart, Dyb, Hagen, & Einarsen, 2003), stress (Nash & Thebarg, 2006) and chronic musculoskeletal pain (Hagen, Einarsen, Zwart, Svebak, & Bovim, 2002; Scher, Stewart, & Lipton, 2006). Improved knowledge of headache triggers (Kelman, 2007; Zivadinov, et al., 2003), and classification of headache disorders (Olesen, 2006b) has also been made in the past few decades.

Numerous clinical trials on finding suitable medication for headache disorders have been performed. Indeed medications such as the triptans marked a triumph in the alleviation of migraine symptoms (Brennum, Kjeldsen, & Olesen, 1992), but no significant advances

have been made in preventative medication. The gold standard for preventative medication is to reduce headache occurrence by half in half of the participants in a clinical trial. This represents failure for half the patients and partial success for the other half. Amitriptyline, the most efficacious preventative medication does not reach this standard in many preventative trials of CTTH (Boline, Kassak, Bronfort, Nelson, & Anderson, 1995; Holroyd, et al., 2001; Pfaffenrath, et al., 1994).

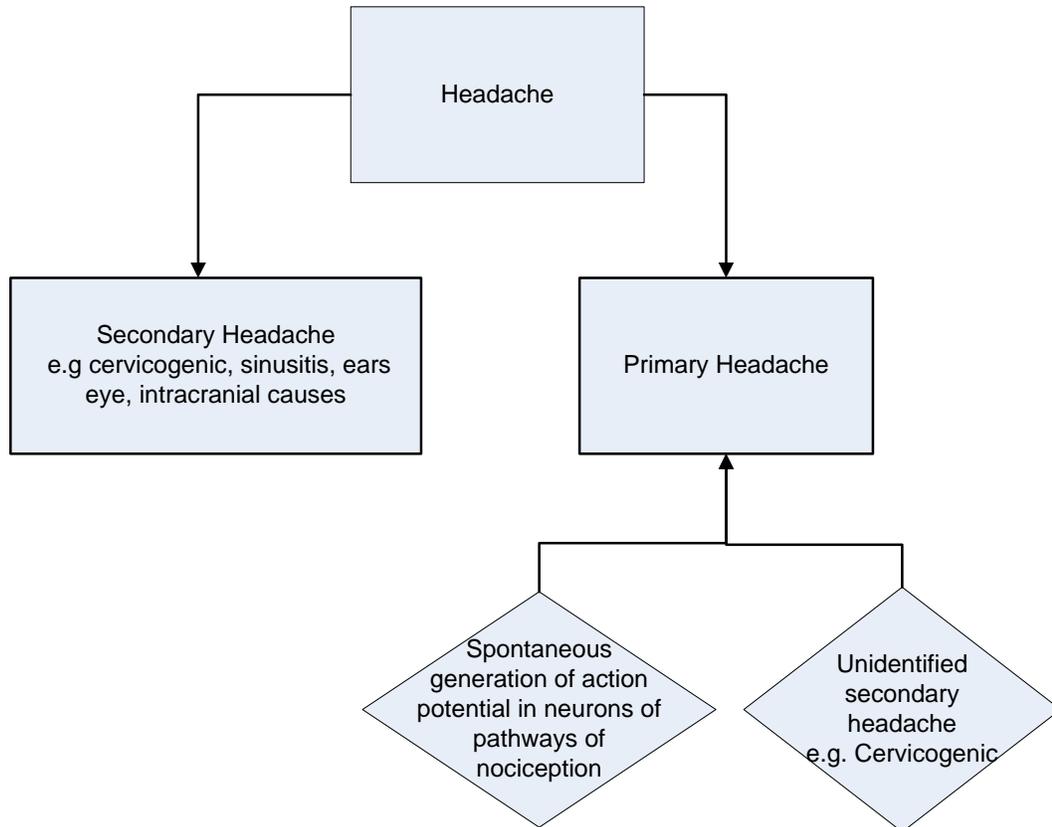
Models of headache causation in the last three decades have concentrated on phenomena found in headache disorder patients such as vasodilatation (M. Ashina, Bendtsen, Jensen, & Olesen, 2000; Christiansen, Iversen, & Olesen, 2000; Holthusen & Arndt, 1995) and muscle tenderness (R. Jensen, Rasmussen, Pedersen, & Olesen, 1993; Langermark & Olesen, 1987), trying to link these phenomena to causation. Central sensitisation of the trigeminocervical nucleus (Dostrovsky & Strausman, 2000; Mosokowitz, 2008) has also been proposed as an important factor in headache causation. The models linking muscle tension and vasodilatation have inconsistencies with the current literature on headache disorders (section 3.8) and the underlying mechanism of central sensitisation still remains unknown (Olesen, 2006a; Thomsen & Olesen, 2000). Furthermore there is no single headache model that explains the many headache phenomena found in the literature.

Several questions remain unanswered. These include;

- What is the pathogenesis of headache disorders from triggers such as emotional stress, alcohol, pain and poor sleep?
- What is the mechanism of action for medications (e.g. β blockers, amitriptyline) used for relieving headache?
- How do some medications (e.g. glyceryl trinitrate, sildenafil, adrenaline) cause headache as a side effect?
- Why do the elderly have a reduction of headache (Thomas, Boardman, & Croft, 2005)?
- Why is the incidence of headache disorders less in tropical countries (Scher, Stewart, & Lipton, 1999)?

Headache is separated into primary headache and secondary headache (Figure 1.1). Primary headache is when no structural cause of headache is found and this PhD relates to primary headache disorders. Headache arising from structures inside the head such as eyes, ears and sinuses is called secondary headache. Referred pain, pain experienced at a site different from the site of tissue damage, from the neck can also be experienced as a headache. Although headaches arising from the neck are an example of secondary headache (cervicogenic) they are not easy to distinguish from primary headache (Antonaci, Ghirmai, Bono, Sandrini, & Nappi, 2001). Figure 1.1 shows a breakdown of primary and secondary headache disorders. Primary headache may be due to spontaneous generation of action potentials in the pathways of nociception (section 4.2), however a proportion of primary headache may in fact be secondary where the structural pathology causing headache has not been identified and is a result of referred pain from the neck.

Figure 1.1: Primary and secondary headache disorder



The pathways of nociception can be divided into peripheral (skin, muscle, bone, joints) and central (dorsal horn and thalamus). Secondary headache pain can be due to the stimulation of nociceptors within the head from pathology such as the jaw joint or infection such as sinusitis. When nociceptors are triggered by stimuli such as heat, cold, pressure and chemicals, electrical impulses are generated and travel from the periphery or from internal organs to the dorsal horn of the spinal cord to the thalamus in the brain and onto the sensory cortex for processing. In primary headache disorders, in the absence of stimuli leading to action potentials at nociceptors, action potentials may be generated by other means in the pathways of nociception.

Nociceptive stimuli activate a wide variety of brain areas including the primary and secondary somatosensory cortices, the anterior cingulate cortex and the insular cortex (Basbaum, Bushnell, & Devor, 2005) which are involved in different aspects of pain perception including spatial, temporal and intensity discrimination, integrating somatosensory information with memory and producing an affective response that includes the autonomic nervous system. The experience of pain itself is a complex perceptual experience which involves the conveying of nociceptive information regarding location, type and intensity of a stimulus combined with emotional and cognitive responses. The experience of pain is the final product of complex information processing in the brain that takes into account emotion, memory and experience (Basbaum, et al., 2005).

1.1 The aims of this PhD

The overall aims of this PhD study were;

1. To examine current headache knowledge and construct a plausible model to explain headache causation that is consistent with the literature on headache disorders.
2. To identify a noninvasive treatment for headaches using the headache causation model developed in this PhD and to investigate its effectiveness by performing a randomised control trial (RCT) using people with CTTH.

3. To promote the headache causation model and noninvasive treatment, if successful, to those involved in the treatment of CTTH including general practitioners and other primary care providers.

My PhD presents the Adrenaline Model for Headache Causation (see chapter 5), a new model that is consistent with the current knowledge on headache disorders. Increased activity of the hypothalamic-pituitary-adrenal (HPA) pathway and SNS by a range of stressors including emotional stress, pain and insomnia can lead to a lowering of the pain threshold due to the stimulation of second messenger cascades in the pathways of nociception by a variety of neurotransmitters and hormones released in the stress response of the body. Second messenger cascades including cyclic adenosine monophosphate (cAMP) have wide ranging physiological effects including opening ion channels that may lower the threshold for nerve transmission leading to sensory amplification of pain, light and sound. The Adrenaline Model of Headache Causation is consistent with the research to date on headache phenomena and predicts why certain preventative medications are effective, why certain medications increase headache risk, why the elderly and people living in the tropics are less plagued by headache and how certain factors can trigger headache. Animal studies examining the effects of the HPA and SNS pathways on hyperalgesia support the Adrenaline Model of Headache Causation.

The new model links several previously available elements of neurophysiology with the medical research on headache disorder. It links the known information on the stress response provided by the SNS and HPA pathway, adrenaline, second messengers and neural sensitisation. Anecdotal evidence from my chronic pain practice and 15 years of experience in dealing with chronic pain patients have helped in the development of the Adrenaline Model of Headache Causation.

In the latter part of this PhD a RCT on subjects with CTTH, The Wellington Education and Self Treatment (WEST) headache trial, was performed to investigate a novel noninvasive treatment predicted by the model. Specifically heat, in the form of sauna, was examined as a treatment strategy. If the treatment is found to be effective in reducing the intensity,

duration and frequency of TTH, then promotion of the Adrenaline Model of Headache Causation and the treatment to therapists who manage CTTH will be carried out by a combination of presentations.

It is my hope that this model stimulates research in different directions based on causation to find cures for individuals who suffer from chronic headache rather than treating headache as a prolonged intermittent lifelong illness. Venturing in new directions with logical reasoning is likely to pave new strategies for this very ancient malady. Headache and migraine has been observed and described through the ages by Hippocrates (c.460-c.370), Galen (AD 131-201), Thomas Willis (1621-1675) to Harold Wolff (1898-1962) among others and almost 500 peer reviewed articles are appearing annually in recent years on this subject. Unfortunately the pathophysiology has been elusive and treatment of these disorders has been based on trial and error, drawing on pharmaceutical interventions from a variety of other disorders (e.g. hypertension, depression, epilepsy).

1.2 Chapter outline for PhD thesis

This thesis is divided into eight chapters as follows:

CHAPTER 1: INTRODUCTION, AIMS AND CHAPTER SUMMARY.

This chapter provides general information on headache disorders and introduces the PhD study and its overall aims.

CHAPTER 2: BACKGROUND - THE STORY BEHIND THIS PHD.

This chapter provides a historical account of the steps that have led to the PhD study with discussion of 15 year's experience and research that has concluded with the development of a new headache causation model outlined in this PhD study (Chapter 5).

CHAPTER 3: LITERATURE REVIEW: CHRONIC TENSION-TYPE HEADACHE.

This chapter sets out to provide background information on headache disorders including prevalence, triggers, comorbid conditions, analysis on RCTs involving people with CTTH,

and examination of current models of headache disorders and experimental induction of headache disorders.

CHAPTER 4: BACKGROUND NEUROPHYSIOLOGY OF THE ADRENALINE MODEL OF HEADACHE CAUSATION.

This chapter sets out to provide a background of the key neurophysiological concepts required to understand the model outlined in Chapter 5, in particular:

- To outline the pathways of nociception
- To give background information on neural sensitisation.
- To outline HPA pathways and SNS of the body and the stress response of the human body

CHAPTER 5: THE ADRENALINE MODEL OF HEADACHE CAUSATION.

This chapter provides a coherent new model of headache causation that fits with the current knowledge on headache disorders. Current headache phenomena that are consistent with this new model are outlined including human and animal studies supporting the model.

CHAPTER 6: THE WELLINGTON EDUCATION AND SELF TREATMENT (WEST) HEADACHE TRIAL: STUDY DESIGN.

This chapter describes the clinical trial design, methods, and data collection and analysis for the WEST headache trial, a RCT investigating sauna for treatment of CTTH.

CHAPTER 7: THE WELLINGTON EDUCATION AND SELF TREATMENT (WEST) HEADACHE TRIAL: RESULTS.

This chapter describes the results of the WEST study including recruitment, attrition and key findings.

CHAPTER 8: THE WEST HEADACHE TRIAL DISCUSSION AND PHD CONCLUSIONS.

This chapter provides a discussion of the WEST headache trial and conclusion to this doctoral study including directions for future research.

Chapter 2

Background - The story behind this PhD

2.1 Introduction

This chapter illustrates the story behind this PhD and spans many years from my early work as a general practitioner to my recent work as a musculoskeletal pain specialist treating chronic pain. This PhD is a result of many years of observation of patients suffering from chronic pain and other medical disorders (Kanji, 2005a, 2005b, 2006a, 2006b, 2008a, 2008b) combined with the medical literature on headache disorders providing background information crucial to forming a new model to explain causation of primary headache. This chapter is written as a narrative because this is the best way to tell this story.

2.2 The journey to this model and PhD

Approximately 17 years ago when I was working in general practice I observed the links between stress and pain. Stress seemed to increase pain intensity and suffering and pain seemed to increase the stress a person suffered, including related disorders of insomnia, anxiety and depression. This relationship was best illustrated by the Repetitive Strain Injury (RSI) epidemic of the 1990s in New Zealand.

The epidemic of repetitive strain injury (RSI) ensured no shortage of patients suffering from chronic pain. Patients presented with the unusual symptom of pain from keyboard use. There was no structural reason found for their pain and the activity of typing itself, lifting fingers against gravity, was innocuous and hardly likely to cause trauma to muscle or tendon. Muscle biopsies in patients were no different to normal people without pain. X-rays and scans including bone scans, CT scans, and MRI scans showed no structural cause for their pain (Quintner, 1991). A population study found that the non-physical stressor of 'dissatisfaction with support from supervisors and colleagues' (Macfarlane, Hunt, & Silman, 2000) is a stronger predictor than the physical stressor of repetitive movement of forearm or wrist in developing RSI.

Patients seen at my clinic for RSI had alleviation of symptoms with local muscle treatments such as acupuncture and even massage therapy but most gains were short term with people returning after a few months with their pain and disability. The one overriding impression from hundreds of patients seen with RSI was that they showed signs of stress. Many of these patients were unable to sleep, developed anxiety and depression. After seeing several patients daily, I was left with a feeling of being defeated and symptoms of tension neck at the end of the working day. As early as 1995 I started reading papers directed at the stress response system of the human body to try and find a link between stress and pain.

In 2002, I completed my specialist training and was vocationally registered in musculoskeletal medicine with the New Zealand Medical Council and began working full time in chronic pain medicine. I recall the uncertainty of going to work as there was no clear path of action to help chronic pain patients, drugs were often unhelpful in eliminating pain and many of these people were in a holding pattern of chronic pain and stress.

I was always interested in injection therapies and many were used in pain medicine such as botulinum toxin (Dodick, et al., 2005; Harden, et al., 2009; Mathew, et al., 2005; Ondo, Vuong, & Derman, 2004) and prolotherapy (injecting combinations of dextrose, glucose, anaesthetic and phenol) (Yelland, Glasziou, Bogduk, Schluter, & McKernon, 2004) with clinical trials often using normal saline as a control. It has been observed in trials that injecting normal saline (placebo control) is as effective as injecting botulinum toxin (Dodick, et al., 2005) or prolotherapy solutions (Yelland, et al., 2004) for chronic pain disorders. The act of injecting myofascial tissues with a solution seems to have efficacy in chronic pain conditions regardless of the solution injected.

Prior to 2004 I was injecting local anaesthetic into myofascial trigger points (a commonly practiced injection technique) to alleviate muscle pain. In 2004, after the prolotherapy study (Yelland, et al., 2004) found saline to be as effective as dextrose solutions for chronic low back pain, I decided to inject normal saline with local anaesthetic into muscle and ligament. I clearly recall the first elderly lady I injected with saline. She presented with muscle pain

at the anterior hip and on injecting these muscles she returned a fortnight later with no symptoms. The injections in the paraspinal muscles in the spine were somehow modifying pain experience. I wrote papers on referred pain (Kanji, 2005a) and the first hypothesis stated that the multifidi (paraspinal spinal muscles close to the spine) were in fact referring pain to the muscles with the same nerve supply (Kanji, 2005b).

Following these papers a case series using saline injections for chronic pain patients was written (Kanji, 2006a). Visual Analogue Scale (VAS) pain scores were recorded out of 10, 0/10 being the lowest pain and 10/10 being the highest pain with both the minimum and maximum pain scores recorded. Maximum daily pain scores in this series reduced from an average of 8.36/10 to 3.29/10, in patients with an average of 6.5 years of chronic pain (Table 2.1). An average reduction in 5 in the VAS score was achieved. A reduction of 2 out of 10 on a 10 point scale correlates with the patient rating of much improved or very much improved (Farrar, Young, LaMoreaux, Werth, & Poole, 2001). The success of treatment was not going unnoticed and newspaper articles were published in the Dominion Post on patients who had been cured of their pain after a decade of suffering from back pain (Hill, 2007) (Appendix 1) and fibromyalgia (Hill, 2008) (Appendix 2). Their sleep, energy, anxiety and depression were also restored. Two further newspaper articles followed in the Citylife Cook Strait News (Appendix 3 and 4), a weekly Wellington newspaper, including a patient that travelled from Geelong, Australia after years of back pain who went home pain free (Stewart, 2008; Wheelan, 2009).

In 2007, I wanted to formulate a scientific rationale for the treatment success and derive a model that explained the success in the treatment of chronic pain disorders. Firstly, I had to explore what the saline and anaesthetic injections were achieving. With further inspection the injections seemed to be in the intercostal space so I went back to the anatomy books to see what sits behind the intercostal spaces. What I found was that the autonomic nervous system had sensory nerves that travelled back to the spinal cord within this space. The autonomic nervous system was broken into the SNS mobilised in emergency situations and the parasympathetic nervous system (PNS) more prominent when resting.

Table 2.1: Results table from the initial case series injecting saline and anaesthetic (10%)
(taken from Kanji 2006a)

| Convergent Referred Muscle Pain | | | | | | | | | |
|--|------------|------------------|-------------------|--------------------|-----------------|-----------------|-----------------|----------|--------------------|
| <i>Table 2 Patients responding to segmental treatment from initial 119 cases</i> | | | | | | | | | |
| | Patient ID | Age | Site | Duration months | Initial consult | | After treatment | | Followup months |
| | | | | | VAS worst | VAS best | VAS worst | VAS best | |
| 1 | 1 | 69 | Left shoulder | 24 | 7 | 3 | 0 | 0 | 12 |
| 2 | 3 | 42 | Lumbar spine | 15 | 7 | 3 | 0 | 0 | 10 |
| 3 | 4 | 36 | Left hip | 7 | 7 | 3 | 0 | 0 | 8 |
| 4 | 5 | 56 | Lumbar spine | 5 | 10 | 5 | 4 | 0 | 5 |
| 5 | 15 | 46 | lumbar spine | 48 | 8 | 4 | 3 | 1 | 5 |
| 6 | 19 | 64 | R Shoulder | 10 | 8 | 4 | 0 | 0 | 7 |
| 7 | 26 | 47 | Lumbar spine | 84 | 9 | 4 | 0 | 0 | 10 |
| 8 | 31 | 47 | left buttock | 4 | 6 | 0 | 0 | 0 | 8 |
| 9 | 32 | 72 | Right hip/knee | 6 | 6 | 2 | 0 | 0 | 5 |
| 10 | 36 | 38 | Lumbar spine | 84 | | | 1 | 1 | 8 |
| 11 | 40 | 35 | R shoulder | 24 | 10 | 6 | 0 | 0 | 4 |
| 12 | 41 | 59 | Cervical spine | 156 | 9 | 5 | 0 | 0 | 4 |
| 13 | 44 | 38 | spine/hip | 24 | 10 | 3 | 0 | 0 | 2 |
| 14 | 46 | 54 | Cervical spine | 48 | 10 | 3 | 0 | 0 | 6 |
| 15 | 48 | 32 | Lumbar spine | 60 | 10 | 2 | 0 | 0 | 9 |
| 16 | 51 | 53 | Thoracic spine | 10 | 7 | 0 | 0 | 0 | 7 |
| 17 | 55 | 77 | Cervical spine | 9 | 10 | 4 | 0 | 0 | 1 |
| 18 | 58 | 25 | Cervical spine | 24 | 7 | 3 | 3 | 0 | 8 |
| 19 | 59 | 34 | Cervical spine | 13 | 10 | 7 | 0 | 0 | 7 |
| 20 | 62 | 70 | R shoulder | 60 | 7 | 3 | 0 | 0 | 7 |
| 21 | 64 | 38 | Lumbar spine | 96 | 5 | 0 | 0 | 0 | 5 |
| 22 | 67 | 56 | Calf pain | 48 | 8 | 0 | 0 | 0 | 6 |
| 23 | 69 | 67 | Right shoulder | 144 | 8 | 5 | 0 | 0 | 7 |
| 24 | 80 | 38 | Right shoulder | 6 | 10 | 5 | 0 | 0 | 6 |
| 25 | 87 | 63 | Cervical spine | 24 | 10 | 4 | 0 | 0 | 6 |
| 26 | 108 | 54 | Right leg | 7 | 9 | 5 | 0 | 0 | 4 |
| 27 | 113 | 18 | Lumbar spine | 3 | 10 | 3 | 3 | 0 | 4 |
| 28 | 114 | 54 | Thoracic spine | 48 | 7 | 4 | 0 | 0 | 4 |
| 29 | 115 | 75 | R knee/leg | 24 | 7 | 2 | 0 | 0 | 1 |
| 30 | 116 | 66 | Lumbar spine | 120 | 8 | 5 | 3 | 0 | 3 |
| 31 | 119 | 61 | Chest post MI | 60 | 8 | 2 | 0 | 0 | 4 |
| | | 1584 | | 1295 | 248 | 99 | 17 | 2 | 183 |
| | | /31 | | /31 | /30 | /30 | /31 | /31 | /31 |
| | | 51 | | 42 | 8.3 | 3.3 | 0.6 | 0.1 | 6 |
| <i>Table 3 Subsequent patients who have responded to segmental treatment</i> | | | | | | | | | |
| | Age | Site | Duration (months) | Initial consult | | After treatment | | | |
| | | | | VAS worst | VAS best | VAS worst | VAS best | | |
| 32 | 64 | Right hip | 18 | 8 | 3 | 2 | 0 | | |
| 33 | 32 | Thoracic spine | 36 | 7 | 2 | | | | |
| 34 | 52 | Cervical spine | 108 | 9 | 6 | 3 | 0 | | |
| 35 | 60 | Left thumb | 60 | 9 | 0 | 2 | 0 | | |
| 36 | 55 | Lumbar spine | 96 | 8 | 0 | 0 | 0 | | |
| 37 | 43 | Lumbar spine | 156 | 8 | 0 | 0 | 0 | | |
| 38 | 72 | Lumbar spine | 14 | 7 | 2 | 0 | 0 | | |
| 39 | 37 | Both forearms | 120 | 8 | 0 | 0 | 0 | | |
| 40 | 87 | Lumbar spine | 6 | 10 | 4 | 0 | 0 | | |
| 41 | 19 | Thoracic spine | 36 | 10 | 4 | 3 | | | |
| 42 | 47 | Cervical spine | 144 | 8 | 2 | 4 | 2 | | |
| 43 | 74 | Lumbar spine/hip | 121 | 10 | 7 | 6 | 0 | | |
| 44 | 34 | Thoracic spine | 14 | 8 | 3 | 0 | 0 | | |
| 45 | 58 | Abdomen | 22 | 9 | 0 | 0 | 0 | | |
| 46 | 78 | Lumbar spine/hip | 60 | 8 | 2 | 0 | 0 | | |
| 47 | 58 | Abdomen | 22 | 9 | 0 | 0 | 0 | | |
| 48 | 78 | Lumbar spine/hip | 24 | 8 | 2 | 0 | 0 | | |
| 49 | 60 | Hip | 18 | 10 | 3 | 0 | 0 | | |
| 50 | 62 | Lumbar spine | 120 | 10 | 7 | | | | |
| 51 | 62 | Chest pain | 24 | 8 | 3 | 0 | 0 | | |
| Totals | 1132 | | 1219 | 172 | 50 | 20 | 2 | | |
| | /20 | | 61 | 8.6 | 2.5 | 1.1 | 0.1 | | |
| | 56 | | | | | | | | |

The autonomic nervous system had representation around the whole body. The nerves entering the spinal cord in the first few intercostal spaces supplied the head, neck and arms. The middle nerves supplied the chest and abdomen while the lower nerves supplied the lower back and legs. This led to my second hypothesis that the structures supplied by the SNS such as sweat glands and blood vessels caused pain accounting for all the negative investigations found in structures such as bone, muscle, joint or ligament.

I wrote a paper describing the afferent pathways of the sympathetic and somatic nervous systems from the periphery to the spinal cord and into the brain as areas for investigating possible sources of pain and referred pain (Kanji, 2008a). Next a paper outlining a theory on headache and chronic widespread pain was written taking into account the possibility of the SNS afferent nerves being involved in pain transmission (Kanji, 2008b).

I started to piece together a hypothesis on headache formation. Either the SNS supplied structures such as sweat glands or blood vessels are causing pain, or some other feature of the SNS and HPA response may be responsible for headache such as sensory amplification due to excess stress chemicals. Sensory amplification was likely as during the fight/flight response our sensations of sight and sound are amplified to help with escaping predators. Pain and touch is also likely to be amplified.

The notion that the SNS causes sensory amplification has a long history. In the 1940s the term reflex sympathetic dystrophy (J. Evans, 1946) started to appear and described an amplification of cutaneous touch and pain receptors leading to the sensation of touch becoming painful, a condition called allodynia, due to SNS hyperactivity. Although the classification of this disorder has evolved to complex regional pain syndrome many still refer to it as reflex sympathetic dystrophy 70 years on. The hallmarks of this condition are redness, colour changes and increased sweating, implicating changes to the control of the blood vessels and sweat gland that are regulated by the SNS.

Several meetings with my PhD supervisors, Associate Professor Rachel Page and Dr Raja Peter, took place over late 2007 and 2008. We discussed further development of the chronic headache causation model and clinical intervention trials. If the sensory amplification could be improved by modulating the SNS and HPA pathways by a treatment that was simple, easy, cheap and available to people suffering chronic headache then this may improve the self-help options available to patients.

Performing saline injections at the level of the intercostal muscles where sympathetic afferent nerves traverse before entering the spinal cord was initially entertained for the clinical trial. Kanji (2008b) tested whether injecting anaesthetic around the afferent sympathetic afferent nerves in the medial intercostal spaces T1 to T5 that supply the head region would alleviate headache and found that injecting the T1 to T5 intercostal spaces with anaesthetic alleviated headache. Injecting the T5 to T9 spaces, which supply the abdominal viscera and lumbar spine region, however did not alleviate headache.

One option that was discussed early for this PhD study was to perform a clinical trial using saline and anaesthetic injections targeting the T1 to T5 sympathetic afferents that supplied the head, neck and arms that entered at the intercostals spaces between the ribs. A control would be to inject lower sympathetic nerves from T8 to L2. The first injections should relieve headache pain if sympathetic afferents were involved with the amplification of somatic pain, or nociception was emanating from structures innervated by the SNS such as blood vessels. The problem with injections into the intercostal regions is the risk of pneumothorax and the precise localisation of the sympathetic afferent nerves. Discussions with Professor Nik Bogduk, Professor of Pain Medicine at Newcastle, Australia advised that to accurately target the sympathetic nerve afferents specialised radiological equipment would be required. If found effective then these injections could only be performed by very few people in the medical profession with image intensifiers, making it expensive and unavailable to the vast majority of headache patients. In the long term this type of intervention would not reach the majority of headache sufferers and a cheaper, more readily available intervention would be more appropriate.

Fortuitously around this time I was asked to attend a gym by a friend. The gym had a sauna and I attended three times a week for a few weeks. I recall feeling relaxed and in particular no longer suffering from tension neck pain that would be present at the end of a busy day seeing patients. During this time I also attended Bikram Yoga, performed at 40 degrees heat, which induces sweating within minutes of starting and runs for 90 minutes. At the end of a session there is a state of profound relaxation achieved. It was during one of these sessions that it struck me that heat and/or sweating may be the mechanism of relaxation. This led me to further reading about the SNS, in particular the sweating pathways, vasodilatation, vasoconstriction, HPA pathways and activation of the fight/flight response.

The overriding thought was that pain was likely to activate the SNS and HPA pathways explaining why people with chronic pain developed symptoms similar to people with chronic or repeated stress such as bereavement, loss, separation, occupational stress among other stressors. The studies (Breslau, et al., 2000; McWilliams, Goodwin, & Cox, 2004; Scott, et al., 2007) clearly showed an association between both chronic pain and headaches to insomnia, depression, anxiety, irritable bowel disorder and Raynaud's syndrome.

By early 2008 I had gained several months of experience with many chronic pain patients' (e.g. fibromyalgia, CTTH) responses to attending sauna for their various pain conditions. Initially patients were skeptical and gentle persuasion was required with sound reasoning for them to trial this type of alternative treatment. However once patients who attended the sauna noticed significant improvements in pain, sleep and mood my recommendation increased from mild to strong. My increasing knowledge of the HPA pathways and SNS gave me greater insights in explaining to patients the possible benefits of attending sauna as a natural treatment with minimal side effects. An increasing number of patients were buying into the explanation and changing their behaviour by attending the sauna however it is important to validate clinical impressions of effectiveness of interventions with an RCT to accept or refute any novel treatment methods as with any medical intervention.

It was at this time a study of the impact of sauna on fibromyalgia was contemplated. This is a condition of widespread pain and tenderness (cutaneous and deeper hypersensitivity).

However the overriding difficulty was the measurement of pain would be difficult unless pain scores were recorded for all parts of the body, by using for instance a body mapping system. The complexity of this was unlikely to make for a well designed study and would be reliant on participants filling in an overly complex chart on a daily basis. This would lead to uncertainty of data collection. Studying patients with headache disorders seemed a good alternative and CTTH was the condition chosen as it is notoriously difficult to manage in the community.

2.3 Summary

Over 15 years of observational practice initially as a general practitioner and then in musculoskeletal medicine treating chronic pain disorders has led to this PhD which allowed me to further develop the new model on headache pain causation and carry out a clinical trial to investigate a noninvasive treatment aimed at the cause of sensory amplification. The next chapter examines the scientific literature regarding CTTH, the chronic pain condition chosen as the study population for the clinical trial (Chapter 6 to 8) performed in this PhD project.

Chapter 3

LITERATURE REVIEW: CHRONIC TENSION-TYPE HEADACHE

3.1 Introduction

Headache disorders are a group of conditions presenting with head pain including TTH, migraine and cluster headache. The International Headache Society (IHS) has divided TTH into infrequent episodic tension-type headache (ETTH) if present less than 12 times per year, frequent episodic TTH if present between 1 and 15 days per month and CTTH if present over 15 days per month (Olesen, 2006b). Chronic daily headache (CDH) is another classification defined as over 15 days of head pain per month with sub-classification depending on headache type such as migraine, tension headache, and new daily persistent headache or hemicrania continua. Migraine is distinguished from TTH by increased pain intensity and the presence of accompanying nausea, vomiting, photophobia and phonophobia. Cluster headache is described as unilateral, excruciating head pain accompanied by autonomic symptoms (Olesen, 2006b). Tension-type headache is the most common of all headache disorders (Olesen, 2006b)

This chapter will outline the literature on CTTH as this is the study population for the clinical trial (Chapters 6 to 8) performed to investigate the effect of heat, in the form of sauna, as a treatment strategy for people with CTTH. The prevalence of TTH (section 3.2), headache and migraine triggers (section 3.3), headache and comorbid conditions of poor sleep, anxiety, depression and musculoskeletal pain (section 3.4), headache and the neck (section 3.5), clinical trial design (section 3.6), review of RCTs for the prevention of CTTH (section 3.7), examination of the current models of headache causation (section 3.8) and experimental induction of headache disorders will be discussed.

3.2 The prevalence of headache disorders

Headache is the most common neurological disorder in the world. In comparing headache prevalence around the globe it is important to ensure a consistency in headache definition. The International Classification of Headache Disorders (ICDH I-1008 and ICDH II-2004) is used worldwide to classify headache disorders to ensure consistent diagnosis of headache type. Three recent reviews of headache prevalence (R. Jensen & Stovner, 2008; Robbins & Lipton, 2010; Stovner, et al., 2007) have all selected population studies that have used this classification system. For comparison of headache prevalence studies the methods of quantification (survey, questionnaire) and time frames of measurement (lifetime, one year) also need to be consistent between studies to make valid conclusions.

In a World Health Organisation initiative (Stovner, et al., 2007), 107 population studies were reviewed and it was calculated that the worldwide prevalence was 47% for current headache, 10% for current migraine and 3% for chronic daily headache and the lifetime prevalence of TTH was 46% and migraine 14%. The prevalence of current TTH was highest in Europe (80%), followed by North America (30%) and lowest in Asia (20%) while migraine was most prevalent in Europe (15%) and least prevalent in Africa (5%). Robbins et al. (2010) also found migraine incidence was lower in Africa than other continents with overall prevalence stated as Global (11%), Africa (5%), Asia (9%), Europe (15%), North America (13%) and Central/South America (9%). A large North American study found the prevalence in both women and men of migraine was highest in Caucasians (20.4%, 8.6%), then African Americans (16.2%, 7.2%) and lowest in Asian Americans (9.2%, 4.2%). Robbins et al. (2010) concluded that although genetics may predispose individuals to attacks, environmental factors play a significant role in modifying that propensity. Jensen and Stovner (2008) also concluded that the prevalence of TTH seems to be much higher in Europe (80%) than in Asia or America (20% to 30%) and migraine is also more prevalent in Europe and North America than it is in Africa.

All three reviews (R. Jensen & Stovner, 2008; Robbins & Lipton, 2010; Stovner, et al., 2007) of headache agree on the prevalence of migraine and TTH being 1.5 to three fold

higher in females compared to males, and peaking between the ages of 30 and 39 and decreasing thereafter with age. Robbins et al. (2010) found the incidence of TTH peaked between the ages of 25 to 34 at 40 per 1000 person years for females and 15 per 1000 person years for males and the incidence of TTH declined with age to below 5 per 1000 person years between 55 to 64 years of age.

The reduced prevalence of headache in the elderly has been studied to investigate whether the decline was associated with not working or due to taking medicine for other conditions (Thomas, et al., 2005). Thomas et al. (2005) found that headache prevalence was similar in people working and retired over the age of 65 and there was no difference in the percentage of daily medication users among headache sufferers compared to non-sufferers.

Several studies reporting one year prevalence for TTH that had sample sizes of over 1000 people (Cheung, 2000; Lavados & Tenhamm, 1998; Queiroz, et al., 2009; Roh, Kim, & Ahn, 1998; Russell, Levi, Saltyte-Benth, & Fenger, 2006; Sakai & Igarashi, 1997; Schwartz, Stewart, Simon, & Lipton, 1998; Takeshima, et al., 2004; Ulrich, Russell, Jensen, & Olesen, 1996) are summarised and shown in Table 3.1. A variety of methods (e.g. questionnaire, telephone interview, personal interview) have been performed to collect data for determining prevalence of TTH in a number of countries (Table 3.1). Table 3.1 shows a wide variation in prevalence of TTH from 83.5 % (Russell, et al., 2006) to 13 % (Queiroz, et al., 2009) that is consistent with the finding in the three reviews (R. Jensen & Stovner, 2008; Robbins & Lipton, 2010; Stovner, et al., 2007) that TTH is likely to be more prevalent in Europe, intermediate in the USA and less prevalent in Asia and South America.

3.3 Headache and migraine triggers

Studies looking at TTH and migraine triggers are based on several types of data including population studies (Ulrich, et al., 1996; Zivadnov, et al., 2003), retrospective questionnaire based enquiry of headache patients seen at various clinics (Andress-Rothrock, King, & Rothrock, 2010; Karli, Zarifoglu, Calisir, & Akgoz, 2005; Kelman, 2007; Yadav, Kalita, & Misra, 2010), prospective diary studies of migraine with correlation about perceived risk

| Reference | Country | Method | Numbers | Age | TTH | | |
|------------------|-----------|---------------|---------|----------|------|--------|-------|
| | | | | | Male | Female | Total |
| Queiroz (2009) | Brazil | T.i. | 3848 | 18-79 | 15.4 | 9.5 | 13 |
| Russel (2006) | Denmark | T.i. and M | 28,195 | 15 to 41 | 78.9 | 92.5 | 83.5 |
| Takeshima (2004) | Japan | P.i. | 4795 | >15 | 16.2 | 26.4 | 21.7 |
| Cheung (2000) | Hong Kong | T.i. and P.i. | 1436 | >15 | | | 26.9 |
| Roh (1998) | Korea | T.i. | 5556 | >15 | 20.2 | 24.3 | 22.3 |
| Schwartz (1998) | USA | T.i. | 13345 | 18-65 | 37.7 | 44.8 | 40.3 |
| Lavados (1998) | Chile | Q | 1385 | >15 | 18.1 | 35.2 | 26.9 |
| Sakkai (1997) | Japan | T.i. | 4029 | >15 | | | 15.6 |
| Ulrich (1996) | Denmark | P.i. and T.i. | 4000 | age 40 | 69 | 85 | 76 |

P.i. = personal interview, T.i. = telephone interview, Q = questionnaire, M = mailout, M = male, F = female, T = total. If no figure quoted then box is empty.

factors (Alstadhaug, Salvesen, & Bekkelund, 2005; Wober, et al., 2007; A. Yang, et al., 2011) in the days leading up to a migraine episode and provocation studies of red wine (Littlewood, et al., 1988) and chocolate (Marcus, Scharff, Turk, & Gourley, 2007).

Zivadinov et al. (2003) examined the frequency of precipitating factors in subjects with migraine and TTH by performing face to face interviews of 2475 positive responders from a sample of 5173 residents in Croatia. A summary of the possible migraine and TTH triggers investigated by Zivadinov et al. (2003) are presented in Table 3.2. The most common precipitating factors in both headache and migraine were stress, frequent travelling, changes in weather and menstruation. They found migraineurs experienced TTH preceded by triggering factors more often than non-migraineurs however this study did not examine whether TTH triggers were different for migraineurs and non-migraineurs.

When studying TTH, people who experience migraine also experience TTH and the triggers for TTH in migraineurs may vary from non-migraineurs. Ulrich et al. (1996) analysed 4000 people from the general population examining TTH in migraineurs and non-migraineurs finding stress and mental tension, and tiredness often precipitated TTH and only migraineurs had episodes of TTH precipitated by alcohol, overmatured cheese, chocolate and physical activity. If TTH triggers differ between migraineurs and non-

migraineurs then certain triggers may cause episodes of TTH due to an inherent quality of the person being a migraineur.

| Table 3.2 A comparison of triggers for TTH and migraine (Zivadinov et al. 2003) | | |
|---|---------------|--------------|
| | Headache type | |
| | TTH (%) | Migraine (%) |
| No. of patients | 1319 | 720 |
| Emotional stress | 49.4 | 57.8 |
| Eating habits | 30 | 32 |
| Changes in sleep | 36 | 40 |
| Menstruation | 46 | 49 |
| Oral contraceptives | 31.5 | 29.5 |
| Various food items | 11.8 | 12.5 |
| Afferent stimulation | 34.7 | 38.9 |
| Physical activity | 36.7 | 29.4 |
| Changes in weather | 44.7 | 54.6 |
| Frequent travelling | 52.5 | 54.6 |
| The incidence of triggers are expressed as percentages | | |

Table 3.3 shows the incidence of various triggers in three recent retrospective clinic based patient studies carried out in migraineurs (Andress-Rothrock, et al., 2010; Kelman, 2007; Yadav, et al., 2010). All three studies consistently showed emotional stress, fasting and sleep deprivation were migraine triggers. Both Andress-Rothrock et al. (2010) and Kelman et al. (2007) found menstruation for females and odours were significant triggers while Yadav et al. (2010) found menstruation to be a less important trigger which the authors commented may be a cultural difference in reporting menstruation as a trigger in India.

Two retrospective studies (Karli, et al., 2005; Scharff, Turk, & Marcus, 1995) comparing TTH and migraine triggers are summarised in Table 3.4 (Karli et al., 2005) and Table 3.5 (Scharff et al., 1995). Karli et al. (2005) found emotional stress was the most common trigger with a similar percentage in both TTH and migraine while fasting, sleep deprivation

| | Study | | |
|----------------------------|--------------|-------------------------|---------------|
| | Yadav (2010) | Andress-Rothrock (2010) | Kelman (2007) |
| No. of patients | 182 | 200 | 1617 |
| F:M numbers | 131F: 51M | 172F:28M | 1363F:254M |
| Condition | Migraine | Migraine | Migraine |
| Any Trigger present | 87.9 | 91 | 75.9 |
| Emotional stress | 70 | 59 | 79.7 |
| Fasting | 46.3 | 39 | 57.3 |
| Physical exertion/exercise | 52.5 | | 21 |
| Traveling | 52.5 | | |
| Sleep deprivation | 44.4 | 53.5 | 49.8 |
| Menstruation | 12.8 | 62 | 65.1 |
| Weather changes | 10.1 | 19 | 53.2 |
| Odours | | 46.5 | 43.7 |
| Alcohol | | | 37.8 |
| bright lights | | 7 | 38.1 |
| Loud noise | | 5 | |
| Neck pain | | | 38.4 |
| food | 0 | 18 | 26.9 |
| Smoke | | | 35.7 |
| Heat | | | 30.3 |

The incidence of triggers are expressed as percentages. F = Female, M = Male. If blank then not reported in the study.

and menstruation were almost twice as likely to trigger migraine as TTH. Odour was a trigger for migraine and not TTH while head and neck movement was a trigger for TTH but infrequent trigger of migraine. In the study by Scharff et al. (1995) with approximately twice the participants, emotional stress, weather changes and odours were present in similar percentages for migraine and TTH and the marked variation found in by Karli et al. (2005) for triggers was absent. A 10% to 20 % variation was present for fasting, changes in sleep and alcohol between TTH and migraine. The small sample size and retrospective nature of both of these studies may limit the conclusions that can be drawn.

A prospective study of headache and migraine triggers is likely to have more validity than retrospective studies due to difficulties recalling information and accuracy of timing of

| Table 3.4 A comparison of triggers for migraine and ETTH presenting to a headache clinic (Karli et al., 2005) | | | |
|---|---------------|-----------------|-------------------|
| | Headache type | | |
| | TTH | Migraine w aura | Migraine w/o Aura |
| No. of patients | 31 | 23 | 33 |
| Emotional stress | 96.8 | 78.3 | 81.8 |
| Fasting | 38.7 | 73.9 | 72.7 |
| Sleep deprivation | 25.8 | 65.2 | 45.5 |
| Menstruation | 32.3 | 56.5 | 60.6 |
| Weather changes | 35.5 | 52.2 | 45.5 |
| Odours | 0 | 30.4 | 27.3 |
| Head and neck movement | 48.4 | 8.7 | 9.1 |
| Exercise | 16.1 | 30.4 | 12.1 |
| The incidence of triggers are expressed as percentages, w = with w/o = without | | | |

| Table 3.5 A comparison of triggers for TTH, migraine and combined migraine and TTH (Scharff et al., 1995) | | | |
|---|---------------|----------|----------|
| | Headache type | | |
| | TTH | Migraine | Combined |
| No. of patients | 52 | 69 | 53 |
| Emotional stress | 74.5 | 72.4 | 70 |
| Fasting | 52.9 | 44.9 | 47.2 |
| Changes in sleep | 58 | 52.2 | 69.2 |
| Menstruation | 60 | 68.1 | 56.8 |
| Weather changes | 48 | 45.5 | 46.2 |
| Odours | 54.9 | 55.1 | 43.4 |
| Glare | 45.8 | 38.8 | 63.5 |
| Physical exertion | 67.3 | 44.9 | 57.7 |
| Alcohol | 31.4 | 35.3 | 32.7 |
| The incidence of triggers are expressed as percentages | | | |

headache symptoms and associated triggers. Wober et al. (2007) performed a prospective study that included 327 migraineurs. All participants kept a diary of headache and migraine occurrence for three months (total of 28,325 diary days). The diary covered 52 items that would potentially trigger migraine and 45 items were lagged by one day to check if their presence the day before may trigger headache or migraine episodes. In migraineurs there was an increased risk of developing non migrainous headache on all days of menstruation and the two days preceding menstruation. The presence of neck muscle tension, stress, psychological tension and tiredness the day before also increased the risk of developing a

headache in migraineurs. Playing sport for less than three hours per month also increased the risk of developing migraine. A holiday or day off reduced the risk of developing headache. The risk of developing migraine increased with menstruation including two days prior to menstruation, daily sunshine duration of over three hours, low pressure over the UK and air advection from the north.

The temporal relationship between weather and headache (A. Yang, et al., 2011) was investigated by studying 52 subjects (mixed population of migraine and TTH), chosen randomly from a community sample who experienced TTH or migraine generated by the Greater Taipei Migraine Study. The 52 subjects kept a diary for 147 days with 1809 diary entries and 195 headache attacks recorded. No relationship was found for headache incidence and the weather data on the day of the headache episodes, however when headache episodes were correlated with weather conditions in the few days leading to the migraine episode, the authors found that cold fronts either play a role in precipitating migraine attacks or at least prime migraine onset.

A double blind provocative study of chocolate and carob in 63 women with chronic headache (migraine and TTH) found chocolate was not likely to trigger headache more than carob (Marcus, et al., 2007). Another migraine provocation study (Littlewood, et al., 1988) was performed on individuals who believed red wine but not alcohol in general provoked their migraine. Red wine with low tyramine content and vodka of equivalent alcohol content to the red wine was tested on these subjects who believed red wine provoked migraine episodes as well as migraine subjects who found red wine did not provoke migraine episodes. Nine of 11 participants who believed red wine provoked migraine developed a typical migraine episode after red wine. Eight of the 11 who believed red wine provoked their typical migraine were challenged with vodka and none experienced a migraine episode. Neither red wine nor vodka provoked migraine in those with migraine who did not believe red wine triggered their migraine episodes. The authors concluded that the migraine provoking agent in red wine is unlikely to be alcohol or tyramine.

Laboratory reproduced psychological stress has been used in clinical trials and found to cause headache, increase muscle tenderness and lower pain threshold. Cathart et al. (2010) carried out a RCT where two groups, CTTH (n=23) and headache free/control group (n=25) were exposed to one hour long stressful mental tasks and a third group of CTTH patients (n=23) were exposed to an hour long neutral task. Headache developed in 91% of the CTTH group and 4% of the control group when exposed to the stressful mental task. Throughout the stressful mental task headache intensity was found to rise in the CTTH group. Seventeen percent of the CTTH group exposed to a neutral task (a task not causing mental stress) developed a headache. Headache sufferers compared to controls had increased muscle tenderness and reduced pain thresholds measured by a pressure algometer (Cathart, Petkov, Winefield, Lushington, & Rolan, 2010). The results of this study showed stress triggers headache and produces hyperalgesia in people with already reduced pain thresholds.

In summary the common triggers of headache and migraine may be divided into those that upset homeostasis and activate the SNS and/or HPA pathways (stress, changes in temperature, hunger and sleep disturbance), those which stimulate sensory input (visual disturbance, sound and odours) and menstruation. A model of headache causation should explain how each of these factors may trigger or exacerbate headache and migraine episodes.

3.4 Headache and associated comorbidities

Headache is comorbid with many conditions including chronic pain, disturbed sleep, anxiety and depression.

3.4.1 Chronic musculoskeletal pain

People suffering from headache disorders are more likely to have chronic pain disorders. The Head Hunt population study in Norway of over 50,000 adults surveyed by questionnaire found people with headaches were twice as likely to have musculoskeletal pain than those without headache disorders (Hagen, et al., 2002). They also demonstrated a

linear relationship between headache frequency and musculoskeletal pain. For those with less than seven days headache per month the increased risk of having chronic musculoskeletal pain was 1.5 fold (CI: 1.4 to 1.6). For those with 7 to 14 days headache per month there was a 3.2 fold (CI: 2.9 to 3.5) increased risk of having chronic musculoskeletal pain and for those with greater than 15 days headache per month a 3.6 fold (CI: 2.9 to 4.5) increased risk (Hagen, et al., 2002). A population study (Strine, Chapman, & Balluz, 2006) in the United States, of 29,828 people, found the increased risk of those reporting severe headache in the previous three months of having a chronic pain condition was 7.6 fold (CI: 5.8 to 10) for men and 5.4 fold (CI: 4.6 to 6.3) for females. A study of 5,692 people in the United States (Von Korff, et al., 2005) with chronic pain conditions found a 5.2 fold (CI: 4.1 to 6.4) increased risk for migraine and a 4.0 fold (CI: 2.9 to 5.3) increased risk for other headache.

3.4.2 Sleep disturbance

Headache and disturbed sleep often coexist in the same patient (Andrea, 2006; Jennum & Jensen, 2002; Rains & Poceta, 2006). Headache and migraine can be provoked by too much or too little sleep. Migraine can also be alleviated by sleep. Sleep deprivation has been found to be a trigger for migraine episodes in several clinic populations (Andress-Rothrock, et al., 2010; Kelman, 2007; Yadav, et al., 2010; Zivadinov, et al., 2003) (section 3.3). It seems there is a reciprocal relationship between headache and sleep but the exact nature of this relationship is not fully understood.

A cross sectional population study (Ødegård SS, et al., 2010) investigated the association between sleep disturbance and headache type using face to face interviews. Among 297 participants 77 were headache free, 135 were diagnosed with TTH, 51 with migraine and 34 with other headache diagnoses. The odds ratio for having severe sleep disturbance with migraine compared to headache free individuals was 5.4 (CI: 2.0 to 15.5) and for TTH 3.3 (CI: 1.4 to 7.3).

A cross sectional postal survey in the United Kingdom (Boardman, Thomas, Millson, & Croft, 2005) investigated sleep problems and headache. There was no specific breakdown

of migraine and TTH in this survey. The survey enquired about sleep problems in the last month by asking about trouble falling asleep, waking up several times a night, trouble staying asleep and waking with the usual amount of sleep with fatigue. Sleep problems were found to be associated with headache disorder and the strength of association increased with severity of headache. Headache was graded according to pain severity and disability into five grades (I to V with V being the most severe). The odds ratio for severe sleep problems was grade I, 1.9 (CI: 0.9 to 4.4), grade II 6.8 (CI: 3.3 to 14), grade III 15.2 (CI: 5.3 to 44), grade IV 48.9 (CI: 11.8 to 202.3) and grade V 39.2 (CI: 12.5 to 122.9). Other cross sectional population studies (Rasmussen, 1993; Strine, et al., 2006) have also found sleep disturbance is comorbid with headache disorders.

3.4.3 Anxiety and depression

Anxiety and depression have an increased prevalence in people who suffer from headache disorders. The World Mental Health Survey Initiative (Scott, et al., 2007) carried out eighteen general population surveys in 17 countries. In all 42,249 people surveyed, people with chronic headache (TTH and migraine were not differentiated) were found to have a 2.5 fold (CI: 2.2 to 2.8) increased risk of depression and a 2.3 fold (CI: 2.1 to 2.5) increased risk of anxiety disorder. Data analysed from the 2002 National Health Interview survey (Strine, et al., 2006) of 29,828 people in the United States looked at severe headache in the past three months and risk of associated anxiety or depression. They found males had a 2.7 fold (CI: 2.2 to 3.3) increased risk while females had a 2.1 fold (CI: 1.9 to 2.3) increased risk of anxiety or depression. The increased association of anxiety with headache disorders has been confirmed in other cross sectional population studies (Boardman, et al., 2005; McWilliams, et al., 2004).

3.5 Headache and the neck

There is support for cervical spine pathology as a cause of chronic headache due to referred pain, pain that is perceived as arising from a location remote to the origin of pain (Arendt-Neilsen & Svensson, 2001). The description of the nerves supplying the neck and their relationship to headache, occipital neuralgia and neck pain have been well described in cadaver studies (Bogduk, 1982). Experimental studies have described stimulation of

muscles supplied by the upper neck that can refer pain to the head (Fenstern, Langton, Jameson, & Schiller, 1954). Experimental studies have also shown that injecting the neck joints with hypertonic saline (zygo-apophyseal joints) refers pain into the head (Dwyer, Aprill, & Bogduk, 1990; Fukui, Osheto, & Shiotani, 1996).

Two studies (Fernandez-de-la-pas-Penas, Alonso-Blanco, Cuadrado, & Pareja, 2006; Fernandez-Mayoralas, Fernandez-de-la-pas-Penas, Palacios-Cena, et al., 2010) have shown that cervical spine range of motion is limited in individuals with CTTH. Both studies used a goniometer to measure range of motion with the assessor blind to whether subjects had CTTH. The first study in 2006 was a blinded control study comparing range of motion of the cervical spine of adults with CTTH and 25 age and gender matched headache free controls. The adults with CTTH were found to have a reduced range of motion. The second study in 2010 performed a similar study using 50 children with CTTH and 40 age and gender matched controls. The group with CTTH was found to have a limited range of motion of the cervical spine compared to the control group. These studies implicate the cervical spine as a possible pain generator causing referred pain in patients classified with CTTH.

Two studies (Govind, King, Bailey, & Bogduk, 2003; van Etteken & Lucas, 2006) have found treatment aimed at the neck have provided relief in a significant proportion of headache patients. In one study of ablative therapies of the cervical spine sensory nerves, with radiofrequency neurotomy, up to 80% of selected patients with chronic headache gained significant relief (Govind, et al., 2003).

A study examining the effect improving control of posterior cervical spine muscles on reducing TTH frequency in people with ETTH compared physiotherapy to physiotherapy plus craniocervical training (van Etteken & Lucas, 2006). Physiotherapy consisted of massage, postural advice and cervical spine mobilisation and craniocervical training incorporated using a latex band to train and/or regain muscle control of cervicospinal and craniocervical muscles. Eighty one participants were randomised to two groups, a control group of 42 participants and craniocervical training group of 39 participants. At six months

follow up the craniocervical training group showed statistically significant reduction in headache frequency, intensity and duration ($p < 0.001$ for all). In this study 85% of participants in the craniocervical training group had a 50% reduction in headache frequency. Almost 50% reported an 80 to 100 percent relief of headache. This study gives some insight that perhaps 50% of patients with primary headache may suffer from referred pain from the neck, as half the participants were almost cured of their TTH when treating the neck.

3.6 Clinical trial design

The second aim of this PhD study was to investigate a noninvasive intervention for the prevention of CTTH. A RCT was chosen as this type of clinical trial design is deemed as providing the best evidence on the efficacy of health care interventions as it has the potential to reduce bias (Moher, et al., 2011). In a RCT randomisation reduces allocation bias while a control group (or placebo) allows some quantification of natural history and/or treatment effect from being involved in a clinical trial against which to compare the intervention of interest. This section will outline certain features of RCT design, sources of bias and potential pitfalls before reviewing clinical trials that have been performed investigating the prevention of CTTH (section 3.7). The review of RCTs discussed in section 3.7 helped determine the RCT study design for this PhD which is described in Chapter 6.

Researchers are often interested in measurements of outcome before and after the intervention to substantiate or negate the effect of an intervention which means pre and post testing is required. Two commonly used study designs are cross over and parallel control (Hopewell, Dutton, Yu, Chan, & Altman, 2010). In a cross over design participants have the study intervention followed by the control treatment or the control intervention followed by the study intervention. There is a washout period in between the two interventions to account for any residual effects of the first intervention. A parallel group trial is when two or more groups are followed simultaneously. A control group should be treated the same as the intervention group to ensure attention paid to subjects is similar.

The Hawthorne effect describes the phenomenon whereby attention paid to subjects in experimental studies may alter their behaviour which may in turn impact on the outcome causing bias (Polgar & Thomas, 2000a). The measurement itself and being involved in a study may change behaviour and affect the outcome of interest and needs to be considered in research design. Ideally the intervention of interest should be the only difference between comparison groups to try and establish the difference made by the intervention. Factors such as the provision of advice sheets, questionnaires filled in, time spent with therapists, place of consultation, skills and qualifications of the clinician performing the consultation or treatments should be similar in different groups to reduce the Hawthorne effect.

3.6.1 Sampling and sample size

A sample of the population with the condition of interest is taken as it is usually impossible and extremely costly to study everyone with the condition and if the sample is representative of the general population then the results of the study may be applicable to the entire population (Polgar & Thomas, 2000b). If the sample is biased, one cannot generalise the results of the trial to the entire population. Most studies of CTTH recruit participants by advertising in newspapers and recruiting patients referred to clinics.

Increasing sample size may not reduce sampling errors greatly and the size of a sample should be balanced against the costs associated with data collection. Sampling error is proportional to $1/\sqrt{n}$ where n is the number of participants. Doubling the sample size results in a reduction of the sampling error by a factor of the square root of 2 (1.41) and a nine fold increase in sample size results in a 3 fold reduction in sampling error (Polgar & Thomas, 2000b). Significant increases in participant numbers are required for small reductions in sampling error once a certain number of participants are reached.

When considering sample size, participant time, travel and occasional discomfort of some interventions need to be factored into the study. It is ethically necessary to use the minimum number of participants as worked out in sample size calculations (section 6.5.1) and sample sizes are worked out for the specific statistical analyses decided upon prior to carrying out the trial.

