The Effect of Electro-Acupuncture on Reducing Opioid Consumption in Patients with Chronic Pain:
A Randomised Controlled Clinical Trial

Run Xiang Guo
Master of Applied Science

2006

RMIT
The Effect of Electro-Acupuncture on Reducing Opioid Consumption in Patients with Chronic Pain:

A Randomised Controlled Clinical Trial

A thesis submitted in fulfilment of the requirements for the degree of Master of Applied Science

Run Xiang Guo

B.Med

School of Health Sciences

RMIT University

August 2006
DECLARATION

I declare that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; and, any editorial work, paid or unpaid, carried out by a third party is acknowledged.

Run Xiang Guo

26 August 2006
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<thead>
<tr>
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<td>AA</td>
<td>Acupuncture analgesia</td>
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<tr>
<td>AE</td>
<td>Adverse events</td>
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<tr>
<td>ANOVA</td>
<td>Repeated measures analysis of variance</td>
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<td>BDI-II</td>
<td>Beck Depression Inventory-II</td>
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<td>BMA</td>
<td>British Medical Association</td>
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<td>BMAS</td>
<td>British Medical Acupuncture Association</td>
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<td>BP</td>
<td>SF-36 bodily pain</td>
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<tr>
<td>BWCPM</td>
<td>Barbara Walker Centre for Pain Management</td>
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<tr>
<td>CAT</td>
<td>Complementary and alternative therapy</td>
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<td>CBT</td>
<td>Cognitive behavioural therapy</td>
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<tr>
<td>CCT</td>
<td>Controlled clinical trials</td>
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<td>CF</td>
<td>Consent form</td>
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<td>CMRB</td>
<td>Chinese medicine registration board</td>
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<td>CNMP</td>
<td>Chronic non-malignant pain</td>
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<td>CNS</td>
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<td>COX</td>
<td>Cyclo-oxygenase</td>
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<td>CSF</td>
<td>Cerebral spinal fluid</td>
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<td>CT</td>
<td>Conventional therapy</td>
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<td>CTN</td>
<td>Clinical Trial Notification</td>
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<tr>
<td>DNIC</td>
<td>Diffuse noxious inhibitory controls</td>
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<td>DOC</td>
<td>Dosage of Opioid Consumed</td>
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<td>Dynorphin A</td>
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<td>EAA</td>
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<td>EI</td>
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<td>EOPs</td>
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<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<td>GLM</td>
<td>General Linear Model</td>
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<td>General practitioner</td>
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<td>HRQL</td>
<td>Health Related Quality of Life</td>
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<td>IASP</td>
<td>International Association for the Study of Pain</td>
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<td>ITT</td>
<td>Intention-to-treat</td>
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<tr>
<td>LOE</td>
<td>level of evidence</td>
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<td>LR</td>
<td>literature review</td>
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<td>MD</td>
<td>Medical doctors</td>
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<td>Abbreviation</td>
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<tr>
<td>MDA</td>
<td>Multidisciplinary assessment</td>
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<td>MEAP</td>
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<td>MH</td>
<td>SF-36 Mental health</td>
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<td>MPM</td>
<td>Multidisciplinary pain management</td>
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<td>MPQ</td>
<td>McGill Pain Questionnaire</td>
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<td>MQS</td>
<td>Medication Quantification Scale</td>
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<tr>
<td>NHMRC</td>
<td>The National Health and Medical Research Council</td>
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<td>NIH</td>
<td>National Institute of Health</td>
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<td>NRS</td>
<td>Numerical rating scales</td>
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<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<td>NSW</td>
<td>New South Wales</td>
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<td>NWC</td>
<td>Number of words chosen</td>
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<tr>
<td>OA</td>
<td>Osteoarthritis</td>
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<td>OLM</td>
<td>Opioid-like pain medications</td>
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<td>PAG</td>
<td>Periaqueductal grey matter</td>
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<td>PF</td>
<td>SF-36 physical functioning</td>
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<td>PI</td>
<td>Participant information</td>
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<td>PNS</td>
<td>Peripheral nervous system</td>
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<td>Preproenkephalin</td>
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<td>Pain rating indexes</td>
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<td>PRI-e</td>
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<td>PRI-m</td>
<td>PRI-miscellaneous</td>
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<td>PRI-sensory</td>
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<td>PWL</td>
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<td>Quality of life</td>
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<td>Research assistant</td>
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<td>RE</td>
<td>SF-36 role emotional</td>
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<td>Real electro-acupuncture</td>
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<td>RP</td>
<td>SF-36 role physical</td>
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<tr>
<td>SD</td>
<td>Standard deviations</td>
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<td>SEA</td>
<td>Sham electro-acupuncture</td>
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<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
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<td>SSR1</td>
<td>Serotonin-selective reuptake inhibitors</td>
</tr>
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<td>START</td>
<td>Selected Targets of Activity ReTraining</td>
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<td>Description</td>
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<tr>
<td>SVH</td>
<td>St. Vincent’s Hospital</td>
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<tr>
<td>TAES</td>
<td>Transcutaneous acupuncture electrical stimulation</td>
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<tr>
<td>TCAs</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>TENS</td>
<td>Transcutaneous electrical nerve stimulation</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<tr>
<td>tw</td>
<td>Treatment week</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>VT</td>
<td>SF-36 vitality</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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RELEVANT CONFERENCE PRESENTATIONS


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SUMMARY

Chronic pain is a common medical condition that affects approximately 20% of young adults and 50% in older people in Australia, with similar prevalence in other Western countries. Clinically, opioids are one of the most commonly used analgesics for the management of this condition. However, opioids have been reported to be closely associated with substantial adverse effects that have significant impact on patients’ quality of life. In addition, dependence on opioids has hindered patients’ participation in programmes that encourage active self-management of chronic pain. Therefore, effective management of chronic pain remained a significant challenge. Identifying and developing non-pharmacological approaches to reduce opioid intake is an important strategy in pain management.

Electro-acupuncture (EA), as part of the acupuncture practice, has a long history of being used as a pain relief therapy. The underlying neural mechanism of EA analgesia is believed to be associated with activation of endogenous inhibitory systems and release of endogenous opioid peptides. In parallel, there have been a number of randomised controlled trials (RCTs) on EA and opioid like medication (OLM) consumption published over the last four decades. Although the quality of the trials varies significantly, the majority of these studies produced consistent and positive findings that EA was effective in reducing OLM consumption for operative and post-operative pain patients, in comparison with sham EA, placebo control or non-EA treatment control. In the meantime, there is inadequate evidence to support any claim of EA for reducing adverse effects of OLM. There have been no RCTs on EA for OLM consumption in patients with chronic pain.

The present study aimed to determine the benefit of EA on OLM consumption and related adverse effects in patients with chronic pain in comparison with sham EA; in addition, the
potential effect of EA on chronic pain related variables such as depression and quality of life was also evaluated.

A randomised, double-blind (patient/assessor) and sham-controlled study was conducted to evaluate the effect of EA in reducing OLM consumption by patients with chronic pain. Thirty-five volunteers met all inclusion criteria after being assessed by medical pain management specialist and thus included in this study. After a two-week baseline assessment, subjects were randomly assigned to one of the two groups using computer software with 17 in the real EA (REA) and 18 in the sham EA (SEA). All subjects were given either REA or SEA treatment twice a week, 30 minutes each session, over a period of six weeks. REA group received 2/100 Hz EA stimulation on the two-paired acupoints, Zusanli (ST36) with Fenglong (ST40), and Hegu (LI4) with Quchi (LI11). SEA group only received superficial needling on non-acupoints without Deqi sensation and electrical stimulation. The assessor and subjects were blinded from treatment allocation.

The primary outcome measures were OLM consumption, related adverse effects, and daily records of the intensity and unpleasantness of pain. The secondary measures were depression and quality of life as measured by the Beck Depression Inventory-II (BDI-II) and SF-36, respectively. Both primary and secondary outcome measures were conducted throughout the baseline and treatment period. Data were analysed with independent t-tests or repeated measure analysis of variance (ANOVA) where appropriate and per protocol analyses were employed.

At baseline, the two groups were comparable in terms of OLM consumption, non-opioid analgesics, the history, diagnosis, duration, and intensity of pain except for the average of pain, which was higher in the SEA group (p < .05). At the end of six weeks of treatment,
subjects reduced 64% and 46% of OLM consumption for REA and SEA groups respectively (p < 0.05). The effect lasted up to four weeks after completion of the six-week treatment. In addition, REA significantly reduced the severity of sedation compared with SEA treatment (p < 0.05). Subjects in the REA also had a lower overall incidence of OLM related adverse effects than those in SEA group. The intensity and unpleasantness of pain as well as depression were reduced during treatment period, however, there were no significant differences between the two groups. Within group comparison, the majority of domains of the SF-36 were not significantly improved except for bodily pain (BP), vitality (VI) and role physical (RP) for both groups. However, no significant group differences in these changes were shown. Both REA and SEA were well tolerated by subjects participated in this trial.

At the end of the treatment period, over 90% of the subjects were satisfied with the interventions given and indicated that they would recommend EA to others. The blinding procedures were successful. In addition, 61% of the subjects thought the interventions were effective for their chronic pain.

The main limitation of this study is the small sample size, which might have contributed to a lack of group difference on pain reduction. In recognition of heterogeneity of chronic pain, variations due to types and locations of pain as well as dosages and forms of OLM also need to be taken into consideration for the interpretation of these findings.

In conclusion, this study demonstrated that alternating 2/100 Hz of REA is more effective in reducing OLM consumption and related sedation for subjects with chronic pain when compared with SEA. The findings suggest that EA may be a safe and effective adjunct therapy in chronic pain management. Further studies with a larger sample size are warranted.
CHAPTER ONE: INTRODUCTION

Pain is the most common human subjective experience. The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Merskey, Lindblom, Mumford, Nathan, & Sunderland, 1994). Chronic pain is mostly defined as pain lasting more than six months and may persist for years (Melzack & Wall, 1996b). Chronic pain is not considered as just a symptom but a medical problem (Helme & Katz, 1993).

Chronic pain is a highly prevalent condition worldwide. Epidemiological studies have indicated that approximately 20% of Australian adults have suffered from chronic pain (Blyth et al., 2001). A similar prevalence of chronic pain is observed in the United States (US) and European countries (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Eriksen, Jensen, Sjogren, Ekholm, & Rasmussen, 2003; National Research Council, 2001). The impacts of chronic pain include physical, psychological and social effects. Chronic pain is also associated with deterioration in the sufferer’s quality of life (QoL) and frequently accompanied by disability (Blyth, March, Brnabic, & Cousins, 2004; Blyth, March, & Cousins, 2003).

Chronic pain conditions are heterogenous, which is evident from the classification of chronic pain. It consists of five axes including regions, systems, temporal characteristics, intensity and etiology. Based on the anatomic locations of the pain, chronic pain can be defined as headache, neck pain, lower back pain and etc. Based on the system affected, it includes pain in the musculoskeletal system, nervous system, respiratory and cardiovascular systems and others. Based on etiology, it includes pain due to injury, degeneration, tumour etc. Based on pathophysiology, it can be further divided into inflammatory and neuropathic pain. The
former arises from inflammation of skin or other tissue; the later is from injury to the peripheral or central nervous system (Basbaum et al., 2005; Merskey & Bogduk, 1994).

Increases in our understanding of the complexity of pain has led to the development of multidisciplinary pain management (Bonica, 1990b; R. Melzack & Casey, 1968). This strategy embraces various therapeutic approaches focused on improving patient’s pain management and quality of life. Opioids are among these therapeutic options and recommended as one of the widely-used analgesics for the management of chronic pain (Grahmann, Jackson, & Lipman, 2004). Australian studies have revealed that an increasing number of patients with chronic pain have been prescribed opioids medication (Bell, 1997; Richards, 1995).

Although the majority of chronic pain may be diminished by opioid treatment (Cowan, Wilson-Barnett, Griffiths, & Allan, 2003a; Jamison, Anderson, Peeters-Asdourian, & Ferrante, 1994), these medications produce a high rate of adverse effects. The most frequently observed symptoms involve both the central nervous and gastrointestinal systems, and drug-dependence has also been documented (Gourlay, 1999; Kalso, McQuay, Edwards, & Moore, 2004). In addition, tolerance to opioid medication which leads to an increased dose is also a significant problem. Recognition of these limitations has hindered the acceptance of opioids in the management of patients with chronic pain, and many clinicians are reluctant to prescribe opioids as a longer-term therapy. Therefore, the use of non-pharmacologic approaches to reduce opioid intake may be beneficial for chronic pain patients.

There are a range of non-pharmacological therapeutic approaches used for managing chronic pain. Acupuncture is one of these therapies increasingly being used by patients and physicians (Aanjesen, Senstad, Lystad, & Kvaerner, 2002; Easthope, Gill, Beilby, & Tranter, 1999;
Easthope, Tranter, & Gill, 2000). Moreover, pain clinics have increasingly employed acupuncture as a treatment option (Woollam & Jackson, 1998). The National Institute Health (NIH), World Health Organization (WHO) and British Medical Association (BMA) have supported the use of acupuncture in the treatment of a wide range of pain conditions, such as post-operative pain, obstetric pain, dental pain, chronic lower back pain, osteoarthritic pain, headache and fibromyalgia (BMA, 2000; NIH, 1998; WHO, 2002).

Electro-acupuncture (EA), based on traditional acupuncture practice, applies needling stimulation and electric pulses to acupuncture meridians and points in order to strengthen the stimulating effect of treatment. Several studies have demonstrated that EA is an effective technique for the management of acute and subacute pain and can reduce opioid-like mediation (OLM) consumption in patients with acute pain (Chen et al., 1998; Lin et al., 2002; Wang et al., 1997). The main underlying mechanism of EA analgesia (EAA) is thought to be activation of endogenous inhibitory systems and the release of endogenous opioid peptides (EOPs) (White, 1999).

A few systematic reviews conclude that the effect of acupuncture on chronic pain is, however, inconclusive (Ezzo et al., 2000; Mendelson, 1977; ter Riet, Kleijnen, & Knipschild, 1990). Clinical studies of acupuncture in the treatment of chronic pain have yet to demonstrate greater pain reduction with real acupuncture when compared with sham acupuncture. These reviews attributed the inconclusive results to poor research methods and small sample sizes employed in clinical trials.

It is reasonable to argue that acupuncture alone cannot sufficiently address the complex factors involved in chronic pain, and therefore, is unable to provide adequate therapeutic
benefit. It is necessary that practitioners and researchers develop an understanding of the specific role of acupuncture in pain management for optimal patient management.

The current study examines the hypothesis that EA may reduce OLM consumption and related side effects in patients with chronic pain. A prospective, randomised, double-blind (patient/assessor), sham-controlled study was designed to test this hypothesis.

This thesis includes the following other chapters:

- Chapter Two describes the epidemiology of chronic pain, its impacts on patients and society, clinical measurements and current management. Neural mechanisms of EAA are discussed. A critical review of RCTs of EA on consumption of OLM in pain patients is conducted to highlight the current state of knowledge.
- Chapter Three provides the general methods of the clinical trial, including sample size and recruitment, eligibility criteria, trial procedures, outcome measures, data collection and analysis.
- Chapter Four reports the short term effects of EA on OLM consumption, pain and related variables. The data are analysed using both per-protocol analysis and intention-to-treat analysis.
- Chapter Five presents the long term effects of EA on OLM consumption, pain and related variables.
- Chapter Six, the final chapter, examines the findings in relation to previous studies, discusses the limitation of the current study and proposes recommendations for future research.
CHAPTER TWO: LITERATURE REVIEW

2.1 Part One - Chronic pain and opioid use

2.1.1 Impact of chronic pain

Numerous prevalence studies of chronic pain indicate the condition is becoming a significant public health burden internationally. Australian epidemiological studies have shown that approximately 20% of adults report chronic pain (Blyth et al., 2001). Comparable prevalence rates have been documented in the US and Denmark (Eriksen et al., 2003; National Research Council, 2001) and greater than half (50.4%) of a community sample in the United Kingdom (UK) (Elliott, Smith, Penny, Smith, & Chambers, 1999) reported suffering due to chronic pain. Moreover, 19% of adult Europeans surveyed in 15 European countries and Israel reportedly suffer moderate to severe chronic pain that negatively impacts on their QoL (Breivik et al., 2006).

Chronic pain has significant health care, social and economic implications worldwide (Bonica, 1990b). Chronic pain is one of the most common reasons that people consult medical practitioners. A recent survey indicated that 78% of chronic pain patients had visited a healthcare practitioner for their pain in the past 6 months (Blyth et al., 2003). Patients with a high level of pain-related disability use health services more frequently than those with a low level of disability (Blyth et al., 2004). The cost of managing pain are enormous with costs estimated at greater than US$150 billion each year in direct medical expenditures in the US (National Research Council, 2001b). In Australia, annual health expenditure for musculoskeletal diseases alone was estimated to be AUS$879 million in 2000-2001 and chronic pain accounted for 19% of the total health system costs (Australian Bureau of
Statistics, 2001). Indirect economic costs associated with the condition include the loss of work productivity (i.e. days at work). A study of 302 patients in Sweden estimated that the annual cost of chronic pain in lost work productivity was estimated at US$16,600 per patient (Ekman, Jonhagen, Hunsche, & Jonsson, 2005).

The impact of chronic pain includes both physical and psychological effects, restricting patient’s daily lives and causing serious social effects. When patients suffer pain for greater than three months, their physical problems may become more complicated, resulting in many changes to their lives as they must try to adapt to their difficulties. These physical effects include interference with daily activities, sleep disturbance, muscular deterioration, and side effects from excessive medications. An Australia study indicated that 11% males and 13.5 % of females reported some degree of interference with daily activities due to pain (Blyth et al., 2001). Poor quality of sleep has been reported in 42% of patients with chronic pain (Becker et al., 1997). Patients with high levels of pain reportedly experience less total sleep time, increased sleep latency and more frequently woke during the night compared with patients reporting low intensity of pain (Morin, Gibson, & Wade, 1998). Patients with chronic pain may also be afraid of physical movement or may limit their movement, resulting in muscular deconditioning, which may lead to further pain aggravation with movement.

The psychological impacts of chronic pain include helplessness, unhelpful beliefs, anxiety, and depression, and associated decline in memory and concentration. A US cross-sectional survey revealed that the prevalence of major depressive disorder was 52% in patients with chronic pain (Elliott, Renier, & Palcher, 2003). Higher estimates were reported in a Hong Kong survey that 71.1% of Chinese patients with chronic pain experienced concurrent depression (Lee et al., 2005). Depression accounted for 35% of memory complaints (Munoz
& Esteve, 2005) and a study of patients referred to a pain centre found that 54% reported problems with short term memory, concentration and attention (McCracken & Iverson, 2001).

Chronic pain contributes significantly to deterioration in Health Related Quality of Life (HRQL) and sufferers have significantly poorer HRQL compared with normal healthy populations (Dysvik, Lindstrom, Eikeland, & Natvig, 2004; Kerr et al., 2004). Becker et al. (1997) studied 150 patients with chronic non-malignant pain (CNMP) and found that HRQL assessed with the Short Form 36 Health Survey (SF-36) were much poorer than in normative samples (Becker et al., 1997). Similarly, Breivik et al. examined the profiles of US interdisciplinary pain management centres and found all CNMP patients (242) had lower than normal SF-36 scores for QoL (Elliott et al., 2003).

Chronic pain is also associated with significant disability. High levels of pain related disability was reported in 27% of the respondents from a Sydney community sample (Blyth et al., 2003). Furthermore, there was a close relationship between the levels of pain related disability and the use of analgesic medication and health services (Blyth et al., 2004; Blyth et al., 2003). Long-term use of analgesics can result in several side effects, such as gastrointestinal problems, constipation, fatigue and concentration difficulty.

2.1.2 Management of chronic pain

An increased understanding of the complexity of pain has resulted in establishment of a conceptual framework utilizing multidisciplinary pain management (MPM) as the main strategy (Bonica, 1990a). MPM programmes have been expanded widely in recent decades and are advocated by the Working Party on the Management of Severe Pain for the National Health and Medical Research Council (NHMRC) in Australia (Atkinson et al., 1988). The
Australian Pain Society also provides a framework for pain management programmes for patients with chronic pain (Australia Pain Society, 2002).

MPM emphasizes a holistic approach to managing pain and improving patients’ QoL rather than attempting solely to reduce or remove pain. The approaches include patient education, cognitive-behavioural therapy, physiotherapy, exercises, and pharmacological treatment. The efficacy of MPM has been demonstrated in different clinical settings, including hospital inpatients and outpatients and home management programs (Becker, Sjogren, Bech, Olsen, & Eriksen, 2000; Chapman, 1994; Helme, Bradbeer, Katz, & Gibson, 1997).

Numerous studies have confirmed that patients obtain benefits from MPM programmes in terms of reduction of pain, improvements in mood, increased activity and return to work (Becker et al., 2000; Helme et al., 1996; Johansson, Dahl, Jannert, Melin, & Andersson, 1998; Robbins et al., 2003). A recent study showed that patients with chronic pain who completed a MPM programme were also able to improve their coping skills and their HRQL (Dysvik et al., 2004). A review concluded that a higher proportion of chronic back pain patients in multidisciplinary clinics had greater levels of functioning than those receiving other therapies (Flor, Fydrich, & Turk, 1992).

2.1.3 Measurements of chronic pain and related variables

As a subjective experience, pain is influenced not only by pathological factors, but also by cultural and social factors (Munden et al., 2003). Individual pain threshold and tolerance may also affect one’s experience of the pain. In particular, chronic pain is a complex and multidimensional condition. It impacts physical, psychological and social aspects of one’s life. Thus, multiple outcome domains, such as physical functioning, emotional
functioning, adverse effects and participant disposition are recommended in the design of clinical trials of the efficacy and effectiveness of treatment for chronic pain (Turk et al., 2003). These measurements commonly include self-reports, behavioural observations, mood inventories, and QoL evaluation.

2.1.3.1 Self report measures

Self-report is one of the most common measurement methods that require patients to record their pain. This method identifies the patients’ subjective view of their pain and roughly assesses the pain experience regarding the intensity, affect, location and quality of the pain (Jensen & Karoly, 2001).

The most common self-reported measure of pain include word descriptor scales, such as verbal and numerical rating scales (NRS), visual analogue scales (VAS) and the McGill Pain Questionnaire (MPQ). Each kind of self-report measurement has different strengths and is chosen depending on the purpose of the study. These methods assess the sensory aspects of pain including its intensity and quality, as well as the affective domain of pain, such as unpleasantness or anxiety (Jensen & Karoly, 2001). Among these methods, the VAS and MPQ are the most frequently used measurements in both clinical and experimental studies, and have been widely recognised as reliable and valid measurement tools.

Visual Analogue Scales

A VAS is a 10 cm long line; the beginning of line indicates “no pain” and the end of the line indicates “the worst pain imaginable” (Huskisson, 1983). Patients are required to draw a perpendicular line on the scale to show the intensity of pain experienced during a specific period of time. A VAS provides consistent results and is used to assess changes in pain severity induced by pain modulation (Price, 1994). The validation and reliability of VAS as a
ratio scale measure for chronic pain has been recognised (Corran, Helme, & Gibson, 1991). A VAS can be and should be used repeatedly when applied to pain measurement.

One must be aware that chronic pain intensity fluctuates and changes may depend upon the patients’ activities. In a clinical study, patients with chronic pain were asked to rate their pain intensity every 2 hours and pain intensity varied over the course of a day (Jensen & Karoly, 2001). It has been shown that current pain levels tend to influence the recall of previous pain. Hence, simple measures of current pain or single time point pain measures are not sufficient. Current pain levels may serve as anchors to influence the averaging of pain (Haythornthwaite & Fauerbach, 2001). It has been recommended that clinical trials on patients with chronic pain should document average pain, highest and lowest levels and present pain experience on a daily basis (Dworkin, Nagasako, Hetzel, & Farrar, 2001).

*The McGill Pain Questionnaire (MPQ)*

Developed by Melzack and colleagues, the MPQ attempts to measure the multiple dimensions of pain experience (Melzack, 1975). It is a frequently used pain assessment tool for both acute and chronic pain (Gagliese & Melzack, 1997; R. Melzack, Abbert, Zackon, Mulder, & Davis, 1987). The questionnaire, using 78 sensory adjectives in 20 categories, consists primarily of three major classes of descriptors reflecting sensory (item 1-10), affective (item 11-15), and evaluative (item 16) aspects of pain. Some miscellaneous descriptors (item 17-20) are also included. In each group, there are 2-6 descriptors to describe the similar aspect of the experience of pain. In any one group, only one word should be chosen to best describe their pain. The questionnaire also contains drawings of the body on which patients can draw the spatial distribution of their pain, and select words describing temporal properties as well as the Present Pain Intensity (PPI) (Melzack & Torgerson, 1971).
The validity and reliability of the MPQ have been tested extensively in acute and chronic pain (Melzack & Perry, 1975; Reading, 1989; Reading, 1982; Wilkie, Savedra, Holzemer, Tesler, & Paul, 1990). The MPQ has been used to distinguish between different pain syndromes. Dubussion and Melzack reported that each type of pain is characterised by a distinctive set of descriptors (Dubussion & Melzack, 1976).

The Gracely Box Scales

Although the MPQ has been widely used and found to measure changes in levels of pain as a response to pain reduction treatments, the MPQ takes time to complete and requires good language skills. Gracely argued that two essential aspects of pain are sensory and affective or unpleasant aspects, and developed the Gracely Box Scales (GBS) to assess them (Gracely, 1983).

The Gracely Box Scales provides quantification by ratio-scaling procedures (Gracely, 1983; Gracely, McGrath, & Dubner, 1978). It has two parts; each consists of 12 verbal descriptors written over a 21-point scale with a minus sign at bottom and a plus sign at the top. Patients are asked to rate the intensity and unpleasantness of their pain by selecting a verbal descriptors adjacent to number, which scales from zero to 20. The verbal descriptor chosen is converted to the nearest number on the ratio scale, and separate score could be obtained by the severity and unpleasantness score (Doctor, Slater, & Atkinson, 1995). A few studies have demonstrated the Gracely Box scales being a valid and reliable instrument with ratio-scale properties (Doctor et al., 1995; Gracely et al., 1978), when tested against pain induced by physical stimuli in health human.
2.1.3.2 Behavioural measurements

There are various definitions concerning pain behaviours. Vlaeyen et al. suggested that chronic pain behaviour may involve nine components. Included are anxiety, attention seeking complaints, verbal pain complaints, medication intake, general verbal complaints, distorted posture and mobility, fatigue, insomnia, and depressive mood (Vlaeyen, Van Eek, Groenman, & Schuerman, 1987).

Observations of pain behaviour not only provide a detailed description of pain behaviour such as facial expression, postures and gross movement, but also help to understand the variables controlling those behaviours. The purpose of the descriptive data is to identify problems that may serve as targets during treatment, to establish an initial baseline measure against which the effects of treatment can be compared, and to assess patient’s response to treatment. Thus, a reliable and valid observation system of pain behaviour requires a high frequency of observation and simple descriptors in order to minimize the inference by the observers (Keefe & Williams, 2001).

Measurements include verbal and nonverbal behaviours. Behavioural measurement indirectly measures the subjective experiences of pain (Melzack & Katz, 1999). However, they do contribute unique information to pain assessment (Hadjistavropoulos & Craig, 2002), and a meta-analysis indicated that self-report of pain intensity and direct observations of pain behaviour are significantly correlated (Labus, Keefe, & Jensen, 2003).

Patients with chronic pain who visit pain clinics and pain management programmes have consistently shown a pattern of pain behaviour of excessive dependence on pain medications. Medication intake and frequency of patients request for medication may be an important measure of pain behaviour (Keefe & Williams, 2001). Jensen et al indicated that pain
behaviour and medication intake was correlated statistically, thus, the behavioural observation can provide reliable and valid information about patients suffering persistent pain (Jensen, Bradley, & Linton, 1989). In addition, behavioural measurements also demonstrate the interference persistent pain exerts on activities of daily living and social roles (Dworkin & Sherman, 1999).

2.1.3.3 Beck Depression Inventory

Depression is often experienced by chronic pain suffers and interacts with chronic pain. Thus, understanding change in the level of a patient’s depression may assist the investigation and evaluation of pain with respect to treatment effects (Moss, Lawton, & Glicksman, 1991).

The Beck Depression Inventory (BDI) was designed to measure cognitive and somatic components of depression, and has become a widely used measurement tool to assess the severity of depression in previously diagnosed patients and to identify possible depression in patients with chronic pain (Beck & Steer, 1987). The inventory consists of 21 items. These items are described according to the severity of the symptoms and attitudes, and each item is rated on a 4-point scale ranging from 0 to 3 levels of severity. Patients endorse one statement in each item that seems to fit best with their mood during the past two weeks (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961).

The reliability and validity of the BDI in chronic pain patients have been well-established (Beck, Steer, & Garbin, 1988; de C Williams & Richardson, 1993; Flor et al., 1992). Several investigations on the BDI have shown its high sensitivity and specificity in identifying depression in patients with chronic pain (Geisser, Roth, & Robinson, 1997). The BDI may also distinguish depressed patients with typical cognitive biases, who require specific treatment for depression together with pain management (Morley, Williams, & Black, 2002).
The BDI-II, revised by Beck and colleagues in 1994, is based on the first version of the BDI. Its purpose is to assess the symptoms corresponding to the criteria for diagnosing depressive disorders listed in the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV, 1994). Research has demonstrated that the BDI-II has adequate reliability and validity (Grothe et al., 2005; Kuhner, Burger, Keller, & Hautzinger, 2006; Osman, Kopper, Barrios, Gutierrez, & Bagge, 2004).

2.1.3.4 Quality of life

One of the commonly used QoL measurements is the SF-36 (Ware, Kosinski, Snow, & Candek, 2000). The SF-36 is a self-administration questionnaire, and assesses patients’ perception of their physical and mental aspects and general well-being in eight domains, including physical functioning (PF), social functioning (SF), bodily pain (BP), general health (GH), vitality (VT), role physical (RP), role emotional (RE) and mental health (MH).

The reliability and validity of the SF-36 is well documented (McHorney, Ware, Lu, & Sherbourne, 1994; Stewart, 1988; Ware, Jr., 2000; Ware, Jr. & Sherbourne, 1992; Ware et al., 2000). It has been used in assessing chronic pain patients’ QoL and evaluating their responses to treatment (Solomon, 1997; Ware & Candek, 1994). There are numerous studies that employ SF-36 for investigating the relationships among QoL, pain severity, and analgesic outcomes (Bombardier & Raboud, 1991; Mauskopf, Austin, Dix, & Berzon, 1994).

A few studies demonstrated that SF-36 scores were reduced in domains of physical, psychological and social well-being in patients with chronic pain (Becker et al., 1997; Kerr et al., 2004; Lee et al., 2005).
2.1.4 Pharmacotherapy

Analgesic pharmacotherapy is the mainstay of management of chronic non-malignant pain. Analgesic medications consist of non-opioid and opioid analgesics. A therapeutic strategy, known as “ladder of analgesia”, was developed by the WHO (WHO, 1996). It is based on three-step analgesia and provides a useful means of determining the type of analgesics to be used for pain of varying severities.

Table 1: Three step pain relief ladder, adapted from WHO’s Pain relief ladder

<table>
<thead>
<tr>
<th>Step</th>
<th>Analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Non-opioid</td>
</tr>
<tr>
<td></td>
<td>+/- adjuvant therapy</td>
</tr>
<tr>
<td></td>
<td>(Aspirin, Paracetamol, Ibuprofen)</td>
</tr>
<tr>
<td>2.</td>
<td>Opioid for mild to moderate pain</td>
</tr>
<tr>
<td></td>
<td>+/- non-opioid</td>
</tr>
<tr>
<td></td>
<td>+/- adjuvant therapy</td>
</tr>
<tr>
<td></td>
<td>(Codeine, Hydrocodone)</td>
</tr>
<tr>
<td>3.</td>
<td>Opioid for moderate to severe pain</td>
</tr>
<tr>
<td></td>
<td>+/- non-opioid</td>
</tr>
<tr>
<td></td>
<td>+/- adjuvant therapy</td>
</tr>
<tr>
<td></td>
<td>(Oxycodone, Morphine, Hydromorphone, Fentanyl)</td>
</tr>
</tbody>
</table>

2.1.4.1 Non-opioid analgesics

Non-opioid analgesics are commonly used to treat either nociceptive or neuropathic pain. They include aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol. In recent years, cyclo-oxygenase-2 (COX-2) inhibitors, such as Celebrex and Mobic, have been developed and are considered to be within the first step of the pain relief ladder (Basbaum et al., 2005). The effectiveness of these agents is mostly limited to the relief of mild pain, but some NSAIDs can reduce moderate pain as well as treat inflammation, in conjunction with opioid analgesics to achieve pain relief (Munden et al., 2003).
NSAIDs and paracetamol are commonly used in chronic pain condition, especially chronic inflammatory musculoskeletal pain. The mechanism of the action of NSAIDs is inhibition of prostaglandin formation through acting on the COX enzyme. NSAIDs have anti-inflammatory, analgesic and antipyretic pharmacologic effects and therefore are commonly used for chronic pain in rheumatoid, osteoarthritis and musculoskeletal pain (Kung, Gibson & Helme 2000). The main side effects of NSAIDs are gastrointestinal upset. Other adverse effects may present with “salicylism” symptoms, and include asymptomatic hepatitis and dilation of peripheral blood vessels (Katzung & Furst, 1998).

Paracetamol has antipyretic activity and minimal anti-inflammatory effects, but has no effect on platelets. The exact mechanism of the antinociceptive effects of paracetamol remains unclear. Clinically, paracetamol has become a commonly used, first-line non-opioid analgesic for chronic pain due to relatively less adverse effect profile and excellent tolerability (WHO, 1996).

