THE HONG KONG POLYTECHNIC UNIVERSITY

SCHOOL OF NURSING

THE RELATIONSHIP OF PLASMA β-ENDORPHINS AND PAIN DIMENSIONS IN CHINESE CANCER PAIN ASSESSMENT TOOL (CCPAT)

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A thesis submitted in partial fulfilment of the requirements for the Degree of Master of Philosophy

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CERTICATE OF ORGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

(Simone Ho Sin Man)

ABSTRACT

Introduction

Cancer pain is a complex, multidimensional phenomenon that contributes to the global problem of optimal pain assessment and management. A bio-psycho-social-cultural link in the context of pain may shed light on pain assessment, and ultimate alleviation, of pain and suffering.

Method

This cross-sectional correlational study investigated the relationship between plasma β-endorphin level (β-end) and CCPAT pain dimensions. β-end was measured in 68 male and 8 female primary liver cancer patients consecutively. The Chinese Cancer Pain Assessment Tool (CCPAT) was employed to obtain weighted scores of functional dimension (FD), psychosocial dimension (PD), pharmacological dimension (PHD), emotional dimension (ED), pain beliefs and meanings dimension (PBMD), pain intensity dimension (PID), and Sum.

Results

Thirty-two (42.1%) patients experienced varying degrees of pain. The mean β-end was 270.4±SEM 11.4 pg/ml. α-corrected correlational matrix showed that the relationships between β-end and the CCPAT pain dimensions were non-significant.

The β-end was higher in the pain group (291.6 ± SEM 18.0 pg/ml) than the no pain group (255.0 ± SEM 14.5 pg/ml).

Discussion

No relationships were found between the studied variables in this cancer population. These findings are inconsistent with the previous study of advanced cancer population. Cancer population that suffers from pain exhibit higher β-end levels suggests that pain pathways stimulate endogenous opiotergic systems, including circulating β-end.

Conclusion

β-end variations in patients who have and have not experienced pain suggest a functional role in cancer pain modulation. Future research is warranted to explore the bio-psycho-social-cultural link in cancer populations which may enhance pain assessment.

SUMMARY OF AWARDS, CONFERENCE PRESENTATIONS AND PUBLICATIONS ARISING FROM THE THESIS

Honours and Awards

1. Young Investigator Award for oral presentation. Multidimensionality of Cancer Pain in Chinese Patients with Primary Liver Cancer. 10th Hong Kong International Cancer Congress, Hong Kong, 19-21 Nov 2003.

Conference Presentations and Publications

1. Ho, S., Chung, J.W.Y., Wong, T.K.S. (*under review – Cancer Nursing*). Multidimensionality of Cancer Pain in Chinese Patients with primary liver cancer.
2. Ho, S.S.M., Chung, J.W.Y., Wong, T.K.S. Multidimensionality of Cancer Pain in Chinese Patients with Primary Liver Cancer. Proceedings, 10th Hong Kong International Cancer Congress, Hong Kong, p.70, 19-21 Nov 2003.
3. Ho, S.S.M., Chung, J.W.Y., Wong, T.K.S. (2004). Promotion of Holistic Health in Cancer Patients: The Mind-body Connection and β-endorphin as a biomarker. Proceedings, International Conference on Health Promotion: Evidence, Practice and Policy, Thailand, p.188, 20-22 Oct 2004.

Public Acquisitions - Seminar by invitation

1. Invited to address Chinese Cancer Pain in Oncology Care Symposium, 23 July 2004 at Cancer Center, Sun Yat-Sen University of Medical Science, Guangzhou, China.

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ABBREVIATIONS

ACTH	Adrenocorticotropin
β-end	Plasma β-endorphin
BCTOS	Breast Cancer Treatment Outcome Scale
BMI	Body mass index
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
CCK	Cholecystokinnin
CCPAT	Chinese Cancer Pain Assessment Tool
CNS	Central nervous system
C-PIVRS	Chinese Pain Intensity Verbal Rating Scale
CRH	Corticotropin-releasing hormone
CSA	Cyclosporine
CSF	Cerebrospinal fluid
CWS	Cold swim stress
ED	Emotional Dimension
EORTC QOQ-C36	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer
FCA	Freund's complete adjuvant
FD	Functional Dimension
FS	Face Scale
GCT	Gate Control Theory
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
GRS	Graphic Rating Scale
HN QOL	Head and Neck Quality of Life Instrument
HPA	Hypothalamic-pituitary-adrenal
HRQOL	Health-Related Quality of Life Scale
HWRL	Hoof withdrawal reflex latency

IASP	International Association for the Study of Pain
IRMA	Immunoradiometric assay
L	Left
LFPX	Light-induced functional pinealectomy
LOC	Locus of control
MPQ	McGill Pain Questionnaire
MSH	Melanocyte-stimulating hormone
M-VAS	Mechanical Visual Analogue Scale
NMDA	N-methyl-D-aspartate
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
OTFC	Oral transmucosal fentanyl citrate
PAG	Periaqueductal gray matter
PBMD	Pain Beliefs and Meanings Dimension
PD	Psychosocial Dimension
PDYN	Prodynorphin
PENK	Proencephalin
PHD	Pharmacological Dimension
PID	Pain Intensity Dimension
PLC	Primary liver cancer
PMDD	Premenstrual dysphoric disorder
POMC	Pro-opiomelanocortin
PPI	Present pain intensity
R	Right
RA	Rheumatoid arthritis
RIA	Radioimmunoassay
RSCL	Rotterdam Symptom Checklist
SD	Standard deviation
SEM	Standard error of mean
SF-MPQ	Short form -McGill Pain Questionnaire
SG	Substantia gelatinosa

SIA	Stress-induced analgesia
STRL	Skin twitch reflex latency
TBI	Total body irradiation
TCES	Transcranial electrostimulation
VAS	Visual Analogue Scale
VAT	Visual Analogue Thermometer
VIP	Vasoactive intestinal polypeptide
VO_2 max	Maximal oxygen uptake
VRS	Verbal Rating Scale
WBPQ	Wisconsin Brief Pain Questionnaire
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Introduction

Pain is an inescapable experience of mankind. Pain is more than a mere physiological phenomenon: there are psychological, social and cultural factors associated with pain that influence an individual's perception and response to it (Fink & Gates, 1995; Helman, 1990). The diversity of these factors is complex and intertwining, contributing to a highly subjective pain experience (Melzack & Wall, 1996). Taken together, accuracy in assessing pain in order to achieve optimal pain management has become a great global challenge to healthcare authorities, healthcare professionals and patients who experience pain (World Health Organization, 1990).

1.2 Prevalence of cancer pain

Pain is one of the most prevalent symptoms in cancer patients worldwide. It has been estimated that more than 9 million people experience pain due to cancer or its treatment (Bonica, 1990). Of these, 30%-50% suffer from moderate to severe pain at varying stages of cancer (Hearn & Higginson, 2003). Notably, approximately 40% experience pain as an early symptom of disease (Ger, Ho, Wang, & Cherng, 1998; Vuorinen, 1993). Unfortunately, 75% in the terminal phase die with inadequate pain control (Bonica, 1990; Hearn & Higginson, 2003).

The magnitude of this international health problem is further reflected by the escalating trend of cancer incidence, mortality and prevalence. Global statistics estimated that there were 10.1 million new cancer cases in year 2000, 6.2 million died from cancer, and 22.4 million people were living with cancer that had been diagnosed within the previous five years (Parkin, 2001). This estimate demonstrates an approximately 22% increase in incidence and mortality compared to a decade ago (Parkin, 2001). The World Health Organization (WHO) has estimated that if the trend continues to rise, the incidence rate could increase by 50% (from 10.1 million in 2000 to 15.7 million in 2020) (World Health Organization, 2003). In the local context, Hong Kong has mirrored the world statistics, with the same percentage increase. There is a rising trend of cancer incidence, and mortality rates of 284 per 100,000 and 126 per 100,000 respectively (Hospital Authority, 2000). In China, it is estimated that there are 1.8 million new cancer cases and 1.4 million deaths attributed to cancer each year (Huang, 2001).

1.3 β-endorphin and pain

β-endorphin has an intriguing and potent analgesic effect that can alleviate pain and produce euphoria (Cabot et al., 1997; Schafer, Mousa, & Stein, 1997). The release of β-endorphin is elicited by stress, exercise, anxiety, emotion and mediators from immune response (Jessop, 1998). Since the discovery of endorphins (endogenous morphine-like chemicals) (Hughes et al., 1975), there has been growing interest with a rapid explosion of in vitro and in vivo research in the field of neurosciences

surrounding investigations of these potent analgesics in our body. There were high hopes for the possibility of developing a more powerful, natural, yet non-addictive analgesia, a substitute for morphine (Levinthal, 1988). Although the functional role of endorphins is still unclear, there is evidence to suggest that they play an important role in pain and mood modulation (Bodnar & Hadjimarkou, 2002; Gabis, Shklar, & Geva, 2003; Ishii, Isono, Inoue, & Hori, 2000; Mousa, Machelska, Schafer, & Stein, 2000).

1.4 Converging lines of research

First, the diagnosis and treatment of cancer, cancer pain and other related symptoms can elicit a highly physically and emotionally stressful experience (Andersen, 1992). Second, increasing evidence suggests that stress levels are associated with maladaptive changes in the hormonal, immune and opioidernegic systems (Clauw & Chrousos, 1997; Gold & Chrousos, 2002). The hypothalamic-pituitary-adrenal (HPA) axis is the major system responsible for stress response. Hyper- or hypo-function of the HPA axis have also correlates with anxiety, depressive states and chronic pain (Blackburn-Munro & Blackburn-Munro, 2001; Holsboer, 1999). Third, these physiological changes may have an important influence on increased sensitivity or reduced tolerance to pain (Takahashi et al., 2000) leading researchers to suggest that the psychological factors that influence hormonal, immune and opioid functions may also influence the outcome of pain. Fourth, psychological intervention and emotional modulation have been developed to reduce emotional distress in cancer patients, and

resulting in pain relief accompanied by increased endorphin release (Amanzio & Benedetti, 1999; O'Callaghan, 1996). These findings are suggestive of a body-mind link in the context of pain.

However, many studies have investigated on β-end and pain, but most of them have failed to report how they are correlated with each other. Those studies that have examined the correlation have produced inconsistent results (direct, inverse or no correlation). Most of the studies have concentrated on the correlation between β-end and the sensory dimension (pain intensity), neglecting the correlation between β-end and the other equally important pain dimensions including the affective and cognitive.

1.5 Aim of the study

For the above rationales, this study is conducted to examine whether the pain dimensions (subjective variables) in cancer patients are correlated with β-endorphin (objective variable), how they are associated, and whether these pain dimensions are able to predict plasma β-endorphin (β-end) levels.