3.6.2 Blinding

Randomised control trials are open or blinded. In open trials the participants and treatment providers are aware of which group participants are allocated to e.g. the intervention group or the control group. Randomised control trials of medications that are open are often referred to as open label (section 3.7). Single blind is when only either treatment providers or participants are aware of the group allocation (usually the treatment provider) and double blind is when both treatment provider and participants are unaware of group allocation. Double blind trials are the gold standard for RCTs especially when performing pharmaceutical trials of tablets or injections.

A double blind trial will reduce the Rosenthal effect where the expectations of the experimenter are conveyed to the experimental subject (Polgar & Thomas, 2000a). If the experimenter believes the intervention will lead to an improvement in the condition then he may treat the control and the intervention group differently. A double blind trial will also reduce the bias of a participant knowing whether he is in the intervention or control group. If a participant knows he is in the intervention group he may believe this will have a greater effect on outcome.

3.6.3 Randomisation and allocation

There are many different methods for allocating participants to groups in a RCT. However random assignment into groups does not guarantee the two groups will be equivalent, rather that there is no reason the two groups should be different. Randomisation can be performed for individual participants by using computerised random number tables or block randomisation can be performed where equal numbers of participants are placed into blocks of a certain number that ensures equal numbers are allocated into each group (Beller, Gebiski, & Keech, 2002).

3.6.4 Questionnaires measuring subjective health status

Questionnaires are used to measure subjective health status as objective measures cannot be taken of such constructs as mood and levels of pain. Research performed on patient outcome measures using questionnaires is only as accurate as the measurement tools. When

measurements for the same individual are reproduced on separate occasions or by different observers then a questionnaire is reliable. Validity is the extent to which the questionnaire measures what is intended. If questionnaires do not measure what is intended or are not reproducible then results of research will be flawed (Juniper, 2009). Psychometrically robust measurement tools increase the probability that questionnaires used to measure subjective health status accurately measure what is intended.

Screening questionnaires have limitations. For example questionnaires screening for depression do not diagnose depression but provide an indication of severity of symptoms for a given period of time (e.g. during the past week). Higher scores often reflect more severe symptoms. Screening questionnaires do not necessarily diagnose the length of time symptoms have been present, degree of impairment and co-morbid psychiatric disorders (Sharp & Lipsky, 2002).

Validation of a questionnaire involves test retest reliability (reproducibility), responsiveness (ability to detect clinically important change), and validity. Face validity is the concept that questions are relevant, content validity is determined by expert consensus and construct validity is determined by correlating subjects' answers to the questions with objective measurements such as interviews (Zarins, 2005). Validated questionnaires are precision measurement instruments (Juniper, 2009) and specificity and sensitivity can gauge whether the questionnaire categorises the participant correctly. Questionnaires with high sensitivity correctly identify those with the condition and questionnaires with high specificity correctly identify those without the condition. The constructs present in the questionnaire can be tested against structured interviews to check sensitivity and specificity of the questionnaire.

Questionnaires used to measure subjective health status also need to be well structured and select appropriate questions to ensure readability for the intended audience (Juniper, 2009). In the RCT described in Chapter 6 the Beck Depression Inventory II was chosen to measure the level of depression, Headache Disability Index to measure headache related disability, Numerical Pain Rating Scale to measure pain intensity and Daily Sleep Interference Scale

to measure sleep disturbance. The validity and reliability of these measurement tools is discussed in Chapter 6.

3.6.5 Pilot studies

Pilot studies have no formal methodological guidance in the literature as to exactly what constitutes a pilot study (Lancaster, Dodd, & Williamson, 2004) however a pilot study has been defined as synonymous with a feasibility study intended to guide the planning of a large scale investigation, in particular testing feasibility of both methods and procedures for later use on a large scale (Thabane, et al., 2010). These procedures include inclusion/exclusion criteria, testing of equipment and materials and educating staff in administration and assessment tools. Testing the randomisation procedures can also be performed in a pilot study. Pilot studies provide an opportunity to model a complex intervention before embarking on a full scale evaluation (Craig, et al., 2008) such as an RCT.

3.6.6 Data handling and analysis

The preferred strategy of data handling in RCTs is intention-to-treat (ITT) analysis, where subjects are analysed according to the group allocation (intended to be treated) rather than how they were actually treated and everyone randomised in the study is included in the analysis regardless of whether they discontinued the intervention or completed the intervention. Intention-to-treat analysis is likely to produce more conservative results and dampen treatment effects due to participants not completing an intervention being included in the analysis (Stanley, 2007).

Strict ITT is difficult to achieve due to missing outcomes and non adherence to the trial protocol. Trials can exclude data due to missing variables or impute data. Concern with missing data should be raised when data is missing due to different reasons in the intervention and control group. In the Consolidated Standards of Reporting Trials (CONSORT) checklist the specific request for intention-to-treat analysis has been dropped in favour of a clear description of exactly who was included in each analysis (Moher, et al., 2011).

Exclusion of patients from analysis can be a source of weakness in an RCT. Dropouts may occur more commonly in the more aggressive therapy arm than the placebo control due to adverse effects of the intervention or protocol violations. Excluding dropouts that occur in one group due to an aspect of the intervention may introduce bias in the results, in particular if dropouts occur more commonly in the aggressive therapy arm than the placebo control arm, the average results in the aggressive therapy arm may be better than the placebo arm as proportionately more non responders than responders are excluded (Stanley, 2007).

The problem of missing data is similar to that of excluding data, if data is missing due to aspects of treatment or disease then problematic bias may occur. Missing data also reduces the number of cases available for analysis and may weaken the power of the study to detect a difference between the groups. Missing values can be imputed by carrying the last result forward or inserting a conservative value, by averaging adjacent values and computerised methods that take into account data from similar patients with complete data. A sensitivity analysis may be performed where two or more methods of data imputation are carried out and results compared. If the results are similar then one may deduce the basic study conclusion does not depend on the imputation method used (Stanley, 2007). Carrying the last result forward is appealing due to its simplicity however has been criticised as it may introduce bias and no allowance is made for imputation of data (Moher, et al., 2011). The handling of missing data is discussed in section 3.7 with several methods used in the RCTs of CTTH identified.

3.7 Review of RCTs for the prevention of CTTH

When treating occasional episodes of TTH analgesic medication is the preferred method of management however when TTH is frequent and conforms to the diagnosis of CTTH medications taken regularly to prevent the onset of headache are preferred (Bendtsen, et al., 2009). This section reviews clinical trials aimed at the prevention of CTTH and included studies that were randomised control trials (RCT) of medications (e.g. amitriptyline, fluoxetine) and other therapies (e.g. relaxation, acupuncture, botulinum toxin).

The search strategy for identification of studies is shown in Table 3.6. Studies were limited to people of 18 years of age and older. When performing this Medline search (1966 to present day), trials that included participants with TTH and ETTH were also found and are shown in Table 3.8. Similar searches were performed using the EMBASE and SCOPUS databases to identify RCTs not available in Medline.

3.7.1 Summary of trials for the prevention of CTTH

Twenty six RCTs of CTTH between 1992 and 2009 were identified (Table 3.7) under the search parameters that addressed preventative treatment of CTTH (Table 3.6). The trial design, number of participants, outcome measures, duration of trial and findings of these 26 studies are summarised in Table 3.7.

Of the 26 RCTs identified in Table 3.7, 20 RCTs were parallel group design and six were cross over design. Only 14 (Bendtsen, Buchgreitz, Ashina, & Jensen, 2007; Bendtsen & Jensen, 2000, 2004; Bendtsen, Jensen, & Olesen, 1996b; Fogelholm & Murros, 1992; Gobel, et al., 1994; Holroyd, et al., 2001; Lindelof & Bendtsen, 2009; Murros, et al., 2000; Pfaffenrath, et al., 1994; Ribeiro, 2000; Shukla, Nag, & Ahuja, 1996; Singh & Misra, 2002; Yurekli, et al., 2008) of the 26 studies used a placebo arm. A placebo arm is recommended by the current guidelines on preventative medication treatment of CTTH (Bendtsen, et al., 2009). The guide states;

That two presumably active drugs are found equally effective in a trial is no proof of efficacy of either, nor of comparability. To refer to the previous efficacy in other trials of an established drug used as a comparator is not enough: it is using historical controls, a method largely discouraged in medicine. Both drugs should also be shown contemporaneously to be superior to placebo (p. 8).

Table 3.6: Medline search strategy for preventative trials of CTTH

MEDLINE data base was searched using the following strategy:

- 1 Headache/ (18954)
- 2 Tension-Type Headache/ (1168)
- 3 Chronic tension type headache.mp. (442)
- 4 Chronic daily headache.mp. (521)
- 5 1 or 2 or 3 or 4 (20212)
- 6 control groups/ or double-blind method/ or random allocation/
(161093)
- 7 exp clinical trial/ (589726)
- 8 Randomi*.mp. [mp=title, original title, abstract, name of substance
word, subject heading word, unique identifier] (404453)
- 9 6 or 7 or 8 (749295)
- 10 5 and 9 (2490)
- 11 exp Migraine Disorders/ (17521)
- 12 5 not 11 (17478)
- 13 9 and 12 (2254)
- 14 2 or 3 (1347)
- 15 9 and 14 (286)
- 16 comment/ or editorial/ or exp "review"/ (2042379)
- 17 15 not 16 (256)

There were a variety of medications examined in 20 of the 26 treatment trials of CTTH (Table 3.7) including antidepressants (amitriptyline, sertraline, citaloprim, desipramine, fluoxetine, paroxetine, and mirtazapine), anxiolytics (alprazolam and buspirone), anticonvulsants (sodium valproate), precursors to serotonin (L-5- hydroxytryptophan), a muscle relaxant (tizanidine), an NMDA receptor antagonist (memantine), anti-inflammatory (ibuprofen) and an antipsychotic (sulpiride). Evidence of dose response effects were tested in only two RCTs (Table 3.7). Murros et al. (2000) tested tizanidine 6mg versus tizanidine 12 mg and found no difference in effect between the two doses. Silberstein et al. (2006) tested several doses of botulinum toxin and found no differences of effect with the different doses trialled.

Eighteen of the 26 RCTs tested pharmaceutical interventions exclusively with 15 of the studies being double blind and three open labelled (Bettucci, et al., 2006; Boz, Altunayoglu, Velioglu, & Ozmenoglu, 2003; Mitsikostas, Gatzonis, Thomas, & Ilias, 1997). All four trials testing botulinum toxin injection therapy (Padberg, de Bruijn, de Haan, & Tavy, 2004; Schulte-Mattler & Krack, 2004; Silberstein, et al., 2006) were double blind. Four of the 26 RCTs included non-pharmaceutical therapies (e.g. acupuncture, relaxation therapy and physical activity) with two of these studies combining pharmaceutical and non-pharmaceutical therapies and two RCTs testing non-pharmaceutical interventions exclusively (Soderberg, Carlsson, & Stener-Victorin, 2006; Wang, Svensson, & Arendt-Nielsen, 2007). None of the four trials testing non pharmaceutical interventions were double blind (Holroyd, et al., 2001; Kiran, Behari, Venugopal, Vivehanandhan, & Pandey, 2005; Soderberg, et al., 2006; Wang, et al., 2007). Three RCTs using non pharmaceutical interventions (Holroyd, et al., 2001; Kiran, et al., 2005; Soderberg, et al., 2006) were open label and one RCT (Wang, et al., 2007) was single blind with patients being blind to the intervention.

| Table 3.7: Chronic tension-type headache; Randomised control trials of preventative measures | | | | | |
|---|---|----------------------------------|--|------------------------------|---|
| Reference Trial design | Groups (N) | Total no. of subjects | Outcome measures | Duration of trial | Findings |
| Lindelof & Bendtsen (2009) DB, Placebo, Cross over | Memantine (29) Placebo (29) | N=29 D=11 C=73% | AUC (intensity x duration) | 10 weeks | Intensity x duration No SSD |
| Yukreli et al. (2008) DB, Placebo, Parallel | Sodium Valproate (23) Placebo (18) | N=41 D=0 | Pain intensity Pain frequency | 12 weeks | Pain intensity No change Pain frequency Valproate 55% reduction.* |
| Wang et al. (2007) SB, Parallel | Electro-acupuncture (18) Sham (18) | N=40 D=4 C=90% | Pain intensity Pain duration | 12 weeks | Daily headache duration No SSD Electroacupuncture 13%/Placebo 12% Headache intensity No SSD Electroacupuncture 20%/Placebo 6% Headache frequency No SSD Electroacupuncture (20%)/Placebo (1%) |
| Bendtsen et al. (2007) DB, Placebo, Parallel | Mirtazapine & Ibuprofen (22) Placebo (21) Mirtazapine 4.5mg (20) Ibuprofen (21) | N=93 D=9 C=90% | AUC (Frequency x intensity) Analgesic intake | 12 weeks | Frequency x intensity No SSD Brufen 400mg day increased 2% after 3 weeks Mirtazapine 20% Mirtazapine and Brufen 13% Placebo 13% |
| Headache index = frequency of headache x intensity of headache. No statistically significant difference = No SSD. Statistically significant difference measures marked with asterix (*). HI = Headache index. Botox = botulinum toxin. AUC = area under curve. DB = double blind. SB = single blind. D = Dropouts for both groups. C = % completers. M = month | | | | | |

| Table 3.7 continued: Chronic tension-type headache; Randomised control trials of preventative measures | | | | | |
|---|--|----------------------------------|---|------------------------------|--|
| Reference Trial design | Groups (N) | Total no. of subjects | Outcome measures | Duration of trial | Findings |
| Bettucci et al. (2006) Open label, Parallel | Amitriptyline (9) Amitriptyline & Tizanidine (9) | N=18 D=0 | Frequency Duration Pain intensity Headache Impact test | 12 weeks | Frequency No SSD Amitriptyline 60% Amitriptyline & Tizanidine 58% Duration No SSD Amitriptyline 38% Amitriptyline & Tizanidine 57% Pain Intensity No SSD Amitriptyline 24% Amitriptyline & Tizanidine 30% |
| Silberstein et al. (2006) DB, Placebo, Parallel | Botox (229) Saline (50) | N=300 D=31 C=90% | Number TTH free days | 90 days | Number TTH free days Day 60 No SSD Placebo= Botox 100= Botox 86 = Botox 50 Headache severity Day 60 No SSD Placebo = Botox 100= Botox 86 = Botox 50 =Botox 150 50% reduction of TTH days Day 90 No SSD Botox A 100U 15/47, 31.9% Botox Usub 100 15/49, 30.6% Botox 86Usub 15/47, 31.9% Placebo 6/50, 12% |

| Table 3.7 continued: Chronic tension-type headache; Randomised control trials of preventative measures | | | | | |
|---|--|--|--|--|--|
| Reference Trial design | Groups | Total no. of subjects | Outcome measures | Duration of trial | Findings |
| Soderberg et al. (2006) Open label, Parallel | Acupuncture (17) Physical training (19) Relaxation training (19) | N=90 D=10(3M) C=89% D=34(6M) C=62% | Headache intensity Headache free days | 4 weeks 3 & 6 month follow-up | Headache intensity No SSD Acupuncture and physical training 33% Relaxation 42% Headache frequency No SSD Acupuncture 1.5%, physical training 20%, relaxation 20% |
| Kiran et al. (2005) Open label, Parallel | Alprazolam (190) Alprazolam and autogenic relaxation (190) | N=380 D= not mentioned | VAS Frequency Duration Headache index | 6 months | Intensity Alprazolam 18% No SSD Autogenic relax 83%* Frequency Alprazolam 20% NO SSD Autogenic relax 80%* Duration Alprazolam 9% No SSD Autogenic relax 81%* Headache index Alprazolam 25% No SSD Autogenic relax 95%* Complete relief Alprazolam 35/190, 18% No SSD Autogenic relax 150/190, 79%* |

| Table 3.7 continued: Chronic tension-type headache; Randomised control trials of preventative measures | | | | | |
|---|---------------------------------------|----------------------------------|---|------------------------------|---|
| Reference Trial design | Groups | Total no. of subjects | Outcome measures | Duration of trial | Findings |
| Padberg et al. (2004) DB, Placebo, Parallel | Botox (19) Saline (21) | N=40 D=0 | VAS Duration | 12 weeks | Days headache No SSD Botox 13%/ Saline 5% Duration No SSD Botox 17%/ Saline 8% Days analgesia No SSD Botox 21%/ Saline 13% |
| Schulte-Mattler et al. (2004) DB, Placebo, Parallel | Botox (53) Saline (54) | N=112 D=5 C=96% | Pain severity Duration Sleep, BDI | 12 weeks | 50% reduction headache days No SSD Botox 4/53, 7.5% Placebo 6/54, 11.1% |
| Bendtsen & Jensen (2004) DB, Placebo, Cross over | Mirtazapine 30mg (22) Placebo (22) | N=24 D=2 C=92% | AUC (intensity x duration) Frequency Duration Intensity | 22 weeks | Intensity x duration Mirtazapine 65% redn.* Placebo 10% increased Headache frequency Mirtazapine 9%* Placebo 0% Duration Mirtazapine 37%* Placebo 13% Intensity Mirtazapine 13%* Placebo 10% |

| Table 3.7 continued: Chronic tension-type headache; Randomised control trials of preventative measures | | | | | |
|---|---|----------------------------------|---|------------------------------|---|
| Reference Trial design | Groups (N) | Total no. of subjects | Outcome measures | Duration of trial | Findings |
| Boz et al. (2003) Open label, parallel | Sertraline 50mg (41) Amitriptyline 25mg (43) | N= 90 D=6 C=93% | VAS Frequency Duration Headache index Drug consumption | 16 weeks | Intensity reduction Amitriptyline 43%*/ sertraline 20%* Frequency reduction Amitriptyline 36%*/ sertraline 21%* Duration Amitriptyline 37%*/ sertraline 22%* Headache index Amitriptyline 70%*/ sertraline 44%* Drug consumption Amitriptyline 38%*/ sertraline 5.2% >50% reduction HI Amitriptyline 31/43*, 72%/ sertraline 18/44*, 44% |
| Singh & Misra (2002) DB, Placebo, Parallel | Sertraline 100mg (25) Placebo (25) | N=60 D=10 C=83% | Severity of headache Headache index | 10 weeks | >50% improvement HI No SSD Sertraline 9/25, 36%/ Placebo 2/25, 8% Analgesic intake Sertraline, 75%*/ Placebo 26% |
| Schmitt (2001) DB, Placebo, Parallel | Botox (28) Saline (24) | N=60 D=3 C=98% | Pain intensity Number of headache free days Analgesic intake | 12 weeks | Pain Intensity No SSD Botox A 23 % Saline 26% Monthly intake analgesics No SSD |

| Table 3.7 continued: Chronic tension-type headache; Randomised control trials of preventative measures | | | | | |
|---|--|----------------------------------|--|-----------------------------------|--|
| Reference Trial design | Groups (N) | Total no. of subjects | Outcome measures | Duration of trial | Findings |
| Holroyd (2001) Open label, Placebo, Parallel | Amitriptyline (53) Stress management (SM) (49) Combination amitriptyline and SM (53) Placebo (48) | N=203 D=59 (6M) C=71% | Headache index scores Days moderate pain Analgesic medication Headache disability | 2 months treatment 6 months | Pain intensity >50% reduction 1 month Amitriptyline & SM 34/53, 64%* > Amitriptyline 20/53, 38% = SM 17/49, 35% = Placebo 14/48, 29% 6 months follow-up pain intensity No SSD Amitriptyline + RT 33% = RT 33% = Amitriptyline 33% |
| Ribeiro (2000) DB, Placebo, Parallel | L-5-hydroxytryptophan (34) Placebo (31) | N=75 D=13 C=83% | Frequency of headache | 12 weeks | No. days headache end of study No SSD Placebo 29.2% / L5HTP 35.7 % No. days HA 2 weeks follow up HTP 55% / Placebo 27.2% |
| Murros et al. (2000) DB, Placebo, Parallel | Tizanidine 6mg (56) Tizanidine 12 mg (49) Placebo (55) | N=185 D=25 C=86% | Pain intensity Duration of headache | 8 weeks | Pain intensity No SSD Tizanidine 6mg 53% Tizanidine 12mg 48% Placebo 52% % days headache free No SDD Tizanidine 6mg 28% Tizanidine 12mg 18% Placebo 12% |

| Table 3.7 continued: Chronic tension-type headache; Randomised control trials of preventative measures | | | | | |
|---|---|----------------------------------|--|------------------------------|--|
| Reference Trial design | Groups | Total no. of subjects | Outcome measures | Duration of trial | Findings |
| Bendtsen and Jensen (2000) DB, Placebo, Cross over | Amitriptyline 75mg (33) Citaloprim 20 (33) Placebo (33) | N=40 D=7 C=83% | Headache intensity Myofascial tenderness | 32 weeks | Intensity x frequency Amitriptyline 30%* Citaloprim 12% 30% reduction of AUC Amitriptyline 19/33* |
| Walker et al. (1998) SB, Parallel | Desipramine 75mg (13) Fluoxetine 20mg (12) | N=37 D=12 C=68% | Pain rating scale Anxiety and depression | 12weeks | Intensity VAS Fluoxetine =desipramine = 36% reduction |
| Mitsikostas et al. (1997) Open label, Parallel | Buspirone30 mg (22) Amitriptyline 50mg (27) | N=49 D=9 C=82% | Days headache/month Frequency drugs | 12 weeks | >50% reduction Headache index No SSD Amitriptyline 65.6% versus Buspirone 54% |
| Bendtsen et al. (1996b) DB, Placebo, Cross over | Amitriptyline 75mg (34) Citaloprim 20mg (34) Placebo (34) | N=40 D=7 C=85% | AUC (intensity x duration) | 32 weeks | Intensity x duration Amitriptyline 37%* > placebo 10% & citaloprim 12% Headache frequency Amitriptyline 25%* Headache intensity No SSD |
| Shukla et al. (1996) DB, Placebo, Cross over | Alprazolam 0.25 (48) Placebo (48) | N=62 D=14 C=77% | Headache frequency/week Headache index | 4 months | Headache index Alprazolam 53%*/ Placebo 40% Reduction in Headache index >50% Alprazolam 20/48, 42%*/ Placebo 10/48, 21% |

| Table 3.7 continued: Chronic tension-type headache; Randomised control trials of preventative measures | | | | | |
|---|---|----------------------------------|---|------------------------------|---|
| Reference Trial design | Groups (N) | Total no. of subjects | Outcome measures | Duration of trial | Findings |
| Pfaffenrath et al. (1994) DB, Placebo, Parallel | Amitriptyline 75mg (67) Amitriptyline-oxide 90mg (66) Placebo (64) | N=197 D=48 C=76% | Primary end point 50% reduction in product duration in hours and days of headache and reduction 50% headache intensity (VAS) 50% reduction headache intensity times duration | 16 weeks | Duration No SSD Amitriptyline 30 % Amitriptylinoxide 36% Placebo 33.3% Intensity No SSD Amitriptyline 24% Amitriptylinoxide 28% Placebo 50% Frequency No SSD Amitriptyline 6% Amitriptylinoxide 6% Placebo increased 7% Duration x intensity No SSD Amitriptylinoxide 30% Amitriptyline 22.4% Placebo 22% >50 % intensity x duration No SSD Amitriptylinoxide 39%, Amitriptyline 25% Placebo 27% |

| Table 3.7 continued: Chronic tension-type headache; Randomised control trials of preventative measures | | | | | |
|---|---|----------------------------------|--|------------------------------|---|
| Reference Trial design | Groups | Total no. of subjects | Outcome measures | Duration of trial | Findings |
| Gobel et al. (1994) DB, Placebo, Parallel | Amitriptyline 75mg (24) Placebo (29) | N=78 D=25 C=68% | Headache duration | 6 weeks | Duration Amitriptyline 29%* placebo 3% reduction |
| Langemark & Olesen (1994) DB, Cross over | Paroxetine 20-30mg (37) Sulpiride 200-400mg (37) | N=50 D=13 C=74% | Headache intensity Analgesic intake | 8 weeks | Headache intensity >50% reduction No SSD Sulpiride 7/24, 29% Paroxetine 6/24, 25% |
| Fogelholm and Murros (1992) DB, Placebo, Cross over | Tizanidine up to 18mg day (37) Placebo (37) | N=45 D=8 C=72% | VAS Verbal rating scale Number of days free headache Analgesic consumption | 14 weeks | Intensity VAS Tizanidine 50% Placebo 25% Increased headache free days Tizanidine 15.4% Placebo 8.7 % |

The number of participants in the trials varied from 18 (Bettucci, et al., 2006) to 380 (Kiran, et al., 2005). Thirteen trials reported less than 50 participants (Bendtsen & Jensen, 2000, 2004; Bendtsen, et al., 1996b; Bettucci, et al., 2006; Fogelholm & Murros, 1992; Langemark & Olesen, 1994; Lindelof & Bendtsen, 2009; Mitsikostas, et al., 1997; Padberg, et al., 2004; Shukla, et al., 1996; Walker, Walker, Robertson, & Stansfeld, 1998; Wang, et al., 2007; Yurekli, et al., 2008), seven trials reported 50 to 100 participants (Bendtsen, et al., 2007; Boz, et al., 2003; Gobel, et al., 1994; Ribeiro, 2000; Schmitt, Slowey, Fravi, Weber, & Burgunder, 2001; Singh & Misra, 2002; Soderberg, et al., 2006), three trials reported between 100 and 200 participants (Murros, et al., 2000; Pfaffenrath, et al., 1994; Schulte-Mattler & Krack, 2004), two trials over 200 participants (Holroyd, et al., 2001; Silberstein, et al., 2006) and one trial between 300 and 400 participants (Kiran, et al., 2005).

Many of the CTTH studies did not show the workings for the minimum number of participants required for the study (Bettucci, et al., 2006; Boz, et al., 2003; Kiran, et al., 2005; Ribeiro, 2000; Schmitt, et al., 2001; Silberstein, et al., 2006; Singh & Misra, 2002; Soderberg, et al., 2006; Wang, et al., 2007; Yurekli, et al., 2008). However several studies did provide sample size calculations which included 5% significance levels and 80% power to determine the number of participants required for the trial (Bendtsen, et al., 2007; Lindelof & Bendtsen, 2009; Padberg, et al., 2004; Schulte-Mattler & Krack, 2004). The standard deviation of the primary measure used to calculate sample size varied from 30% (Bendtsen, et al., 2007) to 40% (Lindelof & Bendtsen, 2009). A 20% to 30% reduction in the primary measurement was often used as a measure of efficacy when performing calculations of participants required in the study (Bendtsen, 2000; Bendtsen & Jensen, 2004; Lindelof & Bendtsen, 2009).

A variety of methods of randomisation were performed in the RCTs for the prevention of CTTH including block randomisation (Bendtsen, et al., 2007; Bendtsen & Jensen, 2004; Bendtsen, et al., 1996b; Lindelof & Bendtsen, 2009; Pfaffenrath, et al., 1994; Schulte-Mattler & Krack, 2004), computerised random number generator (Bettucci, et al., 2006; Murros, et al., 2000) and in the majority of trials the method of randomisation was not

stated (Bendtsen, et al., 2007; Bendtsen & Jensen, 2000; Bendtsen, et al., 1996b; Boz, et al., 2003; Fogelholm & Murros, 1992; Gobel, et al., 1994; Holroyd, et al., 2001; Kiran, et al., 2005; Langemark & Olesen, 1994; Mitsikostas, et al., 1997; Padberg, et al., 2004; Silberstein, et al., 2006; Singh & Misra, 2002; Walker, et al., 1998; Wang, et al., 2007; Yurekli, et al., 2008). Three trials mentioned using sealed envelopes but did not mention how participants were randomised to the groups (Schmitt, et al., 2001; Shukla, et al., 1996; Soderberg, et al., 2006).

The duration of trials varied from 8 weeks (Murros, et al., 2000) to 32 weeks (Bendtsen & Jensen, 2000; Bendtsen, et al., 1996b) with 15 of the 26 trials being of 12 weeks duration or less (Bendtsen, et al., 2007; Bettucci, et al., 2006; Langemark & Olesen, 1994; Lindelof & Bendtsen, 2009; Mitsikostas, et al., 1997; Murros, et al., 2000; Padberg, et al., 2004; Ribeiro, 2000; Schmitt, et al., 2001; Schulte-Mattler & Krack, 2004; Silberstein, et al., 2006; Singh & Misra, 2002; Walker, et al., 1998; Wang, et al., 2007; Yurekli, et al., 2008).

Intervention studies of CTTH used several measures as the primary measure including headache intensity (Kiran, et al., 2005; Padberg, et al., 2004), intensity multiplied by duration (Bendtsen, et al., 2007; Lindelof & Bendtsen, 2009) and number of days free of TTH (Silberstein, et al., 2006). Headache intensity was the most common primary measure employed in 14 (Bendtsen, 2000; Boz, et al., 2003; Fogelholm & Murros, 1992; Kiran, et al., 2005; Langemark & Olesen, 1994; Murros, et al., 2000; Padberg, et al., 2004; Schmitt, et al., 2001; Schulte-Mattler & Krack, 2004; Singh & Misra, 2002; Soderberg, et al., 2006; Walker, et al., 1998; Wang, et al., 2007; Yurekli, et al., 2008) of the 26 RCTs for CTTH.

All RCTs of CTTH (Table 3.7) required patients to fill in headache diaries. Headache diaries commonly included a measure of headache intensity such as the Visual Analogue Scale (VAS) (Bendtsen & Jensen, 2000, 2004; Boz, et al., 2003; Fogelholm & Murros, 1992; Kiran, et al., 2005; Murros, et al., 2000; Padberg, et al., 2004; Pfaffenrath, et al., 1994; Soderberg, et al., 2006; Wang, et al., 2007; Yurekli, et al., 2008), Numerical Pain Rating Scale (NPRS) (Bendtsen, et al., 1996b; Holroyd, et al., 2001; Mitsikostas, et al., 1997; Silberstein, et al., 2006; Walker, et al., 1998) or Verbal Rating Scale (Bettucci, et al.,

2006; Langemark & Olesen, 1994; Lindelof & Bendtsen, 2009; Ribeiro, 2000; Schulte-Mattler & Krack, 2004; Shukla, et al., 1996; Singh & Misra, 2002). Schmitt et al. (2004) used the West Haven-Yale Multidimensional Pain Inventory. Frequency of TTH and number of hours experienced per day were another two common diary entries (Kiran, et al., 2005; Padberg, et al., 2004; Soderberg, et al., 2006). One trial did not measure headache intensity (Gobel, et al., 1994).

Randomised control trials for the prevention of CTTH (Table 3.7) often had a baseline diary period before the intervention of either two week (Murros, et al., 2000; Ribeiro, 2000) or four week duration (Bettucci, et al., 2006; Padberg, et al., 2004). The duration for 15 of 26 trials for CTTH (Table 3.7) was 12 weeks or less including the baseline diary. Typically studies had a baseline and follow-up period where diaries were completed. Data from the treatment period was often subtracted from the baseline to obtain a measure of change. Several studies (Bendtsen, et al., 2007; Bettucci, et al., 2006; Schmitt, et al., 2001; Silberstein, et al., 2006) collected one month baseline diary followed by two month diary collection and compared the three different periods (Month 1 to baseline, Month 2 to baseline and Month 3 to baseline). Some studies used shorter baselines and follow-up (Murros, et al., 2000; Soderberg, et al., 2006) and only two parallel group studies performed long term follow-up after the RCT intervention period (Boz, et al., 2003; Holroyd, et al., 2001; Kiran, et al., 2005; Soderberg, et al., 2006).

Depression has been measured in trials of CTTH by the Hamilton Depression Rating Scale (Walker, et al., 1998) and Beck Depression Inventory (BDI) (Fogelholm & Murros, 1992; Murros, et al., 2000; Schulte-Mattler & Krack, 2004). Scales of depression were utilised to either screen patients with significant depression (Schulte-Mattler & Krack, 2004) or to examine depression pre-post intervention (Fogelholm & Murros, 1992; Murros, et al., 2000; Schulte-Mattler & Krack, 2004; Walker, et al., 1998). Headache disability has been measured in very few trials of CTTH e.g. Holroyd et al. (2001).

Several trials for prevention of CTTH (Bendtsen, et al., 2007; Bendtsen & Jensen, 2004; Bendtsen, et al., 1996b; Bettucci, et al., 2006; Fogelholm & Murros, 1992; Gobel, et al., 1994; Holroyd, et al., 2001; Kiran, et al., 2005; Lindelof & Bendtsen, 2009; Padberg, et al.,

2004; Pfaffenrath, et al., 1994; Ribeiro, 2000; Schmitt, et al., 2001; Schulte-Mattler & Krack, 2004; Silberstein, et al., 2006; Soderberg, et al., 2006; Walker, et al., 1998; Wang, et al., 2007; Yurekli, et al., 2008) used statistical tests such as independent samples *t*-test or Mann-Whitney U and Wilcoxon signed tests to test for statistically significant differences between the final and initial data between the placebo and intervention groups or two intervention groups when placebo was not used. Two trials used repeated measures ANOVA statistical analysis for improvement of headache parameters (Boz, et al., 2003; Murros, et al., 2000).

The handling of missing data and exclusion of data in preventative trials for CTTH included exclusion of missing data (Bendtsen, et al., 2007; Bendtsen & Jensen, 2004; Fogelholm & Murros, 1992; Lindelof & Bendtsen, 2009; Schmitt, et al., 2001), not mentioning how missing data was handled (Bendtsen & Jensen, 2000; Bendtsen, et al., 1996b; Bettucci, et al., 2006; Kiran, et al., 2005; Langemark & Olesen, 1994; Mitsikostas, et al., 1997; Murros, et al., 2000; Pfaffenrath, et al., 1994; Shukla, et al., 1996; Singh & Misra, 2002; Wang, et al., 2007; Yurekli, et al., 2008) while one RCT mentioned intention to treat methodology but there was no mention of how missing data was actually handled (Silberstein, et al., 2006). Certain trials did not explicitly describe the handling of missing data but stated analysis was performed using SPSS (Boz, et al., 2003; Gobel, et al., 1994; Padberg, et al., 2004; Ribeiro, 2000; Schulte-Mattler & Krack, 2004; Walker, et al., 1998). Intention to treat with last measure carried forward was implemented in one study (Soderberg, et al., 2006) with the assumption that there was no change for non completers while another study (Holroyd, et al., 2001) imputed both the last measure carried forward and performed a sensitivity test with imputing the average final figure for the group allocation, finding no significant differences in outcomes from using the two methods.

The number of participants completing RCTs varied from 62% (Soderberg, et al., 2006) to 100% (Bettucci, et al., 2006; Padberg, et al., 2004). The loss of participants to follow-up increased with increasing length of time to follow-up in the trial by Sodeberg et al. (2006). The three month follow-up rate was 89% and the six month follow-up rate was 62%.

Amitriptyline has been the most consistently effective preventative medication for CTTH. Bendtsen et al. (1996b) found a 37% reduction in headache index for amitriptyline compared to 10% for placebo. Bendtsen et al. (2000) reported amitriptyline reduced headache index by 30% that was statistically significant compared to placebo (percentage reduction not reported). Gobel et al. (1994) showed a reduction in duration of headache (29%) but no reduction in analgesic consumption at six weeks. Other trials reported a reduction in headache frequency of 60% (Bettucci, et al., 2006) and reduction of headache index of 65% (Mitsikostas, et al., 1997). However in the largest trial (197 participants) looking at the effectiveness of amitriptyline, when measuring responder rate (50% reduction of headache index) the placebo response was 27% compared to amitriptyline response of 25% (Pfaffenrath, et al., 1994) with no statistically significant difference between groups.

Other antidepressants have on the whole been found to be less effective than amitriptyline. Mirtazapine was found to have some benefit (9% reduction in headache frequency, 37% reduction in headache duration and 13% reduction in headache intensity) for CTTH in a small study of 20 participants (Bendtsen & Jensen, 2004) but a larger study (Bendtsen, et al., 2007) of 84 participants found no benefit over placebo. Desipramine and fluoxetine showed a 36% reduction in pain intensity (Walker, et al., 1998) while citaloprim (Bendtsen, et al., 1996b) was found to be ineffective in the treatment of CTTH.

Valproic acid, an anticonvulsant, did not improve pain intensity but did improve frequency of headache by 55% (Yurekli, et al., 2008). Buspirone, an anxiolytic, was shown to be effective (54% achieved a 50% reduction of headache index) but less effective than amitriptyline (66% achieved a 50% reduction of headache index) (Mitsikostas, et al., 1997). Alprazolam reduced headache index by 53%, and 42% of participants in the alprazolam group achieved a 50% reduction in headache index (Shukla, et al., 1996) and in another study alprazolam achieved a 25 % reduction in headache index (Kiran, et al., 2005). Memantine (Lindelof & Bendtsen, 2009), L-5-hydroxytryptophan (Ribeiro, 2000) and tizanidine (Murros, et al., 2000) were all found not to be superior to placebo. Interestingly tizanidine reduced headache intensity by 53% while placebo reduced headache intensity by

52%, a higher than usual placebo response. The authors concluded that the unexpectedly strong placebo response “supported the view that psychophysiological mechanisms are of considerable importance in sustaining CTTH” (Murros, et al., 2000).

Preventative treatment aimed at the muscles using acupuncture, electro-acupuncture and botulinum toxin have been reported for CTTH (Table 3.7). In several trials of botulinum toxin (Padberg, et al., 2004; Schmitt, et al., 2001; Schulte-Mattler & Krack, 2004; Silberstein, et al., 2006), it was demonstrated that botulinum toxin injections provided no more effective treatment than placebo for CTTH (Table 3.7). Electro-acupuncture was no more effective than sham acupuncture (Wang, et al., 2007) and when tested against relaxation therapy and physical training, acupuncture was not statistically different with headache frequency reducing approximately 20% with relaxation therapy and physical training while reducing only 1.5% in the acupuncture group. The lack of effect of treatment aimed at muscles may give an indication that the phenomenon of myofascial tenderness does not cause headache pain but is a coincidental finding.

A study of autogenic relaxation (Rajyoga meditation) combined with alprazolam versus alprazolam alone with 380 people (Kiran, et al., 2005) found that 150/190 (79%) of the autogenic relaxation group versus 35/190 (18%) in the alprazolam only group obtained complete relief of their headache.

In summary the 26 trials identified for the prevention of CTTH has shown that RCT study design has been either cross over or parallel group design. Most RCTs of medications (both tablet and injections) were double blind and most non pharmaceutical RCTs were single blind (participant being blind to allocation) or open. The duration of most parallel group trials was of 12 week duration. The primary outcome measure varied in trials with headache intensity being the most common with number of days headache and headache index also being used as primary outcome measures in RCTs. Participant numbers were less than 50 in half the trials identified. Randomisation methods and handling of missing data was not mentioned in the majority of RCTs. Most studies analysed differences of outcome between groups from the final to the initial period.

Overall there is a paucity of RCTs on which to base management for the prevention of CTTH, furthermore the effectiveness of interventions trialed for CTTH in 16 of the 26 RCT studies had no statistically significant difference between the active treatment and control/placebo. Ten trials showed efficacy for the prevention of CTTH. One small trial of tizanidine (Fogelholm & Murros, 1992) had positive results while in a larger trial tizanidine was shown to be no better than placebo (Murros, et al., 2000). Three smaller trials of amitriptyline versus placebo (Bendtsen & Jensen, 2000; Bendtsen, et al., 1996b; Gobel, et al., 1994) with a total of 112 participants showed a positive result while the largest placebo control trial of amitriptyline (Pfaffenrath, et al., 1994) with 197 participants showed amitriptyline to be no better than placebo. In one trial (Holroyd, et al., 2001) amitriptyline was shown to be no different to relaxation therapy at one and six months. Five medication trials (Bettucci, et al., 2006; Boz, et al., 2003; Langemark & Olesen, 1994; Mitsikostas, et al., 1997; Walker, et al., 1998) showed a positive result and did not use a placebo. The placebo response has been shown to have an effect of over 50% (Murros, et al., 2000) in reducing outcome measures rendering the five medication trials not using a placebo to be inconclusive. This leaves the trial of autogenic meditation which is a large trial of 380 participants having positive effects as the most successful management strategy for the prevention of CTTH.

3.7.2 Responder rate for clinical trials for the prevention of CTTH

Nine of the 26 studies of CTTH (Table 3.7) reported the percentage of participants achieving a 50% reduction (responder rate) using a variety of outcome measures (frequency x severity, frequency x duration x intensity, mean VAS, days with headache/month) and are shown in Table 3.8. Two studies reported the percentage of participants achieving a 50% reduction in number of headache days (Mitsikostas, et al., 1997; Silberstein, et al., 2006). Silberstein et al. (2006) found botulinum toxin provided approximately 30% of participants a 50% reduction in headache days per month. Amitriptyline 50 mg and buspirone 30 mg (Mitsikostas, et al., 1997) achieved a greater than 50% reduction in number of days headache per month in 61% and 54% of participants respectively.

| Reference | Treatment including placebo | No. of participants responding | Measure | >=50% reduction |
|-------------------------------|--|---------------------------------------|--------------------------------------|---------------------------|
| Silberstein et al. (2006) | Botox A 100U | 15/47 | Headache days | 31.9% |
| | Botox Usub 100 U | 15/49 | Headache days | 30.6% |
| | Botox Usub 86U | 15/47 | Headache days | 31.9% |
| | Placebo | 6/50 | Headache days | 12% |
| Kiran et al. (2005) | Alprazolam 0.25bd combined with autogenic relaxation | 150/190 | Frequency x severity | 79% |
| | Alprazolam 0.25bd | 35/190 | Frequency x severity | 18% |
| Schulte-Mattler et al. (2004) | Botox 500U | 4/53 | Duration x intensity | 7.5% |
| | Placebo | 6/54 | Duration x intensity | 11.1% |
| Boz et al. (2003) | Amitriptyline 25mg | 31/43 | Frequency x duration x intensity | 72% |
| | Sertraline 50mg | 18/44 | Frequency x duration x intensity | 44% |
| Singh and Misra (2002) | Sertraline 100mg | 9/25 | Frequency x duration x intensity | 36% |
| | Placebo | 2/25 | Frequency x duration x intensity | 8% |
| Holroyd et al. (2001) | Amitriptyline 75mg & stress management | 34/53 | Mean VAS | 64% |
| | Amitriptyline 75mg | 20/53 | Frequency x duration x intensity | 38% |
| | Stress management | 17/49 | Mean VAS | 35% |
| Mitsikostas et al. (1997) | Amitriptyline 50mg | 17/28 | Days with headache/month | 61% |
| | Buspirone 30 mg | 12/22 | Days with headache/month | 54% |
| Shukla et al. (1996) | Alprazolam 0.25tds | 20/48 | Frequency x duration x intensity | 42% |
| | Placebo | 10/48 | Frequency x duration x intensity | 21% |
| Pfaffenrath et al. (1994) | Amitriptyline-oxide 90mg | 26/66 | Frequency x duration x intensity | 39% |
| | Amitriptyline 75mg | 17/67 | Frequency x duration x intensity | 25% |
| | Placebo | 17/64 | Duration x frequency & 50% intensity | 27% |

Table 3.8 shows that only one trial (Mitsikostas, et al., 1997) achieved the desired efficacy of a preventative medication (Loder, 2008) which is reducing the desired outcome measure

of headache frequency by 50% in 50% of participants. The number of headache days per month reduced 61% with amitriptyline 50mg and 54% with buspirone 30mg. Two other trials showed a 50% reduction of headache index in over 50% of participants for autogenic relaxation (Kiran, et al., 2005) and amitriptyline 25mg (Boz, et al., 2003). Amitriptyline 75mg and stress management (Holroyd, et al., 2001) showed a 50% reduction of headache intensity for 50% of participants at one month after the trial began but the six month measures of responder rate were not reported.

3.7.3 Summary of preventative trials that include TTH, ETTH and CTTH participants

Along with the 26 RCT studies (Table 3.7) identified by the search parameters outlined in Table 3.6, a further 14 trials were identified that were not exclusively CTTH but included participants with mixed populations of TTH, ETTH and CTTH (Table 3.9). The trials date from 1995 (Boline, et al., 1995) to 2009 (Harden, et al., 2009) with between 21 (Rollnik, Tanneberger, Schubert, Schneider, & Dengler, 2000) and 126 (Boline, et al., 1995) participants. Two important historic clinical trials (Diamond & Baltes, 1971; Lance & Curran, 1964) were also found from reading the literature and are included in Table 3.9. Both of these trials do not use the International Headache Society criteria for CTTH (Olesen, 2006b) as they were performed before the term CTTH was defined but are the earliest studies of amitriptyline for TTH, hence are included in this summary. Thirteen of 16 RCTs (Boline, et al., 1995; Bove & Nilsson, 1998; D'Souza, Lumley, Kraft, & Dooley, 2008; Endres, et al., 2007; Harden, et al., 2009; Karakurum, et al., 2001; Karst, et al., 2001; Melchart, et al., 2005; Rollnik, et al., 2000; Straube, et al., 2008; van Etekenoven & Lucas, 2006; White, et al., 2000; Zissis, et al., 2007) were parallel group and three were cross over design (Diamond & Baltes, 1971; Lance & Curran, 1964; Torelli, Jensen, & Olesen, 2004).

The trials of pharmaceutical interventions used a placebo and most were double blind (Diamond & Baltes, 1971; Harden, et al., 2009; Rollnik, et al., 2000; Straube, et al., 2008; Zissis, et al., 2007). Trials of needling (acupuncture or dry needling) (Endres, et al., 2007; Karakurum, et al., 2001; Karst, et al., 2001; Melchart, et al., 2005; White, et al., 2000) all included a sham or minimal acupuncture group as a control and were single blind with the

participants not advised if they were the active intervention or sham intervention. Dropouts for the RCTs varied from 0% (Lance & Curran, 1964) to 34% (Zissis, et al., 2007).

Headache frequency was the most common primary measure employed by eight of the 14 RCTs that used the International Headache Society definition of cases (Endres, et al., 2007; Harden, et al., 2009; Melchart, et al., 2005; Straube, et al., 2008; Torelli, et al., 2004; van Ettekooven & Lucas, 2006; White, et al., 2000; Zissis, et al., 2007) while headache intensity was employed as the primary measure in five of the RCTs (Bove & Nilsson, 1998; D'Souza, et al., 2008; Harden, et al., 2009; Karst, et al., 2001; Rollnik, et al., 2000) and headache index was used as a primary measure in one RCT (Karakurum, et al., 2001).

Amitriptyline was found to be similar to placebo (Diamond & Baltes, 1971) and inferior to spinal manipulation four weeks after therapy stopped (Boline, et al., 1995). Boline et al. (1995) found spinal manipulation reduced frequency of headache by 32% and intensity by 39% while amitriptyline achieved 7% and 5% respectively four weeks after treatment stopped.

Venlafaxine showed an overall 21% reduction in headache frequency and approximately half of the participants achieved a 50% reduction in frequency while a third of the placebo group achieved a 50% reduction in frequency (Zissis, et al., 2007).

Botulinum toxin was not statistically superior to placebo in several studies (Harden, et al., 2009; Rollnik & Dengler, 2002; Rollnik, et al., 2000; Straube, et al., 2008). Harden et al. (2009) found 2/8, 25% of the botulinum toxin group and 4/10, 40% of the saline group achieved a 50% reduction in headache intensity. Rollnik et al. (2002) found botulinum toxin reduced headache intensity by 8% while placebo achieved a 17% reduction.

Acupuncture was not statistically superior to sham acupuncture (Endres, et al., 2007; Karst, et al., 2001; Melchart, et al., 2005; White, et al., 2000). Karst et al. (2001) found

| Table 3.9: Randomised control trials of preventative measures for TTH, ETTH and CTTH | | | | | |
|---|--|------------------------------|---|---|--|
| Reference | Groups (N) | Total no. of subjects | Outcome measures | Duration | Findings |
| Harden et al. (2009) Placebo, DB, parallel | Botox (12) Saline (11) | N=23 D=4 C=83% | VAS | 12 weeks | 50% reduction VAS No SSD Botox 2/8, 25% Saline 4/10, 40% |
| Straube et al. (2008) Placebo, SB, parallel, multicentre | TTH Botox 420U (28) Botox, 210U (33) Saline (62) | N=118 D=7 C=94% | Headache free days Pain intensity BDI | 12 weeks | All measures No SSD |
| D'Souza et al. (2008) Parallel | ETTH Written emotional disclosure (WED) (17) Relaxation training (RT) (17) | N=51 D=1 C=98% | Headache severity Headache frequency Headache disability | 12 weeks | RT>WED=Control RT 49%* reduction frequency 26%* reduction headache severity 76%* reduction headache disability |
| Zissis et al. (2007) Placebo, DB, parallel | TTH (>5 days month) Venlafaxine (34) Placebo (26) | N=60 D=20 C=66% | Frequency | 12 weeks | Frequency Venlafaxine 21%* Placebo 0% |
| Endres et al. (2007) Parallel | ETTH and CTTH Acupuncture Chinese (209) Sham (200) | N=409 D=11 C=97% | >50% reduction headache days | 6 weeks treatment 6 months follow-up | >50% reduction headache days Acupuncture 33% Sham 27% No SSD |
| Van Ettekovén & Lucas (2006) Parallel, SB | ETTH and CTTH Physiotherapy (42) Cranio-cervical training & Physiotherapy (39) | N=81 D=3 C=96% | Headache frequency Intensity QOL MHLC Multi-dimensional locus of control | 6 Weeks Follow up 6 months | At 6 months > 50% reduction frequency PT and cranio-cervical training 85%* Physiotherapy 35% 80-100% reduction frequency PT and Cranio-cervical training 48%* |

| Table 3.9 continued: Randomised control trials of preventative measures for TTH, ETTH and CTTH | | | | | |
|---|--|------------------------------|---|-----------------|--|
| Reference | Groups (N) | Total no. of subjects | Outcome measures | Duration | Findings |
| Melchart et al. (2005) Parallel, SB | ETTH and CTTH Acupuncture (132) Minimal acupuncture (63) Wait list (75) | N=270 D=26 C=90% | Number of days headache | 16 weeks | >50% reduction headache days Acupuncture 46% = Minimal acupuncture 35% Wait list 4% No SSD No. days headache No SSD Acupuncture 43% = Minimal acupuncture 39% Wait list 6% Hours headache No SSD Acupuncture 43% = Minimal acupuncture 34% Wait list 3% Analgesic intake No SSD Acupuncture 53% = Minimal acupuncture 38% Wait list 6% |
| Torelli et al. (2004) Cross over | CTTH, ETTH & TTH Physiotherapy (50) Observation (50) Cross over design | N=50 D=13 C=74% | Headache frequency Headache duration Pain intensity | 32 weeks | Headache frequency 14/48, 29% > 50% reduction Pain intensity, duration and analgesic use no change |
| Karakurum et al. (2001) Parallel, SB | TTH,ETTH,CTTH Dry Needling (15) Subcutaneous needling (15) | N=30 D= not mentioned | Headache index | 6 weeks | Headache index No SSD Subcutaneous needling 57% Dry needling 64% |

| Table 3.9 continued: Randomised control trials of preventative measures for TTH, ETTH and CTTH | | | | | |
|---|---|---|--|------------------------------|--|
| Reference | Groups (N) | Total no. of subjects | Outcome measures | Duration | Findings |
| Karst et al. (2001) Placebo, parallel, SB | TTH Acupuncture (34) Placebo (35) | N=69 6W D=8 C=88% 6M D=14 C=80% | Pain intensity | 6 weeks 5 month follow-up | Frequency per month No SSD Acupuncture 16% Placebo 21% VAS No SDD Acupuncture 25% Placebo 31% |
| Rollnik et al. (2000) Placebo, DB, parallel | TTH Botox A (10) Placebo (saline) (11) | N=21 D=0 C=100% | Pain intensity Frequency Duration of headaches | 12 weeks | VAS No SDD Botulinum 8% Placebo (saline) 16.5% Frequency No SDD Botulinum 10.3 Placebo (saline) 0.5% |
| White et al. (2000) Parallel, multicentre | ETTH Acupuncture (25) Sham control (25) | N=50 D=14 C=72% | Number of days with headache | 12 weeks | Days with headaches No SSD Acupuncture 40% Sham 36% Duration of headache No SSD Acupuncture 40% Sham 36% Severity of headache No SSD Acupuncture 22% Sham 10% |

| Table 3.9 continued: Randomised control trials of preventative measures for TTH, ETTH and CTTH | | | | | |
|---|--|------------------------------|---|--|---|
| Reference | Groups | Total no. of subjects | Outcome measures | Duration | Findings |
| Bove & Nilsson (1998) Parallel, SB | ETTH Soft tissue & spinal manipulation (38) Soft tissue & placebo laser (37) | N=75 D=27 C=64% | Pain intensity Duration/day Daily analgesic use | 19 weeks | Daily hours headache No SSD Manipulation 45% Placebo laser 44% Analgesic consumption No SSD Manipulation 42% Placebo laser 28% Pain intensity No SSD Manipulation 5% Placebo laser 30% |
| Boline et al. (1995) Parallel | TTH Amitriptyline (56) Spinal manipulation (70) | N=150 D=24 C=84% | Intensity Frequency OTC medications SF36 health status | 6 weeks treatment Follow up 4 weeks later | 6 weeks No SSD Spinal manipulation = amitriptyline 4 weeks after treatment Frequency Manipulation 32%* Amitriptyline 7% Intensity Manipulation 39%* Amitriptyline 5% |
| Diamond & Baltes (1971) Cross over | TTH Amitriptyline 10 (30) Amitriptyline 25 (30) Placebo (30) | N=90 D=33 C=63% | Patient rating scale headache | 4 weeks | Patient rating scale headache Amitriptyline 10 = amitriptyline 25 = placebo No SSD at 4 weeks |
| Lance & Curran (1964) Cross over | ETTH and CTTH 27 in each group | N=27 D=0 C=100% | Self report | 8 weeks | Self report Amitriptyline 34%* substantially improved compared to placebo |

acupuncture reduced headache frequency by 16% while placebo achieved a 21% reduction in headache frequency. Pain intensity also reduced 25% in the acupuncture group and 31% in the placebo group. A study of subcutaneous dry needling (similar to acupuncture) found subcutaneous needling achieved a 57% reduction in headache index and deep muscle needling achieved a 64% reduction in headache index (Karakurum, et al., 2001). Physiotherapy provided 29% of participants a greater than 50% reduction in symptoms compared to an observation group (Torelli, et al., 2004). Physiotherapy and craniocervical training achieved a 50% reduction in headache frequency in 85% of participants while physiotherapy achieved 50% reduction in headache frequency in 35% of participants (van Ettekooven & Lucas, 2006).

In ETTH spinal manipulation (45% reduction duration, 42% reduction analgesic consumption, 5% reduction pain intensity) was as effective as placebo laser (44% reduction duration, 28% reduction analgesic consumption, 30% reduction pain intensity) (Bove & Nilsson, 1998) while relaxation training provided a 49% reduction in frequency of headache (D'Souza, et al., 2008).

The preventative studies of mixed TTH show that any form of needling may have some benefit in CTTH with subcutaneous needling having similar effect to deep muscle needling (Karakurum, et al., 2001) and there are no advantages in injecting botulinum toxin over normal saline (Harden, et al., 2009; Rollnik & Dengler, 2002; Rollnik, et al., 2000; Straube, et al., 2008). Craniocervical training had impressive results (van Ettekooven & Lucas, 2006) with 85% of participants achieving a 50% reduction in headache frequency with a possible explanation being that cervicogenic headache may be difficult to separate from TTH as treatment of the neck gave excellent results for those suffering from TTH.

3.7.4 Clinical trials for analgesia for acute episodes of TTH

Analgesic medications are taken to abort acute attacks of TTH. This section examines a selection of RCTs that represents the different analgesic medication types commonly available for TTH that are presented in Table 3.10. Participant numbers ranged from 40 (Cerbo, et al., 2005) to 5419 (Rabello, Forte, & Galvao, 2000). Studies looked at

improvement of headache pain intensity for between 90 minutes (Cady, Gutterman, Saiers, & Beach, 1997) and six hours (Diamond, Balm, & Freitag, 2000; Prior, Cooper, May, & Bowen, 2002) after taking analgesic medication. The different types of analgesic medication studied for the acute management of TTH include various nonsteroidal anti-inflammatory medications including ketoprofen (Mehlich, Weaver, & Fladung, 1998), indomethacin (Cerbo, et al., 2005), diclofenac (Kubitzek, Ziegler, Gold, Liu, & Ionescu, 2003), ibuprofen (Diamond, et al., 2000; Packman, et al., 2000), naproxen (Pini, et al., 2008) and aspirin (Steiner, Lange, & Voelker, 2003). In all six studies, it was shown that NSAIDS provide a statistically significant reduction in headache intensity compared to the placebo arm.

Sumatriptan (Cady, et al., 1997; Lipton, et al., 2000), acetaminophen (paracetamol) (Pini, et al., 2008; Prior, et al., 2002; Rabello, et al., 2000; Steiner, et al., 2003), and metamisol (Martinez-Martin, et al., 2001) were also trialled for TTH and had greater analgesic effect than placebo. Caffeine increased the analgesic effect in acute TTH when combined with ibuprofen (Diamond, et al., 2000) and paracetamol (Pini, et al., 2008; Rabello, et al., 2000).