The COX-2 inhibitors selectively block one of the two major isoforms of the COX enzyme, COX-2, and produce analgesic effects of NSAIDs without intestinal damage. However, one of them, Vioxx, has been recently taken off the market due to an increased rate of cardiovascular complications (Basmaum et al., 2005)

2.1.4.2 Opioid analgesics

Opium is an addictive narcotic drug which is extracted from the unripe seed pods of the opium poppy. It was commonly used as an analgesic until the development of morphine. Opium contains many different compounds, and morphine is the principal active agent. Other constituents of opium include alkaloids such as codeine, papaverine and thebaine (Way, Howard, & Way, 1998)
Opioids contain derivatives of the opium plant, and other synthetic drugs that imitate natural narcotics. The term opioid applies to any substance which produces a morphine-like effect that antagonists to the µ-opioid receptor, such as naloxone or naltrexone (Portenoy, 1999). Based on the interactions of opioid analgesics with opioid receptors, the classification of opioid analgesics can be divided into pure agonists such as Morphine, Oxycodone and Methadone, and other mixed or partial agonist-antagonists, for example, Nalbuphine and Buprenorphine (Table 2).

The pure agonists selectively bind to and activate µ receptors to produce clinical analgesia. The mixed opioid agonist-antagonist drugs are capable of producing agonistic effects at κ receptors, while at µ receptors the effects are antagonistic. The partial agonist drugs, although act selectively at the µ receptor but generate less intrinsic efficacy, have a 'ceiling response' above which an increase in dose does not produce an additional increase in effect (Portenoy, 1999).

<table>
<thead>
<tr>
<th>Endogenous Opioid Peptides</th>
<th>Opioid receptors</th>
<th>Natural opioids (agonists)</th>
<th>Semisynthetic opioids (agonists)</th>
<th>Synthetic opioids (agonists)</th>
<th>Opioid antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endorphins</td>
<td>µ</td>
<td>Morphine</td>
<td>Oxycodone</td>
<td>Pethidine</td>
<td>Naloxone</td>
</tr>
<tr>
<td>Enkephalin</td>
<td>δ</td>
<td>Codeine</td>
<td>Hydrocodone</td>
<td>Fentanyl</td>
<td>Naltrexone</td>
</tr>
<tr>
<td>Dynorphin</td>
<td>κ</td>
<td></td>
<td>Hydromorphone Oxymorphone Heroin</td>
<td>Tramadol Methadone</td>
<td></td>
</tr>
</tbody>
</table>

The dose of opioid required may vary between patients, depending on the degree to which a patient develops tolerance to medication, pain threshold, experience with pain, and the condition being treated (Galbraith, 2001). Each patient must be assessed individually.
In the clinical setting, different opioids have been generated from three molecules, Oxycodone, Hydromorphone, and Oxymorphone. Each has similar analgesic activity although their potency and duration of effect are quite different. The strength of all analgesics can be expressed by comparison with the equivalent dose of morphine. Table 3 summarises the morphine equivalence of commonly used opioid-containing substances (Halpern, 1989; Margoles, 1999; Twycross, 1999).

The central nervous system (CNS) produces analgesic peptides acting at \( \mu \) and other receptors. The main compounds released are EOPs such as \( \beta \)-endorphins, enkephalins and dynorphins. There are three main opioid receptors: \( \mu \), \( \delta \) and \( \kappa \), that are widely distributed in the spinal cord, brainstem and peripheral tissues. The functions of various receptors are different, as summarised in Table 4. They may promote the opening of potassium or inhibit the opening of calcium channels, which is a process further mediated by G-protein, affecting descending modulatory pathways of pain (Portenoy, 1999).

### Table 3: Morphine dose equivalent to various opioid-like or opioid-containing substances (mg, p.o.)

<table>
<thead>
<tr>
<th>Substances</th>
<th>Morphine</th>
<th>Codeine</th>
<th>Hydrocodone</th>
<th>Meperidine</th>
<th>Levorphanol</th>
<th>Fentanyl</th>
<th>Pentazocine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30</td>
<td>200</td>
<td>60</td>
<td>300</td>
<td>4</td>
<td>0.2</td>
<td>165</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>60</td>
<td>7.5</td>
<td>30</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>30</td>
<td>150</td>
<td>30</td>
<td>300</td>
<td>4</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>60</td>
<td>80</td>
<td>60</td>
<td>20</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>150</td>
<td>200</td>
<td>150</td>
<td>300</td>
<td>150</td>
<td>1.65</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Function of receptors in CNS

<table>
<thead>
<tr>
<th>Endogenous peptides</th>
<th>( \beta )-endorphins</th>
<th>Dynorphins</th>
<th>Enkephalins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor</td>
<td>( \mu ) (mu)</td>
<td>( \kappa ) (kappa)</td>
<td>( \delta ) (delta)</td>
</tr>
<tr>
<td>Receptor location</td>
<td>Dorsal horn of spinal cord</td>
<td>Thalamus</td>
<td>Spinal cord</td>
</tr>
<tr>
<td>Function</td>
<td>Analgesia, Major unwanted side effects, sedation, dependence</td>
<td>Analgesia, Sedation, dysphoria, few unwanted effects, no dependence</td>
<td>Analgesia</td>
</tr>
</tbody>
</table>
Opioid binding to presynaptic receptors in the CNS inhibits the release of neurotransmitters, while binding to postsynaptic receptors directly inhibits the firing of neurons in pain pathways and modulates the descending inhibitory pathways from the brain to prevent transmission of pain impulses.

Exogenous opioid analgesia and other pharmacological effects are induced by copying the function of endogenous peptides in the CNS and peripheral nervous systems (PNS). Most exogenous opioid drugs being used in clinical practice are morphine-like pure agonists that selectively bind to μ receptors. It is thought that μ receptors are responsible for most of the analgesic effects, and for some major unwanted effects, such as respiratory depression, sedation and dependence (Quinn, Coupar, Keily, & Burcher, 1990). Morphine also acts on δ and κ receptors, which partially produce analgesia at the spinal level. Thus, even a receptor-selective ligand can initiate actually at multiple synapses and transmitters (Way et al., 1998).

Opioid receptor systems are complex and changeable. The expression of opioid receptor may vary depending on the type of noxious stimuli, disease processes or the characteristics of the particular analgesic used. For example, nociceptive pain may increase numbers of receptors while neuropathic pain may decrease numbers of receptors, Neuropathic pain may therefore respond less well to opioid analgesics (Rang, Dale, Ritter, & Moore, 2003).

The role of opioid analgesics in chronic non-malignant pain relief

While the use of morphine and other strong opioids for control of severe pain in cancer is fully acknowledged and endorsed, their use for CNMP has been debatable, but is gaining acceptability in the management of chronic osteoarthritis (Caldwell et al., 2002; Ringe, 2003), fibromyalgia (Grahmann et al., 2004), chronic musculoskeletal pain (Dominick et al., 2004;
Khor, 2003), other nociceptive pains (Jadad, Carroll, Glynn, McQuay, & Moore, 1992), and neuropathic pain, particularly in peripheral pain syndromes (Rossi, 2004) and low back pain (Bartleson, 2002). The consumption of morphine and other opioids has significantly increased and currently accounts for 40-90% of CNMP cases (Clausen, 1997; Richards, 1995). In the US, opioid prescriptions doubled for chronic pain during 1980 to 2000 (Caudill-Slosberg, Schwartz, & Woloshin, 2004). In Australia, the use of Schedule 8 oral opioids has increased from 117 to 578 kg during the period 1986-1995. In New South Wales (NSW), the authority prescription of opioids for non-malignant pain have increased 73% during 1990-1996 (Bell, 1997). Moreover, the use and prevalence of narcotic analgesics are higher in patients suffering neurological or non-musculoskeletal conditions as the primary cause of pain (Kung et al., 2000).

The administration of opioid to patients with CNMP is reportedly associated with a 72.5% to 83% improvement in their condition (Cowan, Wilson-Barnett, Griffiths, & Allan, 2003b; Jamison, Anderson, Peeters-Asdourian, & Ferrante, 1994). Some chronic pain patients have achieved considerable benefits in terms of improved pain control, functional improvement and improved QoL (Ballantyne & Mao, 2003; Breivik, 2005; Maier, Hildebrandt, Klinger, Henrich-Eberl, & Lindena, 2002). A recent systematic review demonstrated that, in the majority of included studies, pain intensity decreased by at least 30% with opioids (Kalso et al., 2003). The benefit of long-term opioid treatment of chronic non-malignant pain, however, only applied to a minority of patients with 44% still on opioids after therapy for between 7 and 24 months (Kalso, Edwards, Moore, & McQuay, 2004).

Problems associated with using opioids
Although strong analgesics such as morphine sufficiently relieve pain, they might produce various adverse effects, such as constipation, nausea, sedation and micturition disturbance (Gourlay, 1999). Studies showed that 58% of the patients on morphine medication experienced moderate to severe adverse effects (Caldwell et al., 2002; Maier et al., 2002). Recently, a systematic review revealed a high rate of adverse events among people using opioids, with 80% of patients suffering from at least one adverse event (Kalso, Edwards et al., 2004).

A large number of patients requiring long-term opioids use may experience problems resulting from physical dependence and addiction (Adriaensen, Vissers, Noorduin, & Meert, 2003; Gourlay, 1999; Tedeschi, 2006). Opioid dependence may be associated with cognitive, behavioural, and physiological symptoms that cause individuals to continue opiate use despite significant physiological and psychological harm caused by the ingestion of the drugs. Dependence may lead to dose escalation. Physical dependence is defined by the development of withdrawal symptoms associated with a sudden decrease in opioid dose, abrupt termination of regular opioid use, or when an opioid antagonist is administered. It may play a considerable role in contributing to persistent pain and global dysfunction in some patients (Gourlay 1999). While tolerance and physical dependence are physical changes in the body, addiction is defined by aberrant changes in behaviour. It is a biopsychosocial disorder characterized by the compulsive use of a drug and the preoccupation with obtaining it, despite evidence that its continued use results in physical, emotional, social or economic harm (Savage et al., 2003). However, if there is no history of addiction in the past, addiction to opioid used to treat non-malignant pain is rare.
An increase in abuse of opioids is a growing problem in public health (Gilson, Ryan, Joranson, & Dahl, 2004). In Denmark opioid abuse is a major problem with 40% of those suffering CNMP considered “problematic opioid users”. Meanwhile, 3-19% of chronic pain patients are estimated to suffer from addictive disorders (Eriksen et al., 2003).

Problems of addiction create dilemmas in the prescription of opioids. A survey of physician’s attitudes toward using opioids for chronic pain revealed that 35% of physicians are never willing to prescribe schedule II opioids (eg, sustained-release morphine) for patients with CNMP (Potter et al., 2001, Feb.). Data from another survey highlight similar results in Canada, with 35% of GPs and 23% of primary care practitioners reporting they would not prescribe opioids for non-malignant pain patients even when pain was considered severe (Morley-Forster, Moulin, Clark, & Speechley, 2003). Concerns about physical dependence, tolerance, and addiction to opioids by patients and physicians are major barriers against their use.

Strategies of employing opioids should be used in order to appropriately manage CNMP (Kalso, McQuay, & Wiesenfeld-Hallin, 1999). Prescription of opioids for patients with chronic pain should be the last solution when other pharmacotherapy fails to produce benefit to the patients. Importantly, the balance between providing pain relief drugs and its potential adverse effects should be considered.

2.1.4.3 Adjuvant analgesics

Adjuvant analgesics are also used to treat chronic pain. These analgesics include antidepressants and anticonvulsants. They may be used alone or in combination with opioids.
Antidepressants include two main types of medication: Tricyclic antidepressants (TCAs) and serotonin-selective reuptake inhibitors (SSRI’s). TCAs are highly effective in neuropathic pain, such as peripheral neuropathy, which often responds poorly to opioids (Bryson & Wilde, 1996; Sindrup & Jensen, 1999). The mechanism of the action for TCAs remains unclear. They may act centrally by inhibiting noradrenalin reuptake at nerve endings and in the spinal cord, and through being a potent blocker of voltage-gated Na channels (Song, Ham, & Shin, 2000). The common drugs include clomipramine, imipramine and amitriptyline. Amitriptyline is one of the most effective antidepressants in pain conditions (Bryson & Wilde, 1996). The SSRI’s include sertraline, fluoxetine and fluvoxamine. These drugs have not demonstrated efficacy in treating persistent pain.

Antidepressants are also effective in lifting mood, improving the sleep quality and QoL and reducing chronic fibromyalgia pain (Arnold, Lu, & Crofford, 2004; O'Malley, Balden, & Tomkins, 2000). Moreover, Tomkins et al reported that these medications have beneficial effects in preventing chronic migraine and tension headache (Tomkins, Jackson, O'Malley, Balden, & Santoro, 2001). Antidepressant medications may cause some adverse effects, such as dry mouth, constipation, blurred vision and drowsiness, and may even affect concentration and judgment. Sexual dysfunction is another adverse effect caused by most antidepressants (Kalso, 2005). The dosages used to manage chronic pain are usually lower than that used to manage depression (McQuay, Carroll, & Glynn, 1992).

Anticonvulsant medications were initially used to manage epilepsy. Now it has been found that some types of chronic neuropathic pain, especially the pain manifested as lancinating or stabbing pain, respond beneficially to anticonvulsants. Blocking of the Na$^+$ channel is one of the mechanisms of anticonvulsant action (Kalso, 2005). Anticonvulsant drugs include
carbamazepine, gabapentin, pregabalin and clonazepam, which likely act on the spinal cord and brain to block messages caused by nerve injury or neuropathic pain. They can also improve mood. Carbamazepine is one of the effective anticonvulsants used to treat chronic pain (Johnson, 1997). The common side effects of these agents are mental and motor dysfunction, such as sedation. Clinically, a lower dosage is recommended for pain control than that used for seizure control.

Other pharmacologic management includes local anaesthetic agents, for instance, sympathetic nerve blocks, nerve blocks and neurolysis, which are employed for neuropathic pain. A systematic review demonstrated the efficacy of intravenous lidocaine in chronic pain (Kalso, Tramer, McQuay, & Moore, 1998).

2.1.5 Non-pharmacological treatment approaches

There are a wide range of non-pharmacological treatment approaches used for managing chronic pain. These therapies may not only reduce the pain, but also offer some other benefits, such as reducing depression, improving mood, changing negative thoughts, restoring functionality and promoting well-being. Many of these approaches can be used alone or combined with analgesics. The combination approach may improve pain relief by enhancing the effects of medications, thus lowering required dosages of the medications.

Non-pharmacological strategies include three major categories: physical therapies, cognitive behavioural therapies, and alternative and complementary therapies.

2.1.5.1 Physical therapies

Physical therapies (PTs) are a common part of pain management programmes. These therapies aim to reverse the effects of deconditioning, which contribute to and can confound
other chronic pain factors. In deconditioning syndrome, the “fear-avoidance” model plays an instrumental role. Pain-related fear of movement, tissue damage, or re-injury can lead to avoidance of movement or can increase the distress associated with specific movements. Deconditioning, disuse atrophy, and lower levels of fitness therefore can perpetuate in a cyclical fashion (Vlaeyen, De Jong, Onghena, Kerckhoffs-Hanssen, & Kole-Snijders, 2002; Vlaeyen & Linton, 2000).

PTs aim to reverse the effects of deconditioning by increasing activity, improving functional status, and reducing the pain causing the disability associated with pain. Then patients can decrease their medication intake, self manage pain and return to work (Harding & Watson, 2000).

PTs include exercise, transcutaneous electrical nerve stimulation (TENS), and relaxation. An appropriate exercise program specifically aims to build muscle strength, increase range of motion, improve balance, and raise pain tolerance. Exercise also makes people feel better and helps relieve some of the side effects seen with medications, for example, constipation. More recently, a summary of systematic review has shown that exercise is effective for patients with a wide range of chronic disorders, for example knee osteoarthritis and low back pain (Smidt, de Vet, Bouter, & Dekker, 2005).

TENS is a popular analgesic option. Its mechanism is unclear; but is probably best explained by the gate control theory, which activates large nerve fibres, inhibits local pain circuits and closes the gate to the entering pain message (Munden et al., 2003). It is believed to be an effective and safe therapy which can provide pain relief in some conditions, such as back pain, arthritis, neuropathic pain, surgical pain, migraine and headache (Hansson & Lundeberg, 1999). The effectiveness of TENS in chronic pain lacks evidence (McQuay, Moore,
Eccleston, Morley, & Williams, 1997) A recent systematic review also demonstrates that it is
difficult to provide useful evidence-based information with TENS for treating chronic pain
(Carroll et al., 2005).

In addition, training patients to use relaxation techniques may assist to control the pain by
reducing muscle tension, and develop a state of emotional calmness (Harding & Watson,
2000). Nevertheless, scientific evidence for the effectiveness of relaxation is lacking
(McQuay et al., 1997).

2.1.5.2 Cognitive behavioural therapies

Cognitive-behavioural therapy (CBT) consists of education, skills acquisition, cognitive and
behavioural rehearsal, and generalisation and maintenance. The goals of this intervention are
to teach patients to effectively manage their problems and provide them with strategies to
monitor the suffering component of pain and to reduce the impact of chronic pain on lifestyle
(Bradley 1996). CBT has been proved useful in a variety of patients with chronic problems,
for instance, low back pain, fibromyalgia and upper limb problems (Flor et al., 1992; Nielson,
Harth, & Bell, 1997; Spence, 1989; Williams, 2003).

CBT interventions for the treatment of chronic pain focus on reductions in pain perception
and pain behaviours. They also aim to reduce or cease the use of pain related medications and
the inappropriate use of health care services, improve physical function, change unhelpful
thinking and return to aspects of life previously restricted by their responses to pain (Nicholas,
2003). General treatment objectives of CBT pain management programs also include
empowering patients to become resourceful and able to problem solve their circumstances
(Bradley 1996), assisting patients to learn self-monitoring and to identify relationships
between cognitions, behaviours and environmental change.
There are numerous controlled studies evaluating CBT programs that have shown benefits in different age populations suffering from chronic pain (Cook, Cinciripini, & Floreen, 1998; Johansson et al., 1998). The patients obtained significant benefits in terms of reductions in analgesic medication use, changes in pain behaviour and improvements in physical functioning and employment status (Johansson et al., 1998; Skinner et al., 1990; Williams et al., 1993). A meta-analysis of 25 randomized controlled trails showed that CBT is very effective in achieving a range of improvements, such as, pain experience, mood/affect, cognitive coping and appraisal, and activity level (Stephen Morley, Eccleston, & Williams, 1999). Several studies have also demonstrated the efficacy of pain management programmes in improving patients’ QoL and well-being (Dysvik, Vinsnes, & Eikeland, 2004; LeFort, Gray-Donald, Rowat, & Jeans, 1998; Patrick, Altmaier, & Found, 2004).

Selections of patients to undergo a CBT program varies depending on the pain management service provided but have in common the following criteria: daily life is seriously affected due to pain, habitual overactivity leading to increased pain, using excessive medication, reducing or withdrawal from work due to pain, and related mood disturbance. Also, the patients must be motivated with a desire to achieve a degree of independence, and a desire to gain control of their lives; and they must not have any major personality or psychiatric disorder.

Given the fact that patients who are referred to pain clinics are already likely to be using opioid-like drugs, reducing the dose of opioid-like drugs to an acceptable and satisfactory level is a useful first strategy in the pain management for patients entering into a CBT programme.
Patients are becoming more willing to accept complementary and alternative therapy (CAT) in order to appropriately manage pain and health problems that do not respond to conventional treatments (Lewith & Machin, 1983; Snyder & Wieland, 2003; White, Resch, & Ernst, 1997). These therapies might have relatively less adverse effects in comparison with western medicines, and predominantly focus on balancing the whole body rather than symptomatic control. A recent survey indicated that 35% patients with chronic pain sought the use of alternative therapy which is higher than previously estimated (Haetzman, Elliott, Smith, Hannafor, & Chambers, 2003). In Australia, 21% of patients with chronic pain consulted an alternative practitioner for pain relief in the previous 6 months (Blyth et al., 2003). Higher rates of alternative medicine usage have been observed in Canada, with 39% of adults reporting use for chronic back pain (Foltz et al., 2005).

Amongst the most commonly used CAT, acupuncture is increasingly chosen by patients and physicians (Aanjesen et al., 2002). In Australia, most GPs accept acupuncture as a common medical practice and about 66%-90% of GPs who participated in two surveys referred their patients to acupuncture treatment at least once in the last one year (Easthope et al., 2000). Another earlier survey of 249 GPs shows that acupuncture is the second most commonly used CAT for chronic pain in Auckland after chiropractic therapy (Marshall et al., 1990), and a UK survey reported that 84% of responders used acupuncture as a treatment method for chronic pain in their pain clinic (Woollam & Jackson, 1998). Survey data from the US reveals that 69% of responders who are pain specialists use or refer their patients to acupuncturists.

Systematic reviews on acupuncture in pain treatment have demonstrated moderate to strong evidence of effectiveness, for dental pain (Ernst & Pittler, 1998), osteoarthritis (OA) pain
(Ezzo, 2001) and neck pain (White & Ernst, 1999). The Consensus Development Panel on Acupuncture of the NIH in the United State concluded that acupuncture is effective for various painful conditions, such as post-operative pain, dental pain, tennis elbow and fibromyalgia (NIH, 1998). A report to the NHMRC in 1989 also pointed out the potential role for acupuncture in Australian health practice. Acupuncture was considered to be useful and safe in producing analgesia for post-operative pain, obstetric pain and dental extraction pain (NHMRC, 1989). WHO commissioned a report in which 293 acupuncture controlled clinical trials were reviewed. Eighty-nine of them were related to pain. Acupuncture was recommended to treat headache, painful condition of the locomotor system, postoperative pain, and pain associated with dentistry and surgery (WHO, 2002).

The role of acupuncture in managing chronic pain, however, remains unclear. The results of one review paper and two systematic literature reviews on clinical trials show that the effect of acupuncture on chronic pain is inconclusive (Ezzo et al., 2000; Mendelson, 1977; ter Riet et al., 1990). Compared to sham, intramuscular, or placebo acupuncture, acupuncture produces improved analgesia. However, it is only occasionally more effective than non-treatment. The three review papers attribute the inconclusive results to poor research methods and small sample sizes employed in included trials.

Other forms of alternative and complementary approaches include relaxation therapy, biofeedback and chiropractic treatment. The main benefits that chiropractic treatment provides are to relieve musculoskeletal pain and disability, and adjust internal organ function. The theory of chiropractic treatment is to restore the free flow of neural impulses, and relieve symptoms by adjusting the spine with regular manipulation. Chiropractic treatment is commonly used for specific conditions, for example, headache, neck, shoulder, back pain and
spinal problems with visceral conditions (Jamison, 1995; Paramore, 1997). A systematic review has shown that chiropractic manipulation is not effective for other non-spinal pain conditions, such as fibromyalgia, dysmenorrhoea and chronic pelvic pain (Ernst, 2003).

### 2.2 Part Two - Neural mechanisms of electro-acupuncture analgesia

EA, developed in 1970s, has been widely studied for its pain relieving effects (Clement-Jones et al., 1980; Han, 1989; Tsui & Leung, 2002b). EA employs pulses of weak electrical current, which are delivered through acupuncture needles to acupoints in and under the skin. EA has been incorporated into studies mainly due to its convenience and ability to deliver stable and consistent stimulation. However, an increasing number of studies have demonstrated that EA may be a more effective means of pain relief than manual acupuncture (Saletu et al., 1975; Tsui & Leung, 2002a; Ulett, Han, & Han, 1998; White, 1999).

The current understanding of the neural mechanisms of EAA is largely based on neural mechanisms of endogenous pain control and EOPs (Han & Terenius, 1982). The following section will address the mechanisms of EAA in three steps. Firstly, the findings from decades of research into neural mechanisms are outlined; secondly, studies on EOPs and EA are summarised; and thirdly, the optimal parameters of EA are discussed.

#### 2.2.1 Neural mechanisms of electro-acupuncture analgesia

Three popular neurophysiologic theories have been proposed to explain EA analgesic mechanisms of action: gate control theory or segmental inhibition (Bekkering & Bussel, 1998; Melzack, 1984), diffuse noxious inhibitory controls (DNIC) (Le Bars, Dickenson, & Besson, 1979) and limbic systems attenuation (Campbell, 1999). A fourth theory, the involvement of EOPs, has also been identified (Han & Terenius, 1982).
The gate control theory states that pain signal conduction along the spinal cord may open or close depending on the nature of the incoming signal (Melzack, 1965). Activation of large myelinated afferent fibres (A-β) in the skin or muscles inhibits incoming pain signals transmitted by small afferent (C) fibres. As a result, pain signals are intercepted before they travel along the ascending pain pathway and register as pain in the brain. It has been hypothesised that EA impulses of high frequency may activate large myelinated afferent fibres (A-β) and prevent pain transmission similarly to TENS (Melzack, 1984). Currently no research has confirmed the association between EAA and A-β afferent fibre involvement.

Developed from gate control theory, segmental inhibition of acupuncture or EA (Bekkering & Bussel, 1998) implies that the interception of pain signals not only reduces pain at the spinal segment level, but can also alter subsequent actions taken by humans or animals following painful stimulation. For instance, the withdrawal reflex, local muscle contraction, and local ischemia, can be suppressed or ceased through acupuncture.

These observed actions of acupuncture are related to the segmental arrangement of the spinal neurons, where information from the skin, muscles, tendons, bones and viscera at the same segment converges on transmission interneurons. Inhibition of these neurons leads to a change of the action taken in response to pain, within the same nerve segment, dermatome, myotome, sclerotome or viscerotome.

EAA can only be partly explained by gate control theory. According to the theory, only concurrent stimulation of A-β fibres and C fibres can intercept painful information from C fibres, and this effect is only brief (lasting a few minutes) (Melzack & Wall, 1996a). This may explain why EA appears to have an immediate effect on the local stimulation area, but fails to
explain why EA often produces analgesia in remote parts of the body, and pain relief which may last up to a few days.

2.2.1.2 Diffuse noxious inhibitory control

Experiments in rats have demonstrated that noxious inputs from one part of the body can inhibit the activity of dorsal horn neurons that lay distant from the stimulated segment. Because such effects are not somatotopically organised, but do concern the whole body, they have been called DNIC. DNIC is the underlying mechanism of the counter-irritation phenomenon, which means that pain in one part of the body inhibits pain responses in another part of the body (Le Bars & Dickenson, 1979). DNIC has been demonstrated in healthy humans by submerging the left hand in the hot water at 47°C which is above pain level. This reduced the participants subjective pain rating and withdrawal reflexes induced by electrical stimulation (ES) to the right ankle (Willer, Roby, & Le Bars, 1984). Interestingly, water temperature appeared to be inversely correlated with subjective degree of pain response and suppression of withdrawal reflexes, in response to electrical stimulation.

Analgesia from DNIC is often short-lasting for a few minutes, widely spread in the body, and is induced by very strong pain stimulation. DNIC may explain why EA produces wide spread analgesia (Zaslawski, Cobbin, Lidums, & Petocz, 2003) and improvement in pain reduction with stronger EA stimulation (Wang et al., 1997). However, it does not explain prolonged analgesic effects in response to EA.

2.2.1.3 Limbic system attenuation

Another proposed analgesic mechanism for AA is the modulation of the hypothalamic-limbic system. The limbic system theory may be derived from the feelings of calm and relaxation
often experienced by patients and healthy humans volunteers during and following acupuncture treatment (Campbell, 1999).

Functional magnetic resonance imaging (fMRI) studies have indicated acupuncture regulates the limbic system. Using fMRI, investigators observed needling LI4 (Hegu) and ST36 (Zusanli) with Deqi sensation effectively deactivated the limbic system, and no such effects were attained with shallow needling of non acupoints (Wu, Hsieh, & Xiong, 1999). Similar results have been demonstrated in other fMRI studies in animals (Chiu & Chung, 2003) and healthy human subjects (Hui et al., 2000; Wu et al., 2002). A recent study supports the hypothesis that the limbic system is central to acupuncture effect regardless of specific acupuncture modality (Napadow et al., 2005).

Chronic pain patients appear to have a highly active limbic system that might be related to greater levels of depression and anxiety experienced by these patients (Apkarian, Thomas, Krauss, & Szeverenyi, 2001). The deactivation effect of acupuncture on the limbic system could contribute to the feeling of enhanced wellbeing in chronic pain patients who have received acupuncture (Paterson & Britten, 2003).

2.2.2 Endogenous opioid peptides and electro-acupuncture analgesia

Studies have demonstrated that both manual acupuncture (Mayer, Price, & Rafii, 1977a) and EA (Cheng & Pomeranz, 1979) mediated-analgesia is modulated through a central mechanism involving the release of EOPs (Han & Terenius, 1982). The present review will briefly discuss acupuncture analgesia (AA) and EOPs from the following aspects: naloxone blockade of AA; the common brain regions involved in morphine analgesia and AA; and release of various EOPs by EA of different frequencies.
2.2.2.1 Naloxone blockade of acupuncture analgesia

The initial evidence suggesting the involvement of EOPs in AA was that naloxone, an opioid receptor antagonist, blocked AA in mice and humans (Mayer, Price, & Rafii, 1977b; Pomeranz & Chiu, 1976). Pomeranz and Chiu performed an experimental study in mice divided into one of the following groups: EA alone, EA plus saline, EA plus naloxone, sham EA at a non-acupoint, naloxone alone, saline alone, and no treatment at all. EA was applied at (an anatomically equivalent point to) LI4 (Hegu). Latency to mouse squeak onset induced by radiant heat was measured as pain threshold. Naloxone, but not saline, was observed to completely block AA. Naloxone alone did not cause analgesia but induced hyperalgesia instead. The results indicated that EAA was likely to be mediated by endorphins in mice and not due to psychological effects (Pomeranz & Chiu, 1976).

Similar results have been noted in a human experiment. Mayer et al. (1977) studied AA on acute laboratory-induced tooth pain in healthy human volunteers. Needling stimulation of LI4 (Hegu) increased the pain threshold measured by ES of dental pulp by an average 27%. The subjects were then injected either naloxone or saline. The results showed that pain threshold was reversed by naloxone injection, but not by saline injection (Mayer et al., 1977b). In contrast, a double blind study conducted by Chapman et al., subjects demonstrating AA during low frequency EA on LI4 received either 1.2 mg naloxone or saline injection. Pain thresholds elevated by EA failed to reverse following administration of naloxone (Chapman, Benedetti, Colpitts, & Gerlach, 1983).

Further studies revealed that naloxone (1 mg/kg) could block analgesia induced by EA at 4 Hz but not by 200 Hz. Cheng and Pomeranz suggested that analgesia induced by low frequency EA is associated with endorphins, whereas analgesia induced by high frequency EA may
occur through non-opioid mechanisms (Cheng & Pomeranz, 1979). In contrast, Han et al. found that analgesia induced with 100 Hz EA was naloxone reversible only with a much higher dosage than that used to block EA induced analgesia at 2 Hz (Han, Ding, & Fan, 1986). These results suggest that the effect of high-frequency EA might also be mediated by EOPs, which is unlikely to be affiliated to mu receptors (Huang, Wang, Han, & Wan, 2002).

2.2.2.2 Similar brain regions involved in morphine and acupuncture analgesia

Previous findings suggest that EA and morphine analgesia share the same or similar mechanisms (Han 1981). Zhou et al. demonstrated that the effect of AA was significantly attenuated when naloxone was microinjected into the nucleus accumbens, amygdala, habenula and periaqueductal grey matter (PAG) of the rabbit but little anti-analgesia effect following injection into other brain regions. Administration of morphine to the same four regions also produced significant analgesia (Zhou, Du, Wu, Jiang, & Han, 1981) suggesting that brain regions involved in morphine analgesia are also involved in AA. Damage of these sites reduced both morphine and AA.

EA release EOPs to produce an analgesic effect. However, repeated application of EA stimulation at short intervals can cause tolerance and dependence similar to observations for morphine (Ren & Han, 1979). This phenomenon has been demonstrated in other studies. A parallel experiment was performed in rats which received either EA or morphine. Rats were given EA at 2-15 Hz for 30 mins at repeated 30 minute intervals. A gradual decline in analgesia was observed. After the sixth EA stimulation, the analgesic effect of EA was only 24% of the original value, whereas, the effect of morphine analgesia was 39% of the original value. The results demonstrated that similar mechanisms underlie acupuncture and morphine tolerance (Han, Li, & Tang, 1981).
It has been considered that subjects responding poorly to EA may genetically lack opioid receptors (Peets & Pomeranz, 1978). The incidence of non-responders in rats accounts for approximately 15%-20% of the experimental animals. Takeshige et al. observed that 40% of rats were poor responders to AA due to a deficiency in total brain endorphins measured by a receptor binding assay (Takeshige, Kamada, Oka, & Hisamitsu, 1978). It has been suggested that endogenous opioids can be released by both EA and morphine. The decreased ability to release opioids and an increased capability of releasing endogenous antagonists to opioids might be the mechanisms underlying the non-responsiveness to EA and morphine (Han, 1989).

2.2.2.3 Release of opioid peptides in the central nervous system induced by electro-acupuncture of different frequencies

Antibody microinjection and radioimmunoassay of spinal perfusate techniques were used to study the types of opioid peptides associated with EAA. The neuropeptides recognised by the antibody injected are selectively inactivated, whereas other peptides are intact and act on the receptors (Han, 1984). Using this technique, a series of studies were performed. Collectively it appears the effect of AA is blocked by enkephalin antibodies at both the spinal cord and PAG; by β-endorphin antibodies at the PAG; dynorphin antibodies following injection into subarachnoid space, and not in the PAG (Han, 1989).

Furthermore, using the same technique, other studies explored whether analgesia induced by 2 and 100 Hz are mediated differentially in the spinal cord by enkephalin and dynorphin, respectively. Rats administered intrathecal injection of enkephalin antiserum resulted in a significant decrease in analgesia induced with 2 Hz stimulation. Rats similarly administered dynorphin antiserum produced an equally remarkable decrease in analgesia induced with 128
Hz EA but did not abolish analgesia induced by EA at 4 Hz (Han, 1993). Furthermore, injection of β-endorphin antiserum into rat PAG resulted in significantly decreased analgesia induced with 2 Hz EA when compared with 15 Hz, and the injection failed to block the analgesic effect of 100 Hz EA (He & Han, 1990). Injection of endomorphins antiserum into the cerebral ventricle of mice (Huang, Wang, Chang, & Han, 2000) and the spine of rats (Zhou Han et al., 1999) dose-dependently reduced the analgesic effect produced by 2 Hz, but not 100 Hz. Taken together, the type of EOPs release depends on the frequency of EA. It seems that EA at 100 Hz stimulates the release of dynorphin in the spine, whereas EA at 2 Hz and 15 Hz stimulates the release of β-endorphin and dynorphin.