This study is a cross-sectional correlational design. A venous blood sample (objective variable) is taken to determine β-end. The pain dimensions (subjective variables) in a cancer pain experience are captured by the Chinese Cancer Pain Assessment Tool (CCPAT) to reveal the functional dimension (FD), psychosocial dimension (PD), pharmacological dimension (PHD), emotional dimension (ED), pain

beliefs and meanings dimension (PBMD), and pain intensity dimension (PID). The results of this research will provide a better understanding of the relationship between β-endorphin and the CCPAT pain dimensions, which may guide healthcare professionals in shaping the future direction of pain treatment modalities.

1.6 Significance of the study

By exploring the relationships between plasma β-endorphin and the weighted scores on various pain dimensions as measured in the CCPAT, this study attempts to tease out these relationships in terms of each pain dimension which may shed light on the role of β-endorphin, as an objective biomarker, to reaffirm the importance of assessing different pain dimensions in cancer pain assessment.

As with many pain researches on assessment, the CCPAT will further reveal the various dimensions of pain among Chinese people. It is hoped to enrich healthcare professionals' understanding of cancer pain with respect to its multidimensional nature, and with the aim of ultimate alleviation, of pain and suffering.

1.7 Research questions

All the research questions were based on previous research findings. A previous study has found correlations between β-endorphin and PD, ED and Sum in a heterogeneous sample of 48 cancer patients (Chung et al., 2002). However, since

varying stages of disease and different types of cancer and treatment may induce variations in pain perception and levels of β-endorphin. Therefore, to reduce extraneous variables and increase research rigor, this study has kept the sample homogeneous by including only primary liver cancer patients of stages I & II to further investigate the correlations between the studied variables. Certain pain dimensions in a cancer population was reported to be predictive of the plasma β-endorphin level (Chung et al., 2002), but it has yet to be confirmed. Little research has been conducted to examine the plasma variations in β-endorphin level in a homogeneous group of cancer patients. Thus, the research questions were formulated to guide the present research to shed light on the role of β-endorphin as an objective biomarker in order to reaffirm the importance of assessing different pain dimensions.

i. What is the correlation between plasma β-endorphin level and the pain dimensions in the Chinese Cancer Pain Assessment Tool (CCPAT)?

ii. Can the weighted scores of the pain dimensions in the CCPAT (independent variables) predict the plasma β-endorphin level (dependent variable)?

iii. Is the plasma β-endorphin level significantly different between the pain and no pain groups?

1.8 Assumption

Based on the nursing literature for understanding the qualitative nature of cancer pain, pain is assumed to be whatever an individual says he or she experiences, and it exists whenever he or she says it does (McCaffery & Beebe, 1989).

1.9 Delimitation

As with correlational study design, causality is always an issue. Therefore careful consideration is required in the interpretation of the data. Due to unforseeable circumstances, nearly half of blood samples were lost leading to a relatively small sample size. This has reduced the power of the study. Thus, generazability of results is limited. A homogeneous group of primary liver cancer patients was recruited for this study. Therefore, the findings may be not generalizable to all cancer patients.

1.10 Organization of thesis

This thesis is divided into nine distinct chapters. Chapter 1 briefly introduces the background of cancer pain and β-endorphin. The converging lines of research and the significance of study are delineated, and research questions are formulated. Chapter 2 presents a critique on the definition of pain highlighting pain concepts and theories, and reviewing the multidimensionality of cancer pain. Chapter 3 is a current literature review of cancer pain measures, highlighting the validity and

reliability of these measures as well as their strengths and weaknesses. Chapter 4 introduces what β-endorphin, explaining what it is and attempting a thorough review of the literature relating to β-endorphin and pain. Chapter 5 describes the design of the study, the instrument employed and the instrument's validity and reliability. The procedure for data collection and the plasma β-endorphin assay are elaborated. Chapter 6 discusses the method, results and implications of the pilot study. Chapter 7 sets forth the scope of the main study. The methods and results of the main study are presented and discussed. Chapter 8 includes an overall discussion of the results obtained. Conclusions are drawn. Finally, chapter 9 delineates the limitations and implications of the present study. Recommendations for future research are made.

CHAPTER 2

LITERATURE REVIEW ON PAIN CONCEPTS

2.1 Introduction

Pain is conceptualized as multidimensional. This chapter provides a review of current literature that underpins the conceptualization of the multidimensional cancer pain experience. It will begin with a critique on the definition of pain. Pain concepts and related classical theories of pain will also be highlighted in chronological order.

2.2 Clarification of terms

i. Pain refers to the general notion of subjective pain experience, which includes cancer pain.

ii. Cancer pain refers to pain caused by tumour involvement. Cancer pain in this thesis does not include pain caused by tumour treatment or pain unrelated to tumour or its treatment.

2.3 Definition of pain

Although pain has been an inescapable since the beginning of mankind, pain researchers are still working towards a definition of pain. Early definitions of pain in the 1960s focused solely on the sensory aspect of pain, neglecting the psychological components of the pain experience (Melzack & Wall, 1996). At the same time, there was criticism that pain was strictly associated with tissue damage. Clinical evidence has already shown that pain can exist even when no pathological origin is apparent. Thus, the restriction contributes to the confinement of assessing and managing pain in a biomedical model, leaving other equally important pain dimensions unidentified. Unfortunately, unidentified pain goes untreated (Cleeland, 1998).

With the evolution of new pain theories, the definition of pain has broadened. The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey & Bogduk, 1994, p.210). Reasons that favour this definition are twofold. First, it delinks the firm association between pain and tissue damage. Second, the addition of emotional dimension supplements the components previously lacking in the definition (Melzack & Wall, 1996).

However, describing pain as an 'unpleasant' experience is far from an accurate description of the real pain experience. If pain is simply 'unpleasant', how can one

explain why this unpleasantness may drive people to bear disfiguring scars from operations, or to even suicidal behaviours. Researchers argue that it is logical to believe that there are some important components missing in this definition. It fails to address the cognitive or evaluative dimensions by which the person perceives and interprets pain. Often, pain is described by cancer patients as a punishment or an enemy (Barkwell, 1991). It was found that those who perceived pain as punishment or an enemy reported increased pain intensity and were more depressed, and did not cope as well as those who believed pain to be a challenge. In connection to cognition, the sociocultural dimension has been ignored, which may offer a still expanded horizon on pain that is specific to an individual's cultural beliefs. People from different cultural backgrounds may ascribe different meanings and beliefs to pain. For example, some Chinese people believe that pain is caused by a blockage of collaterals and channels (Chung, Wong, & Yang, 2000).

In light of the diversity of the pain experience, no current definition has fully satisfied the criteria of embracing the rich phenomenon of pain. A major pitfall is clearly exists, which may be better seen by the following analogy: it is like attempting to describe the visual world solely in terms of light flux and paying no attention to pattern, colour, texture, shades and shapes, and many other dimensions of a visual experience (Melzack & Wall, 1996). The subjectiveness and uniqueness of the pain experience adds to the complex pain phenomenon. Taken together, the assessment of pain and its subsequent management have created a great challenge for healthcare professionals.

2.4 Pain concepts and theories

The earliest concept of pain considers it as a punishment from God resulting from the fall of mankind (Bible, 2004; Parris, 2003). The word 'pain' originates from the Latin 'poena', meaning punishment. Later, pain was ascribed to demons and evil spirits. From ancient times, two schools of thoughts have surrounded the question of where pain arises from (heart versus brain). Ancient civilizations (the ancient Egyptians, Indians, Mesopotamians, and ancient Chinese) had similar views on the heart as being the primary organ, while some believed it to be the centre of pain (Lai, 2002). In 500 B.C., the ancient Greeks were the first to postulate the brain as the centre of sensation. Plato (427-347 B.C.) pointed out that all peripheral stimulation ended in the brain. This theory was further advanced by Aristotle (384-322 B.C.) who believed that the heart was the centre for processing pain where pain is felt. He also considered pain to be an emotional quality or *quale*, rather than a sensation which is opposite to pleasure. Galen (A.D. 130-200) extended the postulation that the centre of sensation and pain was the brain.

Empirical observations are classified by concepts. Concepts are abstractions. Essentially, concepts are the building blocks in a theory. A theory provides a rational explanation of observed facts or phenomena (Portney & Watkins, 2000). In other words, as the concept of pain is like a piece of a puzzle, the notion of a theory is an attempt to arrange these pieces of clues and guesses together to make a coherent picture in order to find the solution to a problem (Melzack & Wall, 1996). From

ancient concepts of pain, many theories have been developed which will be discussed the following section. However, it is important to note that a theory on its own is not sufficient to provide answers to problems. A theory has to be tested in research to provide evidence in support of the postulation.

2.4.1 Descartes' theory of pain pathway

While pain is a very subjective and personal experience, for the past three hundred years, the vast majority of pain research has emphasized the mechanistic nature of pain as the key focus (Horn & Munafo, 1997). Perhaps the most classical theory of pain was described by Descartes in 1664. Descartes' concept of the pain system was of a straight channel that begins in the skin and terminates in the brain (Melzack & Wall, 1996). It was illustrated by a person whose foot comes near a fire (Figure 2.1). He postulated that the system is similar to the bell-ringing mechanism in a church wherein a man pulling one end of the rope inside the church sets off the bell striking at the other end in the belfry. Descartes' theory has been criticized for its apparent simplicity, to purely emphasizing the mechanistic nature of pain physiology, and dismissing the psychological factors in the pain experience (Horn & Munafo, 1997).

Figure 2.1 Descartes' theory of pain pathway

2.4.2 Evolution of pain theories

Despite the critisms of Descartes' bell-alarm system, several major theories have evolved and developed from it (Horn & Munafo, 1997; Melzack & Wall, 1996). However, these developments did not begin until the 19th century, when Muller (1842) proposed the doctrine of specific nerve energies. He suggested that specific energy inherent in the sensory nerves is responsible for differentiating the quality of sensation. This concept was similar to that of Descartes, in which the sensory pathway, including pain, was conceived as a straight-through system from the sensory nerves in the sensory organ to the brain centre. Thus, his theory received similar criticism.