In summary analgesic medication for TTH which has efficacy includes various non steroidal anti-inflammatories, paracetamol, sumatriptan and metamisol. Caffeine has been shown to increase analgesic effect when combined with paracetamol and ibuprofen. It is difficult to compare different analgesics tested in different trials due to the differing outcome measures in various trials such as the measurement of relief (e.g. meaningful improvement, complete relief, mean pain relief intensity) and number of hours to relief (e.g. 2 hours, 4 hours and six hours). In direct comparisons of medications in the same trial, different doses of diclofenac (12.5mg, 25mg) or ibuprofen (400mg) were equally effective (Kubitzek, et al., 2003), aspirin (500mg or 1000mg) and paracetamol (500mg or 1000mg) had similar efficacy (Steiner, 2000), paracetamol 1000mg had similar efficacy to naproxen 375mg (Prior, et al., 2002) and was less efficacious than ibuprofen 400mg (Schachtel, Furey, & Thoden, 1996). The mechanism of action of these analgesic medications will be examined further in section 5.3.1.

| Table 3.10: Clinical trials reporting acute analgesic treatment for episodes of TTH | | | | |
|---|--|------------------------------|--|--|
| Reference | Groups (N) | Total no. of subjects | Outcome measures | Results |
| Pini et al. (2008) Placebo, DB, cross over, multicentre | Acetaminophen 1000 & caffeine 130mg (99) Naproxen 500mg (99) Placebo (99) | 99 | Patient preference of improvement at 4 hours | Acetaminophen 1000 & caffeine 130mg 33%* Naproxen 500mg 45%* Placebo 23% |
| Hirata et al. (2007) DB, parallel, multicentre | Etizolam 0.5mg & mefanamic acid 250mg (72) Mefanamic acid 250mg (72) | 144 | Pain relief | Etizolam & mefanamic acid 61% Mefanamic acid 250mg 50% reduction No SSD |
| Cerbo et al. (2005) DB, parallel, multicentre | Combination indomethacin & prochlorpromazine & caffeine (Indoprocaf) (27) Nimesulide (NSAID) (27) | 54 | 50% reduction of pain at 2 hours | Indoprocaf 75% Nimesulide 30% No SSD |
| Kubitzek et al. (2003) Placebo, DB, parallel | Diclofenac 12.5 (160) Diclofenac 25 (156) Ibuprofen 400 (151) Placebo (153) | 620 | Improvement 2 hours | All > placebo but no difference between active drugs 72% >50% improvement 20% total relief |
| No SSD = No statistically significant difference; *Statistically significant result at $P < 0.05$. SB = single blind, DB= double blind IV = intravenous, IM = intramuscular | | | | |

| Table 3.10 continued: Clinical trials reporting acute analgesic treatment for episodes of TTH | | | | |
|--|---|------------------------------|---------------------------------------|---|
| Reference | Groups | Total no. of subjects | Outcome measures | Results |
| Steiner et al. (2003) Placebo, DB, parallel | Aspirin 500mg (111) Aspirin 1000mg (103) Paracetamol 500mg (105) Paracetamol 1000mg (111) Placebo (112) | N = 638 | Total or worthwhile relief at 2 hours | Aspirin 500mg 70%*, 1000mg 76%* Paracetamol 500mg 64%, 1000mg 71%* Placebo 55% |
| Prior et al. (2002) Placebo, DB, parallel, multicentre | Acetaminophen 1000 (321) Naproxen 375 (321) Placebo (321) | N = 963 | Improvement at 2 hours | Acetaminophen 36.8%* Naproxen 31.5%* Placebo 25.9% |
| Bigal et al. (2002) Placebo, DB, parallel, | TTH episode at Hospital ED IV chlorpromazine (30) Placebo IV saline (30) | N = 60 | 60 min pain free | IV chlorpromazine 83.3%* Placebo IV saline 26.7% |
| Martinez-Margin et al. (2001) Placebo, DB, parallel multicentre | Metamisol 0.5g (102) Metamisol 1g *108) Acetylsalicylic 1000mg (102) Placebo (105) | N = 417 | > 50% Pain intensity 4 hours | Metamisol 0.5g 71%* Metamisol 1g 74%* Acetylsalicylic acid 1000mg 69%* Placebo 52% |
| Lipton et al. (2000) Placebo, DB, crossover | Sumatriptan (249) Placebo (249) | N = 249 | Meaningful relief 4 hours | Sumatriptan 78%* Placebo 50% |

| Table 3.10 continued: Clinical trials reporting acute analgesic treatment for episodes of TTH | | | | |
|--|---|------------------------------|---|---|
| Reference | Groups | Total no. of subjects | Outcome measures | Results |
| Diamond et al. (2000) Placebo, DB, parallel, multicentre | Ibuprofen 400mg + caffeine 200mg (97) Ibuprofen 400mg (99) Caffeine 200mg (57) Placebo (48) | N = 301 | Meaningful improvement six hours | Ibuprofen + caffeine 80%* Ibuprofen 67%* Caffeine 61% Placebo 56% |
| Rabello et al. (2000) No placebo | Acetaminophen 1000mg and caffeine 130mg | N = 5490 | Complete relief 2 hours | 76%* |
| Packman et al. (2000) Placebo, DB, parallel | Soluble Ibuprofen 400mg (60) Acetaminophen 1000mg (62) Placebo (32) | N = 154 | Complete relief 3 hours | Soluble Ibuprofen 75%* Acetaminophen 32% Placebo 13% |
| Mehlich et al. (1998) Placebo, DB, parallel | Ketoprofen 12.5 (158) Ketoprofen 25 (156) Acetaminophen 1000 (166) Placebo (151) | N = 703 | Mean pain relief intensity absolute difference at 4 hours | Ketoprofen 25, 5.33* Ketoprofen 12.5, 5.23 Acetaminophen 1000, 5.01 Placebo, 4.75 - |

| Table 3.10 continued: Clinical trials reporting acute analgesic treatment for episodes of TTH | | | | |
|--|--|------------------------------|--|--|
| Reference | Groups | Total no. of subjects | Outcome measures | Results |
| Harden et al. (1998) Placebo, DB, parallel | TTH episode hospital setting Ketorolac IM 60mg (8) Meperidine 50mg + Promethazine (7) Placebo normal saline (6) | N = 30 | Pain relief at 1 hour | Ketorolac IM 60mg* Meperidine 50mg + Promethazine IM Normal saline IM |
| Cady et al. (1997) Multicentre longitudinal case series | Sumatriptan 6mg (43) | N = 43 | Improvement of headache 90 minutes | 97% responded to sumatriptan* |
| Schachtel et al. (1996) Placebo, DB, parallel | Ibuprofen 400mg (153) Acetaminophen 1000mg (151) Placebo (151) | N = 455 | Pain relief VAS at 4 hours | Complete relief 4 hours Ibuprofen 63%* Acetaminophen 1000mg 34%* Placebo 7% |
| Brennum et al. (1992) Placebo, DB, crossover | Sumatriptan subcutaneous inject 2mg and 4mg (36) Placebo injection (36) | N = 36 | At 2 hours pain much better or complete relief | Sumatriptan 2 mg 42%* Sumatriptan 4mg 33%* Placebo 8% |

3.8 Models of tension-type headache

3.8.1 Introduction

Muscle (myofascial) tenderness (Fernandez-de-la-pas-Penas, Cuadrado, Arendt-Nielsen, Simons, & Pareja, 2007), vasodilatation (M. Ashina, Bendtsen, Jensen, Sakai, & Olesen, 2000), and central nervous system sensitisation (Bendtsen, 2000) have all been associated with headache disorders. Myofascial tenderness has been proposed as the cause of central sensitisation while vasodilatation of blood vessels has been promoted as the pain producing entity in headache disorders.

3.8.2 Vasodilatation and headache

Vasodilatation has been the most widely disseminated theory on headache causation (Goadsby, 2005). The fact that glyceryl trinitrate (GTN), a drug prescribed to dilate blood vessels around the heart, caused headache as an adverse effect has perpetuated this theory (Empl & Giovannoni, 2003). Glyceryl trinitrate induced headache has served as a useful model to investigate headache disorders because GTN tablet preparations and infusions induce headache and migraine symptoms similar to that experienced by patients in everyday life (Christiansen, et al., 2000). Glyceryl trinitrate can induce headache in headache free volunteers (Christiansen, et al., 2000) and induce headache at a lower dose of GTN in CTTH patients than headache free controls (M. Ashina, Bendtsen, Jensen, & Olesen, 2000). Glyceryl trinitrate can induce attacks of cluster headache (Ekbom, Sjostrand, Svensson, & Waldenlind, 2004) and migraine (Christiansen, Thomsen, Daugaard, Ulrich, & Olesen, 1999).

Tolerance develops with nitrates and this was mapped against cerebral artery diameter and headache activity (Christiansen, et al., 2000). The middle cerebral artery vasodilatation did not show a temporal relationship with headache but the superficial temporal artery vasodilatation did show a temporal relationship with headache. The authors concluded that if vasodilatation is important in the development of headache, then it is the vasodilatation of the extra cerebral arteries that are important in its development.

Many studies however show no consistent relationship between headache and vasodilatation of the cerebral vessels. A study measuring vasodilatation of the cerebral and meningeal vessels by MRI scan showed no differences during headache or non headache periods when provoked by glyceryl trinitrate (Schoonman, van der Grond, Kortmann, & van der Geest, Ferarri, 2008). Other factors that contradict the vasodilatation theory of headache causation is that there is no consistent vasoconstriction that occurs after treatment of migraine pain with triptans (Gori, et al., 2005). Vasodilators such as vasointestinal protein (Rahmann, et al., 2008) did not induce migraine and sildenafil (Viagra) (Kruuse, Thomsen, Birk, & Olesen, 2003) provoked migraine without cerebral vasodilatation.

An intravenous infusion of GTN was performed in CTTH patients and headache free controls to check for sensitisation of myofascial tissues (M. Ashina, Bendtsen, Jensen, Sakai, et al., 2000). Measures taken in this study included muscle hardness, total tenderness score, pressure pain thresholds and heat pain thresholds. Measurements were taken before the infusion, at 60 minutes and 120 minutes after the infusion. It was observed that a more severe headache was induced in headache patients compared to the controls but there was no change in the sensitivity of the pericranial myofascial pain pathways. They concluded that peripheral and central sensitisation was not involved in the mechanisms of GTN induced immediate headache.

To test whether headache patients produced increased nitric oxide, the NO metabolite nitrite (NO_2^-) was measured in cluster headache patients and controls after administering GTN sublingually. The data did not support a basal hyperactivity of the nitric oxide system, and the increase in metabolites was similar in headache patients and controls (Costa, et al., 2003).

Glyceryl trinitrate leads to the production of nitrous oxide that causes the production of second messenger cGMP that leads to a reduction of intracellular calcium, leading to vasodilatation in smooth muscle (S. Yang & Cox, 2007). The Adrenaline Model of Headache Causation (Figure 5.3) proposes that cGMP simultaneously opens ion channels at

the sensory neurons leading to generation of action potentials in the pathways of nociception (section 4.2) to create co-incidental headache symptoms. Vasodilatation is co-incidental to the headache pain rather than causative.

3.8.3 Muscle tenderness and headache

Many studies have examined the relationship of muscle tenderness (S. Ashina, Bendtsen, Ashina, Magerl, & Jensen, 2006; S. Ashina, Jensen, & Bendtsen, 2003; Bendtsen & Jensen, 2000; R. Jensen, Bendtsen, & Olesen, 1998; R. Jensen, et al., 1993; Langermark & Olesen, 1987; Schoenen, Bottin, Hardy, & Gerard, 1991), sensory thresholds (S. Ashina, et al., 2003; Drummond, 1986), electrical thresholds (Bendtsen, Jensen, & Olesen, 1996a), mechanical nerve sensitivity (Fernandez-Mayoralas, Fernandez-de-la-pas-Penas, Ortega-Santiago, et al., 2010) and muscle contraction (Leistad, Sand, Westgaard, Nilsen, & Stovner, 2005) with headache disorders.

Pericranial muscle tenderness has been shown to be greater in headache patients compared to headache free controls (Drummond, 1987; R. Jensen, et al., 1998). Jensen et al. (1998) studied 29 participants with frequent ETTH, 29 participants with CTTH and 30 subjects that were headache free. An examiner blind to the subject diagnoses performed standardised examination to determine pericranial tenderness. Muscle tenderness was determined in nine pairs of pericranial muscles bilaterally and rated on an intensity scale from 0 to 3 where 0 is no pain and 3 is maximum tenderness. Subjects with ETTH (tenderness score =15.3) and CTTH (tenderness score =18.5) had significantly higher total tenderness scores than headache free controls (tenderness score =4.3). Drummond (1986) assessed pressure pain threshold in the forehead, temples, occiput and neck of 102 patients with migraine or TTH and 35 age and gender matched controls. Pressure pain threshold was reduced in headache and migraine patients compared to controls in the neck and scalp that persisted in the absence of headache symptoms. In patients experiencing unilateral symptoms, scalp tenderness was greater in the unilateral side with symptoms but was also present in the non affected side when compared to the control group.

Muscle tenderness however is not restricted to the head and neck and is found throughout the body (S. Ashina, et al., 2006; S. Ashina, et al., 2003; Schoenen, et al., 1991). The increased muscle tenderness may indicate a cause and effect relationship where the headache has caused muscle tenderness or muscle tenderness has caused headache, or as this PhD study proposes, both headache and muscle tenderness coexist due to a similar pathophysiology. If the muscle tenderness was a cause of pain then muscle tenderness would be expected to be found in the region of pain experience (pericranial) only and generalised muscle tenderness would be accompanied by generalised pain rather than headache pain alone.

In headache patients there is an increased sensitivity to several types of stimuli including pain, thermal, and electrical stimuli when compared to headache free controls. Studies found suprathreshold pain (S. Ashina, et al., 2006), thermal thresholds (Langermark, Jensen, Jensen, & Olesen, 1989) and electrical thresholds (Bendtsen, et al., 1996a) to be lower in headache patients.

Measures of pain sensitivity and sensory thresholds have also been found to be lower in a generalised distribution for headache patients when compared to headache free controls. Bove and Nilsson (1999) studied pressure pain threshold and pain tolerance in ETTH subjects after testing with painful mechanical stimuli and found reduced pressure pain threshold was found in the Achilles region as well as the trapezius muscle. The threshold was lower for both tender and non tender regions of the muscle. Increased mechanical nerve sensitivity (Fernandez-Mayoralas, Fernandez-de-la-pas-Penas, Ortega-Santiago, et al., 2010) was also found throughout the body in headache patients when compared to controls. The lowered sensory threshold seen in headache patients are consistent with a reduction of sensory thresholds for all sensory stimuli rather than just pain and is present throughout the body rather than restricted to the pericranial region.

A study was performed to compare pain thresholds to electrical and pressure pain thresholds of the trapezius muscle and the anterior tibial muscle, as well as to examine whether the differences in pain thresholds was due to the muscle itself or the overlying skin

(S. Ashina, et al., 2003). Electrical pain and sensory thresholds were measured by intramuscular electrical stimulation. The sensitivity of the trapezius muscle was found to be greater than the anterior tibial muscle and the difference in pain thresholds was due to muscle differences rather than differences in the skin. The authors concluded a higher concentration of sensory nerves in the trapezius muscle compared to the anterior tibial muscle did not explain the difference in pain thresholds. The density of nociceptors, greater spinal representation or greater sensory cortical representation of the trapezius muscle compared to the anterior tibial muscle may explain the increased pain sensitivity (S. Ashina, et al., 2003).

Bove and Nilsson (1999) tested whether increased muscle tenderness and pain sensitivity are found in headache patients regardless of whether the headache is present or absent at the time of testing. Twenty subjects with ETTH were subjected to painful mechanical stimuli in a range of muscles when they were experiencing a headache and when headache was absent. The pain sensitivity of the myofascia was constant and did not vary with the presence or absence of headache pain.

Pain sensitivity of pericranial muscles and a lower limb muscle was tested in a group with CTTH and a healthy control group by injecting hypertonic saline (Schmidt-Hansen, Svensson, Bendtsen, Graven-Nielsen, & Bach, 2007). Headache patients were tested on the days that headache was present and on days when headache was absent. Headache patients demonstrated lower pain thresholds, increased pain and greater spread of pain than healthy controls. There was no difference in pain threshold, pain evoked or spread of pain when tested in the absence or presence of a headache. Ashina et al. (1999) also demonstrated that trapezius muscle hardness (as a measure for muscle contraction) did not differ on days with headache and days without headache for patients with CTTH.

In migraine patients an extreme form of sensitivity called allodynia (when non painful stimuli such as touch are experienced as pain) occurs. Patients with transformed migraine (frequent migraine) had a lower pain threshold in the head, forearm and shin compared to people with no migraine (Cook, Eliasziw, & Becker, 2007). Allodynia was found in 75% of

the migraine sufferers confirming earlier studies that found allodynia in 79% of people with migraine (Burstein, Yarnitsky, Goor-Aryeh, Ransil, & Bajwa, 2000). These studies show that a generalised hypersensitivity occurs in migraine as well as CTTH.

Muscle contraction has been of interest in headache patients and electromyography (EMG) studies have shown nil to minimal increase in EMG activity of muscles between headache patients and controls, and when subject to mental stress EMG activity did not increase with the development of headache in TTH patients (Leistad, et al., 2005). Christiansen et al. (2005) showed that sustained muscle contraction in both the leg and trapezius muscle can cause headache rather than muscle tension in the neck alone. Sustained muscle contraction of the trapezius muscle and the anterior tibial muscle (control) were performed in ETTH patients and headache free controls. The ETTH group developed an increased frequency of headache compared to the control group when performing static contraction of both trapezius muscle and the anterior tibial muscle.

The question of whether inflammation in muscles is causing pain has been studied. Ashina et al. (2003) compared interstitial concentration of inflammatory mediators including prostaglandin E₂, adenosine 5-triphosphate, glutamate, bradykinin and other metabolites in headache patients as well as age and gender matched headache free controls. They tested tender points in muscles, and non tender points as well as concentrations before and after static muscle contractions. There was no difference in resting concentration of inflammatory mediators or metabolites at rest or after exercise in the two groups. The authors concluded that tender points in the trapezius muscle are not sites of ongoing inflammation.

Despite researchers proposing that myofascial tenderness leads to central sensitisation and subsequent headache (S. Ashina, et al., 2003; Bendtsen, 2000; Fernandez-de-la-pas-Penas, et al., 2007) the fact that muscle and surrounding tissue tenderness (myofascial tenderness) can be present with or without the presence of headache and muscle tenderness and is generalised in people with headache, may put in doubt that it is the cause of the headache but perhaps a coexisting condition. For a cause and effect relationship between myofascial

tenderness and headache disorders the myofascial tenderness would be present when headache is present and absent when headache is absent, and myofascial tenderness would be expected to be present in the head and neck region only which has been shown by many researchers not to be the case (S. Ashina, et al., 2006; S. Ashina, et al., 2003; Schoenen, et al., 1991).

Bendtsen (2000) states the main problem in CTTH may be sensitisation at the level of the dorsal horn/trigeminal nucleus due to prolonged nociceptive inputs from pericranial myofascial tissues. Furthermore the increased nociceptor stimulation of supraspinal structures results in increased facilitation and decrease in inhibition of pain transmission over the level of the spinal dorsal horn and/or trigeminal nucleus resulting in increased pericranial muscle activity or release of neurotransmitters in the myofascial tissues. By such mechanisms the central sensitisation may be maintained even after the initial eliciting factors have been normalised. No mention is made of the initiating stimulus causing the pericranial muscle tenderness, but he does mention that identifying the source of pericranial muscle tenderness is important to reduce the development of central sensitisation. This presents a rather circular model between two phenomena found in CTTH.

3.8.4 Sensitisation of the trigeminocervical nucleus

The trigeminocervical nucleus is a relay centre in the brainstem through which all sensations such as pain from the head and upper neck reach the thalamus and then sensory cortex. If a structure is creating nociception in the head and upper neck region the nerves transmitting pain must pass through this relay centre. After entering this relay the sensory nerves travel to the thalamus (the major sensory centre in the brain), then onto the sensory cortex where processing of sensations such as touch, pain, cold and heat occur. Once sensations are processed, the sensory cortex will communicate to other parts of the brain and ultimately with the muscles and joints to take action if required, e.g. withdraw a hand from a hot object.

Headache has been thought of as a condition with a source of nociception (structure producing pain) with signals travelling through the trigeminocervical nucleus to the

thalamus and sensory cortex (Dostrovsky & Straussman, 2000). There has been no source of nociception found within the skull that accounts for the pain of headache or migraine in primary headache disorders including both TTH and migraine. The somatic structures of the upper cervical spine may create headache by transmitting nociception from the upper cervical spine therefore the trigeminocervical nucleus may be an important pathway for referred pain in the head arising from the upper neck. The lower cervical spine may also cause headache through increased receptive fields leading to convergence of pathways from the lower neck and the upper neck, which transmits nociception via the trigeminocervical nucleus. Neck pain has been found to be more commonly associated with migraine than nausea in a prospective observational cross sectional study of 113 migraineurs (Calhoun, et al., 2010).

However the lower cervical spine (and other structures) may also refer pain into the head due to increasing receptive fields in the pathways of nociception proximal to the trigeminocervical nucleus, hence this nucleus may not always be a relay centre in the pathways of nociception in primary headache disorders.

Increased sensitivity of the trigeminocervical nucleus has been considered to explain symptoms of headache and heightened sensitivity to light (photophobia) and sound (phonophobia) (Goadsby, 2005). However the relevance of the trigeminocervical nucleus in headache disorders is put in doubt as patients suffering from cluster headache have had surgical section of the trigeminocervical nerve roots and failed to obtain relief of their cluster headache and still responded to sumatriptan. Postoperative MRI scans confirmed the nerve pathways were no longer intact (Matharu & Goadsby, 2002). The surgical section of the trigeminocervical nerve roots eliminates the sensory afferent pathways of nociception from the skull and upper cervical spine to the thalamus. Either a referred source of pain from somewhere other than the upper neck and head, or spontaneous generation of action potentials within the central pathways of nociception (thalamus or somatosensory cortex) may be perpetuating pain when the pathways from the trigeminocervical nucleus have been surgically sectioned.

3.8.5 Mast cell degranulation, neurogenic inflammation and migraine

Neurogenic inflammation has been proposed to explain the headache associated with migraine. The major elements of neurogenic inflammation include vasodilatation, plasma extravasation and mast cell degranulation (Messlinger, 2009; Theoharides, Donelan, Kandere-Grzybowska, & Konstantinidou, 2005). Neurogenic inflammation can be induced by local or antidromic stimulation of meningeal afferents that releases pro-inflammatory neuropeptides from these nerves (Moskowitz, 1993). Messlinger (2009) states there is not much evidence for an important role of neurogenic inflammation during the onset of migraine headache, as it depends on the massive activation of meningeal afferents and no spontaneous process that causes primary activation of meningeal afferents has been found. Furthermore selective and potent inhibitors of plasma protein extravasation were ineffective in the acute treatment of migraine (Panconesi, Bartolozzi, & Guidi, 2009).

Theoharides et al. (2005) states neither cortical spreading depression nor vascular theories of migraine explain the initial triggering events of migraine that could involve emotional, physical or oxidative stress. Theoharides et al. (2005) presents a model with similarities to the Adrenaline Model of Headache Causation in that it involves the HPA pathways. He states that stress triggers CRH release from the hypothalamus, which activates CRH receptors on the sensory nuclei of the trigeminal nerve triggering dura mast cells, either directly or synergistically with CRH. This may trigger mast cell degranulation with the release of vasoactive, proinflammatory and neurosensitising mediators which increase vascular permeability and contribute to the pathogenesis of migraines. The mast cells are located perivascularly in close association with neurons especially in the dura, making them an attractive proposition in the pathogenesis of headache disorders. Theoharides et al. (2005) concludes that mast cells may serve as both the sensor and effector cells in migraines locally in the meninges as well as in the hypothalamus. Interleukin 1 and interleukin 6 both of which are released from mast cells could trigger CRH secretion and CRH can also stimulate interleukin 6 release.

A significant detractor of this theory is that certain conditions with significant mast cell degranulation such as anaphylaxis are not accompanied regularly by headache or migraine. In a review article of anaphylaxis (Kemp & Lockey, 2002) the signs and symptoms of this syndrome are listed as diffuse erythema, pruritis, urticaria, and/or angioedema, bronchospasm, laryngeal oedema, hyperperistalsis, hypotension, and/or cardiac arrhythmias. Other symptoms can occur such as nausea, vomiting, lightheadedness, headache, feeling of impending doom and unconsciousness. If mast cell degranulation and subsequent release of contents is to explain migraine then the absence of migraine being a substantial feature of anaphylaxis is inconsistent with the model.

3.9 Experimental induction of headache disorders

A variety of chemical infusions other than nitrates have been performed to study the pathophysiology of headache disorders. Overall substances such as histamine and PGE₂ that attach to receptors and stimulate the production of second messengers such as cGMP, cAMP and inositol trisphosphate (IP₃) induce headache (Krabbe & Olesen, 1980; Kruuse, et al., 2003; Lassen, et al., 2002; Lassen, Thomsen, & Olesen, 1995; Schytz, et al., 2008; Schytz, Wienecke, Olesen, & Ashina, 2009; Schytz, Wienecke, Oturai, Olesen, & Ashina, 2009; Wienecke, Olesen, Oturai, & Ashina, 2009) while those that do not stimulate second messengers significantly e.g. noradrenaline do not induce headache (Hansen, et al., 2006; Lindholdt, et al., 2008).

Prostaglandin E₂ (PGE₂) infusions caused headache in healthy volunteers who do not regularly suffer from headache (Wienecke, et al., 2009). Prostaglandin E₂ attaches to EP₂ and EP₄ receptors leading to increased cAMP (Hata & Breyer, 2004).

Histamine infusion caused headache in 96% (24/25) of migraine patients and no headache in migraine free controls (Krabbe & Olesen, 1980). Histamine₁ receptors are found in the thalamus and increase production of several second messengers including activation of phospholipase C (PLC) promoting 1) inositol triphosphate (IP₃)-dependent release of Ca²⁺ from intracellular stores and 2) diacylglycerol (DAG)-sensitive activation of protein kinase C (PKC), nitric oxide (NO), and cGMP (Haas, Sergeeva, & Selbach, 2008). The H₁ receptor blocker mepyramine almost immediately abolished the headache. Histamine

infusion also caused severe headache in 20 migraine patients that was prevented by pretreatment with mepyramine (Lassen, et al., 1995).

Infusion of noradrenaline (Lindholdt, et al., 2008) did not create headache in normal volunteers. Significant amounts of noradrenaline are unlikely to enter into the brain as it does not cross the blood brain barrier (Edvinsson & Tfelt-Hansen, 2008) and hence the central nervous system effects of noradrenaline that results in arousal is absent. The central nervous system activation of several neurotransmitters (section 4.5.1) is absent.

Furthermore noradrenaline infusion causes a slight elevation of cAMP compared to adrenaline (MacGregor, Prielipp, Butterworth, James, & Royster, 1996) and this may be inadequate to create action potentials in peripheral nociceptors leading to headache in headache free individuals who do not have central or peripheral sensitisation of their sensory pathways. If participants had headache disorders with central and peripheral sensitisation then noradrenaline may have caused headache similar to histamine infusion (Krabbe & Olesen, 1980).

Pituitary adenyl cyclase activating peptide (PACAP₃₈) was infused in 12 healthy subjects and 12 migraine sufferers (Schytz, Wienecke, Oturai, et al., 2009). Pituitary adenyl cyclase activating peptide₃₈ caused headache in all healthy subjects and 11 out of 12 migraine sufferers. Migraine was induced in seven of the 12 migraine patients while placebo failed to induce migraine. Increased flushing, palpitations and heat sensations were reported after PACAP₃₈ infusions compared to placebo. These reactions signaled activation of the autonomic nervous system.

Vasoactive intestinal peptide (VIP) induced minimal headache in migraine sufferers and no migraine in controls (Hansen, et al., 2006; Rahmann, et al., 2008). Marked dilatation of the cranial arteries was reported and provides further data against a purely vascular origin of migraine (Rahmann, et al., 2008). Pituitary adenyl cyclase activating peptide₃₈ has been shown to stimulate adenyl cyclase 1000 times more than VIP in cultured neural cells (Miyata, et al., 1989) and the reduced production of cAMP may explain the lack of effect of VIP compared to PACAP₃₈ in inducing headache and migraine.

Calcitonin gene related peptide (CGRP) infusion induced headache in all migraine patients (N = 11) whereas a placebo infusion, on the same group (N = 11) failed to induce headache (Lassen, et al., 2002). Calcitonin gene related peptide attaches to G protein coupled receptors and stimulates the action of adenylyl cyclase which results in cAMP production. Calcitonin gene related peptide immunoreactive cells are found in 40% to 50% of dorsal root ganglia neurons, trigeminocervical nucleus and CGRP receptors are found in the thalamus. Calcitonin gene related peptide can therefore act at several sites to reduce nerve thresholds (Van Rossum, Hanisch, & Quiron, 1997).

Sildenafil is a selective inhibitor of cGMP hydrolysing phosphodiesterase and stops the hydrolysis of cGMP which leads to an increased concentration of cGMP levels. When sildenafil was infused in migraine patients, 10 out of 12 patients tested developed migraine while placebo only induced migraine in two out of the 12 patients tested (Kruuse, et al., 2003). There was no associated dilatation of the middle cerebral artery.

Carbachol, an acetylcholine analogue, produced headache in normal volunteers (Schytz, Wienecke, Oturai, et al., 2009), and induced headache in 15 of the 18 migraine patients in the study while a placebo infusion induced headache occurred in eight of the 18 migraine patients (Schytz, Wienecke, Olesen, et al., 2009). Both M₁ muscarinic receptors and M₃ receptors are G protein coupled receptors that upregulate phospholipase C and, therefore, inositol triphosphate and intracellular calcium as a signaling pathway and muscarinic receptors are present in the thalamus.

The Adrenaline Model of Headache Causation outlined in Chapter 5 proposes this increase in second messengers leads to action potentials in the pathways of nociception causing headache.

3.10 Summary

Vasodilatation, muscle tension, mast cell degranulation and sensitisation of the trigeminocervical nucleus do not adequately explain headache phenomena found in the literature. The relationship between headache and muscle tenderness is likely to be

coincidental and caused by a similar pathogenesis. This is further supported by the two main therapies aimed at improving muscle tenderness, botulinum toxin injections and acupuncture, having no greater effect than placebo in reducing CTTH (Padberg, et al., 2004; Schmitt, et al., 2001; Schulte-Mattler & Krack, 2004; Silberstein, et al., 2006; Soderberg, et al., 2006; Wang, et al., 2007). Vasodilatation is not consistent with headache induction or treatment and sensitisation of the trigeminocervical nucleus does not explain the generalised phenomena of muscle tenderness found in headache disorders.

Chapter 4 will outline the neurophysiological background for the headache causation model that has been developed during this PhD study, by examining the SNS, HPA pathways, second messenger systems and nerve sensitisation. Chapter 5 will outline in detail the new headache causation model developed and designated the Adrenaline Model of Headache Causation.

Chapter 4

BACKGROUND NEUROPHYSIOLOGY OF THE ADRENALINE MODEL OF HEADACHE CAUSATION

4.1 Introduction

There are three probable causes for pain experienced in the head during a headache; nociception, referred pain or sensory nerve depolarisation without tissue damage. Nociception (section 4.2) is the encoding and processing of noxious stimuli that will explain headache induced by sinusitis, brain tumours and ear infections among others. The pain experienced during a headache may be referred pain (Kellgren, 1938) where pain is experienced in the head but originates at another source such as the neck (cervicogenic headache). The production of action potentials in the pathways of nociception without tissue damage is one of the key concepts investigated in this PhD thesis to explain primary headache disorders.

This chapter outlines neurophysiological background for the Adrenaline Model of Headache Causation developed in this PhD study and outlined in Chapter 5. In particular nociception (section 4.2), synaptic transmission and metabotropic receptors (section 4.3), neural sensitisation (section 4.4) and the SNS and HPA pathways (section 4.5) will be discussed.

4.2 Nociception

Nociception is the process of detection and transmission of painful stimuli (Connors, 2003a) from nociceptors, through to the dorsal horn, thalamus and onto the sensory cortex where signals are processed (Figure 4.1). At each level there are excitatory and inhibitory influences that are both ascending (peripheral to central nervous system) and descending (central to peripheral nervous system) as shown in Figure 4.1. The balance between inhibitory pathways and excitatory pathways will determine the transmission of an action potential (Heinricher, 2005).

Figure 4.1: Modulation of the pathways of nociception

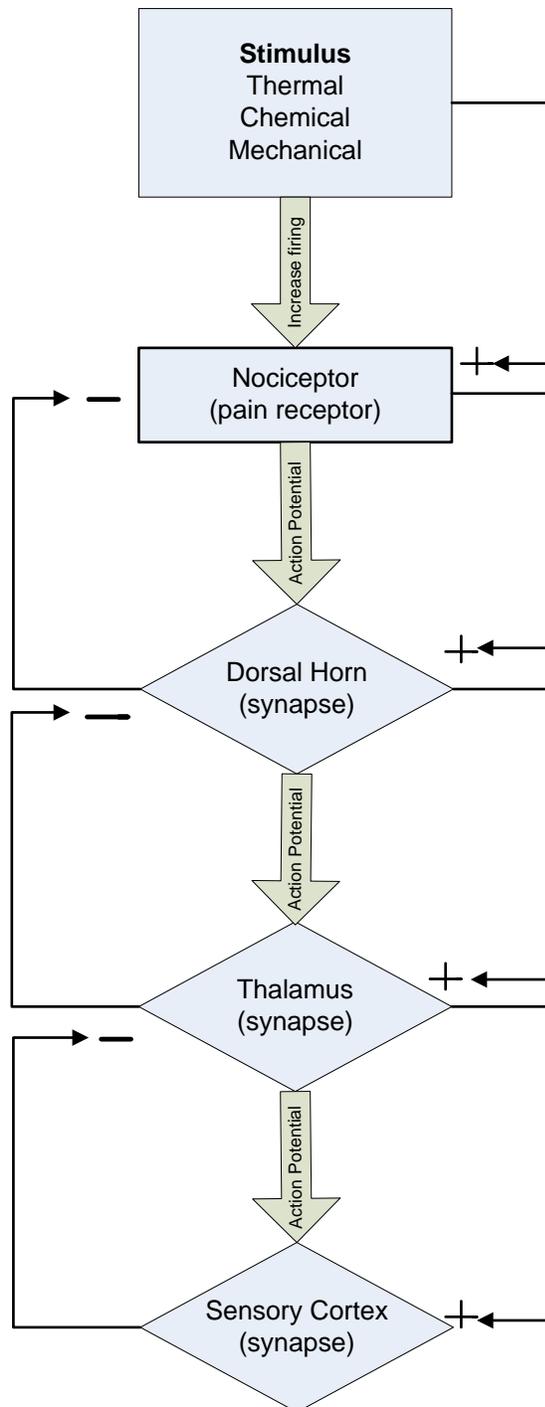


Figure 4.1 + = stimulates, - = inhibits. Adapted from Heinricher (2005).

Transient receptor potential (TRP) channel proteins are found on the peripheral nociceptor membrane. These channel proteins regulate the flow of different ions between the cell and its environment. The gating of these channels may be direct by voltage or ligand binding or indirect via cascade of molecular events and production of second messengers that lead to channel opening. Several physical parameters affect channel opening including mechanical force, pH, osmolarity and biochemical interactions with external ligands or cellular proteins (Pedersen SF, Owsianik G, & B., 2005). The Adrenaline Model of Headache Causation outlined in Chapter 5 proposes that adrenaline is a significant contributor to peripheral sensitisation of the nociceptor by attaching to β adrenoreceptors and stimulating the cAMP second messenger cascade that results in opening of nociceptor TRP channel proteins, causing an increased sensitivity to mechanical pressure and perhaps explaining the widespread muscle tenderness found in headache patients (S. Ashina, et al., 2006).

Descending pathways modulate pain at the level of the spinal cord. The periaqueductal gray projects to the rostroventral medulla which projects two types of neurons to the dorsal horn that are characterised by their firing patterns: “on cells” and “off cells” (Heinricher, 2005). The balance of “on cells” and “off cells” determines whether this pathway has a pro-nociceptive or anti-nociceptive effect. Opiates act indirectly by increasing the firing of “off cells” and reducing the firing of “on cells”. If “off cells” dominate then nociception may be inhibited but if “on cells” dominate then the threshold for nociceptive stimuli is lowered. Neurotransmitters involved in the descending control of nociception include serotonin, gamma-amino-butyric acid (GABA) and noradrenaline. Neurotransmitters do not necessarily have a simple inhibition or excitation of the pathways of nociception and their ultimate action may depend on the concentration of their various receptors present. Both serotonin and noradrenaline may reduce or increase the threshold of action potentials produced at the dorsal horn via descending pathways.

The thalamus is the last subcortical structure through which auditory, somatosensory and visual information must pass before reaching the sensory cortex and is important in modulating the flow of sensory information to the cortex. The thalamus is influenced by

neural pathways from the cerebral cortex (cortico-thalamic), brainstem, spinal cord dorsal horn (spinothalamic) and hypothalamus (McCormick & Bal, 1994). The thalamus consists of relay neurons (from the thalamus to the cortex) that have inhibitory influences from GABAergic interneurons. Ascending stimulatory pathways from the brainstem include cholinergic, noradrenergic, serotonergic, and histaminergic neurons (McCormick & Bal, 1994). Postsynaptic influences are also present from serotonergic, β adrenergic and histaminergic neurons as well as the release of nitric oxide. In addition to these metabotropic receptors there are also ionotropic receptors (glutamate and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid- AMPA) influencing the thalamus. The balance of stimulatory and inhibitory neurotransmitter pathways relaying to the thalamus determine whether action potentials are transmitted to the sensory cortex to relay nociceptive information.

Thalamocortical and thalamic reticular neurons exhibit two distinct firing modes, producing action potentials as calcium spike mediated high frequency bursts or as tonic trains (Kim & McCormick, 1998). Activation of single action potentials or low frequency spike trains resulted in post synaptic potentials that were 0.5mV to 2mV in amplitude and are present during slow wave sleep. Activation of calcium spike mediated bursts of action potentials in the presynaptic cell increased post synaptic potentials to an average of 3.0 mV for the EPSP barrage because of temporal summation and/or facilitation. In the wakeful state trains of action potentials are present (Kim & McCormick, 1998). During the burst mode transmission detailed sensory information is blocked and during the tonic mode sensory information is relayed to the sensory cortex.

4.3 Synaptic transmission and metabotropic receptors

Sensory neurons transmitting nociception relay at the dorsal horn in the spinal cord and thalamus in the brain at synaptic connections where neurotransmitters (e.g. acetylcholine, dopamine, noradrenaline, histamine) are released across the synapse (Connors, 2003b). Once the neurotransmitter has bound to the receptor it can stimulate or inhibit second messenger cascades such as cAMP or cyclic guanosine-monophosphate (cGMP). An increased concentration of second messengers can lead to the opening of ion channels in the

postsynaptic region and the formation of an excitatory postsynaptic electrical potential (EPSP) and if enough of these EPSPs are formed then an action potential may be produced at the axon hillock.

The activation of metabotropic receptors can lead to gaseous messengers such as carbon monoxide (CO) and nitric oxide (NO) and non gaseous second messengers (cAMP, cGMP, calcium). Both of these gaseous messengers activate guanyl cyclase to stimulate the synthesis of cGMP, which like cAMP, is a freely diffusible cytoplasmic second messenger (Roman, 2003). Alpha and β adrenergic receptors, muscarinic acetylcholine receptors, GABA_b receptors, certain glutamate receptors and serotonin receptors are metabotropic receptors. Metabotropic receptors are important in setting the threshold for action potential and in initiating the action potential. Metabotropic receptors produce second messengers able to act on channels located throughout the neuron including the dendrite, axon, presynaptic terminals and growth cones (Connors, 2003b).

Table 4.1 summarises the receptors once activated, that can lead to stimulation or inhibition of adenylyl cyclase which ultimately determines the production of the second messenger cAMP. The chemicals that can cause an increase in cAMP production include serotonin, adrenaline, prostaglandin and CGRP and those that can reduce cAMP production include serotonin, noradrenaline and opioids. Nitric oxide and activation of H₁ receptors can lead to stimulation of guanyl cyclase and the production of cGMP. After a second messenger cascade has been stimulated the increase in second messenger is depleted by enzymes called phosphodiesterases which inactivate second messengers. Medications called phosphodiesterase inhibitors (e.g. Viagra) prevent the depletion of second messengers within cells and increase their concentration.

Synapses can also modulate the effect of another neuron (Connors, 2003b) without causing an action potential itself. An example is noradrenaline released from neurons from the locus coeruleus onto the pyramidal neurons of the cerebral cortex. Noradrenaline attaches to β receptors on the pyramidal neurons but does not stimulate an action potential in the resting neuron. A pyramidal cell however will respond more powerfully to an excitatory input from

| Stimulation of adenylyl cyclase | Inhibition of adenylyl cyclase |
|---|--|
| Serotonin receptors 5-HT ₄ , 5-HT ₆ , 5-HT ₇ | Serotonin receptors 5-HT _{1A} , 5-HT _{1B} , 5-HT _{1D} , 5-HT _{1E} , 5-HT _{1F} |
| Adrenergic receptors β_1 , β_2 , β_3 | Adrenergic receptors α_2 |
| PGE ₂ , EP ₂ and EP ₄ | Opioid receptors μ , κ |
| CGRP | |

other synapses, hence noradrenaline can modulate the cells' response to other inputs. Therefore the release of noradrenaline, while not directly producing action potentials, may reduce the threshold at which stimuli can cause action potentials in the neurons of the cerebral cortex (Connors, 2003b).

The Adrenaline Model of Headache Causation described in Chapter 5 proposes that an increase in second messengers increases the excitability of the pathways of nociception, effectively lowering the threshold for which action potentials are propagated.

4.4 Neural sensitisation

Repeated stimulation of the pathways of nociception can produce neural sensitization, whereby a reduced intensity of stimulus or reduced duration of stimulus can produce an action potential and transmit nociception. Peripheral sensitisation is the term used to describe sensitisation that occurs in the peripheral nociceptors and central sensitisation is the term used to describe this process in the central nervous system. Sensitisation can occur due to an increased efficiency of the synapse and by increasing the number of synapses present (Siegelbaum, Schwartz, & Kandel, 2000).

Metabotropic receptors can create a short acting sensitisation by modulating the strength and efficiency of fast synaptic transmission of ionotropic receptors lasting seconds to minutes by, increasing the efficiency of neurotransmitter production, release and binding to the post synaptic membrane (Siegelbaum, et al., 2000). An increase in presynaptic formation of neurotransmitter can occur by increasing production of the substrate or

enzyme involved in the production of the neurotransmitter. An increased number of vesicles containing neurotransmitter can be released causing increased post synaptic receptors to be occupied, increasing the number of EPSPs that summate. The number of failures of transmission in presynaptic neurotransmitter release is in the order of 60% but after sensitisation the number of failures reduces to 20% (Kandel, Kupferman, & Iversen, 2000). These changes together with resetting the resting membrane potential increase the likelihood of an action potential being generated.

Longer term changes can occur at the synapse due to repeated stimulation of metabotropic receptors, resulting in the synthesis of new proteins leading to the formation of new synapses, that can create long term synaptic changes lasting hours, days or longer (Connors, 2003b). Nerve sensitisation is important in the amplification of sensory messages, development of conditioned responses and long term memory (Kandel, et al., 2000).

4.5 The sympathetic nervous system and the hypothalamic-pituitary-adrenal pathways

The hypothalamus is the main control centre of the body for the HPA pathway (Richerson, 2003). Temperature, sleep, hunger, thirst, fatigue, emotions (anger, excitement, frustration) and circadian rhythms are monitored and if a change occurs in the body, the hypothalamus acts with the SNS to return the body to its preset state (Iversen, Iversen, & Saper, 2000). The hypothalamus is also involved with emotional responses and behaviour such as pleasure, fear, frustration and rage by regulating the release of cortisol from the adrenal cortex via what is termed the HPA pathways (Iversen, et al., 2000).

The locus coeruleus is one of many brainstem nuclei of the SNS involved in the stress response, that has widespread projections in the brain as well as the spinal cord dorsal horn. As well as releasing noradrenaline the locus coeruleus promotes the secretion of corticotrophin releasing hormone (CRH) from the hypothalamus to stimulate the HPA pathways to release cortisol. CRH neurons also have a reciprocal projection to the locus coeruleus promoting noradrenaline release during stress (McCann, et al., 2000).

The HPA and SNS pathways are significant players in the stress response of the body and the hypothalamus and SNS communicate with each other in a coordinated response to a variety of stressors (Pike, et al., 1997) to release adrenaline, noradrenaline and cortisol from the adrenal gland. Adrenaline secretion is under the control of the HPA axis at two levels. ACTH increases the secretion of the precursors to adrenaline (dopamine and noradrenaline), while cortisol up-regulates phenylethanolamine-N-methyl-transferase (PNMT), the enzyme responsible for transforming noradrenaline to adrenaline (Barrett, 2003).

In the presence of severe or chronic stress (major surgery, lingering affective disorders, chronic infections, chronic autoimmune diseases) the adrenal gland as the end organ of the human stress system undergoes many changes due to the influence of the HPA and SNS pathways (Bornstein & Chrousos, 1999). Under chronic stress, ACTH triggers an upregulation of enzymes responsible for the production of cortisol and adrenaline and changes occur in the adrenal gland including cellular hypertrophy, hypervascularisation and hyperplasia. Once a person has undergone a major or prolonged stressor the upregulation of enzymes and cellular hypertrophy, lead to the adrenal gland producing more adrenaline and cortisol for any given stimuli even after the chronic stressor has subsided.

Pike et al. (1997) measured the SNS and HPA responses to an acute psychological stressor and a control video in 11 individuals with chronic life stress versus 12 individuals without chronic life stress. To categorise individuals into the two groups for this study, consultations included formal psychiatric diagnostic interview, medical history, physical examination and blood tests including adrenaline, noradrenaline, β -endorphin, ACTH, and cortisol. Both groups showed similar elevations of adrenaline during the video control and the group with chronic life stress showed greater elevations in adrenaline when subjected to the acute psychological stressor.

Although adrenaline released from the adrenal gland does not pass through the blood brain barrier the central effects of adrenaline administration or acute stress indicates adrenaline has access to the brain. Adrenaline can cause tension and restlessness as well as panic

attacks (Wortsman, 2002). To measure changes in the brain blood vessels from noradrenaline and adrenaline infusions, measures were taken of cerebral metabolism (cerebral oxygen consumption) and cerebrovascular resistance in 16 volunteers. Saline infusion was used as a control. The infusion of adrenaline was often accompanied by palpitations, tremor of the hands and a sense of excitement or apprehension. Cerebral blood flow increased and cerebral oxygen consumption increased from adrenaline infusion but not in response to saline or noradrenaline infusion. The authors concluded that the brain shares in the metabolic augmentation which is produced by adrenaline throughout the body (King, Sokoloff, & Wechsler, 1952). Adrenaline infusion can also cause changes in the electroencephalogram wave frequency and amplitude in humans (Axelrod, Weil-Malherbe, & Tomchick, 1959) indicating a cerebral action of adrenaline.

One source of brain adrenaline from the plasma is from two areas of the hypothalamus that are devoid of a blood brain barrier (Wortsman, 2002). To investigate the distribution of adrenaline, radioactive adrenaline was infused into cats and it was found the concentration within the hypothalamus was 10% to 15% of the plasma level (Axelrod, et al., 1959; Weil-Malherbe, Axelrod, & Tomchick, 1959). Other sources of adrenaline in the brain are found co-stored with noradrenaline in noradrenergic terminals, and brainstem neurons containing the enzyme phenylethanolamine N-methyltransferase that synthesises adrenaline from noradrenaline (Mefford, 1988). Rat studies have shown a depletion of brain adrenaline after administration of 2-cyclooctyl-2-hydroxyethylamine (CONH), a potent phenylethanolamine N-methyltransferase inhibitor. The infusion of COHN produced a reduction in adrenaline levels in the brainstem and hypothalamus (Liang, Tessel, Grunewald, & Borhardt, 1982). Furthermore stress has been shown to cause a marked depletion of hypothalamic adrenaline (Mefford, 1988). During the acute stress response adrenaline produced by the adrenal gland as well as adrenaline stored in the brain contributes to the central nervous system effects of adrenaline.

4.5.1 SNS and HPA response to various stressors

During stress the activity of the SNS leads to both sympathetically mediated neural and endocrine (adrenal catecholamine) responses in the body simultaneously. The response is

thought to be coordinated by the hypothalamus and locus coeruleus (among other brain centers) that innervate both sympathetic outflow systems that regulate blood vessel tone and adrenal release of catecholamines (Jansen, Nguyen, Karpitskiy, Mettenleiter, & Loewy, 1995). At normothermic conditions the SNS exerts a vasoconstrictor tone on the peripheral vasculature.

Sympathetic sudomotor tone is controlled from the preoptic-anterior hypothalamus and increases with rising temperature, and emotional stress can also increase sweating (Vorkamp, Foo, Khan, Schmitto, & Wilson, 2010). The temperature regulating centers in the hypothalamus receive feedback from thermal receptors in the skin, a major thermoregulatory organ in the body. When the skin senses cold, several changes occur including inhibition of sweating and promoting skin vasoconstriction to reduce heat loss. As the skin and/or core temperature increases the central nervous system SNS outflow reduces to reduce the sympathetic vasoconstrictor tone of the peripheral blood vessels to increase skin blood flow and the SNS sudomotor tone may increase to enhance sweating (Wong, Wilkins, & Minson, 2004). Sympathetic tone in this thesis refers to the outflow from the central nervous system that controls both sympathoadrenal release of catecholamines and the vasoconstrictor tone of blood vessels and does not refer to sudomotor activity.

Measurement of SNS activity has included heart rate variability (HRV), sympathetic skin responses (SSR), sympathetic skin nerve activity (SSNA) and sympathetic muscle nerve activity (SMNA). Heart rate variability depends on the balance of SNS and PNS activity with a low frequency of HRV associated with SNS activity and a high HRV associated with increasing PNS activity (Acharya, Joseph, Kannathal, Lim, & Suri, 2006). Sympathetic skin response is a technique that reflects the voltage change on the surface of the skin in response to stimuli and is thought to measure SNS vasoconstrictor and sudomotor activity (Yagiz On, Colakoglu, Hepguler, & Asit, 1997). Sympathetic muscle nerve activity is thought to measure SNS outflow to muscle (Victor, Leimbach, Seals, Wallin, & Mark, 1987). Plasma catecholamine levels have also been used in the measurement of SNS activity and may reflect both SNS postganglionic release of

noradrenaline as well as adrenal release of noradrenaline and adrenaline (Sothman, Hart, & Horn, 1992). However the overall activity of the SNS will depend on several factors including the release of noradrenaline as well as the number and sensitivity of receptors therefore even in states of lower basal noradrenaline serum concentrations, if receptor numbers and sensitivity is increased then overall activity of the SNS may not be lowered despite a reduced level of measured serum noradrenaline. A further discussion of serum noradrenaline levels with respect to headache disorders occurs in section 5.2.

4.5.2 Sympathetic tone

The SNS is always active to a variable level and sympathetic tone changes in the human body in response to several stimuli. Stimuli including psychological stress (Pike, et al., 1997), sleep disturbance (Burgess, Trinder, Kim, & Luke, 1997), fasting (Segel, Paramore, & Cryer, 2002), alcohol (van de Borne, Mark, Montano, Mion, & Somers, 1997), exercise (Kotchen, et al., 1971), viral illness (Mason, Buescher, Belfer, Artenstein, & Moughey, 1979) and pain (Danilov, et al., 1994) will increase sympathetic tone and sympathetic tone is reduced by relaxation (Lucini, et al., 1997; Pike, et al., 1997), heat (Yagiz On, et al., 1997), regular exercise (Murros, et al., 2000), sleep (Trinder, et al., 2001) and ageing (Seals & Esler, 2000).

Sleep deprivation and alcohol have been shown to increase sympathetic tone. Sympathetic nervous system activity was measured in subjects during 36 hours of sleep deprivation finding an increase in sympathetic tone (Zhong, et al., 2005). The effects of alcohol on SNS activity were examined in 16 healthy individuals by measuring blood pressure, heart rate, heart rate variability, muscle sympathetic nerve activity, forearm vascular resistance and minute ventilation after oral alcohol intake (van de Borne, et al., 1997). Acute increases in alcohol were found to increase sympathetic muscle nerve activity and increase heart rate but did not increase blood pressure probably due to the vasodilatation effects of alcohol.

To investigate the local effect of heat on pain, Yagiz On et al. (1997) performed a randomised trial recording the sympathetic skin response (SSR) amplitudes in both hands in response to a painful stimulus in the peroneal nerve in the leg, before and after the

application of heat on one hand. The plantar and palmar SSR activity was recorded as these regions represent the emotional sweating areas that are activated primarily by mental and emotional stimuli such as pain, fear, excitement, arithmetic testing and problem solving (Yagiz On, et al., 1997). This study sought to investigate the effect of therapeutic heat in healthy participants subject to painful electrical stimulation of the peroneal nerve in the leg. They found SSR amplitudes at the palmar surface of both hands reduced with heat which in turn increased pain threshold to the painful stimuli in the leg. The authors concluded the analgesic effect of heat may be caused by a suppression of cortical pain sensation.

Bilateral SSR was evaluated in 25 healthy participants subject to painful electrical stimulation with the finding that SSR amplitude and duration increased with increased intensity of pain (Danilov, et al., 1994). HPA activity has also been found to be attenuated in those responding to a pain management course. A prospective study followed 18 participants undergoing a one month multidisciplinary pain management course. Salivary cortisol (K. Evans, Douglas, Bruce, & Drummond, 2008) was measured for several days before and after the course. Cortisol levels did not change significantly in the whole group (there was substantial variation among the group) but many of the participants regularly experienced very high levels of cortisol with a disruption of the normal diurnal pattern of cortisol secretion. Reductions in pain were accompanied by reductions in morning cortisol levels after controlling for depression.

Measurements of sympathetic activity have been reported in migraine patients (Anthony, 1981) with measurements of adrenaline, noradrenaline, cAMP, free fatty acids and serum dopamine-beta-hydroxylase (DBH) in a group of ten migraine patients before, during and after a migraine attack. All measurements except for adrenaline showed statistically significant elevations during the migraine. Adrenaline was measured before, during and after a migraine attack. In this study blood samples were taken four hourly before, during and after the migraine. The half life of adrenaline is approximately 1.2 minutes (Ward, et al., 1983) and sampling for adrenaline levels needs to be continuous before during and after the stimulus that has caused the migraine to detect changes in adrenaline levels. The timing of the samples by Anthony (1981) was every four hours and unlikely to detect changes in

adrenaline levels before, during and after a migraine. Noradrenaline is released by both the SNS as well as the HPA pathways and hence levels of noradrenaline may be found elevated.

Plasma adrenaline measured by continuous blood withdrawal with an indwelling venous catheter has found blood adrenaline to be elevated by venepuncture, mental arithmetic tests, anticipation and the initial periods of a vigilance task, public speaking, vigorous physical exercise and submerging the hand in ice water (Ward, et al., 1983). Dimsdale and Moss (1980) performed catecholamine measurements in response to public speaking in junior doctors and state that because the half life of adrenaline is brief, care should be taken in obtaining blood samples. They used portable non-obtrusive blood withdrawal pumps which took baseline samples, samples within the first three minutes of speaking and then at 15 minutes during the speech. They found adrenaline levels were elevated approximately 400% in the first three minutes compared to baseline and elevated approximately 300% at 15 minutes. They found the elevated levels of adrenaline were statistically significant at 3 minutes but not at 15 minutes. Noradrenaline levels were elevated approximately 200% at both three minutes and 15 minutes. This was a statistically significant elevation at both times.

Plasma adrenaline and noradrenaline was measured after exhaustive treadmill exercise or a 30 minute stressful interview (Olehansky & Meyerhoff, 1991). Graded exercise to exhaustion (approximately 15 minutes in duration) increased adrenaline by 201% and noradrenaline by 239% immediately after completing exercise. After the stressful interview adrenaline levels increased 82% and noradrenaline increased 67%. The noradrenaline and adrenaline response to graded exercises was studied (Kotchen, et al., 1971) by measuring plasma levels in six healthy subjects at three different workloads calculated as 40%, 70% and 100% of VO_2 max. Noradrenaline was elevated significantly at 70% and 100% maximum intensity and adrenaline was only elevated significantly after maximal exercise. The SNS and HPA pathways elicit a graded response to exercise, with minimal response to mild and moderate exercise and a marked response to exercise at maximal intensity.

Plasma ACTH levels have been measured in response to sitting in a sauna for 30 minutes at 90°C. Baseline measures of 27.5 +/- 4.4 increased to 79.3 +/-3.1 at the end of the sauna and then 36.5, 30 minutes after the sauna. An episode of sauna bathing is likely to have similar effects on the HPA and SNS pathways as an episode of exercise as ACTH response has been found to correlate with the adrenaline response in the presence of stressors (Goldstein & Kopin, 2008).