Studies utilising radioimmunoassay further confirmed the EA frequency-dependent EOPs release. It was found that 2 Hz EA significantly increased the release of the immunoreactive-Met5-enkephalin whereas 100 Hz EA increased the release of dynorphins (Fei, Xie, & Han, 1987).

Frequency-dependent opioid release initially observed in animal models has also been confirmed in humans. Transcutaneous acupuncture electrical stimulation (TAES) was given to 37 patients at LI4 and ST36 with either 2 or 100 Hz for 30 minute. Met-enkephalin-Arg-Phe (MEAP) in the cerebrospinal fluid (CSF) was significantly increased upon 2 Hz EA, and dynorphin A (Dyn A) was increased at 100 Hz EA (Han et al., 1991; Ho & Wen, 1989), also showed that following EA at a frequency of 2-3 Hz, no significant change of dynorphin immunoreactivity in the CSF was detected compared with before EA (Ho & Wen, 1989).

Rats made tolerant to 2/15 Hz were still reactive to a frequency of 100 Hz, and vice versa. This phenomenon further proves that EA at different frequencies produces analgesia via different pathways. EAA at 2 Hz is mediated by μ/δ-receptors, 100 Hz-EAA by κ-receptor,
and 2/100 Hz-EAA by combined action on all of three receptors in the CNS (Chen et al., 1992; Han, 2003). All three kinds of EOPs, β-endorphin, met-enkephalin, and dynorphin could be fully released to maximise the analgesic effect when using alternate 2/100 Hz (Chen, Guo, Chang, & Han, 1994; Chen & Han, 1992; Han et al., 1999). Table 5 summarises the EA frequency, the types of EOPs and opioid receptors.

Table 5: Summary of EOPs upon EA

<table>
<thead>
<tr>
<th>Types of EOPs</th>
<th>EA frequency</th>
<th>Types of opioid receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enkephalin</td>
<td>2 Hz</td>
<td>µ,δ; can be blocked by naloxone</td>
</tr>
<tr>
<td>Dynorphins</td>
<td>100 Hz</td>
<td>κ; relatively resistant to naloxone</td>
</tr>
<tr>
<td>β-Endorphin</td>
<td>2 and 15 Hz</td>
<td>µ,δ, κ; can be blocked by naloxone</td>
</tr>
</tbody>
</table>

A recent study demonstrated that peripheral release of opioids also plays a role in AA. Using a rat model of unilateral inflammatory hyperalgesia, pain behavioural changes were measured by paw withdrawal latency (PWL) to a noxious thermal stimulation. The results showed that rats receiving EA produced a significantly longer PWL, lasting up to three hours following EA treatment, compared with the non-EA controls. The analgesic effect was blocked totally by naloxone administrated at the inflammatory site 30 mins following EA treatment. The results suggested that EA might have induced peripheral EOPs release and activates peripheral opioid receptors (Zhang, Yu, Lee, & Lao, 2005).

2.2.3 Optimal parameters of electro-acupuncture for analgesia

In general, the parameters of EA include frequency, intensity, size of electrodes, pulse duration and depth of stimulation. So far, there is no common understanding of optimal parameters for the best possible analgesia. In a recent review, Zheng concluded that the ideal parameter of EA may vary according to the condition of the patient. Alternating frequency with strong but tolerable intensity of stimulation is recommended. EA with needles applied at
traditional acupoints may offer extra analgesic (Zheng, 2001). This section summarises recent evidence from animal studies and aims to gain further understanding of the ideal parameters of EA.

As discussed previously, the frequency of EA seems to play an important role in the releases of EOPs. On the basis of experimental data, to obtain the maximal release of central opioid peptides, an alternate frequency between 2/15 or 2/100 Hz may be the ideal to produce EAA and minimise tolerance (Han, 2003). Evidence from clinical trials currently is not consistent with this conclusion and details will be discussed in the Part three of this chapter.

Intensity of ES is another factor determining the effectiveness of EA. In one experiment, anaesthetised rats were given EA on the hind limbs at intensity of 1, 10 and 20 times the threshold of muscle contraction. The radian heat-induced latency of the tail withdrawal reflex was measured as pain threshold. EA at 20 times threshold increased the latency by 74% for more than 75 minutes after the treatment; EA at 10 times threshold increased the latency by 50% for 10 minutes, whereas EA at the threshold intensity had no effect. The results suggested that the powerful and persistent antinociceptive effect was elicited by high-intensity (Romita, Suk, & Henry, 1997). Furthermore, a recent study of EA on persistent hyperalgesia and Fos protein expression in rats supported the above finding. It was found that most anti-hyperalgesia was induced by ES at 3 mA when compared to EA 1 mA and 2 mA (Lao et al., 2004).

The depth of stimulation comprises another important factor. One study investigated the effects of EA on pain threshold in various tissues in healthy humans. The EA consisted of both insulated and non-insulated acupuncture needles. Non-insulated needles induced a significantly increased pain threshold in the skin, fascia and muscles, whereas insulated
needle induced analgesia only in the muscles and periosteum. The results indicated that insulated needles could produce an analgesic effect at a deeper level compared with uninsulated needles. It therefore suggests that the depth of stimulation might play an important role in the depth of analgesic effects (Ishimaru, Kawakita, & Sakita, 1995).

The effect of the duration of the pulse has yet to be clearly evaluated and there remains no agreement on an appropriate EA pulse width for AA. A range of pulse widths have been used, varying from 0.1 to 5 ms (Huang et al., 2000; Cheng Huang et al., 2002; Ishimaru et al., 1995; Koo, Park, Lim, Chung, & Chung, 2002; Romita et al., 1997). One previous study showed that with a pulse duration of 0.2 ms at 10 times threshold, a brief analgesic response was produced but the persistent response was markedly attenuated; whereas ES with a pulse width of 5 ms or 2 ms produced persistent responses (Romita et al., 1997). A more recent study showed within a given period of time and at a frequency of 10 Hz EA, short term anti-hyperalgesia was induced with 2 ms /10 Hz EA stimulation, which was similar to that induced with 0.1 ms/ 100 Hz. It appears that effects produced by increased pulse width is the same as by increased frequency, as the amount of stimulation to acupoint was increased by either pulse width or frequency within a given time unit (Lao et al., 2004).

The ideal duration of EA stimulation has been suggested to be 30 minutes, which is the induction period necessary for the full development of AA in humans (Research Group of Acupuncture Anesthesia, 1973).

Taken together, it is clear that optimal parameters of EA for pain control are ES with an alternate frequency at 2/100 Hz with high intensity. The depth of stimulation is likely to be associated with the depth of analgesia produced. Results from clinical acupuncture research will be useful for understanding ES parameters and their effects on pain.
2.3 Part Three - A critical review of randomised controlled trials of electro-acupuncture on consumption of opioid like medication in pain patients

2.3.1 Aims

The aims of this review were to investigate whether EA can reduce the consumption of OLM, OLM related-side effects, and pain in pain patients, and to identify the ideal electrical parameters of EA for this function.

2.3.2 Methodology

2.3.2.1 Search strategies

RCTs for EA in pain conditions were searched through commonly used health databases including Pubmed, the Cochrane Library and EMBASE (all from their inception to February 2005). A combination of the following keywords was used for the search: electro-acupuncture, electroacupuncture, TENS, transcutaneous acupuncture electrical stimulation (TAES), electrical stimulation (ES), opioids, analgesia, morphine, acute pain and chronic pain. The search was limited to clinical trials and English language papers. No time limit was placed on the search.

2.3.2.2 Selection criteria

Inclusion criteria

To be included, a study had to fulfil the following criteria:

- English language;
randomised controlled clinical trials;
study population was patients with acute or chronic pain;
the study intervention had ES via acupuncture needle or surface electrodes on
classified acupoints;
parameters of ES were reported; and
outcome measures included the dosage of OLM, or the reduction of OLM
consumption;

Exclusion criteria

• TENS used on non-acupoints, or
• Trials in which participants were morphine addicts

2.3.2.3 Methods of the review

Data extraction

Each eligible study was reviewed and the following information extracted: author, publication
year, condition, sample size, intervention, parameters of EA, duration of treatment, acupoints
used, acupoints stimulated with EA, methods of sham EA, control intervention, pain intensity
or reduction, OLM consumption and related side effects. Where reduction of pain or OLM
consumption was measured in different time periods in included studies data was obtained
from total recovery period.

Quality assessment

The quality of reports/methodological quality of included trials was assessed using the Jadad
scale (Jadad et al., 1996; Melchart et al., 2001). The scale includes items on:
• random allocation (1 point if allocation was described as randomised + 1 point if an appropriate method to generate the random sequence was described)
• double-blinding (1 point if there was a statement that patients and evaluators were blinded + 1 point when the blinding method was described and appropriate)
• reporting of withdrawals / dropouts (1 point if dropouts and withdrawals, as well as the reasons, were listed independently for each treatment group)

The total score was obtained by adding the scores for each item together. The maximum score is 5. Studies scoring 3 or more points were considered high quality.

**Outcome assessment**

For assessing effectiveness of EA on the consumption of OLM, related side effects and pain, the results were classified the following three categories:

- positive when the consumption of OLM, related side effects, and pain in the real acupuncture treatment group were significantly less than that of the control group;
- neutral when there were no significant difference between the groups;
- negative when these variables in the REA group were significantly higher than the control group. A $P$-value less than 0.05 was considered as significant.

The level of evidence (LOE) of single RCTs was assessed by using the Oxford Level of Evidence grading. When the Jadad score of a clinical trial was equal or more than three, it was considered as high quality, and 1b was assigned. If the score was less than three points, then the LOE was assigned 2b (Centre for Evidence-based Medicine, 2001).
Evidence evaluation

A best evidence synthesis method was used to evaluate the overall effectiveness of EA on reducing the consumption of OLM, related side effects and pain intensity. There are four levels of evidence (van Tulder, Cherkin, Berman, Lao, & Koes, 1999):

- strong evidence - multiple, relevant, high-quality RCT with generally consistent results
- moderated evidence - one relevant, high-quality RCT and one or more relevant, low quality RCT with generally consistent results
- limited evidence - multiple relevant on low quality RCT with generally consistent results
- Inconclusive evidence - only one relevant, low-quality RCT, no relevant RCT or RCT with conflicting findings

2.3.3 Results

2.3.3.1 Literature search results and study population

In total, 25 studies were identified from 1966 - 2005. Key data from the remaining 11 studies are summarised in (Table 6). All of them examined EA in the management of various acute pain and sub-acute pain syndromes, including pain during surgery, such as oocyte aspiration, lower abdominal surgery, hysterectomy, hemorrhoidectomy, colonoscopy, gynaecologic surgery and postoperative pain. No studies examining EA on the consumption of OLM in patients with chronic pain were identified.

Fourteen studies were excluded from this review. Detailed reasons for exclusion are listed in Table 7. Of these, four studies did report the use of analgesics but did not report the type of
analgesic or no OLM consumption was measured, or no ES was delivered. These studies were excluded. 10 studies on chronic pain were also excluded because they did not measure OLM consumption.
<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>Sample size, Intervention</th>
<th>Parameters of EA described</th>
<th>Acupoints used</th>
<th>Acupoints stimulated with EA and Duration of stimulation</th>
<th>Methods of Sham EA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gejervall, et al. 2005</td>
<td>During oocyte aspiration</td>
<td>N=160; EA + PCB vs. CA + PCB</td>
<td>Square-wave pulses with alternating polarity. 2 and 80 Hz. Intensity was high enough to induce strong paraesthesia or muscles contraction</td>
<td>KI11, ST29, LI10, LI 4, ST36, GV20</td>
<td>LI4, LI10, ST29 and KI11; 30-45 min before oocyte aspiration</td>
<td>N/A</td>
</tr>
<tr>
<td>Humaidan et al., 2004</td>
<td>During oocyte retrieval</td>
<td>N= 200; EA+ PCB vs. CA+PCB</td>
<td>20 Hz at a continuous pulses duration of 0,5 ms. Intensity was high under pain threshold.</td>
<td>LI4 (bil), SP6 (bil), GV20, 2 points in the low abdomen</td>
<td>LI4 (bil); a few minutes prior to OPU</td>
<td>N/A</td>
</tr>
<tr>
<td>Stener-Victorin, et al., 2003</td>
<td>During oocyte aspiration</td>
<td>N=268; EA+ PCB vs. Alfentanil nil +PCB</td>
<td>continuous square-wave pulses of alternating polarity with a 2 and 80 Hz; intensity was strong to induce paraesthesia or muscles contractions</td>
<td>GV20, ST29 (bil), TE5 and LI4 (bil), ST36 (bil)</td>
<td>80 Hz at ST29, 2 Hz at TE5 and LI4; 30 min before OPU</td>
<td>N/A</td>
</tr>
<tr>
<td>Lin, et al., 2002</td>
<td>After Lower abdominal surgery</td>
<td>N=100; No EA control vs. sham-EA vs. LF-EA vs. HF-EA</td>
<td>2 Hz or 100 Hz at constant current of 0.5 mA, 1ms square pulse tolerable intensity</td>
<td>ST36</td>
<td>ST36; 20 min pre-operation</td>
<td>Needle insertion with the indicator light on but with no actual current</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>N</td>
<td>Condition</td>
<td>Frequency</td>
<td>Efficacy</td>
<td>Needle/ES description</td>
</tr>
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</tr>
<tr>
<td>Sim et al., 2002</td>
<td>Post Gynecologic lower abdominal surgery</td>
<td>90</td>
<td>Control group (placebo EA for 45 min before induction of GA) vs. preoperative EA vs. postoperative EA</td>
<td>2 Hz, 100 Hz</td>
<td>ST36 (bil), PC6 (bil)</td>
<td>2 Hz at ST36 and PC6, 100 Hz at the skin incision; 45 minutes of EA before induction of GA; 45 minutes of EA on arrival to the recovery area</td>
</tr>
<tr>
<td>Chen, et al., 1998</td>
<td>Abdominal hysterectomy or myomectomy procedures</td>
<td>100</td>
<td>Sham-TENS vs. Nonacupoint-TENS at the shoulder vs. TENS at the level of the surgical incision vs. acupoint-TENS</td>
<td>DD model, alternating 2 and 100 Hz every 3s, Intensity was tolerable.</td>
<td>ST36</td>
<td>ST36, started in the PACU and continued using 30 min every 2 h until pain was controlled with oral analgesic medication.</td>
</tr>
<tr>
<td>Wang, et al., 1997</td>
<td>Undergo elective lower abdominal surgery</td>
<td>101</td>
<td>Sham TASE vs. Low intensity TASE vs. High intensity TASE</td>
<td>DD mode, alternating 2 and 100 Hz every 3s, Intensity was low at 4-5 mA and high at 9-12 mA depending on the treatment group</td>
<td>L14</td>
<td>Two at the LI 4 and the opposite of the ST 36; the other two were at either side of the skin surgical incision; started in the PACU and continued 30 min every 2 h until pain was controlled with oral analgesic medication.</td>
</tr>
<tr>
<td>Christensen et al., 1993</td>
<td>Before and during Hysterectomy surgery</td>
<td>50</td>
<td>PCA + EA vs. PCA</td>
<td>Constant current, pulse width 320 ms, 12V, chain freq.10 and 100 Hz</td>
<td>GV2, GV4, BL32 (bil), SP6 (bil), ST36</td>
<td>GV2, GV4, BL32 (bil), SP6 (bil), ST36; 20 min before incision and throughout the operation</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Outcome 1</td>
<td>Outcome 2</td>
<td></td>
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</tr>
<tr>
<td>Christensen, et al., 1989</td>
<td>Postoperative pain (Lower abdominal surgery)</td>
<td>N=20</td>
<td>PCA + EA vs. PCA</td>
<td>Constant current, pulse width 320 µs, 12V, chain freq. 10 and 100 Hz</td>
<td>GV2, GV4, BL32(bil), SP6 (bil)</td>
<td></td>
</tr>
<tr>
<td>Kho, Eijk, Kapteijns, &amp; van Egmond, 1991</td>
<td>During surgery for retroperitoneal lymph node dissection</td>
<td>N=29</td>
<td>CATA vs. MFA</td>
<td>10 Hz, 40 mA, 0.5% pulse width and 40 volts, WQ-6F (10Hz up to 20 mA, and a 0.7msec pulse width)</td>
<td>BL14, BL17, BL19 and BL23</td>
<td></td>
</tr>
<tr>
<td>Chiu et al., 1999</td>
<td>Undergoing hemorrhoidectomy</td>
<td>N=60</td>
<td>TENS + PCA at the acupoints vs. TENS + PCA at non acupoints</td>
<td>Alternating 2 and 100 Hz, 300µ sec pulse, 20-30 mA, The intensity was adjusted until rhythmic flexion of thumb and index finger</td>
<td>LI4, LU7</td>
<td></td>
</tr>
</tbody>
</table>

Note: EA, electro-acupuncture; CA, conventional analgesia; DD: Dense-and-Disperse; ES: electrical stimulation; PCB, paracervical block; HF, high frequency; LF, Low frequency; bil, bilateral; OPU, ovum pick-up; GA, general anaesthesia; CATA, combined acupuncture and stimulation analgesia; MFA, moderate-dose fentanyl; TENS, transcutaneous electrical nerve stimulation; PCA, patient-controlled analgesia; freq., frequency; GA, general analgesia; PACU, postanesthetic care unit
<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>Sample size, Intervention</th>
<th>Measures</th>
<th>Results</th>
<th>Reasons for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanti, et al., 2003</td>
<td>Colonoscopy</td>
<td>N=30; EA vs. sham vs. no acup.</td>
<td>Demand for sedative drugs, pain, discomfort, anxiety</td>
<td>Pain level and dose of additional midazolam boluses requirement were sig. lower in the EA group.</td>
<td>Consumption of OLM was not measured.</td>
</tr>
<tr>
<td>Meng, et al., 2003</td>
<td>CLBP</td>
<td>N=55; EA+ medication vs. medication alone</td>
<td>Roland score</td>
<td>EA had a sig. decrease in modified Roland score at week 6; No group difference in medications changes.</td>
<td>Medications were NSAIDs, non-narcotic analgesics, and muscle relaxants</td>
</tr>
<tr>
<td>Zhu, et al., 2002</td>
<td>CNP</td>
<td>N=29; EA. vs. sham EA</td>
<td>Pain, analgesic medication count</td>
<td>No group difference in reducing pain intensity and pain pill count.</td>
<td>Types of analgesic was not reported</td>
</tr>
<tr>
<td>Ekblom, et al., 1991</td>
<td>operative removal of impacted mandibular third molars</td>
<td>N=110; Preoperative-acup. vs post operative-acup. Vs. No acup.control</td>
<td>Intraoperative, postoperative pain intensity and consumption of analgesics</td>
<td>Intraoperative pain intensity higher in the preoperative acup. than the no acup. control and experienced higher pain intensity immediately postoperatively compared with postoperative-acup. and non acup. control. Consumption of analgesics was higher in preoperative acup. compared with the non acup. control.</td>
<td>No ES was applied</td>
</tr>
<tr>
<td>Tsukayama, et al., 2002</td>
<td>Low back pain</td>
<td>N=20; EA vs TENS</td>
<td>Pain relief scale, LBP score</td>
<td>Reduction in pain relief was greater in EA than TENS.</td>
<td>OLM was not measured</td>
</tr>
<tr>
<td>Carlsson and Sjolund 2001</td>
<td>CLBP</td>
<td>N=55; Acup. vs. EA vs. mock-EA</td>
<td>Pain intensity, analgesic intake, quality of sleep and activity level</td>
<td>There was a sig. improvement of quality of sleep, reduction of analgesics intake in EA from a mean of 29.6 to 11 tables/person/wk, 32.3 to 31.8 in placebo group.</td>
<td>Types of analgesic was not reported</td>
</tr>
<tr>
<td>Stener-Victorin, et al., 1999</td>
<td>During oocyte aspiration</td>
<td>N=150; EA+ PCB vs. Alfentanil +PCB</td>
<td>Pain, anaesthesia, discomfort</td>
<td>No significant group difference in terms of pain related to operation, adequacy of anaesthesia during operation and nausea. The EA group experienced sig. longer discomfort than alfentanil group during oocyte aspiration</td>
<td>Types of analgesic was not reported</td>
</tr>
<tr>
<td>Study</td>
<td>Condition</td>
<td>Sample Size</td>
<td>Intervention</td>
<td>Outcome Measures</td>
<td>Findings</td>
</tr>
<tr>
<td>------------------------</td>
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<td>----------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wang, et al., 1997</td>
<td>Colonoscopy</td>
<td>N=99; EA vs. CMA</td>
<td>Pain tolerance score, side effects</td>
<td>Analgesic efficacy of both groups were the same but with less side effects such as nausea, vomiting and dizziness in the EA group</td>
<td>Consumption of OLM was not measured.</td>
</tr>
<tr>
<td>Thomas and Lundberg, 1994</td>
<td>CLBP</td>
<td>N=40; Acup. vs. LF-EA vs. HF EA</td>
<td>Activities of daily life, pain</td>
<td>Long term improvement in LF &amp; HF than controlled group, both after treatment and follow up</td>
<td>Consumption of OLM was not measured.</td>
</tr>
<tr>
<td>Deluze, et al., 1992</td>
<td>Fibromyalgia</td>
<td>N=70; EA vs. sham EA</td>
<td>Pain threshold, number of analgesic tablets used, regional pain score, VAS</td>
<td>7/8 outcome measures improved in EA group whereas none were in sham group. Pain threshold improved by 70% in the EA group. Number of analgesic tablets was reduced in the EA group than Sham EA.</td>
<td>Types of analgesic was not reported</td>
</tr>
<tr>
<td>Eriksson, Lundeberg et al., 1991</td>
<td>OA</td>
<td>N=32; EA; EA in patients pretreated with naloxone</td>
<td>affective and sensory of pain</td>
<td>EA significantly reduce of pain on the affective than sensory; Pain reduction was not significant after pretreatment with naloxone or diazepam.</td>
<td>No control group, experiments</td>
</tr>
<tr>
<td>Lundeberg et al., 1991</td>
<td>OA</td>
<td>N=58; LF-EA vs. HF-EA vs. Acup. vs. sham Acup.</td>
<td>Pain intensity and unpleasantness</td>
<td>All groups produced significant pain reduction on the affective than sensory.</td>
<td>OLM was not measured.</td>
</tr>
<tr>
<td>Ng, Leung &amp; Poon, 2003</td>
<td>OA</td>
<td>N=24; LF EA vs. LF TENS vs. no treatment control</td>
<td>Pain and TUGT</td>
<td>There was sig. reduction of knee pain in both EA and TENS groups; TUGT score of EA group was sig. lower that that of the control group.</td>
<td>OLM was not measured.</td>
</tr>
<tr>
<td>Allais, et al., 2002</td>
<td>Migraine</td>
<td>N=160; Acup. vs. CT</td>
<td>Pain, analgesic intake</td>
<td>The number of analgesic intake was sig. in acup. group than CT group during the treatment.</td>
<td>No ES was applied; Types of analgesic was not reported</td>
</tr>
</tbody>
</table>

Note: Acup., Acupuncture; EA, electro-acupuncture; sig., significantly; LBP, lower back pain; NSAIDs, non-steroidal anti-inflammatory drugs; CLBP, chronic lower back pain; OA, osteoarthritis; CNP, chronic neck pain; CMA, conventional meperidine analgesic; HF, high frequency; LF, Low frequency; sig., significant; TENS, transcutaneous electrical nerve stimulation; TUGT, Timed Up-and-Go Test score; CT, conventional therapy; ES, electrical stimulation.
2.3.3.2 Study interventions

EA was applied in nine studies while TENS was used in two (Chen et al., 1998; Chiu et al., 1999). EA was given as a combination method with conversational analgesia in six studies (Christensen, Noreng, Andersen, & Nielsen, 1989; Christensen et al., 1993; Gejervall et al., 2005; Humaidan et al., 2004; Kho, Eijk, Kapteijns, & van Egmond, 1991; Stener-Victorin et al., 2003). Another five studies used sham/placebo acupuncture-controlled (Chen et al., 1998; Chiu et al., 1999; Lin et al., 2002; Sim et al., 2002; Wang et al., 1997). These sham/control groups used non-functional EA devices with no electrical current or non-insertion of needles or at non-acupoints.

2.3.3.3 EA Parameters

Apart from EA intensity, which was adjusted below pain threshold to induce non-painful local muscle contraction, other EA parameters including frequency, duration, shape and width of pulses, acupoints stimulated, and the use of needles or surface electrodes varied widely.

Different frequencies of EA were employed, including fixed frequency at 2 & 80 Hz, 10&100 Hz, 20 Hz and 10 Hz respectively; or alternating frequencies between 2 & 100 Hz; or 2 & 100 Hz at the same time on different points and 2 Hz or 100 Hz in different groups (Table 6).

Duration of EA stimulation was another key parameter. The total duration of EA stimulation varied from a few minutes prior to surgical operation, 20-45 minutes before surgery, or stimulation throughout the whole operation (Humaidan et al., 2004; Lin et al., 2002; Sim et al., 2002); to 45 minutes after surgery (Sim et al., 2002).

There are three patterns observed in the selection of acupoints. In most cases, either LI4 or ST36 or both were used. In addition, some studies also applied stimulation at the local
incision area (Chen et al., 1998; Sim et al., 2002; Wang, Chang, Liu, & Ho, 1997). Some others selected classic acupoints based on meridian theory. For example, SP6 was used in two occasions (Christensen et al., 1989; Christensen et al., 1993) for lower abdominal surgery; and GV 20 or PC6 was selected to calm the patients (Gejervall et al., 2005; Humaidan et al., 2004; Sim et al., 2002; Stener-Victorin et al., 2003) (Table 6).

2.3.3.4 Outcome

The reported outcome measures were consistent in included studies. OLM consumption, related side effects and pain intensity were reported. Of these, nine studies reported that the postoperative OLM requirements in the EA group was significantly less than that of the control group, while two studies yielded no significant difference in OLM consumption between the EA and control group after operation (Christensen et al., 1993; Sim et al., 2002) (Table 8).

Four of 11 studies reported that the EA treatment could significantly reduce OLM related side effects, such as nausea, vomiting, dizziness and pruritus compared with the placebo/control groups; four reported no significant different and three did not report data (Table 8). Similarly, only three of 11 studies showed significant reduction in postoperative pain with EA compare with placebo/controls; five reported no significant difference, two reported more pain in the EA group compared with controls and another study did not measure pain outcome (Table 8).
### Table 8: Results of Outcome Measures

<table>
<thead>
<tr>
<th>Study</th>
<th>Consumption of OLM (EA vs. sham/control) / percentage of reduction</th>
<th>Related side effects (EA vs. sham/control)</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gejervall, et al. 2005</td>
<td>+; NA</td>
<td>Nausea: neutral</td>
<td>At recovery: -</td>
</tr>
<tr>
<td>Humaidan et al., 2004</td>
<td>+; NA</td>
<td>Did not measure</td>
<td>-</td>
</tr>
<tr>
<td>Stener-Victorin, et al., 2003</td>
<td>+; NA</td>
<td>Nausea: +</td>
<td>+</td>
</tr>
<tr>
<td>Lin, et al., 2002</td>
<td>Sig. reduced by 61, 43, 21% in the high-, low- and sham-EA, respectively.</td>
<td>Nausea and vomiting in the Low- and High EA groups: +</td>
<td>neutral</td>
</tr>
<tr>
<td>Sim et al., 2002</td>
<td>The 24h total: neutral</td>
<td>Nausea, vomiting, drowsiness and pruitis: neutral</td>
<td>neutral</td>
</tr>
<tr>
<td>Chen, et al., 1998</td>
<td>Acupoint group compared with sham group: 39%; compared with non-acupoint group: 38%</td>
<td>Nausea and dizziness: +</td>
<td>+</td>
</tr>
<tr>
<td>Wang, et al., 1997</td>
<td>Decreased 65, 34 and 23% with high-TAES, low-TAES, and sham TAES respectively.</td>
<td>Nausea, vomiting, dizziness and pruritis in the high-TAES: +</td>
<td>neutral</td>
</tr>
<tr>
<td>Christensen et al., 1993</td>
<td>neutral</td>
<td>Did not measure</td>
<td>neutral</td>
</tr>
<tr>
<td>Christensen, et al., 1989</td>
<td>During the total recovery period: +; NA</td>
<td>Nausea and drowsiness: neutral</td>
<td>neutral</td>
</tr>
<tr>
<td>Kho, Eijk, Kapteijns, &amp; van Egmond, 1991</td>
<td>+; NA</td>
<td>Nausea and vomiting: neutral</td>
<td>Did not measure</td>
</tr>
<tr>
<td>Chiu et al., 1999</td>
<td>+; NA</td>
<td>Did not measure</td>
<td>+</td>
</tr>
</tbody>
</table>

*Note: + indicates outcome variable in the EA group was significantly less than that of the sham/control group; - indicates outcome variable in the EA group was significantly higher than that of the sham/control group; TAES: transcutaneous acupoint electrical stimulation; NA, percentage of OLM reduction was not available.*

#### 2.3.3.5 Methodological quality and direction of outcomes

Of the 11 RCTs, six studies were of high quality and five studies were of low quality (Table 9). The six high quality studies reported positive results in reduction of OLM consumption. Thus, significant correlation was found between methodological quality and direction of...
positive trial outcomes. However, no significant correlation was found between side effects and pain. Four of the five low-quality studies also reported positive results in reduction of OLM consumption, two reported positive results in OLM related side effects and one reported positive results in pain.

Table 9: Assessment of Methodological Quality: Jadad Scale of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Jadad Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Described as Randomised</td>
</tr>
<tr>
<td>Gejervall, et al., 2005</td>
<td>1</td>
</tr>
<tr>
<td>Humaidan et al., 2004</td>
<td>1</td>
</tr>
<tr>
<td>Stener-Victorin, et al., 2003</td>
<td>1</td>
</tr>
<tr>
<td>Lin, et al., 2002</td>
<td>1</td>
</tr>
<tr>
<td>Sim et al., 2002</td>
<td>1</td>
</tr>
<tr>
<td>Chen, et al., 1998</td>
<td>1</td>
</tr>
<tr>
<td>Wang, et al., 1997</td>
<td>1</td>
</tr>
<tr>
<td>Christensen et al., 1993</td>
<td>1</td>
</tr>
<tr>
<td>Christensen, et al., 1989</td>
<td>1</td>
</tr>
<tr>
<td>Kho, Eijk, Kapteijns, &amp; van Egmond, 1991</td>
<td>1</td>
</tr>
<tr>
<td>Chiu et al., 1999</td>
<td>1</td>
</tr>
</tbody>
</table>
2.3.3.6 Levels of evidence

The studies fell into two categories: comparing EA with or without conventional therapy (CT) either with no EA (CT only), or with sham EA. Four of six studies comparing combination therapy with CT alone were rated high quality and two were low quality (Table 9). The results of reduction of OLM requirements during surgery were conflicting. OLM reduction was considered positive in five studies and neutral in one study (Christensen et al., 1993). Thus, there is stronger evidence that EA is as effective as or more effective than CT in reducing OLM requirements during surgery.

Among them, one study reported positive result for nausea, two were neutral and two had inadequate data. For pain intensity, one yielded positive result, three neutral and one had inadequate data. Therefore, the evidence is inconclusive that EA is more effective than CT in reducing OLM related side effects and pain.

Two of five studies comparing EA with SEA were rated as high-quality (Chiu et al., 1999; Lin et al., 2002) and three were low-quality (Chen et al., 1998; Sim et al., 2002; Wang et al., 1997). Their results in reduction of postoperative OLM consumption were consistent with all reporting positive results. There is therefore stronger evidence that REA is more effective than sham/placebo EA in reducing postoperative OLM consumption.

Three of these studies reported positive results for side effects, such as nausea and vomiting, one was neutral and one had inadequate data. Similarly, in pain intensity, two reported positive results and another two had inadequate data. Thus, there is inconclusive evidence that REA is more effective than sham/placebo EA in reducing OLM related side effects and postoperative pain than sham/placebo EA.
2.3.4 Discussion

2.3.4.1 Methodological quality

Methodological quality is an essential factor in interpreting the validity of outcomes. In general, most studies reported an appropriate method of randomisation. It is notable, however, that only one study in this review achieved two points for blinding, the rest of studies either did not apply an adequate double blinded approach or could not blind the patients because SEA was not used (Table 9).

Randomised placebo controlled double-blind trials are the most appropriate approach to evaluate efficacy of drug or therapy as double-blinding can minimise bias associated with patient, investigators, or assessor expectation of treatment outcome (Goldstein, 1962). It is almost impossible to successfully apply double blinding to clinical acupuncture research because blinding of the investigator (acupuncturist) delivering the treatment is too difficult. Alternative double-blinding methods need to be further developed. Furthermore, only six of 11 studies adequately reported drop out/withdrawal in their studies.