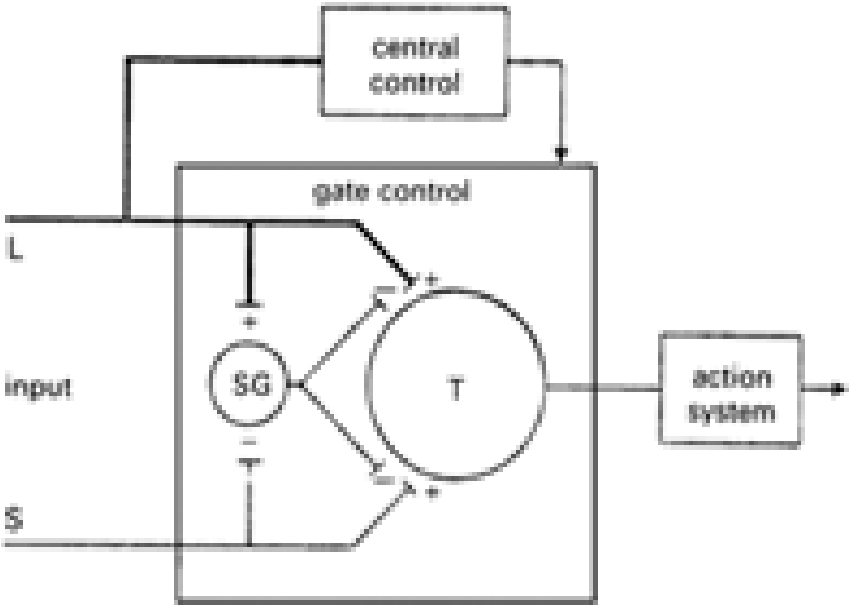
Von Frey (1894) expanded Muller's concept wherein the specificity theory was extended. In an attempt to solve the puzzle of pain, he further proposed that specific pain receptors in body tissue transmit messages via specific pain fibres through a pain pathway, which terminates in a pain centre in the brain. This part of the theory became the basis of the modern-day specificity theory (Melzack & Wall, 1996). The strength of Von Frey's theory is demonstrated by its physiological assumption about the specialization of skin receptors. However, its major flaw is that implies linear causality without considering the factors between the stimulus and response that may modulate pain (Everson, 1991). Again, this theory is influenced by Descartes' concept of assuming a conceptual nervous system which depicts a rigid and direct connection from the receptor to the brain. The notion of the direct link to the nervous system is further refuted by clinical evidence such as the amputee with phantom limb pain or chronic pain patients without obvious organic pathology (Horn & Munafo, 1997).

Contrasting with the physiological evidence of receptor specificity, the postulation of pattern theory emerged. In pattern theory, Goldscheider (1884) argued that pain is determined by critical factors, stimulus intensity and central summation (Melzack & Wall, 1996). It was suggested that the two patterns of neural transmission, spatial and temporal, produce different intensity and duration of pain sensation (Horn & Munafo, 1997).

In summary, despite more than three centuries of research into the theories of pain, scholars, healthcare researchers and clinicians have not been able to epitomize the subtleties of pain as a subjective and private experience. The assumption of the linear model of pain causation, to the extent that pathology directly equates with pain without accommodating psychological factors, led to neurosurgery wherein the pain pathway is incised (nerve block) to alleviate pain. Unfortunately, it was soon discovered that neural pathway injury further exacerbates pain. Although the controversies have not been compromised to integrate the diverse theoretical mechanisms, these pain theories have influenced research and therapy for pain (Horn & Munafo, 1997). Nevertheless, each successive theory has made an important contribution towards an understanding of the complex pain phenomenon, which was previously inexplicable (Melzack & Wall, 1996).

2.4.3 The Gate Control Theory of pain

Not until the late 20th century was the active role of the brain process, or specifically psychological processes, exemplified by Melzack and Wall (1965), as opposed to a passive receptive role. They proposed in the Gate Control Theory (GCT) that nociceptive signals traveling from the periphery to the central nervous system (CNS) are modulated by a ‘gate’ situated in the substantia gelatinosa (SG) at the dorsal horn of the spinal cord (Figure 2.2).



+ = excitation; – = inhibition

Figure 2.2 Schematic diagram of the Gate Control Theory (from Melzack and Wall, 1965, p. 971).

This neural mechanism of opening or closing a hypothetical gate is determined by the amount of excitatory activity in small-diameter (S) and large-diameter (L) nerve fibres. S (A-delta and C) and L (A-beta) nerve fibres project to the SG and converge into the first central transmission cells (T) in the dorsal horns. The activity in the S nerve fibres will enhance the neural transmission by opening the gate, while activity in the L nerve fibres has an inhibitory effect by closing the gate. A schematic diagram of the Gate Control Theory presented above shows that the inhibitory effect exerted by the SG on afferent nerve fibres is increased by activities in the L nerve fibres and decreased by activities in the S nerve fibres.

Melzack and Casey (1968) expanded the theory by integrating three parallel processing systems related to the nociceptive stimulation that contribute to the subjective experience of pain. These systems are the sensory-discriminative, motivational-affective, and cognitive-evaluative dimensions of pain. All three systems interact with each other. The brain structures involved in the modulation of sensory input are the ventrobasal thalamus and the somatosensory cortex; reticular and limbic structures activation underlies the powerful affect, and neocortical structures processes the evaluation of input.

It was proposed that when the integrated firing level of the T cells at the dorsal horn reaches or exceeds a critical level, these responsible action systems and responses are triggered (Figure 2.3). The output from the T cells projects to the sensory-discriminative system, where perceptual information is processed regarding the location, magnitude and spatiotemporal characteristics of the noxious stimulus. Concomitantly, the ouput of the T cells also projects to the motivational-affective system, where the motivational tendency toward flight or fight and the negative affect of unpleasantness are evoked.

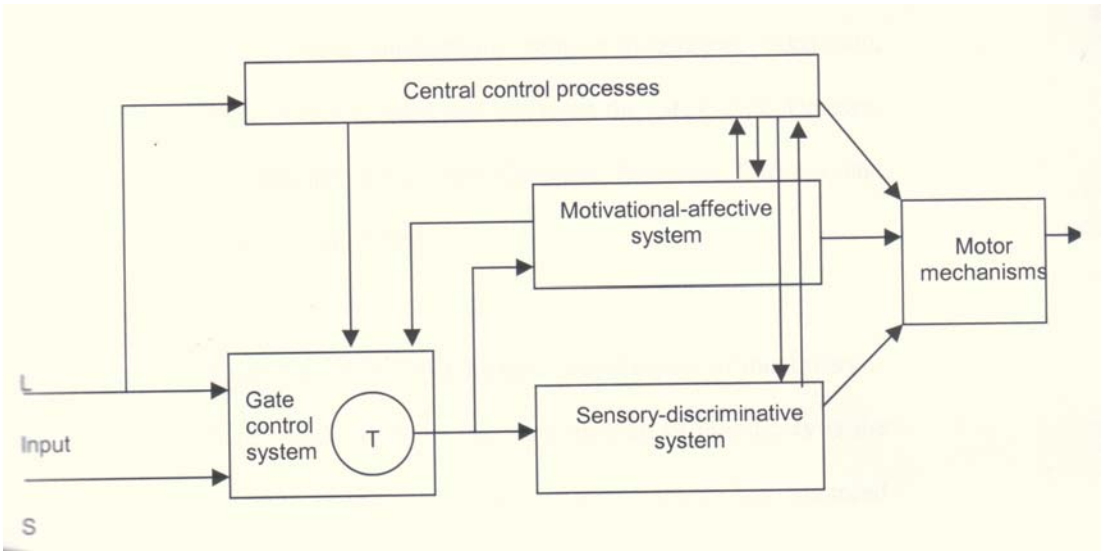


Figure 2.3 Conceptual model of sensory, motivational and central control determinants of pain (from Melzack and Wall, 1996, p.191).

In addition, the noxious stimulus triggers activity in the higher central control processes (as represented by a line from the L nerve fibres to the cognitive-evaluative system), which in turn project back to the gate-control system, and to the sensory-discriminative and motivational-affective systems. It is important to note that pain information signals must be modulated at the gate, and allowed to pass (gate opens), before pain is felt. Cognitive processes are known to influence even simple reflexes, which previously were thought to be solely spinal process and are now recognized to extend throughout the entire CNS (Melzack & Wall, 1996). This is illustrated by the fact that a person picking up a hot cup of tea in an expensive cup is not likely to drop the cup, but jerkily returns it to the table, and then attends to the scalded hand. Thus, the complex sequences of behaviour in a person experiencing pain are determined by sensory, motivational, and cognitive processes acting on motor mechanisms (Melzack & Casey, 1968).

Cognitive processes such as anxiety, attention, memory, anticipation and past experience are able to enhance the transmission by opening the gate. By contrast relaxation, concentration on other stimuli, touch, massage, medication, and the release of opioids tend to inhibit the transmission by closing the gate (Doody, Smith, & Webb, 1991; Melzack & Wall, 1996). Recent observations have noted another inhibitory structure within the brain stem, the periaqueductal gray matter (PAG) (Lee, Park, Won, Park, & Sohn, 2000; Sohn et al., 2000). Transcranial electrostimulation and electrical stimulation to the PAG in chronic pain patients results in pain relief with a significant increase in serum and ventricular β-endorphin levels (potent endogenous opioid) (Gabis et al., 2003; Hosobuchi, Rossier, Bloom, & Guillemin, 1978; Ignelzi & Atkinson, 1980). This can be evidenced by blocking analgesia with naloxone (Airapetov, Zaichik, Trukhmanov, Lebedev, & Sorokoumov, 1985).

The GCT is now well accepted as the classical pain theory. Most importantly, the value of the GCT is its ability to unravel the puzzle of the psychophysical relationship between injury and pain (Horn & Munafo, 1997). This can account for those who do not feel pain with apparent injury and those who complain of pain without any apparent injury. Psychological, physiological and behavioural dimensions are integrated into a single holistic system representing a conceptual leap which has improved understanding and development in pain studies and management (Grahek, 1991).

Since the advent of this newly-evolved pain definition and theory, the multidimensional aspect of pain assessment has been incorporated. Thus psychological and behavioural interventions have been implemented in conjunction with the biomedical approach of pharmacological and nerve block treatments (Hasenbring, Ulrich, Hartmann, & Soyka, 1999; Sullivan & Neish, 1999; Weisenberg, 1987). Nevertheless, the multifaceted dimensions including functional, psychosocial, pharmacological, emotional, and cultural components of the pain experience have been under-explored. Revelation of these important pain dimensions will foster better pain treatment decisions.

2.5 Multidimensionality of pain

For over three decades, the conceptualization of pain as a multidimensional phenonmenon has evolved from the GCT (McGuire, Yarbro, & Ferrell, 1995). According to the GCT, the subjective pain experience determined by the interaction among sensory-discriminative, motivation-affective and cognitive-evaluative components. This complex interplay contributes to the total pain experience at the holistic level of an individual.

The concept of total pain in its stronger and definitional sense includes physical symptoms, mental distress, social and emotional components (Saunders, 1964). In addition to these multi-faceted components, literature has incorporated other components into the totality of the cancer pain experience, such as functional

constraints, spiritual suffering, belief challenge and social estrangement (Urba, 1996) as well as psychosocial, spiritual, interpersonal, and financial components (Mystakidou, Liossi, Fragiadakis, Georgaki, & Papadimitriou, 1998).

At present, the multidimensional framework is depicted as physiological, sensory, affective, cognitive, behavioural, and sociocultural (Ahles, Blanchard, & Ruckdeschel, 1983; Barkwell, 1991; McGuire, 1992; McGuire et al., 1995; Pallis & Mouzas, 2004; Zimmerman, Story, Gaston-Johansson, & Rowles, 1996). Each dimension will be discussed, with relevant research work critically reviewed. It is important to note that this framework is still undergoing evolution (McGuire et al., 1995). Identification of relevant pain dimensions may facilitate ascertaining the etiology of pain and provide the basis for multidisciplinary interventions to achieve pain relief.