A meta-analysis of HPA and SNS responses (Goldstein & Kopin, 2008) found psychological stress, heat and cold all elicit HPA and SNS responses, with cold exerting a greater elevation in plasma noradrenaline compared to ACTH and adrenaline. In response to hypoglycaemia, plasma adrenaline and ACTH increased proportionately greater than noradrenaline. Across the 15 stressors mean adrenaline response was graded from 0 (no release) to 4 (maximum release) with results ranging from 0.0 (cold exposure, no hypothermia) to 3.9 (hypoglycaemia), ACTH responses ranged from 0.0 (cold exposure, no hypothermia) to 3.5 (exercise, severe exercise to exhaustion) and noradrenaline responses ranged from 1.0 (hypoglycaemia) to 3.5 (exercise, severe/exhaustion). Goldstein and Kopin (2008) found that mean adrenaline responses were strongly correlated with mean ACTH responses for stressors and less strongly correlated with noradrenaline. Table 4.2 summarises the responses of adrenaline, noradrenaline and ACTH to a variety of stressors.

| Stressor | Adrenaline | Noradrenaline | ACTH |
|---|------------|---------------|------|
| Hypoglycaemia | 3.9 | 1 | 2.6 |
| Psychological stress | 3 | 2.5 | 2 |
| Mild hypothermia | 1 | 1 | 2 |
| Cold, no hypothermia | 0 | 2.6 | 0 |
| Severe Exercise | 3.3 | 3.5 | 3.5 |
| No response (0) to extremely large response (4) | | | |

4.5.3 The effects of repeated relaxation therapy and exercise on the SNS and HPA pathways

The effect of mental relaxation to blunt the autonomic excitatory responses was tested in an RCT (Lucini, et al., 1997) with three groups that were subjected to relaxation training

(N=13), sham relaxation (N=12) and β adrenergic blockade (N=13). Markers of SNS activity including heart rate variability were measured in response to standing and stressful arithmetic tasks, before and after three months of relaxation and sham relaxation. The β adrenergic blockade group had measures of SNS activity before and after a four day course of atenolol (β Blocker). Autonomic excitatory responses significantly blunted in the relaxation training and β adrenergic blockade group, but not in the sham relaxation group. The authors concluded that SNS excitation accompanying simple standardised physical and mental stressors can be significantly reduced in healthy individuals by a three month relaxation programme.

A review of RCTs on the effects of repeated aerobic exercise for over four weeks duration for blood pressure effects (Cornelissen & Fagard, 2005) concluded that endurance training reduced blood pressure through a reduction in vascular resistance in which the SNS seemed to be involved. Noradrenaline levels reduced an average of 29% (CI: 17.6 to 39.8, $P < 0.001$) in the 30 study groups of hypertensive individuals. A RCT on the effects of one hour exercise three times a week for four months on heart failure patients (Roveda, et al., 2003) showed that SNS activity in the peroneal nerve was elevated compared to a control group (without heart failure, who did not exercise regularly) and reduced to the same level as another control group who performed regular exercise, after the four months of exercise. Evidence from animal studies and human studies to a lesser extent also show that exercise training reduces SNS reactivity to stressors, perhaps by altering neural plasticity in the neural networks that regulate SNS activity in the brain (Mueller, 2007).

The lowering of SNS activity with regular exercise is not found in all studies. Sothmann et al. (1992) randomised 24 healthy individuals who did not regularly exercise into two groups and measured plasma adrenaline and noradrenaline responses to a stressful task. One group performed aerobic exercise three times a week for 16 weeks and the stressful tasks were repeated. No differences in noradrenaline or adrenaline response were found between the two groups at the end of the study when the same stressful activity was repeated. Sympathetic nervous system activity may be reduced in individuals with elevated sympathetic tone (hypertension, heart failure) but perhaps sympathetic tone is not attenuated in healthy individuals without an initial elevated sympathetic tone?

4.5.4 The effects of sauna bathing on the SNS and HPA pathways

This section details the research on the endocrine effects of sauna on human subjects with particular reference to the HPA and SNS pathways. A search of Web of Science, EBSCO, and Ovid Medline was performed using “far-infrared sauna” OR “sauna” OR “thermal therapy”. The above search was combined by using AND with “autonomic nervous system” to identify relevant articles on the effects of sauna on the autonomic nervous system. Articles were restricted to the English language and human subjects. Articles were found exploring the endocrine effects of a single episode of sauna bathing (typically 15 to 30 minutes) and on the effects of repeated exposure to sauna bathing. The key articles are discussed below.

The effect of a single episode of sauna bathing on several measures of SNS and HPA pathways showed plasma noradrenaline, adrenaline, ACTH, prolactin, and cortisol were studied in eight males and eight females (Jezova, Kvetnansky, & Viggas, 1994). Repeated blood samples (via an indwelling catheter) were taken 15 minutes prior to the sauna and twice while in the sauna and at 15 and 30 minutes after the sauna. Noradrenaline, adrenaline, ACTH and prolactin increased during sauna exposure and returned to normal within approximately 60 minutes. Cortisol showed an initial decline in the first 15 minutes and then increased at 30 minutes. The authors concluded that a single episode of sauna bathing activates the pituitary-adrenocortical and sympathetic-adrenomedullary system. Several other studies have measured noradrenaline (reflecting HPA and SNS activity) and also showed a rise in serum noradrenaline levels with single episodes of sauna bathing (Kauppinen, Pajari-Backas, Volin, & Vakkuri, 1989; Kukkonen-Harjula, et al., 1989; Leppaluoto, et al., 1986; Vaha-Eskeli, et al., 1992).

Several studies have found a rise in serum adrenaline levels (reflecting HPA activity) with a single exposure to sauna bathing (Kauppinen, et al., 1989; Kukkonen-Harjula, et al., 1989; Leppaluoto, et al., 1986; Tatar, Viggas, Jurcovicova, Kvetnansky, & Strec, 1986; Vaha-Eskeli, et al., 1992) however there are also several studies showing no change in adrenaline during a single episode of sauna bathing (Hussi, et al., 1977; Kukkonen-Harjula, et al.,

1989; Laatikainen, Salminen, Kohvakka, & Pettersson, 1988). Jezova et al. (1994) states that studies not showing a rise in adrenaline levels may be erroneous because blood samples were not taken within the sauna but afterwards. Adrenaline has a short half-life of a few minutes (Dimsdale & Moss, 1980) and therefore adrenaline may have returned to baseline levels prior to the collection of the blood sample. For example Laatikainen et al. (1988) (found no increase in adrenaline levels) took blood samples prior to the sauna, after the sauna and 30 and 60 minutes later compared to Tatar et al. (1986) (found an increase in adrenaline levels) took samples via an indwelling catheter prior to the sauna and every 10 minutes in the sauna (sauna exposure of 30 minutes) and 30 minutes after the sauna. In order to detect changes in adrenaline concentration in the blood, the timing of the blood samples is important and it appears that continuous sampling via an indwelling catheter as performed by Tatar et al (1986) and Jezova et al. (1994) is the best method.

Cortisol (reflecting HPA activity) has been found to rise (Kauppinen, et al., 1989), remain unchanged (Laatikainen, et al., 1988) or fall (Kukkonen-Harjula, et al., 1989) during a single exposure to sauna bathing. Jezova et al. (1994) measured serum cortisol and found that cortisol reduced for the first 15 minutes while in the sauna and then had a rise at 30 minutes while participants were still in the sauna, then cortisol peaked at 45 minutes, 15 minutes after participants left the sauna. Jezova et al. (1994) state that a decrease, increase or no change in cortisol levels may be found depending on the timing of the sample collection. Kauppinen et al. (1989) discussed possible reasons for variable findings including when the blood samples were collected (whether samples were taken in the sauna or before and after) and the time of the day studies were conducted, since cortisol has a circadian rhythm.

There have been several other hormones and metabolites that have been measured in response to a single episode of sauna bathing. For instance melatonin did not change during a single exposure to sauna bathing (Kauppinen, et al., 1989) while beta endorphin has been found to increase after single exposure to sauna bathing (Kukkonen-Harjula, et al., 1989). Growth hormone, testosterone, prostaglandin E₂ and thromboxane A₂ were found not to rise from a single exposure to sauna bathing (Kukkonen-Harjula, et al., 1989).

A controlled experimental study looking at the urinary excretion of adrenaline and noradrenaline in a single episode of sauna bathing showed increased excretion of adrenaline and noradrenaline in the urine (Huikko, Jouppila, & Karki, 1966). An examination of the effect of a single episode of sauna bathing on heart rate variability (HRV) in ten patients (Gayda, et al., 2012) showed a decrease in HRV. This reduction in HRV reflects an increase in SNS activity which normalised after 15 to 120 minutes. These two studies as well as the aforementioned studies demonstrate an overall trend toward an increase in activity of the SNS and HPA pathways in response to a single episode of sauna bathing.

Two key studies have looked at the effect of repeated sauna bathing on a number of parameters. In an RCT of 30 subjects with congestive heart failure the effect of repeated sauna on the frequency of premature ventricular contractions was conducted (Kihara, et al., 2004). Treatment consisted of 10 sauna bathing exposures of 15 minutes duration over two weeks. Heart rate variability increased in the sauna group (113 +/- 8 to 142 +/- 10) compared to the control group (111 +/- 10 to 112 +/- 11) demonstrating a reduction in SNS activity with repeated sauna therapy. The incidence of premature ventricular contractions also reduced in the sauna group (3161 +/- 1104 to 848 +/- 415) compared to the control group (3048 +/- 914 to 3097 +/- 1033). Miyamoto et al. (2005) studied 15 hospitalised patients with congestive heart failure who underwent 15 minutes of sauna bathing for two weeks. Plasma adrenaline and noradrenaline concentrations both showed statistically significant reductions in the sauna group compared to the control group, 40 +/- 42 pg/ml versus 21 +/- 23 pg/ml ($p < 0.05$) and 633 +/- 285 pg/ml versus 443 +/- 292 pg/ml ($p < 0.01$) respectively. These results from the above two studies indicate there is a reduction in SNS activity in patients with congestive heart failure.

The studies examined in this section show that a single episode of sauna bathing leads to an increase in SNS and HPA activity. Repeated sauna bathing may have an opposite effect by reducing SNS activity in patients with congestive heart failure (Kihara, et al., 2004; Miyamoto, et al., 2005). There are no studies that examine the effect of repeated sauna bathing on individuals without congestive heart failure.

4.5.5 Sauna as an intervention for patients with chronic pain

To identify relevant articles on the effects of sauna on chronic pain, a literature search of Web of Science, EBSCO and Ovid Medline was performed using “far-infrared sauna” OR “sauna” OR “thermal therapy”. The above search was combined by using AND with “pain”. Articles were restricted to the English language and human subjects. Clinical trials of sauna for chronic pain conditions were restricted to RCTs but due to the lack of RCTs prospective case series were included if there were more than 10 participants. This search identified one RCT (Masuda, Koga, Hattanmaru, Minagoe, & Tei, 2005) and three case series (Matsumoto, Shimodozono, Etoh, Miyata, & Kawahira, 2011; Matsushita, Masuda, & Tei, 2008; Oosterveld, et al., 2009).

Masuda et al. (2005) performed an RCT with 46 chronic pain patients. Group A attended a four week inpatient multidisciplinary treatment including cognitive behavioural therapy, rehabilitation and exercise therapy while group B were treated with the same inpatient multidisciplinary treatment combined with repeated sauna once a day for four weeks. The Visual Analogue Scale (VAS) pain score, number of pain behaviours, self rating depression scale and anger scores decreased significantly after treatment in both groups. Pain behaviour was assessed using 11 items: (a) request for an analgesic agent, (b) request for a compress or massage, (c) complain of stubborn pain, (d) change in expression or posture due to pain, (e) complain that they cannot take care of themselves due to pain, (f) request for help in eating, bathing and excretion, (g) complain of sleeplessness due to pain, (h) complain of pain to family by telephone or calling them to hospital, (i) reject rehabilitation because of pain, (j) complain of dissatisfaction and blame the neutral attitude of the therapist, and (k) overreact to pain by gait disturbance, crying, hysterical reaction. The number of pain behaviours per day was counted by the doctor, nurse, clinical psychologist and other staff. All parameters reduced more in group B after treatment with the reduction in anger scores showing statistical significance. Two years after treatment 17 (77%) of patients in group B returned to work compared to 12 patients (50%) in group A ($P < 0.05$). The treatment was rated satisfactory or very satisfactory by 13 (55%) in group A and 18 (82%) in the sauna group.

Two cases series have reported a positive effect of regular sauna bathing on patients with chronic widespread pain (fibromyalgia). The first study (Matsushita, et al., 2008) reported a case series of 13 patients with fibromyalgia who attended a sauna for 15 minutes followed by lying down with a blanket for 30 minutes on two to five days per week. Visual analogue scores for pain and Fibromyalgia Impact Questionnaire (FIQ) were recorded before therapy, after the first session, after the 10th session and then at an average of 14 months follow-up. The mean VAS pain score reduced from 6.9 +/- 1.6 to 4.2 +/- 1.5 ($P < 0.05$) immediately after the first session. After the 10th session VAS pain score was 3.3 +/- 1.1 ($P < 0.05$) and at average 14 months follow up was 3.9 +/- 2.2 ($P < 0.05$). The FIQ score before therapy was 44.8 +/- 13.5, after 10 sessions 29.3 +/- 7.9 ($P < 0.05$) and at 14 months average follow up 27.0 +/- 11.4 ($P < 0.05$). The researchers concluded that the effects were dramatic and further clinical studies in larger populations were required to confirm the effects of this method of treatment.

To investigate the benefit of repeated sauna three times a week and underwater exercise twice a week for 12 weeks duration, 44 patients with fibromyalgia of five to 24 months duration were followed in a case series (Matsumoto, et al., 2011). Pain, symptoms and quality of life were measured using VAS (/10), FIQ and the Short Form 36 questionnaires (SF-36) respectively. All of the patients experienced significant reductions in pain of 31% to 77% after the 12 week programme with continued improvements seen at six month follow up. The average VAS pain score reduced from 7.5 +/- 1.3 prior to treatment, to 3.1 +/- 1.1 ($P < 0.05$) after 12 weeks and 3.7 +/- 0.9 ($P < 0.05$) at six months. The FIQ score decreased significantly from 44.8 +/- 3.6 to 27.1 +/- 5.6 after 12 weeks to 28.6 +/- 5.2 ($P < 0.05$) after six months. In all eight domains of the SF-36 questionnaire there were statistically significant improvements in quality of life measures after treatment that was maintained at six months. Furthermore 21 of the 32 patients who had quit their job or taken a leave of absence returned to work and showed an improved physical functioning following sauna therapy.

A pilot study investigating sauna bathing twice a week for four weeks on patients with ankylosing spondylitis (n=17) and rheumatoid arthritis (n = 17) (Oosterveld, et al., 2009)

showed no significant reduction of pain, stiffness or fatigue measured by VAS scales after sauna bathing twice weekly. At four weeks there were improvements of approximately 10% to 15% in all three parameters but none of the changes reached statistical significance. After repeating power calculations for a controlled clinical study it was deemed that 25 patients in each group are required. The sauna was well tolerated with no significant side effects in this study.

Two cohort studies (Matsumoto, et al., 2011; Matsushita, et al., 2008) and one RCT (Masuda, Koga, et al., 2005) showed a positive effect of sauna bathing on chronic pain patients while an underpowered pilot study showed no effect. There were no dropouts or side effects mentioned in the above studies. Overall it would seem sauna bathing may be a safe and effective therapy for certain chronic pain conditions without too many side effects. It also has the potential to be self directed which reduces the costs of engaging therapists on a regular basis (several times a week).

4.5.6 The psychological effects of sauna bathing

This section details a literature review of clinical trials looking at the psychological impact of sauna bathing, in particular depression, stress and insomnia. A search of Web of Science, EBSCO and Ovid Medline was performed using “far-infrared sauna” OR “sauna” OR “thermal therapy”. The above search was combined by using AND with “anxiety disorder”, “insomnia”, “stress” and “depression” to identify relevant articles on the effects of sauna on psychological health. Articles were restricted to the English language and human subjects. When combining with either anxiety disorder, insomnia and stress, zero articles were identified. When combining with depression one RCT explored the effects of repeated sauna on patients with mild depressive illness (Masuda, Nakazato, Kihara, Minagoe, & Tei, 2005) and one article showed the effects of a single session of sauna on mental health (Hayasaka, et al., 2008).

Masuda et al. (2005) performed an RCT of 28 patients with mild depressive illness that were randomised into two groups of 14 patients in an inpatient multidisciplinary setting for a four week programme. Both groups attended occupational and physical therapy once a

day for five days a week and the thermal therapy group attended a 15 minute sauna followed by 30 minutes lying down once a day for five days per week. The non thermal group placed in a supine position for 45 minutes once a day for five days in the week. Somatic and mental complaints and depressive mood were evaluated by the Japanese versions of the Cornell Medical Index and the Zung Self Rating Depression Scale respectively. The Cornell Medical Index somatic complaints scale was significantly reduced in the thermal therapy group and changes in the Zung Self Rating Depression Scale did not reach statistical significance between the two groups. Hayasaka et al. (2008) studied the effects of a single exposure of varying time lengths (5 minutes to greater than 40 minutes) to a charcoal kiln sauna on 45 volunteers. Participants completed the Profile of Mood States and State-Trait Anxiety Inventory before and after the sauna. All mood scales and anxiety measures improved after the sauna exposure ($P < 0.001$).

Overall no conclusions can be drawn on the psychological impact of regular sauna bathing due to the lack of studies in this field.

4.6 Summary

This chapter has outlined the pathways of nociception, metabotropic receptors and generation of second messengers, neural sensitisation, the SNS and HPA response to stressors including sauna bathing. The effects of sauna bathing on chronic pain and psychology have been reviewed. In the Adrenaline Model of Headache Causation outlined in Chapter 5, hyperactivity of the SNS and HPA pathways is proposed as the significant contributor to the development of peripheral and central nervous system sensitisation in the pathways of nociception.

Chapter 5

THE ADRENALINE MODEL OF HEADACHE CAUSATION

5.1 Introduction

The Adrenaline Model of Headache Causation has been developed during this PhD project using the information discussed in Chapters 2 to 4. The Adrenaline Model of Headache Causation combines the knowledge from the literature on headache disorders including prevalence (section 3.2), headache triggers (section 3.3), RCTs of preventative interventions (section 3.7), current models of headache causation (section 3.8) and experimental induction of headache disorders (section 3.9) with the neurophysiology of nociception (section 4.2), synaptic transmission and second messengers (section 4.3), neural sensitisation (section 4.4), and the stress response (section 4.5) together with my clinical experience in chronic pain over the past 15 years outlined in Chapter 2.

The Adrenaline Model of Headache Causation is different to other models proposed in that it identifies a likely source of neural (central and peripheral) sensitisation. The model has been developed by examining the variety of phenomena associated with headache disorders in an attempt to piece together a model that is consistent with these phenomena. Previous models have looked at certain phenomena in isolation (e.g. vasodilatation and muscle tenderness) relating the phenomena to headache and trying to develop a cause and effect.

5.2 The Adrenaline Model of Headache Causation

Transmission of painful stimuli requires transmission of action potentials in the pathways of nociception. The initiation of nociception would normally be expected to start with action potentials being formed in the peripheral nociceptor and transmitted through the dorsal horn, thalamus and onto the somatosensory cortex (Figure 4.1). In primary headache disorders there is no known source of nociception. In migraine, headache is clinically the most important symptom, with the origin of pain also unknown (Messlinger, 2009). The Adrenaline Model of Headache Causation proposes that the stress pathways (significantly the SNS and HPA pathways) increase neuronal excitability (reduce threshold of

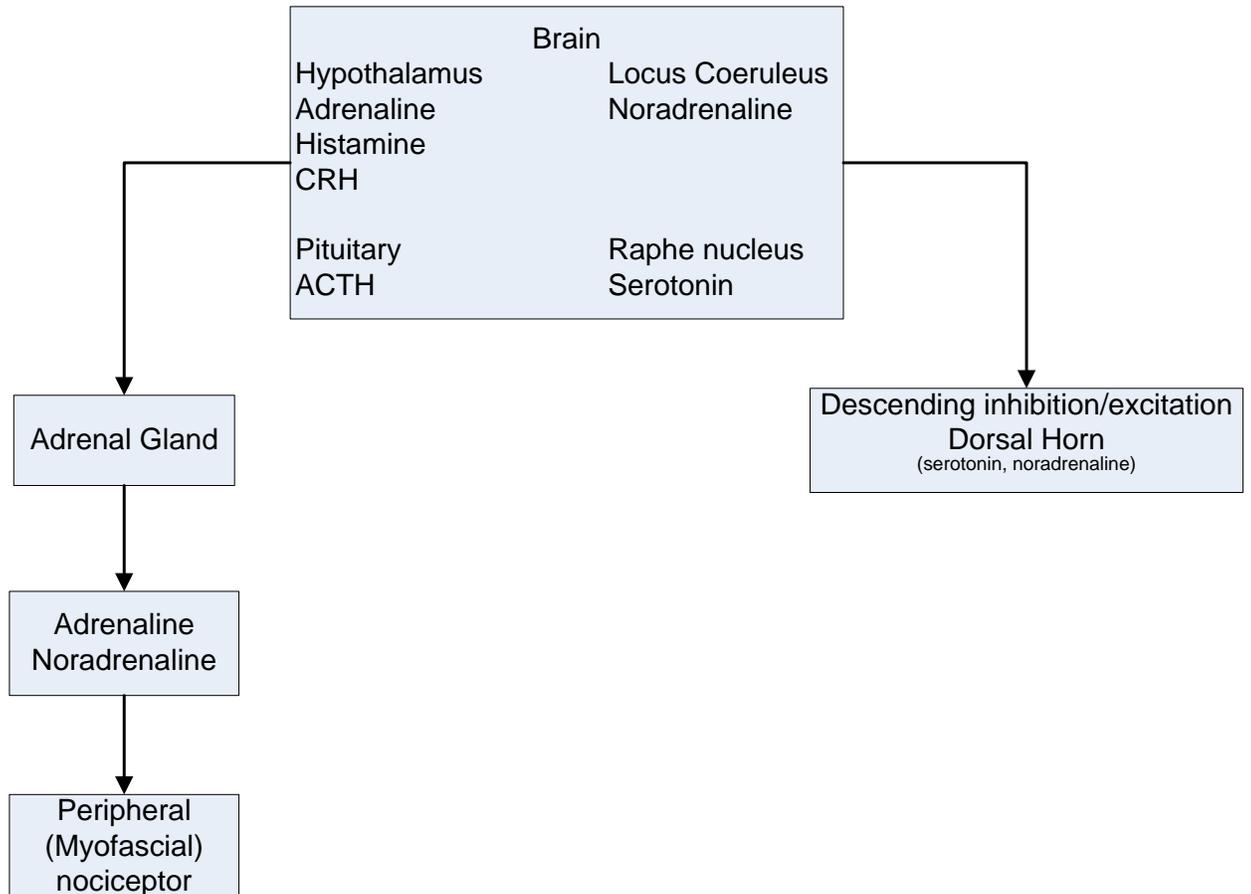
transmission) in the pathways of nociception through neurotransmitters binding to metabotropic receptors, activating second messenger cascades with subsequent development of central and peripheral sensitisation. Headache triggers (section 3.3) create headache episodes in people with central and peripheral sensitisation, more easily than in individuals without central or peripheral sensitisation due to this neuronal excitation (section 4.4). The lowered threshold for action potential transmission in the pathways of nociception may also lead to transmission of nociception from structures (e.g. pericranial muscles or cervical spine structures) that do not cause pain in the absence of neuronal excitability.

Central sensitisation is likely to be due to the effects of stressors (section 4.5) activating several pathways in the brain resulting in the release of CRH, ACTH, adrenaline, noradrenaline, serotonin and histamine as shown in Figure 5.1. The descending noradrenergic and serotonergic pathways may contribute to reducing thresholds at the dorsal horn. Peripheral sensitisation may be explained by adrenaline (and noradrenaline to a lesser extent) binding to β receptors with subsequent formation of cAMP which activates the transient receptor potential (TRP) channel proteins (section 4.2) and reduces the threshold for the production of action potentials in peripheral nociceptors found in the skin and muscle. In the Adrenaline Model of Headache Causation neuronal excitability in the central nervous system is likely to play a major role in the causation of headache disorders, with peripheral sensitisation playing a lesser role.

The thalamocortical projection fibres operate in two modes, the tonic mode during wakefulness and Rapid Eye Movement (REM) sleep and the burst mode during slow wave sleep (McCormick & Bal, 1994). As stated before (section 4.2) during the burst mode transmission of detailed sensory information is blocked whereas during the tonic mode sensory information is relayed to the sensory cortex. Several inputs into the thalamus depolarise thalamic neurons shifting them to the tonic mode and therefore enhancing transmission of nociceptive and other sensory stimuli. The noradrenergic input from the locus coeruleus, histaminergic projections from the hypothalamus and serotonergic projections from the raphe nuclei, all depolarise thalamic neurons toward the tonic mode

(Nolte, 2002). Reciprocal corticothalamic fibres are however numerically the largest input to the thalamus and have been shown in animal studies to change thalamic mode from burst to tonic (McCormick & von Krosigk, 1992).

Figure 5.1: The contribution of the stress response to the development of central and peripheral sensitisation



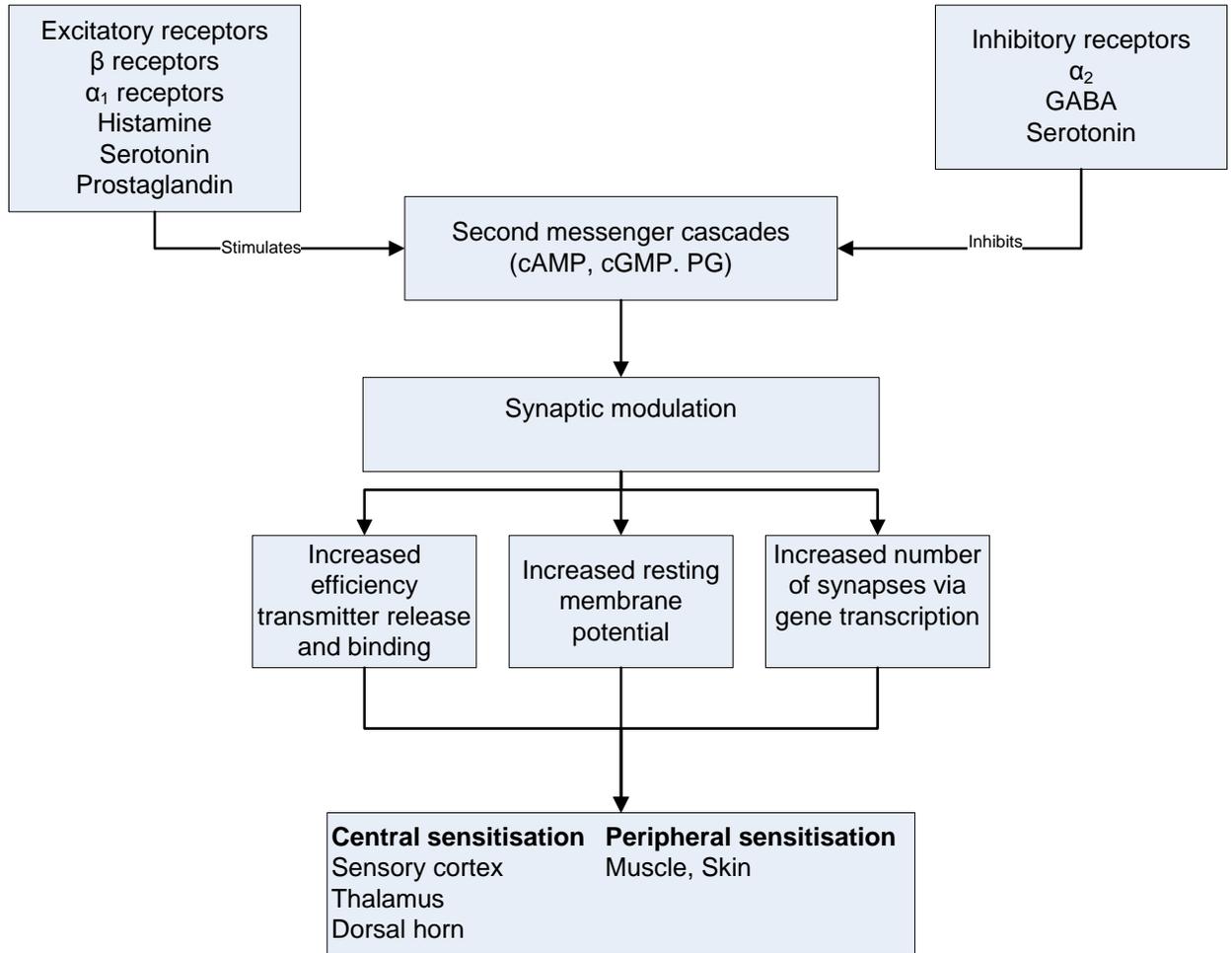
Noradrenergic cells in the dorsolateral pontine tegmentum and locus coeruleus are a major source of noradrenergic projections to the spinal cord. Noradrenaline can reduce nociception by attaching to the α_2 receptor in the dorsal horn (G-coupled inhibitory receptor reducing activity of adenyl cyclase with subsequent reduction in cAMP), however the influence of noradrenergic projections to the spinal cord can also be facilitatory when mediated by α_1 receptors which activates phospholipase C and increases intracellular IP3 and calcium. The noradrenergic descending system therefore can inhibit or facilitate the

transmission of nociception in the spinal cord (Heinricher, 2005). The α_1 receptor has lower affinity to noradrenaline than α_2 receptors (Carrasco & Van de Kar, 2003) and at lower concentrations of noradrenaline, α_2 receptor activity may dominate while α_1 receptor activity starts only at higher concentrations. Although the exact mechanism of this dual action is unknown during times of low central nervous system SNS outflow from the brain, the transmission of nociception may be inhibited at the dorsal horn by noradrenaline and during times of increased SNS activity, transmission of nociception may be increased.

Metabotropic receptors are important in setting the threshold for action potential and in initiating the action potential (Connors, 2003b). Various metabotropic receptors are likely to influence the transmission of action potentials in the pathways of nociception (Figure 5.2). Certain serotonin receptors ($5HT_2$), histamine receptors, prostaglandin receptors, α_1 and β receptors are likely to increase second messengers leading to opening of ion channels and reducing the action potential threshold in the pathways of nociception (Figure 5.2). GABA, α_2 receptors and certain serotonin receptors ($5HT_1$) reduce second messengers, leading to closing of ion channels and subsequent reduction in the threshold of generating action potentials in the pathways of nociception (Figure 5.2).

Once peripheral and central sensitisation has occurred, the threshold for the generation of action potentials in the pathways of nociception is reduced and the transmission of nociceptive signals that does not usually reach the threshold for generating an action potential (e.g. pericranial muscles) without sensitisation, may now reach the threshold for generating an action potential in the pathways of nociception. This may explain a role for myofascial tissue in creating nociception. Myofascial tenderness is present in people with headache regardless of the presence or absence of headache. If the HPA and SNS pathways are activated then both the action of adrenaline on peripheral nociceptors (generating action potentials) and the proposed lowered threshold for nociception in the central nervous system, may contribute to the experience of pain from myofascial tissue.

Figure 5.2: The action of metabotropic receptors in setting neuronal excitability in the pathways of nociception



Headache triggers (section 3.3) that activate the SNS and HPA pathways (stress, changes in temperature, vigorous exercise, poor sleep, fasting) may activate second messenger cascades that create EPSP that may exceed the threshold of action potentials in the pathways of nociception when central sensitisation is present, explaining how these triggers generate headache. A prolonged or substantial stress will result in up regulation of the adrenal gland (section 4.5), resulting in increased sensitivity of the neuroendocrine response to stressors increasing the neurotransmitters and adrenal catecholamines sustaining lower thresholds for the transmission of nociception in the pathways of nociception, creating periods of higher headache frequency.

Nociceptive stimulation has been found to activate the locus coeruleus in animal studies (Voisin, Guy, Chalus, & Dallel, 2005) therefore pain itself may lead to increased nociceptive transmission by activating the SNS. In effect chronic pain may lead to the amplification of pain, if the SNS is responsible for setting the pain threshold in the pathways of nociception.

The Adrenaline Model of Headache Causation may explain the amplification of pain anywhere in the body. People with headache may experience either amplified pain from structures around the head and neck (referred pain) due to sensitisation of the pathways of nociception to cause headache. In people without sensitisation of the pathways of nociception, pain is not experienced, as action potentials are either inhibited and/or the severity of stimulus and duration of stimulus required is greater to reach action potential. The head and neck may also have relatively large receptive fields in the thalamus and/or sensory cortex making them prone to developing pain more frequently than other parts of the body.

Central and peripheral sensitisation has been the favoured explanation for the development of TTH and migraine by prominent researchers in the field of headache in the last decade (Bendtsen, 2000; Dodick & Silberstein, 2006; Goadsby, 2005; R. Jensen, 2003; T. Jensen, 2001). The experimental induction of headache by several infusions (section 3.8) has shown that an increase in secondary messengers such as cAMP, cGMP and others is likely to play a role in the induction of headache. Second messengers have the ability to open ion channels leading to action potentials at the peripheral myofascial nociceptors, dorsal horn and thalamus.

Several models of headache causation outlined in section 3.8 relate phenomena commonly associated with headache (e.g. vasodilatation, muscle tenderness and reduced pericranial pain threshold) to headache disorders, but fail to pinpoint the mechanism by which stress and other triggers cause generalised muscle tenderness, reduced sensory threshold and headache pain. Analysis of these current models of headache causation, studies on headache induction and experience in managing chronic pain patients, has led to the

Adrenaline Model of Headache Causation (Figure 5.3) outlined in this chapter in an endeavour to link the headache phenomena, triggers and studies of headache pathophysiology.

Current models of headache causation do not fully explain many of the research findings around headache disorders. In particular current headache models do not explain how triggers such as change in temperature, alcohol and stress cause episodes of headache; why the prevalence of headache is reduced in the elderly; why the prevalence of TTH is lower in Africa and Asia compared to Europe; how preventative measures including relaxation and exercise may improve headache and how medications can create headache or abort headache.

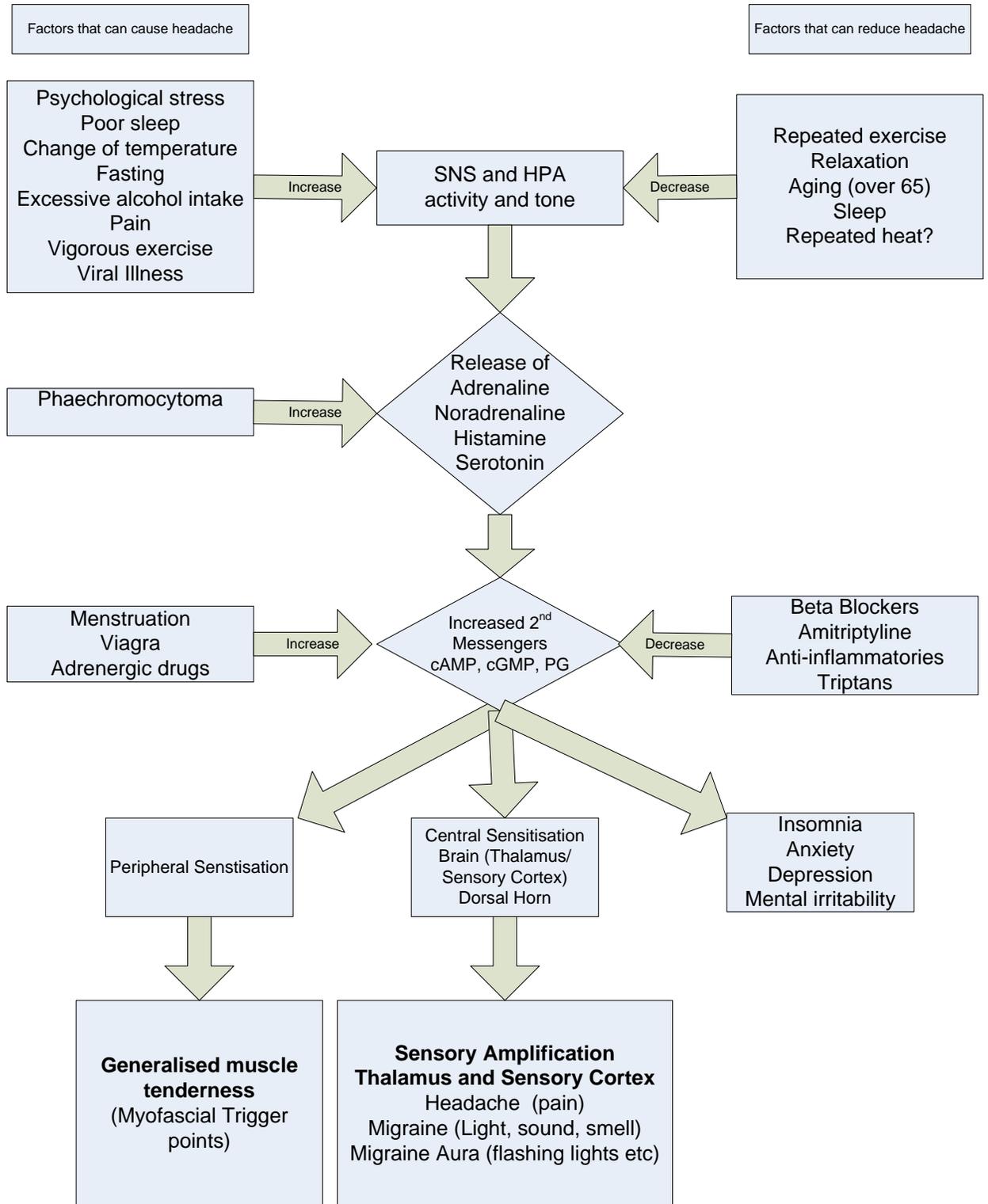
Jensen (2001) states there's quite an explosion of new information on the mechanisms of pain over the previous two decades, however there has been no similar improvement in our handling of patients with chronic pain including headache disorders. Despite another decade passing this statement is still valid.

An overview of the Adrenaline Model of Headache Causation is shown in Figure 5.3. Increased sympathetic tone increases the likelihood of developing headache disorders while those factors that reduce sympathetic tone may improve headache disorders. It has been shown that psychological stress (Pike, et al., 1997), sleep disturbance (Burgess, et al., 1997), fasting (Segel, et al., 2002), alcohol (van de Borne, et al., 1997), vigorous exercise (Kotchen, et al., 1971), viral illness (Mason, et al., 1979), pain (Danilov, et al., 1994), cold (Vybiral, Lesna, Jansky, & Zeman, 2000) and heat (Vescovi, et al., 1992) can activate the SNS and/or HPA pathways. Heat (Yagiz On, et al., 1997), relaxation (Lucini, et al., 1997; Pike, et al., 1997), ageing (Seals & Esler, 2000), regular exercise (Mueller, 2007) and sleep (Burgess, et al., 1997; Hornyak, Cejnar, Elam, Matousek, & Wallin, 1991; Zhong, et al., 2005) can result in a reduction of SNS tone. Heat, exercise, relaxation and sleep are changeable factors that can be manipulated to reduce sympathetic tone and perhaps reduce headache symptoms.

The headache disorders including TTH and migraine may have similarities in that central sensitisation may occur in both groups and lead to increasing frequency of episodes of TTH or migraine. Migraine is also different in that it is at the severe end of a spectrum perhaps due to a genetic predisposition of neuronal excitability being present (Messlinger, 2009). People who experience migraine may also experience TTH, however a person who experiences TTH is unlikely to experience migraine unless a person has genetic predisposition for migraine. Migraine patients are characterised by neuronal excitability that is generalised to all senses leading to increased sensitivity to pain, light (photophobia), sound (phonophobia), touch (allodynia) and smell (hyperosmia) and the threshold of stimuli that triggers episodes of TTH episodes is likely to vary for migraineurs and non migraineurs. Ulrich et al. (1996) investigated the triggers for TTH in migraineurs and non migraineurs and found only migraineurs developed TTH precipitated by alcohol, overmatured cheese, chocolate and physical activity (Ulrich, et al., 1996). Migraineurs may require less activation of the pathways that lead to headache episodes shown in Figure 5.3, due to their increased neuronal excitability.

Phonophobia has been investigated in migraine sufferers and migraine free controls to establish whether phonophobia is a manifestation of loudness recruitment in the cochlear apparatus (Woodhouse & Drummond, 1993). Auditory discomfort thresholds were measured in 16 migraine patients when experiencing migraine and without migraine symptoms, and 16 headache free individuals. The auditory discomfort threshold decreased significantly during attacks of migraine, which was different from those with loudness recruitment from cochlear injury and in most cases phonophobia was not associated with hearing loss for low intensity sounds. The authors concluded the data did not support phonophobia was of cochlear origin but more likely to be due to central sensory processing mechanisms. Auditory discomfort thresholds were similar in migraine patients not experiencing current symptoms and migraine free individuals. Visual discomfort thresholds were measured during the same study and found to be lower in

Figure 5.3: The Adrenaline Model of Headache Causation



migraine patients when not experiencing symptoms than migraine free individuals. Visual discomfort thresholds and auditory discomfort thresholds reduced in migraine sufferers when they experienced a migraine episode. This study highlights that the increased light and sound sensitivity that occurs with migraine patients is likely to be due to alterations in central sensory processing.

Nosedá and Burstein (2000) have looked at mechanisms to explain photophobia and in particular how light can increase headache pain intensity (Nosedá & Burstein, 2011). They traced light sensitive neurons and found they converged with dura sensitive neurons at the posterior thalamus. With single unit recording and neural tract tracing, they found dura sensitive neurons in the posterior thalamus whose activity was modulated by light. Even in blind individuals who could perceive light, light aggravated their migraine symptoms. They concluded that a group of photoreceptors project onto the neurons on the thalamus that also process pain signals; thereby explaining how light aggravates headache pain.

The catecholamine response to light changing from low luminosity to high luminosity was examined using urinary excretion of adrenaline in 26 migraineurs and 25 controls with back pain (Stoica & Enulescu, 1988). A statistically significant increase in adrenaline levels was found in the migraineurs when exposed to light with high luminosity. Bright light and glare have been found to trigger migraine (Kelman, 2007; Scharff, et al., 1995) and TTH (Scharff, et al., 1995) and the increase in SNS and HPA activity may be the mechanism of this trigger, which is consistent with the Adrenaline Model of Headache Causation.

Hyperosmia is present in migraine patients and persists between episodes of migraine. Olfaction thresholds for acetone and vanillin together with an unpleasantness rating were measured in 20 migraine sufferers and 21 headache free controls (Snyder & Drummond, 1997). The olfactory threshold was lower for vanillin in migraine patients compared to headache free controls and they detected the acetone at a lower concentration than controls. The Adrenaline Model of Headache Causation proposes an increase in SNS and HPA activity (as well as other pathways involved in the stress response e.g. serotonin, histamine) are important in initiating and maintaining central and peripheral sensitisation and also may

trigger episodes of headache in the presence of central and peripheral sensitisation, however a review article examining studies of noradrenaline levels in headache disorders has found plasma noradrenaline is lower in headache patients than headache free controls (Peroutka, 2004). Peroutka (2004) reviewed six studies that investigated the levels of noradrenaline in headache disorders finding noradrenaline levels are lower in patients with headache disorder compared to headache free controls and they concluded sympathetic hypofunction is present in headache disorder patients.

Of all the studies reviewed by Peroutka (2004) the duration of migraine was longstanding e.g. 19.8 years (Havanka-Kanniainen, Juujarvi, Tolonen, & Myllyla, 1987) and 8.6 years (Mikamo, Takeshima, & Takahasi, 1989) and all studies measured noradrenaline in a non headache period. Although four (Gotoh, Komatsumoto, Araki, & Gomi, 1984; Mikamo, et al., 1989; Nagel-Leiby, Welch K, G, Grunfeld, & Brown, 1990; Takeshima, Takao, Urakami, Nishikawa, & Takahasi, 1989) of the six studies did show a lower level of noradrenaline in migraine patients than headache free controls, one study (Havanka-Kanniainen, et al., 1987) showed no statistically significant difference between noradrenaline levels between migraineurs and controls. Another study compared levels of noradrenaline in migraineurs to controls that were undergoing acute stressful episodes (e.g. first 24 hours of a stroke and surgical intervention) (Martinez, Castillo, Pardo, Lema, & Noya, 1993) and found that the levels of noradrenaline were likely to be markedly elevated in acute stressful episodes, and concluding that noradrenaline levels are lower in migraineurs than headache free individuals may be erroneous from this particular study.

Sympathetic nervous system activity has been investigated by measuring the cardiovascular reflexes after infusions of noradrenaline and clonidine in both migraineurs in a headache free period (n=13) and in migraine free controls (n=18) (Cortelli, et al., 1991). The results showed that migraineurs during the headache free interval have a normal central sympathetic response, rather than sympathetic hypofunction.

Several studies have examined SNS activity in headache sufferers by measuring noradrenaline level changes from supine posture to an upright posture. Gotoh et al. (1984)

studied 10 patients with classic migraine, 10 with common migraine and 11 headache free controls and found the resting levels of noradrenaline were lower in the classic migraine group (80.9 pg/ml) and common migraine group (77.1 pg/ml) compared to the headache free control group (151.7 pg/ml). However on postural change from supine to the upright position the increase in plasma noradrenaline was similar in all three groups (classic migraine 43.2 pg/ml, common migraine 49.2 pg/ml and control 49.2 pg/ml). Similar findings on testing changes in noradrenaline on postural change from supine to standing was found in two other studies (Havanka-Kanniainen, et al., 1987; Mikamo, et al., 1989). Therefore although the baseline levels of noradrenaline are lower in migraine and headache patients than headache free controls, the increase in noradrenaline on changing from the supine to upright position parallels the rise in controls. Baseline noradrenaline levels are approximately 60% of controls in both supine and standing positions (Peroutka, 2004). Overall baseline noradrenaline levels are lower in headache and migraine patients than headache free controls, however the function of the SNS as measured by noradrenaline changes in posture from supine to standing is still intact. An alternative conclusion may be that the SNS has reset noradrenaline levels to a new baseline with SNS function intact, with no absolute SNS hypofunction present.

Alpha adrenergic supersensitivity has been demonstrated by injecting phenylephrine (selective α_1 adrenergic agonist) in migraine and migraine free controls (Bocconi, Allesandri, Fusco, & Cangi, 1989). Phenylephrine increased blood pressure, mean arterial pressures, and heart rate significantly more in migraineurs than controls. This suggests that a lowering of the noradrenaline level is accompanied by an increase in adrenergic receptor sensitivity. If similar rises in noradrenaline occur to changes in posture and other stressors and there is an adrenergic receptor sensitivity, the net result may be an increase in the production of second messengers, subsequent opening of ion channels and increased transmission of action potentials in the pathways of nociception. Consequently the lower levels of basal noradrenaline may reflect a resetting of basal levels of noradrenaline and paradoxically there may be an actual increased effect of SNS activation on neurons (via second messengers after noradrenaline binds to metabotropic receptors) in the presence of lowered baseline noradrenaline levels.

The levels of noradrenaline may be elevated in the early phase of headache (first few months or years) and at some point perhaps due to pre-synaptic α_2 autoreceptors there is a reduction in baseline noradrenaline levels and an increase in adrenergic receptor sensitivity. A similar pattern for serum cortisol was found by Kiran et al. (2005) who measured cortisol in 380 patients with CTTH, finding plasma cortisol was higher in those with less than five years headache duration (7.13 mg/dl +/- 2.01) compared to those with greater than five years headache duration (5.22 mg/dl +/- 2.09). After eight weeks of treatment (autogenic relaxation), cortisol returned to levels similar to those with headache of less than five years duration (7.27 mg/dl +/- 3.35) with no significant change in cortisol levels in those with less than five years of headache. This lower cortisol in those with greater than five years of headache may reflect a similar phenomenon, in that a resetting of hormone level has occurred that was accompanied by return to normal levels after treatment. In future studies of migraine and headache prevention, noradrenaline levels taken before and after treatment may show a return to normal levels of noradrenaline similar to cortisol with a reduction of headache activity? Overall the above may point to adrenergic receptor sensitivity being a significant determinant of headache activity, rather than absolute baseline noradrenaline levels.

A similar finding is seen in hypertension where overwhelming evidence is found for increased sympathetic activity (Julius & Majahalme, 2000) where levels of noradrenaline are increased in young patients with hypertension that reduces in older patients (Julius & Nesbitt, 1996) which is thought to be due to emerging adrenergic receptor hypersensitivity, that requires less sympathetic drive to maintain elevated blood pressure.

A review of complex regional pain syndrome (CRPS) (Drummond, 2010) found sympathetic dysfunction with noradrenaline levels that were lower within the affected limb, adrenergic supersensitivity with increased α_1 receptors found in skin biopsies taken from affected limbs compared to pain free controls and that sympathetic arousal can evoke pain in CRPS patients. A similar pathophysiology of sympathetic dysfunction and adrenergic receptor sensitivity may be present in both headache disorders and CRPS.

Levels of hormones and neurotransmitters other than noradrenaline released in the stress response have been studied in headache disorders. Adrenaline has been found to be elevated in headache patients compared to headache free controls in headache free periods reflecting increased activity of the HPA pathways. Adrenaline levels in cerebrospinal fluid and plasma has been found to be similar in migraine in the headache free period and for participants undergoing acute stressful episodes (Martinez, et al., 1993) and a significant positive correlation was found between cerebrospinal adrenaline levels and severity of classic migraine. Elevated plasma adrenaline and thromboglobulin (reflects platelet turnover) has been found in hypertension with a positive correlation found between these two factors in hypertension (Julius & Majahalme, 2000). Plasma thromboglobulin has been measured in migraine, muscle contraction headache and headache free controls with thromboglobulin being significantly higher in both headache groups compared to headache free controls.

A review article of serotonin levels in headache sufferers (Hamel, 2007) stated that consistent increased plasma serotonin levels were found during migraine attacks and low plasma serotonin levels were found in migraine patients between attacks and altogether these observations lead to a conclusion that low serotonin may form the biochemical basis of migraine aetiology, and a sudden increase in serotonin release is part of the triggering event that culminates in a migraine episode. Low serotonin levels present between migraine episodes may reflect a resetting of the levels similar to noradrenaline together with the possibility of receptor sensitivity, which may explain the reduced baseline levels of serotonin and raised serotonin levels during attacks.

5.3 Phenomena explained by the Adrenaline Model of Headache Causation

The Adrenaline Model of Headache Causation (Figure 5.3) presented in this PhD study may explain many headache phenomena found in the literature of CTTH including prevalence (section 3.2), headache triggers (section 3.3), headache comorbidities (section 3.4), medications prescribed for headache (section 3.7), muscle tenderness (section 3.8.3)

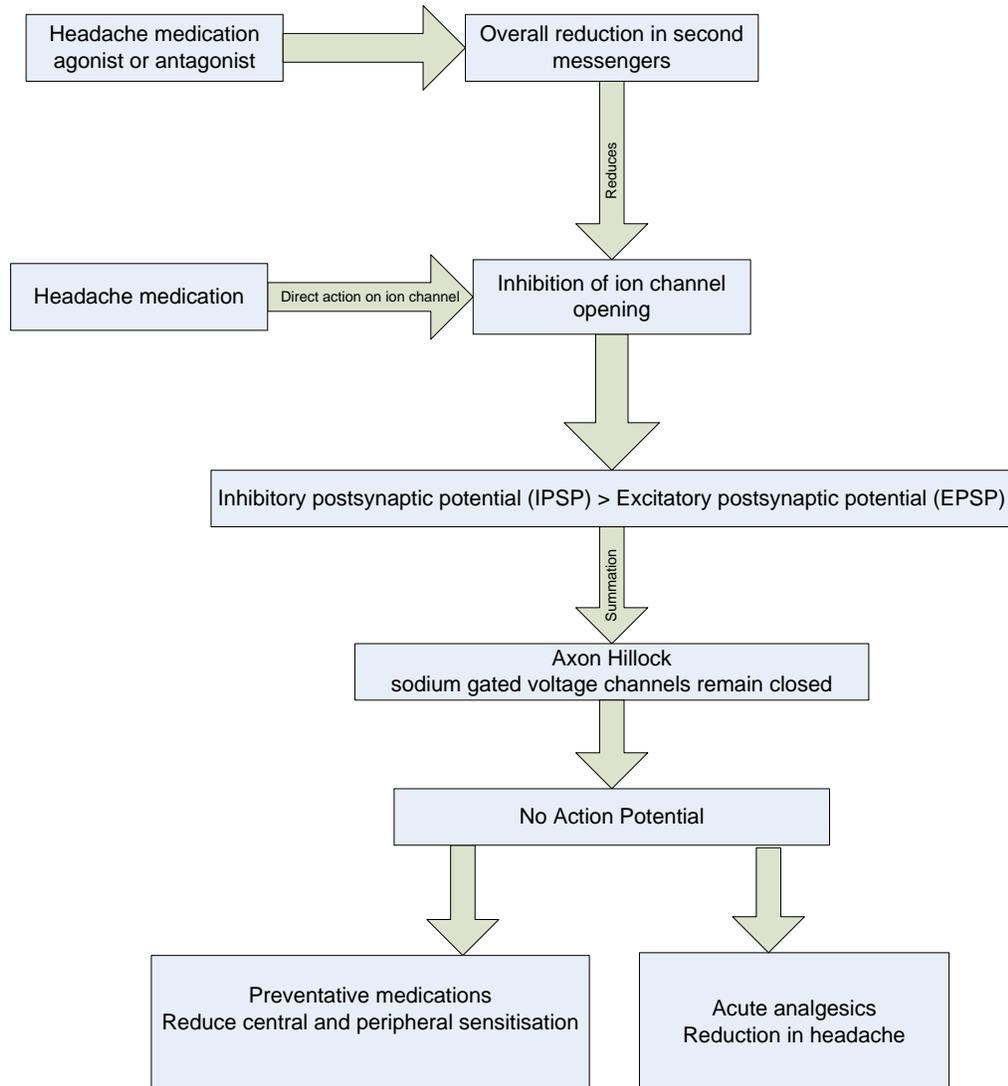
and experimental reproduction of headache (section 3.9). These phenomena will be discussed in the context of the Adrenaline Model of Headache Causation.

5.3.1 The mechanism of action of headache medication

Most medications that reduce headache (section 3.7) inhibit the production of second messengers that may reduce the generation and propagation of action potentials in the excitatory pathways of nociception. They may also facilitate neural pathways that inhibit nociception. Medications can act as an agonist (a drug that binds and activates a receptor) or an antagonist (a drug that binds and prevents the agonist binding to the receptor) depending on the actions of the receptor. If the receptor results in an increase in second messenger production when stimulated (e.g. β receptors) then medications reducing headache may be antagonists (e.g. β blockers) and if the receptor results in a subsequent reduction in second messengers when stimulated (e.g. $5HT_1$) then an agonist (triptans) may alleviate headache (Figure 5.4). Many receptors have subtypes, some of which increase second messengers and some which reduce second messengers e.g. serotonin $5HT_1$ receptor stimulation reduces second messengers and $5HT_2$ receptor stimulation increases production of second messengers, therefore medications with serotonin agonist properties (triptans acting via $5HT_1$ receptors) may reduce headache activity while medication with serotonin antagonist activity (methysergide and cyproheptadine via $5HT_2$ receptors) may reduce headache activity.

The central nervous system stress response includes the release of noradrenaline, adrenaline, serotonin and histamine. Medications that alleviate headache act at several receptor sites (Table 5.1) including histamine receptors, serotonin receptors, β receptors and α_2 receptors, to reduce the production of second messengers and subsequent formation of an action potential. Medications can also act directly at the ion channel e.g. sodium valproate to block inflow of ions needed for the generation and propagation of an action potential (Table 5.1).