2.3.4.2 Effectiveness of EA

Overall, the existing evidence strongly supports that EA with or without CT is more effective than either sham EA/TENS plus CT or CT alone in reducing the OLM consumption during or after operations. This review shows inconclusive evidence that EA is more effective in reducing incidence of opioid-related side effects and pain compare with SEA or CT. None of the included studies undertook research on opioid consumption in chronic pain patients. No evidence can be obtained regarding the effect of EA on reducing OLM consumption in patients with chronic pain.
Our findings are different from that of Lee and Ernst, which concluded that AA during surgery was inconclusive (Lee & Ernst, 2005). The difference may be attributed to the aim of the reviews. The aim of Lee and Ernst’s paper was to assess the effectiveness of acupuncture as an adjunctive method to standard anaesthetic procedures during surgery, while the current review was to investigate whether EA can reduce the consumption of OLM, related-side effects and pain in patients during and after operations. Thus, the included papers were different from Lee and Ernst. Our assessment of two papers common to both reviews was consistent with that of Lee and Ernst (Sim et al., 2002; Stener-Victorin et al., 2003). However, we assessed pain intensity in the Sim et al. (2002), but Lee and Ernst did not. Pain directly after oocyte aspiration was not significantly different in the Stener-Victorin et al paper (2003). However, reduction in pain outcomes 2 hours after oocyte aspiration was significantly less in the EA group compared to alfentanil group. The rest of the 17 papers in Lee and Ernst’s review were not included in the current review due to the use of manual acupuncture only or the dosage of OLM was not reported.

We searched a number of different sources to identify all relevant studies. Only 11 RCTs were eligible for evaluation. The limitation was that our search did not yield studies published in language other than English. The exclusion of Chinese publications where acupuncture is widely accepted is noted. Since the majority of Chinese literature has not been covered by most of the English databases, some eligible studies in China might have been omitted. However, the evidence has to be interpreted with caution since publication bias is acknowledged and it has been shown that published reports from China are almost exclusively positive (Vickers 1998).
2.3.4.3 Design of a control intervention

Inclusion of a relevant control group excludes confounding factors such as the practitioners’ expectation, patients’ beliefs and attitudes, the natural history of the condition, psychological effects of needling and the therapeutic relationship. Sham/placebo controls are designed to address these factors. Although an adequate control (e.g. sham acupuncture) is necessary it is also important to assess the success of blinding. Control interventions in the present review are generally categorised into two major types: no EA control and placebo EA/TENS. Blinding patients is impossible when comparing EA with no EA group. Thus, sham design is essential.

Sham EA design in clinical trials has not been standardised. The investigators have designed various placebo techniques that possess both advantages and disadvantages. The sham procedures used in the current review were inserting needles at non-acupoints, or tapping a plastic needle tube on the bone near the acupoints first, then taping needles to the skin without skin penetration, or using a stimulator with a light on but without electrical current (Table 6). The method of inserting needles at non-acupoints has been reported as effective in terms of producing positive results in several studies (Chen et al., 1998; Chiu et al., 1999). It is a reasonably credible method as participants are unlikely to know true acupoints and the outcome influenced by the participants’ needling experience may be reduced to a minimal level. This technique, however, may still produce some physiologic impacts as any form of needling seems to generate an analgesic effect through counterirritation and possibly endorphin release (Vickers, 1996a). Therefore, the depth of insertion may be an important factor for the analgesic effects.

Sham points should be selected away from the acupoints and from the meridians. There are two methods being employed to determine the location of sham points. One method is
locating the point 1-2 cm away from real acupoints (Vincent & Richardson, 1986). Another was proposed by Zaslawski and colleagues that the sham acupoints should be located far away from any known meridians or known extra-points. In the second method, they tested the sites of sham points on the limbs that were four body units below the knee or elbow (Zaslawski et al., 1997), and the depth of needling insertions was enough to keep the needle upright without inadequate sensation in order to maintain the blind status of a naïve subject. The results demonstrated that this method appeared to offer a credible sham acupuncture control (Zaslawski et al., 1997).

Sham EA/TENS involves the use of a non-functional EA stimulator or TENS machine with the indicator lights on only. This control strategy is known as mock TENS, and has been adopted by a number of studies (Chen et al., 1998; Lin et al., 2002; Sim et al., 2002; Wang et al., 1997). The mock TENS without needling produces little to zero physiological effect. The disadvantage of this method seems to be less credible because the participants may distinguish this stimulation from real acupuncture where needle insertion is applied (Vickers, 1996b).

Sham acupuncture includes invasive and non-invasive approaches. The latter could be delivered with placebo needles developed by Park and colleagues (Park et al., 2002). A review however showed that there was no difference between the two types of sham procedures (Dincer & Linde, 2003). The placebo acupuncture reported in the current review is tapping a plastic needle tube on the bone near acupoints to produce discernible sensation then taping needles to the skin without skin penetration (Sim et al., 2002). It appears consistent with actual needle insertion as the patients may feel slight sensation with little physiological action. However, the disadvantage of this procedure was easily visualised by the participants when the selected acupoints are in the upper limb. Thus, this method may remain a problem in maintaining blinding of participants.
Overall, an ideal acupuncture placebo should minimize psychological and physiological impacts on the research outcomes. The most appropriate sham control would be inserting needles at non acupoints without Deqi sensation, with a depth of insertion enough to ensure needles remained standing and with mock electrical stimulation.

2.3.4.4 EA Parameters

This review shows no agreement on the ideal parameters of EA stimulation for OLM reduction. The commonly used frequencies were 2, 10 and 100 Hz, and the results did not seem to be affected by frequency used. Only one study comparing different frequencies of EA showed that stimulation of 100 Hz produced a greater OLM reduction than that of 2 Hz (Lin et al., 2002). Comparing the efficacy of the different EA intensity, Wang et al. showed that EA at a high intensity produced a higher reduction of postoperative OLM requirement and side effects (nausea, vomiting, dizziness and pruritus) than low intensity EA (Wang et al., 1997). The duration of ES also influenced the analgesia effect. The ideal duration has not been identified, but most of studies applied EA prior to surgery for operative condition and EA after surgery for postoperative condition.

2.3.4.5 The selection of electrical stimulation acupoints

The current review indicates that ES applied at the acupoints was more effective than that at non-acupoints sites in reducing OLM consumption, related side effects and pain (L. Chen et al., 1998; Chiu et al., 1999). The majority of these studies selected ST36 and LI4 for EA. This approach is consistent with studies in healthy humans subjects in which stimulation of ST36 or LI4 increased pain threshold (Han et al., 1991; Research Group of Acupuncture Anesthesia, 1973). Other acupoints stimulated with EA were SP6, PC6, LI10, ST29, KI11, GV2, GV4, BL32, BL23 and LU7. Some of them were selected for their calming effects, while others were based on meridian theory.
2.3.5 Conclusion

There is strong evidence that EA reduces the opioid consumption during or after surgery, and is more effective than either no EA (CT alone) or SEA treatment. There is inconclusive evidence that EA reduces side effects, like nausea and dizziness, from OLM, and postoperative pain, and is more effective than SEA treatment. The effects of EA require the stimulation frequency at fixed 2, 10 or 100 Hz or alternating between 2 and 100 Hz with high intensity.

Future studies needed to examine whether the EA can reduce OLM consumption in patient with chronic pain, and whether the EA is more effective in reducing OLM side effects and pain than SEA.

2.4 Part Four - Research aims

The aims of the present study were to assess the effectiveness of real electro-acupuncture (REA) in comparison with sham electro-acupuncture (SEA) on:

- reducing opioid consumption in patients with chronic pain;
- reducing opioid related side effects in patients with chronic pain;
- chronic pain related variables including depression and quality of life.
3.1 Trial design

The trial is a prospective, randomised, double-blind (patient/assessor), sham controlled clinical trial. This project was conducted with approval from the Human Research Ethics Committees (HREC) of RMIT University (Project No. 27/03) and St. Vincent’s Hospital (SVH) (Project No. 132/03 CTN), Melbourne. A Clinical Trial Notification (CTN; 031/2004) was approved by the Therapeutic Goods Administration (TGA).

3.2 Participants

Patients who had suffered non-malignant pain for over three months and subsequently required administration of OLM were eligible to participate in the trial. All participants were volunteers recruited from the Barbara Walker Centre for Pain Management (BWCPM) at SVH Melbourne or SVH website, or responding to newsletters circulated through Centre Melbourne, Eastern and Northern Divisions of General Practices.

3.3 Selection Criteria

The eligibility of study participants was determined by respecified inclusion and exclusion criteria, as listed below.

3.3.1 Inclusion Criteria

Patients aged 18 years or greater, suffering from non-malignant pain longer than three months, and who were using opioid-like pain medications for pain control, were eligible for the study. In addition, prospective participants were required to have sound English reading,
comprehension and written skills, and be able and willing to participate in the study for the eight week duration of the study.

3.3.2 Exclusion Criteria

The following patients were excluded from the study if they had:

- Pacemaker
- Severe arrhythmia or heart failure
- Epilepsy
- Pregnancy
- Severe depression diagnosed with BDI-II > 29
- Previous experience with EA in the last six months
- Previous experience or exposure to cognitive-behavioural therapy (CBT) programmes.

The first three exclusion criteria were required as EA may disrupt the pacemaker function, as well as trigger epilepsy or arrhythmia. There is limited evidence suggesting acupuncture is dangerous to pregnant women, however, pregnancy was excluded due to the frequency of spontaneous miscarriage in the first trimester and evidence of acupuncture use to induce labour in China (BMAS, 2000). Patients with severe depression were excluded due to the requirement for comprehensive concomitant management by a psychologist or psychiatrist. Patients with previous EA experience were excluded to ensure participants remained blinded to treatment allocation. No previous experience or exposure to CBT was required as the purpose of this study was to help patients reduce their medication with EA before taking part in the CBT programme.

Participants were informed that they were free to withdraw from the study at any time. Written informed consent was obtained prior to study enrolment. An assessment of
participants’ competence to give consent was assessed by the BWCPM. The recruitment process allowed patients adequate time to consider the detailed patient information and consent to participate in the trial by completing an Expression of Interest (EI). The EI was then returned to the investigator by the patient in a pre-paid envelope. Participants were given further opportunity to further discuss the project and ask for more information preceding their participation.

3.4 Procedure for recruitment

Recruitment took place over an 18 month period and was carried out in one of the following five ways:

- Patients who were yet to have a Multidisciplinary Assessment

Patients referred to BWCPM, usually by their GPs, were placed on a waiting list for around 18 months before receiving a multidisciplinary assessment (MDA). There were approximately 200 patients in this group at recruitment. As patients had not yet been assessed by a pain specialist doctor and provided information about the study, patients were mailed a pamphlet (Appendix 1) and a letter of invitation (Appendix 2) informing them that an EA study was being conducted in the Centre. The HREC at SVH approved the pamphlet. Patients who phoned voluntarily to enquire about the study and who expressed an interest in participating were entered into a database. The EI (Appendix 3) and screening Questionnaires (Appendix 4) were then sent to each of the potential participants (PP).

- Patients who were discharged from the Centre

A total of 800 patients were discharged from the Centre. A research assistant and investigator had approval to access patient files and identified PP according to the inclusion and exclusion
criteria. A letter of invitation was then sent to potential participants identified. Participants who replied by phone to express an interest in the study were entered into the database and sent the same screening questionnaires.

- Patients with a MDA but were not candidates for the Selected Targets of Activity ReTraining programme (START) (i.e. CBT programme)

The Centre for Pain Management has developed an intensive outpatient CBT programme, called START, conducted by clinical psychologists, medical specialists, physiotherapists and clinical nurse consultants. The aim of START is to help patients minimise the distress and daily dysfunction associated with persistent pain. START teaches skills to help patients manage their pain more effectively. Some patients were considered not suitable for the START programme according to the exclusion criteria of the START programme. This group of patients were invited to participate in the study.

- Patients who were on the waiting list for the START programme

START is a programme for groups of up to 12 outpatients. After a multidisciplinary assessment, patients considered appropriate for the multidisciplinary pain management programme are placed on a waiting list for a few months before entry into the programme. The Figure 1 illustrates the methods used to sort participants who were being processed at the BWCPM.
During the initial recruitment period, we realised that the process used was slow. In order to speed up the recruitment process, the following strategies were developed and approved by the HREC at SVH. Doctors from outpatient’s clinics at SVH, Melbourne including Rheumatology, Orthopaedics, Neurology and General Medicine were informed about the study through the website of SVH (Appendix 5) and through letters to Heads of Unit (Appendix 6). Also, advertisements in the newsletter of the Divisions of General Practice in letters to GPs were used to invite the GPs to refer participants to the trial (Appendix 7).

PP were informed of the study at the BWCPM with an EI form and pamphlet containing information about the study. After reading the EI, PP filled out and returned the EI in a pre-
paid envelope to the investigator. The investigator then interviewed eligible participants at the centre. Figure 2 illustrates the recruitment procedures.

Figure 2: A Flow Chart Illustrating Participants Recruitment

![Flow Chart Illustrating Participants Recruitment](image-url)
3.4.1 Randomisation

Patient recruitment was made difficult due to the significant travel required for a face-to-face interview and attendance twice weekly for six weeks. For this reason, a block randomisation method with 40 subjects in each block was used. Random numbers (40 numbers) were generated using a computer generated sequence of numbers. Following baseline assessment, participants were asked to select a sealed opaque envelope containing a unique random number which allocated the participant to the real electro-acupuncture (REA) or sham electro-acupuncture (SEA) group.

3.4.2 Blinding

Successful blinding is a challenge in clinical trials of electro-acupuncture as the patient is able to see and feel subcutaneous needling and electrical stimulation. However, patient blinding is important to prevent bias in clinical studies of manipulative or ritualised procedures, such as acupuncture.

A conventional double-blind trial attempts to blind both the patients and the person delivering the treatment. In the current study, performance bias was minimised by blinding the patient and outcomes assessor from the treatment allocation. The acupuncturist (study investigator) was unable to be blinded. Describing this procedure as a modified double-bind (patient/evaluator) trial is acceptable when intervention characteristics preclude investigator blinding (Jadad et al., 1996); The investigator delivering the treatment was blinded to treatment outcome and discussion of acupuncture with patients during treatment was limited. A research assistant (RA) entering outcome data was blinded to treatment allocation during the trial period. A second independent investigator who carried out the telephone consultation of participants’ OLM reduction was also blinded to the group assignments.
3.4.3 Drop outs

Any participant who dropped out of this study was analysed according to the intention-to-treat (ITT) method.

3.5 Materials and Methods

3.5.1 Materials

3.5.1.1 Electro-acupuncture stimulation equipment

EA was applied using a modified EA stimulator (MME 501, Meyer Medical Electronics, Australia) that was battery operated. As this stimulator is not registered or listed within Australia by the TGA, the trial was placed under the CTN scheme.

The stimulator was originally designed to deliver ES of 1-500 Hz in frequency and constant or dense/disperse (D/D) square waves with a pulse width of 50–70 microseconds. In the current study, the D/D delivering mode was replaced with alternating frequency of 2 and 100 Hz. Each frequency was delivered for 6 seconds. It was operated on 8 AA batteries.

3.5.1.2 Needles

“Hwato” brand individually wrapped, sterilised, and disposable needles with guide tubes were used in this study. The needles are manufactured by Suzhou Medical Instrument Factory of China and are approved and listed by the TGA of Australia. The needles selected in the present study were 0.25mm in diameter. The lengths of the needles were 30mm - 40 mm. The depth of insertion of the needles varied depending on the acupoints selected. Used needles were placed into a sharps disposal bin. The same quality of needles was used in the REA and the SEA group.
Real and sham EA treatments were delivered by an acupuncturist who is registered with the Chinese Medicine Registration Board (CMRB) of Victoria, Australia.

3.5.2 Real electro-acupuncture treatment

3.5.2.1 Selection of acupoints

Location of acupoints adopted in the present study followed the standard nomenclature of acupoints published by WHO (1993). The acupoint selection was adopted from an authorised book of Chinese medicine compiled by the State Administration of Traditional Chinese Medicine (Ming & Yang, 1997) and empirical experience. Paired acupoints selected for ES were Hegu (LI4), and Quchi (LI11), as well as Zusanli (ST36) and Fenglong (ST40). Each pair of acupoints was connected to an electrical stimulator.

Secondary acupoints were selected to reduce the side effects of OLM, to relieve insomnia and promote calmness. A total of nine acupoints were chosen for every participant. They included four primary acupoints and five secondary acupoints which always included Shenmen (HT7), Sanyingjiao (SP6), and YinTang (EX-3). In addition, more supplementary acupoints could be added according to participants’ other accompanying complaints, or as a result of side effects from any medication. Table 10 summarises the acupoints used in the study.
### Table 10: Selected Acupoints

<table>
<thead>
<tr>
<th>Primary acupoints</th>
<th>Hegu (LI 4) (negative), Quchi (LI 11) (positive); Zusanli (ST36) (negative), Fenglong (ST40) (positive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary acupoints 1) Insomnia</td>
<td>Shenmen (HT7) (bilateral), Sanyingjiao (SP6) (bilateral), Yintang (EX-3)</td>
</tr>
<tr>
<td>2) Reducing side effects from drugs</td>
<td>Nausea Neiguan (PC 6)</td>
</tr>
<tr>
<td></td>
<td>Vomiting Geshu (BL 17), Neiguan (PC 6)</td>
</tr>
<tr>
<td></td>
<td>Constipation Tianshu (ST 25) (bilateral), Zhigou (SJ 6)</td>
</tr>
<tr>
<td></td>
<td>Fatigue / General weakness Guanyuan (RN 4), QiHai (RN 3)</td>
</tr>
<tr>
<td></td>
<td>Drowsiness/ Sedation Yinglingyun (SP 9)</td>
</tr>
<tr>
<td></td>
<td>Profuse sweating Fuliu (KI 7), Hegu (L 14)</td>
</tr>
<tr>
<td></td>
<td>Night sweat Fuliu (KI 7), Yinxi (HT 6)</td>
</tr>
<tr>
<td></td>
<td>Cough Lieque (LU 7), Feishu (BL 13)</td>
</tr>
<tr>
<td></td>
<td>Insomnia Taixi (KI 3)</td>
</tr>
<tr>
<td></td>
<td>Skin pruritus Xuehai (SP 10)</td>
</tr>
</tbody>
</table>

#### 3.5.2.2 Needling technique

The participants in the real treatment group were required to be in a supine posture. After the acupoints were located, and skin sterilised, filiform disposable needles were inserted into the acupoints. The depth of needle insertion depended on the acupoints selected. Further manipulation was then delivered to achieve Deqi sensation that was characterised as a numb, heavy, sore and/or distending sensation.

#### 3.5.2.3 EA stimulator

A pair of acupoints was used to make a circuit for conducting the electric current. In the present study, The MME 501 electrical stimulator was connected to the needles placed on the paired acupoints, of LI4 and LI11, and acupoints ST36 and ST40 via two pairs of wired clips after obtaining Deqi sensation. The black clips (negative) were connected to LI4, ST36, and red clips (positive) to LI11, ST40, respectively. The stimulator was then switched on, and the intensity was gradually increased from zero to reach a strong but comfortable level. The sensation of EA is numbness, distension and tingling. Any possible muscle contraction was explained to participants prior to the treatment. After 5 minutes of electrical stimulation, the intensity was adjusted to reach a tolerable level. Adjustments were done during a stimulation.
of 100 Hz, i.e. the dense period. After 30 minutes of EA stimulation, the intensity knob was turned down to zero, the stimulator was switched off, and the needles were gently removed.

During the treatment, the acupuncturist was not allowed to communicate with participants about the treatment and its effect.

3.5.3 Sham electro-acupuncture treatment

3.5.3.1 Location of sham acupoints

Methods of locating sham acupoints in the present study were adapted from one commonly used approach (Vincent & Richardson, 1986) and one validated approach (Zaslawski et al., 1997). In sham acupuncture, the same number of acupoints as for REA was used for each participant. For each real acupoint, there was a corresponding sham acupoint, and their method of location is described in Table 11.
Table 11: Location of Sham Acupoints

<table>
<thead>
<tr>
<th>Sham acupoints corresponding to</th>
<th>Method of location of sham acupoints</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hegu (L14)</td>
<td>On dorsal aspect of the hand between second &amp; third metacarpal bones, about 1.5 cm proximal to metacarpal pharyngeal joint; insertion is transverse &amp; caudal.</td>
<td>Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Quchi LI 11</td>
<td>On the posterior surface of the forearm, four body units distal to the olecranon.</td>
<td>Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Shenmen (HT7)</td>
<td>On the palmar surface of the arm, four body units distal to the elbow crease</td>
<td>Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Yintang (EX- NH 3)</td>
<td>1.5 cm above and lateral to the real acupoint</td>
<td>Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Zusanli (ST 36)</td>
<td>On the posterior aspect of the leg. Six body units inferior to the popliteal crease and one body unit lateral to the midline</td>
<td>Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Fenglong (ST 40)</td>
<td>On the posterior aspect of the leg. Eight body units inferior to the popliteal crease and one body unit lateral to the midline</td>
<td>Modified from Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Sanyinjiao (SP 6)</td>
<td>On the medial aspect of the leg. Four body units inferior to the popliteal crease</td>
<td>Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Yinlingquan (SP9)</td>
<td>At the centre of the medial aspect of the thigh</td>
<td>Fanti et al., 2003</td>
</tr>
<tr>
<td>Geshu (BL 17)</td>
<td>Three body units lateral to the spinous process of the sixth cervical vertebrae</td>
<td>Modified from Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Feishu (BL 13)</td>
<td>Four body units, below spinous process of the T3</td>
<td>Modified from Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Tianshu (ST 25)</td>
<td>One body unit lateral to the anterior midline, and one body unit superior to the umbilicus.</td>
<td>Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Neiguan (PC 6)</td>
<td>1.5 cm lateral of the real acupoint.</td>
<td>Vincent &amp; Richardson, 1986</td>
</tr>
<tr>
<td>Zhigou (TE 6)</td>
<td>On the posterior surface of the forearm, five body units distal to the olecranon</td>
<td>Modified from Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Fuliu (KI 7)</td>
<td>One body unit directly above the real acupoint</td>
<td>Modified from Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Yinxī (HT 6)</td>
<td>1.5 cm right lateral of the real acupoint</td>
<td>Vincent &amp; Richardson, 1986</td>
</tr>
<tr>
<td>Lièque (LU 7)</td>
<td>1.5 cm left lateral of the real acupoint</td>
<td>Vincent &amp; Richardson, 1986</td>
</tr>
<tr>
<td>Taixi (KI 3)</td>
<td>One body unit above the real acupoint</td>
<td>Modified from Zaslawski et al., 1997</td>
</tr>
<tr>
<td>Xuehai (SP 10)</td>
<td>One body unit lateral to the real acupoint</td>
<td>Modified from Zaslawski et al., 1997</td>
</tr>
</tbody>
</table>
3.5.3.2 Needling technique

In the SEA group, the needling depth was approximately 5 mm, so that the insertion was superficial, but deep enough to keep the needle standing. Neither manipulation technique, nor Deqi was applied. A minimum of nine needles was applied and was equivalent to real acupuncture.

3.5.3.3 Sham EA stimulator

After inserting the needles, a modified, non-functioning, (but with a flashing light) MME 501 EA stimulator was connected to the needles placed at the unilateral sham acupoints L14, LI11 and ST36, ST40. No electrical current was passed through. No adjustment was applied during the treatment. The participants were told that they might or might not feel any sensation, because only a very weak current was delivered. Table 12 is a comparison of the REA and SEA procedures.

| Table 12: A Comparison between Real Electro-Acupuncture (REA) and Sham Electro-Acupuncture (SEA) |
|-------------------------------------------------|---------------------------------|---------------------------------|
| **Needle instruments**                          | **REA**                         | **SEA**                         |
| “Hwato” brand needles                           | “Hwato” brand needles           |                                 |
| **Acupoints**                                   | ST 36 (-) + ST 40 (+)           | Off meridian real acupoints     |
|                                                 | LI 4 (-) + LI 10 (+)            |                                 |
| **Depth**                                       | Depending on the acupoints selected. | Shallow insertion, enough depth to keep the needle in place |
| **Stimulation**                                 | Obtain Deqi sensation           | No Deqi                         |
| **EA stimulator**                               | MME 501, Myer Australia        | Modified MME 502, Myer Australia |
| **Parameter**                                   | Alternating frequency at 2 /100 Hz at an acceptable intensity. | Non functional EA stimulator with flashing light only. |
| **Duration**                                    | 30 minutes                      | 30 minutes.                     |
| **Treatment Frequency**                         | Twice a week for six weeks      | Twice a week for six weeks      |
3.6  Outcome Measures

3.6.1  Primary Outcome Measures

The primary outcome measures were assessed daily at baseline and during treatment, one week immediately after completion treatment, and one week in every four during follow up. The McGill Pain Questionnaire was an exception and was assessed in the same way as the secondary outcome measures.

3.6.1.1  Subject Diary (Appendix 8)

Participants were asked to complete a daily Subject Diary in which they recorded the number of pain medications they were taking, especially OLM, the severity of any related side effects, and the amount of pain that they were experiencing. This weekly Subject Diary took subjects approximately five minutes to complete at the end of the day. Also, the participants were asked to record any AE associated to acupuncture treatment. The participants were requested to complete the Subject Diary independently and bring it to the centre weekly. The Subject Diary continued for a two-week run-in period, a six-week treatment period, one week of early follow up immediately after treatment, and for a further three-week period starting on the fourth week after the end of the treatment.

Instructions for using the Diary were provided and a sample showing how to use the scale enclosed and how to record the pain medication doses was enclosed. The participants were instructed only to rate the intensity and unpleasantness of the pain for which they were referred to the BWCPM. The detailed content of the Diary is described as follows.
Pain scale

Pain severity was measured by asking participants to rate their pain on a VAS of 10 centimetres length with “no pain at all” and “worst pain imaginable” at the two ends. Patients recorded the average level of pain, present pain, and the highest and lowest level of pain that they experienced today.

Time that pain lasted on each day

Participants were also required to draw a line representing a period of time within 24 hrs that they experienced pain.

Severity and unpleasantness of pain on each day

Participants were also asked to tick one of the boxes numbered from 0 to 20 that stated the severity and unpleasantness of their pain on each day.

Medication usage

Daily use of opioid and other pain medications was recorded by the participants. Doses of opioid were converted to daily equivalents of morphine in milligrams according to the Conversion Table 3. For example, a participant took Endone 5 mg and Tramadol 100 mg daily. These medications were conversed to the doses of morphine equivalent that was 25 mg daily. \[5 \text{ mg (Endone)} \times 30 \text{ mg (morphine)} \div 30 \text{ mg (Oxycodone)} + 100 \text{ mg (Tramadol)} \times 30 \text{ mg (morphine)} \div 150 \text{ mg (Tramadol)}\]. An individual medication reduction schedule was formulated by a medical doctor and was released to the participant by the second investigator.

The consumption of non-opioid analgesics was recalculated with Medication Quantification Scale (MQS) (Harden et al., 2005). Each non-opioid analgesic for every participant was given a score based on the drug class, dosage, and detriment weight. The MQS scores for each
non-opioid medication were then summed to obtain a total score representing the consumption of non-opioid analgesics.

Side effects of pain medication

Participants were asked to mark the side effects of pain medication on VAS of 10 centimetres ranging between 0 (no symptoms at all) and 10 (very severe symptoms) at the end of each week throughout the study.

Report of adverse events (AE) for acupuncture

Participants were asked to record any perceived AE associated with acupuncture treatment, and the management of the symptoms at the end of each week throughout the treatment period. Common AE include fainting, infection, dizziness, bruising, pain and lethargy. Meanwhile, the severity of AE was categorised into: 0 (not at all), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe), and 5 (extremely severe).

3.6.1.2 The McGill Pain Questionnaire

Participants were asked to choose as many as words as required from the descriptive words of the MPQ to describe their pain during the baseline, 3rd and 6th week of treatment, and at the 4th, 8th and 12th week after the treatment. The basic scoring method of the MPQ followed the instructions from the study by Melzack (1975). Accordingly, results were categorised into three main scores. The first is the Pain Rating Index (PRI), which is based on the rank values of the words and is the total sum of all the 20 subclasses; and the second is the total number of words chosen (NWC). The third is the PPI, which is the number-word combination chosen as the indicator of overall pain intensity at the time of administration of the questionnaire. The Pain Rating Index scores are also subdivided into the following scores:
• The score of groups 1-10 to assess sensory components (PRI-s)
• The score of groups 11-15 to assess affective components (PRI-a)
• The score of groups 16 to assess evaluative components (PRI-e)
• The score of groups 17-20 to assess miscellaneous components (PRI-m)

The word in each subclass implying the least pain is given a score of one, the next word is given a score of two, and for subsequent words a score is given determined by their placement. Participants were told that only one descriptor in any group should be chosen and not all groups need be included (Melzack, 1975).

3.6.2 Secondary Outcome Measures

The Secondary Outcome Measures were assessed at baseline, 3rd and 6th week during the treatment and at the 4th, 8th and 12th week after the treatment. The outcome measures are described below:

3.6.2.1 Beck Depression Inventory-II (BDI-II)

The questionnaire used in this study was BDI version II, a self-reporting scale. It is comprised of 21 items and takes approximately 5-10 mins to complete. The participants were asked to choose one provided statements they felt “best describes the way they had been feeling in the past two weeks, including today” (Beck, Rush, Shaw, & Emery, 1979).

The summary of the rating for the 21 items is the total score on the BDI-II. Each item is rated on a 4-point scale ranging from 0-3. For items with multiple responses, the response with the higher rating is recorded. For Items 16 and 18, each of them contains seven options rated, in order, as 0, 1a, 1b, 2a, 2b, 3a, 3b. This is to differentiate between increases and decreases in behaviour or motivation. The maximum total score that can be obtained is 63. Higher scores
indicate more severe depressive symptomatology. Scores in the categories 0-13, 14-19, and 20-28 indicate minimal, mild, and moderate depressive symptomatology, respectively, and a score equal to or higher than 29 is an indicator of severe depressive symptomatology.

3.6.2.2 General Quality of life (SF-36)

The SF-36 quality of life questionnaire was used to assess the impact of pain on each patient’s social activities and work during the previous 4 weeks. The instruments assess eight health domains including physical functioning (PF), role physical (RP), social functioning (SF), mental health (MH), vitality (VT), role emotional (RE), bodily pain (BP) and general health (GH). Each domain is scored from 0 to 100; a higher score indicates better health.

3.6.2.3 Participants’ perception of EA treatment (Appendix 9)

The participant’s perception was reported at the end of the treatment stage using Questionnaire Forms (Wang et al., 1997). The questionnaire consisted of four questions including participants’ view on effective of treatment, real treatment, paying for treatment in the future and recommendation to others.

3.7 Procedure of the study

3.7.1 Initial examination and assessment

After PP returned their EI in a pre-paid envelope to the investigator, individual phone calls were made to them to ascertain and identify Inclusion/Exclusion Criteria. Once eligible, volunteers who met the basic selection criteria were identified, the investigator then invited them for an initial assessment.
The initial assessment was conducted at the BWCPM, St. Vincent’s Hospital. During the assessment, the following procedures were undertaken:

- The Investigator greeted the PP. A verbal explanation concerning the study and PI (Appendix 10) was given, and any questions comprehensively answered prior to signing of the Consent Form (CF) (Appendix 11). A CF was provided to each PP to be read, signed, and witnessed.
- A copy of the signed CF was given to each of the participants for their own records.
- During the assessment interview, the BDI-II was given to the PP to complete. PP whose score was less than or equal to 29 were recruited into the baseline, and asked to complete the questionnaires summarized in Table 13.

### Table 13: The Summary of Instruments Used in Different Stages

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Instruments</th>
<th>Initial assessment</th>
<th>Baseline Stage (2 weeks)</th>
<th>Treatment Stage (6 weeks)</th>
<th>Follow up Stage 1\textsuperscript{st}, 4\textsuperscript{th}, 8\textsuperscript{th}, 12\textsuperscript{th} week after completion of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td>Subject Diary (Weekly)</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MPQ</td>
<td></td>
<td>3\textsuperscript{rd}, 6\textsuperscript{th}</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td>BDI-II</td>
<td>√</td>
<td>3\textsuperscript{rd}, 6\textsuperscript{th}</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SF-36</td>
<td>√</td>
<td>3\textsuperscript{rd}, 6\textsuperscript{th}</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Demographic and general information</td>
<td></td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perception of EA treatment</td>
<td></td>
<td></td>
<td></td>
<td>6\textsuperscript{th}</td>
</tr>
</tbody>
</table>

#### 3.7.2 Baseline stage

Once the participants completed the initial assessment, and written informed consent was obtained, they had a two-week baseline period prior to the treatment. During the baseline period, participants were required to fill out the weekly Subject Diary for two weeks, and to
post back a completed baseline week one Diary to the investigator with the pre-paid envelope, and asked to bring the baseline week two Diary with them on their next visit.

3.7.3 Treatment stage

Before administering the treatment, the investigator assessed the medications the participant was taking, especially opioid medications, as documented in the baseline Subject Diary. The participants were excluded if they were not taking opioid medication. Once the participants were eligible to participate in the study after the baseline period, each received treatment twice a week for a total of 12 sessions, delivered over a period of six weeks. The participants were required to record pain medication, related side effects, intensity of pain, and adverse events of acupuncture in the Subject Diary daily. Each participant was asked to fill out their perception of EA at the end of the treatment.

3.7.4 Follow up stage

After completion of EA treatment, the participants were assessed at three months follow up. The follow up procedure was to evaluate any potential long-term effects of EA. The participants were asked to complete the Subject Diary at 1st, 4th, 8th and 12th week during this stage, and were re-assessed with the secondary outcomes.

3.7.5 Telephone consultation

The purpose of the telephone consultation was to explain to participants how to reduce their OLM and avoid bias in the REA and the SEA groups. The second investigator indicated participants how to reduce their pain medication on the basis of a well-established individual plan for reducing OLM for each participant. The participants were informed at the second and
fifth week during the treatment and the third, sixth, and ninth week during the follow up stages.

Figure 3 illustrates the procedure of the present study.
3.7.6 Sample size calculation

The sample size was calculated based on one of the primary outcome measures, which was the Dosage of Opioid Consumed (DOC). A previous study had reported that the mean DOC in postoperative patients when treated with sham EA was 30.2 mg with a standard deviation of
14.4 mg (Lin et al., 2002). In order to detect a difference of 30% or more in mean DOC between the two groups (REA and SEA), 44 participants were required in each group to reject the null hypothesis with 80% power and at a 5% significance level (two-tailed) (Warren S.B., Dennis B., Thomas, & B.H., 1988). Considering a 30% drop out rate, the total number of participants required to be randomised was 101.