2.5.1 Physiological dimension

The physiological dimension of pain is depicted as the organic etiology (cause) and duration of pain, and the response of the endogenous opioids to pain (McGuire et al., 1995). In brief, classical cancer pain differentiation is delineated as pain caused by tumour involvement (bone tumour invasion, compression of nerve roots), pain caused by tumour treatment (surgeries, radiation and chemotherapy), and pain unrelated to tumour or its treatment (Bonica, 1980). Additional work has been carried out on specific pain syndromes relating to cause of pain that are common in

cancer patients, such as somatic, visceral, and neuropathic pain (Kelly & Payne, 1991; Payne, 1987). Examples of neuropathic pain that is often experienced by cancer patients are hyperalgesia, the response of increased pain to painful (noxious) stimuli, and allodynia, where pain is evoked by non-painful (non-noxious) stimuli.

The duration of pain is generally classified into the dichotomy of acute or chronic pain (McGuire et al., 1995). Endogenous opioids are considered to have analgesic properties and play the role of modulating perception and response to pain. Detailed properties, functions and research related to endogenous opioids, specifically β-endorphin, will be discussed in chapter 4.

A vast amount of research has been conducted on tumour-related and tumour treatment-related pain in cancer patients. This literature demonstrates the existence of a physiological dimension in various cancer diagnoses or sites such as the lung (Potter & Higginson, 2004), breast (Roemer-Becuwe, Krakowski, & Conroy, 2003), head and neck (Whale, Lyne, & Papanikolaou, 2001), prostate (Rodrigues, Hering, & Campagnari, 2004), gynaecologic (Yavuz, Eroglu, & Ozsoy, 2004), gastrointestinal (Befon, Mystakidou, Lyra, Tubanakis, & Vlahos, 2000), liver (Li et al., 1994), and myeloma (Diaz, Soutelo, Quiroga, Palmer & Lutfi, 2004).

A prospective study that recruited 2266 cancer patients from a pain clinic (Grond, Zech, Diefenbach, Radbruch, & Lehmann, 1996) reported that most of the patients suffered from pain that was tumour-related (85%) or tumour-treatment related (17%).

Another prospective international survey (Caraceni & Portenoy, 1999) showed that among 1095 cancer patients with severe pain, 80% of pain was due to cancer and 18% was caused by cancer treatment. Tumour-related pain was classified as originating from nociceptors in the soft tissue (45%), bone (35%), or visceral structures (33%), or as having neuropathic origin (34%).

It is important to bear in mind that the size, type or location of the tumour or the extent to which the visceral organ are involved may not be associated with pain intensity and quality (sensory dimension). Recent literature, together with clinical findings, has shown that certain solid visceral organs such as the lung, liver and kidney might be grossly destroyed by a tumour, yet the patient experiences no pain (Mantyh, Clohisy, Koltzenburg, & Hunt, 2002). Conversely, a small kidney tumour can cause severe pain because it depends on trigger factors such as distension, ischemia, inflammation, compression and infiltration (Ness & Gebhart, 1990). This is because visceral pain occurs by activation of nociceptors that are embedded in visceral organs but respond to mechanical stimuli ‘stretch’ (Cervero & Laird, 1999). Therefore visceral pain is closely connected to the nature of provoking stimuli rather than to tissue injury (Ness & Gebhart, 1990).

Identification of different pain syndromes and etiology provides important data for comprehensive pain assessment of the cancer pain experience which can foster appropriate pain treatment decisions (Turk & Okifuji, 2001).

2.5.2 Sensory dimension

The sensory dimension of pain refers to the location, intensity and quality of pain (McGuire et al., 1995). The pain location provides information on the etiology of pain and the extent of the functional status that may be interfered with. Pain intensity is the most often measured dimension of pain, with a wide range of pain assessment scales. Words commonly used to describe pain intensity are mild, moderate, severe, excruciating and intolerable. It is highly subjective and influenced by the individual's pain threshold (the least stimulus intensity at which an individual perceives pain). The quality of pain is depicted as how the pain actually feels, such as sharp, dull, tender, burning, aching, and stabbing (McGuire et al., 1995).

2.5.2.1 Pain intensity

Pain intensity is a dominant factor in determining the effects of pain on the patient and the effectiveness of pain interventions (Anderson & Cleeland, 2003). The main focus of pain research has been investigating pain intensity.

In Jensen's critical review (2003) of pain measures in adult cancer patients, he found that of 164 articles reviewed, the majority of studies (74.4%) examined pain intensity, and some (29.3%) assessed pain intensity and pain interference in a combined single composite score. There are few studies that examine the prevalence and intensity of pain at the early stage of diagnosis. In a recent systematic review (Hearn &

Higginson, 2003) of the literature between 1980 and 2000, only 2 out 54 studies focused on the early stage of the disease (Ger et al., 1998; Vuorinen, 1993). Ger et al. (1998) interviewed 296 subjects in a prospective study to examine the presence and intensity of pain. They found that 38% had cancer-related pain. Of these, 31% were suffering from significant average pain of more than or equal to 5 on a 10-point scale, and 65% had significant worst pain of more than or equal to 5 on a 10-point scale. Vuorinen (1993) recruited a newly diagnosed cancer population to investigate only the prevalence and not the intensity of pain. A total of 240 subjects responded to a pain questionnaire. The results showed that 28% reported having pain. Clearly, there is a lack of studies investigating pain intensity in newly diagnosed cancer populations.

In the studies that have investigated pain intensity, most of them concentrated on advanced or terminal disease. In the same review by Hearn and Higginson (2003), 26 of the studies involved advanced or terminal cancer populations. Unfortunately, it was found that 75% of cancer patients in the terminal phase die with inadequate pain control (Bonica, 1990; Hearn & Higginson, 2003). The average sample size in these studies was 537.6 ranging from 52 to 3577 advanced cancer patients. The study with the largest sample was a prospective one involving 3577 advanced cancer patients over a 9-year period in a home palliative setting (Mercadante, 1999). The presence and intensity of pain were recorded at regular intervals from when the patients were first referred to the palliative programme, after 1 week, and in the last week of life. It was reported that 70.3% had pain at referral. The mean intensity on a 0-10 visual

analogue scale (VAS) was 4.4 at referral, 2.5 after 1 week, and 2.3 in the last week of life.

In another prospective study, a population of 1640 advanced cancer patients was assessed at admission to 7 palliative care units in an international study Europe, the United States, and Australia (Vainio & Auvinen, 1996). The authors found that 72% had pain on admission and 51% had moderate to severe pain. A retrospective survey conducted in Hong Kong (Chung, Yang, & Wong, 1999) to review the significance of current pain in 100 cancer patients in hospices and oncology units reported that 77% had current pain and the majority had mild pain. The remaining 26 studies in the systematic review (Hearn & Higginson, 2003) involved general cancer populations and showed that 30%-50% had moderate to severe pain intensity at varying stages of cancer (Hearn & Higginson, 2003; Mercadante, 1997; Portenoy & Lesage, 1999).

Although numerous studies have revealed the pain intensity among cancer patients, there are several problems associated with the generalizability of the study results. First, the study designs are limited by the inconsistencies between prospective (Mercadante, 1999; Vainio & Auvinen, 1996) and retrospective designs (Addington-Hall & McCarthy, 1995; Chung, Yang, et al., 1999). Retrospective designs may contribute to potential recall bias, leading to measurement error. Also, there may be observer bias in those studies where only the caregivers were interviewed and not the patient who was in pain (Addington-Hall & McCarthy, 1995; Bucher, Trostle, &

Moore, 1999). Caregivers including significant others or family members tend to overestimate the level of pain intensity in cancer patients (Jensen, 2003). Second, most of the studies were conducted in healthcare settings (Caraceni & Portenoy, 1999; Ger et al., 1998; Grond et al., 1996) rather than in communities of people (Greenwald, Bonica, & Bergner, 1987), rendering the data less generalizable (Hearn & Higginson, 2003).

Third, the measures of pain intensity are inconsistent. The wide range of methods or tools used compounds the difficulties in pain assessment. Jensen (2003) reports that these single-item tools used to assess cancer pain intensity include the Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), and Verbal Rating Scale (VRS), and those much less often used include the Mechanical Visual Analogue Scale, Graphic Rating Scale (GRS), Face Scale, Finger Dynamometer, and various combination scales. While a single-item tool measures one dimension of pain, a multiple-item tool measures more than one dimension, or multidimensions. Multiple-item tools include the most frequently used Brief Pain Inventory (BPI), others include the Rotterdam Symptom Checklist, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer (EORTC QlQ-C36), the Head and Neck cancer questionnaire, and the Head and Neck Quality of Life Intstrument (HN QOL). A detailed discussion of the pain assessment tools will follow in chapter 3.

Fourth, cancer pain is not well defined. Studies have reported that cancer patients have more than one pain (Caraceni & Portenoy, 1999; Twycross, 1997), with varying duration (Caraceni & Portenoy, 1999; Glover, Dibble, Dodd, & Miaskowski, 1995). Most of these studies do not state whether the pain is acute or chronic, and do not address the pathology of pain (nociceptive or neuropathic), or its etiology (tumour-related, tumour treatment-related, or concurrent disorder). Fifth, the discrepancies in reporting may be related to differences in culture, family network support, perceptual processes in abstractions and the properties of pain assessment tools (Chung, Wong, et al., 1999).

2.5.2.2. Pain interference (Functional dimension)

Pain interference refers to the extent to which pain interferes with daily functioning, also known as the functional dimension. The scale most commonly used to measure cancer pain interference is the Brief Pain Inventory (BPI). The BPI consists of 7 day-to-day functional activities with which cancer pain can interfere. These are general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life on 0-10 NRS scales. Subjects are asked to indicate the extent to which pain interferes with daily functioning, where 0=does not interfere and 10=completely interferes.

The newly developed Chinese Cancer Pain Assessment Tool (CCPAT) is a culturally specific pain measure (Chung, Wong, & Yang, 2001). This tool was developed from

a triangulation study involving cancer patients, doctors and nurses of the same culture. The CCPAT consists of functional, psychosocial, pharmacological, and emotional factors, as well as pain beliefs and meanings and pain intensity dimensions. The functional dimension includes the influence of pain on functional activities such as appetite, eating habits, self-care and daily activities, entertainment, sleep and rest, housework, and walking ability. Chung et al. (2000) revealed the importance of including appetite, sleep and rest in pain assessment for Chinese cancer patients. Appetite has an important role in maintaining health and fighting illness, since "to cure and to eat are of the same origin". Sleep and rest are equally important because the Chinese believes that energy restoration helps in fighting illness and pain.

Many studies have demonstrated that pain interferes with daily functioning (Caraceni et al., 1996; Cleeland & Ryan, 1994; Ho, Chung, & Wong, 2003; Ho, Chung, & Wong, 2004; Mystakidou et al., 2001). However, studies have demonstrated that the association between pain intensity and pain interference is nonlinear using the BPI (Daut & Cleeland, 1982) or CCPAT (Ho et al., 2003).