Figure 5.4: The mechanism of action of headache medication



Headache disorder medication is used both to abort acute attacks and as a preventative measure. The acute treatment of headache disorder (migraine and/or TTH) medications includes the use of ergotamine, the triptans, anti-nausea medications and NSAIDs or combinations of the aforementioned. While triptans are mostly reserved for migraine they also have efficacy for TTH (Cady, et al., 1997; Lipton, et al., 2000). Ergotamine has both α_2 adrenergic and serotonergic agonist activity (Table 5.1). Both ergotamine and dihydroergotamine are agonists at the serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F} receptors. When these drugs bind to their specific receptors, it results in the reduction of

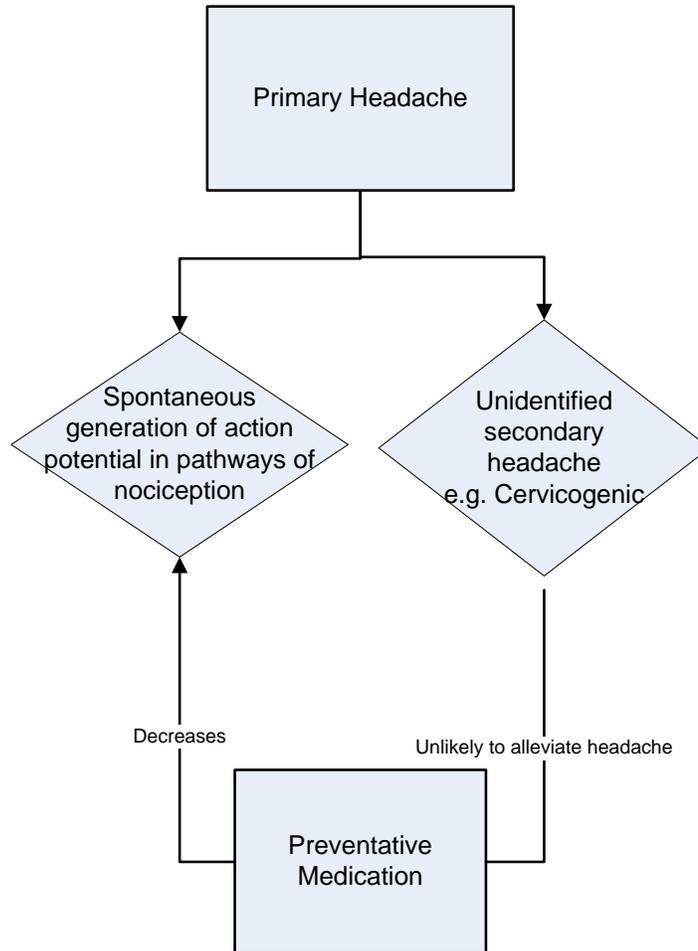
| Table 5.1 Headache medication receptor sites of action and changes in second messengers or ion channel | | | | | | |
|--|--|--|----------------------------------|--|----------------------------|--------------------------------|
| Headache medication | | | Agonist or Antagonist | | receptor or ion channel | second messenger or ion change |
| Triptans | | | Agonist | | 5HT _{1B,1D,1F} | reduces cAMP |
| Ergotamine/dihydroergotamine | | | Agonist | | 5HT _{1A,1B,1E,1F} | reduces cAMP |
| | | | Agonist | | α_2 | reduces cAMP |
| NSAID | | | Antagonist | | EP ₂ | reduces cAMP |
| B Blocker | | | Antagonist | | β_2 | reduces cAMP |
| Amitriptyline/desipramine | | | Antagonist | | H ₁ | reduces cGMP |
| | | | Antagonist | | M ₃ | reduces cGMP |
| | | | Reduces β receptor density | | β | reduces cAMP |
| | | | | | sodium | reduces sodium |
| | | | | | calcium | reduces calcium |
| Buspirone | | | Agonist | | 5HT _{1A} | reduces cAMP |
| Alprazolam | | | Agonist | | GABA _A | increases chloride |
| Calcium channel blocker | | | | | calcium | reduces calcium |
| sodium valproate | | | | | sodium | reduces sodium |

adenyl cyclase activity and the subsequent reduction in cAMP production (Silberstein, Freitag & Bigal, 2008).

Non steroidal anti-inflammatory medications reduce the production of second messengers by inhibiting the production of prostaglandins. Prostaglandin E₂ (PGE₂) binds to the prostaglandin E₂ receptor (EP₂) to increase the subsequent production of cAMP (Hata & Breyer, 2004), therefore a reduction of prostaglandins reduces generation of second messengers and transmission of pain in the pathways of nociception.

Preventative medication is prescribed for people who suffer frequent headache symptoms (section 3.7). Preventative medication is not effective for a proportion of patients. This may reflect the inability to tolerate the medication due to side effects, or may reflect the heterogeneous population of people enrolled in a clinical trial of headache disorders. Some patients diagnosed with primary headache disorder may have undiagnosed pathology that is causing their headache and will not respond to preventative medication (Figure 5.5).

Figure 5.5: Response of primary headache disorders to preventative medications



Preventative medication that has support for migraine prevention include β blockers without partial agonist activity (Tfelt-Hansen, 2006), sodium valproate (D'Amico, 2007), and some calcium channel blockers (Tfelt-Hansen, 2006). The other properties of β blockers such as cardioselectivity, penetration into the central nervous system, or membrane stabilising activity are not important in their ability to prevent migraine attacks (Tfelt-Hansen & Shanks, 2000). Beta blockers block adrenaline binding to both β_1 and β_2 receptors and hence stop the production of cAMP and may reduce subsequent formation of action potentials in the pathways of nociception. A review of RCTs of β blockers for migraine prevention has concluded that they are superior to placebo (Weerasuriya, Patel, & Turner, 1982). There are no RCTs of β blockers for CTTH.

The mechanism of action of β blockers has been elusive in the management of migraine and the mode or even the site of action of these drugs is unknown (Weerasuriya, et al., 1982) in relation to the management of headache pain. Only those β blockers without partial agonist properties have been found effective. The Adrenaline Model of Headache Causation explains the benefits of β blockade as this reduces the production of cAMP and ensuing neural sensitisation (Figure 5.3).

A RCT for migraine prevention showed a combination of cyproheptadine and propranolol (Rao, Das, Taraknath, & Sarma, 2000) was found to be superior to placebo and both propranolol or cyproheptadine taken individually. Cyproheptadine has antihistamine, antiserotonergic (5-HT₂ receptor antagonist) and blocks calcium channels. This combination of medication improving migraine is consistent with the Adrenaline Model of Headache Causation.

Headache prevention medication may act directly on ion channels to inhibit action potentials and nerve transmission. Calcium channel blockers reduce the influx of calcium into cells while sodium valproate suppresses the sodium channel. Both will reduce the membrane potential of the neuron and reduce the likelihood of action potential generation and propagation, therefore helping prevent the transmission of pain.

Amitriptyline, the most effective preventative medication in CTTH prevention trials (sections 3.7, 3.71 and 3.72), has the following actions;

1. H₁ receptor antagonist that blocks histamine action and reduces the production of intracellular cGMP.
2. Anticholinergic, blocking muscarinic (M₃) receptors on the vasculature, reducing nitric oxide and subsequent production of cGMP.
3. α_1 receptor antagonist, reducing intracellular IP₃ and calcium production (α_1 receptors found throughout the central and peripheral nervous system.)
4. Inhibits the reuptake of noradrenaline and serotonin, increasing both noradrenaline and serotonin at the synapse. Noradrenaline binding to the α_2 receptor and serotonin

binding to the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F} results in the reduction of second messengers.

5. Decreased β adrenoreceptor density (Silberstein, et al., 2007) which will result in a subsequent reduction of cAMP.
6. Inhibits sodium channels and calcium channels that further inhibit nerve transmission.

Amitriptyline therefore reduces second messengers through several receptors and also directly inhibits ion channels to inhibit generation of action potentials and subsequent transmission of pain thus accounting for its effectiveness in several clinical trials of CTTH (section 3.71). The effect of amitriptyline is only modest and reduces headache activity between 30% (Bendtsen, 2000) and 60% (Bettucci, et al., 2006). This may reflect the development of tolerance to medication, or that neural sensitisation only plays a role in a proportion of people with CTTH. In a proportion of people with CTTH an unidentified source of nociception such as the cervical spine (section 3.5) may be the significant source of pain with sensitisation playing a lesser role in the generation of headache pain.

A series of studies have shown neurons in the thalamic nuclei are inhibited in reaching the threshold of -55mV to generate action potentials by propranolol (β blocker) through the β adrenoreceptor (Shields & Goadsby, 2005), triptans through 5-HT_{1B/1D} receptors (Shields & Goadsby, 2006) and anxiolytics (alprazolam) through GABA receptors (Shields, Kaube, & Goadsby, 2003). These studies are consistent with the Adrenaline Model of Headache Causation (Figure 5.3).

5.3.2 Treatment other than drugs improving headache

Relaxation therapies have been found to be as effective as medication in the management of CTTH. Stress management (Holroyd, et al., 2001) produced a 50% reduction in headache intensity in 33% of participants, the same as amitriptyline. Meditation (Kiran, Behari, Venugopal et al., 2005) has been found to be the most successful therapy for CTTH with 79% reporting complete relief of their headaches (section 3.7). Relaxation training significantly blunted SNS response when patients were placed under psychological stress

(Lucini, et al., 1997). Both relaxation (Lucini, et al., 1997) and regular exercise (Mueller, 2007) have been shown to reduce SNS activity, that may explain their effectiveness in headache disorders which is consistent with the Adrenaline Model of Headache Causation (Figure 5.3).

Two reviews looking at the effectiveness of aerobic exercise as an intervention for headache disorders found no RCTs for the effects of aerobic exercise in the management of headache disorders (Busch & Gaul, 2008; Friction, Velly, Ouyang, & Look, 2009). Most published reports were small case series of less than a dozen participants. One study (Narin & Pinar, 2003) was a control trial of 40 migraine patients. Measurements of VAS and headache disability were recorded by questionnaire prior to the study and after the study. The 40 participants were allocated alternately to two groups of 20. The exercise regime consisted of a variety of aerobic exercises for one hour three times a week for eight weeks. The VAS score reduced from 8.5 +/-0.8 to 7.0 +/-0.9 in the control group and from 8.8 +/- 1.7 to 4.0 +/- 1.4 in the exercise group. Headache intensity, frequency and Pain Disability Index showed over 50% reduction in the exercise group with only mild reductions in the control group. Despite the non random allocation of participants the baseline characteristics of the groups were similar. Unfortunately the measurements taken were not collected by a diary but from a questionnaire at the start and finish of the trial. Accurate recall of frequency of headache (number of days) and duration (hours) is compromised by the lack of a diary, however this would also apply to the control group.

A randomised trial comparing 40 minutes of aerobic exercise three times a week, relaxation therapy or topiramate for migraine (Varkey, Cider, Carlsson, & Linde, 2011) found that all three interventions were similar in efficacy, with all groups reducing approximately one migraine episode per month from an average of approximately seven episodes per month. The responder rate (>50% improvement) was 23% in the relaxation group, 30% in the exercise group and 31% in the topiramate group. In conclusion, aerobic exercise performed approximately three times a week is likely to be beneficial for the treatment of migraine but the clinical evidence is scarce. There are no RCTs examining exercise as an intervention for TTH or CTTH.

Peripheral vasoconstriction results from increased sympathetic tone. Hand temperature in headache patients and normal controls has been measured and found to be significantly lower in the headache disorder patients (Blanchard, Morrill, Wittrock, Scharff, & Jaccard, 1989) indicating increased sympathetic tone in headache disorder patients. A review found hand warming using biofeedback to be effective in the management of headache disorders with an effect size of approximately 55% improvement (Nestoriuc, Martin, Rief, & Andrasik, 2008). Warming the hands produces vasodilatation and feedback to the SNS to reduce sympathetic tone. These findings are consistent with the Adrenaline Model of Headache Causation (Figure 5.3) that proposes a reduction of SNS activity reduces transmission of action potentials in the pathways of nociception.

5.3.3 Medications that cause headache as a side effect

Medications that cause headache as a side effect, may increase the concentration of second messengers that may lead to action potential generation and propagation in the pathways of nociception. They can be agonists at receptors that increase second messengers, antagonists at receptors that reduce second messengers, or drugs that prevent the breakdown of second messengers.

Adrenergic agonist medications (e.g. salbutamol, salmeterol, terbutaline, and isoprenaline) list headache as a common side effect and lead to an increase in cAMP via the β_2 receptor. Glyceryl trinitrate causes headache and has been used in headache trials (section 3.9) to induce headache (Christiansen, et al., 2000) and migraine (Christiansen, et al., 1999). The mechanism of action has been historically explained in terms of the vasodilatation caused by nitric oxide. Nitric oxide activates cGMP, a second messenger, (Costa, et al., 2003) similar to cAMP. Cyclic GMP opens ion channels and may result in depolarisation of the nerve cell membrane and create action potentials in the pathways of nociception causing headache. The vasodilatation produced may be coincidental to the headache caused.

Phosphodiesterases (PDE) are enzymes that break down second messengers, cAMP and cGMP, and reduce their concentration within cells. Phosphodiesterase inhibitors increase

the concentration of second messengers and have headache as a common side effect. Medications such as sildenafil (Viagra) (Kruuse, et al., 2003) and cilostazol used for erectile dysfunction, and theophylline used in asthma may cause headache by increasing second messenger concentration, leading to generation of action potentials in the pathways of nociception.

5.3.4 Medication overuse headache

Medication overuse headache occurs when the overuse of all forms of analgesic medication for the acute relief of headache can result in an increased frequency of headache (Diener & Limmroth, 2004). A mechanism that may explain medication overuse analgesia is desensitisation. With repeated presentation of a neurotransmitter the activation of the receptor can cause a lesser response when subsequently activated. Long term desensitisation can occur when the number of receptors reduce, leading to a reduced intracellular response (Sibley & Lefkowitz, 1985). Beta receptors display desensitisation due to degradation of receptors with subsequent reduced production of cAMP, and new protein synthesis is required to produce new receptors (Hertel & Perkins, 1984). Medication overuse headache may be a condition whereby analgesia becomes ineffective for headache disorders, rather than worsening the condition, as people are taking analgesia more frequently due to their escalating headache frequency.

5.3.5 Pheochromocytoma

Pheochromocytoma (a tumour that produces adrenaline) increases headache activity, chest pain and abdominal pain (Zelinka, Eisenhofer, & Pacak, 2007). The adrenaline leads to an increase in adrenergic activity leading to the increased production of cAMP that may create action potentials in the pathways of nociception resulting in pain (Figure 5.3).

5.3.6 Headache comorbidity

People who suffer from CTTH have an increased probability of experiencing other symptoms including chronic pain, sleep disturbance, anxiety, depression, Raynaud's syndrome and irritable bowel syndrome. Hypothalamic disturbance has been implicated in the comorbidity of symptoms with headache disorders. Measurements of plasma prolactin,

melatonin, growth hormone and cortisol was performed hourly for 12 hours in 17 chronic migraine patients and 17 age matched migraine free controls to investigate hypothalamic hormone secretion (Peres, et al., 2001). An abnormal pattern of hypothalamic hormone secretion was found in chronic migraine with increased cortisol concentrations, and lower melatonin concentrations in those patients with chronic migraine and insomnia.

5.3.6.1 *Chronic pain*

Pain activates the SNS and HPA pathways. Chronic pain is also accompanied by psychological stress and disturbed sleep that both stimulate the SNS and HPA pathways. Elevated SNS and HPA activity may explain the comorbidity of chronic pain and headache disorders.

5.3.6.2 *Insomnia and anxiety*

The SNS and HPA are instrumental in the fight/flight response when faced with physical threat and they are designed to maintain alertness, as sedation would be counterproductive to survival. The increased alertness may lead to poor sleep and anxiety by the actions of the stress response (release of histamine, serotonin, noradrenaline and adrenaline) in the brain, particularly in the reticular activation system which plays an important role in cortical arousal (Connors, 2003b). Although speculative, the action of these neurotransmitters in increasing arousal may be through the increase in second messengers in the pathways that activate cortical arousal, explaining the comorbidity of headache with insomnia and anxiety.

5.3.6.3 *Depression*

Depression has been linked to increased sympathetic tone and hence comorbidity of headache and depression may be due to increased sympathetic tone. Sympathetic nervous system activity has been measured by measuring noradrenaline produced by the sympathetic efferent nerves (excluding noradrenaline produced by the adrenal medulla) in 17 depressed individuals and 36 control subjects without depression (Veith, et al., 1994). The appearance of noradrenaline into the extravascular and vascular compartments was found to be significantly elevated in the depressed individuals, with the rate of clearance

similar in both groups. A review article has found several studies showing increased SNS activity in depressed individuals compared to controls (Carney, Freedland, & Veith, 2005).

5.3.6.4 *Raynauds Phenomenon*

Raynaud's syndrome describes the symptom of cold hands and cold feet. The odds ratio of having Raynaud's syndrome is 1.7 (CI: 0.7 to 4.5) if you suffered from a headache in the last three months (Boardman, Thomas, Croft, & Millson, 2003). People with Raynaud's syndrome have a higher incidence of migraine with an odds ratio of 5.4 (CI: 2.8 to 10.3) (O'Keeffe, Tsapatsaris, & Beetham, 1992). Both headache disorders and Raynaud's syndrome may be comorbid due to hyperactivity of the SNS.

5.3.6.5 *Irritable bowel syndrome (IBS)*

During the fight/flight response blood flow is constricted to the abdominal viscera and digestive enzyme production is reduced and likely to contribute to symptoms of irritable bowel syndrome. The prevalence odds ratio for a person experiencing irritable bowel syndrome is 1.6 (CI: 1.4 to 1.7) if a patient experiences migraine (Cole, Rothman, Cabral, Zhang, & Farraye, 2006). Irritable bowel syndrome and headache disorders may be comorbid due to both conditions having increased HPA and SNS activity.

5.3.7 *The reduced prevalence of headache found in the elderly*

Headache complaints decrease in prevalence with increasing age (section 3.2). Work status or consumption of medication for other conditions did not account for this reduction in headache prevalence (Von Korff, Dworkin, Le Resche, & Kruger, 1988). A survey carried out in Seattle of 1500 people enrolled in a group health programme found the prevalence of head pain reduced to 0% of males and 2% of females at the age of 65, compared to peaks of 21% and 35% in the 25 to 44 age group respectively. The release of adrenaline reduces with ageing and although levels of adrenaline are similar due to reduced clearance, there is a significant attenuation of adrenaline release in response to stress in the elderly (Seals & Esler, 2000). There is also a 40% reduction in the number of neurons in the locus coeruleus in the elderly (Vijayashankar & Brody, 1979). The reduced HPA and SNS activity may be a reason for the decline in headache symptoms in the over 65 age group.

5.3.8 The reduced prevalence of headache found in warmer climates

The prevalence of TTH is lower in warmer climates (section 3.2). A prospective diary study found cold fronts either play a role in precipitating headache attacks or have some role in priming effect on headache occurrence (A. Yang, et al., 2011). The prevalence of TTH was highest in Europe (80%), followed by North America (30%) and lowest in Africa and Asia (20%) (Stovner, et al., 2007). Temperature variation with reduced prevalence in warmer climates may be partly responsible for this trend.

As body temperature increases, the skin is important in moving heat from the core to the environment primarily by convection (Nadel, 2003) and blood flow increases to the skin to improve convection as core temperature rises. Thermal receptors are present in the skin providing feedback to the hypothalamus. Normally the SNS exerts a vasoconstrictor effect on the blood vessels of the skin and to increase blood flow to the skin, the sympathetic tone is reduced to allow dilatation of skin blood vessels. When environmental temperature rises, thermal receptors on the skin feed back to the SNS to reduce sympathetic tone (section 4.5.2).

Vasodilatation is the result of reducing the smooth muscle contraction in the vessel wall which requires a reduction in the stimulus for contraction, namely intracellular calcium that leads to the phosphorylation of the light chain of myosin (Benoit & Taylor, 1997). The three main ways in which vasodilatation can occur are via calcium channel blockade (calcium channel blockers), cAMP mediated (e.g. β_2 , Histamine₁, Prostaglandin D₂, E₂ and prostacyclin) reduction of intracellular calcium and cGMP mediated (e.g. NO) reduction of intracellular calcium. Nitrous oxide mediates vasodilatation by stimulating the production of cGMP which leads to the reduction of intracellular calcium in smooth muscle. The second messengers cGMP and cAMP increase neuronal excitability and relax smooth muscle which is likely to explain the co-occurrence of vasodilatation and headache pain. Second messengers such as cAMP and cGMP play a role in vasodilatation by relaxing the blood vessel wall (Haynes, Robinson, Saunders, Taylor, & Strada, 1992) with increasing temperature. After vasodilatation of smooth muscle both cAMP and cGMP are depleted by

being broken down to AMP and GMP respectively by their phosphodiesterases (Francis & Corbin, 1999).

In heating the skin initial vasodilatation is thought to be mediated by sensory nerves and later NO is thought to be the significant contributor to vasodilatation (Charkoudian, Eisenach, Atkinson, Fealey, & Joyner, 2001). Heating of the skin does not consistently cause headache despite the production of NO. A possible explanation is that NO produces cGMP which is depleted by vasodilatation and increased levels of cGMP may not persist for long enough to create neuronal excitability. Exercise and sauna bathing are both accompanied by vasodilatation which may result in a neutral state with respect to the levels of second messengers produced (both producing an increase in HPA and SNS pathway mediated increase in second messengers followed by a depletion with vasodilatation), whereas repeated psychological stress may result in a net increase in second messengers (from HPA and SNS activation) and no corresponding rapid depletion.

The reduced sympathetic tone and consumption of second messengers to affect vasodilatation, may both contribute to an overall reduction of second messengers with increasing temperature. The reduction of second messengers and inhibition of subsequent action potentials in the pathways of nociception may account for the reduced incidence of headache disorders in tropical climates (section 3.2).

Local effects of heat on sympathetic skin responses (SSR) have been investigated (Yagiz On, et al., 1997) and showed that heat reduced SNS response. Application of heat (e.g. wheat pack, hot water bottle, infrared heat lamp, electric blankets) is often used to alleviate pain at a local area and a reduction of sympathetic tone and depletion of second messengers from vasodilatation, resulting in inhibition of action potentials may explain the rationale for the beneficial effect of heat application.

5.3.9 The reduced prevalence of headache found with regular exercise

Population cross sectional studies provide support that regular exercise may reduce the risk of headache and migraine as there is a consistent reduction of headache and migraine risk

in those that exercise regularly. A cross sectional survey from Japan of 12,988 subjects aged between 20 and 79 receiving health checks at a Tokyo clinic, found 15.4% of women and 5.4% of males who filled out a self administered questionnaire suffered from headache. The odds ratio of those performing exercise 1, 2, 3, 4, or 5 days a week was below the reference of those seldom exercising (Yokoyama, et al., 2009). A Danish population questionnaire study of 31,865 individuals found the odds ratio of migraine reduced with increasing exercise (Le, Tfelt-Hansen, Skytthe, Kyvik, & Olesen, 2011). An RCT of exercise, relaxation and topiramate found that all three interventions similarly reduced migraine episodes (Varkey, Cider, Carlsson, & Linde, 2008). Regular exercise has been found to reduce sympathetic tone, especially in individuals with elevated sympathetic tone (section 4.5.3) and this reduction in sympathetic tone may reduce headache disorder activity which is consistent with the Adrenaline Model of Headache Causation.

5.3.10 Headache triggers

The triggers of headache include psychological stress, menstruation in females, fasting, changes in weather conditions and temperature, sleep disturbance and physical activity (section 3.3). These triggers all activate the SNS and HPA pathways (DeRosa & Cryer, 2004; Kotchen, et al., 1971; Pike, et al., 1997; Segel, et al., 2002; van de Borne, et al., 1997; Zhong, et al., 2005). In the presence of neural sensitisation (section 4.4), these triggers may activate the HPA and SNS pathways and lead to action potentials in the pathways of nociception, leading to headache episodes (Figure 5.6). Figure 5.7 shows that the same triggers may not lead to an action potential in people without neural sensitisation as the EPSP fades away, as it is not amplified at the synapse. An upregulation of the stress pathways are likely to increase the chances of developing headache episodes from triggers.

The timing of migraine headache also correlates with sympathetic tone which is consistent with the Adrenaline Model of Headache Causation. The timing of migraine headaches was investigated by examining the 24 hour distribution of migraine in a prospective study of 89 females over 12 consecutive months with participants recording timing of migraine (Alstadhaug, Salvesen, & Bekkelund, 2008). The study recorded 2,314 migraine episodes and found migraine peaked between the hours of 10am and 4 pm and was lowest in the

Figure 5.6: Headache triggers with sensitisation of pathways of nociception

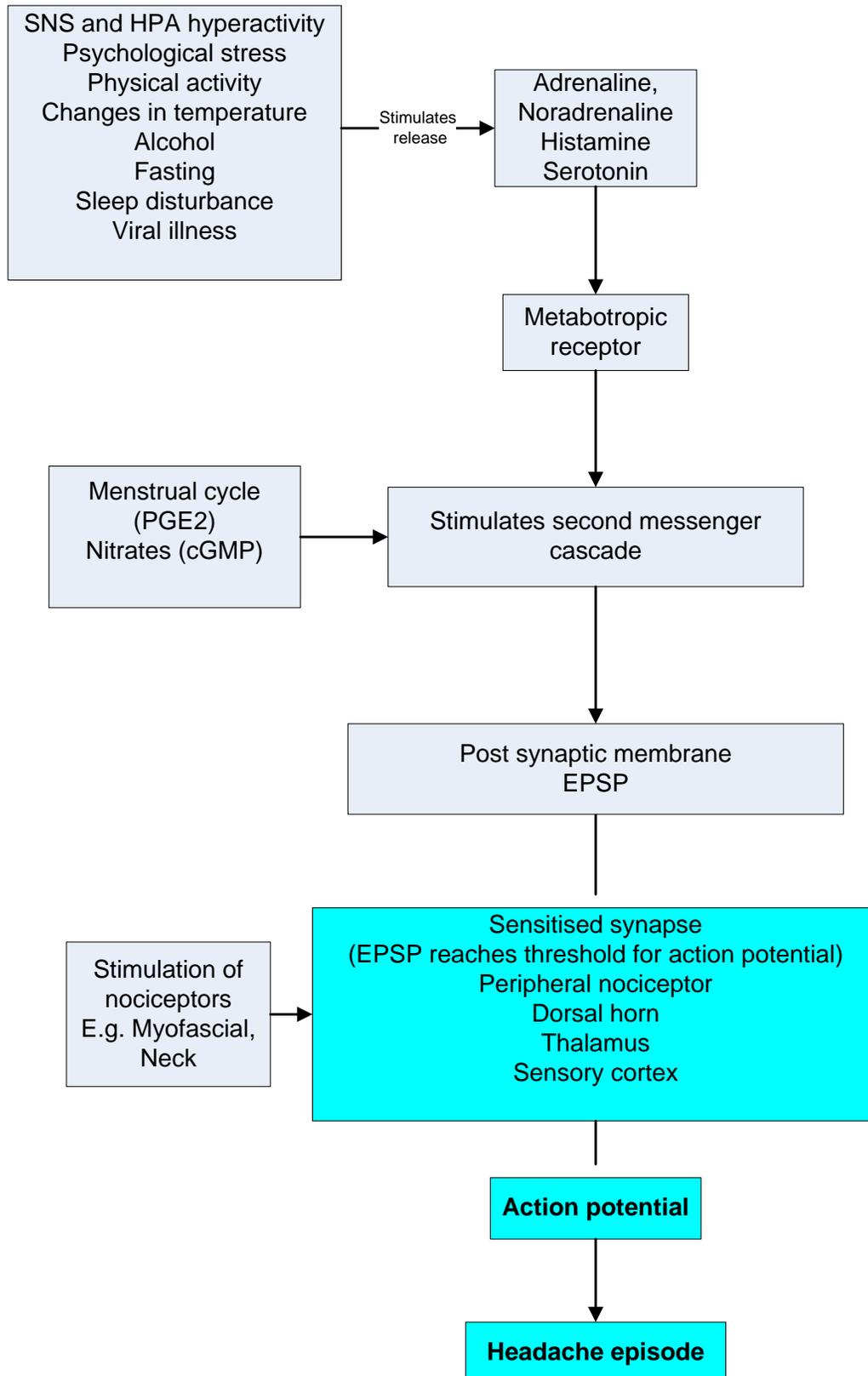
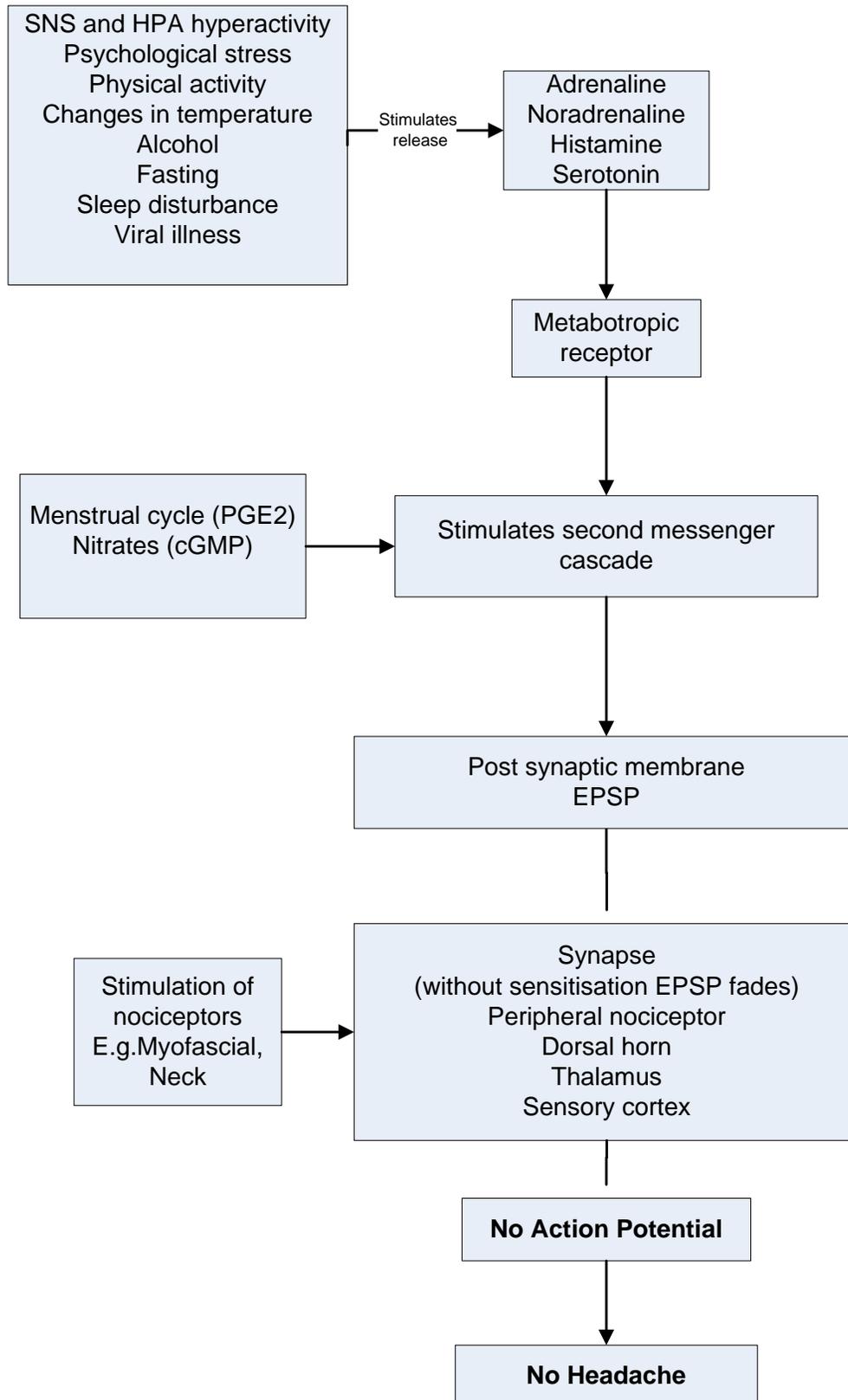


Figure 5.7: Headache triggers without sensitisation of pathways of nociception



early hours of the morning. This 24 hour temporal distribution of migraine also correlates with the variation of sympathetic tone in 24 hours, with an increased tone present during increased onset of migraine episodes and a reduced sympathetic tone present during periods of reduced onset of migraine episodes. The sympathetic tone measured in 20 healthy individuals by heart rate variability monitoring, also peaked between the hours of approximately 10am to 4 pm and was lowest in the early hours of the morning (Nakagawa, et al., 1998). The timing of migraine episodes during the hours of increased sympathetic tone is consistent with the Adrenaline Model of Headache Causation, which proposes an increase in sympathetic tone may lower threshold for action potential in the pathways of nociception.

5.3.10.1 *Psychological stress*

Stress is known to be a predisposing factor for the onset of CTTH, accelerates the progression of headache disorder into a chronic condition and precipitates individual headaches (Nash & Thebarger, 2006). Psychological stress stimulates the HPA and SNS pathways leading to the release of noradrenaline, adrenaline and other neurotransmitters and a subsequent activation of second messenger cascades (Larsson, Martinsson, Olsson, & Hjemdahl, 1989). Larsson and colleagues (1989) tested the rise in plasma adrenaline, heart rate, blood pressure and cAMP after adrenaline infusion, placebo infusion (normal saline) and mental stress. Both adrenaline infusion and mental stress evoked a rise in adrenaline and cAMP while placebo infusion did not. The rise in cAMP and generation of action potentials in the pathways of nociception may lead to central and peripheral sensitisation as well as trigger acute episodes of headache once central and peripheral sensitisation is established.

Cortisol release in the stress response may contribute to sensitisation of the pathways of nociception by increasing the production of adrenaline. Both adrenaline and noradrenaline can act at the different adrenergic receptors with differing affinities. Noradrenaline is generally classified as β_1 selective and adrenaline as mixed β_1 and β_2 receptor agonist (MacGregor, et al., 1996). Both adrenaline and noradrenaline via the α_1 receptor can excite neural transmission and via α_2 receptors inhibit neural transmission. The final action of

these catecholamines is likely to depend on the relative concentration of adrenaline and noradrenaline, the concentration of receptors at the effector sites and their affinities to the receptors. Noradrenaline released from the locus coeruleus can act on α_2 receptors in low concentration and act on α_1 receptors at higher concentrations, due to its lower relative affinity to α_1 receptors (Ramos & Arnsten, 2007).

5.3.10.2 *Menstruation*

As noted in section 3.3 several studies revealed that menstruation was a significant trigger for headaches in females (Andress-Rothrock, et al., 2010; Kelman, 2007; Wober, et al., 2007). Prostaglandin E₂ (PGE₂) and Prostaglandin F (PGF) are known to increase at the luteal and menstrual phases of the menstrual cycle and are elevated in women suffering from dysmenorrhea compared to women not suffering from dysmenorrhea (Benedetto, 1989). These prostaglandins bind to EP₂ and EP₄ receptors and increase cAMP (Hata & Breyer, 2004) that may generate action potentials in the pathways of nociception explaining menstrual migraine and headache (Figure 5.6).

5.3.10.3 *Food*

Chocolate has been implicated as a food trigger for migraine headache. Cacao contains phenylethylamine that causes the release of vasoactive amines including adrenaline. Tyramine is an amine derived from tyrosine and is found in cheese, cured meats, smoked fish, fermented food and other foods. Tyramine's primary effect is the release of noradrenaline and adrenaline (Okaa, Ohuchia, Yoshida, & Imaizumia, 1966). The link was initially observed in people eating aged cheese while taking monoamine oxidase inhibitors, as they developed headache and hypertensive crises (Sun-Edelstein & Mauskop, 2009). Although this may explain a mechanism for food triggers, most studies (Kelman, 2007; Marcus, et al., 2007) investigating migraine triggers are retrospective studies, and further prospective studies or control experimental studies are required to confirm if food does actually trigger episodes of headache or migraine.

5.3.10.4 *Viral illness*

Headache and generalised myalgia is common with viral illnesses. The HPA and SNS are activated causing a rise in adrenaline and cAMP during a viral illness (Mason, et al., 1979). Mason et al. (1979) measured adrenaline and noradrenaline blood levels that showed a 60% rise in levels after the onset of an adenovirus respiratory infection. Histamine was also measured during an infection with influenza A viral infection and showed a rise during infection (Gentile, Doyle, Fireman, & Skoner, 2001). Adrenaline will result in production of cAMP while histamine will stimulate the production of cGMP. Both second messengers will potentiate action potentials in the pathways of nociception leading to headache pain and myalgia.

5.3.10.5 *Alcohol*

Delayed alcohol induced headache has been described as diffuse, bilateral and throbbing, and migraine sufferers are at increased risk of developing headache after alcohol consumption (Kuster, Piraja da Silva, Aquino, Ziviani, & Domingues, 2006). Alcohol may also cause hypoglycaemia that may contribute to the development of a hangover headache (section 5.3.10.7). The “hangover” headache caused by heavy alcohol consumption can be explained by the Adrenaline Model of Headache Causation (Figure 5.3) due to stimulation of the increased SNS activity and HPA activation overnight leading to subsequent production of second messengers and the generation of action potentials in the pathways of nociception.

Alcohol has been shown to increase sympathetic nerve activity by up to 239 +/- 22% of baseline values in 16 healthy male subjects (van de Borne, et al., 1997). The morning plasma cortisol has also been shown to be increased in alcoholics while drinking but reduced to normal on abstinence (Merry & Marks, 1972) demonstrating activation of the HPA pathways.

5.3.10.6 *Changes of climate*

Body temperature is monitored by the hypothalamus with feedback from thermal receptors in the skin to maintain a constant core temperature. Changes in weather may cause changes in skin temperature, that may activate both the HPA and SNS pathways and this may explain why changes of temperature trigger headache.

5.3.10.7 *Hypoglycaemia*

Glucose levels are monitored by the hypothalamus and a drop in glucose is a threat to life and a significant physiological stress (Spat, 2007) to the human body that activates the stress response of the body (HPA and SNS pathways) (Segel, et al., 2002), and generation of action potentials as proposed in the Adrenaline Model of Headache Causation (Figure 5.3). Fasting is a significant trigger for headache occurrence (section 3.3).

5.3.11 Experimentally induced headache

Infusions of PGE₂ (Hata & Breyer, 2004), histamine (Krabbe & Olesen, 1980; Lassen, et al., 1995), pituitary adenylyl cyclase activating peptide (PACAP₃₈) (Schytz, Wienecke, Oturai, et al., 2009), calcitonin gene related peptide (CGRP) (Van Rossum, et al., 1997), sildenafil (Kruuse, et al., 2003) and carbachol (Schytz, Wienecke, Oturai, et al., 2009) all stimulate the formation of headache or migraine (section 3.9). The headache produced can be explained by the fact that all of these neurotransmitters activate second messenger cascades, open ion channels leading to an action potential in the pathways of nociception, resulting in the transmission of pain (Figure 5.2 and Figure 5.3).

PGE₂ attaches to the EP₂ and EP₄ receptors triggering production of cAMP (Hata & Breyer, 2004), histamine is an agonist at the H₁ receptor and leads to production of cGMP (Lassen, et al., 1995), PACAP₃₈ stimulates cAMP (Schytz, et al., 2008), CGRP acts on the G protein coupled receptors increasing cAMP production (Van Rossum, et al., 1997) and carbachol acts on the muscarinic and nicotinic receptors that act via the nitric oxide pathways to increase cGMP (Schytz, Wienecke, Olesen, et al., 2009).

Noradrenaline (Lindholdt, et al., 2008) did not produce headache in headache free volunteers. Although adrenaline and noradrenaline both have affinity to the β_2 adrenoreceptor, noradrenaline has a low affinity for β_2 adrenoreceptor while adrenaline has a high affinity for the β_2 adrenoreceptor (Molinoff, 1984). Noradrenaline stimulated cAMP production only one third as much as adrenaline when attaching to the β_2 adrenoreceptor and the half effective concentration (EC_{50}) for noradrenaline was 10 fold higher than adrenaline (MacGregor, et al., 1996).

Headache was induced by sildenafil (Viagra) in a group of migraine sufferers (Kruuse, et al., 2004). Measurements taken included cAMP, cGMP and CGRP with no statistically significant difference in levels noted. Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 that would be expected to increase cGMP, rather than cAMP. Closer examination of the data of this study shows the level of cGMP rises from a baseline of 4.2nmol/L to 5nmol/L, 60 minutes after ingesting sildenafil, while the level of cGMP (3.5nmol) remained the same after ingesting placebo. The level of cAMP was 8.3 nmol and remained unchanged at 60 minutes after administering sildenafil. Although not statistically significant, the increased levels of cGMP may explain the presence of headache according to the Adrenaline Model of Headache Causation (Figure 5.3), as subjects with neural sensitisation in the central nervous system will only need a slight rise in second messengers to lead to action potential generation and subsequent headache symptoms.

5.3.12 The development of fibromyalgia (chronic widespread pain) from focal pain

The development of fibromyalgia has been linked to tissue injury that does not heal for several months. One hundred and two patients with whiplash and 59 patients with leg fractures (control), all previously without pain syndromes were followed and 21% of those with whiplash injury developed fibromyalgia while 1% of the leg fracture group developed fibromyalgia. Fibromyalgia did not develop until a mean of three months after the whiplash injury. The patients with whiplash who developed fibromyalgia had higher pain intensity scores measured by VAS (Buskila, Neumann, Vaisberg, Alkalay, & Wolfe, 1997).

The development of fibromyalgia after tissue injury and ongoing focal pain may be explained by the Adrenaline Model of Headache Causation (Figure 5.3). The development of central sensitisation leads to amplification and spread of pain (due to increased receptive field) and peripheral sensitisation leads to widespread muscle tenderness due to the increased SNS activity. The subsequent poor sleep, fatigue, social and occupational difficulties activate the SNS and HPA pathways that may perpetuate symptoms.

5.4 Animal studies of SNS and HPA pathways and hyperalgesia

Several experiments using rats have been performed looking at stimulation of the SNS and HPA axis, and effects of adrenaline and second messengers on the development of hyperalgesia (Dina, Gear, Messing, & Levine, 2007; Khasar, et al., 2008; Khasar, Dina, Green, & Levine, 2005, 2009; Khasar, Gear, & Levine, 2003; Khasar, Gold, Dastmalchi, & Levine, 1996; Khasar, Gold, & Levine, 1998; Khasar, Green, Gear, Isenberg, & Levine, 2003; Khasar, Green, & Levine, 2005; Khasar, Green, Miao, & Levine, 2003; Khasar & Levine, 1996; Khasar, Lin, et al., 1999; Khasar, McCarter, & Levine, 1999; Khasar, Miao, Gear, Green, & Levine, 2003; Khasar, Miao, Janig, & Levine, 1998a, 1998b; Khasar, Reichling, Green, Isenberg, & Levine, 2003; Taiwo & Levine, 1991). These experiments support a role for the SNS and HPA axis production of adrenaline in the development of hyperalgesia.

Khasar et al. (1999) showed that injection of adrenaline into the dorsum of the hindpaw of the rat produced a dose dependent increase in mechanical pain sensitivity. This was blocked significantly by intradermal injection of propranolol, a β receptor antagonist, but not by phentolamine, an α_1 receptor antagonist. Indomethacin (prostaglandin synthase inhibitor) had no effect on hyperalgesia suggesting the prostaglandin system is not operating in the development of hyperalgesia. Injection of isoprenaline, a β receptor agonist, also caused mechanical pain sensitivity that was blocked by propranolol but not phentolamine or indomethacin. The hyperalgesia produced in the hindpaw by adrenaline is consistent with the Adrenaline Model of Headache Causation (Figure 5.3) as adrenaline acting on the β receptor produces cAMP, opens ion channels and is capable of generating action potentials in the peripheral nociceptors. Hyperalgesia was attenuated by inhibitors of the cAMP

pathways, inhibitors of protein kinase A and inhibitors of protein kinase C. Lumbar sympathetic chains were removed from L1 to L4 to remove the sympathetic innervation of the hindpaw. A sham procedure was performed on the control animals. They found that the elimination of sympathetic innervation had no effect on the hyperalgesia produced by adrenaline. They concluded that adrenaline produced from the adrenal gland acting via the β adrenoreceptor is the cause of hyperalgesia due to a direct action of adrenaline on sensory nerve terminals in the skin. In the same study adrenaline was also found to sensitise small diameter neurons in the dorsal root ganglions in culture that was mediated by β adrenergic receptors (Khasar, McCarter, et al., 1999). In conclusion, adrenaline produced cutaneous mechanical hyperalgesia and sensitised cultured dorsal root ganglion neurons, via an action at the β adrenergic receptor mediated by cAMP second messenger pathways that is consistent with the Adrenaline Model of Headache Causation (Figure 5.3).

The tetrodotoxin resistant voltage gated sodium channel (TTX-R I_{NA}) has been investigated to determine its contribution to mechanical nociceptive threshold and the production of hyperalgesia (Khasar, Gold, et al., 1998). Decreased expression of this sodium channel may inhibit pain while increased expression of this sodium channel may produce hyperalgesia. Prostaglandin E_2 is known to cause hyperalgesia and Khasar and colleagues (1998) investigated whether PGE_2 induced hyperalgesia was mediated by the TTX-R I_{NA} channel at both the nociceptor and dorsal horn. Due to the lack of agonists or antagonists for TTX-R I_{NA} , antisense oligodeoxynucleotides (ODNs) were used to selectively knock-down expression of protein encoded by targeted mRNA. Treatment with antisense ODNs increased mechanical nociceptive threshold and blocked PGE_2 induced hyperalgesia in both the peripheral nociceptor and the dorsal root ganglion neurons, compared to rats treated with sense and mismatched ODNs. The study showed that the production of hyperalgesia is mediated by the sodium channel when stimulated by PGE_2 . Prostaglandin E_2 stimulates the production of second messengers, generating action potentials by opening sodium channels as proposed by the Adrenaline Model of Headache Causation.

Studies have investigated the effect of cAMP on hyperalgesia of the primary afferent nociceptor of the rat. The intradermal injection of forskolin, a direct activator of cAMP,

resulted in a dose dependent hyperalgesia in the rat (Taiwo & Levine, 1991). In the same study hyperalgesia was prolonged by phosphodiesterase inhibitors (section 5.3.2) that increase cAMP, and antagonised by an analog of cAMP that prevents the phosphorylation of the cAMP protein kinase. An analogue of cAMP, 8 bromo cAMP, produced a dose dependent hyperalgesia in the hindpaw of the rat that is not affected by sympathectomy, or blockade of the cyclo-oxygenase pathway of arachidonic acid by indomethacin (Taiwo, Bjerknes, Goetzl, & Levine, 1989).

Rat studies have investigated the role of cGMP in the modulation of thalamic neurons. An analogue of cAMP, 8 bromo-cGMP, applied to thalamic neurons lowered the threshold of the neurons to produce an action potential. The somatosensory and visual responses of thalamic neurons were enhanced to 274 +/- 76% and 217 +/- 69% of controls values (Shaw, Charles, & Salt, 1999). This study shows second messengers cause membrane depolarisation of thalamic nuclei as predicted by the Adrenaline Model of Headache Causation (Figure 5.3). Shields and Goadsby (2005) investigated the effect of β antagonists on thalamocortical activity, in response to superior sagittal sinus stimulation by microiontophoretic injection onto thalamic neurons, and found the β_1 adrenoreceptors were involved in inhibition of thalamic activity, as β_2 antagonists and β_3 antagonists had no effect on thalamic inhibition while β_1 antagonists inhibited thalamocortical activity.

Physiological stress has also been tested to find its role in hyperalgesia and what organ is responsible for hyperalgesia. Unpredictable sound stress has been used to provoke physiological stress and found to enhance mechanical hyperalgesia. Removal of the adrenal gland reversed the effect of sound stress hyperalgesia while sympathectomy had no effect on the development of hyperalgesia. This suggests the enhancement of mechanical hyperalgesia is mediated by the adrenal release of adrenaline rather than noradrenaline release from postganglionic sympathetic nerves (Khasar, Green, et al., 2005).

Furthermore prolonged muscle and cutaneous hyperalgesia can last for up to 28 days following unpredictable sound stress, showing long term enhancement of sensory pathways (Khasar, et al., 2009) that outlast physiological stress due to sensitisation of sensory

pathways. Surgical adrenal medullectomy abolished induced muscle and cutaneous hyperalgesia and administration of stress levels of adrenaline to rats with adrenal medullectomy reintroduced the hyperalgesia. Both HPA release of cortisol and SNS release of adrenaline were important in creating hyperalgesia (40% greater decreased minimum pain threshold for mechanically evoked hindpaw withdrawal compared to control) after unpredictable sound stress (Khasar, et al., 2008).

Rats have been fed alcohol diets to investigate the effects of alcohol on hyperalgesia and found hyperalgesia from alcohol was mediated by the SNS release of adrenaline and HPA axis release of cortisol, mediated by both the β_2 adrenergic receptor and the glucocorticoid receptor (Dina, et al., 2007). Hyperalgesia was reversed with adrenal medullectomy as well as inactivation of the β adrenergic receptors and glucocorticoid receptors.

When the major parasympathetic nerve, the vagus nerve, was severed (Vagotomy) hyperalgesia occurred in rats through SNS release of adrenaline (Khasar, Green, Miao, et al., 2003; Khasar, Miao, et al., 1998b) suggesting a tonic inhibitory role of the PNS on the SNS release of adrenaline. Oestrogen regulates plasma adrenaline in female rats that may explain the differential sensitivity to β_2 adrenergic agonists and lower nociceptive threshold found in female rats (Khasar, Dina, et al., 2005).

The animal studies discussed show that adrenaline released from the adrenal gland is capable of causing sensitisation at the peripheral nociceptor (Taiwo, et al., 1989), dorsal horn (Khasar, McCarter, et al., 1999) and the thalamus (Shaw, et al., 1999). The mechanism of hyperalgesia operates via the β adrenergic receptor and subsequent production of cAMP that targets the TTX-R I_{NA} . The Adrenaline Model of Headache Causation is supported by these animal studies.

5.5 Human studies of SNS and HPA pathways and hyperalgesia

A selection of studies investigating the effects of stimuli including catecholamines, SNS and HPA activation on pain are presented in this section. The development of headache and muscle tenderness has been investigated by subjecting CTTH patients and headache free

controls to a stressful and neutral task (Cathart, et al., 2010). Ninety-one percent of the CTTH group developed a headache during the stressful task versus 17% performing the neutral task. In the control group 4% developed a headache when performing the stressful task versus 0% of the control group performing the neutral task. Headache was induced in the CTTH group subjected to stress within 30 minutes. Muscle tenderness in both CTTH groups (subject to stress or neutral task) was higher than the headache free control group at baseline and mean pressure pain threshold was lower in both CTTH groups than the headache free controls. The mean pressure pain threshold reduced and muscle tenderness increased in the CTTH group exposed to the stressful task, while both remained constant in the CTTH group exposed to the neutral task. A stressful task therefore lowers pain threshold and increases muscle tenderness, while simultaneously inducing headache pain in patients with CTTH.

Pressure pain thresholds and sensitivity to sharpness in the forehead were measured in 34 individuals with ETTH and 32 headache free controls, before and after hand immersion in painfully cold water (cold pressor test) (Drummond & Knudsen, 2010). Prior to the cold pressor test, pressure pain threshold in the forehead and sensitivity to sharp stimulus was similar in both groups. In the ETTH group pressure pain threshold reduced and mild headache developed after cold pressor test, with no change in the sharpness rating. The control subjects after the cold pressor test did not develop headache, pressure pain thresholds did not change and sharpness ratings decreased after immersion. The cold pressor test increases SNS activity with increases in heart rate that are blocked by β adrenergic blockade (Victor, et al., 1987). Increases in noradrenaline and mean arterial pressure also accompany the cold pressor test. This study showed an increase in SNS activity by the cold pressor test, may have induced headache in headache patients and reduced pressure pain thresholds.

Both noradrenaline and adrenaline have been investigated to examine their effect on hyperalgesia and shown to lower sensory thresholds. The effect of adrenaline and placebo infusions on subjective pain, threshold of pressure pain and heat pain were performed on 24 healthy students (Janssen, Arntz, & Bouts, 1998). Subjective pain showed an increase and

heat pain threshold reduced due to adrenaline infusion. Pressure pain threshold did not change, but this was thought to be due to large within-subject variation for this measurement. To determine the effect of noradrenaline on heat hyperalgesia, the forearm skin of 10 healthy subjects was sensitised by topical capsaicin at sites of noradrenaline or saline iontophoresis (Drummond, 1995). Heat hyperalgesia persisted at the sites of noradrenaline application after withdrawal of the noradrenaline, whereas heat hyperalgesia decreased as inflammation subsided in the saline group.

5.6 Summary

The central nervous system stress response and sympathoadrenal release of adrenaline and subsequent increase in second messengers cascades, may reduce the sensory threshold of peripheral nociceptors, the dorsal horn neurons and the thalamic neurons and may account for central and peripheral sensitisation seen in chronic pain and headache disorders. An increase in second messengers (sometimes due to headache triggers) can also cause depolarisation of neurons leading to action potentials in the pathways of nociception in the presence of central and peripheral sensitisation and lead to episodes of headache.

The Adrenaline Model of Headache Causation (Figure 5.3) predicts that reducing SNS and HPA activity by the use of regular heat, relaxation, regular exercise and sleep may improve symptoms of CTTH. The latter part of this PhD thesis (Chapters 6 to 8) describes an RCT performed to investigate repeated sauna as an intervention for CTTH patients.

Chapter 6

THE WELLINGTON EDUCATION AND SELF TREATMENT (WEST) HEADACHE TRIAL: STUDY DESIGN

6.1 Introduction

The first aim of this PhD study was to develop a model of headache causation that is consistent with many of the headache phenomena found in the literature. One of the predictions of the Adrenaline Model of Headache Causation is that an increase in SNS and HPA activity stimulates second messenger cascades in the pathways of nociception, namely, the peripheral nociceptor, dorsal horn, thalamus and sensory cortex. This may increase the sensitivity of the pathways of nociception which increases the risk of developing headache. Conversely a reduction in SNS tone and HPA activity may reduce the occurrence of headache.

Regular exercise, heat, relaxation and improving sleep are mutable factors that reduce SNS tone and may reduce headache activity in CTTH. Repeated exercise (Varkey, et al., 2008) and repeated relaxation therapy (Holroyd, et al., 2001; Varkey, et al., 2008) have both been found to improve headache disorders. Both have been found to reduce SNS activity (Lucini, et al., 1997; Mueller, 2007). Repeated sauna bathing has been found to reduce SNS activity in patients with congestive heart failure (Kihara, et al., 2004; Miyamoto, et al., 2005) and may also be a useful intervention to reduce headache intensity in patients experiencing tension-type headache.

The second aim of this PhD study was to examine the effectiveness of a noninvasive treatment on CTTH sufferers. Sauna was chosen as a possible noninvasive treatment based on anecdotal experience (Chapter 2) and because it has been shown to reduce SNS activity. The aim of the clinical trial was to investigate if repeated sauna bathing reduced headache intensity for those experiencing CTTH. In studying patients with CTTH, the SNS activity is likely to be elevated by effects of pain and common comorbid conditions such as poor sleep. The Adrenaline Model of Headache Causation has identified heat as a possible

means for reducing sympathetic tone that may in turn reduce headache intensity (sections 4.5.2 and 5.2).

This chapter outlines the design of the WEST headache trial which was performed to examine if regular sauna bathing reduces headache intensity in CTTH. The analysis of RCTs in section 3.7 has helped formulate the design of this current RCT. This chapter outlines specific objectives and null hypotheses (section 6.2), WEST headache trial protocol (section 6.3), interventions (section 6.4), study participants and recruitment (section 6.5), data collection, handling and analysis (section 6.6 to section 6.8).

6.2 Specific objectives and null hypotheses

This research project sought to answer the following research objectives with respect to CTTH.

6.2.1 Primary objective of the clinical trial

To investigate whether education, sauna and soft tissue massage will reduce headache pain intensity more effectively than education and soft tissue massage as measured by NPRS scores.

6.2.2 Secondary objectives of the clinical trial

1. To investigate whether education, sauna and soft tissue massage will reduce headache duration more effectively than education and soft tissue massage, as measured by duration of headache in hours/day.
2. To investigate whether education, sauna and soft tissue massage will result in a greater proportion of patients gaining a 50% reduction of headache index (intensity times duration), than education and soft tissue massage.
3. To investigate whether education, sauna and soft tissue massage will improve sleep more effectively than education and soft tissue massage, as measured by a numerical rating scale for sleep disturbance.

4. To investigate whether education, sauna and soft tissue massage will improve depression more effectively than education and soft tissue massage as measured by BDI.

5. To investigate whether education, sauna and soft tissue massage will improve HDI more effectively than education and soft tissue massage.

6.2.3 Null hypotheses

These primary and secondary objectives of this clinical trial can be framed as null hypotheses in the tradition of scientific enquiry:

Null hypothesis I: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage for the reduction of intensity of headache pain as measured by NPRS scores.

Null hypothesis II: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage for the reduction of headache duration as measured by hours of headache per day.

Null hypothesis III: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage for the number of CTTH patients reducing headache index by 50%.

Null hypothesis IV: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage in improving sleep disturbance as measured by a numerical rating scale (/10) for sleep disturbance.

Null hypothesis V: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage in improving depression as measured by BDI.

Null hypothesis VI: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage in reducing headache disability as measured by the HDI.

6.3 WEST headache trial protocol

The study design chosen for the WEST headache trial was a two group parallel RCT. A within group design such as a cohort study following patients with CTTH and taking measurements before and after treatment was an option to evaluate sauna bathing in patients with CTTH. Three studies of sauna bathing for chronic pain (Matsumoto, et al., 2011; Matsushita, et al., 2008; Oosterveld, et al., 2009) employed a cohort study design. Each participant serves as his or her own control with the time period before treatment compared to the time period after the treatment for measures such as headache intensity, duration and other parameters (Grady, Cummings, & Hulley, 2001).

A pilot study was not performed prior to the clinical trial in this PhD project however pre study testing was performed. The PI had experience of the effects of repeated sauna bathing on several patients with chronic pain over at least 12 months prior to this PhD study and found that eight weeks of regular attendance was sufficient to reduce pain intensity. Therefore the dose of the intervention was ascertained. The diary was developed and tested on clinic patients prior to the RCT to test these for readability and any difficulties participants may face when filling in the headache diary. The validated questionnaires were also filled in by patients in the clinic to ensure these were easy to understand and fill in. Staff at the Southern Cross Specialist Centre was also trained to administer the questionnaire prior to the RCT starting.

The options to perform an observational study such as a cohort study were considered. The cohort study would have been simpler to perform and could have served as a pilot study on which to base a future RCT with information gained to compute sample size, recruitment trends and a chance to trial questionnaires and procedures. The cohort study would not have given the PI experience on aspects of RCTs such as randomisation and statistical analysis comparing two groups. The major disadvantages of within group designs is the lack of concurrent controls and improvements may be due to regression to the mean (participants

recruited into the trial are at their worst and would expect to improve spontaneously back to their baseline symptoms) or perhaps seasonal trends (if winter was the worst period for TTH then if the study started in winter there would be an improvement as the weather improved) (Grady, et al., 2001).