3.8 Data collection and analysis

3.8.1 Data collection

Data were collected during baseline, treatment stage and follow-up stage by a RA. The RA checked the completion of the Subject Diary and prepared a summary of medication used for telephone consultation. The methods employed in the present study were to ensure successful blinding of the acupuncturist and other investigators. Reports of AE from acupuncture in the Diary were checked by the acupuncturist weekly to ensure safe practice.

All raw data from the Subject Diary were entered directly into Excel spread sheets. After the calculation of weekly means of variances, data were finally exported to Statistical Package for the Social Sciences (SPSS, version 13.0 for Windows) for statistical analysis. The SF-36 value was calculated according to the manual for each of the subscales.

3.8.2 Data analysis

The data were summarised as mean ± standard deviations (SD). Per protocol analysis was performed for participants who completed the study. The data missed in the Subject Diary were replaced by carrying last value forward; the data missed in the BDI-II and SF-36 questionnaires were dealt with according to the manual of BDI-II and SF-36. In addition,
participants who dropped out during the study were also recorded, and their primary outcome measure was analysed using the intention-to-treat analysis.

The participants’ socio-demographic characteristics and the classification of diagnosis were analysed with chi-square or t-test. The data of primary and secondary outcomes measures for short term effects were analysed employing repeated measure of General Linear Model (ANOVA) with Bonferroni corrected tests, paired-samples t-test and independent-sample t-tests; and the data for long term effects were analysed using the paired sample t-test. Due to the evaluative (PRI-e) component of the questionnaire being composed of only one group of descriptors and the remaining four groups being composed of miscellaneous descriptors (PRI-m), the decision was made to exclude these from individual analysis. Scores from these groups were included in total scores.

The incidence of side effects of OLM and adverse effects of EA were compared between the two groups using chi-square analysis. Additionally, the perception of EA was crosstabulated with the group they were in and a chi square test performed, as appropriate.

On the basis of the above methods, the data were generally analysed on the following aspects:

- Comparison of the consumption of analgesics, particularly that of OLM, over time within and between groups.
- Comparison of the severity of opioid related side effects within and between groups.
- Comparison of the average intensity and duration of pain within and between groups.
- Comparison of the severity and unpleasantness of pain within and between groups.
- A comparison of MPQ (total and sub-category scores) within and between groups.
- Comparison of the degree of depression and QoL within and between groups.
• Analysing the long term effect of EA.

When the probability value was less than 0.05, the difference was considered to be statistically significant. Figures and charts were constructed in Window XP 2003 from the Microsoft Company.
CHAPTER FOUR: SHORT TERM EFFECTS OF ELECTRO-ACUPUNCTURE ON OPIOID MEDICATION CONSUMPTION, PAIN AND RELATED VARIABLES

This chapter presents the analysis of data obtained from the treatment period of the study. Per protocol analysis was employed to analyse both the primary and secondary outcomes, and these results are presented in details. Intention-to-treat analysis was also employed, a summary of the results is presented, and the detailed results are included in Appendix 13. A detailed description of these two analysis methods has been provided in the Methods chapter.

4.1 Allocation of participants

Between April 2004 and September 2005, 82 patients with CNMP were assessed for study inclusion. Of these, 40 participants were excluded for not meeting the inclusion criteria as shown in Table 14. Forty-two participants were enrolled during the two-week baseline period. Of these, seven were excluded from this data analysis. Five patients failed to return by the end of the baseline period and two discontinued as they had previously been scheduled for surgery. A total of 35 participants were randomly allocated to either the SEA or the REA group. Of the 35 enrolled participants, 26 completed the treatment, with four dropping out from the SEA group, and five from the REA group. A statistical test could not be conducted to find out if there were any differences between the groups as the numbers in each category were very small. The reasons for dropping out are summarised in Table 15 and the study flowchart is illustrated in Figure 4.
### Table 14: Reasons for the Participant Exclusion

<table>
<thead>
<tr>
<th>Reasons for Exclusion</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>English is not good enough to understand the questionnaires</td>
<td>3</td>
</tr>
<tr>
<td>Severe depression symptomatology diagnosed with BDI-II</td>
<td>11</td>
</tr>
<tr>
<td>Had experience of EA in the previous six months</td>
<td>2</td>
</tr>
<tr>
<td>Not taking opioids</td>
<td>8</td>
</tr>
<tr>
<td>GP did not agree the patient to participate in the study</td>
<td>1</td>
</tr>
<tr>
<td>Not interested in participating in the study</td>
<td>1</td>
</tr>
<tr>
<td>Didn't want to be in the sham acupuncture group</td>
<td>1</td>
</tr>
<tr>
<td>Transportation problems</td>
<td>4</td>
</tr>
<tr>
<td>Had malignant pain</td>
<td>2</td>
</tr>
<tr>
<td>Fear of needles</td>
<td>1</td>
</tr>
<tr>
<td>Pacemaker in site</td>
<td>1</td>
</tr>
<tr>
<td>Failed to complete the questionnaires</td>
<td>3</td>
</tr>
<tr>
<td>Could not come regularly for treatment</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>40</strong></td>
</tr>
</tbody>
</table>

### Table 15: Reasons for Dropping out Prior to Randomisation

<table>
<thead>
<tr>
<th>Dropped out reasons</th>
<th>SEA group</th>
<th>REA group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=4</td>
<td>N=5</td>
</tr>
<tr>
<td>Could not tolerate needling sensation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Had aggravation of symptoms</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Had transportation problems</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Reason unclear</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Had baby-sitting problems or family issue</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Work commitment</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4</strong></td>
<td><strong>5</strong></td>
</tr>
</tbody>
</table>
Figure 4: A Study Flowchart

82 Chronic pain patients assessed for eligibility

42 Entered baseline stage

35 Randomised

17 Allocated to the REA group
  5 Dropped out
    1 Could not tolerate the sensation of needling
    1 Had aggravation of symptoms
    1 Had transportation problems
    1 Reason unclear
    1 Had baby-sitting problems
    12 completed the study

18 Allocated to the SEA group
  4 Dropped out
    2 Had transportation problems
    1 Had to go back to work
    1 Had a family issue
    14 Completed the study

9 Completed follow up assessment
  (3 months after the end of treatment)
  3 lost to follow up
  (Unable to contact)

14 Completed follow up assessment
  (3 months after the end of treatment)

12 were included in per protocol analysis of the treatment effects

14 were included in per protocol analysis of the treatment effects

12 were included in the analysis of long term effects

14 were included in the analysis of long term effects

40 Excluded
Failed to meet inclusion criteria

5 Never returned by the end of the baseline stage,
2 were scheduled for surgery

42 Entered baseline stage

35 Randomised

17 Allocated to the REA group
  5 Dropped out
    1 Could not tolerate the sensation of needling
    1 Had aggravation of symptoms
    1 Had transportation problems
    1 Reason unclear
    1 Had baby-sitting problems
    12 completed the study

18 Allocated to the SEA group
  4 Dropped out
    2 Had transportation problems
    1 Had to go back to work
    1 Had a family issue
    14 Completed the study

9 Completed follow up assessment
  (3 months after the end of treatment)
  3 lost to follow up
  (Unable to contact)

14 Completed follow up assessment
  (3 months after the end of treatment)

12 were included in per protocol analysis of the treatment effects

14 were included in per protocol analysis of the treatment effects

12 were included in the analysis of long term effects

14 were included in the analysis of long term effects

Note: REA, real electro-acupuncture; SEA, sham electro-acupuncture
Per protocol analysis included data from participants who completed the six-week treatment. In total, 26 participants were included in the per protocol analysis and the 35 patients randomised in the intention to treat analysis. Table 16 summaries the number of participants and outcome measures analysed by per protocol or intention-to-treat method. In the following sections, all data presented were analysed with per protocol method.

4.2 Socio-demographic data

The results of the univariate analyses regarding the age, gender, education level, marital status, living status for the two groups are presented in Table 17. There was no significant group difference, and the two groups were comparable in all these measures (Table 17).
Table 16: Number of Participants and Outcomes were Analysed Using per protocol and Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th></th>
<th>Per protocol</th>
<th>Intention-to-treat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage of OLM</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>OLM related adverse events</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Intensity and unpleasantness of pain</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of depression</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>QoL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 17: Demographic Variables at Baseline in Each Group

<table>
<thead>
<tr>
<th>Demographic Variables</th>
<th>Intention-to-treat</th>
<th>Per protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEA group</td>
<td>REA group</td>
</tr>
<tr>
<td></td>
<td>N=18</td>
<td>N=17</td>
</tr>
<tr>
<td>Age (yrs) (Mean ± SD)</td>
<td>48.4 ± 10.5</td>
<td>51.1 ± 13.0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (N, %)</td>
<td>9 50%</td>
<td>9 53%</td>
</tr>
<tr>
<td>Female (N, %)</td>
<td>9 50%</td>
<td>8 47%</td>
</tr>
<tr>
<td>Marital status (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>9 7</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>3 3</td>
<td></td>
</tr>
<tr>
<td>Separated</td>
<td>0 1</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>2 4</td>
<td></td>
</tr>
<tr>
<td>De facto</td>
<td>3 2</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td>Education level (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 or more years of formal education</td>
<td>15 10</td>
<td></td>
</tr>
<tr>
<td>Less than 9 years</td>
<td>3 7</td>
<td></td>
</tr>
<tr>
<td>Living status (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>4 2</td>
<td></td>
</tr>
<tr>
<td>With spouse /partner and children</td>
<td>8 7</td>
<td></td>
</tr>
<tr>
<td>With spouse /partner only</td>
<td>4 4</td>
<td></td>
</tr>
<tr>
<td>With child /children only</td>
<td>0 1</td>
<td></td>
</tr>
<tr>
<td>With other relatives</td>
<td>2 2</td>
<td></td>
</tr>
<tr>
<td>With friends /housemates</td>
<td>0 1</td>
<td></td>
</tr>
</tbody>
</table>
4.3 Classifications of diagnosis in Western Medicine

The participants were diagnosed by the doctors according to the Classification of Chronic Pain Definitions published by the International Association for the Study of Pain (IASP) (Merskey & Bogduk, 1994). A multiplex coding system was used, which consists of five axes plus an optional letter used as a suffix. These axes include: Axis I - Regions, the major body region or site of the reported pain; Axis II - Systems, the body system which abnormal functioning produces the pain; Axis III - Temporal characteristics of pain, pattern of occurrence; Axis IV - Patients statement of intensity and Time since onset of pain; Axis V - Etiology, the presumed etiology of the pain problem. By applying this coding scheme, a five-digit numerical code was generated that represented each participant’s diagnosis. The letters S and R were added after the digits a coding to identify spinal and radicular pain respectively. Where both occur in the same location, the letter C, for combined spinal and root pain, is preferred. For instance, the digital portion of the code for the syndrome of severe tension headache of more than 6 months’ duration is 033.97c. If a participant had pain in more than one region, two codes were completed for that participant. In this study, the primary pain means the condition that drove the participant to be treated in this study; second and third pains are referred to the pains located out of the site of primary pain.

According to this coding system, many participants presented with both primary and second pains. The distribution of primary pain in the SEA and the REA groups are described in detail below (Figure 5).

**Axis I distribution (regions):** Half the participants (50%) in the REA group were grouped into region 500 which indicates lower back, lumbar spine, sacrum and coccyx pain. Greater than
one third of participants (35.7%) in the SEA group were coded in region 900 which indicates more than three major sites of pain (Figure 5-Axis I).

**Axis II distribution (Systems):** The majority of patients in the SEA (79%) and REA (92%) groups presented with musculoskeletal system and connective tissue pain (category 4) (Figure 5-Axis II).

**Axis III distribution (Temporal Characteristics of pain: Pattern of Occurrence):** A significant proportion of SEA (86%) and REA (92%) group participants suffered continuous, or nearly continuous, fluctuating severity pain (category 4) (Figure 5-Axis III).

**Axis IV distribution (Patient’s Intensity of Pain):** Half of the participants in both groups had a medium level of pain intensity for greater than 6 months. Severe pain lasting longer than 6 months represented 35.7% and 50%, of patients in the SEA and the REA groups, respectively (Figure 5-Axis IV).

**Axis -V distribution (Etiology):** The most common etiological factors identified were degenerative and mechanical causes which made up 50% and 58.3% participants in the SEA and the REA groups, respectively. Trauma/operation/burns were the second most common etiological factors for both the SEA and REA comparison groups (Figure 5-Axis V).
Figure 5: Coding Site of Primary Pain in Each Group

**Axis I - Region**

<table>
<thead>
<tr>
<th>Code number</th>
<th>Number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>000</td>
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</tr>
<tr>
<td>100</td>
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<tr>
<td>800</td>
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<tr>
<td>900</td>
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</tbody>
</table>

**Axis II - Systems**

<table>
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<th>Number of participants</th>
</tr>
</thead>
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<td>60</td>
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<td>1</td>
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<td>80</td>
<td>1</td>
</tr>
<tr>
<td>90</td>
<td>1</td>
</tr>
</tbody>
</table>

**Axis III - Temporal Characteristics of Pain: Pattern of Occurrence**

<table>
<thead>
<tr>
<th>Code number</th>
<th>Number of participants</th>
</tr>
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<tr>
<td>6</td>
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</tr>
<tr>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

1. head, face, and mouth 000
2. cervical region 100
3. upper shoulder and upper limbs 200
4. thoracic region 300
5. abdominal region 400
6. lower back, lumbar spine, sacrum, and coccyx 500
7. lower limbs 600
8. pelvic region 700
9. anal, perineal, and genital region 800
10. more than three major sites 900

1. nervous system and special senses; physical disturbance 00
2. nervous system (psych and social) 10
3. respiratory and cardiovascular 20
4. musculoskeletal system and connective tissue 30
5. cutaneous and subcutaneous and associated glands 40
6. gastrointestinal 50
7. genito-urinary 60
8. other organs or viscera 70
9. more than one system 80
10. unknown 90

1. not recorded, not applicable, not known 0
2. single episode, limited duration 1
3. continuous/ nearly continuous, nonfluctuating 2
4. continuous/ nearly continuous, fluctuating severity 3
5. recurring irregularly 4
6. Recurring regularly 5
7. Paroxysmal 6
8. sustained with superimposed paroxysms 7
9. other combinations 8
10. none of the above 9
Data concerning a second diagnosis were reported by 66.7% and 35.7% participants in the REA and the SEA group. The result obtained was similar to the primary pain. The majority of participants in both groups had a second pain of the musculoskeletal system, which was continuous or nearly continuous/fluctuating, severe lasting more than 6 months and associated with degeneration. The majority of participants in the REA group had a second pain in the lower back/lumbar spine/sacrum region, whereas those in the SEA group were likely to report pain in the coccyx or cervical region.

In addition, two participants in the REA group had a third diagnosis, which was also coded as musculoskeletal pain in the lower back and lower limbs of continuous or nearly continuous
character with medium or severe fluctuation. The pain was associated with degeneration and lasted more than 6 months.

In summary, most participants in the REA group were suffering from pain in the lower back / lumbar spine/ sacrum and coccyx region (region, 500), and in the SEA group had pain in more than three major sites. The majority of participants in both groups had pain in the musculoskeletal system (system, 30), continuous or nearly continuous/ fluctuating, medium intensity, lasting more than 6 months and associated with degeneration. Overall, there were no significant differences between the two groups in terms of primary and second diagnoses of pain (Table 18).

### Table 18: Comparison of Primary and Second Diagnoses Variables by Participants Completed Study in Each Group

<table>
<thead>
<tr>
<th></th>
<th>Primary diagnoses</th>
<th></th>
<th>Second diagnoses</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \chi^2 ) value</td>
<td>df</td>
<td>p-value</td>
<td>( \chi^2 ) value</td>
</tr>
<tr>
<td>Region</td>
<td>6.552</td>
<td>5.0</td>
<td>0.256</td>
<td>3.846</td>
</tr>
<tr>
<td>System</td>
<td>1.187</td>
<td>2.0</td>
<td>0.553</td>
<td>0.677</td>
</tr>
<tr>
<td>Character</td>
<td>0.895</td>
<td>2.0</td>
<td>0.639</td>
<td>4.128</td>
</tr>
<tr>
<td>Intensity</td>
<td>2.026</td>
<td>3.0</td>
<td>0.567</td>
<td>5.254</td>
</tr>
<tr>
<td>Etiology</td>
<td>3.198</td>
<td>3.0</td>
<td>0.362</td>
<td>1.499</td>
</tr>
</tbody>
</table>

### 4.4 Baseline clinical characteristics

#### 4.4.1 Clinical characteristics at baseline

Twenty-six of 35 participants completed the six-week treatment with the Subject Diary information. Participants’ clinical characteristics at baseline in terms of consumption of OLM, dosage of non-opioid analgesics, pain history, intensity and unpleasantness of pain, depressive symptoms and quality of life in the two groups are presented in Table 19. Pain was measured using VAS, GBS and MPQ respectively. The two groups were comparable with respect to all
of the clinical characteristics except that the average pain level reported by the SEA group was higher than that reported by the REA group [5.8 ± 1.7 (SD) vs. 4.5 ± 1.3 (SD), $t = 2.133$, $p < .05$].

Participants were taking various types of OLM or mixed OLM. The major types of OLM were codeine, oxycodone, morphine and tramadol. In the REA group, the majority of participants took tramadol, whereas codeine was most commonly taken in the SEA group. The numbers of participants who took different types of opioid are presented in Table 19.
Table 19: Comparison of Baseline Clinical Characteristics Variables of Participants Who Completed the Study

<table>
<thead>
<tr>
<th>Clinical characteristics of participants who completed the study</th>
<th>SEA N=14</th>
<th>REA N=12</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumption of OLM (mg/weekly)</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Types of OLM §</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic name:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>11</td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>3</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>3</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>MQS</td>
<td>6.19</td>
<td>6.98</td>
<td>5.57</td>
<td>9.58</td>
</tr>
<tr>
<td>Pain history (yrs)</td>
<td>13.3</td>
<td>11.2</td>
<td>15.6</td>
<td>12.6</td>
</tr>
<tr>
<td>Present pain intensity -VAS</td>
<td>5.9</td>
<td>1.7</td>
<td>4.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Highest levels of pain-VAS</td>
<td>7.0</td>
<td>1.6</td>
<td>6.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Lowest levels of pain-VAS</td>
<td>3.9</td>
<td>2.3</td>
<td>2.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Average pain-VAS †</td>
<td>5.8</td>
<td>1.7</td>
<td>4.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Duration of pain (hrs/day)</td>
<td>16.0</td>
<td>4.6</td>
<td>16.9</td>
<td>6.1</td>
</tr>
<tr>
<td>Severity of pain - GBS</td>
<td>14.3</td>
<td>2.6</td>
<td>12.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Unpleasantness of pain - GBS</td>
<td>12.7</td>
<td>2.7</td>
<td>10.9</td>
<td>3.2</td>
</tr>
<tr>
<td>PRI-sensory</td>
<td>18.1</td>
<td>8.4</td>
<td>14.2</td>
<td>8.6</td>
</tr>
<tr>
<td>PRI-affective</td>
<td>4.8</td>
<td>4.1</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>PRI-evaluative</td>
<td>2.8</td>
<td>1.7</td>
<td>2.3</td>
<td>1.7</td>
</tr>
<tr>
<td>PRI-miscellaneous</td>
<td>5.7</td>
<td>4.3</td>
<td>3.0</td>
<td>2.5</td>
</tr>
<tr>
<td>PRI-total</td>
<td>31.4</td>
<td>16.0</td>
<td>22.3</td>
<td>12.2</td>
</tr>
<tr>
<td>Present Pain Intensity (PPI)</td>
<td>3.0</td>
<td>1.1</td>
<td>2.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Depressive symptoms (BDI-II)</td>
<td>17.8</td>
<td>8.5</td>
<td>15.9</td>
<td>6.2</td>
</tr>
<tr>
<td>SF-36 Physical Functioning (PF)</td>
<td>36.5</td>
<td>22.0</td>
<td>52.1</td>
<td>24.4</td>
</tr>
<tr>
<td>SF-36 Role Physical (RP)</td>
<td>12.5</td>
<td>29.2</td>
<td>10.4</td>
<td>16.7</td>
</tr>
<tr>
<td>SF-36 Bodily Pain (BP)</td>
<td>22.5</td>
<td>12.2</td>
<td>29.2</td>
<td>16.8</td>
</tr>
<tr>
<td>SF-36 General Health (GH)</td>
<td>44.6</td>
<td>20.1</td>
<td>40.9</td>
<td>18.5</td>
</tr>
<tr>
<td>SF-36 Vitality (VT)</td>
<td>26.3</td>
<td>21.5</td>
<td>38.8</td>
<td>19.1</td>
</tr>
<tr>
<td>SF-36 Social Functioning (SF)</td>
<td>47.9</td>
<td>21.9</td>
<td>51.0</td>
<td>18.8</td>
</tr>
<tr>
<td>SF-36 Role Emotional (RE)</td>
<td>52.8</td>
<td>48.1</td>
<td>33.3</td>
<td>37.6</td>
</tr>
<tr>
<td>SF-36 Mental Health (MH)</td>
<td>56.9</td>
<td>18.7</td>
<td>63.0</td>
<td>17.2</td>
</tr>
</tbody>
</table>

Note. * indicates p < .05 is significant, two-tailed, independent-sample t –tests; † indicates average pain was significantly higher in the SEA group than that of the REA group; § indicates the number of participants who took various OLM

4.4.2 Side effects of opioid like medication at baseline

Table 20 shows that the number and percentage of participants who experienced side effects of OLM at baseline. The incidence of side effects was greater in the SEA group compared to
the REA group. On average, the incident rate of side effects was 6.3 in the SEA group and 4.7 in the REA group. The most common complaint was drowsiness in the SEA group (85.7%) and fatigue in the REA group (75%). The second most common complaints were fatigue and lethargy in the SEA group and constipation in the REA group. There were no statistically significant differences between the two groups for any side effects except for drowsiness ($\chi^2 = 5.539, p = .019$).

Table 21 shows the average severity of side effects that participants experienced in each group at baseline. The most severe symptom reported in the SEA group was drowsiness, and fatigue in the REA group. There was no statistically significant difference in the severity of side effects between two groups except for drowsiness and sedation, with the SEA group experiencing more severe symptoms.

In summary, the most commonly experienced and severe side effects were drowsiness in the SEA group and fatigue in the REA group.
### Table 20: Number and % of Participants Who Experienced Side Effects at Baseline

<table>
<thead>
<tr>
<th>Experienced Side Effects at Baseline</th>
<th>SEA N=14</th>
<th>REA N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>21.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>71.4</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>12</td>
<td>85.7*</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>8</td>
<td>57.1</td>
</tr>
<tr>
<td>Sedation</td>
<td>8</td>
<td>57.1</td>
</tr>
<tr>
<td>Lethargy</td>
<td>10</td>
<td>71.4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>Nightmares</td>
<td>5</td>
<td>35.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>35.7</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>6</td>
<td>42.9</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td></td>
</tr>
</tbody>
</table>

Incident rate: 6.3 | 4.7

Note: * indicates p < .05 is significant, chi-square tests.

### Table 21: Comparison of the Average Severity of Side effects of OLM in Each Group at Baseline

<table>
<thead>
<tr>
<th>Average severity of side effects of OLM at baseline</th>
<th>SEA N=14</th>
<th>REA N=12</th>
<th>t</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.9</td>
<td>1.4</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.4</td>
<td>0.9</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.5</td>
<td>2.6</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.5</td>
<td>3.7</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3.8</td>
<td>2.6</td>
<td>1.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1.8</td>
<td>2.3</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Sedation</td>
<td>1.8</td>
<td>2.3</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2.6</td>
<td>2.6</td>
<td>1.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.6</td>
<td>2.2</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Nightmares</td>
<td>0.9</td>
<td>1.8</td>
<td>1.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.3</td>
<td>2.1</td>
<td>2.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>2.6</td>
<td>3.7</td>
<td>1.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Note: * indicates p < .05 is significant, two-tailed, independent - samples t -tests.
4.5 The effects of EA on the primary outcomes during the treatment period

4.5.1 Dosages of opioid like medication consumption

Weekly dosages of OLM consumption were analysed with the General Linear Model (GLM) for repeated measures. There was a significant time effect \[ F (6, 144) = 13.73, p = .000 \] and group by time interaction \[ F (6,144) = 2.431, p = .029 \] but without significant group effect \[ F (1, 24) =1.278, p = .27 \], indicating that dosages of OLM were reduced in both groups over the six-week treatment period. The reduction of weekly OLM consumption between baseline and at the end of the treatment was more rapid in the REA group than the SEA group, with 64% and 46% reduction rates, respectively (Figure 6).

Paired-sample t-tests were used to assess differences within groups. The results showed that significant decreases of OLM were obtained at the end of 3rd and 6th week in the REA group, and the end of 6th week in the SEA group when compared with the baseline value \( p < .05 \). These results suggested that the effect occurred soon after the commencement of REA treatment and more slowly after the SEA treatment.
Note: †† indicates significant differences within the REA group at the time points when compared with the baseline. * indicates significant differences within the SEA group at the time points when compared with the baseline. p < .05, paired-simple t-tests.

4.5.2 Side effects of opioid like medication

Table 22 shows the number and percentage of participants who experienced side effects associated with OLM at the end of the treatment. The results showed that there was a higher incidence of side effects in the SEA group than the REA group at the end of the treatment. On average, the incident rate of side effects was 2.9 in the SEA and 2.3 in the REA group after completion of the treatment. However, chi-square tests indicate that there were no significant differences between two groups for any side effects.

The severity of each side effect was analysed individually with the GLM for repeated measures. There were significant time effects for sedation \([F (6,138) = 4.753, p = .000]\), drowsiness \([F (6,138) = 4.030, p = .001]\), dizziness \([F (6,138) = 2.241, p = .043]\), blurred version \([F (6,138) = 3.126, p = .007]\), lethargy \([F (6,138) = 2.830, p = .013]\), anxiety \([F
(6,138) = 2.171, p = .046], and constipation [F (6,138) = 2.309, p = .0037], indicating the severity of side effects were reduced during the treatment period. Significant group by time interactions were observed only for sedation [F (6,138) = 3.176, p = .006] and drowsiness [F (6,138) = 3.087, p = .007]. The reduction of the severity of sedation in the REA group (100%) was greater than that in the SEA group (89%). However, the reduction of drowsiness was greater in the SEA group than in the REA group, with 66% vs. 43%, respectively (Table 23).
Table 22: Number and % of Participants Who Experienced Side effects at the End of the treatment

<table>
<thead>
<tr>
<th>Experienced side effects of OLM at the end of the treatment</th>
<th>SEA N=14</th>
<th>REA N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>21.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3</td>
<td>21.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>64.3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>5</td>
<td>35.7</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>Sedation</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5</td>
<td>35.7</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3</td>
<td>21.4</td>
</tr>
<tr>
<td>Nightmares</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>4</td>
<td>28.6</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Incident rate</td>
<td>2.9</td>
<td></td>
</tr>
</tbody>
</table>

Table 23: Average Severity of Side effects of OLM in Each Group at baseline and the End of the Treatment

<table>
<thead>
<tr>
<th>Average severity of side effects of OLM at the end of the treatment</th>
<th>Baseline</th>
<th>At the end of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEA N=14</td>
<td>REA N=12</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Drowsiness*</td>
<td>3.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Sedation†</td>
<td>1.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Nightmares</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>2.6</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Note: † indicates statistically significant difference within the REA group at the end of the treatment when compared with the baseline. * indicates statistically significant difference within the SEA group at the end of the treatment when compared with the baseline.
4.5.3  The effects of EA on the intensity and unpleasantness of pain

4.5.3.1  Pain assessed with Visual Analogue Scale

Weekly means of present pain, average pain, and highest and lowest levels of pain were analysed with VAS. There was a significant time effect for the average pain, highest level of pain and present pain [average pain: F (6, 144) = 3.313, p = .004; highest level of pain: F (6,144) = 3.697, p = .001; present pain: F (6, 144) = 2.189, p = .047]. However, there was no group by time interaction. The results showed during the six-week treatment period, the average pain, highest level of pain, and present pain were reduced in both groups (p <.05), and the reduction was similar in both groups (p >.05) (Table 24).

There were neither significant time effects nor group by time interaction for the lowest level of pain and duration of pain. The results showed that the lowest level of pain and duration of pain were not changed in both groups over the six-week treatment period (Table 24).

Within group comparisons of average pain in the REA group indicated a significant reduction (p <. 05) at the 3rd and 6th week when compared with baseline value. In the SEA groups, significant differences were only found at the 3rd week, but not at the 6th week (Figure 7).
### Table 24: Comparison of Pain Assessed With VAS at Baseline and at the End of the Treatment in Each Group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At the end of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEA N=14</td>
<td>REA N=12</td>
</tr>
<tr>
<td></td>
<td>Mean     SD</td>
<td>Mean     SD</td>
</tr>
<tr>
<td>Average Pain</td>
<td>5.8  1.7</td>
<td>4.5  1.3</td>
</tr>
<tr>
<td>Present pain</td>
<td>5.9  1.7</td>
<td>4.9  1.5</td>
</tr>
<tr>
<td>Highest of pain</td>
<td>7.0  1.6</td>
<td>6.4  1.4</td>
</tr>
<tr>
<td>Lowest of pain</td>
<td>3.9  2.3</td>
<td>2.6  1.1</td>
</tr>
<tr>
<td>Duration of pain (hour)</td>
<td>16.0  4.6</td>
<td>16.9  6.1</td>
</tr>
</tbody>
</table>

**Figure 7: Weekly Average Pain Scores Assessed With VAS in Each Group Across All the Time Points**

Note: † indicates statistically significant difference within the REA group at the time points when compared with the baseline. * indicates statistically significant difference within the SEA group at the time points when compared with the baseline.
4.5.3.2 Pain assessed with Gracely Box Scales

The results showed that there was a significant time effect in the severity and unpleasantness of pain across all the time points [severity of pain: $F (6, 144) = 3.750, p = .002$; unpleasantness of pain: $F (6, 144) = 2.578, p = .021$], with neither group by time interaction nor group effect, indicating that both groups had less pain over the six-week treatment period. However, the reductions in the severity and unpleasantness of pain were similar in both groups.

The results also showed that when compared with the baseline, unpleasantness of pain in the REA group was significantly reduced from the 2nd week to the 5th week ($p < .05$), but not at the 6th week. There was no significant difference in the SEA group over the six-week treatment period (Figure 8).

![Figure 8: Weekly Unpleasantness of Pain Scores Assessed with GBS in Each Group across All the Time Points](image)

Note: † indicates significant difference within the REA group at the time points when compared with the baseline.
4.5.3.3 Pain assessed with McGill Pain Questionnaire

Weekly MPQ scores were analysed with the GLM for repeated measures. The results showed that there were neither time effects nor group by time interactions, indicating there were no statistically significant changes at the end of the six-week treatment in both groups in the following MPQ measures: PRI-sensory, PRI-affective and PRI-Total (Table 25). PRI-evaluative and PRI-miscellaneous were not analysed as discussed earlier.

4.5.3.4 Correlations of Visual Analogue Scale, Gracely Box Scales and McGill Pain Questionnaire at the end of the treatment

Data were analysed with Pearson r to assess the correlations between VAS and GBS, VAS and MPQ, and MPQ and GBS that were obtained at the end of the treatment. The VAS measures of present pain, average pain and highest level of pain were highly correlated with GBS measures of both severity and unpleasantness of pain. Highest level of pain and average pain were also correlated with MPQ evaluative, miscellaneous and total scores, but not MPQ sensory and affective scores; and present pain was only correlated with MPQ evaluative score. The GBS severity and unpleasantness of pain were correlated with all of MPQ measures (Table 26).

4.5.3.5 Correlation of reduction of pain and reduction of OLM consumption

Data were analysed with Pearson r to assess the correlation between OLM consumption and intensity of pain before the treatment; and the reductions of pain and OLM consumption at the end of treatment week 6. None of these variables were well correlated apart from a weak correlation between reductions in OLM consumption and pain in REA group only (Pearson r = .612*).
### Table 25: Comparison of MPQ PRI Scale Score at Baseline and at the End of the Treatment in Each Group

<table>
<thead>
<tr>
<th></th>
<th>Baseline SEA N=14</th>
<th>Baseline REA N=12</th>
<th>At the end of the treatment SEA N=14</th>
<th>At the end of the treatment REA N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>PRI - sensory</td>
<td>18.1</td>
<td>8.4</td>
<td>14.2</td>
<td>8.6</td>
</tr>
<tr>
<td>PRI - affective</td>
<td>4.8</td>
<td>4.1</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>PRI - Total</td>
<td>31.4</td>
<td>16.0</td>
<td>22.3</td>
<td>12.2</td>
</tr>
</tbody>
</table>

### Table 26: Correlation Between VAS, GBS and MPQ Scores in 26 Participants at Treatment Week Six

<table>
<thead>
<tr>
<th></th>
<th>Present pain</th>
<th>Highest level of pain</th>
<th>Average pain</th>
<th>GBS - Severity of pain</th>
<th>GBS - Unpleasantness of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRI - sensory</td>
<td>0.184</td>
<td>0.318</td>
<td>0.341</td>
<td>.411(*)</td>
<td>.391(*)</td>
</tr>
<tr>
<td>PRI - affective</td>
<td>0.169</td>
<td>0.244</td>
<td>0.266</td>
<td>.445(*)</td>
<td>.417(*)</td>
</tr>
<tr>
<td>PRI - evaluative</td>
<td>.681(**)</td>
<td>.656(**)</td>
<td>.727(**)</td>
<td>.684(**)</td>
<td>.638(**)</td>
</tr>
<tr>
<td>PRI - miscellaneous</td>
<td>0.324</td>
<td>.407(*)</td>
<td>.486(*)</td>
<td>.513(**)</td>
<td>.513(**)</td>
</tr>
<tr>
<td>PRI - total</td>
<td>0.3</td>
<td>.405(*)</td>
<td>.450(*)</td>
<td>.531(**)</td>
<td>.508(**)</td>
</tr>
<tr>
<td>Present pain intensity</td>
<td>.925(**)</td>
<td>.913(**)</td>
<td>.849(**)</td>
<td>.842(**)</td>
<td></td>
</tr>
<tr>
<td>Highest levels of pain</td>
<td></td>
<td>.919(**)</td>
<td>.874(**)</td>
<td>.788(**)</td>
<td></td>
</tr>
<tr>
<td>Average pain</td>
<td></td>
<td></td>
<td>.856(**)</td>
<td>.819(**)</td>
<td></td>
</tr>
<tr>
<td>GB-Severity of pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.898(**)</td>
</tr>
</tbody>
</table>

Note: ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed), Pearson r tests.
4.6 The effects of EA on secondary outcomes during the treatment period

4.6.1 Severity of depression

The data on severity of depression were analysed with the GLM for repeated measures. There was a significant time effect \[F (2, 46) = 3.722, p = .032\] but without group by time interaction \[F (2, 46) = .838, p = .439\], indicating the severity of depression was reduced in both REA group (10.7%) and SEA group (23%) across all the time points, and the reduction was similar between the two groups (Figure 9).