Ho et al. (2004) recruited 22 male and 5 female hospitalized Chinese liver cancer patients consecutively with a mean age of 43.7 (SD ± 9.9) years. A significant number reported the influence of pain on their functional activities such as sleep (76%) and housework (64%). More than half reported interruption to daily activities like shopping (56%), eating habits (52%) and resting in bed during the daytime (56%) due to pain. T-test demonstrated a significant difference in the functional dimension

scores of 42.7 (± 11.2) and 31 (± 11.3) between the pain and no pain groups respectively ($p<0.05$). Among the pain groups (no pain, mild, moderate and severe pain), the interference of pain on the patients' lives in terms of their function was not as much when the pain intensity was low. The CCPAT revealed that the composite scores were most salient with moderate pain. It has been suggested that as the pain intensity reaches a certain level, the functioning of the patient becomes interrupted and even impaired (Cleeland, Ladinsky, Serlin, & Nguyen, 1988).

Although studies have found an association between pain intensity and pain interference, findings in other research support the notion that pain intensity and pain interference are distinct dimensions of pain (Ferrans & Ferrell, 1992; Klee, Groenvold, & Machin, 1997). Klee et al. (1997) investigated pain intensity and pain interference by using a cancer-specific quality of life measure in 1041 women with breast or gynaecologic cancer. They found that women with gynaecologic cancer had greater pain interference than those with breast cancer however the pain intensity scale (4-point VRS) was not able to distinguish these two cancer groups. Thus, the findings support that pain intensity and pain interference are both measures of pain but are distinctly different components of pain.

2.5.2.3. Pain location

The pain location provides information on the etiology of pain (McGuire et al., 1995). In cancer pain research, a pain drawing is used to assess the pain site. This drawing consists of an outline of a human body, and subjects are asked to indicate the pain location by putting a mark or shading the corresponding area on the drawing.

Only limited number of studies have reported the location of pain (Caraceni & Portenoy, 1999; de Wit et al., 1997; Grond et al., 1996; Twycross, 1997; Twycross & Fairfield, 1982). A recent review (Jensen, 2003) reported that among 164 articles on the measurement of pain, only 1.8% included pain location. A prospective study with 383 hospitalized cancer patients who were about to be discharged assessed them on the number of pain locations, pain duration and intensity (de Wit et al., 1997). The study found that patients had a mean of 1.8 pain locations.

Two prospective cross-sectional studies included larger samples of 1095 and 2266 general cancer patients attending pain clinics (Caraceni & Portenoy, 1999; Grond et al., 1996) to investigate the pain intensity, types and numbers of pain. Caraceni and Portenoy (1999) found that 25% of cancer patients experienced two or more pains, whereas Grond et al. (1996) reported that 77% experienced pain, and among those who had pain, 30 % had one pain, 39% had two pains and 31% had had three or more pains. In advanced cancer patients, 85% have been reported to have more than one pain, and among those 40% have four or more pains (Twycross, 1997).

In those studies that did investigate the site of pain, the primary cancer sites included were lung (Potter & Higginson, 2004), breast (Roemer-Becuwe, Krakowski, & Conroy, 2003) , head and neck (Whale et al., 2001), prostate (Rodrigues et al., 2004), gynaecologic (Yavuz et al., 2004), gastrointestinal (Befon et al., 2000), liver (Li et al., 1994), and myeloma (Diaz et al., 2004). However, Jensen's critical review (2003) reports that in most of the subjects studied (68%), no specific cancer diagnoses or sites were provided. Also, in those studies that did specify cancer diagnoses or sites, the sites most often studied were breast (14%), lung (11%), prostate (10%), head and neck (7%), metastatic (6%), gynaecologic (4%), myeloma (4%), gastrointestinal (2%), colon, rectal, or colorectal (2%), and genital (2%) cancer. He further points out that many of the cancers were less represented by subjects including melanoma, oral, lymphoma, liver, bone, hematologic, brain, cervical, stomach, orofacial, esophageal, reproductive, soft tissue, bladder, nasopharyngeal, testicular, kidney, and thoracic (all less than 1%).

The major flaws in these studies are that they exclude the cancer sites of the studied subjects and are limited to certain cancer sites. It is impossible to interpret these results in a meaningful way because one of the key factors is missing. It is important to assess the pain location as it provides information on the cause of pain, whether it is related to tumour or tumour treatment, and the extent to which functional status that may be interfered with.

2.5.2.4 Pain quality

In addition to the pain intensity dimension, pain has many sensory and affective qualities. The sensory quality refers to how the pain feels. The affective dimension will be discussed in the next section. The most commonly used tool to measure cancer pain quality is the McGill Pain Questionnaire (MPQ), but the short form McGill Pain Questionnaire (SF-MPQ) has also been used. The MPQ contains choices from 78 possible word selections or pain descriptors that are categorized into four major dimensions: sensory, affective, evaluative, and miscellaneous, as well as pain intensity. The SF-MPQ consists of a subset of 15 descriptors taken from the sensory and affective dimensions.

A number of studies have been conducted to examine pain quality in various groups of cancer patients using the MPQ (Caraceni, 2001; Dobratz, 2001; Mystakidou et al., 2001; Wilkie, Huang, Reilly, & Cain, 2001). However, in Jensen's comprehensive review of 164 articles (2003), only 10.4% of the studies assessed pain quality.

A recent study has explored the differences in the words used to describe the quality of nociceptive and neuropathic pain in 123 lung cancer patients (Wilkie et al., 2001). Patients reported 457 pain sites: 343 (75%) were nociceptive sites whilst 114 (25%) were neuropathic. Pain quality descriptors used to describe nociceptive pain sites include lacerating, stinging, heavy, and suffocating. Throbbing, aching, numb,

tender, punishing, pulling, tugging, pricking, penetrating, punishing, miserable, and nagging are the descriptors chosen for neuropathic pain site.

Wilkie et al. (2001) also found that ten words were predictive of 78% of the pain sites with 81% sensitivity to nociceptive pain and 59% sensitivity to neuropathic pain. However, some pain quality descriptors that had previously been associated with neuropathic pain such as burning, shooting, flashing, tingling, itching, and cold, did not differentiate between neuropathic pain and nociceptive pain. They concluded that the inconsistency may be attributed to the less frequent selection of MPQ words and insufficient neurological examination recorded in the data in previous literatures and research.

Another descriptive study recruited 76 terminal cancer patients to depict the pain quality of advanced cancer pain in a home hospice (Dobratz, 2001). They reported that the four main pain patterns selected by these patients were tiring and exhausting (11.5%), troublesome and annoying (8.8%), dull and aching (7.7%), and nauseating and sickening (6.8%).

Clearly, there is a lack of studies that examine pain quality. Also, studies are inconclusive of pain quality or the pattern of pain quality because of the relatively small sample sizes, and large variations in the samples (different cancer types, stages, etiology of cancer pain, and pain syndromes) (Dobratz, 2001; Wilkie et al., 2001).

2.5.3 Affective dimension

The affective dimension of pain experience encompasses mood states or emotional responses to pain, personality traits and psychiatric problems (Briley, 2003; Fishbain, Cutler, Rosomoff, & Rosomoff, 1997). Emotional responses include anxiety, depression, mood changes, irritability, anger, hostility, and helplessness. Apart from the MPQ and SF-MPQ, a number of single-item affective scales are used to measure the affective dimension. These scales include the VAS of affective pain, NRS of affective pain, and VRS of affective pain.

2.5.3.1 Pain affect and intensity

Although numerous studies have focused on the physiological and sensory dimensions (pain intensity) of cancer pain, fewer studies have revealed the affective or emotional dimension of the cancer pain experience (Sela, Bruera, Conner-spady, Cumming, & Walker, 2002). The relationship between cancer pain and pain affect has also been investigated.

Studies have been conducted to examine the relationship between pain affect and intensity (Kremer, Atkinson, Jr., & Ignelzi, 1982; Smith, Gracely, & Safer, 1998). One study investigated whether an increase in present pain intensity by physical therapy will affect the pain ratings in intensity and affective scores (Smith et al., 1998). Thirty-two cancer patients were recruited to undergo a session of physical

therapy whereby the movement exacerbated the pain. The results showed that pain therapy increased the pain intensity but not the unpleasantness rating. The findings support the distinction between pain intensity and pain affect (unpleasantness).

Kremer et al. (1982) compared how pain intensity influences the affective dimension in cancer patients and benign low back pain patients using the MPQ. They reported that cancer patients reported higher affective scores than low back pain patients, even with low pain intensity. They suggested that one possible explanation for the difference in reporting the affective dimension of pain is that cancer patients may have greater worry or fear in relating pain to their cancer diagnosis.

Although the affective dimension using the MPQ has been positively associated with pain intensity (Ahles et al., 1983), low associations have been demonstrated in studies between MPQ–affective dimension and pain intensity (Chung et al., 2001; Wilkie, Keefe, Dodd, & Copp, 1992). It has been concluded that these data indicate that MPQ-affective dimension and other single-item affective scales (unpleasantness) are tapping into different components of pain, and that these affective scales measure psychological distress more than pain intensity (Jensen, 2003).

2.5.3.2 Anxiety, depression and pain

The association between cancer pain and anxiety, depression, or a combination of the two is interrelated (Lawlor, 2003). The relationship between pain and anxiety is

complex and bidirectional (Thielking, 2003). Anxiety and excessive worry can contribute to emotional and psychological distress, which in turn aggravate pain experience (Lee, 2002). On the other hand, cancer pain can have a negative effect on mood resulting in anxiety, depression and even suicidal thoughts (Strang, 1998).

Supporting evidence has been demonstrated in studies that have investigated the relationship between cancer pain and anxiety in cancer populations (Glover et al., 1995; Thielking, 2003). Thielking (2003) reports that patients who have tumour or tumour treatment-related pain are more anxious than cancer patients without pain. Glover et al. (1995) included 369 oncology outpatients in a study to determine the mood states in patients who had cancer-related pain and those who did not experience pain. They found that the patients who had cancer-related pain rated significantly higher anxiety, depression and anger than those who were pain-free. They concluded that increases in pain intensity correlate with increased mood states including anxiety and depression in patients who experienced cancer-related pain. However, the exact causal relationship between cancer pain and anxiety remains to be established.

Nonpharmacological interventions have been implemented on cancer pain patients in an attempt to investigate the effect of psychoeducation and supportive psychotherapy on emotional distress particularly anxiety and depression, as well as pain level (Ferrell, Rhiner, & Ferrell, 1993; Spiegel & Bloom, 1983). Ferrell et al. (1993) reported that cancer patients have a reduced anxiety level and a decrease in pain

intensity following participation in three sessions of a psychoeducation programme. By contrast, Spiegel and Bloom (1983) showed that patients who received one year of supportive psychotherapy were significantly less anxious and depressed but reported no change in pain level.

The comorbid presentation of pain and depression is observed in as many as 50% of patients who suffer from chronic pain conditions (Gallagher, 2003). It has been suggested that pain and depression may share a common underlying mechanism (Blackburn-Munro et al., 2001). The HPA axis is postulated. Many chronic pain patients, including cancer patients, develop depression. However, the results are not definitive as to whether depressed patients tend to report more pain or whether patients experiencing chronic pain are more likely to be depressed (McGuire et al., 1995).