The randomisation procedure of this RCT was based on computer generated random numbers. Randomisation of matched pairs may have been an option to ensure matching of characteristics such as age, sex and headache severity between the two groups. This design may reduce confounding variables on the outcome measures, however to match pairs the clinical trial could not get underway until enough participants enrolled to begin the matching process. Due to time constraints a classic randomisation was adopted rather than matched pairs.

Researchers are often interested in measurements of outcome before and after the intervention to substantiate or negate the effect of an intervention, which means pre and post testing is required. Two commonly used study designs are cross over and parallel control (Hopewell, et al., 2010). A parallel group trial is when two or more groups are followed simultaneously. In a cross over design participants have the study intervention followed by the control treatment, or the control intervention followed by the study intervention. There is a washout period in between the two interventions to account for any residual effects of the first intervention. This approach increases statistical power and reduces the numbers of participants required, however disadvantages include carryover effect and increased length of time for the trial to be performed. The carryover effect is the residual effect of the intervention on the outcome after it has been stopped and a washout period can be introduced to eliminate the carryover effect. A cross over design has been used in six RCTs for CTTH (section 3.7) (Bendtsen & Jensen, 2000, 2004; Fogelholm & Murros, 1992; Langemark & Olesen, 1994; Lindelof & Bendtsen, 2009; Shukla, et al., 1996). The carryover effect and washout period of sauna bathing are unknown and a parallel group design was selected over a cross over design for this PhD study.

The WEST headache trial was designed to be single blind with participants not knowing whether they were allocated to the intervention or control group, which is consistent with trials of non pharmaceutical intervention trials of CTTH (section 3.7). The information sheet for the trial (Appendix 5) states there are two treatment groups of which one will attend the sauna, however no mention is made whether this is the intervention group or control group and several participants commented that they thought the sauna group was the control or inactive treatment group. None of the nonpharmaceutical trials reviewed in section 3.7 (Holroyd, et al., 2001; Kiran, et al., 2005; Soderberg, et al., 2006; Wang, et al., 2007) were double blind with both treatment provider and participant blind to treatment allocation.

While an RCT on sauna bathing for CTTH may address whether this intervention may be a worthwhile intervention to relieve pain and other headache parameters, the design chosen is unable to prove the Adrenaline Model of Headache Causation or provide a direct link between SNS tone and the presence or severity of CTTH. Thus far research has shown that repeated sauna bathing reduces SNS activity in patients with an elevated SNS tone (e.g. congestive heart failure) (Kihara, et al., 2004; Miyamoto, et al., 2005). Research in the form of one RCT (Masuda, Koga, et al., 2005) and two cohort studies (Matsumoto, et al., 2011; Matsushita, et al., 2008) has also shown that regular sauna bathing has the potential to be a useful intervention for chronic pain. The PI's principal aim in carrying out an RCT was to test whether regular sauna bathing, a self directed non invasive therapy, may offer pain relief for patients suffering from chronic pain. Unfortunately if headache intensity reduces from regular sauna bathing, the mechanism by which sauna bathing is acting will be unproven. There are no measures of SNS activity in the trial design. Discussions were held with supervisors on measuring serum noradrenaline and other parameters of SNS activity. The drawbacks of taking serum samples of SNS markers were increased costs (no budget was available for personnel to take bloods or for the required assays) and subjecting participants to blood tests (that may have made participation in this RCT less attractive). If this RCT showed positive results, then funding agencies may be more likely to provide funding in future studies to allow measurements such as noradrenaline levels and HRV before and after the intervention period. It would be interesting to see whether pain reduced

in parallel with SNS tone or was independent of a change in SNS tone but this will have to be addressed in the future.

The WEST headache trial was to include a baseline observation period of four weeks followed by an intervention period of eight weeks. The timeline is shown in Figure 6.1. Several trials looking at the prevention of CTTH had a four week baseline diary and eight weeks of treatment (Bendtsen, et al., 2007; Bettucci, et al., 2006; Padberg, et al., 2004; Ribeiro, 2000; Schmitt, et al., 2001). This timeframe was deemed as adequate to identify a treatment effect of sauna bathing as identified from anecdotal evidence with test subjects with CTTH who underwent sauna bathing prior to the WEST headache trial (Chapter 2).

Once participants contacted the Southern Cross Hospital or the PI, they were screened by the PI in a telephone interview to ensure they met the inclusion criteria and no exclusion criteria were present. A detailed analysis of the type of headache the potential participants experienced was discussed, to ensure other headache disorders such as migraine or cluster headache were excluded. Participants were then advised about the study and if they were interested in participating were sent an information sheet (Appendix 5) and a four week headache diary (Appendix 6) to record headache intensity (NPRS) and headache duration (hours/day). Participants were asked to make their initial appointment once they completed their four week headache diary. Once they completed their baseline diary they attended the initial consultation with the PI.

Prior to the initial consultation a questionnaire (Appendix 7) was filled in to obtain baseline data including demographic information, medication usage, sleep disturbance score (Vernon, Brandenburg, Alvir, Griesing, & Revicki, 2008), BDI (Beck, Steer, & Carbin, 1988) and HDI (Jacobsen, Ramadan, Aggarwal, & Newman, 1994). The questionnaire was administered by a nurse at the Southern Cross Specialist Centre. Participants were also given a consent form to read.

The initial consultation was approximately 45 minutes duration. Participants were given an explanation of the trial and questions about the trial were answered. A consent form was

signed by participants if they wished to enter the trial (Appendix 8). The participant's diary was checked to ensure they met the CTTH criteria of 15 headaches per month. A clinical history and examination were performed to exclude any obvious secondary cause of headache and confirm the headache conformed to the International Headache Society definition of CTTH. The Adrenaline Model of Headache Causation was explained to all participants with a handout given to them for future reference (Appendix 9) and how to perform soft tissue massage also with a handout (Appendix 10). The intervention group was given cards that allowed complementary attendance at the Wellington City Council swimming pool saunas and advised to attend three times a week for 20 minutes.

Participants were given an eight week daily headache diary to record headache intensity and duration. All participants were phoned two weeks into their treatment to ensure there were no difficulties with their treatment or adverse effects. After the eight week headache diary participants attended the final consultation. Prior to the final consultation the study questionnaire including BDI, HDI and sleep disturbance scores were administered by the nurse. At the final consultation participants were questioned about difficulties in completing the treatment assigned and compliance.

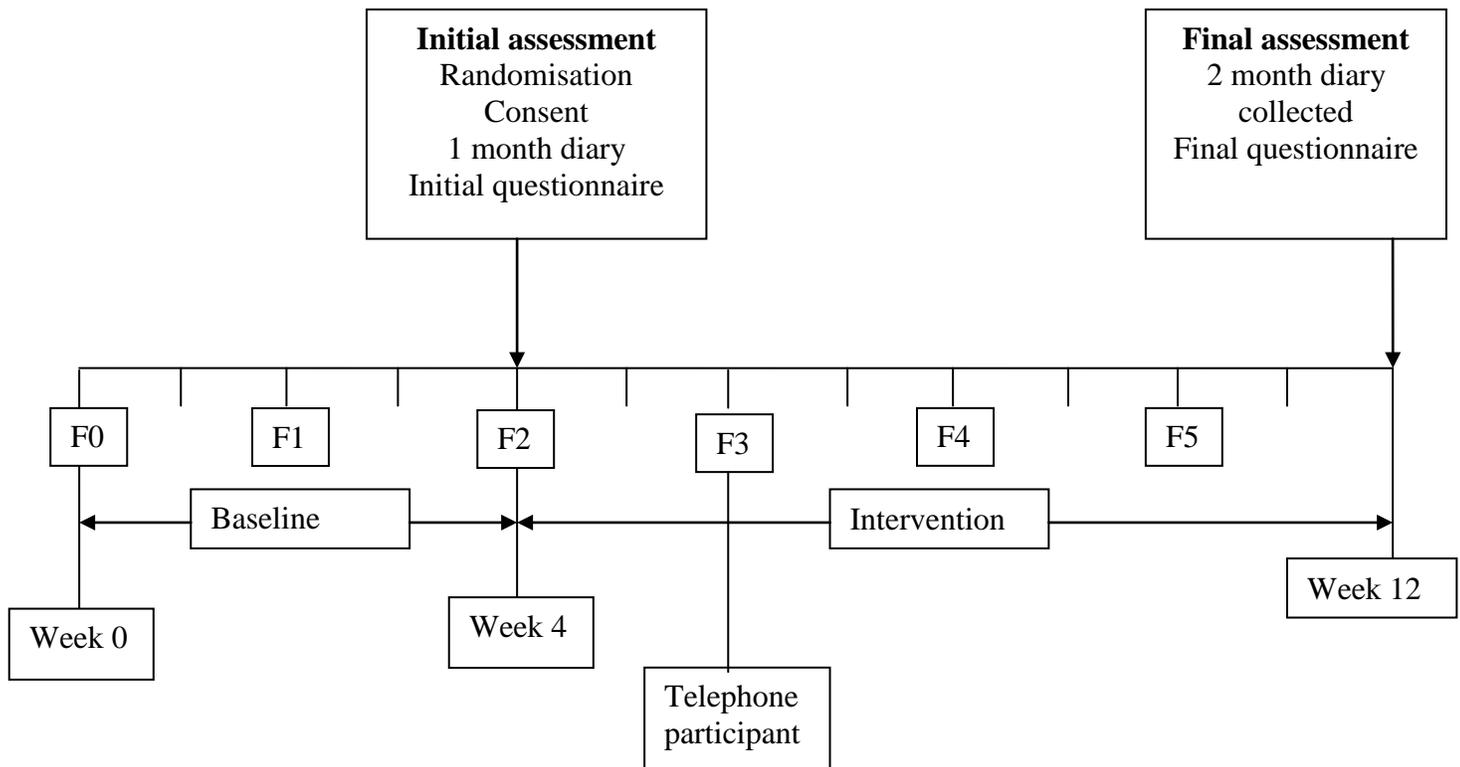
Both groups received the same education outlining the Adrenaline Model of Headache Causation with handout (Appendix 9) and training for soft tissue massage with a handout (Appendix 10). The number of appointments, time spent at appointments, data collected and consultation were the same for all participants in the study. The only difference was the instruction to attend the sauna for the intervention group (Appendix 11).

6.4 The study interventions

The interventions chosen were education on the headache model developed, repeated sauna bathing and soft tissue massage. Education regarding the model of headache causation is required when advising someone to attend the sauna to improve compliance and give a rationale of why someone suffering from CTTH should attend. Identical education on the Adrenaline Model of Headache Causation was given to both groups with a handout (Appendix 9). The soft tissue massage was included for both the sauna and control group,

so that the control group was undertaking some intervention and both groups would be blind as to whether they were the active intervention group or the control group. The technique of soft tissue massage was described to both groups together with a handout (Appendix 10).

Figure 6.1: Timeline of the WEST headache trial



6.4.1 Education

Education about the Adrenaline Model of Headache Causation was performed in the initial consultation with a handout given to patients in both groups. Education on headache causation consisted of:

1. The HPA and SNS pathways
2. Stress and the fight/flight response
3. Pathways of pain

4. Neural sensitisation
5. Generation of headache

Education about the treatment of headache was performed at the initial consultation with a handout on treatment (Appendix 10) that consisted of advice on sleep, stress and soft tissue massage.

6.4.2 Soft tissue massage

A treatment that could be performed by both groups was required to ensure the control group was blinded to the fact that they were not the intervention group. As patients with CTTH have generalised muscle tenderness, a well recognised technique of ischaemic deep tissue massage was chosen as a treatment that would be performed by both the control and intervention groups. A handout was written with diagrams and instructions (Appendix 10). This form of massage was self directed, easy to perform, required no funding and may reduce muscle tenderness which is commonly present in CTTH.

6.4.3 Sauna

The duration and dose of sauna for this trial was determined by following patients referred to my chronic pain clinic with CTTH, who were willing to try the sauna for management of their symptoms. They were followed with headache diaries that recorded the presence of headache and the pain severity using the NPRS from 0 to 11. Of 10 initial patients seven noted good improvement over two months, attending the sauna for 20 minutes three times a week. Many CTTH trials were 6 to 12 weeks in duration (section 3.7) and together with experience from several test subjects, the dose of the sauna to be used in the clinical trial for this PhD study was 20 minutes three times a week for eight weeks.

Venues with saunas in Wellington include private gyms and public swimming pools owned by the Wellington City Council (WCC). The WCC operates several swimming pools in the greater Wellington area (Kilbirnie, Oriental Bay, Tawa and Johnsonville). A presentation was given by the PI of the study to the WCC Chief Executive Officer, Gary Poole, and several councillors explaining the rationale for the study and to seek the use of WCC sauna

facilities. The WCC agreed to complementary admission to the saunas operated at the WCC public swimming pools for study participants, on presentation of a card stating their participation in the WEST headache trial.

If sauna turned out to be an effective means for reducing headache intensity, frequency and duration of headache, it would be an intervention that is self directed and available for most individuals suffering from CTTH. The sauna is a self administered treatment that requires minimal therapist input or time. In the Wellington region the cost of attending the sauna per session (\$4.40 to \$7.00) is markedly less than attending therapists for CTTH (Physiotherapist \$40.00 to \$70.00 per visit: Osteopath \$50.00 to \$100.00 per visit: Chiropractor \$60.00 to \$90.00 per visit and Doctor \$75.00 to \$225.00 per visit).

6.5 Study participants and recruitment

The target population for this study were people with CTTH as classified by the International Headache Society (Lenaerts & Newman, 2008): A disorder evolving from episodic tension-type headache, with daily or very frequent episodes of headache lasting minutes to days. Headaches are present over 15 days per month for the previous 3 months. The pain is typically bilateral, pressing or tightening in quality and of mild to moderate intensity, and it does not worsen with routine physical activity. There may be mild nausea, photophobia or phonophobia.

Inclusion criteria for the WEST headache trial included ages 18 to 70 years and the presence of CTTH as classified by the International Headache Society. Exclusion criteria included a known cause of symptoms such as sinusitis, eyesight or ear problems, cancer, acute infections including viral illness, previous spinal surgery, cancer and pregnancy or intended pregnancy. Participants with more than one migraine per month were excluded. Pregnancy or intended pregnancy was an exclusion criterion as sauna may have some effects on lowering blood pressure in pregnant women and this may cause fainting.

Recruitment included newspaper advertising and enrolling patients referred to the Wellington Pain and Headache Clinic, Southern Cross Hospital, with frequent TTH. This

recruitment strategy mirrored recruitment methods in several other RCTs for CTTH (Bendtsen, et al., 2007; Lindelof & Bendtsen, 2009; Schmitt, et al., 2001). Advertising was placed in the Citylife and Wellingtonian newspapers to recruit potential participants for the study. The Citylife Newspaper ran a front page article to highlight this clinical trial (Appendix 3). In the newspaper article people with TTH over 10 days in a month were invited, if interested, to phone the study setting Southern Cross Specialist Centre, Southern Cross Hospital, Newtown, or email the PI.

The sample chosen included people who read the particular newspapers where advertisements were placed and patients referred to the clinic. The newspapers are delivered to most households in the greater Wellington City area so potentially the entire population with frequent TTH was exposed to the advertising. The readership may depend on those who are fluent in reading the English language and the sample chosen may have missed those with CTTH who are immigrants and/or who do not have a good command of the English language. Patients referred to the Wellington Pain and Headache Clinic may not be representative of the entire population with CTTH, as this is a private clinic and affordability to attend the clinic will determine those who attend. The external validity of the sample (the extent to which study findings can be generalised to the entire population with CTTH) may be compromised by the above and people in poorer socioeconomic groups and immigrants who cannot read English may not be represented in the same proportion as the general population. The recruitment process occurred between September 2008 and March 2009.

6.5.1 Determination of sample size

To determine sample size for a study that will be analysed with a *t*- test the null hypothesis must be stated, an estimate of effect size determined (difference in the mean value of the outcome variable between groups), an estimate of the variability of the outcome variable as its standard deviation must be made as well as setting α (level of statistical significance) and β (probability of failing to reject the null hypothesis when it is actually false) (Browner, Newman, Hearst, & Hulley, 2001).

Previous research on the management of acute benign headache (Frank, Olson, Shuler, & Gharib, 2004) found a mean value on the VAS at presentation of 8/10 with a standard deviation of 1.5. The same study found that the mean change from baseline on the VAS in the placebo group was 1.5. In another paper on the prevention of CTTH (Padberg et al., 2004) a mean VAS headache intensity of 40/100 mm (equivalent to 4/10) was expected with an expected reduction of 8 mm for a placebo and 18 mm for an intervention group (botulinum toxin). Although the paper didn't explicitly state the standard deviation used in the power calculation this can be calculated from the nominated number of participants, 40 with 80% power and a significance level of 5% and equals a standard deviation of 1.1. A number of other RCTs have used a sample size of 40 participants (Bendtsen, 2000; Lindelof & Bendtsen, 2009; Yurekli, et al., 2008), consistent with a clinically important effect size of 0.9 standard deviations.

The sample size in the WEST headache trial was based on a 1.5 difference in NPRS between the control and intervention group. Headache intensity was expected to be approximately 4 to 5 out of 10 and 1.5 represented an approximate 30% reduction in intensity. This is a clinically significant difference in change of pain intensity. In order to have 80% power, at an alpha value of 0.05 to detect a difference of 1.5 units between two randomised groups, 17 participants need to be randomised into each of two groups, a total of 34 participants. We aimed to recruit 40 participants to allow for dropouts.

6.5.2 Randomisation process

Participants who did not meet the criteria for CTTH such as experiencing 15 days headache per month were excluded prior to randomisation at the initial consultation (Figure 6.1). Participants meeting the inclusion criteria were randomised to the control group (education and soft tissue massage) or the intervention group (education, soft tissue massage and sauna). A computerised random number table was used by Bettuci et al. (2006) in their trial of CTTH and this method appealed for this RCT due to its ease of use. Participants were allocated to their group on the basis of a computerised table of random numbers from 1 to 44. Once the table of random numbers was generated participants enrolled into the study were sequentially placed into their random group assignment by the PI. Randomisation was

not blinded to the PI; however participants were blind as to whether they were in the control or the active treatment group.

6.6 Data collected

A consensus conference with representation from academia, governmental agencies, and the pharmaceutical industry met and concluded that chronic pain trials should consider outcomes in six core domains; pain, physical functioning, emotional functioning, patient global ratings of satisfaction, negative health states and adverse effects and patient disposition (Turk & Dworkin, 2004). In this study headache intensity pain (NPRS), physical functioning (HDI) and emotional functioning (BDI) were measured. Negative health states including side effects were also addressed.

Guidelines published for preventative trials of medications for CTTH (Bendtsen, et al., 2009) suggest to use number of days a headache is present as the primary measure rather than headache intensity. There is however some debate regarding the validity of using the number of days a headache is present as the primary measure and headache pain intensity was the most common primary outcome measure in reviewed clinical trials of preventative measures for CTTH (section 3.7). If the number of days a headache is present is taken as the primary measure, and assuming the same intensity of headache is experienced, one hour of headache in a day and 16 hours headache per day would both represent one day of headache in that month, however the pain experience, distress and disability are different. In this study headache intensity was chosen as the primary outcome measure.

6.6.1 Demographic data

Data on several demographic and clinical variables were collected from all participants at the first appointment at week four of the study. These included:

- Age
- Gender
- Number of years with headache
- Current medications

- Past medical history
- Surgical history

6.6.2 Headache intensity and duration

A daily headache diary that recorded headache intensity using NPRS score and duration (number of hours) was sent to participants after telephone screening to collate the first four weeks of data (Appendix 7). Participants circled a number to represent their worst intensity of their headache on a NPRS. Headache duration was measured by daily headache diary, participants circled a number from 1 to 16 to represent the number of hours they experienced a headache on that day. The mean duration was calculated per fortnight.

Headache intensity in RCTs of CTTH is measured by Visual Analogue Score (VAS), Numerical Pain Rating Scale (NPRS) or Verbal Rating Scale (VRS). The VAS is presented as a 10cm line anchored by descriptions of pain (One end - no pain, other end - worst pain imaginable). The patient marks a point on the 10cm line between the two descriptors and a millimeter scale is used to measure the pain intensity. The NPRS is commonly an 11 point scale where 0 is no pain and 10 is the worst pain imaginable. The VRS comprises a four point scale for severity of headache (0 = no headache, 1 = mild headache, 2 = moderate headache and 3 = severe headache).

A review (Williamson & Hoggart, 2005) found that NPRS and VAS were more sensitive than the VRS in determining headache intensity. They also found the NPRS provided interval data and is as sensitive as the VAS is easy to administer and record, and patients prefer the NPRS over both the VAS and VRS. The review concluded that the NPRS is probably more useful for audit or research than the VAS or the VRS. Another trial (Downie, et al., 1978) comparing an 11 point NPRS, 4 point VRS and VAS also concluded that the 11 point NPRS performed better than both the VRS and the VAS with less measurement error, probably due to the VRS having too few choices and the VAS offering too great a freedom of choice which may be confusing.

A review article of 10 studies of chronic pain looking at clinically relevant reductions in pain intensity on an 11 point NPRS found a reduction of 30% or two points on the scale, was consistent with a patient rating of much improved or very much improved (Farrar, et al., 2001). Both VAS and NPRS have a high number of response categories allowing precise quantification of pain but is limited by having only one dimension. Other pain measures such as the McGill pain questionnaire are multi-dimensional measuring sensory, affective and evaluative dimensions of pain (Melzack, 1987) however it takes considerably longer to fill in. On the basis of these studies headache intensity was measured using NPRS and the daily headache diary included headache intensity and headache duration (number of hours per day).

6.6.3 Sleep disturbance

Sleep disturbance has not been measured in previous trials of CTTH (Table 3.7) however one trial (Schulte-Mattler & Krack, 2004) measured sleep duration in hours. The Adrenaline Model of Headache Causation proposes that sleep disturbance and pain are comorbid due to both being influenced by sympathetic tone (increased sympathetic tone increasing both pain intensity and sleep disturbance). If heat reduced pain intensity there may also be an improvement in sleep disturbance.

Sleep disturbance was measured using a numerical rating scale of sleep disturbance with 0 being no sleep disturbance and 10 being maximum sleep disturbance as in the Daily Sleep Interference Scale (DSIS) (Vernon, et al., 2008). Sleep disturbance was measured in the initial and final questionnaire. The DSIS has demonstrated robust test–retest reliability, good construct and discriminant validity and responsiveness in painful diabetic peripheral neuropathy and post herpetic neuralgia (Vernon, et al., 2008) as well as rheumatoid arthritis (Wolfe, Michaud, & Li, 2006). A 1 to 2 point change on the DSIS may be interpreted as an important difference.

6.6.4 Depression

The Beck Depression Inventory (II) questionnaire (Beck, et al., 1988) was used to measure depression at the first consultation and the final consultation eight weeks later. Very few trials for the prevention of CTTH reviewed in section 3.7 measured depression with the BDI questionnaire being utilised by Schulte-Mattler et al. (2004). The BDI was preferred for this study due to the PI's previous experience using this scale in clinical practice, ease of administration and robustness of this scale. The BDI (II) is a self report instrument that takes approximately 5 to 10 minutes to complete and produces a single score for depression. Each of the 21 items has a four point scale from 0 to 3 that is summed to give the score for BDI. A total score of 1 to 13 is considered minimal depression, 14 to 19 mild depression, 20 to 28 moderate depression, and 29 to 63 severe depression. The BDI has been used for 35 years and a meta-analysis of the BDI's internal consistency estimates, yielded a mean coefficient α of 0.86 for psychiatric patients and 0.81 for nonpsychiatric subjects.

6.6.5 Headache disability

The headache disability index (HDI) (Jacobsen, et al., 1994) was used to measure headache disability in the questionnaire at the first consultation and the final consultation eight weeks later (Figure 6.1). The HDI is a questionnaire with 25 items with two subscales, functional impairment and emotional impairment. Each item of the HDI has a possible score of 0, 2 or 4 with a maximum score of 100. The functional impairment subscale has 12 items (maximum score 48) and the emotional impairment subscale has 13 items (maximum score 52). An increasing score relates to increasing disability with no numerical subscale present to determine levels of disability (mild, medium or severe disability). A total 29 point change must occur before the changes in HDI can be attributed to treatment effects (Jacobsen, et al., 1994).

Headache disability has been measured in very few trials of CTTH e.g. Holroyd et al. (2001). The HDI measures the functional and emotional impact of headache on everyday life. The questionnaire takes a few minutes to fill in and was chosen for this study as it has

internal consistency, test-retest reliability, convergent validity and discriminative validity (Jacobsen, et al., 1994).

6.7 Data handling

The 12 weeks of the trial were broken down into fortnights (F) named F0 (weeks 1 & 2), F1 (weeks 3 & 4), F2 (weeks 5 & 6), F3 (weeks 7 & 8), F4 (weeks 9 & 10) and F5 (weeks 11 & 12) (Figure 6.1). F0 and F1 represent the first month of the study. F1 was taken as the baseline measure as this was the fortnight immediately prior to the intervention and patients had two weeks' experience in completing the daily headache diary, ensuring any initial difficulties with filling in the questionnaire had been overcome prior to the intervention starting. Many studies had compared data using the timeframe of a month (Bendtsen, et al., 2007; Bettucci, et al., 2006; Padberg, et al., 2004; Ribeiro, 2000; Schmitt, et al., 2001) with a few trials collating data in fortnights (Ribeiro, 2000; Wang, et al., 2007). Data in this trial was collated two weekly so that comparisons could be made two weekly to ascertain the length of period required to attend the sauna before a statistically and clinically important change occurred (section 7.4.1). Attending the sauna for 20 minutes three times a week requires travelling time and sauna bathing time which is significantly more time than required to take tablets so it was important to try and establish what is the minimum dose required. Data was also analysed monthly so that comparisons could be made with other RCTs of CTTH and comparisons could be made with the fortnightly analysis to check for bias in reporting results in the WEST headache trial.

6.8 Data analysis

The pain diary scores, BDI, HDI and sleep disturbance scores were entered into excel worksheets by an assistant who was not involved with the running of the trial and blind to the group allocation in the trial. Once the spreadsheets collating pain scores and durations were finished they were transferred to SPSS version 17 and SAS 9.2 (SAS Institute Inc., Cary, NC). The data for headache intensity and duration was averaged over fortnights for analysis. The baseline data was the average intensity and duration at F1 (weeks 3 & 4) and the final data was at F5 (weeks 11 & 12). The fortnights designated F0, F1, F2, F3, F4 and

F5 represent fortnights ending in weeks 2, 4, 6, 8, 10 and 12 respectively. Data was also collated into months for analysis as many CTTH headache trials report monthly measures.

The primary prespecified analysis of the primary outcome was individual 2 sample *t*-tests for the mean difference in the NPRS. Independent sample *t*-tests were carried out for final minus initial BDI scores, DSIS and HDI scores. There was one observation per participant for the above scores. A *p* value of < 0.05 and/or 95% CI not inclusive of 0 would be considered indicative of statistical significance. Independent sample *t*-tests were performed as it is a well established standard method for comparing means of distributions and is robust for non normal distributions. Differences in the primary and secondary outcomes between groups was the most common method of analysis in the RCTs identified in Table 3.6, with 19 out of 26 RCTs for prevention of CTTH (Bendtsen, Buchgreitz, Ashina, & Jensen, 2007; Bendtsen & Jensen, 2004; Bendtsen, Jensen, & Olesen, 1996; Bettucci, et al., 2006; Fogelholm & Murros, 1992; Gobel, et al., 1994; Holroyd, et al., 2001; Kiran, et al., 2005; Lindelof & Bendtsen, 2009; Padberg, de Bruijn, de Haan, & Tavy, 2004; Pfaffenrath, et al., 1994; Ribeiro, 2000; Schmitt, Slowey, Fravi, Weber, & Burgunder, 2001; Schulte-Mattler & Krack, 2004; Silberstein, et al., 2006; Soderberg, et al., 2006; Walker, Walker, Robertson, & Stansfeld, 1998; Wang, et al., 2007; Yurekli, et al., 2008) performing various statistical tests such as independent samples *t*-test or Mann-Whitney U and Wilcoxon signed tests to test for statistically significant differences between the final and initial data between the control and intervention groups.

Two additional measures, headache index and responder rate, were determined using the data collected. Headache index was determined by multiplying the mean duration of headache by the mean severity of headache. The responder rate is the number of people reaching a 50% reduction in a headache activity measure and is important because in clinical practice if patients gain 50% improvement in symptoms in chronic pain this is a clinically significant outcome. When using mean values of a group response, treatments can emerge that are statistically significant if many of the group respond to treatment with small improvements. Treatment success, patients gain 50% improvement in symptoms, may be masked if a proportion of the group have poor outcomes balancing the good outcomes. It is

important to report the proportion of the group that improve over 50% (responders) to see the proportion in the population that may respond to the treatment under investigation.

To investigate the main effects of treatment group and time and their interaction, a secondary analysis of the headache intensity and duration using a mixed model analysis of variance was performed. The fixed effects were group and time and their interaction. The random effect was the participant with a compound symmetry covariance structure for repeated measurements. The difference between the sauna and control group in the final measures for the dependent variables of sleep disturbance, BDI and HDI before and after the trial were analysed using analysis of variance to explore differences between the groups, adjusting for the levels before treatment. Histograms were examined to assess whether the data is normally distributed. These showed the data was reasonably consistent with a normal distribution.

There was missing data due to loss of final diaries. The reasons for absent data were the same in both groups and not due to the intervention performed. All participants with complete data were analysed according to their group allocation.

6.9 Settings and location of the study

The consultation for participants and filling in the questionnaires was performed at Southern Cross Specialist Centre, Southern Cross Hospital, 90 Hanson St, Newtown, Wellington. This is a private hospital that is owned by New Zealand's major health insurance company, Southern Cross. This facility is well known to many people who live in the Wellington region and was easy to find for most participants.

6.10 Ethics committee approval and lodgement of trial

Once the details of the WEST headache trial study population, sample size, interventions and statistical handling were finalized, an ethics committee application was lodged for the clinical trial. The Upper South A Regional Ethics Committee gave ethics approval for this study (approval number URA/08/08/054) (Appendix 12). The trial was registered with the

Australian New Zealand Control Trial Registry (ANZCTR), ACZCTR registration number 12609000746235 (Appendix 13).

6.11 Summary

The WEST headache trial aims to evaluate the effectiveness of a noninvasive intervention in reducing headache intensity and a number of other outcome measures (e.g. headache duration, sleep disturbance, depression). The Adrenaline Model of Headache Causation was used to help identify the noninvasive treatment for the WEST headache trial. Sauna bathing was chosen as the intervention and if proven to be effective will be a mostly self directed, relatively cheap treatment for CTTH sufferers. Chapter 7 presents the results of the WEST headache trial.

Chapter 7

THE WELLINGTON EDUCATION AND SELF TREATMENT (WEST) HEADACHE TRIAL: RESULTS

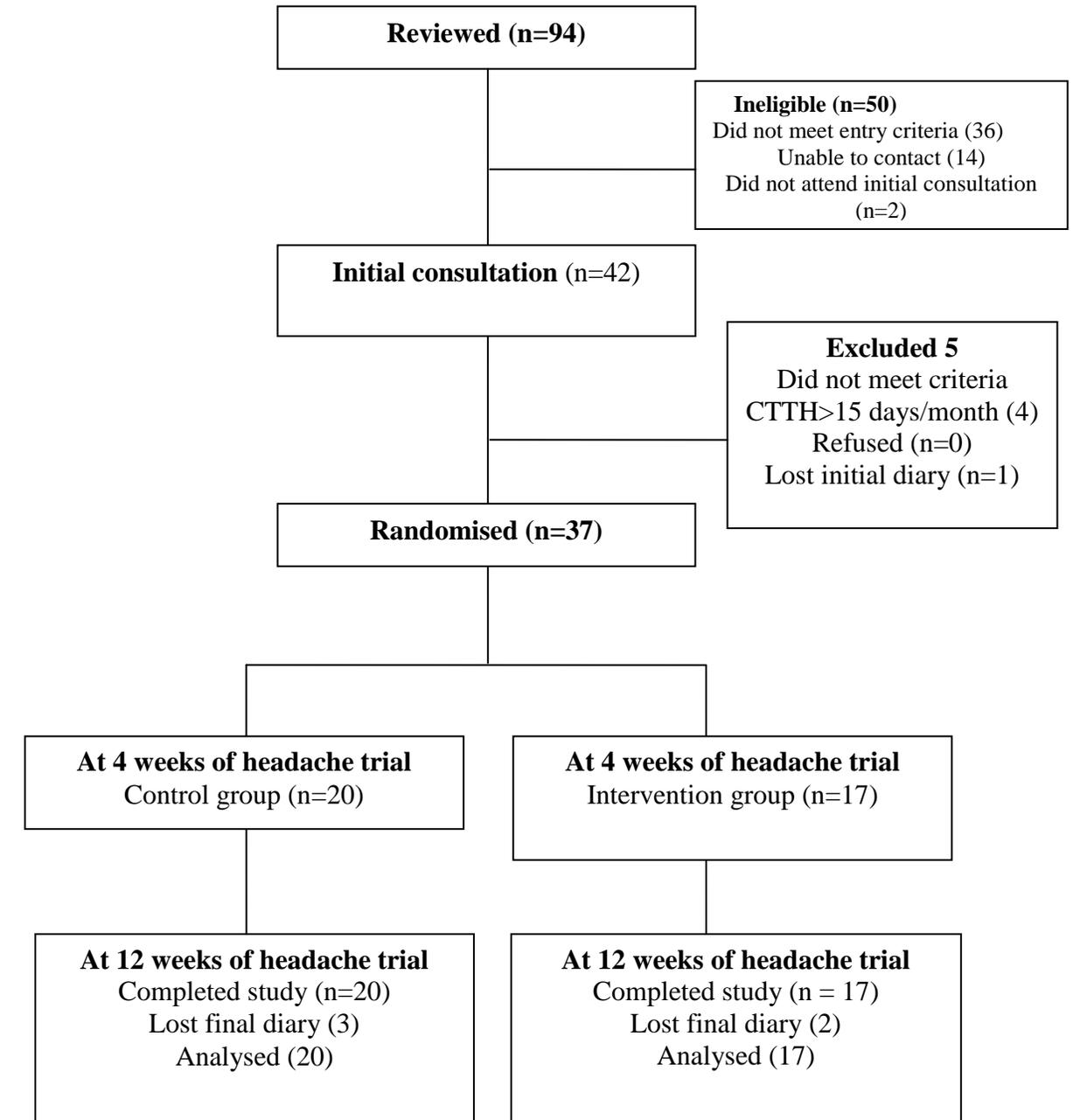
7.1 Introduction

This chapter provides the results of the WEST headache trial of sauna bathing as a preventative treatment for CTTH and describes demographic profiles of participants (section 7.1), recruitment and attrition (section 7.2) as well as the changes in the recorded measures of headache pain intensity (section 7.4), headache duration (section 7.4), sleep disturbance (section 7.5.1), depression (section 7.5.2), headache disability (section 7.5.3) and headache index (section 7.5.4). The trial was essentially a self directed treatment with only one consultation to explain the model and treatment protocol and one consultation at the end of the eight week intervention.

7.2 Recruitment and attrition

The flow of participants in the WEST headache trial is shown in Figure 7.1. Ninety-four potential subjects expressed interest in the study, responding to the different recruitment procedures (section 6.5). Fourteen people were unable to be contacted and after five attempts by telephone and email they were excluded from the study. Eighty people were screened in a structured telephone interview for eligibility by the PI and 36 were excluded from the study. Exclusions were due to not meeting the criteria for CTTH by either frequency of headache, type of headache or pain being at a body site other than the head. A total of 50 participants were excluded and a total of 44 participants were sent an initial headache diary and information sheet outlining the trial. Forty two participants made it to the initial consultation (at 4 weeks) at the Southern Cross Specialist Centre between January and August 2009, which also included their initial consultation, consent and randomisation into treatment groups.

Figure 7.1 Flowchart of participants in the WEST headache trial



Of the 42 participants enrolled in the clinical trial four did not meet the criteria of CTTH (15 headaches per month) as evidenced from their first month headache diary and were excluded from the trial, whereas one participant lost their initial diary and was also excluded as it was unknown whether this participant met the entry criteria of 15 days headache per month. Seventeen participants with CTTH were randomised to the intervention (sauna) group and 20 to the control group.

There were no dropouts from either intervention or control group due to side effects and all participants were analysed according to the group in which they were randomised. Of the 17 in the intervention group, 2 participants lost or misplaced their final eight week diary. Of the 20 participants in the control group, 3 participants lost or misplaced their final eight week diary. Imputation of missing data is a very complex issue and was not prespecified when planning the trial, obtaining Ethics Committee approval or registering the trial therefore imputation of data was not performed. The last observation carried forward is now known to be an inappropriate method of data imputation leading to significant biased results (Moher, et al., 2011). If people drop out because they have improved markedly or become worse then results will be biased by carrying the last observation forward and does not improve the quality of the analysis. Hence in this study data was handled by SPSS version 17 where data is included in the means for initial and final scores, but excluded by default in the measures of difference, as there is no difference of scores when only an initial (or final) outcome measure is present.

In the WEST headache trial there are a different number of participants providing initial data compared to final data, due to five participants not providing the final data (losing their final diary). This resulted in the mean difference between initial data minus final data not always being equal to the subtraction of initial and final data presented in the results Table 7.3. For example in the initial NPRS for the control group (3.5) there were 37 full sets of data and the mean is taken for this set. In the final NPRS data for the control group there were only 32 complete sets of NPRS data with a mean of 3.1. The mean is taken for the 37 initial data and the mean is taken from the 32 participants who provided the final diary. The

mean difference is calculated by SPSS by taking only the 32 participants who provided complete data and equals 0.3. Therefore 3.5 minus 3.1 did not equal 0.3. The same problem was present for incomplete questionnaires for BDI, HDI and sleep disturbance whereby the difference between the initial and final data does not equal the difference seen in Table 7.3.

7.3 Demographic characteristics and baseline clinical characteristics of the control and intervention groups

Demographic and baseline clinical characteristics of the 37 participants are presented in Table 7.1. The mean (SD) age for the control group was 44.7 (10.6) and for the intervention group was 38.9 (16.8). The percentage of females in the control group was 80% and in the intervention group was 71%. The mean (SD) number of years headache experienced in the control group was 18.9 (12.9) and for the intervention group was 14.4 (13.8). The mean (SD) number of days headache per 28 days in the control group was 22.9 (5.1) and in the intervention group was 25.7 (4.2).

| Characteristic | Control (n= 20) | Intervention (n=17) | Total (n=37) |
|---|----------------------------|--------------------------------|-------------------------|
| Mean (SD) age (years) | 44.7 (10.6) | 38.9 (16.8) | 42.0 (13.9) |
| Mean (SD) duration of headaches (years) | 18.9 (12.9) | 14.4 (13.8) | 16.8 (13.3) |
| Mean (SD) Number of headaches/month | 22.9(5.1) | 25.7 (4.2) | 24.3 (4.8) |
| Females n (%) | 16 (80.0%) | 12 (70.6%) | 28 (75.6%) |
| Males n (%) | 4 (20.0%) | 5 (29.4%) | 9 (24.3%) |
| Taking preventative medication (amitriptyline or nortriptyline) | 3 (15%) | 5 (29%) | 8 (22%) |
| F1 headache intensity (NPRS/10) | 3.5 (1.8) | 4.3 (1.7) | 4.0 (1.8) |
| F1 headache duration (hours) | 6.6 (5.5) | 8.3 (5.5) | 7.4 (5.5) |
| Sleep disturbance | 3.2 (2.2) | 3.3 (2.5) | 3.2 (2.3) |
| Beck Depression Inventory | 11.1 (9.3) | 13.0 (10.2) | 11.9 (8.9) |
| Headache Disability Index | 48.7 (22.1) | 48.0 (27.9) | 48.4 (24.6) |
| Data expressed as mean (standard deviation) or Number of participants (%) and taken from initial questionnaire and baseline daily headache diary. F1= Fortnight 1 | | | |

The mean (SD) headache intensity at baseline in the control group was 3.5 (2.0) and in the intervention group was 4.3 (1.7). The secondary measure of headache duration in hours per day in the control group was 6.6 (5.5) and in the intervention group was 8.3 (5.5). The

secondary measure of sleep disturbance in the control group was 3.2 (2.2) and in the intervention group was 3.3 (2.5). The secondary measure of BDI in the control group was 11.1 (9.3) and in the intervention group was 13.0 (10.2). The secondary measure of HDI in the control group was 48.7 (22.1) and in the intervention group was 48.0 (27.9). Eight participants were taking preventative medications for headache, three participants in the control group and five participants in the intervention group. The eight participants were taking antidepressants as their preventative medication; six were taking amitriptyline whilst two were taking nortriptyline (both drugs are tricyclic antidepressants).

7.4 Headache intensity and duration

The outcome measurements of mean (SD) headache intensity (NPRS), duration (hours/day) and number of days' headache present per fortnight for the WEST headache trial at measurement time points designated F0, F1, F2, F3, F4 and F5 (F = fortnight) are presented in Table 7.2. The fortnight prior to the intervention starting was designated as the first fortnight (F1) and was taken as the baseline measure in this study with F5 representing the final score. Comparisons between the control and intervention group for headache pain intensity and duration of headache are presented in Table 7.3.

A bar plot of the change in mean headache intensity is shown in Figure 7.2. The mean (SD) initial headache intensity (F1) for the control group was 3.5 (2.0) and the final score was 3.1 (1.9) with a mean difference of 0.3 (1.1), a reduction of 8% in headache intensity. The mean initial headache intensity score for the intervention group at F1 was 4.3 (1.7) and the final score at F5 was 2.6 (1.9) with a mean difference of 1.9 (2.5), a reduction of 44% in headache intensity (Table 7.3). The mean difference of headache intensity between the two groups was 1.6 (95% CI: 2.9 to 0.2, $p = 0.027$) which was statistically and clinically significant (greater than 30% reduction of NPRS) (Table 7.3).

Table 7.2: Fortnightly mean measures of headache intensity, duration, and number days headache present

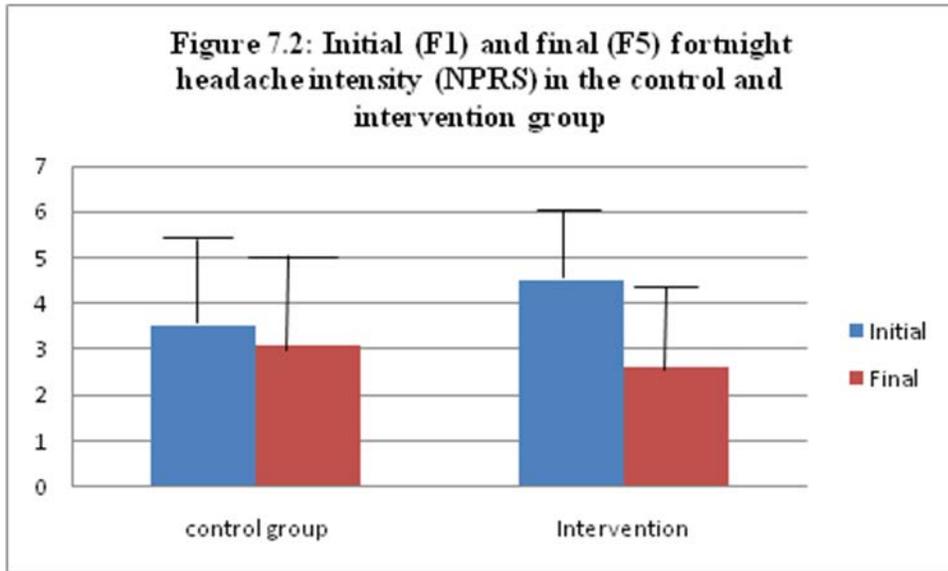
| Outcome measure | Group | F0 | F1 | F2 | F3 | F4 | F5 |
|-------------------------------|--------------|------------|------------|------------|------------|------------|------------|
| Headache Intensity (NPRS) | Control | 3.5 (1.8) | 3.5 (2.0) | 3.4 (1.6) | 3.3 (1.9) | 3.0 (1.6) | 3.1 (1.9) |
| | Intervention | 4.5 (1.7) | 4.3 (1.7) | 3.5 (1.7) | 2.8 (1.5) | 2.5 (1.6) | 2.6 (1.9) |
| Headache duration (hours/day) | Control | 7.0 (5.3) | 6.6 (5.5) | 6.2 (5.1) | 6.1 (5.5) | 5.6 (4.6) | 6.1 (4.8) |
| | Intervention | 8.4 (5.3) | 8.3 (5.5) | 7.4 (5.5) | 6.2 (5.5) | 5.3 (5.3) | 5.7 (5.9) |
| No. of days headache present | Control | 11.7 (2.4) | 11.1 (3.0) | 11.6 (3.0) | 11.7 (3.4) | 10.7 (4.2) | 10.7 (4.2) |
| | Intervention | 12.9 (2.0) | 12.8 (1.7) | 11.2 (4.2) | 10.6 (3.7) | 9.9 (4.4) | 9.6 (4.8) |

Data is expressed as mean (SD). Fortnights are designated as F0, F1, F2, F3, F4 and F5 with F1 representing the initial score (weeks 3 & 4) and F5 representing the final score (weeks 11 & 12). Data taken from daily headache diary.

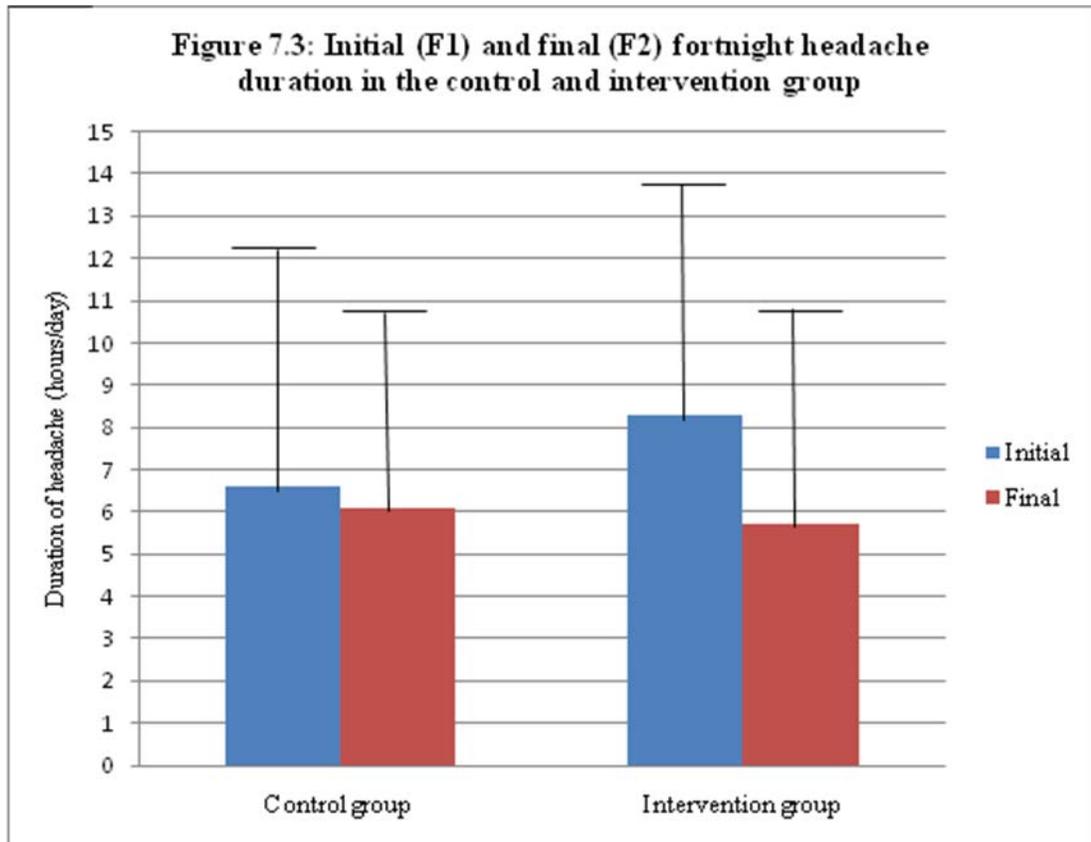
Table 7.3: Summary of differences between intervention and control group for primary and secondary outcome measures

| Outcome measures | Control group | | | Intervention group | | | Mean difference | p |
|---------------------------|---------------|-------------|-------------|--------------------|-------------|-------------|---------------------|-------|
| | Baseline | Final | Change | Baseline | Final | Change | | |
| Primary outcome | | | | | | | | |
| Headache Intensity | 3.5 (2.0) | 3.1 (1.6) | 0.3 (1.1) | 4.3 (1.7) | 2.6 (1.6) | 1.9 (2.5) | 1.6 (0.2 to 2.9) | 0.027 |
| Secondary outcomes | | | | | | | | |
| Duration hours/day | 6.6 (5.5) | 6.1 (4.8) | 0.8 (3.4) | 8.3 (5.5) | 5.7 (5.9) | 3.4 (4.7) | 2.6 (-0.1 to 5.3) | 0.055 |
| Number of days/fortnight | 11.1 (3.0) | 10.7 (4.2) | 0.8 (3.5) | 12.8 (1.7) | 9.6 (4.8) | 3.5 (4.6) | 2.7 (-0.2 to 5.6) | 0.067 |
| Sleep disturbance | 3.2 (2.2) | 2.2 (2.0) | 0.9 (3.3) | 3.3 (2.5) | 2.6 (2.3) | 0.6 (2.4) | 0.4 (-2.6 to 1.9) | 0.74 |
| Beck Depression Inventory | 11.1 (9.3) | 7.1 (3.9) | 2.7 (5.1) | 13.0 (10.1) | 7.4 (4.2) | 6.1 (8.3) | 3.4 (8.2 to-1.5) | 0.169 |
| Headache Disability Index | 48.7 (22.1) | 36.0 (18.8) | 16.5 (17.2) | 48.0 (28.0) | 32.2 (20.4) | 19.8 (24.1) | 3.3 (-21.0 to 14.4) | 0.7 |

Data expressed as mean (SD). Headache intensity, duration and number of days headache/fortnight determined by daily headache diary using baseline fortnight Weeks 3 & 4 (F1) and final fortnight weeks 11 & 12 (F5) data. Sleep disturbance, Beck Depression Inventory and Headache Disability Index determined by Initial and Final Questionnaire.

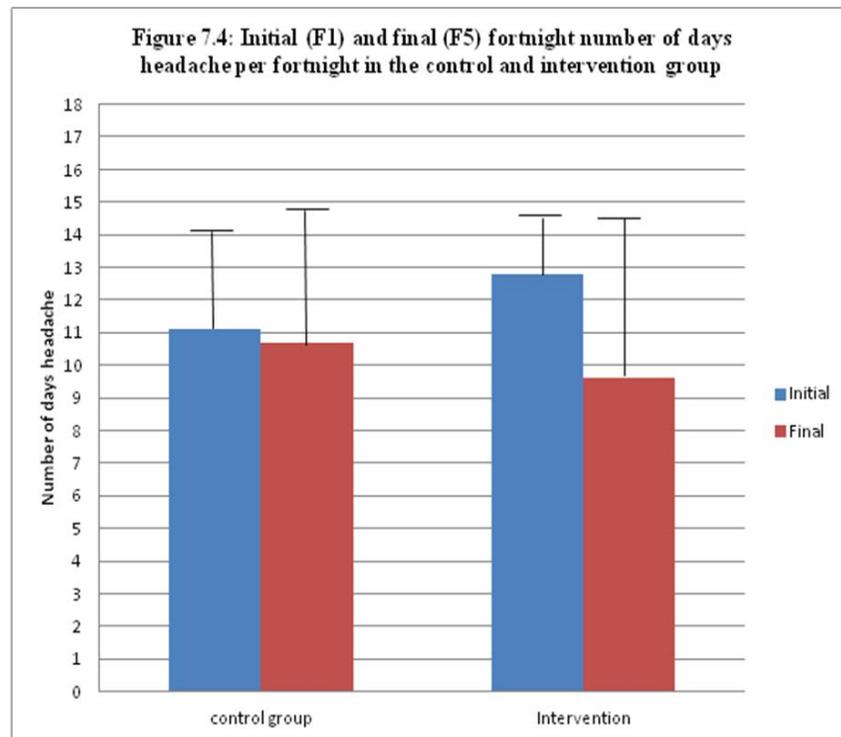


A bar plot of the change in mean headache duration is shown in Figure 7.3. The mean (SD) initial headache duration (hours/day) for the control group at F1 was 6.6 (5.5) and the final headache duration was 6.1 (4.8) with a mean difference of 0.8 (3.4), a reduction



of 12% in headache duration. The mean duration of headache at F1 for the intervention group was 8.3 (5.5) and the final headache duration at F5 was 5.7 (5.9) with a difference of 3.4 (4.7), a reduction of 40% in headache duration (Table 7.3). The mean difference of headache duration between the two groups was 2.6 (95% CI: -0.1 to 5.3, $p = 0.055$) (Table 7.3).

A bar plot of the change in mean number of days' headache per fortnight for the control and intervention group is shown in Figure 7.4. The mean (SD) number of days' headache per fortnight at F1 for the control group was 11.1 (3.0) and the final number of days' headache per fortnight was 10.7 (4.2) with a mean difference of 0.8 (3.3), a reduction of 7% in number of days' headache per fortnight (Table 7.3). The mean number of days' headache per fortnight at F1 for the intervention group was 12.8 (1.7) and the final number of days' headache per fortnight at F5 was 9.6 (4.8) with a mean difference of 3.5 (4.6), a reduction of 27% in mean number of days' headache per fortnight (Table 7.3). The mean difference of number of days headache per fortnight between the two groups was 2.7 (95% CI:-0.2 to 5.6, $p = 0.067$) (Table 7.3).



7.4.1 Comparisons of headache intensity at each fortnight

The headache intensity scores were analysed at each fortnight to determine when the differences in the scores became statistically and clinically significant within the 8 week intervention trial.

Comparisons of headache intensity between groups from the initial fortnight (F1) and F4, F3, F2 are presented in Table 7.4. A clinically relevant (30% reduction in NPRS) and statistically significant change ($P < 0.05$) in headache intensity is apparent between the initial fortnight and F4, six weeks after entering the intervention group. Although a statistically significant change in headache intensity is seen at F3, the change is not clinically significant as it does not reach a 30% reduction in NPRS.

| Table 7.4: Headache intensity comparisons between initial fortnight (F1) and F4, F3, F2 | | | |
|--|----------------|---------------------|----------------|
| | Control | Intervention | p-value |
| F1 minus F4 | | | |
| Initial | 3.5 (1.8) | 4.3 (1.7) | |
| F4 | 3.0 (1.6) | 2.5 (1.6) | |
| Difference | 0.4 (1.0) | 2.0 (2.2) | |
| Mean Difference | | 1.5 (2.8 to 0.3) | 0.014 |
| F1 minus F3 | | | |
| Initial | 3.5 (1.8) | 4.3 (1.7) | |
| F3 | 3.3 (1.9) | 2.8 (1.5) | |
| Difference | 0.4 (1.0) | 1.4 (1.1) | |
| Mean Difference | | 1.3 (2.1 to 0.5) | 0.002 |
| F1 minus F2 | | | |
| Initial | 3.5 (1.8) | 4.3 (1.7) | |
| F2 | 3.4 (1.6) | 3.5 (1.7) | |
| Difference | 0.2 (1.2) | 0.7 (1.5) | |
| Mean Difference | | 0.8 (1.8 to -0.2) | 0.1 |
| Data are expressed as mean (SD). Intensity was determined from the daily headache diary. F = Fortnight, F1 = Weeks 3 & 4 (baseline), F2 = Weeks 5 & 6, F3 = Weeks 7 & 8, F4 = Weeks 9 & 10 | | | |

7.5 Secondary outcome measures

The between group comparisons for the secondary measures of sleep disturbance, depression and headache disability are presented in Table 7.3.

7.5.1 Sleep disturbance

In the control group mean (SD) baseline sleep disturbance was 3.2 (2.2) and at the final consultation was 2.2 (2.0), a mean reduction of 0.9 (3.3). The mean baseline sleep disturbance in the intervention group was 3.3 (2.5) and 2.6 (2.3) at the final consultation, a mean (SD) reduction of 0.6 (2.4). The mean (SD) difference of sleep disturbance between the two groups was 0.4 (95% CI: -2.6 to 1.9, $p = 0.74$) (Table 7.3).

7.5.2 Depression

Measurement of depression was performed using the BDI. A total score of 1 to 13 is considered minimal range, 14 to 19 mild, 20 to 28 moderate and 29 to 63 severe depression. Table 7.5 shows the numbers of participants in each group within these ranges at the initial and final consultation. The number of participants with scores above 13 reducing to 13 or

| | Control group | | Intervention group | |
|---------------------------------------|----------------------|--------------|---------------------------|--------------|
| | Initial | Final | Initial | Final |
| Minimal depression (1 to 13) | 11 | 17 | 10 | 15 |
| Mild depression (14 to 19) | 6 | 2 | 4 | 1 |
| Moderate depression (20 to 28) | 1 | | 1 | |
| severe depression (29 to 63) | 1 | | 2 | |

Beck Depression Inventory scores from the initial and final questionnaire completed at week 5 and week 12. Missing variables account for numbers of results not being equal.

below in the control group was 6 and in the intervention group was also 6. In the control group mean (SD) baseline BDI score was 11.1 (9.3) and at the final consultation was 7.1 (3.9), a reduction of 2.7 (5.1), representing a reduction in BDI of 25%. In the intervention

group baseline BDI score was 13.0 (10.1) and 7.4 (4.2) at the final consultation, a decrease of 6.1(8.3), representing a reduction of 45%. The mean difference of BDI scores between the two groups was 3.4 (95% CI: -1.5 to 8.2, $p = 0.169$) (Table 7.3).