![Figure 9: A Comparison of Severity of Depression Assessed With BDI-II in Each Group Across All the Time Points](image)

4.6.2 Quality of life (SF-36 Health survey)

During the treatment period, one participant from the SEA group failed to complete items in the domain of physical functioning; and two did not complete items in the domains of role physical, bodily pain, general health, vitality and role emotional. In the REA group, one participant did not respond to the items in the domain of general health. Data from these
participants were not analysed according to the guidelines of dealing with missing data in the manual of SF-36.

Eight domains of SF-36 were analysed individually with the GLM for repeated measures. The main effect of time was significant in bodily pain (BP) \(F(2, 44) = 5.324, p = .008\), vitality (VT) \(F(2, 44) = 3.420, p = .042\) and role physical (RP) \(F(2, 44) = 4.838, p = .013\), with no group by time interaction. These results indicate that the scores of BP, VT and RP in the both groups were increased after the six-week treatment when compared with baseline, and the improvement were similar in both groups \((p > .05)\) (Figure 10).

### 4.6.3 Non-opioid analgesics assessed with MQS

Dosages of non-opioid analgesics, as indicated with MQS, at the baseline and at the end of the treatment period were analysed with ANOVA to detect the difference between groups and over time. MQS did not change significantly in either group \((tw 6: REA 4.98 \pm 8.66 vs. SEA 4.12 \pm 6.87)\).
Figure 10: The Eight Domains of SF-36 Health Scale Scores in Each Group at the Baseline and at the End of the Treatment Period
4.7 Summary

The results obtained from the per protocol analysis are summarised below.

At the end of the six-week treatment period, the consumption of OLM was significantly reduced in both groups. However, there was no significant difference between the two groups. There was a more rapid decline in consumption of OLM in the REA group than the SEA group. Some side effects related to OLM including drowsiness, dizziness, blurred vision, sedation, lethargy, anxiety and constipation were reduced in both groups. Reductions in the severity of these symptoms were similar in both groups except for sedation and drowsiness. The reduction of sedation was greater in the REA group than that in the SEA group, and reduction of drowsiness was greater in the SEA group.

The intensity of pain including average pain, present pain and highest level of pain, severity of pain and unpleasantness of pain were significantly reduced in both groups. Reduction in pain was similar in both groups. Lowest level of pain, duration of pain and pain measured by the MPQ scores were not significantly reduced in both groups.

The severity of depression was significantly reduced in the both groups, there were no group difference. The scores of SF-36 were increased in the domains of the BP, VI and RP in the both groups by a similar degree.

In summary, the results of the primary outcomes obtained from the intention-to-treat analysis were generally consistent with the per protocol analysis method except the side effects of OLM. Differences were that the REA group had lower severity of drowsiness than the SEA group.
4.8 Adverse events of EA

There were a total of 345 treatments comprising 187 SEA and 158 REA sessions. Fifty-two adverse events (AE) were recorded, 19 in the SEA group and 33 in the REA group. The rate of AE incidences per treatment in the REA group (21%) was greater than the SEA group (10%). The most frequently reported AE by the SEA group was needling pain, followed by bruising and in the REA group, bruising, followed by needling pain (Table 27). Other AE included minor itching, headache, sweating, and stiffness of neck in the SEA group, and blurring vision, tingling, sore, cramp, muscle spasm, tenderness, tiredness and weariness in the REA group.

The level of impact of each AE on life was recorded. The majority participants who experienced an AE reported no or mild impact on life. Approximately 26% and 24% participants in the SEA and REA groups, respectively, reported moderate to severe impact on their life. Often these events were alleviated by rest and disappeared over time. There were no instances where an AE required any special medical management (Table 27).

4.9 Credibility of blinding process

Credibility of the blinding process was assessed with participants’ perception of EA treatment with data collected at the end of the treatment. Twenty-three participants including 10 participants from the REA group and 13 from the SEA group completed a four-item questionnaire, which was designed to assess whether the participants could differentiate the REA from SEA treatment. No statistically significant differences were detected between the two groups in respect to their perception of the effectiveness of the treatment, allocation of real treatment, would like to pay for the service and recommend the treatment to others. The results indicated that the blinding procedure was successful (Table 28). Of the 23 participants
who completed the recommendation item of the questionnaire, 96% of them would recommend the treatment to others although only 61% thought the treatment was effective.

Table 27: The Incidents and Impact of A.E of EA Reported by Participants in each Group

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>SEA*</th>
<th>REA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact on life</td>
<td>Not at all</td>
<td>Min.</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bruising</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Lethargy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total incidents of A.E</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Total treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidences /per treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Min., minimal; Mod., moderate; Sev., severe.

Table 28: Number of Participants’ Perception of Treatment in Each Group at the End the Treatment

<table>
<thead>
<tr>
<th></th>
<th>SEA</th>
<th>REA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=13</td>
<td>N=10</td>
</tr>
<tr>
<td>Effective of treatment</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>Allocation of real treatment</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>Pay for service in the future</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>Recommend the treatment to others</td>
<td>Yes</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>
CHAPTER FIVE: LONG TERM EFFECTS OF ELECTRO-ACUPUNCTURE ON OPIOID LIKE MEDICATION CONSUMPTION, PAIN AND RELATED VARIABLES

This chapter presents the analysis of data obtained from the 12-week follow-up period of the study. The statistical methods used were paired sample t-test within each group to assess whether the outcomes obtained at the end of the treatment period were maintained. In total, 26 participants completed the treatment period. Three of them from the REA group failed to return for their follow-up assessment that included one dropping out at post-treatment week 8 (pw 8) and the other two at pw 12. Their missing values were replaced with last observed data values carried forward for the follow-up data analysis except for the SF-36 survey. The missing data in the SF-36 survey were analysed according to the guidelines for dealing with missing data in the manual of SF-36.

5.1 The effects of EA on the primary outcomes during the follow-up period

5.1.1 Dosages of opioid like medication consumption

Figure 11 illustrates the consumption of OLM in the REA and SEA groups during the 12-week follow up period. Paired sample t-tests showed that the weekly dosages of OLM in the REA group at post treatment week 8 and week 12 (pw 8 and pw 12) were significantly higher than that at the end of the treatment (pw 8: 198.9 ± 146.8 mg/wk, pw 12: 215.8 ± 177.4 mg/wk). On the contrary, the changes in the dosage of OLM in the SEA group were not statistically significant during the 12-week follow-up period when compared with the end of
treatment (113.9 ± 139.2 mg/wk). This indicates the reduction of dosage of OLM observed during the treatment period in the REA group was maintained for only four weeks after treatment, whereas the reduction in the SEA group was maintained throughout the follow-up period.

5.1.2 Side effects of opioid like medication

Results of paired sample t-tests showed that there were no significant changes in both groups for all of the OLM related-side effects during the 12-week follow-up period. Table 29 lists the average severity of side effects of OLM at the end of 6-week treatment and at pw 12. The most severe symptom reported by the SEA group was fatigue followed by drowsiness; and was constipation in the REA group followed by lethargy.
Figure 11: Consumption of OLM (Morphine Equivalent) (mg/weekly) In Each Group During the 12 Week Follow Up Period

Note: † indicates significantly increased within the REA group at the time points when compared with tw 6

Table 29: Average Severity of Side Effects of OLM in Each Group at tw 6 and pw 12

<table>
<thead>
<tr>
<th>Average severity of side effects of OLM</th>
<th>At tw 6</th>
<th></th>
<th></th>
<th>At pw12</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEA 14</td>
<td>REA 12</td>
<td>SEA 14</td>
<td>REA 12</td>
<td>SE</td>
<td>REA 12</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.6</td>
<td>1.3</td>
<td>0.2</td>
<td>0.4</td>
<td>0.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.2</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.1</td>
<td>2.4</td>
<td>0.2</td>
<td>0.4</td>
<td>0.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.9</td>
<td>2.1</td>
<td>1.5</td>
<td>1.7</td>
<td>2.0*</td>
<td>2.9</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1.3</td>
<td>2.1</td>
<td>0.9</td>
<td>1.6</td>
<td>1.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0.4</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
<td>0.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Sedation</td>
<td>0.2</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1.0</td>
<td>1.5</td>
<td>1.0</td>
<td>1.8</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.4</td>
<td>0.8</td>
<td>0.3</td>
<td>0.9</td>
<td>0.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Nightmares</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.3</td>
<td>0.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.4</td>
<td>0.9</td>
<td>1.4</td>
<td>2.9</td>
<td>0.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>1.5</td>
<td>2.9</td>
<td>0.8</td>
<td>2.6</td>
<td>1.1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Note: * indicates the most severe symptom reported at pw 12 in each group.
5.1.3 The effects of EA on the intensity and unpleasantness of pain

5.1.3.1 Pain assessed with Visual Analogue Scale and Gracely Box Scales

Results of paired sample t-tests for pain intensity, severity and unpleasantness, and duration of pain showed that there were no statically significant changes in either group during the 12-week follow-up period when compared with the treatment week six (Table 30).

Table 30: Pain Assessed with VAS and GBS in Each Group at tw 6, pw 1 and pw 12

<table>
<thead>
<tr>
<th></th>
<th>At tw 6</th>
<th></th>
<th>At pw 1</th>
<th></th>
<th>At pw 12</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEA N=14</td>
<td>REA N=12</td>
<td>SEA N=14</td>
<td>REA N=12</td>
<td>SEA N=14</td>
<td>REA N=12</td>
</tr>
<tr>
<td>Present pain intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS</td>
<td>Mean 5.4 SD 2.4</td>
<td>Mean 5.4 SD 2.2</td>
<td>Mean 5.1 SD 2.4</td>
<td></td>
<td>Mean 5.1 SD 2.4</td>
<td></td>
</tr>
<tr>
<td>Highest levels of pain</td>
<td>Mean 6.1 SD 2.1</td>
<td>Mean 6.1 SD 2.1</td>
<td>Mean 5.7 SD 2.5</td>
<td></td>
<td>Mean 5.7 SD 2.5</td>
<td></td>
</tr>
<tr>
<td>VAS</td>
<td>Mean 3.6 SD 2.5</td>
<td>Mean 3.6 SD 2.3</td>
<td>Mean 3.2 SD 2.2</td>
<td></td>
<td>Mean 3.2 SD 2.2</td>
<td></td>
</tr>
<tr>
<td>Lowest levels of pain</td>
<td>Mean 5.1 SD 2.1</td>
<td>Mean 5.1 SD 2.0</td>
<td>Mean 4.6 SD 2.1</td>
<td></td>
<td>Mean 4.6 SD 2.1</td>
<td></td>
</tr>
<tr>
<td>Average pain - VAS</td>
<td>Mean 15.6 SD 3.7</td>
<td>Mean 15.8 SD 4.5</td>
<td>Mean 17.7 SD 5.3</td>
<td></td>
<td>Mean 17.7 SD 5.3</td>
<td></td>
</tr>
<tr>
<td>Duration of pain</td>
<td>Mean 13.3 SD 3.6</td>
<td>Mean 13.4 SD 2.8</td>
<td>Mean 13.1 SD 3.6</td>
<td></td>
<td>Mean 13.1 SD 3.6</td>
<td></td>
</tr>
<tr>
<td>Severity of pain - GBS</td>
<td>Mean 11.9 SD 4.0</td>
<td>Mean 12.1 SD 2.9</td>
<td>Mean 11.6 SD 3.7</td>
<td></td>
<td>Mean 11.6 SD 3.7</td>
<td></td>
</tr>
<tr>
<td>Unpleasantness of pain</td>
<td>Mean 11.9 SD 4.0</td>
<td>Mean 12.1 SD 2.9</td>
<td>Mean 11.6 SD 3.7</td>
<td></td>
<td>Mean 11.6 SD 3.7</td>
<td></td>
</tr>
</tbody>
</table>

5.1.3.2 Pain assessed with McGill Pain Questionnaire Scores

Results of paired sample t-tests for PRI-sensory and PRI-affective showed that there were no significant changes in either group during the 12-week follow-up period when compared with the treatment week six except for the PRI-total. In the REA group, PRI-total at pw 12 was significantly increased when compared with treatment week six values (t = -2.397, p = .035), whereas no significant difference was found in the SEA group (Table 31). PRI-evaluative and PRI-miscellaneous were not analysed as discussed earlier.
### Table 31: Pain Assessed With MPQ in Each Group at tw 6 and pw 12

<table>
<thead>
<tr>
<th></th>
<th>At tw 6</th>
<th></th>
<th>At pw 12</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEA</td>
<td>REA</td>
<td>SEA</td>
<td>REA</td>
</tr>
<tr>
<td></td>
<td>N=14</td>
<td>N=12</td>
<td>N=14</td>
<td>N=12</td>
</tr>
<tr>
<td>PRI - sensory</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>17.1</td>
<td>7.3</td>
<td>13.6</td>
<td>6.4</td>
</tr>
<tr>
<td>PRI - affective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.9</td>
<td>3.7</td>
<td>2.8</td>
<td>3.2</td>
</tr>
<tr>
<td>PRI - Total</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>29.6</td>
<td>13.9</td>
<td>22.3</td>
<td>13</td>
</tr>
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<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Note: * indicates p < 0.05 when compared with the data at tw 6.

#### 5.2 The effects of EA on secondary outcomes during the follow-up period

#### 5.2.1 Severity of depression

The severity of depression during the 12-week follow-up period was analysed with the paired sample t-tests within group. The results showed that the severity of depression was not significantly changed during the whole follow-up period when compared with treatment week six for both groups. This indicated that depression in both groups was maintained during the follow-up period (Table 32).

#### 5.2.2 Quality of life (SF-36 Health survey)

Twelve participants in the SEA group and eight in the REA group completed all items of the SF-36 survey during the whole study period, respectively, and were included in the analysis. Of these, one participant in the REA group failed to complete the general health items domain, and was excluded from analysis.

Eight domains of the SF-36 were analysed individually with paired sample t-tests within group. The results showed that there were no significant changes on eight domains during the whole follow-up period compared with the treatment week six in both groups (Table 32).
Therefore, the improvements on bodily pain and mental health during the treatment period in both groups were maintained throughout the whole follow-up period (Table 32).

Table 32: Depression and QoL in Each Group at tw 6 and pw 12

<table>
<thead>
<tr>
<th></th>
<th>At tw 6</th>
<th></th>
<th>At pw 12</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEA N=14</td>
<td>REA N=12</td>
<td>SEA N=14</td>
<td>REA N=12</td>
</tr>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Depressive symptoms (BDI-II)</td>
<td>13.7</td>
<td>10.0</td>
<td>14.2</td>
<td>7.5</td>
</tr>
<tr>
<td>SF-36 Physical Functioning (PF)</td>
<td>43.1</td>
<td>24.1</td>
<td>55.4</td>
<td>21.5</td>
</tr>
<tr>
<td>SF-36 Role Physical (RP)</td>
<td>28.8</td>
<td>33.6</td>
<td>33.3</td>
<td>38.9</td>
</tr>
<tr>
<td>SF-36 Bodily Pain (BP)</td>
<td>32.5</td>
<td>20.5</td>
<td>35.8</td>
<td>16.8</td>
</tr>
<tr>
<td>SF-36 General Health (GH)</td>
<td>47.1</td>
<td>22.0</td>
<td>45.4</td>
<td>17.1</td>
</tr>
<tr>
<td>SF-36 Vitality (VT)</td>
<td>36.7</td>
<td>25.8</td>
<td>44.6</td>
<td>20.9</td>
</tr>
<tr>
<td>SF-36 Social Functioning (SF)</td>
<td>49.1</td>
<td>24.5</td>
<td>50.2</td>
<td>23.8</td>
</tr>
<tr>
<td>SF-36 Role Emotional (RE)</td>
<td>52.8</td>
<td>41.4</td>
<td>55.6</td>
<td>29.7</td>
</tr>
<tr>
<td>SF-36 Mental Health (MH)</td>
<td>60.7</td>
<td>23.6</td>
<td>66.3</td>
<td>18.2</td>
</tr>
</tbody>
</table>

5.3 Summary

At the end of the follow-up, the reduction of OLM intake obtained during the treatment period in the REA group was maintained for four weeks after treatment, and significantly increased at post treatment week 8 and the end of the follow-up, compare to the end of the treatment. However, the reduction of OLM intake obtained during the treatment period in the SEA group was maintained throughout the follow-up period. The severity of OLM-related side effects was not significantly changed in both groups throughout the follow-up period.

The intensity and unpleasantness of pain remained stable in both groups throughout the follow-up period. The secondary outcomes were not significantly changed in both groups during follow-up period.
CHAPTER SIX: DISCUSSION

The aims of the current study were to evaluate the short and long-term effect of REA on the reduction of OLM consumption, related side effects, and pain in patients with chronic pain in comparison with SEA. The results of the present study demonstrated that REA significantly reduced OLM consumption and sedation related to OLM in comparison to SEA. However, the reduction of OLM consumption was short lasting, being maintained for only four weeks after REA treatment. Pain intensity and unpleasantness were reduced in both groups to a similar degree. Due to the small sample size, these results should be interpreted with caution.

6.1 Population sample

Participants were volunteers mainly referred by medical doctors in the metropolitan Melbourne area and the majority of them were from a multidisciplinary pain management centre. In comparison to other studies of acupuncture for chronic pain patients in the community, the present group were older and had more severe pain for a longer duration of time (Carlsson & Sjolund, 2001; Leibing et al., 2002; Mendelson et al., 1983). The consumption of OLM was, however, comparable to that of musculoskeletal pain patients in other studies (Kalso, McQuay et al., 2004).

Participants of this study were all adults aged between 39 and 78 years. The mean age was 50.8 (SD 9.7) years in the SEA group and 56.1 (SD 9.6) years in the REA group. Participant age was therefore similar to results of an Australian study that reported that the prevalence of chronic pain peaked in the 45-64 year age group (Blyth et al., 2004). The majority of participant’s chronic pain was in the musculoskeletal system, with conditions such as lower back and lumbar spine pain due to degenerative disease. Not unexpectedly, this is higher than
European and Australia data reporting that about 45-50 % of chronic pain patients in the community suffer from pain in the low back (Breivik et al., 2006; Jensen, Thomsen, & Hojsted, 2006).

Pain chronicity across the participants varied greatly. The mean duration of pain was 15.6 years (SD 12.6) in the REA group and 13.3 years (SD 11.2) in the SEA group. The median pain chronicity was 9.6 years and 13 participants experienced their pain for over 10 years. Australia wide, 21% of the population are reported to have suffered pain greater than 10 years (Blyth et al., 2003). The pain duration of patients included in the present study was longer than that of a CBT programme in the same pain management clinic, which is less than 7 years (Bradbury, 2003), and of other acupuncture studies of chronic pain, which were about 9.6 years (Carlsson & Sjolund, 2001; Leibing et al., 2002; Mendelson et al., 1983).

In the present study, chronic pain of moderate intensity occurred in 50% of participants. Severe pain occurred in 50% and 35.7% of the REA and SEA groups, respectively. The prevalence of severe pain in the present study was higher than that of other convenience sample studies (Kalso, McQuay et al., 2004).

6.2 Credible sham EA design

The blinding of participants was successful as there were no differences in the patients’ perception of treatment received when comparing those allocated to REA or SEA at the end of the treatment period. The patient’s judgement appears to have been made on the basis of perceived success of the treatment.
A series of strategies were applied in the present study to ensure the credibility of the sham EA intervention. Firstly, superficial needling was applied on non-acupoints without stimulation (Vincent & Richardson, 1986). This method attempts to mimic acupuncture technique and minimize afferent stimulation. This method has been successfully used as the control in many previous studies (Chen et al., 1998; Chiu et al., 1999). Almost half (n = 27) of 45 RCTs identified in a systematic review employed this technique (Dincer & Linde, 2003). The location of sham acupoints in the present study has previously been evaluated and considered an effective and credible placebo control (Zaslawski et al., 1997). Secondly, participants with little knowledge of acupuncture were recruited so that they could not identify real from sham treatment on the basis of experience. Thirdly, this study employed a mock EA device with flashing light but no electrical current that appeared to meet the requirements of an appropriate control. Using non-functioning electrical acupuncture in sham control has been widely used as is considered a suitable and valid procedure (Chen et al., 1998; Lin et al., 2002; Sim et al., 2002; Wang et al., 1997). Participants were told that it was normal that they might or might not feel any stimulation sensation. Combination of sham intervention and mock EA appears to be a valid approach to the issue of placebo in controlled studies of EA.

### 6.3 Short and long term effects of electro-acupuncture on OLM reduction

The main findings from the present study showed that REA produced a 64% decrease in OLM intake after treatment. The dose of OLM intake was 126.1±97.3 mg/week of morphine equivalent (i.e. 18.0 mg/day) at the end of REA treatment, which is lower than
musculoskeletal pain patients’ intake in other dose reduction studies (Kalso, McQuay et al., 2004).

The group difference in reduction of OLM consumption noticed in this study was unlikely to be due to an initial difference between groups. REA and SEA groups were comparable in key variables such as age, pain history, intensity and unpleasantness of pain at worst with the exception of average pain intensity. Although the REA group consumed a higher dosage of OLM at the baseline than the SEA group did, there was no group different in OLM dosage. In addition, the use of ANOVA with repeated measure reduced the between subjects variance and increased the sensitivity of tests. It assessed both within subject changes over time as well between subject differences (Hills, 2003). However, the possibility that the REA group with a higher initial OLM dose might have experienced a quick reduction by a large amount cannot be either excluded or substantiated.

The group differences noticed in the study is also unlikely due to the blinding process inherent in the study design. The modified double-blind (patient/evaluator), sham-controlled design has eliminated the impact of patient bias on the result and, as it is not possible to blind the investigator (acupuncturist) in acupuncture studies, the assessor (an independent research assistant) collecting and summarising the data was blinded to treatment allocation. Describing the study design in this manner is consistent with current quality assessment of RCT recommendations (Jadad et al., 1996).

6.3.1 The short term effect of EA on OLM consumption

The present study demonstrated that the reduction of OLM consumption was statistically significantly rapid in the REA group (64%) compared to the SEA group (46 %) over the six-
week trial period. This result is consistent with other clinical studies on postoperative OLM requirement reporting that the decrease in postoperative OLM requirement was 38%-65% in the EA/TAES group (Chen et al., 1998; Lin et al., 2002; Wang et al., 1997). The 46% reduction in the SEA is, however, higher than the 21-23% reduction reported by other studies in patients with acute pain (Lin et al., 2002; Wang et al., 1997). No data from chronic pain patients are available.

The strong effect of SEA on OLM reduction can be attributed to several factors. The present study was to investigate the patients with chronic pain whereas previous studies were conducted in acute pain patients. An earlier review showed that chronic pain is associated with significant placebo analgesia effects, reducing pain in 30-35% of patients. Moreover, needling in sham acupoints appears to work in nearly 33-50% of patients compared with an effectiveness rate of 55-85% of cases receiving needling at true acupoints (Vincent & Richardson, 1986). This sham acupuncture effect is rarely seen in acute laboratory-induced pain (Vincent & Lewith, 1995). The study shown that despite almost 40% noticed a difference in treatment type between needles, there were no differences in outcome between real and placebo needling, indicting that the latter is not an inert control as previously thought (White, Lewith, Hopwood, & Prescott, 2003).

Secondly, the reduction in SEA could be caused by non-specific effects. It is reported that any penetration of needling on the body can produce physiological effects (Ghia et al., 1976; Lewit, 1979). Evidence was also found that acupuncture stimulation at non-classical acupoints might still produce analgesia possibly through DNIC (Le Bars, Villanueva, Bouhassira, & Willer, 1992; Vincent & Lewith, 1995). A few recent clinical trials in migraine, neck pain and fibromyalgia and OA, all shown that SEA is as effective as REA (Assefi et al., 2005; Linde et
al., 2005; Scharf et al., 2006; Zhu & Polus, 2002). Thirdly, prolonged superficial insertion into the skin might still produce a non-specific endorphin response (ter Riet, de Craen, de Boer, & Kessles, 1998), thereby reducing OLM intake even in the sham acupuncture group.

Moreover, additional encouragement offered by a third researcher, despite being blinded from the treatment allocation, could be another factor. The researcher telephoned the participants four times through the trial, and this may have been viewed positively by these patients and improved outcome. Indeed, in some pain management clinics, encouragement is the only method to assist patients to reduce OLM prior to a CBT programme (Bradbury, 2003).

All the above-mentioned factors could also be used to explain the effects of REA, which was associated with statistically significant 18% reduction. This can possibly be attributed to specific treatment characteristics, including Deqi sensation produced, the utilisation of the 2/100 EA stimulation and the acupoints selected. These factors have been proven to be essential to acupuncture analgesia (Chen et al., 1994; Chen & Han, 1992; Fei et al., 1987; Han, 2003; Han et al., 1999; Kong et al., 2005; Wang, Yao, Xian, & Hou, 1985). Which of these factors, alone or in combination, cannot be confirmed from the current study.

Apart from the percentage difference, REA had a more rapid, although shorter duration of action compared to the SEA group. The significant reduction in the REA appeared at treatment week three, while this was not evident in the SEA group until week six. The quick onset of REA effect parallels other studies in post-operative pain (Lin et al 2002). The REA group consumed less than half of morphine intake of the SEA group in the first eight hours following operating procedure in the study by Lin et al.
6.3.2 The long term effects of REA on OLM consumption

The effect of REA lasts up to four weeks after treatment whereas the effect of SEA was sustained throughout the 12-week follow up period. As previous studies focused on post-operative pain, the duration of REA effect on OLM consumption is unknown. Studies on chronic pain have indicated the long term effects of acupuncture vary from four to 52 weeks (Berman et al., 2004; Grant, Bishop-Miller, Winchester, Anderson, & Faulkner, 1999; Leibing et al., 2002; Vickers et al., 2004; Witt et al., 2005).

The difference of long-term effects between REA and SEA may have been due to the high opioid consumption of REA at baseline and the consequent ease with which it might be reduced more, the number of treatments in total, or the short-term effect of EA. A lower dose of OLM was ingested by patients in the SEA group (212.3 ± 177.8 mg/weekly) compared to the REA group (348.5 ± 303.7mg/weekly) at baseline. It is possible that OLM at a low dose is relatively easier to maintain at lower levels.

Repeated treatments are important to induce better and longer-term effects. Animal studies showed that repeated EA treatment could increase synthesis of neuropeptides in brain areas involved in pain control, and these began three weeks into the treatment and lasted for seven weeks (Bucinskaite et al., 1996). Repeated treatments also reduced mechanical hyperalgesia (C. Huang et al., 2004) and produced cumulative effects (Cui et al., 2005). Human clinical studies have also demonstrated more benefit by repetition of treatment (Martelete & Fiori, 1985; Price, Rafii, Watkins, & Buckingham, 1984). A chronic pain treatment review indicated that six or more treatments was more likely to produce significantly more positive results than fewer treatments (Ezzo et al., 2000). A 12-session treatment protocol in the current study should have been adequate to produce a long-term benefit, but this was not observed in the
REA group. The most parsimonious explanation is that REA has a short-term effect on OLM consumption.

Two analgesic points, ST36 and LI4, were selected for electrical stimulation in the present study. When one or both points are stimulated, pain threshold is significantly increased (Han et al., 1991), the limbic system is deactivated (Chiu et al., 2003; Hui et al., 2000; Wu et al., 1999; Wu et al., 2002), EOPs are released and postoperative analgesics requirement is reduced (Chen et al., 1998; Chiu et al., 1999; Lin et al., 2002; Wang et al., 1997). According to this hypothesis, the current study would be expected that this type of EA would stimulate the release of EOPs, and therefore replaced the use of exogenous OLM. The release of EOP often is short lasting for a few days. An animal study showed that after one session of EA, the prepro-enkephalin (PPE) mRNA expression in the brain increased at four hours after treatment, peaked at 48 hours, and then declined by 50% at 72 hours (Guo et al., 1996). The results indicate that after a single REA treatment the release of EOP could continue for more than three days, and therefore a treatment effect might last a similar duration. It is not clear from the literature whether, and for how long, repeated treatments prolong PPE mRNA expression and related effects.

It appears logical that discontinuation of EA stimulation would lead to a reduction of EOP release and OLM consumption would therefore increase again. This is consistent with what was observed in the current study. The increase of OLM consumption in the REA group commenced at one week after the treatment, and continued to the end of the 12-week follow up. On the other hand, the consumption of OLM in the SEA group fluctuated, and overall remained the same. The discrepancy in this change indicates that the reduction seen in the REA may be due to specific effects of EA, whereas that in SEA is explained by either non-
specific effects or factors other than EA. Further studies are required to replicate these secondary outcome observations. Such studies will need to include further controls and measurement of biologic substrates in order to confirm these observations and their associated putative mechanisms.

Currently CBT is considered an effective strategy for pain management and reducing OLM (Bradbury, 2003). The pre-requisite for entering the programme is to reduce opioid intake to an arbitrary predetermined level, for example, 60mg/day oral morphine. The time taken to reduce OLM to this level before the programme is variable and individual to each patient. No specific assistance is offered to achieve this goal except for patient education, counselling and exercise. Whatever its mode of action, EA seems to offer the potential for additional assistance to these patients, and could easily be incorporated in a multidisciplinary pain management programme.

6.4 The effects of EA on OLM related-side effects

The incidence of OLM related side effects was lower in the REA group than the SEA group at the end of the treatment. REA significantly reduced the severity of sedation compared with SEA treatment. This is consistent with previous study findings that reported that the real TAES group achieved a lower sedation score than the sham-TAES, although there were no statistically significant differences in the pain and nausea scores among groups (Chen et al., 1998). The effect observed in the current study may be due to decreased Tramadol consumption by the majority of participants in the REA group. Tramadol is known to produce sedation (MIMS online).
The severity of drowsiness was significantly reduced in the SEA group compared with the REA group. This may be due to the fact that most of participants in the SEA group took codeine phosphate that may cause drowsiness. Previous studies have also shown that the incidence of other opioid-related side effects, such as nausea and dizziness, were significantly reduced in the real TAES group compared with the sham groups (Chen et al., 1998). However, the present study found that common OLM-related side effects, such as dizziness, anxiety, lethargy and constipation, were reduced in both groups, and the group differences were not significant.

6.5 The effects of EA on pain intensity

Average pain was reduced following treatment in both groups, and the REA group (22%) tended to produce greater pain reduction than the SEA group (12%). However, there was no significant difference between the groups. Obviously, the small sample size contributes to a lack of group difference.

The reduction of pain is comparatively small in comparison to the figures reported by other authors, in which pain reductions were 56%, 40% and 19% in real acupuncture group, sham acupuncture and no treatment or standard control, respectively (Leibing et al., 2002). Similarly, in another epidemiological study of acupuncture for chronic headaches, pain reduction was about 50% after acupuncture treatment (Melchart et al., 2006).

This discrepancy is likely to be explained by the difference of the primary aims between the present study and previous studies. The current study was designed to evaluate the effect of EA on reducing the OLM consumption rather than pain level. The acupoints selected aimed to effectively stimulate the release of EOPs, but not specifically pain reduction. The primary
acupoints electrically stimulated were LI4 and ST36 and local acupoints or trigger points at the site of pain were not chosen. The local points may be essential for pain relief.

The finding in this study demonstrates that the reduction of OLM consumption is not necessarily related to the reduction of pain or the levels of pain intensity. This is likely due to a variety of psychosocial factors involved in chronic pain. As mentioned in chapter Two, 11 studies have measured postoperative OLM requirement and pain in acute pain patients and nine reported significantly reduced OLM requirement. Of these, six reported a significant reduction in OLM requirement after REA, although pain relief was not significantly different between the REA and control groups (Christensen et al., 1993; Gejervall et al., 2005; Humaidan et al., 2004; Kho et al., 1991; Lin et al., 2002; Wang et al., 1997). Only three out of nine studies found both postoperative pain and OLM requirement were significantly less in the REA group than those in sham/standard treatment control group (Chen et al., 1998; Chiu et al., 1999; Stener-Victorin et al., 2003).

In the current study, there was no correlation between the OLM consumption and pain level at baseline. After treatment, a weak correlation was present between reductions in OLM consumption and decreased pain in the REA group but not the SEA group. This may imply that OLM reduction maybe associated with pain relief in some patients, perhaps those with more evidence of activated nociceptor systems in the pathogenesis of their pain.

The patients in the REA group took the equivalent to 18mg/day of morphine at the end of the treatment and the reduction of pain intensity was 22%. This compares to 30% of mean pain relief at daily doses of 30-120 mg morphine in chronic pain patients as studied by Kalso et al (Kalso, McQuay et al., 2004). The OLM usage after REA treatment in the present study seems
to produce stronger pain reduction per unit of morphine but with a lesser pain reduction than found in this study.

The lack of a strong correlation between OLM consumption and pain might be explained by the complexities of pain pathogenesis and the fact that its relief cannot be simply induced by analgesics or acupuncture, with an associated inappropriate level of OLM intake by some patients.