2.5.3.3 Other affective dimensions

Other affective dimensions include emotional responses such as frustration, anger, fear, exhaustion, helplessness and hopelessness. A recent study examined pain intensity and affect in 52 male and 59 female outpatients with advanced cancer attending a pain clinic (Sela et al., 2002), using the VAS to quantify overall pain intensity and the accompanying affect. Six separate VASs were used to measure frustration, anger, fear, exhaustion, helplessness and hopelessness. The results showed that 60% of males and 58% of females rated pain intensity as 90 to 100. Females scored higher than males on all of the emotional scales, with a significant

difference for fear and hopelessness. A high level of frustration was observed in these patients, while anger was found to be moderately high and a relatively lower level of fear was reported. The exhaustion scores were high and strongly correlated with cancer pain, whereas levels of helplessness were found to be moderate and there was only a limited correlation between pain intensity and hopelessness.

No consistent set of affective factors has been identified, but extensive literature indicates that these factors play an important role in pain perception and response to pain (Ahles & Martin, 1992). Other studies have produced inconsistent results in the correlations between pain and anxiety, mood states, hostility, extroversion, and neuroticism (McGuire, 1987). The relationship between cancer pain and pain affect remains questionable (Sela et al., 2002). Sela et al. (2002) conclude that controversy exists with respect to whether increased pain intensity contributes to heightened emotional responses or whether changes in affect amplify pain perception.

2.5.4 Cognitive dimension

The cognitive dimension is defined as the way pain influences an individual's thought processes, and the individual's perception of the meaning of pain and of oneself (Ahles et al., 1983). These thought processes include attitudes, beliefs, perception, knowledge about pain, and attention to pain perception and response, which are influenced by social learning, cultural background, past life experience, and locus of control.

There are a limited number of studies that examine the cognitive dimension of pain and the relationship between the cognitive dimension and pain intensity. Cancer patients often view pain as a sign of progressive disease (Levin, Cleeland, & Dar, 1985; Spiegel & Bloom, 1983). Studies have shown that patients with this cognitive view report higher anxiety levels, more mood disturbance and depression, and more pain (Ahles et al., 1983; Spiegel & Bloom, 1983). This may be attributed to the fact that the cognitive appraisal of pain is considered as a future threat by cancer patients (Arathuzik, 1991).

One study recruited 32 cancer patients to investigate whether an increase in present pain intensity will affect the pain ratings in intensity and affective scores (Smith et al., 1998). The results showed that beliefs about the cause of pain also influence the pain intensity. Cancer patients who believed that the pain was due to cancer reported significantly higher pain intensity and pain affect than those who did not believe that the pain was due to cancer.

Another study showed that among 100 cancer patients, pain was perceived as a punishment (23%), an enemy (20%), or a challenge (36%) (Barkwell, 1991). The results further indicated that patients who perceived pain to be a punishment and an enemy were in greater pain, more depressed, and poorer in coping than those who thought it was a challenge.

Most of studies have been conducted among Caucasians in exploration of the cognitive meaning and perception they ascribe to pain, and how they cope with pain. There is a lack of studies that investigate the cognitive appraisal of pain among Chinese people. Research findings have demonstrated cultural differences in the perceived meaning of pain using the CCPAT to capture the essence of Chinese culture in pain beliefs and meanings (Chung et al., 2000; Ho et al., 2003). In these studies, most Chinese patients believed that pain is physical and mental torture, which causes discomfort, and that cancer means suffering. It was thought that pain serves as a reminder to treasure one's health, and to accept reality. Also, facing pain is a challenge. However, the generalizability of this study is low due to the small sample size.

The role of attention towards pain remains unclear. A review of various studies suggested that focusing on somatic symptoms such as pain may contribute to elevated anxiety and pain level (Ahles & Martin, 1992). Various forms of distraction such as counselling or music therapy may alleviate pain related to attention (O'Callaghan, 1996). The interplay between the cognitive, affective and sensory dimensions of pain is complex and intertwining (McGuire et al., 1995). However, it is important to unravel how the cognitive dimension interacts with other pain dimensions. The significance of this dimension rests on the individual's coping strategies, expression and behaviours attributed to the meaning of pain, as well as his/her decisions and compliance with treatment options.

2.5.4.1 Pharmacological dimension

The pharmacological dimension refers to the individual's attitudes and knowledge about the use of analgesics. These include the perception of analgesics as being effective, the willingness to comply with doctor's orders for analgesics, and concerns. Attitudes and perception towards analgesics may influence an individual in the choice of pharmacological means for pain relief. The placebo effect may also have a role in nociception.

Undoubtedly, one of the major barriers related to patients being treated for cancer pain are misconception and fear about the use of opiates (Ward et al., 1993). These findings are echoed by studies that were conducted among Chinese palliative (Chung, French, & Chan, 1999) and hospitalized patients (Lin & Ward, 1995; Wills & Wootton, 1999). Despite the existence of the pharmacological dimension, studies that use a pain assessment tool to quantify this dimension in cancer patients are lacking.

A pilot study involving 22 male and 5 female hospitalized Chinese liver cancer patients examined different pain dimensions using the CCPAT, including the pharmacological dimension (Ho et al., 2003). The results show a high compliance rate (70%) with the doctors' prescriptions for analgesics. Less than half of the

patients (41%) perceived the analgesics as ineffective, or concerned about tolerance to narcotics (44%).

Although the pharmacological dimension is known to have an effect on the pain outcome, there is minimal research that has considered this dimension as a pain measure. It is important to include the pharmacological dimension in cancer pain assessment and to examine the placebo effects on these patients.

2.5.5 Behavioural dimension

The behavioural dimension of pain includes behaviours related to pain (McGuire et al., 1995). These behaviours may reflect the presence and severity of pain and behaviours undertaken to control pain, which may or may not be conscious and deliberate. Behaviours that can be observed are grimacing, moaning, rubbing of affected area, limiting movement to guard pain, resting and lying down, or taking medication (LeResche & Dworkin, 1984; Wilkie & Keefe, 1991). The critical review on the behavioural dimension is not discussed in this thesis since the present study concentrates on the subjective reporting of pain rather than observations made by assessors. Studies related to the behavioural dimension have potential observer bias leading to measurement errors.

2.5.6 Sociocultural dimension

The sociocultural dimension of pain includes demographic and cultural variables such as sex, age, race, religion, ethnic background, social support and cultural practices that may relate to pain experience. Studies that have examined the sociocultural dimension are related to coping styles, expression of pain, and psychosocial support.

Studies have involved subjects from six different ethnic and cultural backgrounds, and examined the variations in pain responses and the association with the locus of control (LOC) (Bates, Edwards, & Anderson, 1993; Bates & Rankin-Hill, 1994). An individual with an external LOC may rely on fate and chance, whereas an individual with an internal LOC may perceive that matters (including pain) are within one's own control. The results showed significant correlations between variations in pain reporting and responses and LOC style, rather than between pain intensity and diagnosis, current medication use, or past pain therapies (Bates et al., 1993). The external LOC group reported a higher mean score of pain than the internal LOC group. Further correlation has been found between LOC style and ethnic and cultural background (Bates et al., 1994). Among the six ethnic groups, the Latino, Italian, French Canadian and Irish had higher external LOC, whereas the Old Americans and Polish had a higher internal LOC. The Old Americans and Polish who had internal

LOC tended to be less expressive or emotional; also believed that non-expression of pain was the ideal pain response.

However, the researchers argue that the results may not reflect the true ethnic background of the subjects being studied because the duration of residency in the country (United States) was not considered. This is attributed to the possibility of a change in LOC style due to the length of residency in a particular country. Longer residency in a different country may contribute to higher adaptation of LOC style specific to that country, since past life experiences, beliefs, attitudes and meanings derived from growing up within different social communities may influence LOC style. It has also been suggested that LOC style may be changed in chronic pain experience (Bates et al., 1994).

Caution must be taken not to label certain cultural groups with expressive or less expressive behaviours, and consideration of individual differences is equally important. In light of these findings, it is plausible that cultural background plays an important mediating role that influences an individual's beliefs and attitudes towards pain, pain reporting and responses, as well as the communication of pain experiences. Therefore, careful selection of an appropriate culturally sensitive pain assessment tool enables researchers to capture the essence of the sociocultural dimension of pain.

2.5.6.1 Psychosocial dimension

The psychosocial dimension refers to family and social support with regard to an individual's cultural background. Some studies have examined the relationship between the psychosocial dimension and pain intensity (Kelsen et al., 1995; Spiegel, Sands, & Koopman, 1994).

In their critical review of cancer pain and psychosocial factors, Zaza and Baine (2002) report that there is a significant relationship between a supportive family environment and reduced pain intensity. Spiegel et al. (1994) revealed that there is a significant relationship between a supportive family environment and reduced pain intensity. Studies in the western culture have suggested that higher pain intensity is associated with less social support and reduced social activities and a less resilient social network.

A recent study demonstrated that among 27 Chinese cancer patients (Ho et al., 2003), most (80%) responded that there were perceived benefits from living with the family. More than half of the patients (56%) indicated that they were overt about their need for others' attention with respect to pain, and reported no apparent concealment of pain. Despite the only 16% of patients reporting perceived discrimination, it is prudent to note that some Chinese people perceive cancer as contagious. This may lead to social stigmatization by the general public, resulting in social separation and isolation.

Further study is warranted to discover whether family and social support in the Chinese context influence pain level. This finding reinforces the clinical implications concerning family support and involvement and in-patient care, particularly during cancer treatment. Assessment for cancer pain with reference to a patient's psychosocial status is shown to be relevant.

2.6 Conclusion

From the ancient beliefs surrounding the phenomenon of pain to the evolution of pain theories and the recent conceptualization of pain as multidimensional, it is clearly important to consider the biological, psychological, social and cultural factors that contribute to the totality of pain experience. Although research and literature support that pain experience results from these pain dimensions, their complex interactions further complicate the subjective pain experience, rendering the assessment of pain extremely difficult. Pain assessment tools are available, spanning from the physiological to the sociocultural dimensions of pain. However, each tool has its own strengths and weaknesses. The next chapter will address issues surrounding the pain assessment tools.

CHAPTER 3

LITERATURE REVIEW ON CANCER PAIN MEASURES

3.1 Introduction

The comprehensive and reliable assessment of pain serves as the cornerstone of effective pain management. This chapter will present a review of current literature on measures used to assess cancer pain. The review will include the validity and reliability of selective common types of cancer pain measures, and critical accounts of these pain measures including the strengths and weaknesses in clinical pain assessment. The pain measure's sensitivity, the number of response options in an instrument and the extent to which a measurement is sensitive to change will also be addressed.

3.2 Clarification of terms

i. "Validity" refers to the extent to which the pain measure is a valid and useful indicator of cancer pain.

ii. "Reliability" refers to the extent to which a measurement is consistent and free from error or reproducibility of results.