7.5.3 Headache disability

In the control group mean (SD) baseline total HDI score was 48.7 (22.1) and 36.0 (18.8) at the end of the trial, a mean decrease of 16.5 (17.2). In the intervention group baseline HDI score was 48.0 (28.0) and at the final consultation was 32.2 (20.4), a mean reduction of 19.8 (24.1) (Table 7.3). The mean difference of HDI between the two groups was 3.3 (95% CI: -21 to 14.4, $p = 0.70$) (Table 7.3). The HDI scores, including the emotional and functional subscales are presented in Table 7.6. A 29 point change must occur before the changes in headache index can be attributed to treatment effects. A 29 point reduction in HDI was registered in one participant in the control group and three participants in the intervention group.

7.5.4 Responder rates for headache intensity, duration and headache index

A responder is a participant who achieves a 50% reduction in the measure of interest, often the headache index. Responder rates of the number of participants reaching a 50% reduction, for headache intensity, headache duration and headache index for participants with complete data (initial and final daily headache diary) are presented in Table 7.7. Forty seven percent of the intervention group and 12% of the control group experienced a 50% reduction of headache intensity. The odds ratio for association between greater than 50% change and allocation to intervention was 6.6 (95% CI: 1.1 to 39.3, $p = 0.031$). Forty three percent of the intervention group and 12% of the control group experienced a 50% reduction of headache duration. The odds ratio for association between greater than 50% change and allocation to intervention was 5.6 (95% CI: 0.9 to 34.5, $p = 0.053$). Seventy one percent of the intervention group and 29% of the control group experienced a 50% reduction of headache index (Table 7.7). The odds ratio for association between

| Outcome measure | Control group | | | Intervention group | | | Mean difference | p |
|-------------------------|---------------|-------------|-------------|--------------------|-------------|-------------|---------------------|-------|
| | Baseline | Final | Change | Baseline | Final | Change | | |
| HDI (total) | 48.7 (22.1) | 36.0 (18.8) | 16.5 (17.2) | 48.0 (28.0) | 32.2 (20.4) | 19.8 (24.1) | 3.3 (-21.0 to 14.4) | 0.7 |
| HDI (Emotional) | 23.4 (11.3) | 15.0 (9.2) | 8.7 (8.9) | 24.3 (13.9) | 14.6 (8.8) | 11.3 (13.7) | 2.7 (-12.5 to 7.1) | 0.578 |
| HDI (Functional) | 25.3 (12.3) | 21.0 (10.4) | 7.8 (9.2) | 23.6 (14.5) | 17.5 (12.6) | 8.5 (10.9) | 0.7 (-9.2 to 7.9) | 0.873 |

Data expressed as mean (SD). HDI = Headache Disability Index. Headache Disability Index determined by Initial and Final Questionnaire.

| Outcome measure | Group | | OR (95%CI) | p |
|-------------------------|------------|--------------|-------------------|-------|
| | Control | Intervention | | |
| Intensity (NPRS) | 2/17 (12%) | 7/15 (47%)* | 6.6 (1.1 to 39.3) | 0.031 |
| Duration(hours) | 2/17 (12%) | 6/14 (43%) | 5.6 (0.9 to 34.5) | 0.053 |
| Headache index | 5/17 (29%) | 10/14 (71%)* | 6.0 (1.3 to 28.5) | 0.022 |

Data expressed as proportion of participants (%). Intensity (NPRS) and duration (hours/day) as determined by daily headache diary. OR = Odds ratio CI = confidence interval. *P < 0.05 is statistically significant

greater than 50% change and allocation to intervention was 6.0 (95% CI: 1.3 to 28.5, $p = 0.022$). There is a statistically significant difference in responder rate for headache intensity and headache index favouring the intervention group.

7.5.5 Monthly comparisons of headache intensity and duration

Although data has been presented for fortnightly measures, many headache studies present data in monthly measures and hence headache intensity, duration and number of days headache experienced per month are presented in Table 7.8 with the comparisons between groups at month 1 and month 3 shown in Table 7.9. Statistical comparisons of headache intensity, duration and number of headache days per month between the control and intervention group are presented in Table 7.9. Mean monthly headache intensity showed 9% reduction in the control group and 42% reduction in the intervention group. The control group showed a 17% reduction in duration of headache (hours/day) whereas the intervention group showed a 40% reduction in headache duration (hours/day). The control group showed an 8% reduction in number of headache days per month compared to a 25% reduction in headache days in the intervention group. The changes in monthly statistics and fortnightly statistics were similar for reduction in headache intensity and duration and minimal bias resulted from presenting fortnightly analysis.

| Outcome measures | Control | | | Intervention | | |
|--|------------|------------|------------|--------------|------------|------------|
| | Month1 | Month2 | Month3 | Month1 | Month2 | Month3 |
| Headache Intensity (NPRS) | 3.4 (1.7) | 3.5 (1.7) | 3.0 (1.7) | 4.5 (1.6) | 3.2 (1.5) | 2.6 (1.6) |
| Headache duration (hours/day) | 7.0 (5.5) | 6.6 (5.1) | 5.8 (4.6) | 8.9 (5.5) | 6.8 (5.2) | 5.5 (5.4) |
| No. of days headache/month | 22.9 (5.1) | 23.3 (6.1) | 21.5 (7.3) | 25.7 (4.2) | 21.9 (7.5) | 19.5 (8.5) |
| Data expressed as mean (SD). Headache intensity, duration and number of days headache present per month determined from daily headache diary | | | | | | |

| Table 7.9: Comparison of Intensity, duration and days headache present per month between groups | | | | | | | | |
|--|----------------------|--------------|---------------|---------------------------|--------------|---------------|------------------------|----------|
| Outcome measures | Control group | | | Intervention group | | | Mean difference | p |
| | Baseline | Final | Change | Baseline | Final | Change | | |
| Primary outcome | | | | | | | | |
| Headache Intensity | 3.5 (1.8) | 3.0 (1.6) | 0.32 (1.1) | 4.50 (1.7) | 2.5 (1.6) | 1.9 (2.5) | 1.53 (2.79 to 0.28) | 0.027 |
| Secondary outcomes | | | | | | | | |
| Duration hours/day | 7.0 (5.4) | 5.8 (4.6) | 1.2 (1.8) | 8.9 (5.5) | 5.5 (5.4) | 3.6 (4.8) | 2.49 (-0.1 to 5.0) | 0.055 |
| Number of days/month | 23.8 (5.1) | 21.5 (7.3) | 1.9 (3.6) | 26.1 (3.5) | 19.5 (8.5) | 6.5 (3.6) | 4.59 (0.1 to 9.1) | 0.046 |
| Data expressed as mean (SD). Baseline = Month 1. Final = Month 3. Headache intensity, duration and number of days headache/month determined by daily headache diary. Sleep disturbance, Beck Depression Inventory and Headache Disability Index determined by Final and Initial Questionnaire. P< 0.05 is statistically significant. | | | | | | | | |

| Table 7.10: Repeated measures of mean (SD) headache intensity and duration for each fortnight | | | | | | | |
|--|--------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Outcome measure | Group | F0 | F1 | F2 | F3 | F4 | F5 |
| Headache Intensity (NPRS) | Control | 3.5 (1.8) | 3.5 (2.0) | 3.4 (1.6) | 3.3 (1.9) | 3.0 (1.6) | 3.1 (1.9) |
| | Intervention | 4.5 (1.7) | 4.3 (1.7) | 3.5 (1.7) | 2.8 (1.5) | 2.5 (1.6) | 2.6 (1.9) |
| Headache duration (hours/day) | Control | 7.0 (5.3) | 6.6 (5.5) | 6.2 (5.1) | 6.1 (5.5) | 5.6 (4.6) | 6.1 (4.8) |
| | Intervention | 8.4 (5.3) | 8.3(5.5) | 7.4 (5.5) | 6.2 (5.5) | 5.3 (5.3) | 5.7 (5.9) |
| Data is expressed as mean (SD). Fortnights are designated as F0, F1, F2, F3, F4 and F5 with F1 representing the initial score and F5 representing the final score. Data taken from daily headache diary. | | | | | | | |

7.5.6 Analysis of variance for headache intensity and duration

The repeated measures for the dependent variables of headache intensity and duration at the time points F1, F2, F3, F4, F5 (Table 7.10) were analysed to compare the control group and intervention group using a mixed model ANOVA analysis. The full factorial model was used in this analysis.

For pain intensity the interaction of group times time was significant.

$$F = 2.95, df = 4,117, p = 0.023$$

For duration the interaction of group times time was not significant.

$$F = 1.66, df = 4,119, p = 0.16$$

The contrasts from the mixed model analysis of variance comparing the difference from baseline of different time points between the control group and intervention group for pain intensity is shown in Table 7.11. The contrasts from the mixed model of analysis comparing the difference from baseline of different time points between the control group and intervention group for duration of headache is shown in Table 7.12 The pain intensity was significantly different between the sauna and control groups at F3, F4 and F5. The duration was significantly different between the sauna and control groups at F3.

Table 7.11 The contrasts from the mixed model analysis of variance comparing the difference from baseline of different time points between the control group and the intervention group for pain intensity

| Time | F | Df | P | Difference in mean change (95%CI) |
|------|------|-------|--------|-----------------------------------|
| F2 | 2.94 | 1,119 | 0.089 | 0.88 (-0.14 – 1.91) |
| F3 | 7.94 | 1,119 | 0.006* | 1.45 (0.43 – 2.48) |
| F4 | 6.48 | 1,119 | 0.012* | 1.31 (0.29 – 2.32) |
| F5 | 8.21 | 1,119 | 0.005* | 1.45 (0.45 – 2.45) |

F2,3,4,5 = fortnight, df = degrees of freedom, p < 0.05 is statistically significant

| Time | F | Df | P | Difference in mean change (95% CI) |
|-------------|----------|-----------|----------|---|
| F2 | 1.08 | 1,121 | 0.30 | 1.22 (-1.11 – 3.56) |
| F3 | 4.84 | 1,121 | 0.030* | 2.60 (0.26 – 4.93) |
| F4 | 3.58 | 1,121 | 0.061 | 2.25 (-0.10 – 4.61) |
| F5 | 3.85 | 1,121 | 0.052 | 2.34 (-0.02 – 4.69) |

F2,3,4,5 = fortnight, df = degrees of freedom, p < 0.05 is statistically significant

Group main effects for change from baseline in pain intensity and duration were estimated with a contrast for the difference between control group and intervention group in the mean change from baseline. The groups were significantly different for pain intensity $F = 10.17$, $df = 1,117$, $p = 0.002$, difference in mean change 1.27 (95% CI 0.48 – 2.07) and duration $F = 5.16$, $df = 1,118$, $p = 0.025$, difference in mean change 2.10 (95% CI 0.27 – 3.93).

There were no significant differences between the groups at baseline for headache intensity $F = 1.36$, $df = 1,117$, $p = 0.25$, mean difference 0.69 (95% CI -0.49 – 1.87) or headache duration $F = 1.13$, $df = 1,118$, $p = 0.29$, mean difference 1.84 (95% CI -1.59 – 5.26). There were significant differences between times for the sauna group for pain intensity $F = 8.54$, $df = 4, 117$, $p = < 0.0001$ and duration $F = 5.10$, $df = 4,118$, $p = 0.0008$. Pain intensity was significantly different from baseline at F2 ($p = 0.034$), F3 ($p = 0.0002$), F4 ($p < 0.0001$) and F5 ($p < 0.0001$) and between F2 and F4 ($p = 0.017$) and F5 ($p = 0.013$). Duration was significantly different from baseline at F3 ($p = 0.003$), F4 ($p = 0.0001$) and F5 ($p = 0.0008$) and between F2 and F4 ($p = 0.032$). There were no significant differences between times for the control group for pain intensity $F = 0.95$, $df = 4,117$, $p = 0.44$ or duration $F = 0.76$, $df = 4,118$, $p = 0.55$.

7.5.7 Analysis of variance for sleep disturbance, BDI and HDI

The difference between the sauna and control group in the difference between the final measures and baseline for the dependent variables of sleep disturbance, BDI and HDI before and after the trial were analysed using analysis of variance. Histograms were

examined to assess whether the data is normally distributed. These showed the data was reasonably consistent with a normal distribution.

The analysis of variance of sleep disturbance revealed no statistically significant difference in the change in sleep disturbance in the sauna group compared to the control group (0.3; 95% CI -1.8 – 2.5; $F = 0.09$, $df = 1, 29$, $p = 0.77$). There were no significant differences between the groups at baseline ($F = 0.02$, $df = 1, 29$, $p = 0.88$), mean difference 0.1 (95% CI -1.4 – 1.6). There were no significant differences between times for the sauna group ($F = 1.89$, $df = 1, 29$, $p = 0.18$) or the control group ($F = 0.61$, $df = 1, 29$, $p = 0.44$).

The analysis of variance of BDI revealed no statistically significant difference in the change in BDI in the sauna group compared to the control group (1.8; 95% CI -3.4 – 6.9; $F = 0.48$, $df = 1, 30$, $p = 0.49$). There were no significant differences between the groups at baseline ($F = 0.52$, $df = 1, 30$, $p = 0.47$), mean difference -1.9 (95% CI -7.1 – 3.3). There was a significant difference between times for the sauna group ($F = 10.20$, $df = 1, 30$, $p = 0.004$), but not for the control group ($F = 3.19$, $df = 1, 30$, $p = 0.085$).

The analysis of variance of HDI revealed no statistically significant difference in the change in HDI in the sauna group compared to the control group (10.8; 95% CI -7.0 – 28.5; $F = 1.55$, $df = 1, 23$, $p = 0.22$). There were no significant differences between the groups at baseline ($F = 0.96$, $df = 1, 23$, $p = 0.33$), mean difference -7.3 (95% CI -22.2 – 7.7). There was a significant difference between times for the sauna group ($F = 15.85$, $df = 1, 23$, $p = 0.0006$), but not for the control group ($F = 1.85$, $df = 1, 23$, $p = 0.19$).

7.6 Adverse effects

Potential adverse effects of attending a sauna include fainting and feelings of claustrophobia. All participants were contacted two weeks after entering the treatment phase to enquire about adverse effects and whether there were any difficulties or problems with respect to the sauna or soft tissue massage. Participants were also asked about adverse effects at the final consultation. There were no reports of adverse effects from the sauna or control group in this trial.

7.7 Communication of results

To provide education on the Adrenaline Model of Headache Causation, discussion with health professionals involved in headache management occurred and several conference presentations were delivered in the last three years (Appendix 14). The health professionals reached included general practitioners, osteopaths, pain specialists, pharmacists, biomedical researchers and physiotherapists.

7.8 Summary

Sauna provided a clinically (30% reduction in NPRS) and statistically significant ($p < 0.05$) reduction in headache pain intensity within six weeks of the intervention phase of the WEST headache trial. A clinically and statistically significant reduction of headache pain intensity did not occur at any point in the trial in the control group. Sauna also provided a clinical and statistically significant improvement in sleep disturbance in this trial. All other secondary outcome measures including duration of headache, number of days with headache, depression and headache disability favoured the intervention group compared to the control group. Chapter 8 will discuss the results and compare them with other studies of CTTH.

Chapter 8

THE WEST HEADACHE TRIAL DISCUSSION AND PHD CONCLUSIONS

8.1 Introduction

This final chapter discusses the major findings of the WEST headache trial, including comparisons of this trial with other CTTH clinical prevention trials as well as implications of the Adrenaline Model of Headache Causation on future research and treatment of CTTH.

8.2 Major findings

The WEST headache trial supports the use of heat in the form of sauna for treating CTTH with the intervention group achieving a 44% reduction in headache intensity. The trial ran for 12 weeks with the treatment protocol of attending the sauna for 20 minutes three times a week being eight weeks in duration. Clinically and statistically significant changes in headache intensity were present by week six of the intervention. Preventative medication (section 3.7) seems to take a similar period of time to reach effectiveness as shown by Holroyd et al. (2001) who found 20/53 (38%) taking amitriptyline, 34/53 (64%) taking amitriptyline and receiving stress management, 17/49 (35%) receiving stress management and 14/48 (29%) taking placebo medication achieved a greater than 50% reduction in pain intensity after one month. Murros et al. (2000) also found reductions in headache intensity after six weeks of treatment with tizanidine.

Heat may work on the pathways of nociception, reducing central and peripheral sensitisation, but is unlikely to be successful in secondary headache where the source of nociception is a structural problem causing the pain such as sinusitis, eye strain or referred pain from the neck. If sensitisation of the pathways of nociception was the sole cause of headache then preventative treatment aimed at neural sensitisation may alleviate headache completely. If headache is partially alleviated, one may conclude that neural sensitisation was contributing to headache severity but not the sole cause. If it is

assumed that current preventative management of headache disorders only reduces neural sensitisation then people not responding to preventative medication may have an unidentified structural cause of nociception. Other reasons for not responding to preventative medication include inadequate dosing and other pathology such as inflammation.

The following null hypotheses stated in section 6.2.3 are refuted;

Null hypothesis I: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage for the reduction of intensity of headache intensity. Education, sauna and soft tissue massage is more effective than education and soft tissue massage alone in reducing intensity of headache as measured by NPRS. The difference in pain intensity scores demonstrates that attending the sauna for 20 minutes three times a week for eight weeks is effective in reducing the intensity of headache for CTTH.

Null hypothesis III: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage for the number of CTTH patients reducing headache index by 50%. Education, sauna and soft tissue massage is more effective than education and soft tissue massage alone in reducing headache index. The WEST headache trial found that attending the sauna for 20 minutes three times a week for eight weeks is effective in reducing the headache index for participants with CTTH.

The following null hypotheses stated in section 6.2.3 are retained;

Hypothesis II: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage for the reduction of headache duration as measured by hours of headache per day. The WEST headache trial found that attending the sauna for 20 minutes three times a week for eight weeks is not effective in reducing headache duration for participants with CTTH.

Null hypothesis IV: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage in improving sleep disturbance. Education, sauna and soft tissue massage is no more effective than education and soft tissue massage alone in reducing sleep disturbance for participants with CTTH.

Null hypothesis V: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage in improving depression as measured by the BDI. The WEST headache trial found that attending the sauna for 20 minutes three times a week for eight weeks is not effective in reducing depression for participants with CTTH.

Null hypothesis VI: Education, sauna and soft tissue massage is no more effective than education and soft tissue massage in reducing headache disability as measured by the HDI. The WEST headache trial found that attending the sauna for 20 minutes three times a week for eight weeks is not effective in reducing headache disability for participants with CTTH.

ANOVA found no statistically significant differences at baseline for headache intensity or duration between the control and intervention group. For headache intensity the differences between the groups differed between the time points. For headache duration the difference between the groups were not statistically significantly different between the time points.

The ANOVA was consistent with the *t*-tests for headache intensity rejecting null hypothesis I finding that education, sauna and soft tissue massage is more effective than education and soft tissue massage alone in reducing headache intensity. A statistically significant difference from baseline was found at F3, F4 and F5 in the sauna group.

The average post treatment change from baseline was statistically significant for headache intensity and headache duration. Headache intensity was statistically significantly different from baseline at all time points for the sauna group. Headache duration was statistically significant from baseline at F3, F4 and F5.

The ANOVA found no statistically significant difference in sleep disturbance, HDI or BDI between the control and intervention groups at baseline. The analysis of variance was consistent with the *t*-test analysis for sleep disturbance, HDI and BDI. Null hypotheses IV, V and VI were retained showing no statistically significant difference in the change from baseline between the control and intervention groups before and after treatment.

8.3 Sample size and attrition

The initial sample size calculation based on a 1.5 difference in NPRS required 34 participants. Forty four participants were recruited into the trial with seven dropouts occurring. This left 37 participants completing the trial and provided the minimum number of participants (n=34) based on the sample size calculation (section 6.51) to determine if a statistically significant difference would occur for headache intensity between the control and intervention group.

8.4 Comparison with previous trials on CTTH

The WEST headache trial is the first study to use sauna as an intervention for CTTH and no comparative studies are available for the treatment of CTTH using sauna as an intervention. Comparison of the WEST headache trial with the results of previous treatment trials on CTTH is seen in Table 8.1. The studies in Table 8.1 either used VAS or NPRS as the primary measure or a secondary measure so that a percentage reduction in headache intensity could be calculated. Reductions in headache intensity ranged from 13% for mirtazapine (Bendtsen & Jensen, 2004) to 83% for autogenic relaxation (Kiran, et al., 2005). The highest percentage reduction by a medication was 59% with the combination of amitriptyline and tizanidine (Bettucci, et al., 2006). Sauna reduced the headache intensity by 44% which is a similar result to several medications trialled for CTTH including sodium valproate, 40% reduction (Yurekli, et al., 2008), amitriptyline, 33% reduction (Boz, et al., 2003), tizanidine, approximately 50% reduction (Fogelholm & Murros, 1992; Murros, et al., 2000), and desipramine and fluoxetine, 33% reduction (Walker, et al., 1998). Medications that showed a lesser reduction in headache intensity include sertraline, 20% (Boz, et al., 2003), mirtazapine, 13% (Bendtsen & Jensen, 2004), and alprazolam, 18% (Kiran, et al., 2005).

The sauna group showed a favourable reduction in headache intensity when compared to botulinum toxin, 23% (Schmitt, et al., 2001) and 16% reduction (Padberg, et al., 2004), acupuncture, 33% reduction (Soderberg, et al., 2006) and physical therapy, 33% reduction (Soderberg, et al., 2006). Relaxation therapy produced a 42% reduction in headache intensity (Soderberg, et al., 2006) which was a similar outcome to the use of sauna.

| Table 8.1: Clinical trials reporting a reduction in headache intensity in trials of CTTH | | | | | |
|---|---|-----------------------|-----------------|-----------------|--|
| Reference | Groups | No of subjects | Measures | Duration | Findings |
| Kanji et al. (2011) (WEST) | Sauna | N = 37 | NPRS | 12 weeks | 44% reduction |
| Yurekli et al. (2008) | Sodium Valproate | N = 41 | VAS | 12 weeks | 40% reduction |
| Wang et al. (2007) | Electro-acupuncture | N = 36 | VAS | 12 weeks | 20% reduction |
| Bettucci et al. (2006) | Amitriptyline & Tizanidine | N = 18 | VAS | 12 weeks | 59% reduction |
| Soderberg et al. (2006) | Acupuncture Physical training Relaxation training | N = 56 | VAS | 4 weeks | Acupuncture 33% Physical training 33% Relaxation 42% |
| Kiran et al. (2005) | Alprazolam Alprazolam and meditation | N = 380 | VAS | 6 months | Alprazolam 18% Alprazolam and Meditation 83% |
| Padberg et al. (2004) | Botulinum | N = 40 | VAS | 12 weeks | Botulinum 16% |
| Bendtsen & Jensen (2004) | Mirtazapine 30mg | N = 20 | VAS | 22 weeks | Mirtazapine 13% |
| Boz et al. (2003) | Sertraline 50mg Amitriptyline 25mg | N = 84 | VAS | 16 weeks | Amitriptyline 43%, sertraline 20% |
| Schmitt et al. (2001) | Botulinum | N = 52 | VAS | 12 weeks | Botulinum A 23 % |
| Murros et al. (2000) | Tizanidine 6mg Tizanidine 12 mg | N = 160 | VAS | 8 weeks | Tizanidine 6mg 53% Tizanidine 12mg 48% |
| Walker et al. (1998) | Desipramine 75mg Fluoxetine 20mg | N = 25 | VAS | 12 weeks | Fluoxetine 36% Desipramine 36% |
| Fogelholm & Murros (1992) | Tizanidine up to 18mg day | N = 37 | VAS | 14 weeks | Tizanidine 50% |

The headache index is often calculated by duration times intensity and seems to be more sensitive than days with headache for preventative trials of CTTH (Bendtsen, et al., 2009). Table 8.2 outlines the studies using a 50% reduction of a headache index. The range of headache index varies from 18% for alprazolam (Kiran, et al., 2005) to 79% for autogenic relaxation (Kiran, et al., 2005). The sauna group had a 79 % reduction of headache index.

| Reference | Treatment including placebo | Numbers responding | Headache index | Percentage responding |
|-----------------------------------|---|---------------------------|-----------------------------|------------------------------|
| Kiran et al. (2005) | Alprazolam 0.25bd & Autogenic relaxation (Meditation) | 150/190 | Frequency x severity | 79% |
| Kanji et al. (2011) (WEST) | Sauna | 11/14 | Duration x intensity | 79% |
| Boz et al. (2003) | Amitriptyline 25mg | 31/43 | Duration x intensity | 72%, |
| Mitsikostas et al. (1997) | Amitriptyline 50mg | 17/28 | Days with headache/month | 61% |
| Holroyd et al. (2001) | Amitriptyline 75 mg & stress management | 34/53 | Mean VAS | 64% |
| Mitsikostas et al. (1997) | Buspirone 30 mg | 12/22 | Days with headache/month | 54% |
| Boz et al. (2003) | Sertraline 50mg | 18/44 | Duration x intensity | 44% |
| Shukla et al. (1996) | Alprazolam 0.25tds | 20/48 | Duration x intensity | 42% |
| Pfaffenrath et al. (1994) | Amitriptyline-oxide 90mg | 26/66 | Duration x intensity | 39% |
| Holroyd et al. (2001) | Amitriptyline 75mg | 20/53 | Duration x intensity | 38% |
| Singh and Misra (2002) | Sertraline 100mg | 9/25 | Duration x intensity | 36% |
| Holroyd et al. (2001) | Stress management | 17/49 | Mean VAS | 35% |
| Pfaffenrath et al. (1994) | Amitriptyline 75mg | 17/67 | Duration x intensity | 25% |
| Kiran et al. (2005) | Alprazolam 0.25bd | 35/190 | Frequency x severity | 18% |

Responder rate defined as participants reaching greater than or equal to 50% reduction in headache index or other measure chosen by the study.

8.5 Sleep disturbance, depression, and headache disability

Sleep disturbance and depression are comorbid with headache disorders (section 3.4) and were measured in the WEST headache trial. Both control and intervention groups showed an improvement in sleep disturbance. In the control group sleep disturbance reduced by 28% and in the intervention group sleep disturbance scores reduced by 18%.

Both control and intervention groups showed a reduction in depression as measured by the BDI. At the initial consultation in the control group, eight people had a BDI score over 13 (mild, moderate or severe depression) and in the final consultation two participants had a score over 13. At the initial consultation in the intervention group seven people had a BDI score over 13 and at the final consultation one participant had a BDI score over 13. Overall the control group had a 25% reduction in mean BDI while the intervention group had a 45% reduction in mean BDI. The reduction in BDI scores in both groups may be attributed to being involved in a clinical trial, the effects of the education and soft tissue massage or some other factor such as social desirability

effects. The education on the Adrenaline Model of Headache Causation and advice on stress management, may have given both groups some insight into their symptoms and a measure of control over their headaches that may have contributed to improving mood over the duration of the intervention period. Schulte-Mattler et al. (2004) measured BDI pre and post intervention and found no statistical significant differences similar to this study. The design of the WEST headache trial and other studies of CTTH measuring depression as a secondary measure however, are not designed to detect a statistically significant difference in BDI as this is not the primary prespecified measure.

Headache disability measures the limitations of symptoms on patients' activities. The changes in headache disability measured by the HDI favoured the intervention group with the control group achieving a 32% reduction in HDI and the intervention group achieving a 40% reduction in HDI. An overall reduction of 29 points is considered a statistically significant reduction in HDI score that can be attributed to treatment and one participant in the control group and three participants in the intervention group achieved a drop of 29 points. The reduction in HDI in both groups may be attributed to being involved in a clinical trial and/or the effects of the education and soft tissue massage. The education on the Adrenaline Model of Headache Causation and advice on stress management, may have given both groups some insight into their symptoms and a measure of control that may have contributed to improving disability associated with headache. Holroyd et al. (2001) measured HDI and found both amitriptyline and stress management reduced HDI by approximately 30% which is a similar reduction to both groups in the WEST headache trial.

8.6 Generalisability of results

The representativeness of the cohort studied and the effects of participation in a randomised trial will affect the generalisability of the trial results. In the WEST headache trial there was a bias in people wishing to try a non drug treatment for CTTH and participants were willing to attend the sauna for three times a week for eight weeks rather than take a tablet once or twice a day. Attending the sauna requires significantly more time and motivation than taking tablets and the population of patients with CTTH may not have the time to carry out sauna treatment excluding them from this treatment.

The changes in headache intensity may represent a regression to the mean as people may be motivated to join a clinical trial when the problem is at its worst, making spontaneous improvement more likely or perhaps reflect the natural history of a condition. The sauna group had headache for an average of 14.4 years and the control group experienced headache for an average of 18.9 years. Both groups experienced headache for several years and regression to the mean or natural history of improvement is unlikely to explain the effect.

8.7 Explanations of the overall response

The Adrenaline Model of Headache Causation (Figure 5.3) shows that heat (Yagiz On, et al., 1997), relaxation (Lucini, et al., 1997; Pike, et al., 1997), regular exercise (Mueller, 2007) ageing (Seals & Esler, 2000) and improved sleep (Burgess, et al., 1997; Hornyak, et al., 1991; Zhong, et al., 2005) all reduce sympathetic tone (section 4.5.2). There are several components of attending a sauna apart from the heat that can contribute to reducing headache intensity for CTTH sufferers. Sitting in a quiet room for 20 minutes three times a week, attending a health facility (gym or public swimming pool), and meeting other people and socialising may all contribute to the effects of attending the sauna. The question that arises is, does the effect of relaxation for 20 minutes, 3 times a week for 8 weeks cause the reduction in headache symptoms and not the heat of the sauna? This proposition is consistent with the Adrenaline Model of Headache Causation and trials of relaxation have shown to be effective in the management of CTTH (Soderberg, et al., 2006). To answer this question the control arm of future trials should include a group that performs relaxation for 20 minutes three times a week, similar to sitting in a cold sauna.

If heat is an effective modality for CTTH there are several possibilities regarding the action of heat on reducing pain including a reduction in sympathetic outflow due to heat reducing vasoconstrictor tone. This may provide negative feedback to reduce SNS activity in the brain and spinal cord as well as reducing sympathoadrenal catecholamine release, resulting in lower levels of central and peripheral sensitisation. Although speculation, the activity of repeated exercise (and perhaps repeated sauna) is likely to take six weeks or longer to reduce sympathetic tone and reactivity explaining the time taken for interventions to become effective. Other explanations by which sauna may

have an analgesic effect is through the release of β endorphin when activating the SNS and HPA pathways and the consumption of second messengers in the vasodilatation process.

8.8 Safety and cost analysis

The main adverse effects with sauna are a reduction in blood pressure that may occur in pregnancy, otherwise there are few risks of attending a sauna. In the WEST headache trial there were no adverse effects reported from those participants that attended the sauna.

The sauna is an intervention that is self directed and requires no input from treatment providers at each session. Once the patient is educated on the Adrenaline Model of Headache Causation (Figure 5.3) compliance is more likely, therefore education is the significant input from health professionals. A sauna is available at most gymnasiums and public swimming pools in New Zealand, and the cost of attending the sauna is relatively cheap (\$4.40 to \$7.00 per visit) with a total cost within the range of \$105.00 to \$168.00. Attending treatment practitioners that manage headache pain in the community including doctors (\$60.00 to \$200.00 per visit), Physiotherapists (\$40.00 to \$70.00 per visit), Osteopaths (\$70 to 100 per visit), Chiropractors (\$60.00 to \$90.00 per visit), Massage Therapists (\$40.00 to \$70.00 per visit). Depending on the therapist often multiple visits are required depending on the type of treatment trialled. For example attending a physiotherapist may take a trial of treatment for 8 sessions at a cost of around \$320.00 to \$560.00. The sauna can be used in conjunction with other treatments including preventative medication.

The initial education and assessment of patients takes approximately 30 to 40 minutes. In New Zealand physiotherapists, practice nurses and osteopaths may be best placed to provide education and subsequent treatment advice based on the Adrenaline Model of Headache Causation as it may incur less cost for patients to attend these practitioners than a medical professional such as a general practitioner for this length of time. Most general practice appointments within New Zealand are approximately 15 minutes which may not be long enough to explain the model and subsequent treatment advice. Many physiotherapists and osteopaths are also trained in teaching methods of relaxation to

patients as well as providing advice on exercise to help sleep disturbance. The only disadvantage of management of CTTH at physiotherapy or osteopathic practices compared to general practice, is that only general practitioners are able to prescribe analgesic or sedative medications to reduce pain levels and improve sleep. A combined approach with general practitioners and allied health professionals may be the most effective treatment in the community.

8.9 Limitations of the WEST headache trial

The primary aim of the trial was to test a self treatment that required minimal therapist input. Both groups were educated on the Adrenaline Model of Headache Causation, while the sauna bathing group was given advice that the sauna is helpful in reducing adrenaline and were given an access card for complimentary sauna attendance. This was designed to be a very pragmatic approach that can be followed by any medical doctor treating CTTH or an allied health professional such as a pharmacist, physiotherapist or osteopath. This trial was part of a PhD study so many of the tasks of the trial including randomisation, consultations and statistical analysis was performed by the PI with assistance from supervisors. The experience has given considerable insight to the PI into the design of RCTs (including faults) and the practical steps required to complete a clinical trial.

Limitations of this clinical trial were present and included the lack of quantification of sauna attendance, lack of an independent person carrying out the randomisation and statistical analysis and the lack of SNS measures. The RCT was not designed to test the Adrenaline Model of Headache Causation and this could be seen as a limitation of the trial. The RCT was designed to examine a non invasive self treatment requiring minimal medical supervision and in this aim it was successful.

The trial design did not answer the question does sauna attendance for 20 minutes three times a week for eight weeks reduce headache intensity, as there is no log of sauna attendance. The RCT only addresses the question - is education on the Adrenaline Model of Headache Causation together with advice on attending the sauna three times a week combined with a free access card for sauna bathing more effective than education on the Adrenaline Model of Headache Causation alone? Sauna attendance was enquired

about during the telephone follow-up at two weeks to address any difficulties in attending. On discussion with participants in the final assessment consultation, participants in the sauna group readily volunteered their experiences of attending the sauna, describing the sauna facilities at the different venues they attended, describing the experience of attending a sauna and some of the effects they experienced such as profound relaxation or feeling uncomfortably hot to begin with. It was apparent that most participants in the sauna group tried the intervention but how often and for how long is not known. Hence a shortcoming of the trial was the lack of diary or log that showed whether the participants in the sauna group attended the intervention or not. Patients may have stayed in the sauna for a shorter or longer duration or attended the sauna more or less than three times a week. For future studies using sauna bathing as a self directed treatment it would be important to include an attendance record for the sauna. The attendance could be recorded with the headache diary or an attendance register at the sauna facility.

There are a multitude of other factors that may have had a bearing on the results of this study including participants starting new exercise programmes, attending their doctors for new medications, buying over the counter medications, having a change in personal circumstances (e.g. bereavement, moving house, separation, employment status etc.). There was no specific advice (i.e. to avoid new medications, starting new exercise programmes etc.) given to participants either in the control or intervention group in this study. An improvement in this study may have been to monitor major lifestyle events (bereavement, separation etc.) that may have altered their headache activity. Another improvement would have been to advise participants not to embark on new treatments (e.g. medications) and/or activities (e.g. exercise) during the study to prevent confounding factors introducing bias into the study results.

The information provided to the participants (Appendix 5) did not disclose which group was the intervention group or control group. At the initial assessment several participants questioned whether the sauna was the control or intervention. From responses in the sauna group many considered this an unlikely form of intervention in a clinical trial run by a medical doctor. Although they were not blind to what intervention they were to receive, they were blind to whether it was the active treatment arm of the trial. If participants in the sauna group were advised they were in the active treatment

group their expectations may be heightened increasing the placebo effect. A double blind design is also possible in non pharmaceutical interventions. To blind the clinician if the intervention was the active or placebo treatment, two extra clinicians would be required. One clinician could have performed consultations for the control group while the other clinician performed consultations for the intervention group, hence a double blind trial can be achieved. Ideally a researcher blind to the group allocation (intervention or control) should perform the randomisation procedures and statistical analysis to prevent bias. Unfortunately both of these improvements in design were out of the scope of this trial due to lack of resources to fund extra clinicians.

The Rosenthal effect is likely to be minimal in this trial due to the only difference between the two groups being that one group was given instructions to attend the sauna within the initial consultation. In this RCT the initial assessment was approximately 45 minutes duration. During this time the PI spent approximately 40 minutes explaining the study protocol, informed consent, going through handouts on the model of headache causation and soft tissue massage for both groups. In the intervention groups approximately five minutes was spent advising participants to attend the sauna and handing over a card that allowed complimentary attendance at the sauna. There was no discussion of the sauna being the intervention and no discussion of what physiological effects the sauna may achieve. The only other clinical contact was a courtesy phone follow up at week 6 of the trial (2 weeks into the intervention) to discuss if there were any problems with the trial interventions.

The Hawthorne effect was minimised as the intervention and control group were treated similarly in most respects. Similarities included the number of consultations, time spent with participants and measures taken. If there was a treatment effect of being involved in the trial it is likely to be similar for both groups. The gathering of data is likely to have introduced minimal bias as all measures were self reported with no measurements taken by the PI.

What other factors may have caused bias in the results? After education on the Adrenaline Model of Headache Causation, participants in both the sauna group and the control group may have sought to reduce their stressors or started to exercise regularly in the knowledge that exercise may reduce headache. Participants in the sauna group

may have gone for a swim as the complimentary entry card to the WCC pools also gave entry to the swimming pool (the sauna is situated next to the pool but within the same entrance). Therefore participants may have performed more regular exercise than the control group. Social factors of talking to receptionists at the pool and other occupants of the swimming pool and/or sauna may have a beneficial effect on participants. The experience of taking time out of their normal routine to attend the sauna may have created a feeling that they were doing something positive about their health, creating a placebo response in itself.

To isolate the effect of heat alone in the prevention of CTTH, the control group could have performed 20 minutes relaxation three times a week as this would have been a better control for the sauna, which would have made only the heat of the sauna and the travel component to the sauna venue different between the two groups.

Five participants lost their completed final diary, resulting in the loss of headache intensity and duration data. Three participants were in the control group and two participants in the intervention group. The loss of data was similar in both groups and not due to protocol violation or side effects. This loss of data threatened to reduce the power of the study to detect a difference of 1.5 on the NPRS but is unlikely to introduce bias in the results as the reasons for loss of data did not vary between the two groups.

For future studies to improve retention of daily diaries an online diary handed in weekly or fortnightly may avoid loss of diaries. If participants have not emailed their diary or completed it online, then correspondence can be made with the participant to complete their daily headache diary. Because the final daily headache diary was eight weeks long in this trial, losing this diary results in the loss of eight weeks' data. Data analysis was performed with SPSS version 17 and in those participants with lost data the difference for their scores is not calculated. The data is included however when calculating the mean measures before and after the intervention, but excluded when calculating differences. Imputing data by carrying the last measure forward would have resulted in no changes to the differences in group scores as the last measure minus the initial measure would equal zero and not change group differences.

The WEST headache trial was performed to investigate whether heat in the form of sauna would improve headache intensity in CTTH sufferers. The WEST headache trial did not attempt to test the Adrenaline Model of Headache Causation directly. To test the model directly an RCT may have required measures of SNS activity when headache patients were in a headache free period and then follow them until they entered a period of frequent headache. An elevation of SNS tone would be expected to precede the occurrence of regular headache according to the Adrenaline Model of Headache Causation. The prospective nature of such a study required for headache patients to switch from being relatively headache free to experiencing 15 episodes of TTH per month may have been difficult. The time taken to change from TTH free to CTTH is an unknown and not within the time scope for this PhD study where the majority of time was devoted to exploring headache literature and formulating a model of headache causation that is consistent with the current knowledge on headache disorders. Furthermore the Principal Investigator (PI) is a clinician interested in alleviating pain so it was decided to investigate a novel, self directed and untested treatment that may help CTTH patients. If a lowering of SNS tone was observed after repeated sauna bathing, this may have been due to reduced pain and does not directly support the proposition that elevated SNS activity causes central and peripheral sensitisation and increased predisposition to headache episodes.

Measurements of SNS activity however would have been useful to perform in this clinical trial to check the changes to SNS activity if any, during the intervention period. Sauna bathing may reduce pain by a completely different mechanism than alteration of SNS tone and if SNS tone did not reduce over the intervention period, this may have pointed to another mechanism of action for heat. Possible measures of SNS tone that may be taken in future trials at regular intervals in both an intervention and control group may include heart rate variability that can be performed with the availability of commercial devices (van de Borne, et al., 1997).

In the current trial biochemical measures of SNS and HPA function such as adrenaline, noradrenaline, cAMP, and cortisol were not undertaken. Adrenaline requires continuous plasma monitoring to ensure timing of samples will detect rises in adrenaline in response to stressors (section 4.5.2 and section 4.5.4). At the start of this PhD and when planning the WEST headache trial, the details of the model including the effect of

adrenaline and other neurotransmitters such as histamine, noradrenaline, serotonin released in the stress response on second messenger pathways was not fully elucidated and measures of neurotransmitters and second messengers were not considered. Cortisol was measured and shown to be low in chronic headache sufferers (over approximately two years' duration) and normal in those with headaches of less than approximately two years (Kiran, et al., 2005). With our population of varying headache duration it is likely that any pattern in cortisol changes would have been missed due to the considerably smaller sample size (37) compared to the 380 CTTH participants studied by Kiran et al. (2005). No RCTs for the prevention of CTTH identified in section 3.7 measured SNS tone or took blood tests for measures of SNS or HPA activity. The WEST headache trial was a pragmatic trial of sauna for the improvement of CTTH rather than a test of the model.

A pilot study would have enhanced the RCT performed in this thesis as testing of the randomisation procedure was not undertaken prior to the RCT and no quantification of sauna attendance was obtained. Flaws in both of these procedures may have been detected prior to proceeding to the RCT by undertaking a pilot study. This may have lead to using an assistant to perform and administer the randomisation, rather than the PI performing this function, to reduce bias. Quantification of sauna attendance may also have been added to the study protocol.

8.10 What the Adrenaline Model of Headache Causation adds to the literature of CTTH.

The Adrenaline Model of Headache Causation provides a rationale for several headache phenomena including a mechanism by which therapies including medications (section 5.3.1) and relaxation therapies (section 5.3.2) may reduce symptoms of CTTH. The model explains a mechanism how experimental infusions of chemicals may induce headache (section 3.9) and is consistent with headache prevalence (section 3.2). The model also provides a possible explanation of the analgesic effect of heat, which is commonly used as direct treatment to alleviate pain.

The Adrenaline Model of Headache Causation is different from other models (section 3.8) in that it examines several headache phenomena and links these to a central model

of headache causation, rather than take one headache phenomena e.g. vasodilatation and muscle contraction or tension to create a model of headache causation. The limitations of trying to relate a single phenomenon to causation of headache, is that it will rarely be consistent with the several headache phenomena found in the literature and are unlikely to address the several questions posed in Chapter 1 namely;

- What is the pathogenesis of headache disorders from triggers such as emotional stress, alcohol, pain and poor sleep?
- What is the mechanism of action for medications (e.g. β blockers, amitriptyline) used for relieving headache?
- How do some medications (e.g. glyceryl trinitrate, sildenafil, adrenaline) cause headache as a side effect?
- Why do the elderly have a reduction of headache (Thomas, et al., 2005)?
- Why is the incidence of headache disorders less in tropical countries (Scher, et al., 1999)?

The Adrenaline Model of Headache Causation provides a useful framework to explain to patients how their current lifestyle, for example job stress, headache triggers and sleep disturbance impact on their symptoms, and provides a rationale for future changes to manage their headache disorder. It allows a more self directed approach to managing CTTH and preventing recurrence by providing patients an understanding of headache disorders.

The Adrenaline Model of Headache Causation allows treatment at a hierarchy of levels where factors are alterable for the treatment of CTTH. As seen in Figure 5.3, the changeable factors that reduce sympathetic tone include relaxation, repeated exercise, heat and sleep. Heat, relaxation therapies, regular exercise and improving sleep hygiene can be used together in the management of CTTH and can be added to medications useful for prevention of CTTH as discussed in Chapter 3. This combination therapeutic approach is utilised in my chronic pain practice as a result of forming this model. It is easy to explain to patients and gives them a reason to follow the course of treatment prescribed.

An attempt can also be made to alter factors that increase SNS and HPA release of adrenaline such as psychological stress (Pike, et al., 1997), sleep disturbance (Burgess, et al., 1997), fasting (Segel, et al., 2002), alcohol (van de Borne, et al., 1997), strenuous exercise (Kotchen, et al., 1971), pain (Danilov, et al., 1994) and cold (Vybiral, et al., 2000).

In patients with maladaptive coping skills leading to psychological stress and activation of the SNS and HPA axis, psychological management such as cognitive behavioural therapy as shown by Holroyd et al. (2001) may help people deal with conflict better and reduce future recurrences of CTTH. The model also highlights the importance of maintaining relaxing hobbies or seeking formal relaxation in the form of Tai chi, yoga or meditation among others.

Several medications examined in trials of CTTH (Table 3.7) including antidepressants (amitriptyline, desipramine, and mirtazapine), anxiolytics (alprazolam and buspirone), a muscle relaxant (tizanidine), an NMDA receptor antagonist (memantine) and an antipsychotic (sulpiride) may act via metabotropic receptors (section 4.3) reducing second messenger cascades and reducing the likelihood of action potential in the pathways of nociception. Medications for acute relief and prevention of migraine also act on several neurotransmitter pathways in the brain that are activated in the stress response (adrenergic, histaminergic, serotonergic and noradrenergic). Although the model has been named the Adrenaline Model of Headache Causation a variety of neurotransmitters released in the central nervous system including serotonin, adrenaline, noradrenaline and histamine, are all integral to the sensory amplification of pain rather than adrenaline alone. The Adrenaline Model of Headache Causation predicts that combinations of medications that block various receptors may be more effective than each taken separately. A combination of medications that blocked the histamine, serotonin, and adrenergic response was found to be more useful than placebo or either tablet alone (Rao, et al., 2000). If lower doses of individual medications in combination are effective, this may reduce side effects compared to taking each medication individually at a higher dose.

8.11 Promotion of the Adrenaline Model of Headache Causation

The promotion of the Adrenaline Model of Headache Causation and heat in the form of sauna as a management option for individuals with CTTH, if found successful, was the third aim of this PhD. The sauna represents a simple, cheap and self directed treatment that has the ability to reduce pain intensity and headache index in those that experience CTTH. Sauna had no side effects in this trial. In order to promote and educate health professionals it was important to identify who manages headache in the community. The following health professionals, pharmacists, general practitioners, pain specialists, clinical psychologists, nurses and physiotherapists were identified by personal communication as dealing with headache patients. Appropriate events including symposia, conferences, educational opportunities and small group sessions were targeted to present the Adrenaline Model of Headache Causation, the WEST headache trial and discussion of sauna as another treatment option for CTTH. Twenty five conference and group presentations (Appendix 14) have been performed in the past few years. To highlight the WEST headache trial and Adrenaline Model of Headache Causation to medical colleagues and headache researchers, in order to have further peer review and feedback, an article on the WEST headache trial and another article on the model are being written for submission to peer reviewed medical journals.

8.12 Questions and future research

The changeable factors that reduce SNS activity are improving sleep, regular exercise, heat and relaxation according to the Adrenaline Model of Headache Causation. Improving sleep has been indirectly studied by the prescription of medication that has sedating effects including amitriptyline (Bendtsen & Jensen, 2000; Bettucci, et al., 2006; Boz, et al., 2003; Gobel, et al., 1994; Holroyd, et al., 2001; Mitsikostas, et al., 1997; Pfaffenrath, et al., 1994), desipramine (Walker, et al., 1998), alprazolam, (Kiran, et al., 2005; Shukla, et al., 1996), buspirone (Mitsikostas, et al., 1997) and sulpiride (Langemark & Olesen, 1994). Relaxation therapies have been studied for CTTH including autogenic meditation (Kiran, et al., 2005), relaxation (Soderberg, et al., 2006) and stress management (Holroyd, et al., 2001). The range of reduction in headache index for these studies is between 18% for alprazolam (Kiran, et al., 2005) to 93% for meditation (Kiran, et al., 2005) (Table 8.2). The WEST headache trial is the first study

to look at the effects of heat in the form of sauna for CTTH patients with a 79% reduction of headache index.

The above therapies may act by reducing sympathetic tone to reduce central and peripheral sensitisation according to the Adrenaline Model of Headache Causation (Figure 5.3). However these therapies may be acting through other mechanisms rather than an effect on sympathetic tone.

There are several questions that arise including:

1. Will a patient respond better to a combined approach where modalities of reducing sympathetic tone are applied simultaneously with or without preventative medication? Holroyd et al. (2001) has answered this question partially with the combination of amitriptyline and stress management providing a 50% reduction in pain intensity at one month in 64%, compared to 38% for amitriptyline, 35% for stress management and 29% for placebo. At six months all three groups had an overall 33% reduction in headache intensity but the improvements in the amitriptyline and stress management group were more rapid. This is clinically important as patients with chronic headache disorders may stop therapy if there is no response and the quicker the response the more likely compliance with treatment will be adhered to. If sleep, heat and relaxation therapies are used in combination with preventative medication, improvements may be quicker. More importantly relapse is less likely if people are aware of behaviour and habits alleviating or contributing to their headache pain. Studies using a combined approach may shed light on whether the combination will provide a more efficacious and quicker response in patients.
2. What do we do with patients who do not respond to improvements in central and peripheral sensitisation? If symptoms fail to settle then investigations to find the source of pathology may be appropriate. Underlying pathology causing nociception and referred pain from the neck will explain headache in a proportion of people experiencing headache. This pathology needs to be identified and treated for successful treatment. Four participants in the WEST headache trial who did not respond to sauna, were further investigated with three

cases of cervicogenic headache being diagnosed on radiology and one case of sinusitis. All four participants experienced improvements once the source of their symptoms were found and managed, despite experiencing headache pain for up to two decades.

Radiology including x-rays often shows narrowed disc space and loss of lordosis and MRI scans often show prolapsed discs with nerve root impingement. Insights into the neck being a cause of headache can be gained from studies treating the neck for TTH. Van Ettehoven and Lucas (2006) showed specifically treating the neck by adding self directed craniocervical training with physiotherapy in a mixed group with ETTH and CTTH resulted in 85% of participants achieving greater than 50% relief, a striking improvement over physiotherapy alone (35% achieved a 50% reduction in headache frequency). Future studies combining a simple self management strategy for the cervical spine with heat, sleep, relaxation and preventative medications may improve the yield of participants improving from headache disorders. In particular those with central and peripheral sensitisation as well as referred pain from the neck may respond.

Migraine is likely to represent the worst end of the headache spectrum whereby a genetic predisposition to central nervous system neuronal excitability is present. Sympathetic tone may however set the threshold of action potentials in the pathways of nociception and govern the frequency of migraine episodes. If this is the case reducing sympathetic tone using heat in the form of sauna may have potential as a treatment for migraine.

The comorbid conditions of anxiety, depression and insomnia may be related to headache disorders due to an elevation of HPA and SNS activity. The WEST headache trial showed a statistically significant improvement in sleep. Seven participants in the sauna group had a BDI over 13 (depression) and six reduced to under 13 after eight weeks attending the sauna. Future studies investigating the effect of heat in the form of sauna for anxiety, depression and insomnia may provide new treatment options for these disorders.

8.13 Summary

The aims of this PhD on headache causation were (section 1.1);

1. To examine current headache knowledge and construct a plausible model to explain headache causation that is consistent with the literature on headache disorders.
2. To identify a noninvasive treatment for headaches using the headache causation model developed in this PhD and to investigate its effectiveness by performing a randomised control trial (RCT) using people with CTTH.
3. To promote the headache causation model and noninvasive treatment, if successful, to those involved in the treatment of CTTH including general practitioners and other primary care providers.

The Adrenaline Model of Headache Causation provides a useful model to explain to patients the origin of TTH and allows self management of symptoms by altering factors that increase or reduce SNS activity together with current therapeutic measures available. The Adrenaline Model of Headache Causation is consistent with headache phenomena found in the literature. The WEST headache trial examined the efficacy of heat in the form of sauna in patients with CTTH. Sauna was as effective as the gold standard medication treatment used for managing CTTH, and produced a 44% reduction in headache intensity within six weeks of treatment. The aims of this PhD have been fulfilled.

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Appendices

Appendix 1: Dominion Post September 26, 2007

NEWS

ACC battler chances on cure

Man who lost payments wins appeal, loses pain

RUTH HILL

IN A perverse way, Jack Sagato Brown could thank ACC for scrapping his entitlement after 16 years.

If he had not had to fight to get it back, he would never have met Geri Kani, who, in the process of helping the Petrie man win his 16-month court battle, also cured him.

The Accident Compensation Corporation cancelled Mr Brown's payments last year, judging his disability was due to aging, not a 1990 injury when he slipped on a building site.

At the time of the injury the doctor told the then 46-year-old that his back had "had it". "My supervisor dropped me home. I couldn't walk or stand or do anything."

Mr Brown's daughter moved in to care for him, and for the next 16 years he relied on ACC.

In February last year, however,

he was told his entitlement was being cancelled under a clinical review, which blamed "major pre-existent degenerative changes", identified on scans taken at the time of the accident and exacerbated by aging.

"My family said, 'You can't win against ACC'. But I knew I was right."

The GP assessing Mr Brown for an invalid's benefit referred him to Dr Kani, who injected steroids and pain relief directly into his back.

Mr Brown woke up the next day after his first full night's sleep in 16 years and inside himself a cup of tea. His daughter asked what he was doing. "I said, 'I feel like a 18-year-old!' And then I went for a walk."

After three sessions with Dr Kani, Mr Brown was able to volunteer at the St Vincent de Paul store, working up to six days a week.

him the good news, Mr Brown was in hospital, after stomach cancer was diagnosed. He has spent six weeks in Hutt Hospital recovering from surgery and complications but the fire is undimmed when he recounts his battle with ACC.

"I knew I was right," Mr Brown's lawyer, Ben Thompson, said. "Typically these are isolated cases. Usually these are men who have worked their bodies hard then got injured and end up on the scrapheap."

Many people did not have the energy or the money to fight unfair decisions. Hundreds could be missing out on entitlements. His firm alone had 70 active ACC back cases.

Trish Fong of John Miller Law, which specialises in ACC cases, said the firm had 1200 active cases of people whose entitlement was threatened by "degeneration".

"There are some doctors who are afraid in the camp that it's all to do with degeneration and ACC is going to seek opinions from them."

People were now entitled to choose their assessor, however, from a list provided by ACC.



Proven right: Jack Sagato Brown was wrongly told by ACC that his back ailment was "major pre-existent degenerative changes". Picture: CRAIG SIMCOX

Dr Kani concluded the pain was the result of a soft tissue injury, not bone degeneration. Mr Brown appealed against ACC's decision in June last year but lost.

Wellington District Court has overturned that decision, reinstating Mr Brown's ACC payment and awarding him \$3300 in costs.

But when his lawyer rang to tell

Appendix 2: Dominion Post February 4, 2008

HEALTH



Recovery: Anne-Marie Van Der Linden has been pain free for 2½ years after having saline injections. Picture: ROSS GIBLIN

The journey back to wellbeing

A CAR crash just before her 30th birthday started Anne-Marie Van Der Linden on a 20-year journey of chronic, debilitating back pain — a journey that looked like it would never end.

Pain was the constant backdrop to her day, but intermittent flare-ups would leave her completely immobile and reliant on other people to wash, dress and feed her. "That was pretty humiliating," says the former social worker.

She was fortunate to have "an incredibly supportive partner" at the time, but the continuing strain of living with chronic pain was certainly a factor in their break-up.

Despite her restrictions, she went back to university and became a lawyer. However, about three years ago, the pain was so bad she was running out of options.

Then one day her GP was talking with his old medical school friend Gireesh Kanji,

who told him about the excellent results he was having treating chronic pain with saline injections. Dr Kanji diagnosed Marie with fibromyalgia, but said he could cure her. "I was sceptical," she admits. "But I had nothing to lose."

Over a period of months, he injected saline into her back at progressively higher points. "He chased it up my back, till one day it was completely gone."

Since then, she has had one relapse in a period of high stress, which is often a trigger for fibromyalgia. One emergency visit to Dr Kanji and her back was returned to normal.

"In the past 2½ years I have not had any painkillers, and that is miraculous."

WITHOUT diet or exercise, Kirsten Eriksen has slimmed down from a size 24 to an 18 in less than a year. But her healthy new figure is the least of her transformation. After more than 15 years of chronic

pain and fatigue, she is off all medication. "My life is so different since I was treated by Dr Kanji — my husband says it's a relief not to be living with a grumpy person who is in pain all the time."

Dr Kanji traced Kirsten's problems back to a gymnastics injury when she was 13, in which she ripped the cartilage in her knee. As the knee healed, she began experiencing aches throughout her body, insomnia and migraines.