As discussed above and in Chapter Two, physiological, psychological and social factors all contribute to the presentation and intensity of pain. Pain management and reduction should consider a coherent and multidisciplinary approach rather than a single treatment approach, whether it is acupuncture, analgesics or psychological counselling alone (Coeytaux et al., 2005; Meng et al., 2003; Stener-Victorin, Kruse-Smidje, & Jung, 2004).

6.6 The effects of EA on depression and QoL

The severity of depression significantly improved in both groups, however the between group difference was not statistically significant. This outcome was not the focus of the current study. Although there is evidence that acupuncture can reduce depression and anxiety (Leibing et al., 2002; Roschke et al., 2000), the selected acupoints used in the present study were not specific to depression and would be considered insufficient to produce such effects. A US study found that acupuncture at specific points improved depression in women more than those treated at non-specific acupoints (i.e. real acupoints not related to depression symptom) (Allen & Schnyer, 1998). The 11% and 23% reduction of depression scores in REA and SEA groups, respectively, might be due to the placebo effect or non specific effects of acupuncture. Nevertheless, the current result is consistent with recent systematic reviews,
which concluded there is inconsistent evidence to determine the efficacy of acupuncture compared to sham acupuncture in treatment for depression (Mukaino, Park, White, & Ernst, 2005; Smith & Hay, 2005).

Acupuncture has been reported to improve QoL in the clinical settings. Patients with chronic disease often reported improved sense of well being and QoL with repeated acupuncture treatments (Paterson & Britten, 2003). The results from clinical trials are mixed, with some reporting improved QoL in patients with pain after acupuncture treatment compared to control treatment (Carlsson & Sjolund, 2001; Coeytaux et al., 2005; Vickers et al., 2004), while others observing no significant differences between acupuncture and control groups (Berman et al., 2004; Grant et al., 1999; Kerr, Walsh, & Baxter, 2003).

In the present study, most domains of the SF-36 were not significantly improved except for BP, VI and role RP after treatment in both groups, and these improvements were not significantly different between groups. A possible explanation for the lack of group difference might be due to the low level of pain reduction. The current results are consistent with a review report which showed that QoL, like mood, are affected by the amount of pain relief achieved (Kalso, McQuay et al., 2004). The same review also reported that only three of eight studies found improvement in function or disability using opioids in chronic pain.

The role of acupuncture in depression and QoL and the respective contributing factors requires further investigation.
6.7 Safety of EA and participants’ satisfaction

The rate of adverse events (AE) per treatment in the REA group (21%) was greater than that in SEA group (10%), but the impact on the patients life reported for AE was essentially the same in the REA group (24%) compared with the SEA (26%) group. The most frequent events were needling pain and bruising in both groups. These AE did not require special medical management.

Types and severity of AE in the current study are consistent with a survey (White, Hayhoe, Hart, & Ernst, 2001) and an electrical acupuncture clinical trial in patients with osteoarthritis in the knee (Berman et al., 2004). The AE rate is however higher than 6.7% and 7% reported by the survey and the clinical trial, respectively. The difference is likely due to the modality of acupuncture and frequency of assessment. The study by White et al examined the AE during acupuncture practice which may be manual or electrical stimulated. In the study by Berman et al, AE was assessed every four weeks. Because AE in that trial were minor and did not require any medical attention as in the current study, it is possible that patients forgot to report events happened a few weeks prior to the assessment. In the current study, AE was assessed weekly, and patients were more likely to remember to report any AE happened.

Similarly, a recent study shows that about 80% of patients with chronic non-cancer pain experienced adverse events of OLM (Kalso, McQuay et al., 2004), but the current study indicated that only 21% had EA related adverse events. REA treatment appears to be relatively safe and well tolerated in the clinical management of chronic pain.

Over 90% participants were satisfied with the interventions received and would be willing to refer the treatment to others, although only 61% perceived the interventions as effective. The
discrepancy between the satisfaction rate and perception of treatment benefit were not clear. The perception of treatment did not entirely depend on the success of OLM reduction or pain because about 15% of the participants who thought they received ineffective treatment had a significant reduction in OLM consumption. Why these patients reduced OLM consumption is unknown. Such information is often qualitative and may be better elicited by semi-structured interview. Future studies should elicit details of how participants perceive the treatments. Whether treatment success is based on meaningful OLM reduction or on the impact of OLM reduction is uncertain.

6.8 Limitations of the study

There are several limitations of the present study that need to be addressed. The most important of these include the small sample size, the sources of participant recruitment, heterogenous participant characteristics and selection of acupuncture points.

The planned sample size was 110 (55 in the each of group). Due to the difficulty in participant recruitment, only 35 participants enrolled within the 18 months period in spite of intense effort and recourse to several recruitment strategies. There are several reasons that may underpin the small sample size, some of which are discussed below.

Firstly, because acupuncture is increasingly used, it has become increasingly difficult to enrol acupuncture-naive subjects. About 10% of responders had acupuncture experience and had to be excluded. Secondly, the sourcing of participants limited the recruitment capability. In the present study, participants were referred by specialists at the pain management centre and outpatient clinics in the hospital, and by local GPs surrounding the hospital premises. Advertisements were placed on the hospital website, and sent to GPs via electronic
newsletters. It is impossible to calculate the referral rate due to these strategies used. About 18 patients were referred through these strategies, which may reflect clinicians’ knowledge and attitude to acupuncture, or patients visiting their GP at times the trial was not being advertised. In a paper by Australian researchers it was suggested that media release to the public was the most effective means of recruiting participants for acupuncture clinical trials (Smith & Coyle, 2006). This strategy was not used in the current study because of the requirement to recruit those on opioids and therefore collaboration from the patients’ regular doctors was considered to be most important.

Most participants were referred from a pain management clinic. Epidemiological surveys suggest that pain clinic samples may differ in many ways from community samples. For example, the association between psychological findings and pain frequency noted in pain clinics is less frequently observed in epidemiological studies (Turk & Melzack, 2001). Their responses to treatment may also be expected to be different from those in the community. Patients referred to pain clinics also have high rates of aberrant drug related behaviour (Portenoy, 1996) and are likely to report low quality of life with inability to cope (Kerr et al., 2004). This is the case in the current study.

In addition, the participants were having pain in different locations, of varying intensity and were taking OLM at different dosages and via oral, parenteral or intradermal routes. This heterogeneity might have resulted in difficulties in further decreasing OLM intake. Moreover, there was a large individual variation of OLM consumption in the REA group which varied from 26.8 to 855 mg/week, and this variation could have impacted on the ability to decrease the consumption unevenly. Further studies should aim to recruit patients taking similar classes and doses of medications and with similar types of pain.
The selection of acupoints LI 4 and ST 36 is both an advantage and a disadvantage to the study. Unlike other studies, pain was not specifically addressed in the current project. On the basis of the principle of traditional Chinese medicine (TCM) the individualised selection of acupoints is an essential practice. However, it is important to point out that this principle restricts the ability of acupuncture clinical studies to undertake randomised, placebo controlled and blinded trials. Therefore, standardised treatment protocols requiring acupuncture at fixed acupoints remains necessary for clinical trial (Hammerschlag, 1998; Vincent & Richardson, 1986). However this narrow selection of acupoints would not be expected to substantially impact on pain located at various parts of the body, and therefore only small reductions in pain and other associated variables, such as depression and QoL, was expected.

The two acupoints were chosen for their likely effect on the primary outcome measure and because of convenience in respect of the need for stimulation. In studies on post-operative pain, chronic musculoskeletal pain and heroin addiction (Cheng & Pomeranz, 1987; Han, 1998; Wang et al., 1997), a TENS like device was given to patients who were taught to stimulate LI 4 and ST 36 daily at home. This simple protocol may decrease drop out rates due to the burden of travelling and may be more acceptable to chronic pain patients, and result in a better outcome.

6.9 Conclusions and implications

The conclusions drawn from this study are that REA is more effective than SEA in reducing self-reported exogenous opioids consumption and related sedation in patients with chronic pain. EA was also shown to be safe and acceptable. The duration of the observed effect,
however, is short term. The findings suggest that EA may be a useful adjunct therapy in chronic pain management.

Chronic pain is multidimensional, and its treatment requires a multidisciplinary approach. Future studies should examine the benefits of using EA in combination with conventional therapies in pain management. This model of EA may offer patients a method for reducing exogenous opioid consumption so that they can participate more effectively in pain management programmes.

Further studies examining the effect of acupuncture on OLM reduction should consider the following issues:

- recruitment of a large sample of participants, preferably chronic pain sufferers from the general community;
- to optimise OLM consumption in terms of types and dose prior to the study;
- to allow self-administration of acupuncture, such as transcutaneous electrical acupuncture stimulation (TEAS), so that participants can treat themselves at home and when needed; and
- to include a qualitative study to understand patients’ needs, perception and judgement of the effectiveness of outcomes.

Further studies should also examine the role of acupuncture in comprehensive pain management programmes, such as with CBT, and compare the performance of patients with and without acupuncture in that environment.
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APPENDICES

8.1 Appendix 1: EA study pamphlet

Volunteers with Chronic Pain Needed Study of Electro- Acupuncture (EA) for Chronic Pain

2004

Chinese Medicine Research Group

RMIT University &

The Barbara Walker Centre for Pain Management

St. Vincent’s Hospital Melbourne
Introduction
Chronic pain is a common complaint. Many patients with severe chronic pain take pain medications, such as opioid-like drugs, for pain relief. These medications may produce side effects, which affect their quality of life.

This study uses EA to scientifically evaluate whether EA reduces chronic pain, as well as reducing the consumption of pain medications and their side effects.

The benefit of participating in the study is that your pain and well-being will be monitored closely, and your pain may be alleviated as a result of treatment given to you.

It is necessary to have a sham group so that the effect of EA treatment can be compared with inactive treatment.

This means you have 50% chance to get into the active treatment group.

About the research
Acupuncture is a clinical procedure in which very fine needles are used to stimulate specific locations on the body surface to achieve therapeutic effects. Acupuncture is a part of Chinese Medicine, and has been used clinically for more than 2,000 years. Its use in western countries has increased over the last three decades.

The combination of acupuncture procedure with battery-operated electrical stimulation is called electro-acupuncture. This treatment method has been widely used in everyday practice for many years.

Electro-acupuncture (EA) is reported to be beneficial and safe for various types of acute pain, (such as pain after operation, pain during labour, dental extraction pain), nausea and vomiting. EA has been shown to be effective in reducing consumption of pain medications for acute pain patients. It is therefore useful to investigate the effect of EA in reducing pain medication and related side effects in patients with chronic pain within a multidisciplinary setting.

Your involvements in the study
If you agree to participate in the study, you will be asked to:

- Visit the clinic twice a week (3 days between the two visits) for six weeks to receive EA or sham treatments. Each session will last approximately 40 minutes.
- During the initial and treatment periods (8 weeks), you will complete a daily record of pain medication consumption, related side effects, pain intensity and duration, which may take you 5 minutes every day.
- During the 3 months follow up, attend the clinic monthly. Each visit may take up to 30 minutes.
- Provide us the name and dosage of medications prescribed by your medical doctor at the BWCPM.
Chinese Medicine Research Group, RMIT University and Barbara Walker Centre for Pain Management, St. Vincent’s Hospital are conducting a research project to evaluate the effect of electrical acupuncture on reducing the consumption of pain medication and pain in patients with chronic pain.

If you meet the following conditions, please contact us:

• Aged between 18 and 80;
• Suffering from non-cancer pain over more than 3 months and using opioid-like drugs for pain control;
• No previous experience with acupuncture (in the last 5 yrs);
• Have not yet undergone cognitive-behavioral therapy program;
• No heart disease;
• Not pregnant.

Research Team members:
Jessica Run Xiang Guo
BMed (Registered Acupuncturist, RMIT University)

Professor Robert Helme
FRACP, PhD (Consultant Neurologist, Barbara Walker Centre for Pain Management, St. Vincent’s Hospital, Melbourne)

Dr Zhen Zheng
BMed, PhD (RMIT University)

A/Prof. Charlie Xue
BMed, PhD (RMIT University)

If you are interested in this study, please discuss it with your doctor, psychologist, physiotherapist, or nurse.

If you would like further information, please contact:

Jessica Guo
Mobile: 0401 259 431
Telephone: (03) 9288 4681 (Message only)
Facsimile: (03) 9288 4660
Appendix 2: Invitation of patients on the waiting list to BWCPM

Dear Patients,

An Electro-Acupuncture Clinical Trial on Chronic Pain

This letter is to inform you about an electro-acupuncture clinical trial on chronic pain, which is now being conducted at the centre.

We understand that you are waiting for assessment at the Barbara Walker Centre for Pain Management (BWCPM). We are working with the Centre on a trial of electro-acupuncture, and agree that if people are waiting for the assessment and wish to try electro-acupuncture we will gladly provide treatment.

Dr Jessica Guo, a registered acupuncturist and a research student from the RMIT University, conducts this trial.

The trial attempts to evaluate the effect of electro-acupuncture on reducing pain medication and pain in chronic pain patients. If you are on pain medication, and you are interested in this trial, please make a phone call to 9925 6563 or 0401 259 431 or email: S3060693@student.rmit.edu.au to Dr. Jessica GUO.

Upon receipt of your information, Dr Guo will contact you to arrange an appointment for a further assessment to confirm your suitability for this study.

This is not part of the clinic assessment, you don’t need to pay for it, but please feel free to participate in this trial. You will be very welcome.

I look forward to hearing from you

Best Regards

Yours sincerely,

Jessica Guo
Division of Chinese Medicine
Health Science
RMIT University

Dr Andrew Muir
Director, Barbara Walker Centre School of
for Pain Management
St Vincent’s Hospital, Melbourne
Appendix 3: Expression of Interest

2003/2005 Study of Electro-Acupuncture

- Expression of Interest

Dear Participants,

Thank you for your interest in participating in the study of electro-acupuncture for chronic pain. Please find enclosed some information about the study.

It contains a number of questions to be completed. Your answer will help us assess whether you are suitable to participate.

In order to provide accurate information for this initial assessment, please read the information carefully prior to completing the forms on pages 1 and 2.

Please return the completed Expression of Interest in the enclosed prepaid envelope. Upon receipt of your information I will contact you to arrange an appointment for further assessment to confirm your suitability for this research.

I look forward to your participation and thank you for taking time to fill in this form.

Yours Sincerely

Jessica Guo

Tel: 9925 6563 or 0401 259 431

Family Name: ____________ First name: __________________

Date of birth: ________________ □ Male □ Female

Address: _____________________________________ Postcode: ________________

Telephone No.(home): ______________ Telephone No. (work): ______________

Other Contact Person: ______________ Address: __________________________________

Telephone No: (Home): ______________ (work) ________________

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1) How long have you had pain?

2) Do you use any pain medication for pain control?
   - Yes  - No

3) If Yes, Please tick (√) the pain medications you are taking at present.
   - Anamorph  - Dilauid  - Durogesic
   - Endone  - Panadeine Forte  - Pethidine Hydrochloride
   - Kapanol  - Ordine  - Physeptone
   - Panadeine  - MS Contin  - OxyContin  - Proladone
   - Tramal
   - MS Mono  - OxyNorm  - Other

4) Do you plan to move during the next 6 months?
   - Yes  - No

5) Can you visit the clinic twice a week for six weeks and monthly for three months?
   - Yes  - No

6) Do you have a pacemaker?
   - Yes  - No

7) Do you suffer from any heart disease?
   - Yes  - No

   If yes, Please give details: _____________________

8) Have you been diagnosed on epilepsy?
9) Have you had acupuncture treatment in the last 5 years?
   ☐ Yes  ☐ No

   If yes, when was the last acupuncture treatment you had?  ________________

10) Have you had been through a multidisciplinary therapy program before?
   ☐ Yes  ☐ No

11) Are you willing and able to participate in the study?
    ☐ Yes  ☐ No

12) Are you currently participating in any research?
    ☐ Yes  ☐ No
Appendix 4: Screening questionnaire

Part 1: PATIENT INFORMATION QUESTIONNAIRE

Date completed: ________________________________

1. (Please circle one) Mr / Mrs / Miss / Ms / Other (Please specify): ________________

2. Surname: ____________________________________________________________

3. Other names: _______________________________________________________

4. Address: ___________________________________________ Postcode: ______

5. Previous address (if you have moved within the last 5 years): ________________

_________________________________________ Postcode: ______

6. Telephone: (H) ___________________________ (W) _________________

7. Have you been to this hospital before? YES / NO (Please circle one)

   If YES, please indicate your UR No. (if known): __________________________

8. Medicare No.: _______________________________________________________

9. Date of birth: _______________________________________________________

10. Country of birth: _________________________________________________

11. Are you of Aboriginal and/or Torres Strait Island descent? YES / NO (Please circle one)

   If YES, please tick one: Aboriginal and Torres Strait
Aboriginal not Torres Strait

Torres Strait

12. Are you an Australian citizen or permanent resident? YES / NO (Please circle one)
   If NO, please give details: ________________________________

13. Do you need an interpreter? YES / NO (Please circle one)
   Please list all the languages you speak: ________________________________

14. Name of your General Practitioner: ________________________________
    Address: __________________________________________ Postcode: _______
    Telephone: __________________________ Fax: _________________

15. Name of your Consulting Specialist Doctor (most recently seen): ________________
    Address: __________________________________________ Postcode: _______
    Telephone: __________________________ Fax: _________________

16. Are you on a Pension? YES / NO (Please circle one)
   If YES, please indicate your Pension No.: ________________________________

17. Do you have private health cover? YES / NO (Please circle one)
   If YES, please indicate: Name of fund: ________________________________
   Membership No.: ________________________________

18. Is this visit related to (please tick one):

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a Workers’ Compensation claim?

a Third Party Accident Compensation claim?

some other legal case?

none of the above?

19. If you answered “none of the above” in Question 18, move on to Question 21.

Otherwise, please indicate who is primarily responsible for your accounts?

(please tick one) Employer Solicitor / Lawyer Insurer

Please provide the following details:

(a) Name of Employer: ________________________________
   Address: ________________________________ Postcode: _________
   Telephone: ___________________________ Fax: ____________

(b) Name of Solicitor / Lawyer: ________________________________
   Address: ________________________________ Postcode: _________
   Telephone: ___________________________ Fax: ____________

(c) Name of Insurer: ________________________________
   Address: ________________________________ Postcode: _________
   Telephone: ___________________________ Fax: ____________
   Claim No.: ________________________________

20. (a) Has your compensation been settled? YES / NO (Please circle one)
(b) If you received compensation, was it satisfactory? YES / NO (Please circle one)

(c) If your case has not been settled, when do you think it will be settled? (please tick one):

- in the next 6 months
- in the next 12 months
- in the next 1-2 years
- more than 2 years
- no idea

21. What is your marital status? (please tick one):

- Married
- Single
- Separated
- Divorced
- De facto
- Widowed

Spouse’s / Partner’s name: ________________________________

22. How many children do you have? ______  How old are your children? _______

23. Do you live … (please tick one):

- alone?
- with spouse / partner and child / children?
- with spouse / partner only?
- with child / children only?
- with other relatives?
- with friends / housemates?

24. What is your highest level of education? (please tick one):

- University
- CAE
- TAFE
- HSC
- Year 11 / Leaving Cert
- Year 10 / SC

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25. For how long have you lived in Australia? (please tick one):

- All my life
- More than 10 years
- Between 6 & 10 years
- Between 2 & 5 years
- Less than 2 years

26. What is / was your main occupation **before** your pain / injury?

27. What is your **current** work status? (please tick one):

- Full time work
- Part time work
- Voluntary work
- Home duties
- Retired
- Student
- Unemployed due to pain
- Retraining
- Unemployed due to other reasons (please specify): ____________

28. What is your **current** source of income? (please tick all that apply):

- Workers’ Compensation insurance
- Sickness Benefits
- Age Pension
- Invalid Pension
- Wages / Salary
- Spouse’s / Partner’s earnings
Questions 29 to 34 are concerned with **paid** work.

29. If you are working, is your work restricted due to pain?

   YES / NO / NOT APPLICABLE (Please circle one)

30. If you are working, how much time have you taken off work due to pain in the last year?

   _____ months / _____ weeks / NOT APPLICABLE

31. If you are not working (and you are not retired), how long is it since you last worked?

   _____ months / _____ weeks / NOT APPLICABLE

32. If you are not working now, do you have a job to go back to?

   YES / NO / NOT APPLICABLE (Please circle one)

33. If you are not working now, have you attempted to return to work in the last year?

   YES / NO / NOT APPLICABLE (Please circle one)

   If YES, how long did it last?

   (If you returned to work more than once, what was the longest period?) (please tick one):

   Less than 1 week         3 - 6 months         1 - 4 weeks

   7 months – 1 year        5 – 12 weeks        More than 1 year
34. If you are not working now, and you would like to return to work, do you feel you are currently able to work at your regular job? (please tick one):

- As much as I could prior to my pain / injury
- Only with reduced hours
- Only with reduced hours and a lot of help
- In my present condition I can’t work at all
- Not applicable

35. Do you know anyone with chronic (long term) pain problems? YES / NO (Please circle one)

   If YES, please describe the nature of their relationship with you (e.g. father, mother, friends, colleagues, etc.):

36. Do you know anyone with chronic (long term) illness which does not involve chronic pain?

   YES / NO (Please circle one)

   If YES, please describe the nature of their relationship with you (e.g. father, mother, friends, colleagues, etc.):

37. Have you ever smoked regularly? YES / NO (Please circle one)

   If you are still smoking regularly, how many cigarettes do you smoke in a normal day? __

38. Do you drink alcohol regularly? YES / NO (Please circle one)

   If YES, (a) on how many days in a week do you usually have a drink? _______

   (b) roughly, how many drinks do you usually have on these days? _______
(c) do you ever drink alcohol to relieve your pain?  YES / NO (Please circle one)

39. How many cups of tea do you drink per day?  ____________________________
   ______

40. How many cups of coffee do you drink per day?  ____________________________
Part 2: PAIN HISTORY

1. Please describe the pain problem that brings you to the clinic.

___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________

2. Please indicate with an X on these figures where your main pain is. Shade any area where your pain spreads. Please number (2, 3, 4, etc) any other areas where you have pain.
3. When did your pain first start? Please be as exact as possible.

   DAY [   ] MONTH [   ] YEAR [   ]

4. If your pain comes and goes, when did the present episode of pain start? (Answer this only if different from Question 1.)
   DAY [   ] MONTH [   ] YEAR [   ]

5. How did your pain begin? (tick ONE; if more than one applies, tick the one which applies BEST)
   1 [   ] Accident at work
   2 [   ] At work, but not involving an accident
   3 [   ] Accident at home
   4 [   ] Car accident
   5 [   ] After surgery
   6 [   ] After an illness
   7 [   ] Pain just began, no clear reason
   8 [   ] Other reason/s (please describe) ____________________________________________

6. Which statement best describes your pain? (If none is exactly like your pain, please tick the closest statement)
   1 [   ] Always present, always the same intensity
   2 [   ] Always present, intensity varies
   3 [   ] Usually present, but have short periods without pain
   4 [   ] Often present, but have pain-free periods lasting up to several hours
   5 [   ] Often present, but am pain-free for much of the day
   6 [   ] Occasionally present for brief periods, but not every day
   7 [   ] Rarely present – have pain episodes every now and then, with days or weeks in between
7. What makes your pain worse? (you may tick more than one)

<table>
<thead>
<tr>
<th>Sitting</th>
<th>Household chores</th>
<th>Cold weather</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standing</td>
<td>Everything</td>
<td>Hot weather</td>
<td>Stress</td>
</tr>
<tr>
<td>Lying-down</td>
<td>Loud noise</td>
<td>Wet weather</td>
<td>Tension</td>
</tr>
<tr>
<td>Lifting</td>
<td>Working</td>
<td>Weather changes</td>
<td>Driving</td>
</tr>
<tr>
<td>Bending</td>
<td>Any movement</td>
<td>Walking</td>
<td>Going up/down stairs</td>
</tr>
<tr>
<td>No clear reason</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>(please describe)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8. What makes your pain better? (you may tick more than once)

<table>
<thead>
<tr>
<th>Sitting</th>
<th>Watching TV</th>
<th>Cold weather</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standing</td>
<td>Working</td>
<td>Hot weather</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Lying-down</td>
<td>Warm/hot bath</td>
<td>Pressure</td>
<td>Rest</td>
</tr>
<tr>
<td>Stretching</td>
<td>Warm/hot shower</td>
<td>Massage/rubbing</td>
<td>Nothing</td>
</tr>
<tr>
<td>Relaxing</td>
<td>Tablets</td>
<td>Walking</td>
<td>Being with other people</td>
</tr>
<tr>
<td>Reading</td>
<td>Hot/cold packs</td>
<td>Keeping busy</td>
<td>Keeping my mind off pain</td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>(please describe)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. Please rate the **intensity** of your pain by circling a number on the following scales. For every question: 0 = “no pain at all” and 10 = “worst pain imaginable”
(a) How intense is your pain at this moment?

0   1   2   3   4   5   6   7   8   9   10

No pain     Worst pain imaginable

(b) What were the highest and lowest levels of your pain in the last week? (make 2 circles)

0   1   2   3   4   5   6   7   8   9   10

No pain     Worst pain imaginable

(c) What was the usual level of pain in the last week?

0   1   2   3   4   5   6   7   8   9   10

No pain     Worst pain imaginable

10. Some of the words below describe your present pain. Underline only those words which best describe it. Use only one word in each group. If more than one word in a group describes your pain, choose the one that describes it best. If no words in a group describe your pain, leave it and go on to the next one.

1. flickering  
   quivering  
   pulsing  
   throbbing  
   beating  
   pounding

2. jumping  
   flashing  
   shooting

3. pricking  
   boring  
   drilling  
   stabbing  
   lancinating

4. sharp  
   cutting  
   lacerating

5. pinching  
   pressing  
   gnawing  
   cramping  
   crushing

6. tugging  
   pulling  
   wrenching

7. hot  
   burning  
   scalding  
   searing

8. tingling  
   itchy  
   smarting  
   stinging

9. dull  
   sore  
   hurting  
   aching  
   heavy

10. tender  
    taut  
    rasping  
    splitting

11. tiring  
    exhausting

12. sickening  
    suffocating

13. fearful  
    frightful  
    terrifying

14. punishing  
    gruelling  
    cruel

15. wretched  
    blinding
11. MEDICATION

(a) Do you think you need more medication, or stronger medication, than you are currently taking?
   To answer, circle one of the numbers on the scale below.

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th>Agree</th>
<th>Unsure</th>
<th>Disagree</th>
<th>Disagree strongly</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Strongly</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td></td>
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<td>3</td>
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<td>4</td>
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<td>5</td>
<td></td>
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</tbody>
</table>

(b) Please list all of the medications you are taking at present:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>How Often?</th>
<th>Any side effects?</th>
<th>Date started</th>
</tr>
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<tbody>
<tr>
<td></td>
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</tbody>
</table>

Please list all the medications you have taken in the past for your pain:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>How Often?</th>
<th>Any side effects?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

(d) Please list any allergies you may have:
12. Since your pain began, which of the following people have you seen about it?

1 [ ] acupuncturist

2 [ ] anaesthetist

3 [ ] chiropractor

4 [ ] homeopath

5 [ ] hypnotherapist

6 [ ] neurologist

7 [ ] neurosurgeon

8 [ ] occupational therapist

9 [ ] orthopaedic surgeon

10[ ] physiotherapist

11[ ] psychologist

12[ ] psychiatrist

13[ ] rheumatologist

14[ ] pain clinic

15[ ] general practitioner

16[ ] other/s (please specify)

13. Which of the above have you found helpful so far?
14. Based on your experiences so far, what do you **realistically expect** will happen to your pain in the coming months? (TICK ONE)

1 [   ] It will get worse

2 [   ] It will not change

3 [   ] It will be reduced by 25%

4 [   ] It will be reduced by 50%

5 [   ] It will be reduced by 75%

6 [   ] It will be completely relieved or cured

15. If your pain could be reduced, but not completely, how much of a reduction would there need to be for you to feel you could live with it?

My pain would need to be reduced by ________% for me to be able to live with it.

16. Do you think that your pain may be due to a serious disease which your doctors have not found or have not told you about? (Circle one)

YES / NO / NOT SURE

Are there any questions you would like answered after your assessment at this pain clinic?

(please write)

………………………………………………………………………………………………………..

………………………………………………………………………………………………………..

17. TIME LINE
List by year (starting at childhood) all illnesses and operations you have had since childhood.
Thank you for completing this questionnaire. It will help us to understand your pain problem.

Finally, for a full assessment and applicable treatment, we need to be able to liaise with your treating practitioners, and where applicable, your legal and insurance representatives. Thus we ask you to sign the following consent:

I give permission for the health professionals of the Barbara Walker Centre for Pain Management to discuss my pain problem with other professionals, and to receive information that is relevant to my pain management.

Signature: _____________________________

Witness: ______________________________

Date: ________________________________ [ ] [ ]
8.5 Appendix 5: Advertisement to website of SVH

VOLUNTEERS NEEDED

An acupuncture trial for patients with chronic pain is being conducted at the Barbara Walker Centre for Pain Management (BWCPM), St Vincent’s Hospital, Melbourne. This trial aims to reduce opioid-like medications consumption.

This study has been approved by Human Research Ethics Committees of St. Vincent’s Hospital and the RMIT University. Please note that this is a research project, and not a clinical service provided by the BWCPM.

The study expects to recruit patients who are suffering from non-malignant pain present for over 3 months and who are using opioid-like medication for pain control. Subjects must have had no experience of electrical acupuncture within the previous six months.

We would appreciate it if you can refer appropriate patients to the study.

For further information, please contact Ms Jessica Guo on 9925 6563 or 0401 259 431, or email: s3060693@student.rmit.edu.au
Appendix 6: Invite Medical Doctors at SVH to refer patients

Dear Dr.

We are writing to inform you of an electro-acupuncture clinical trial for patients with chronic pain, which is being conducted at the Barbara Walker Centre for Pain Management. This study has been approved by Human Research Ethics Committees of the St. Vincent’s Hospital and the RMIT University.

This trial is a randomized, single blind and sham controlled acupuncture study. It is evaluating the effect of electro-acupuncture on reducing pain and pain medication in patients with chronic pain. The patients will receive 12 sessions of treatments in a period of six weeks, and will be followed up monthly for three months.

This trial is neither a part of the clinic assessment, nor a treatment provided by the BWCPM. It is a research project to help better understand the use of electro-acupuncture in pain management.

We would appreciate if you or your staff could refer any suitable patients to the study. We have attached a brochure regarding this study for your use and/or for display in the waiting room of your clinic.

If you would like any further information about this study, please don’t hesitate to contact Jessica Guo on 9925 6563 or 0401 259 431, or by email: s3060693@student.rmit.edu.au.

Jessica Guo (B.Med) is a Registered Acupuncturist and a Student Researcher from the Division of Chinese Medicine, School of Health Sciences, RMIT University.

Yours sincerely,

Professor Robert Helme  
Consultant Neurologist  
Principal Researcher  
Barbara Walker Center for Pain Management  
St Vincent’s Hospital, Melbourne

Dr Andrew Muir  
Director, Barbara Walker Center for Pain Management  
St. Vincent’s Hospital, Melbourne
Appendix 7: Advertisement sent to GPs

VOLUNTEERS NEEDED

A randomised placebo controlled acupuncture trial for patients with chronic pain is being conducted at the Barbara Walker Centre for Pain Management (BWCPM), St Vincent’s Hospital, Melbourne. This trial aims to reduce opioid-like medications consumption.

This study has been approved by Human Research Ethics Committees of St. Vincent’s Hospital and the RMIT University. Please note that this is a research project, and not a clinical service provided by the BWCPM.

The study expects to recruit patients who are suffering from non-malignant pain present for over 3 months and who are using opioid-like medication for pain control. Subjects must have had no experience of electrical acupuncture within the previous six months.

We would appreciate it if you can refer appropriate patients to the study.

For further information, please contact Ms Jessica Guo on 9925 6563 or 0401 259 431, or email: s3060693@student.rmit.edu.au
8.8 Appendix 8: Subject Diary

Subject Diary

Please circle the relevant week

Pre-treatment: Week 1 2
During treatment: Week 1 2 3 4 5 6
Post treatment: Week 4 8 12

Period: From / / to / /

Please complete Four Forms:

Form 1 Pain Intensity (VAS)
Form 2 Pain medications Taken
Form 3 Side Effects of Pain Medications
Form 4 Report of Adverse Event

We hope and expect you will be able to reduce your opioid medications during the study
Explanation on how to use the Subject Diary

Welcome to the study. Please complete this diary, as it is a very important part of the assessment.

Your Diary gives us information about

- the dosage of pain medications you are taking
- the severity of related side effects
- the amount of pain you are experiencing and
- aspects of your life which may be affected by the pain

Please take 5 minutes each day to fill in the diary, and do so at the end of the day.

Please only rate the intensity and unpleasantness of the pain for which you are referred to Barbara Walker Centre for Pain Management.

When you finish a one-week assessment, please check whether you have filled in the date and your name. Return it to the Barbara Walker Centre for Pain Management, St. Vincent’s Hospital when you come for treatment.

The data collected may be published as group data, and no personal information will be identified.

Thanks for your co-operation.
The following are examples of how to use the scale enclosed and how to record the pain medication doses on Form 2.

For example, if you draw a line on the scale, the distance from 0 to the line is 3.5 cm, which means your pain is 3.5 out of 10.

1) How intense is your pain at this moment?

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>worst pain</td>
</tr>
<tr>
<td>At all</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>imaginable</td>
</tr>
</tbody>
</table>

If you draw a line from 6:50 am to 9:10 pm, which means your pain never stops during this period time. You may use more than one line over the 24hrs, if you need to.

4) When did you feel the pain today?

<table>
<thead>
<tr>
<th>6am</th>
<th>8am</th>
<th>10am</th>
<th>12pm</th>
<th>2pm</th>
<th>4pm</th>
<th>6pm</th>
<th>8pm</th>
<th>10pm</th>
<th>12am</th>
<th>2am</th>
<th>4am</th>
<th>6am</th>
</tr>
</thead>
</table>

Pain Medication Taken

Please put the number associated the pain medications in the related columns (see the listed of pain medications below).