3.3 Significance of pain assessment

Systemic and objective assessment of pain is fundamental and essential to the achievement of pain relief (Chung, 2002; Horn & Munafo, 1997) because unidentified or underestimated pain may lead to untreated pain or undertreatment of pain (Anderson et al., 2000). The significance of pain assessment is embedded in its aims and purposes which will be highlighted here. First, pain assessment identifies the individuals who have pain and are reluctant to report it. Second, it provides quantitative and qualitative data on the nature, characteristics and impact of pain, whereby a more accurate picture of the pain experience is captured. This impact includes its effect on patients and their families.

Third, it guides the healthcare professionals' clinical decisions regarding pain treatment, interventions and modalities, since the selection of choices is dependent on the causes of pain. Fourth, by monitoring the changes in pain status, it evaluates the effectiveness (including the progress and outcome) of current therapeutic interventions, and the efficacy of different pain treatments. Fifth, in chronic pain situations such as cancer pain, it facilitates the prevention of delayed treatment and further disability, the prediction of prognosis and estimation of resources and facilities required for provision of care. Finally, by assigning a measurement of pain, the patient will possess a better sense of control over the condition, and thus better coping abilities (Cork, Isaac, Elsharydah, Zavisca, & Alexander, 2004).

Therefore, the importance of accurate pain assessment cannot be overemphasized. Apart from appropriate timing of assessment, including baseline and ongoing assessments, the careful selection of appropriate cancer pain measures for a given patient population and clinical situation is one of the key factors for accuracy in pain assessment (McGuire et al., 1995).

3.4 Common types of cancer pain measures

Studies have examined a wide variety of cancer pain measures that assess a spectrum of pain dimensions including pain intensity, pain interference, pain quality, and pain affect or unpleasantness (Ahles et al., 1983; Caraceni et al., 2004; Cork et al., 2004; DeConno et al., 1994). The types of cancer pain measures used in these studies include single-item pain measures and multiple-item pain measures which are based on self-reporting of pain (Jensen, 2003; Valley, 2003). For example, Visual Analogue Scales (VAS) (Ahles, Ruckdeschel, & Blanchard, 1984), Numerical Rating Scales (NRS) (Paice & Cohen, 1997), Verbal Rating Scales (VRS) (Tannock et al., 1989), and the Chinese Pain Intensity Verbal Rating Scale (C-PIVRS) (Chung, Wong, Yang, & Tan, 1998), Graphic Rating Scales (GRS) (McMillan, Williams, Chatfield, & Camp, 1988), Face Scales (FS) (Ramer et al., 1999), and the Mechanical Visual Analogue Scale (M-VAS) (Ramer et al., 1999) are single-item pain measures.

Examples of multiple-item pain measures include the Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994), the McGill Pain Questionnaire (MPQ) (Wilkie et al., 1992), the Rotterdam Symptom Checklist (de Haes, van Knippenberg, & Neijt, 1990), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer (EORTC QLQ-C36) (Klepstad et al., 2002), the Head and Neck Quality of Life Instrument (HN QOL) (Terrell, Nanavati, Esclamado, Bradford, & Wolf, 1999), the Breast Cancer Treatment Outcome Scale (BCTOS) (Stanton, Krishnan, & Collins, 2001), and the Chinese Cancer Pain Assessment Tool (CCPAT) (Chung et al., 2001). Each scale can be used on its own or in conjunction with other scales to meet the different needs of patients (Chung, 2002). Determining factors for the usefulness of pain measures in clinical assessment include validity, reliability and sensitivity (Jensen, 2003), and these will be addressed in the following review.

3.5 Cancer pain measures for pain intensity

By far, single-item pain measures are the most commonly used. These pain measures are popular in clinical use because they are simple, easy to use and cost-effective (Valley, 2003). The primary weakness is the risk of attempting to translate the complex dynamic process of pain experience into oversimplified numerical models (Horn & Munafo, 1997).

3.5.1 Single-item pain measures for cancer pain intensity

Most studies have investigated cancer pain intensity using single-item pain measures (Ahles et al., 1984; Paice & Cohen, 1997; Tannock et al., 1989) while some studies have used multiple-item pain measures (Cleeland & Ryan, 1994; de Haes et al., 1990).

3.5.1.1 Visual Analogue Scale (VAS)

A Visual Analogue Scale (VAS) is commonly used to measure pain intensity. It is usually a 10-cm horizontal line anchored by 0 and 10 at each end, where 0 represents no pain and 10 represents pain as bad as it could be (Appendix 1). The user is instructed to report pain by marking one point along the line that is analogous to the level of pain. The VAS score is determined by measuring the distance between 0 and the marked point (usually in millimetres). Thus, the scale provides finely graded options from 0 to 100 points. The line orientation can also be vertical or curved (Sriwatanakul et al., 1983), and the direction of the numbers can be reversed (Yakut, Bayar, Meric, Bayar, & Yakut, 2003).

Many studies have demonstrated that the VAS has well-established criterion validity and consistent sensitivity to changes in cancer pain in relation to pain treatment or time (Grossman et al., 1992; Paice & Cohen, 1997; Ramer et al., 1999; Wilkie,

Lovejoy, Dodd, & Tesler, 1990). Criterion validity refers to associations of pain measures with outcome criteria. The primary criterion of pain measures in clinical pain assessment is the sensitivity to treatment or to changes in pain over time (Jensen, 2003). The test-retest reliability of VAS has been examined and shown to be high in a number of studies (Gallagher, Bijur, Latimer, & Silver, 2002; Grossman et al., 1992).

The sensitivity of the VAS is an advantage as it provides infinite options between 0 and 100 and is highly sensitive to change (Rosier, Iadarola, & Coghill, 2002). However Jensen, Turner and Romano (1994) concluded that the discriminative function of a scale may be lost by using too many responses. Their study examined 124 chronic pain patients whose pain intensity was assessed using the 101-point NRS pre- and post-treatment. The pain intensity measured was for least, most, current, and average pain. The results were recoded to form seven scales ranging from 2 to 101 points. The sensitivity of the scales was examined to determine the number of levels needed. They concluded that 10- and 21- point scales had retained more information than scales with levels less than 11, and that scales reduced to 11 or 21 points provided sufficient meaningful discrimination. Thus, the higher sensitivity of a scale does not imply greater discriminative power.

Clinically, the VAS is simple, practical, and easy and quick to use particularly for patients with language difficulties (Ahles et al., 1984; Kelly, 2001; Wallenstein, 1984). although the VAS is a well-studied method for measuring acute and chronic

pain (Carlsson, 1983; Katz & Melzack, 1999; Scott & Huskisson, 1976), some studies have shown several limitations to its use. Substantial potential measurement errors are related to the user. The abstract concept of visualizing pain and relating it to the distance along the VAS is difficult for some patients to grasp (Cork et al., 2004; Ferraz et al., 1990). Many patients find it difficult to judge the distance accurately such as children, the elderly, and those with cognitive or visual impairment or who are too sick (Chung, 2002), or patients with psychomotor impairment (Herr, Spratt, Mobily, & Richardson, 2004). Therefore, failure in using VAS (4-11%) has been reported when compared with other simple scales (Jensen, Turner, & Romano, 1994), although it was argued that better explanation of the use of the scale significantly reduced the failure rates (Wilkie et al., 1990). Investigators have assumed that the failure rate is affected by older age, when abstract thinking becomes poorer (Herr et al., 2004; Kremer, Atkinson, & Ignelzi, 1981; Scott & Huskisson, 1976).

Related to the conceptualization of pain, scale orientation (horizontal versus vertical) has been found to alter pain reporting in patients from different cultural backgrounds. One study showed that the horizontal VAS has higher sensitivity than the vertical one when administered to a group of German-speaking patients with chronic low back pain who also reported higher scores on the vertical scale (Ogon, Krismer, Sollner, Kantner-Rumplmair, & Lampe, 1996). The authors concluded that the horizontal scale was preferable. In a constrasting study, the vertical VAS was demonstrated to have significantly less error than the horizontal scale in a group of Chinese patients with postoperative pain, therefore the vertical scale is more beneficial for use in the

Chinese population (Aun, Lam, & Collett, 1986). Inconsistent results were produced because of the scale orientations. These results may be attributed to the traditional Chinese cultural customs of reading vertically downwards (Aun et al., 1986). Studies have shown that cultural factors will affect how a single dimension of pain (pain intensity) is reported. Thus, in more complex situations such as cancer pain, it is imperative that distinct cultural influences are incorporated into the multidimensional assessment of pain.

Further, the abstraction elicits practical limitations in the clinical setting, because it is more time-consuming to use (Cork et al., 2004). Also, the requirement of pen and paper further reduces its practicality. A scale on paper causes other technical problems leading to measurement error. One is inaccuracy in the length of the line (10 cm) in the process of making duplications from a photocopying machine (Jensen, Karoly, & Braver, 1986). This may be due to photocopying techniques, and the quality of paper and machine used. Another type of measurement error is caused by the assessor having to measure the distance in order to determine the score (Chung, 2002), compared to direct scoring in the numeric rating scales. To reduce assessor-related errors, an instrument known as the Visual Analogue Thermometer (VAT) has been developed. This instrument will be discussed in the section under Mechanical Visual Analogue Scale (M-VAS).

When applying statistical analyses to the data obtained by any instrument, the level of measurement must be considered (Portney & Watkins, 2000). Studies have shown

evidence of the ratio scaling properties of the VAS, which demonstrates a high power function predictive of the ratio of pain sensation (Price & Harkins, 1992). It has been argued that the scores obtained by the VAS are non-linear, and therefore the analysis is prone to bias (Langley & Sheppeard, 1985). Further, the researchers argue that the VAS can only be considered as an ordinal (rank-ordered) versus a ratio scale. A true ratio scale gives the actual amount of the variable being measured as indicated by the numeral (or score) on the scale, and can be subjected to all mathematical and statistical manipulations such as summation, deduction, multiplication and division. That is to say, a score of 40mm cannot be considered to be twice as painful as a score of 20mm. By the same token, the same score obtained from two different subjects may not indicate an identical amount of pain. Statistical limitation exists due to manipulative restrictions in the ordinal data. However, the VAS is often treated as a ratio level of measurement (Phillip, 1990; Price, McGrath, Rafii, & Buckingham, 1983) with which parametric statistic is conducted, leading to potential measurement errors.

VAS has its limitations, but in view of its well-established validity and reliability, it is considered the gold standard for validation of newly developed pain measures and is widely used in clinical and research settings (Campbell & Lewis, 1990; Wallenstein, 1984). It is important to note that the orientation of pain measures (horizontal versus vertical) may have implications for specific cultures, since a previous study has suggested that Chinese patients may be more accustomed to a vertical scale.

3.5.1.2 Numeric Rating Scale (NRS)

A Numeric Rating Scale (NRS) consists of a range of numbers, and there are numerous variations of NRS. The most commonly used NRS consists of 0 to 10, or sometimes 0 to 100 or other ranges along a horizontal axis (0 representing 'no pain' and 10 or 100 representing 'pain as bad as it could be') (Appendix 1). The user is instructed to write down a number, or circle or state the single number that best represents the level of pain intensity. Pain intensity is interpreted by the magnitude of the numeral rated. Larger numerals indicate greater pain intensity.