She was diagnosed with fibromyalgia, but the drugs she was prescribed led to other problems. Her weight ballooned as her over-active pain receptors and heavy-duty drugs made her body think it was hungry, while making her too tired to exercise.

Since being treated last February, the 29-year-old is a new woman. "My GP told me I was going to be on those drugs for the rest of my life ... but now I feel my life is really beginning."

Appendix 3: Citylife newspaper October 21, 2008

South & East

Citylife

WIN: a **DOUBLE PASS** to Homegrown



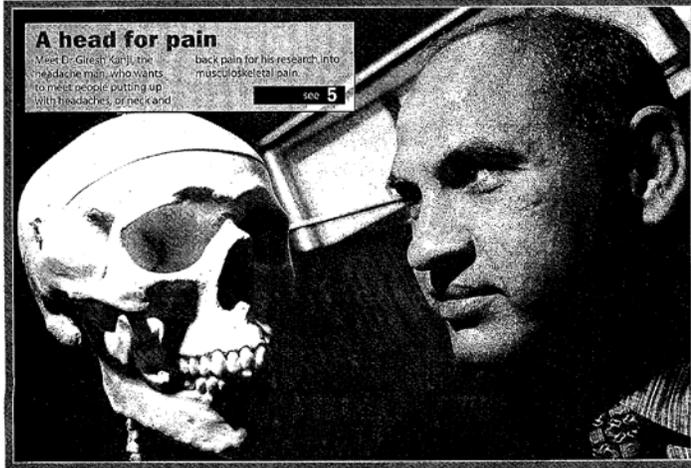
vodafone
Homegrown

October 21 - 27, 2008 Building community and business networks

A head for pain

Meet Dr. Giresh Kanji, the headache man who wants to meet people putting up with headaches, or neck and back pain for his research into musculoskeletal pain.

see 5



Life's a beach as Babylon opens

see 5



Look who's

October 21 - 27, 2008 | Citylife SOUTH & EAST NEWS | 5

In pursuit of your pain

Everyday hundreds of people suffer from aches and pains without ever really knowing their cause. Dr Giresh Kanji wants volunteers to help research this suffering. Rachele Stewart reports.

Rachele Stewart
rachel@citylife.co.nz
09 486 551-5071

Dr Giresh Kanji is on a mission to find out just what causes long-term aches and pains in people.

"Many patients I see with long term pain have no diagnosis of their pain," says Dr Kanji, who is seeking volunteers for a trial.

"I have been doing musculoskeletal pain medicine since 1999 but full time musculoskeletal medicine for the past five years. I have been interested in people suffering from chronic pain conditions and the drastic effects it has on people's health."

Dr Kanji says many pain problems that can't be diagnosed can be the result of referred pain, which occurs when the brain confuses hip pain with back pain or shoulder pain with neck pain, or neck pain

with head pain.

"There have been over a dozen people who have presented with back pain from four to 25 years who in fact have internal hip injury. Most of these people have had significant falls or motor vehicle trauma.

"The impact is often taken by the hip region in the first instance as this is the region that hits the ground initially in most falls," he says.

"The hip and the back have a similar nerve supply that enters the spinal cord and then the brain." If no diagnosis is made to determine where pain is coming from it can lead to years of suffering and taking unnecessary medication.

"One lady fell off a tree 25 years ago and has been treated for back pain since this time. Investigations have confirmed her hip is the likely source of her pain.

"She never thought her hip was the source of pain and all her treat-

ment had been directed to the back." He is starting a clinical trial on chronic tension type headaches for which he is now recruiting participants.

"Many patients I see with headaches have no diagnosis of their headache," he says.

"In this respect the method I use is to exclude the different causes of headache. This usually results in finding the cause of headache."

Dr Kanji says the three most common types of headaches he sees are tension headaches and neck injuries causing headache.

Other common causes of headaches are local conditions that cause irritation around the head region such as sinuses, ears and eyes.

Dr Kanji aims to test simple methods to treat tension type headaches.

Anyone interested in taking part in the trial can email him on drkanji@strc.co.nz.



COMMUNITY LIFE

In this weekly column, local service organisations offer advice and insights on current issues.

Christmas can be a stressful time, especially for your wallet. Even more painful can be the months after Christmas, when the credit card bill arrives and the kids need books for school and maybe new uniforms. But it doesn't have to be that way. Christmas shouldn't be just about spending lots of money you don't have and having to face the consequences later.

In fact you can have a great Christmas spending very little, a sort of "Scrooge Christmas" if you like.

That doesn't mean going around with a long face muttering "bah, humbug" and kicking poor people into the gutter. A "Scrooge Christmas" can be fun.

Set yourself a strict budget for Christmas spending and stick to it. Make Christmas presents rather than buying them – a present that involves your time and love is worth far more than one that sends you broke.

Set children the task of using their imagination.

Appendix 4: Citylife newspaper December 9, 2009

Citylife Cook Strait News | Wednesday, December 9 2009

Getting your head around pain

Dr Giresh Kanji loves explaining to people how pain works, but he is at his most passionate when he talks about the people who have left his care smiling after years of putting up with pain.

His aim is to discharge people either pain free or with a diagnosis so they know what is causing their pain.

Dr Kanji's research include:

- Investigating the sympathetic nervous system:

"The system is involved in primitive reflexes such as the fight flight response required when humans were hunter gatherers. Unfortunately pain releases the same stress chemicals, adrenaline and cortisol but people with chronic pain often are restricted in physical activity and cannot consume stress chemicals by exercising, creating more risk for stress symptoms. The development of suffering from chronic pain is likely to be due to the release of stress chemicals leading to insomnia, anxiety, depression and irritability."

- Using interventions that consume stress chemicals:

"From my reading and clinical experience exercise and heat are the two interventions that burn stress chemicals. We have used saunas to treat pain. It helps unwind the amplified brain. This may reduce the need for."

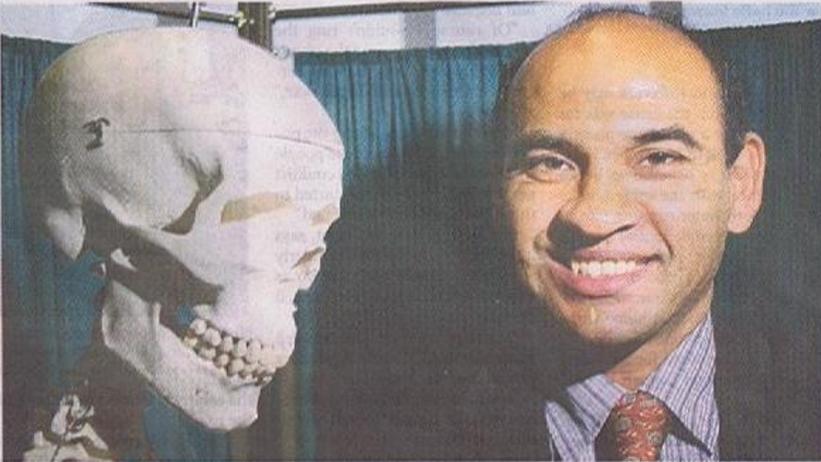
- Chronic headache disorders:

Three to four per cent of people suffer from daily headaches. "A clinical trial on chronic tension type headaches has just been completed and is currently being analysed. The preliminary results show statistical significance against a control group for reduced pain intensity."

- Finding the source of pain:

"If the source of pain can be found then treatment can be directed. Referred pain is felt at one place but arising from another remote site. Chronic pain is frequently experienced at a site different from where pain is experienced. In one research paper I did, studying 40 people who had back pain for two to 20 years, eight were

This week we introduce for readers a new column on pain, written by Dr Giresh Kanji, a specialist in musculoskeletal pain. *Bernie Whelan* introduces Dr Kanji.



solved by hip surgery, arthroscopy of the hip, and 30 improved by giving them exercises for the hip."

- The link between pain and stress:

"The vicious cycle of pain and stress is something long-term pain sufferers live with. It's like sleeping with a tiger 24-7." The stress link is an area Dr Kanji intends to continue opening up because the evidence continues to mount. "A model has been created to explain chronic pain symptoms is like putting a jigsaw together, helping patients understand the diverse problems they encounter."

- Dr Kanji's column will appear weekly in Cook Strait News
- Ph (04) 910 2178

Feeling relief

Phillip Tring

Phillip brought nine years of constant daily pain from Melbourne to Dr Kanji in October and returned to Australia without 95 per cent of it. It had started with a disc prolapsed and spread over the years.

Phillip was treated with injections of saline and anaesthetic to reduce the referred muscle pain. He was also started on core strengthening exercises and stretches/strengthening for his hip regions. After three weeks Phillip returned home without the constant daily pain.

Phillip was contacted six weeks after returning to Victoria and was pain free over 95% of the time with mild pain in the right groin after exercise that settles with stretching within a few minutes. He is attending the gym several times a week. He is sleeping well and taking no painkillers or other

tablets at present. Phillip is looking at returning to the work force after Christmas.

Ann-Marie Van der Linden

Ann-Marie suffered from widespread pain since 1998 after a motor vehicle accident. Poor sleep, poor mood, and major problems performing normal daily activities had plagued her life for the past seven years on a daily basis. Ann-Marie presented in May 2005 when Dr Kanji started experimental treatment with saline injections.

After four months Ann-Marie was discharged pain free and able to participate in full activities and remains pain free at the current time.

Appendix 5: Information sheet for the WEST headache trial



Institute of Food, Nutrition and Human Health

INFORMATION SHEET

Wellington Education and Self Treatment (WEST) Headache Trial

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Introduction

You are invited to take part in a headache treatment trial to test a hypothesis on headache causation and self treatment. The WEST headache trial is a clinical trial to evaluate an education and self treatment approach to headache disorders. The study is for a PhD carried out by Dr Giresh Kanji. You have two weeks to decide if you would like to participate in the study and have the right to refuse to participate in this study at any time. The above principal investigator and supervisors can

be contacted with any problems or questions you would like answered before deciding to participate.

About the Study

What are the aims of the study?

The aims of the study are to test two treatments for people suffering from headaches using education and self treatment.

How are participants selected for this study, and who will select them?

Participants will be recruited from the general population by the Principal Investigator (Dr Giresh Kanji) and the PhD Supervisors (Dr Rachel Page and Dr Raja Peter). The study will require a minimum of 60 people to ensure the research produces valid results. The study will be held at Southern Cross Specialist Centre, 90 Hanson St, Newtown, Wellington and will take place over 13 weeks.

What will happen during the study?

After recruitment participants will be placed into two groups of 20 using chance (randomisation). Both groups will be given advice on headache causation and both groups will be given self treatment methods aimed at the cause of headaches. Self treatments include Soft Tissue Massage (an easy technique that can be self administered). One group will also be asked to attend a sauna three to four times per week.

The treatments are noninvasive and there are no injections or medications in the treatments. Handouts will be given to participants providing information on causation of headaches and the treatment that they will be trying in the study. Participants have the right to stop the trial at any time. Participants are not required to change their current treatment including medications for headaches during the trial.

Both groups will fill in a headache pain diary (twice per day), for one month prior to the consultation. Both groups will complete a questionnaire, prior to the consultation, that will take approximately 15 minutes. The consultations will take place at Southern Cross Specialist Centre,

Newtown Wellington. The initial consultation is expected to take 45 minutes and follow up consultations are expected to take 30 minutes.

Follow up consultation of both groups will occur at 13 weeks. Prior to the consultation the headache pain diary will be collected by a nurse and the questionnaire will be completed. There is no blood or other samples taken during the consultations.

Timeline of the study

After recruitment (using exclusion and exclusion criteria)

| Week 1- 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 to 12 | Week 13 |
|------------|---|--------|--------------------|--------|-----------------|---|
| Pain diary | Initial consultation/ Questionnaire/ Hand in pain diary | | Phone follow up | | Pain diary | Follow up consultation/ Questionnaire/ Hand in pain diary |

Participants Rights

You are under no obligation to accept this invitation to participate in this research. If you decide to participate you have the right to:

Decline the answer to any particular question;

Withdraw from the study at anytime;

Ask any questions about the study anytime during participation;

Provide information on the understanding that your name will not be used unless you give permission to the researcher;

Be given access to a summary of the project findings when it is completed.

Support

If there are any adverse reactions from the self treatment then you are able to contact the principal investigator by phone or email as they occur. If you have any particular questions please do not hesitate to contact the principal investigator or the supervisors.

Benefits, Risk and Safety

What are the benefits of the study?

The study aims to provide simple treatments for people suffering from recurrent headaches. These simple treatments can then be used in General Practice by other doctors if found successful. These treatments involve no pain tablets so side effects associated with medication are eliminated.

Treatment is also self directed and this will empower patients to treat themselves.

What are the risks and/or inconveniences of the study?

There are no medications being looked at in this study. There will be the inconvenience of traveling to Southern Cross Specialist centre and time required off work which unfortunately cannot be compensated by the study. The self treatment will require 5 to 20 minutes four times a week.

The selection criteria for participation in this study include:

Age 21 to 70 years

Two years duration of headaches

The criteria for Chronic Tension-type Headache as defined by the International Headache Society that includes headaches being present for at least 15 days of the month.

The exclusion criteria for participation in this study are as follows:

Known cause of symptoms such as acute sinusitis, eyesight or ear problems,

Current diagnosis of cancer

Acute infections including viral illness

Previous spinal surgery

Pregnancy or intended pregnancy. Blood pressure is usually lowered during pregnancy and there may be a small risk of fainting while attending the sauna. If participants become pregnant during the trial then their doctors will be contacted and consultation will occur with the participant and their doctor as to the individual risk of continuing in the trial. The decision to stop them completing the trial will be made by the participant, their doctor (and/or maternity caregiver) and the researchers.

Previous neurosurgery

Costs for the study

There is no monetary compensation offered for participation in the study. Participants will have to pay for their travel and other costs incurred due to participation in the study. The education about headache causation and self treatment requires no injections or procedures that are likely to put participants at risk or cause discomfort.

This study is looking at two treatments aimed at the cause of headaches. The advantages of the treatments being studied compared to normal medical treatment is that people can treat themselves and reduce prescription medicine intake if the treatment is found successful. If there are any accidental occurrences during the trial such as falling over then patients should be covered under the Accident Compensation Corporation (ACC) Act as specified in New Zealand.

Participation

Your participation is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part you will receive the usual treatment/care. If you do agree to take part you are free to withdraw from the study at any time, without having to give a reason and this will in no way affect your future health care/continuing health care. Participation in this study will be stopped should any harmful effects appear or if the medical doctor (Principal Investigator of the study) feels it is not in the participant's best interests to continue.

General

Your General Practitioner will be advised of your participation in the study if you wish. Further information about the study can be obtained by contacting the Principal Investigator or the Supervisors. An interpreter can be provided if required. You may have a friend, family or whanau support to help you understand the risks and/or benefits of this study and any other explanation you may require. You do not have to answer all the questions on the Questionnaire and you may choose at any time whether you wish to answer the questions or not.

You will be issued a card to confirm your participation in a clinical trial. This card should be presented at the time of any medical treatment received during your participation in the trial. If you have any questions or concerns about your rights as a participant in this research study you can contact an independent health and disability advocate. This is a free service provided under The Health and Disability Commissioner Act.

Telephone: (NZ wide) 0800 555 050

Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)

Email (NZ wide): advocacy@hdc.org.nz

Confidentiality

No material which could personally identify you will be used in any reports on this study. Participants will remain anonymous and the only people to sight the data will be Dr Giresh Kanji, Dr Rachel Page and Dr Raja Peter. The data will be kept safely under lock and key with access only to the above people. Your name will not appear on the PhD thesis or any research papers which are published. The data will appear grouped and include no markings that can be traced back to you. The data will be kept for ten years and then destroyed in accordance with current research procedures.

Results

Results of this trial will be sent to all participants in the mail and will be forwarded for publication to the appropriate journals. There may be a delay of six months before the results are sent out to the participants.

Statement of Approval

This study has received ethical approval from the Upper South A Regional Ethics Committee.

Please feel free to contact the researcher if you have any questions about this study.

Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

WEEK ONE DATE:**Monday**

Circle your worst headache pain intensity today

| | | | | | | | | | | |
|------|---|------|----------|---|--------|---|----------|---|---|----|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| None | | Mild | Moderate | | Severe | | The Most | | | |

Imaginable

Circle the number of hours you have experienced a headache today

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16**Tuesday**

Circle your worst headache pain intensity today

| | | | | | | | | | | |
|------|---|------|----------|---|--------|---|----------|---|---|----|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| None | | Mild | Moderate | | Severe | | The Most | | | |

Imaginable

Circle the number of hours you have experienced a headache today.

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16**Wednesday**

Circle your worst headache pain intensity today

| | | | | | | | | | | |
|------|---|------|----------|---|--------|---|----------|------------|---|----|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| None | | Mild | Moderate | | Severe | | The Most | Imaginable | | |

Circle the number of hours you have experienced a headache today.

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

Appendix 7: Initial and final questionnaire



Institute of Food, Nutrition and Human Health

Wellington Education and Self Treatment (WEST)

Headache Trial

Initial Questionnaire

Date:

Surname:

First Name:

Middle Name:

Home Phone:

Cell Phone:

Work phone:

Fax No.:

Email:

Height:

Weight:

How many years have you suffered from headaches?

List your current medications

List your past medical history

List any surgical procedures that have been performed.

Please rate the below factors by circling a number that represents your level using the scale below. You may indicate half if you wish by circling the line between the numbers.

A. Sleep Disturbance

How much has your pain interfered with your sleep in the past week?

| | | | | | | | | | | |
|------|------|---|----------|---|--------|---|----------|---|---|----|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| None | Mild | | Moderate | | Severe | | The Most | | | |

Imaginable

Circle the number that most represents the way you feel.

- | | | |
|----|--|---|
| 1. | I do not feel sad. | 0 |
| | I feel sad | 1 |
| | I am sad all the time and I can't snap out of it. | 2 |
| | I am so sad and unhappy that I can't stand it. | 3 |
| 2. | I am not particularly discouraged about the future. | 0 |
| | I feel discouraged about the future. | 1 |
| | I feel I have nothing to look forward to. | 2 |
| | I feel the future is hopeless and that things cannot improve. | 3 |
| 3. | I do not feel like a failure. | 0 |
| | I feel I have failed more than the average person. | 1 |
| | As I look back on my life, all I can see is a lot of failures. | 2 |
| | I feel I am a complete failure as a person. | 3 |
| 4. | I get as much satisfaction out of things as I used to. | 0 |
| | I don't enjoy things the way I used to. | 1 |
| | I don't get real satisfaction out of anything anymore. | 2 |
| | I am dissatisfied or bored with everything. | 3 |
| 5. | I don't feel particularly guilty | 0 |
| | I feel guilty a good part of the time. | 1 |
| | I feel quite guilty most of the time. | 2 |
| | I feel guilty all of the time. | 3 |
| 6. | I don't feel I am being punished. | 0 |
| | I feel I may be punished. | 1 |
| | I expect to be punished. | 2 |
| | I feel I am being punished. | 3 |
| 7. | I don't feel disappointed in myself. | 0 |
| | I am disappointed in myself. | 1 |
| | I am disgusted with myself. | 2 |
| | I hate myself. | 3 |

- | | | |
|-----|---|---|
| 8. | I don't feel I am any worse than anybody else. | 0 |
| | I am critical of myself for my weaknesses or mistakes. | 1 |
| | I blame myself all the time for my faults. | 2 |
| | I blame myself for everything bad that happens. | 3 |
| 9. | I don't have any thoughts of killing myself. | 0 |
| | I have thoughts of killing myself, but I would not carry them out. | 1 |
| | I would like to kill myself. | 2 |
| | I would kill myself if I had the chance. | 3 |
| 10. | I don't cry any more than usual. | 0 |
| | I cry more now than I used to. | 1 |
| | I cry all the time now. | 2 |
| | I used to be able to cry, but now I can't cry even though I want to. | 3 |
| 11. | I am no more irritated by things than I ever was. | 0 |
| | I am slightly more irritated now than usual. | 1 |
| | I am quite annoyed or irritated a good deal of the time. | 2 |
| | I feel irritated all the time. | 3 |
| 12. | I have not lost interest in other people. | 0 |
| | I am less interested in other people than I used to be. | 1 |
| | I have lost most of my interest in other people. | 2 |
| | I have lost all of my interest in other people. | 3 |
| 13. | I make decisions about as well as I ever could. | 0 |
| | I put off making decisions more than I used to. | 1 |
| | I have greater difficulty in making decisions more than I used to. | 2 |
| | I can't make decisions at all anymore. | 3 |
| 14. | I don't feel that I look any worse than I used to. | 0 |
| | I am worried that I am looking old or unattractive. | 1 |
| | I feel that there are permanent changes in my appearance that make me look unattractive. | 2 |
| | I believe that I look ugly. | 3 |
| 15. | I can work about as well as before. | 0 |
| | It takes an extra effort to get started at doing something. | 1 |
| | I have to push myself very hard to do anything. | 2 |
| | I can't do any work at all. | 3 |

- | | | |
|-----|--|---|
| 16. | I can sleep as well as usual. | 0 |
| | I don't sleep as well as I used to. | 1 |
| | I wake up 1-2 hours earlier than usual and find it hard to get back to sleep. | 2 |
| | I wake up several hours earlier than I used to and cannot get back to sleep. | 3 |
| 17. | I don't get more tired than usual. | 0 |
| | I get tired more easily than I used to. | 1 |
| | I get tired from doing almost anything. | 2 |
| | I am too tired to do anything. | 3 |
| 18. | My appetite is no worse than usual. | 0 |
| | My appetite is not as good as it used to be. | 1 |
| | My appetite is much worse now. | 2 |
| | I have no appetite at all anymore. | 3 |
| 19. | I haven't lost much weight, if any, lately. | 0 |
| | I have lost more than five pounds. | 1 |
| | I have lost more than ten pounds. | 2 |
| | I have lost more than fifteen pounds. | 3 |
| 20. | I am no more worried about my health than usual. | 0 |
| | I am worried about physical problems such as aches and pains, or upset stomach, or constipation. | 1 |
| | I am very worried about physical problems and it's hard to think of much else. | 2 |
| | I am so worried about my physical problems that I cannot think about anything else. | 3 |
| 21. | I have not noticed any recent change in my interest in sex. | 0 |
| | I am less interested in sex than I used to be. | 1 |
| | I have almost no interest in sex. | 2 |
| | I have lost interest in sex completely. | 3 |

HEADACHE DISABILITY INDEX

Please read carefully: The purpose of the scale is to identify difficulties that you may be experiencing because of your headache.

Please tick "YES", "SOMETIMES", or "NO" to each item. Answer each question as it pertains to your headache only.

| | | | |
|--|------------|------------------|-----------|
| E1. Because of my headaches I feel handicapped. | YES | SOMETIMES | NO |
| F2. Because of my headaches I feel restricted in performing my routine daily activities. | YES | SOMETIMES | NO |
| E3. No one understands the effect my headaches have on my life. | YES | SOMETIMES | NO |
| F4. I restrict my recreational activities (eg, sports, hobbies) because of my headaches. | YES | SOMETIMES | NO |
| E5. My headaches make me angry. | YES | SOMETIMES | NO |
| E6. Sometimes I feel that I am going to lose control because of my headaches. | YES | SOMETIMES | NO |
| F7. Because of my headaches I am less likely to socialize. | YES | SOMETIMES | NO |
| E8. My spouse (significant other), or family and friends have no idea what I am going through because of my headaches. | YES | SOMETIMES | NO |
| E9. My headaches are so bad that I feel that I am going to go insane. | YES | SOMETIMES | NO |
| E10. My outlook on the world is affected by my headaches. | YES | SOMETIMES | NO |
| E11. I am afraid to go outside when I feel that a headaches is starting. | YES | SOMETIMES | NO |
| E12. I feel desperate because of my headaches. | YES | SOMETIMES | NO |
| F13. I am concerned that I am paying penalties at work or at home because of my headaches. | YES | SOMETIMES | NO |
| E14. My headaches place stress on my relationships with family or friends. | YES | SOMETIMES | NO |
| F15. I avoid being around people when I have a headache. | YES | SOMETIMES | NO |
| F16. I believe my headaches are making it difficult for me to achieve my goals in life. | YES | SOMETIMES | NO |
| F17. I am unable to think clearly because of my headaches. | YES | SOMETIMES | NO |

| | | | |
|--|------------|------------------|-----------|
| F18. I get tense (eg, muscle tension) because of my headaches. | YES | SOMETIMES | NO |
| F19. I do not enjoy social gatherings because of my headaches. | YES | SOMETIMES | NO |
| E20. I feel irritable because of my headaches. | YES | SOMETIMES | NO |
| F21. I avoid traveling because of my headaches. | YES | SOMETIMES | NO |
| E22. My headaches make me feel confused. | YES | SOMETIMES | NO |
| E23. My headaches make me feel frustrated. | YES | SOMETIMES | NO |
| F24. I find it difficult to read because of my headaches. | YES | SOMETIMES | NO |
| F25. I find it difficult to focus my attention away from my headaches and on other things. | YES | SOMETIMES | NO |

Appendix 8: Consent form



Institute of Food, Nutrition and Human Health

Wellington Education and Self Treatment (WEST)

Headache Trial

CONSENT FORM

This consent form will be held for a period of ten (10) years

Full Name - printed

.....

REQUEST FOR INTERPRETER

| | | | |
|-------------|--|-----|-------|
| English | I wish to have an interpreter. | Yes | No |
| Maori | E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero. | Ae | Kao |
| Cook Island | Ka inangaro au i tetahi tangata uri reo. | Ae | Kare |
| Fijian | Au gadreva me dua e vakadewa vosa vei au | Io | Sega |
| Niuean | Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu. | E | Nakai |
| Samoan | Ou te mana'o ia i ai se fa'amatala upu. | Ioe | Leai |
| Tokelaun | Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika | Ioe | Leai |
| Tongan | Oku ou fiema'u ha fakatonulea. | Io | Ikai |
| | | | |

| Please tick the Yes/No box for each statement. | Yes | No |
|--|-----|----|
| I have read and I understand the information sheet dated 8/9/2008 for volunteers taking part in the study designed to test specific education and self treatment for headaches. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given. | | |
| I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study. | | |
| I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care. | | |
| I have had this project explained to me by Dr Giresh Kanji | | |
| I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study. | | |
| I understand that the treatment, or investigation, will be stopped if it should appear harmful to me | | |
| I understand there is no monetary compensation provided for in this study. | | |
| I have had time to consider whether to take part. | | |
| I know who to contact if I have any side effects arising from the study | | |
| I know who to contact if I have any questions about the study | | |
| I wish to receive a copy of the results | | |
| I agree to my GP or other current healthy provider being informed of my participation in this study/the results of my participation in this study | | |

I _____ (full name) hereby consent to take part in this study.

Signature

Full names of Researchers

Contact Phone Number for researchers

Project explained by

Project role

Signature

Date

Appendix 9: Handout on headache causation



Institute of Food, Nutrition and Human Health

Wellington Education and Self Treatment (WEST) Headache Trial

Headache Causation: The Stress Response and Chronic Headaches

Dr Giresh Kanji (MbCHb, PGDip MusMed, FRNZCGP, PGDip BusInfo, FAFMM, MMgt)

Musculoskeletal Pain Specialist

Southern Cross Hospital

90 Hanson St, Newtown, Wellington.

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Introduction

Adrenaline and cortisol are hormones that play a central role in the stress response of the body to a range of stressors including pain, psychological stress, viral illness, alcohol, extreme heat and cold. Adrenaline is a "fight or flight" hormone, and plays a central role in the short-term stress reaction. Cortisol is a slightly longer acting hormone that also increases the effects of adrenaline in the body. Both are designed to protect individuals against threatening situations or in emergencies. In evolutionary terms this hormone helped the survival of the fittest animals.

Adrenaline

Prior to modern civilization human beings were busy hunting for food and avoiding being eaten by predators. When faced with a tiger the release of adrenaline helps the body to cope with the physical demands of fighting the tiger or running from the tiger. The intense physical act of running away or fighting burned up the extra adrenaline produced and stopped the long term effects of adrenaline on the body.

As humans have become city dwellers the need to run from threat or hunt for food has decreased. In modern society pain, psychological stress, viral illness, alcohol, caffeine, bad memories and perceived threat release adrenaline and cortisol. Bad experiences (trauma) can lead to release of adrenaline during dreams or nightmares without conscious control.

The significant problem with releasing adrenaline for pain or stress is that no vigorous physical activity follows to use up the excess adrenaline. This means adrenaline stays in the body for longer than expected and the body and brain becomes sensitised to adrenaline which can cause significant distress. Adrenaline exerts its effect on the body by attaching to adrenaline receptors throughout the body. Often medications such as β blockers target these receptors for relieving headache pain.

Effects of adrenaline stimulation:

When the body reacts to signals of threat the sympathetic nervous system creates several changes in the body preparing the body to fight or take flight (run from danger). These changes include:

An increase in the force of contraction and heart rate. Blood pressure will increase and palpitations or awareness of increase heart beat may result.

Suppression of stomach and intestinal action. This is because digestion is not important for fighting or running away. An increase in blood flow to skeletal muscles (e.g. in legs), heart and the brain to enhance the fight/flight response. The blood flow to skin decreases and may result in cold hands and cold feet. Production of glucose for providing energy for the increased physical effort that may be required during the fight/flight response. Excess glucose is released in the blood stream to service other organ tissues for energy production. The increased levels of glucose in the blood stream can aggravate diabetes. Fats in the body can be mobilised and broken down to be used to produce glucose as well and hence aggravate possible problems associated with blood glucose levels remaining high.

An increased in alertness. If faced with a threat such as a tiger then being alert is beneficial to fight or run. If there is no tiger or physical threat then the increased alertness can lead to

disturbed sleep as the body is alert to deal with a perceived threat. It is as though one is sleeping with a tiger in the bed. So the alertness can be experienced as anxiety.

Cortisol

Cortisol is a stress hormone released by the adrenal gland that has a daily variation, with the highest levels present in the early morning, and the lowest levels present around midnight (Figure 1). In conditions of long term stress, pain or infection the release of cortisol may burnout so the morning levels end up being similar to the low levels at night (Figure 2). Low levels of cortisol cause fatigue. After long periods of stress or chronic pain the low cortisol in the morning makes you feel tired like at night. Cortisol also increases the body's sensitivity to adrenaline and can aggravate symptoms of the fight flight response.

Figure 1: Normal pattern for cortisol levels

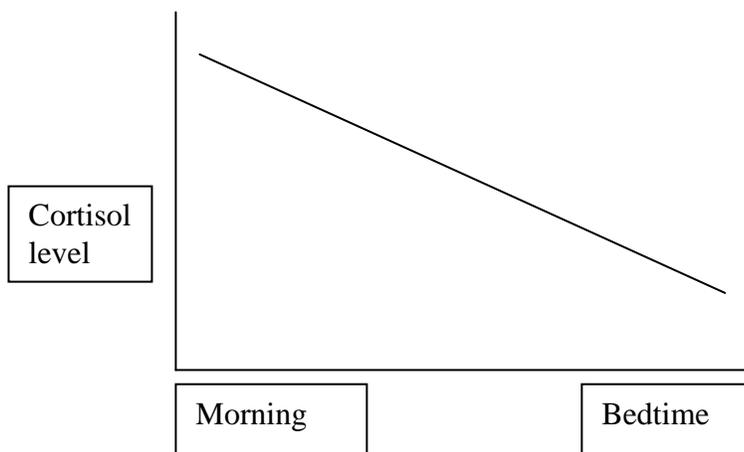
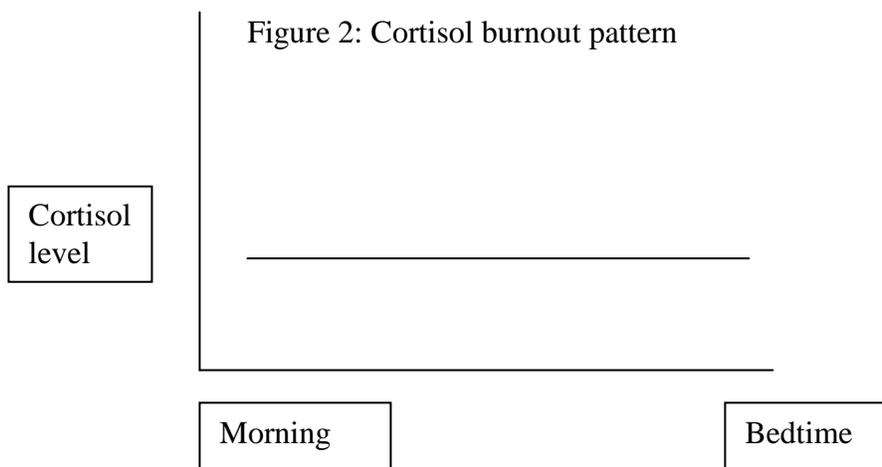


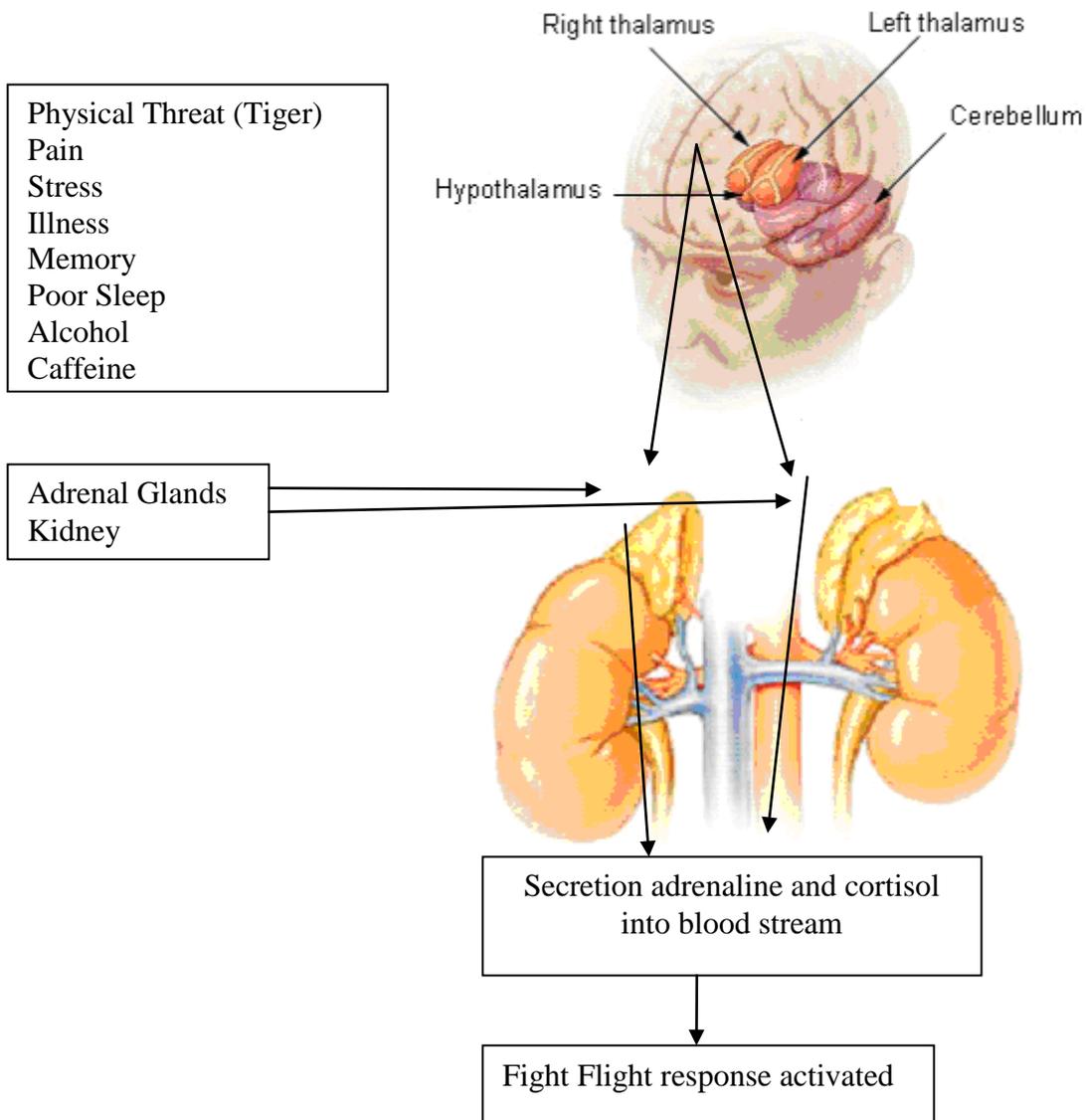
Figure 2: Cortisol burnout pattern



The pathways of the sympathetic nervous system

The hypothalamus (a centre in the brain) sends nerve impulses to the spinal cord that sends signals to the adrenal gland, a small gland that sits above the kidney. The sympathetic nerves weave through the adrenal gland and signal the release of adrenaline.

Figure 3: The pathways of the sympathetic nervous system



Sensitisation

Adrenaline is produced for vigorous physical activity to either run or fight. When running or fighting the adrenaline is used up. When the fight/flight response is activated for pain, stress, viral illness or alcohol there is no vigorous physical activity that follows. The excess

adrenaline then stays in the brain pathways and causes sensitisation of adrenaline pathways in the brain.

Normally nerves work in relays. At the relay (synapse) there are chemical messengers (adrenaline among others) that are released across the gap to activate the next nerve. Figure 4 shows normal transmission with the electricity traveling in nerve D being similar to A. Figure 5 shows the effect of sensitisation of nerves with increases in nerve synapses that allow increased adrenaline to cross the synapse and increase the electricity (increasing the strength of transmission) in nerve D.

Figure 4 Normal transmission of electricity in a nerve

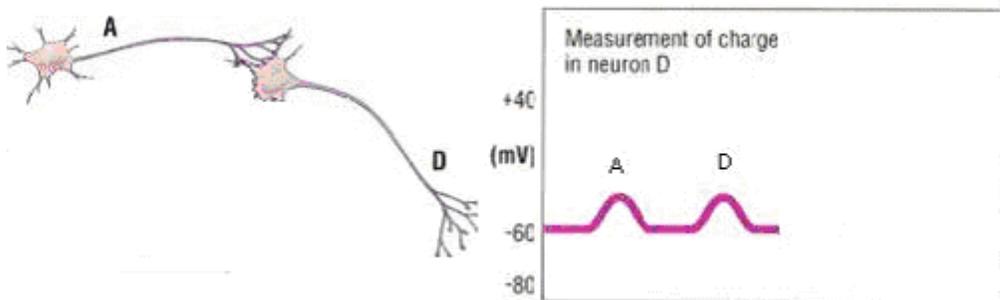
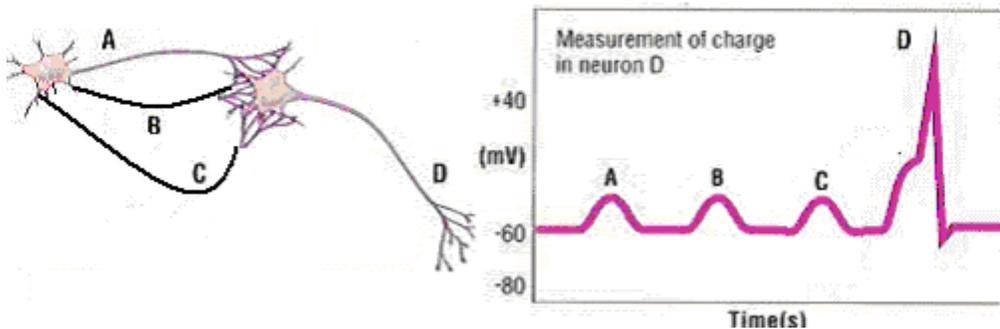


Figure 5 The Sensitisation of Nerves by Increased synapses.



Sensitisation of the adrenaline pathways in the brain can create insomnia, anxiety, headaches and other pain, mental irritability and cause concentration and memory difficulties. There is a pain filter that blocks messages of pain being received by the brain from muscle contraction points. The messages from broken bone or torn muscles pass through the filter to warn the brain of body damage. Once the brain pathways are sensitised holes appear in the filter and pain from contracted muscle points can reach the brain and create discomfort in a wide variety of body sites.

Treatment of headaches is aimed at reducing cortisol and adrenaline action in the body and hence improving sleep and stopping signals of pain being received by the brain from the muscle contraction points.

Appendix 10: Treatment handout for education and soft tissue massage



Institute of Food, Nutrition and Human Health

Wellington Education and Self Treatment (WEST) Headache Trial

Self Treatment for Headaches

Dr Giresh Kanji (MbCHb, PGDip MusMed, FRNZCGP, PGDip BusInfo, FAFMM, MMgt)

Musculoskeletal Pain Specialist

Southern Cross Hospital

90 Hanson St, Newtown, Wellington.

drkanji@southerncrosspain.co.nz

www.southerncrosspain.co.nz

The strategies for self treatment include reducing factors that increase cortisol and adrenaline release in the body, depleting adrenaline and cortisol regularly as well as treating muscle tension points with soft tissue massage. This handout will outline all three strategies for reducing headaches.

Poor sleep

Poor sleep causes cortisol and adrenaline to be released. Between seven and eight hours sleep is required to maintain good morning levels of cortisol otherwise people suffer from tiredness. If a patient has trouble getting to sleep or wakes early in the morning with difficulty returning to sleep then the following strategies may help.

No caffeine after midday. This includes tea, coffee, caffeinated energy drinks, copious amounts of chocolate among others. For people with poor sleep these increase adrenaline and may increase alertness promoting poor sleep.

No stimulating activity such as work, using a computer, vigorous exercise a few hours prior to sleeping. These activities increase cortisol and/or adrenaline and will promote wakefulness. Regular rigorous exercise for 30 minutes per day will promote good sleep when performed at least two hours before going to sleep. Having a regular sleep time may help establish a routine of sleep.

Occupational Stress

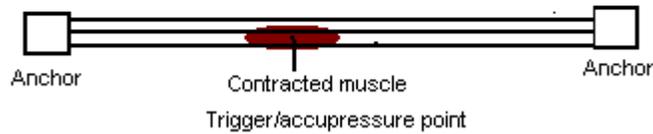
Work stress is a significant contributor to everyday stress. In particular working prolonged hours and into the evening will prevent you feeling refreshed. During the day it is important to have regular breaks including a lunch break to prevent the buildup of stress during the day.

SOFT TISSUE MASSAGE

Soft tissue massage is a technique that can relieve tender muscles without any pain. It is based on two basic principles. The first principle is that muscle is like a piece of string between two anchors. The second principle is that muscles contract when breathing in and relax when breathing out.

The muscle is like piece of string between two fixed points (Figure 1). Between these two fixed points there is spasm of the muscle and an underlying tender point often called a trigger point.

Figure one showing muscle and contracted muscle point



Pushing on the tender point stretches the muscle underneath. Figure two shows the stretched muscle.

Figure two showing lengthening of the muscle

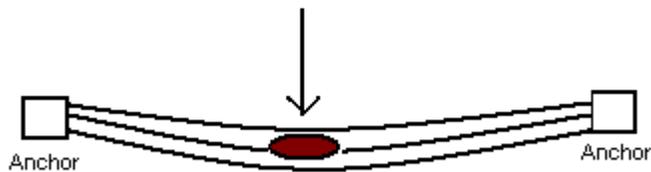
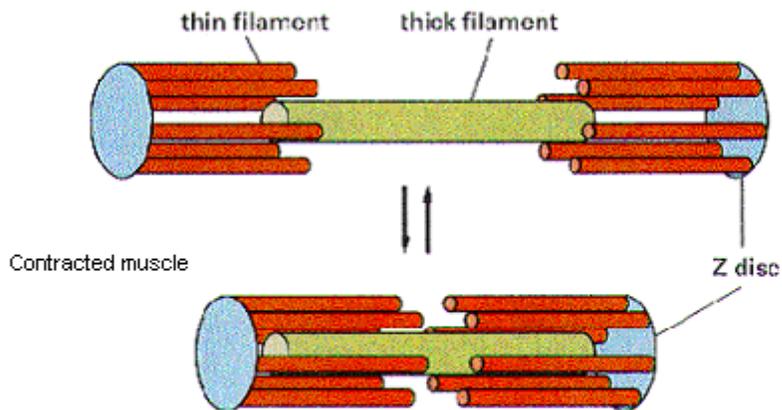


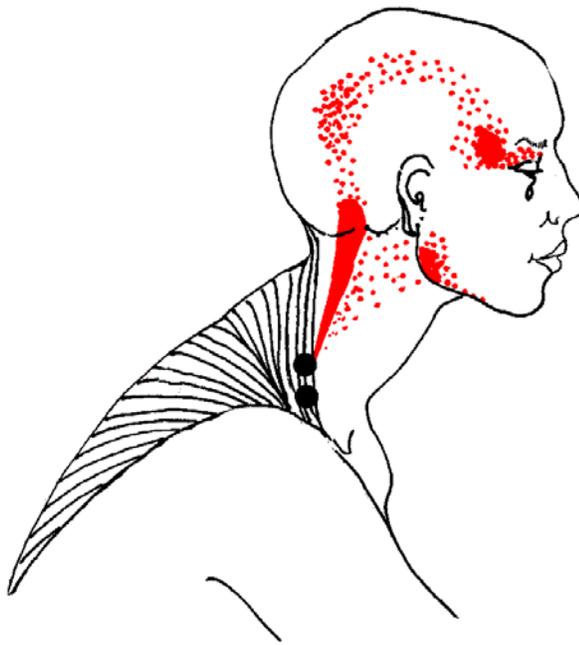
Figure 3 showing relaxed muscle and contracted muscle.

Relaxed muscle



The muscles can refer pain in certain patterns far away from the muscles themselves. Figure 3 shows referral from the trapezius muscle of the neck.

Figure 4 The referral pattern from contraction points in the trapezius muscle.



Steps for Soft Tissue Massage

Step 1. Press on the muscle points as shown on diagram 6 and 7. These points are approximate only and pressing over a region will identify the very tender muscle points that are the contraction points.

Step 2. Mark the very tender points with a pen

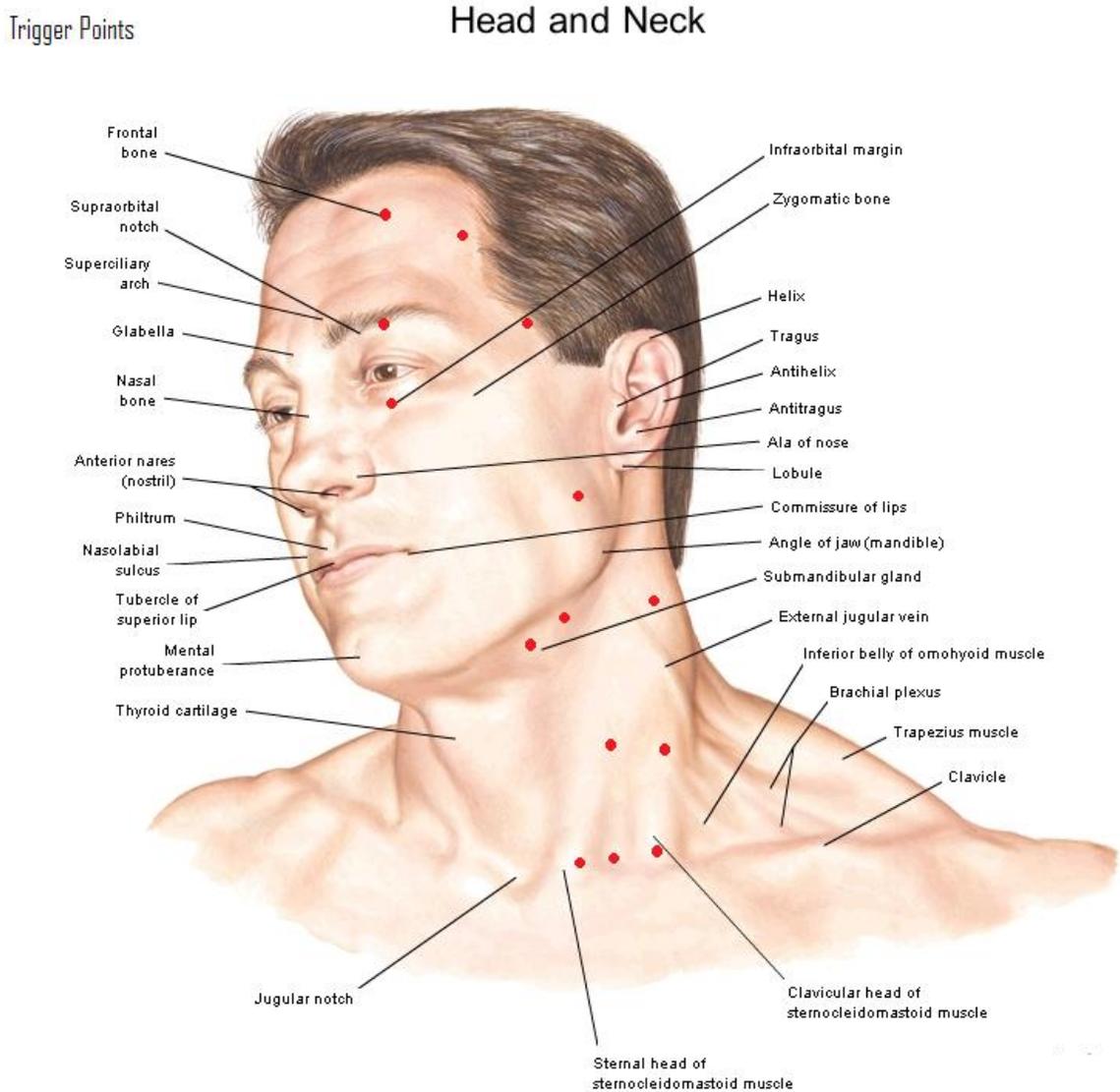
Step 3. Gently press on the very tender point without causing pain. If pressing creates pain then the muscle will contract (spasm) and not relax.

Step 4. Take approximately 10 deep breaths while pressing gently on the muscle. As you breathe out the muscle relaxes and your finger presses more deeply into the muscle stretching it.

Step 5. Initially not all the tenderness may subside but if you perform 5 to 10 points per day they will slowly subside.

For tender muscle points in the back of the neck and shoulders a golf ball may be used to lie against to locate the points and then lean slowly back onto while breathing to treat them.

Figure 6. Common muscle contraction sites of the head and neck



Appendix 11: Addendum to treatment handout for sauna group

The handout for the sauna group was identical to Appendix 10 above with this addendum for the sauna group.

Sauna's and Sweating

Sweating helps diminish the chemicals that produce adrenaline in the body. The deep relaxation felt after a sauna is likely to be linked to the depletion of cortisol and adrenaline as well as other affects from the heat. The heat stresses the body. The body tries to restore the normal body temperature by sweating. This is an active process that requires energy (1/2 a calorie is burned for every 1 ml of sweat produced). During this process cortisol/adrenaline is depleted as well as acetylcholine (the chemical responsible for muscle contraction).

Attending a sauna three times a week for 20 minutes is recommended. The Wellington City Council have arranged for three months access to all their pools for participants to attend the sauna at no charge to the participants.

Appendix 12: Ethics committee approval

**Health
and
Disability
Ethics
Committees**

21 October 2009

Dr Giresh Kanji
29 Aparima Avenue
Miramar
Wellington

Upper South A Regional Ethics Committee

Ministry of Health
4th Floor, 250 Oxford Tce
PO Box 3877
Christchurch
Phone (03) 372 3037
Fax (03) 372 1015

Email: uppersouth_ethicscommittee@moh.govt.nz

Dear Dr Kanji,

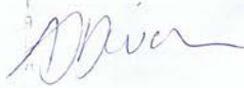
Wellington Education and Self Treatment (WEST) Headache Trial. A randomised, blind controlled trial.

**Investigator: Dr G Kanji, Dr R Page, Dr R Peter
Locality: Southern Cross Specialist Care Centre
Ethics ref: URA/08/08/054**

Thank you for the progress report for the above study, which was considered by the Upper South A Regional Ethics Committee at its meeting on 19 October 2009.

Ethical approval is confirmed for a further 12 months from the report due date. We look forward to receiving another report from you in September 2010.

Yours sincerely



Alieke Dierckx
Upper South A Ethics Committee Administrator
Alieke_dierckx@moh.govt.nz

Appendix 13: Australia/NZ trial registration document

| | |
|-------------------------|---------------------|
| Request Number: | 083685 |
| ACTR Number: | ACTRN12609000746235 |
| Trial Status: | Registered |
| Date Submitted: | 8/03/2009 |
| Date Registered: | 27/08/2009 |

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| | |
|-----------------------------------|--|
| Public title: | In chronic tension type headache sufferers is sauna or soft tissue massage more effective than their current care in reducing headache severity and frequency. |
| ANZCTR registration title: | In chronic tension type headache sufferers is sauna or soft tissue massage more effective than their current care in reducing headache severity and frequency |
| Secondary ID: | |
| UTN: | |
| Trial acronym: | WEST Headache trial |

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Appendix 14: List of conference, symposia and group presentations

The following conferences, symposiums or clinical practitioners were addressed by the author to outline the headache causation model and preliminary or final results of the WEST headache trial

- 1) The causation of chronic pain disorders, oral presentation to Proactive Physiotherapy, Wellington, August, 2008.
- 2) The causation of headache disorders, oral presentation to Wellington Indian Association, Wellington, December, 2008.
- 3) The causation of headache disorders: Confirmation of thesis, oral presentation, Massey University, Wellington, May, 2009
- 4) Original research: The Wellington Education and Self Treatment (WEST) headache randomised control trial of sauna, preliminary results, oral presentation at Pharmacy Society of New Zealand Symposium, Christchurch, May, 2009.
- 5) Original research: The Wellington Education and Self Treatment (WEST) headache randomised control trial of sauna, preliminary results, oral presentation at Pharmacy Society of New Zealand Symposium, Rotorua, May, 2009.
- 6) Original research: The Wellington Education and Self Treatment (WEST) headache randomised control trial of sauna, preliminary results, oral presentation at Wellington General Practice Peer review Group, May, 2009.
- 7) Original research: The Wellington Education and Self Treatment (WEST) headache randomised control trial of sauna, preliminary results, oral presentation at Pharmacy Society of New Zealand Symposium, Wellington, June, 2009.

- 8) Original research: The Wellington Education and Self Treatment (WEST) headache randomised control trial of sauna, preliminary results, oral presentation at Pharmacy Society of New Zealand Symposium, Auckland, June, 2009.
- 9) Chronic pain in children, oral presentation at New Zealand National Orthopaedic Nurses conference, Wellington, September, 2009.
- 10) Chronic headaches and other medical syndromes: The mismatch of the human body to the current environment, oral presentation New Zealand Post Graduate Conference, Wellington, November, 2009.
- 11) A model of the development of chronic pain syndrome/Fibromyalgia, oral presentation at National Association of Opioid Treatment Providers meeting, Wellington, March, 2010.
- 12) The Wellington Education and Self Treatment (WEST) randomised control trial of sauna for chronic tension-type headache – oral presentation at the Australasian Faculty of Musculoskeletal Medicine (AFMM) Retreat, Orewa Beach, March, 2010.
- 13) The development of chronic pain disorders: The Wellington Education and Self Treatment (WEST) randomised control trial of sauna for chronic tension-type headache, oral presentation at Spine in Action: Low Back Pain Can Chronicity Be Prevented, Auckland, March, 2010.
- 14) The development of chronic pain syndromes and headache disorders, oral presentation to Newtown Physiotherapy practice, Wellington, March 2010.
- 15) The causation of headache disorders, oral presentation at 3 Minute Thesis presentation competition, Massey University, Winner of competition, Wellington, May, 2010.

- 16) The causation of headache disorders, oral presentation at 3 Minute Thesis Presentation Competition, National Final, Massey University, Runner up prize, Palmerston North, May, 2010.
- 17) The development of chronic pain syndromes and headache disorders: Kilbirnie Physio and Rehab clinic, Wellington, June 2010.
- 18) The Wellington Education and Self Treatment (WEST) randomised control trial of sauna for chronic tension-type headache, Massey University College of Science Seminar presentation, Wellington, July, 2010.
- 19) The Wellington Education and Self Treatment (WEST) randomised control trial of sauna for chronic tension-type headache, Poster presentation at Wellington Health and Biomedical Research Society 79th Scientific Meeting, Wellington, August, 2010.
- 20) The Wellington Education and Self Treatment (WEST) randomised control trial of sauna for chronic tension-type headache, insights into chronic pain and headache disorders, Royal New Zealand College of General Practitioners Annual Conference (Research Day), Christchurch, September 2010.
- 21) The development of chronic pain syndromes, New Zealand National Orthopaedic Nursing Association Conference, Wellington, September, 2010.
- 22) The causation of headache disorders: The Wellington Education and Self Treatment (WEST) headache trial- oral presentation open to the public at Bikram Yoga Studio, Wellington, September, 2010.

- 23) Original research: The Wellington Education and Self Treatment (WEST) headache trial of sauna for CTTH – oral presentation at Teamphysio Sports and Rehab, Lower Hutt, October 2010.

- 24) Original research: The Wellington Education and Self Treatment (WEST) headache trial of sauna for CTTH - oral presentation at the Wellington Health and Biomedical Research Society 80th Scientific Meeting, Wellington, November, 2010.

- 25) Original research: The Wellington Education and Self Treatment (WEST) headache trial of sauna for CTTH – oral presentation at Peer Review meeting Waiwhetu Medical Centre, Lower Hutt, December 2010.