<table>
<thead>
<tr>
<th>Date</th>
<th>Medication 1</th>
<th>Medication 15</th>
<th>Medication 17</th>
<th>Medication 18</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/05/04</td>
<td>3</td>
<td>15</td>
<td>17</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Doses Taken</td>
<td>Doses Taken</td>
<td>Doses Taken</td>
<td>Doses Taken</td>
<td>Doses Taken</td>
</tr>
<tr>
<td>1-2 am</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4 am</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-6 am</td>
<td></td>
<td></td>
<td>100 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-8 am</td>
<td>5 mg</td>
<td>5 mg</td>
<td>500 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-10 am</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11am-12 pm</td>
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</tr>
<tr>
<td>1-2 pm</td>
<td></td>
<td></td>
<td>500 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4 pm</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>5-6 pm</td>
<td></td>
<td></td>
<td>100 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-8 pm</td>
<td>10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-10 pm</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>11am-12 pm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15 mg</td>
<td>5 mg</td>
<td>1000 mg</td>
<td>200 mg</td>
<td></td>
</tr>
</tbody>
</table>

List of Pain Medications:
1. Anamorph
2. Dilaudid
3. Durogesic
4. Pethidine Hydrochloride
5. Endone
6. Ordine
7. Physeptone
8. Panadeine Forte
9. Kapanol
10. OxyContin
11. Proladone
12. Panadeine
13. MS Contin
14. OxyNorm
15. Tramal
16. MS Mono
17. Others
18. Celebrex
(The participants were asked to fill out this sheet daily for seven days)

**Pain Intensity (VAS)**

1) How intense is your pain **at this moment?**

   ![](image1.png)

2) What are the **highest and lowest** levels of your pain today?

   ![](image2.png)

3) What is the **average** level of pain today?

   ![](image3.png)

4) When did you feel the pain today?

   ![](image4.png)
5) How **strong** is the average level of your pain today?

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>EXTREME INTENSE</td>
</tr>
<tr>
<td>19</td>
<td>VERY INTENSE</td>
</tr>
<tr>
<td>18</td>
<td>INTENSE</td>
</tr>
<tr>
<td>17</td>
<td>STRONG</td>
</tr>
<tr>
<td>16</td>
<td>SLIGHTLY INTENSE</td>
</tr>
<tr>
<td>15</td>
<td>BARELY STRONG</td>
</tr>
<tr>
<td>14</td>
<td>MODERATE</td>
</tr>
<tr>
<td>13</td>
<td>MILD</td>
</tr>
<tr>
<td>12</td>
<td>VERY MILD</td>
</tr>
<tr>
<td>11</td>
<td>WEAK</td>
</tr>
<tr>
<td>10</td>
<td>VERY WEAK</td>
</tr>
<tr>
<td>9</td>
<td>FAINT</td>
</tr>
<tr>
<td>8</td>
<td>NO PAIN SENSATION</td>
</tr>
</tbody>
</table>

6) How **unpleasant** is the average level of your pain today?

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>20</td>
<td>EXTREME INTENSE</td>
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<tr>
<td>19</td>
<td>VERY INTENSE</td>
</tr>
<tr>
<td>18</td>
<td>INTENSE</td>
</tr>
<tr>
<td>17</td>
<td>STRONG</td>
</tr>
<tr>
<td>16</td>
<td>SLIGHTLY INTENSE</td>
</tr>
<tr>
<td>15</td>
<td>BARELY STRONG</td>
</tr>
<tr>
<td>14</td>
<td>MODERATE</td>
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<td>13</td>
<td>MILD</td>
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<tr>
<td>12</td>
<td>VERY MILD</td>
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<td>11</td>
<td>WEAK</td>
</tr>
<tr>
<td>10</td>
<td>VERY WEAK</td>
</tr>
<tr>
<td>9</td>
<td>FAINT</td>
</tr>
<tr>
<td>8</td>
<td>NO PAIN SENSATION</td>
</tr>
</tbody>
</table>

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**Pain Medication Taken**

Please put the number associated the pain medications in the related columns (see the listed pain medications below).

<table>
<thead>
<tr>
<th>Time</th>
<th>Medication Doses Taken</th>
<th>Medication Doses Taken</th>
<th>Medication Doses Taken</th>
<th>Medication Doses Taken</th>
<th>Medication Doses Taken</th>
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</thead>
<tbody>
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<td>1-2 am</td>
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<td>3-4 am</td>
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<td>5-6 am</td>
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<td>7-8 am</td>
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<tr>
<td>9-10 am</td>
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<tr>
<td>11 am-12 pm</td>
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<td>1-2 pm</td>
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<tr>
<td>11 pm-12 am</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
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<td></td>
</tr>
</tbody>
</table>

**List of Pain Medications:**

1. Anamorph
2. Dilauidid
3. Durogesic
4. Pethidine Hydrochloride
5. Endone
6. Ordine
7. Physeptone
8. Panadeine Forte
9. Kapanol
10. OxyContin
11. Proladone
12. Panadeine
13. MS Contin
14. OxyNorm
15. Tramal
16. MS Mono
17. Others_________
Side Effects of Pain Medication

(Fill in this form at the end of the week)

The severity of each symptom is defined by the scale below (0 = no symptom; 10 = very severe symptoms). Please indicate your response.

1. Nausea
   [ ]
   0 (No symptom at all) — 10 (Very severe)
2. Vomiting
   [ ]
   0 (No symptom at all) — 10 (Very severe)
3. Dizziness
   [ ]
   0 (No symptom at all) — 10 (Very severe)
4. Fatigue
   [ ]
   0 (No symptom at all) — 10 (Very severe)
5. Drowsiness
   [ ]
   0 (No symptom at all) — 10 (Very severe)
6. Blurring of vision
   [ ]
   0 (No symptom at all) — 10 (Very severe)
7. Sedation
   [ ]
   0 (No symptom at all) — 10 (Very severe)
8. Lethargy
   [ ]
   0 (No symptom at all) — 10 (Very severe)
9. Anxiety
   [ ]
   0 (No symptom at all) — 10 (Very severe)
10. Nightmares
    [ ]
    0 (No symptom at all) — 10 (Very severe)
11. Constipation
    [ ]
    0 (No symptom at all) — 10 (Very severe)
12. Other (please describe)
    [ ]
    0 (No symptom at all) — 10 (Very severe)
Report of Adverse Events for Acupuncture

(Fill in this form at the end of the week)

(Completed by patients)

Please record any unexpected symptoms during your acupuncture treatment or after your treatment. You don’t need to fill in the form if you don’t have any discomfort, you still need to return this to us even it is not filled.

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Date</th>
<th>How long does it last</th>
<th>Impact on your life</th>
<th>How do you manage it?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not at all (0)</td>
<td>Minimal (1)</td>
</tr>
<tr>
<td>Fainting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8.9 Appendix 9: Perception of EA treatment

Perception of EA treatment

1) Do you think your treatment is effective?
   □ Yes   □ No

2) Do you think you are in the real acupuncture treatment group?
   □ Yes   □ No

3) Would you like to pay for the service in the future?
   □ Yes   □ No

4) Would you like to refer acupuncture to your friends when they suffer pain?
   □ Yes   □ No
8.10 Appendix 10: Participant Information

ST. VINCENT’S HOSPITAL

PARTICIPANT INFORMATION

Version: Two
Dated: 15 March 2004
Site: St. Vincent’s Hospital, Melbourne

NAME OF PARTICIPANT: [omegaprivate]
U.R.NO: [omegaprivate]
FULL PROJECT TITLE: The effect of electro-acupuncture on reducing pain medication consumption in patients with chronic pain

Principal Researcher: Prof. Robert D Helme
Associate Researcher(s): Dr. Zhen Zheng
A/Prof. Charlie Xue
Research student: Jessica Run Xiang Guo

This Participant Information and Consent Form is 8 pages long. Please make sure you have all the pages.

1. Your Consent
You are invited to take part in this research project.

This Participant Information contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project. You are free to withdraw at any time but your data will be retained because it is necessary for the validity of this project.
You will be given a copy of the Participant Information and Consent Form to keep as a record.

2. **Purposes and Background**

The purpose of this project is to examine whether electro-acupuncture reduces chronic pain, as well as reducing the dosage of pain medications, in particular, opioid-like medications, and their related side effects.

Many patients with severe chronic pain take strong pain medications, such as opioid-like medications, for pain relief. These medications may produce side effects, which affect their quality of life.

Acupuncture is a clinical procedure, in which very fine needles are used to stimulate specific locations on the body surface to achieve therapeutic effects. Acupuncture is a part of Chinese Medicine, and has been used clinically for more than 2,000 years. Its use in western countries has increased over the last three decades. The combination of acupuncture procedure with battery-operated electrical stimulation is called electro-acupuncture. This treatment method has been widely used in everyday practice for a number of decades.

Electro-acupuncture (EA) is reported to be beneficial and safe for various types of acute pain, such as pain after operation, pain during labour, dental extraction pain, nausea and vomiting, and has been shown to reduce the consumption of pain medications in acute pain patients. It is therefore useful to investigate the effect of EA in reducing pain medication dosage and their related side effects in patients with chronic pain within a multidisciplinary setting.

The device is an acupuncture stimulator manufactured by the Meyer Medical Electronics. It has a width of 205 mm, length 175 mm and height 80 mm and consists of a black plastic box and 4 pairs of metal stimulator clips. This instrument will be used to stimulate acupoints with electrical pulses via stimulator leads.

The electrical stimulation machine to be used in this study is a modified version of an EA machine that has not been approved for marketing by the Therapeutic Goods Administration (TGA) of Australia and therefore its use in this study is experimental.

A total of 120 people will participate in this project.

You are invited to participate in this research project because you suffer from chronic pain and take pain medications including opioid-like medication for pain relief. This trial has been initiated by the above mentioned researchers.

The results of this research project will be used to help researcher Ms Jessica Run Xiang Guo to obtain the degree of Master of Applied Sciences (Chinese Medicine) from the RMIT University.

3. **Procedures**

Participation in this project will involve a two-week initial monitoring and measurements, a six-week treatment and a twelve-week follow up. You will be asked to:

- Visit the clinic twice a week (3 days between visits) for six weeks to receive electro-acupuncture or sham treatments. Each treatment will last for 25 minutes.

- Complete a daily record of pain medication consumption and related side effects, pain intensity and duration, which may take you 5 minutes daily for 6 weeks.
Attend the clinic monthly, for three months, for follow-up appointments. Each appointment may take 30 minutes.

Allow us to obtain the name and dosage of medications prescribed by your medical doctor at the Barbara Walker Centre for Pain Management.

It is necessary to have an inactive treatment group who will receive sham acupuncture, so that the true effect of electro-acupuncture treatment can be demonstrated. Sham acupuncture is a form of placebo treatment with minimal effect on your body. It is used to show whether the real treatment has a true effect. Once you have met the inclusion and exclusion criteria, you will be allocated randomly into one of the two groups (using real or sham acupuncture). Please note that you will have a 50% chance of being placed in an inactive treatment group. However, acupuncture in this project is not intended to replace any other therapy.

In both treatment groups, six to ten needles for each treatment will be inserted. The area of insertion will depend on the location of pain and Chinese Acupuncture theory.

Needles may be inserted in legs, arms, trunk or scalp, and then an electrical stimulator will be connected to the needles.

Project will be conducted at Barbara Walker Centre for Pain Management, St. Vincent’s Hospital, Melbourne.

4. Possible benefits
The benefit of participating in the study is that your pain and well-being will be monitored closely, and your pain may be alleviated as a result of treatment given to you.

We cannot guarantee or promise that you will receive benefit from this project.

5. Possible Risks
Possible risks, side effects and discomfort may be associated with the electro-acupuncture procedure.

Acupuncture has been reported to be associated, in a very few cases, with minor risks, such as fainting, infection, and minor bruising, as needles may puncture small blood vessels during the procedure. Precautions will be taken to avoid inserting needles too deeply or into nerves, arteries or internal organs. There is no evidence that acupuncture treatment may result in psychological damage. Only disposable needles will be used and they are much thinner than needles used for injection. The acupuncturist is a registered practitioner with the Chinese Medicine Registration Board of Victoria.

Electro acupuncture is widely used in everyday practice with an excellent safety profile. EA provides stronger stimulation than regular acupuncture. In a very few cases, therefore, fainting may happen if some people have an enhanced response to acupuncture treatment. Bending of needles can also happen if you alter posture too much during the treatment or if muscle contraction is too strong as a result of strong electrical stimulation. Caution will be taken to avoid such risks. In addition, any electrical current when passed through a human body may interfere with the human electromagnetic field. For this reason, people who have severe heart diseases, epilepsy or wear a pacemaker are not suitable for electro acupuncture. If you have any of the above-mentioned conditions, you will be excluded from the study.
Some people may experience minor pricking sensations during initial treatment with electro acupuncture. This normally is reduced in later treatment.

The effects of electro acupuncture on the unborn child and on the newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the first six weeks of the study. You must not participate in the study if you are pregnant or trying to become pregnant, or breast-feeding. If you do become pregnant whilst participating in the study you should advise the principal researcher immediately. He/she will withdraw you from the study. You must not continue in the study if you become pregnant.

There may be additional unforeseen or unknown risks.

6. Other Treatments Whilst on Study
It is important to tell your doctor and the research staff about any treatments or medications you may be taking, including non-prescription medications, vitamins or herbal remedies and any changes to these during your participation in the study.

7. Alternatives to Participation
The electro-acupuncture procedure is a potential alternative to pain medications, in particularly opioid-like medications. In this research project, patients will able to continue with their routine therapies.

8. Privacy, Confidentiality and Disclosure of Information
Patients’ personal information and other relevant data will be stored in a password protected computer program. Only researchers involved in the project have the access to the data. The information will be retained by the RMIT University for 15 years. At the end of the period, the documents will be destroyed according to the University’s document disposal procedure.

Any information obtained in connection with this research project that can identify you will remain confidential and will only be disclosed with your permission, except as required by law. If you give us your permission by signing the Consent Form, we plan to share the results with others researchers through conferences and publications in academic journals.

Your health records and any information obtained during the study are subject to inspection (for the purpose of verifying the procedures and the data) by the Australian Government’s Therapeutic Goods Administration (TGA) and authorised auditors or representatives from the sponsor, St Vincent’s Hospital, Melbourne or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

In any publication, information will be provided in such a way that you cannot be identified.

9. New Information Arising During the Project
During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person(s) supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.
10. Results of Project
The participants will be informed of the summary of the results in writing when the research project is completed.

11. Further Information or Any Problems
If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact the researcher Ms Jessica Guo. The researchers responsible for this project are Ms Jessica Guo on 0401 259 431 or E-mail s3060693@student.rmit.edu.au, and Prof Robert Helme on 9288 4681.

12. Other Issues
If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact the Patient Representative at St Vincent’s Hospital on 9288 2211, or the Secretary of the Human Research Ethics Committee at the St Vincent’s Hospital on 9288 3930, or the Secretary, RMIT Human Research Ethics Committee, University Secretariat, RMIT, GPO Box 2476, Melbourne, 3001. Tel: 9925 1745.

You will need to tell the secretary the name of one of the researchers given in section 11 above.

13. Participation is Voluntary
Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the pain management clinic.

You are free to withdraw from this study at any stage but your data will be retained because it is necessary for the validity of this project.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

14. Reimbursement for your costs
You will not be paid for your participation in this trial.

15. Ethical Guidelines
This project will be carried out according to the National Statement on Ethical Conduct in Research Involving Humans (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.
The ethical aspects of this research project have been approved by the Human Research Ethics Committees of RMIT University and St. Vincent’s Hospital, Melbourne.

16. Injury
In the event that you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you.

17. Termination of the Study
This research project may be stopped for a variety of reasons. These may include unacceptable side effects, the procedure being shown not to be effective, and not needing further investigation.
8.11 Appendix 11: Consent Form

St Vincent’s Hospital

Consent Form

Version: Two

Dated: 15 March 2004
Site: St Vincent’s Hospital, Melbourne

Full Project Title: The effect of electro-acupuncture on reducing pain medication consumption in patients with chronic pain

I have read, or have had read to me in my first language, and I understand the Participant Information version 2 dated 15 March 2004.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this project according to the conditions in the Participant Information.

I will be given a copy of the Participant Information and Consent Form to keep.

I understand that the researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

Participant’s Name (printed) ……………………………………………………

Signature        Date

Name of Witness to Participant’s Signature (printed) …………………………………

Signature        Date

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher’s Name (printed): Jessica Guo …………………………………………

Signature        Date
8.12 Appendix 12: Guideline of reduction of OLM

Medical Doctors’ Role in the Clinical Trial of Electro- Acupuncture and Opioid Like Medication (OLM) Consumption in Chronic Pain Patients

Dear Doctor

Thank you for participating in this 20-week clinical trial. The following outlines how you might help us with this trial.

- **Assess the use of opioid like medications (OLM) regularly**, at baseline, 3rd week and 6th week during the intervention stage, and 1st, 2nd, and 3rd month during the follow up stage.

- **Help patients to identify the targeted medication;** and fill in the given Targeted Medication Form. Patients will be guided to reduce short acting OLM first, and then long acting OLM.

- **Encourage patients to reduce their analgesic intake, especially OLM at each consultation.** To assist you with this task, at each consultation, you will be provided with a summary of the analgesic consumption recorded by patients daily.

- Patients may be encouraged to reduce their OLM when
  - Their pain has diminished in the last 2 weeks, or
  - They experience a better sense of well-being, or
  - Both.

- The following advice can be given, such as “**I suggest you reduce opioids by half to one tablet per day for the next week, and then think about reducing one tablet per day again the following week**”.

- Finally, we strongly encourage you **not to discuss the acupuncture procedure** with the patients.

Thank you again for participating in the trial.

Trial Team
8.13 Appendix 13: Results analysed with Intention-to-treat

8.13.1 Intention-to-treat analysis of baseline clinical characteristics

8.13.1.1 Clinical characteristics at baseline

Clinical characteristics in terms of consumption of OLM, pain history, intensity of average and unpleasantness of pain, depression and quality of life in the two groups were also comparable when the intention to treat analysis was employed in this study (Table 13-1). The results are consistent with per protocol analysis.

8.13.1.2 Side effects of opioid like medication at baseline

The side effects of OLM were assessed at baseline. There was a higher incidence of the side effects in the SEA group than in the REA at baseline. On average, participants reported 6.6 side effects per person in the SEA group and 5.4 side effects per person in REA group. The commonest complaint was drowsiness in the SEA group, accounting for 89% (16 participants), and fatigue in the REA group, with 76% (13 participants). The second most common complaint was fatigue and lethargy in the SEA group and constipation and lethargy in the REA group (Table 13 - 2). However, chi-square tests indicate that there were no significant difference between two groups for any side effects except for constipation ($\chi^2 = 5.042$, $p = 0.025$) and drowsiness ($\chi^2 = 5.536$, $p = .019$).

Table 13 - 3 shows the average severity of side effects that participants experienced in each group at baseline. In the SEA group, most severe symptoms reported were drowsiness and fatigue, and in the REA group were lethargy and fatigue. There was no significant difference on the severity of side effects between two groups except for sedation ($t = 2.533$, $p = .016$) and drowsiness ($t = 2.036$, $p = .05$), with the SEA group experiencing more severe symptoms (Table 13 - 3).

In summary, results about the incidence and severity of side effects related to OLM at baseline were similar when analysed with intention-to-treat methods to those analysed with per protocol methods.
Table 13-1: Comparison of Baseline Characteristics for Randomised Participants in Each Group

<table>
<thead>
<tr>
<th>Baseline characteristics for randomised participants</th>
<th>SEA N=18</th>
<th>REA N=17</th>
<th>t</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumption of OLM (mg/weekly)</td>
<td>295.5</td>
<td>461.6</td>
<td>-1.283</td>
<td>.208</td>
</tr>
<tr>
<td>Pain history (yrs)</td>
<td>13.0</td>
<td>19.8</td>
<td>-1.067</td>
<td>2.94</td>
</tr>
<tr>
<td>Present pain intensity -VAS</td>
<td>5.6</td>
<td>4.9</td>
<td>1.196</td>
<td>.240</td>
</tr>
<tr>
<td>Highest levels of pain-VAS</td>
<td>7.0</td>
<td>6.5</td>
<td>.993</td>
<td>.328</td>
</tr>
<tr>
<td>lowest levels of pain-VAS</td>
<td>3.8</td>
<td>2.6</td>
<td>1.675</td>
<td>.103</td>
</tr>
<tr>
<td>Average pain-VAS</td>
<td>5.5</td>
<td>4.6</td>
<td>1.578</td>
<td>.122</td>
</tr>
<tr>
<td>Duration of pain (hrs/day)</td>
<td>15.6</td>
<td>16.8</td>
<td>-.707</td>
<td>.484</td>
</tr>
<tr>
<td>Severity of pain-GBS</td>
<td>14.0</td>
<td>12.7</td>
<td>1.278</td>
<td>.210</td>
</tr>
<tr>
<td>Unpleasantness of pain -GBS</td>
<td>12.4</td>
<td>11.1</td>
<td>1.283</td>
<td>.208</td>
</tr>
<tr>
<td>PRI-sensory</td>
<td>18.5</td>
<td>15.8</td>
<td>.956</td>
<td>.346</td>
</tr>
<tr>
<td>PRI-affective</td>
<td>4.4</td>
<td>3.2</td>
<td>1.204</td>
<td>.313</td>
</tr>
<tr>
<td>PRI-evaluative</td>
<td>2.8</td>
<td>2.5</td>
<td>.654</td>
<td>.518</td>
</tr>
<tr>
<td>PRI-miscellaneous</td>
<td>5.8</td>
<td>4.3</td>
<td>1.214</td>
<td>.233</td>
</tr>
<tr>
<td>PRI-total</td>
<td>31.6</td>
<td>25.8</td>
<td>1.200</td>
<td>.239</td>
</tr>
<tr>
<td>Present Pain Intensity (PPI)</td>
<td>2.8</td>
<td>2.7</td>
<td>.315</td>
<td>.755</td>
</tr>
<tr>
<td>Depressive symptoms (BDI-II)</td>
<td>19.0</td>
<td>18.4</td>
<td>.247</td>
<td>.806</td>
</tr>
<tr>
<td>SF-36 Physical Functioning (PF)</td>
<td>36.5</td>
<td>52.1</td>
<td>-1.244</td>
<td>.223</td>
</tr>
<tr>
<td>SF-36 Role Physical (RP)</td>
<td>12.5</td>
<td>10.4</td>
<td>-.140</td>
<td>.890</td>
</tr>
<tr>
<td>SF-36 Bodily Pain (BP)</td>
<td>22.5</td>
<td>29.2</td>
<td>-1.001</td>
<td>.324</td>
</tr>
<tr>
<td>SF-36 General Health (GH)</td>
<td>44.6</td>
<td>40.9</td>
<td>.582</td>
<td>.565</td>
</tr>
<tr>
<td>SF-36 Vitality (VT)</td>
<td>26.3</td>
<td>38.8</td>
<td>-1.194</td>
<td>.241</td>
</tr>
<tr>
<td>SF-36 Social Functioning (SF)</td>
<td>47.9</td>
<td>51.0</td>
<td>-.330</td>
<td>.974</td>
</tr>
<tr>
<td>SF-36 Role Emotional (RE)</td>
<td>52.8</td>
<td>33.3</td>
<td>1.258</td>
<td>.217</td>
</tr>
<tr>
<td>SF-36 Mental Health (MH)</td>
<td>56.9</td>
<td>63.0</td>
<td>-.217</td>
<td>.830</td>
</tr>
</tbody>
</table>

Note. p < .05 is significant, two-tailed.
Table 13 - 2: Number and % of Participants Who Experienced OLM Side effects at Baseline

<table>
<thead>
<tr>
<th>Side effects of OLM</th>
<th>SEA N =18</th>
<th>REA N =17</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>10</td>
<td>56</td>
<td>7</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>17</td>
<td>4</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>56</td>
<td>5</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>78</td>
<td>13</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>16</td>
<td>89</td>
<td>9</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td>9</td>
<td>50</td>
<td>6</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>11</td>
<td>61</td>
<td>5</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td>14</td>
<td>78</td>
<td>11</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>10</td>
<td>56</td>
<td>7</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nightmares</td>
<td>7</td>
<td>39</td>
<td>6</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
<td>39</td>
<td>13</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other symptoms</td>
<td>7</td>
<td>39</td>
<td>6</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
<td>92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident rate</td>
<td>6.6</td>
<td>5.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 13 - 3: Comparison of Average Severity of Side effects of OLM for Randomised Participants in Each Group at Baseline

<table>
<thead>
<tr>
<th>Side effects of OLM at baseline</th>
<th>SEA N =18</th>
<th>REA N =17</th>
<th>t</th>
<th>p- value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.1</td>
<td>1.5</td>
<td>1.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.3</td>
<td>0.8</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.4</td>
<td>2.3</td>
<td>0.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.8</td>
<td>3.0</td>
<td>2.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3.8</td>
<td>2.6</td>
<td>2.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1.5</td>
<td>2.1</td>
<td>0.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Sedation</td>
<td>1.8</td>
<td>2.2</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2.7</td>
<td>2.4</td>
<td>2.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.6</td>
<td>2.0</td>
<td>1.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Nightmares</td>
<td>0.9</td>
<td>1.8</td>
<td>0.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.9</td>
<td>2.9</td>
<td>2.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>2.4</td>
<td>3.6</td>
<td>1.3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Note: * indicates p < .05 is significant, two-tailed, Independent - samples t -test.
8.13.2 The effects of EA on the primary outcomes during the treatment period

8.13.2.1 Dosage of opioid like medication consumption

Dosage of OLM was significantly reduced in both SEA and REA groups at the end of the treatment [SEA group: 219.1 ± 293.0 (SD) mg/week vs. REA group: 250.5 ± 410.2 (SD) mg/week, F (6, 198) = 13.44, p = .000], and a significant group by time interaction occurred, indicating that OLM reduction of the REA group was more rapid (39%) than that of the SEA group (26%) [F (6, 198) = 2.948, p = .009].

Paired-samples t-tests showed that significant decrease were found in the REA group at the end of 3\textsuperscript{rd} and 6\textsuperscript{th} week, and the end of the 6\textsuperscript{th} week in the SEA group when compared to baseline (p < .05). However, there was no significant difference between two groups at the end of six-week treatment (t = -.261, p = .795) (Figure 13-1).

![Consumption of OLM (Morphine Equivalent) mg/Per Week](image)

Figure 13-1: Consumption of OLM (Morphine Equivalent) mg/Per Week in Each Group across all of Time Points

8.13.2.2 Side effects of opioid like medication

Table 13-4 shows the number and percentage of participants who experienced side effects at the end of the treatment. The results showed that there was a higher incidence of side effects in the SEA group than the REA group at the end of the treatment. On the average, the incident rate of side effects was 3.7 in the SEA and 3.0 in the REA group after completion of the treatment. However, chi-square tests indicate that there were no significant differences between two groups for any side effects.
The results of GLM for repeated measure showed that the majority of the side effects were significantly reduced ($p < .05$) except the symptoms of nausea, vomiting and nightmares in both groups, and the reductions of severity of the side effects were similar in both groups. There were significant group by time interaction for sedation [$F (6,198) = 3.629, p = .002$], drowsiness [$F (6,198) = 3.761, p = .001$]. The results indicated that the REA group had lower severity of sedation and drowsiness overall than in the SEA group (Table 13-5). This is different from per protocol analysis where REA is better with sedation, and SEA is better with drowsiness.
Table 13-4: Number and % of Participants Who Experienced Side effects of OLM at the End of the Treatment

<table>
<thead>
<tr>
<th>Side effects of OLM at the End of the Treatment</th>
<th>SEA N = 18</th>
<th>REA N = 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>67</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Sedation</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Lethargy</td>
<td>9</td>
<td>50</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>Nightmares</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>51</td>
</tr>
<tr>
<td>Incident rate</td>
<td>3.7</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 13-5: Average Severity of Side effects of OLM in Each Group at the End of the Treatment

<table>
<thead>
<tr>
<th>Average severity of side effects of OLM</th>
<th>Baseline</th>
<th>At the end of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEA N=18</td>
<td>REA N= 17</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Sedation</td>
<td>1.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Nightmares</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>2.4</td>
<td>3.6</td>
</tr>
</tbody>
</table>
8.13.3 The effects of EA on Intensity and unpleasantness of pain

8.13.3.1 Pain assessed with VAS

The results showed that there were significant time effects of the average pain and highest level of pain [average pain: F (6, 198) = 3.686, p = .002; highest level of pain: F (6,198) = 4.301, p = .000], and a non significant group by time interaction. This analysis showed that the intensity of average pain and highest levels of pain in both SEA and REA groups decreased over the six-week treatment period, and the reduction of pain was similar in both groups (Table 13-6).

The lowest level of pain, present pain and duration of pain did not change over the six-week treatment period in both groups (Table 13-6).

Table 13-6: Comparison of Pain Assessed With VAS at Baseline and at the End of the Treatment in Each Group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At the end of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEA N=18</td>
<td>REA N=17</td>
</tr>
<tr>
<td>Average pain</td>
<td>Mean SD</td>
<td>Mean SD</td>
</tr>
<tr>
<td>5.5 1.7</td>
<td>4.6 1.6</td>
<td>4.9 2.0</td>
</tr>
<tr>
<td>present pain</td>
<td>5.6 1.7</td>
<td>4.9 1.7</td>
</tr>
<tr>
<td>Highest of pain</td>
<td>7.0 1.4</td>
<td>6.5 1.4</td>
</tr>
<tr>
<td>Lowest of pain</td>
<td>3.8 2.2</td>
<td>2.6 1.8</td>
</tr>
<tr>
<td>Duration of pain</td>
<td>15.6 4.6</td>
<td>16.8 5.3</td>
</tr>
</tbody>
</table>

The findings of the paired-sample t-tests showed that the average pain in the REA group was significantly reduced between the 3<sup>rd</sup> and 6<sup>th</sup> week when compared to baseline (p < .05). However, it was not found in the corresponding time in the SEA group (Figure13-2). It might be pain reduction is not significant enough to produce group by time interaction.
Figure 13-2: Average of Pain Score Assessed With VAS in Each Group across Time

![Graph showing VAS scores over time for REA and SEA groups.]

Note: † indicates significant differences within the REA group at the time points when compared to baseline. * indicates significant difference within the SEA group at the time points when compared to baseline.

8.13.3.2 Pain assessed with Gracely Box Scales

The results showed that there was a significant time effect in the severity and unpleasantness of pain across all the time points [severity of pain: F (6, 198) = 3.046, p = .007); unpleasantness of pain: F (6, 198) = 2.575, p = .020)], without group by time interaction (Table 13-7), indicating that the severity and unpleasantness of pain were significantly reduced within both groups over the treatment period when measured with the GBS and the reduction was similar in both groups (Figure 13-3).

Table 13-7: Comparison of GBS at Baseline and at the End of the Treatment in Each Group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At the end of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEA N=18</td>
<td>REA N=17</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Severity of pain</td>
<td>14</td>
<td>2.5</td>
</tr>
<tr>
<td>Unpleasantness of pain</td>
<td>12.4</td>
<td>2.7</td>
</tr>
</tbody>
</table>
8.13.3.3 Pain assessed with MPQ

Weekly MPQ scores were analysed with the GLM for repeated measures. The results showed that there were no time effects on the following MPQ measures: PRI-s, PRI-a, PRI-m and PRI-Total except PRI-e \( [F (1, 33) = 5.439, p = .027] \). However, there was no group by time interaction for all MPQ measures, indicating that there were no significant changes in both groups on the following MPQ measures: PRI-s, PRI-a, PRI-m and PRI-Total except PRI-e, and the reduction of PRI-e in both groups was not significantly different (Table 13-8).

**Table 13-8: Comparison of MPQ PRI Scale Score at Baseline and at the End of the Treatment in Each Group**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At the end of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEA N=18</td>
<td>REA N=17</td>
</tr>
<tr>
<td><strong>PRI-sensory</strong></td>
<td>Mean 18.5 SD 8.1</td>
<td>Mean 15.8 SD 8.4</td>
</tr>
<tr>
<td><strong>PRI-affective</strong></td>
<td>Mean 4.4 SD 3.7</td>
<td>Mean 3.2 SD 3.3</td>
</tr>
<tr>
<td><strong>PRI-total</strong></td>
<td>Mean 31.6 SD 14.5</td>
<td>Mean 25.8 SD 14.0</td>
</tr>
</tbody>
</table>
### Appendix 14: Comparison of consumption of OLM at the Baseline, \(tw\) 3 and \(tw\) 6

Comparison of consumption of OLM at the Baseline, \(tw\) 3 and \(tw\) 6 week

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At (tw) 3</th>
<th>At (tw) 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>SEA (N = 14)</strong></td>
<td>212.3</td>
<td>177.8</td>
<td>140.7</td>
</tr>
<tr>
<td><strong>REA (N = 12)</strong></td>
<td>348.5</td>
<td>303.7</td>
<td>240.1</td>
</tr>
</tbody>
</table>

### Appendix 15: Comparison of consumption of OLM at \(tw\) 6, \(pw\) 4, \(pw\) 8 and \(pw\) 12

Comparison of consumption of OLM at \(tw\) 6, \(pw\) 4, \(pw\) 8 and \(pw\) 12

<table>
<thead>
<tr>
<th></th>
<th>At (tw) 6</th>
<th>At (pw) 4</th>
<th>At (pw) 8</th>
<th>At (pw) 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td><strong>SEA (N = 14)</strong></td>
<td>113.9</td>
<td>139.2</td>
<td>119.6</td>
<td>166.1</td>
</tr>
<tr>
<td><strong>REA (N = 12)</strong></td>
<td>126.1</td>
<td>97.3</td>
<td>164.8</td>
<td>148.9</td>
</tr>
</tbody>
</table>