NRS are less often used in research than VAS (Jensen, 2003). The findings in studies support the validity and reliability of NRS as being similar to that of VAS. Most studies have demonstrated very strong associations between NRS and VAS (DeConno et al., 1994; Jensen et al., 1986; Paice & Cohen, 1997). Studies have shown that the NRS is sensitive to changes in pain associated with physical therapy and pain treatment (Grond et al., 1999; Smith et al., 1998). Portenoy et al. (1999) further supported the validity of NRS in a randomized double-blinded study examining the effectiveness of a new opioid (oral transmucosal fentanyl citrate - OTFC) for cancer-related breakthrough pain. Ascending doses of OTFC (200, 400, 600, 800, 1200 or 1600 mg) were randomly given to ambulatory cancer patients. An NRS was used to monitor the changes in pain intensity level. They reported that the responses on the NRS showed an appropriate dose response to treatment with OTFC.

The NRS is superior to the VAS in several aspects. First, the result is simple to record as there is no need for the assessor to measure the distance from zero. Second, the NRS is more flexible as it can be used in the verbal or written format. The verbal version is quicker to administer (no paper or pen required) and can be easily used by those patients who are very sick as cancer progresses (Valley, 2003). Third, it tends to be more easily understood than the VAS since numerals may eliminate cultural and linguistic problems as the are easier to comprehend: for example, 8 is a higher value number than 4. Fourth, it is the most familiar scale used by elderly patients (Herr & Mobily, 1993).

One study investigated the reliability of pain measures among 66 literate and 25 illiterate patients with rheumatoid arthritis from an outpatient clinic (Ferraz et al., 1990). Patients were asked to score their pain intensity on three scales, a Visual Analogue Scale (VAS), a Numerical Rating Scale (NRS) and a Verbal Rating Scale (VRS) on two occasions, before and after consultation with the doctor. The scales were presented randomly. The results showed highest correlations between the two measurements in the NRS, 0.963 for the literate and 0.947 for the illiterate, compared to 0.937 and 0.712 respectively for the VAS, and 0.901 and 0.802 for the VRS. The study thus clearly demonstrated that the NRS is more reliable when used among illiterate patients.

NRS has similar weaknesses to the VAS because of the requirement of the abstract concept of relating pain to a number, especially in cognitively impaired older patients (Herr & Mobily, 1993). Another drawback is that the assigned numbers are on the ordinal level of measurements (Chung, 2002). This incurs statistical constraints in analytic manipulations. As argued above, the intervals between numbers on the ordinal scale cannot be assumed to be consistent or equidistant. Although nine is always represents greater pain intensity than one, this scale is not sensitive enough to determine what the actual difference is (Portney & Watkins, 2000). Thus, ordinal scales lack arithmetic properties, and therefore the results are not arithmetically meaningful. Despite the weaknesses in the NRS, it is also embraced by healthcare professionals for its simplicity and clarity, as it is easy to understand, use, and interpret (Jacox, Carr, & Payne, 1994; McCaffery & Pasero, 1999). It is also easy to record and cost-effective. No special training is required to administer this scale (Valley, 2003).

Although studies have provided supporting evidence to demonstrate the validity and reliability of the NRS and suggested that it may be more reliable than the VAS, cancer patients tend to be an older population whose may be and cognitive judgement may be influenced by the use of opioids. These factors may affect their understanding of the numerals and what they represent in terms of pain intensity. Thus, it is important to consider these factors when selecting pain measures for cancer pain intensity.

3.5.1.3 Verbal Rating Scale (VRS)

A Verbal Rating Scale (VRS) consists of a set of pain descriptors or phrases. In cancer pain literature, the number of descriptors ranges from 4 to 8 words (Jensen, 2003). The most often used words include 0 = none, 1 = mild, 2 = moderate, and 3 = severe, representing varying degrees of pain intensity (Valley, 2003). Users are asked to select a single word or phrase that best describes their pain level, and their score is the number associated with the word or phrase chosen.

Like the VAS and NRS, some studies have demonstrated that the VRS is sensitive to changes in pain level with cancer pain treatment (Portenoy et al., 1999; Tannock et al., 1989). The VRS shows high intercorrelation with other pain measures such as the VAS, thus demonstrating its validity (DeConno et al., 1994; Jensen et al., 1986). Although studies have found that test-retest reliability has low to moderate stability (Ellershaw, Peat, & Boys, 1995; Sneeuw et al., 1997), patients prefer using the VRS than to using the VAS because words are easily understood. Evidence has supported that the VRS has a higher completion rate than the VAS (Kremer et al., 1981).

Like to the NRS, rank ordering scales impose similar arithmetic problems of non-parametric data. A non-continuous scale with indistinguishable distance between each rank cannot produce mathematically meaningful data. Another weakness is the restricted number of possible responses, with the results that patients cannot accurately describe their pain. Despite these limitations, the VRS has the advantage

of being simple and easy to use, as words are often more easily understood by patients than numbers.

3.5.1.4 The Chinese Pain Intensity Verbal Rating Scale (C-PIVRS)

While most pain intensity measures have been developed in the Western culture and translated from English to be used in another culture, the Chinese Pain Intensity Verbal Rating Scale (C-PIVRS) was developed within the Chinese population (Appendix 2) (Chung et al., 1998). The strength of the C-PIVRS is that it is culturally sensitive, and the terminology or pain descriptors used are more familiar and unique to the Chinese people (Chung et al., 1998). Another advantage is that the C-PIVRS is vertically oriented. It has been suggested that Chinese people may relate to the pain intensity better on a vertical scale than on a horizontal scale, since Chinese people traditionally read from top to bottom (Aun et al., 1986). It has been reported that up to 19% of Chinese patients were not able to complete the VAS properly (Chung et al., 1998). Also, the VRS has an advantage in containing words that would be more comprehensible to patients.

The C-PIVRS was tested for validity and reliability among 50 healthy Chinese subjects, using the VAS as a gold standard for comparison (Liu, Chung, & Wong, 2003). They found that the C-PIVRS is highly correlated with the VAS. Factor analysis showed that a single factor emerged in both scales, that is, they both measure only one dimension (pain intensity). The test-retest reliability of the C-

PIVRS was satisfactory and both scales were highly consistent for pain measurement under similar conditions (Liu et al., 2003).

3.5.1.5 Graphic Rating Scale (GRS)

A Graphic Rating Scale (GRS) is similar to a VAS. The GRS consists of specific markers along the 100mm horizontal line with numbers and words associated with each marker. An example of a GRS consists of numbers 1 to 5 along the continuum with the words no pain, slight pain, moderate pain, very bad pain, and pain as bad as can be along each marker (Appendix 3). Users are asked to circle the number or word descriptor that best represents their pain intensity level. A limited number of studies have used a GRS to investigate the pain intensity of cancer patients (Greenwald et al., 1987; McMillan et al., 1988). Greenwald et al. (1987) used a GRS to determine pain intensity in cancer patients at different stages receiving care in the community and treatment centres. They found that cancer patients with pancreatic cancer reported greater pain than those with lung, prostate, and cervical cancer, and that the GRS was associated with diagnosis. McMillan (1988) demonstrated that a 0-10 GRS was sensitive to changes in pain level. There is a lack of studies that demonstrate the validity, reliability and sensitivity of the GRS, and further research will be warranted to establish the usability of this pain measure.

3.5.1.6 Face Scale (FS)

A Face Scale (FS) consists of drawings of facial expressions that represent increasing levels of pain intensity (Appendix 3). Users are asked to select the drawing that best represents their pain level. A small number of studies have examined pain intensity using a face scale with cancer patients (Ramer et al., 1999; Shannon, Ryan, D'Agostino, & Brescia, 1995).

One study investigated the intercorrelations between pain measures in 51 cancer pain patients from different ethnic groups (English-, Korean-, or Spanish-speaking) (Ramer et al., 1999). The pain measures used were the VAS, FS and Memorial Pain Scale (MPS). The authors found that the FS showed strong associations with the VAS. Another study tested the feasibility of pain measures in a group of far advanced cancer patients using the FS, the McGill Pain Questionnaire (MPQ), or the Memorial Pain Assessment Card (Shannon et al., 1995). They found that 81% of cancer patients were able to complete the FS (compared with 75% who were able to complete the VAS and 89% the VRS). Shannon et al. (1995) commented that these findings suggest that the FS may be a potentially valid measure for cancer pain intensity. However, there are not sufficient studies yet to merit the use of this pain measure among cancer patients.

3.5.1.7 Mechanical Visual Analogue Scale (M-VAS)

The Mechanical Visual Analogue Scale (M-VAS) is very similar to the VAS. It consists of a pointer that can slide along the straight line between no pain and pain as bad as it could be on a plastic scale, therefore instead of marking along the line with a pen the user moves the slider (Choiniere & Amsel, 1996). The pain score is indicated by the pointer, thus no measuring is required. Only a few studies have demonstrated that the M-VAS is strongly associated with the VAS (Grossman et al., 1992; Ramer et al., 1999). Grossman et al. (1992) also showed the high reliability of the M-VAS ($r = 0.95$).

In addition, a recently developed electronic format of VAS may help to eliminate technical errors. The electronic VAS has been incorporated in a hand-held Palmtop computer with the use of a touch screen, where the score is entered by moving the mark along the line with a stylus (Jamison et al., 2002). However, the researchers argue that these new tools require higher concentration, dexterity and psychomotor skills to manipulate the pointer or stylus. Therefore, the tools have limitations in their use by very sick or weak patients such as cancer patients with advanced disease and those who are physically impaired. Also, the feasibility and practicality of their clinical use will need to be supported by further studies.

In summary, single-item pain measures for cancer pain intensity have been widely used despite the existence of potential measurement errors. Many weaknesses are related to the inherent nature of the scale. The validity and reliability of pain measures are one of the important determinants in the selection criteria. However a single-item pain measure can only measure a single dimension of pain (pain intensity) and fails to reveal the complexities of the multidimensional components in a real pain experience. To use the analogy by Melzack (1975, p.278), "to describe pain solely in terms of intensity is like specifying the visual world only in terms of light flux without regard to pattern, colour, texture, and the many other dimensions of visual experience".

3.5.2 Multiple-item pain measures –pain intensity

To compensate for this deficiency, multiple-item pain measures have been developed to capture a better picture of the cancer pain experience. Some multiple-item pain measures have incorporated a single-item pain measure. Effective pain treatment modalities for pain which involves multidimensional components cannot merely depend on a single pain measurement (Bruckenthal, 2000).

There are a variety of multiple-item pain measures that are used to measure pain the intensity of cancer patients' pain. These pain measures include the Health-Related Quality of Life Scale (HRQOL), the Rotterdam Symptom Checklist (RSCL), the

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer (EORTC QLQ-C36), the Head and Neck Quality of Life Instrument (HN QOL), and the Breast Cancer Treatment Outcome Scale (BCTOS). However, much less research has been conducted to examine their validity, reliability and sensitivity (Cleary, Morrissey, & Oster, 1995; de Haes et al., 1990; Sigurdardottir, Bolund, Brandberg, & Sullivan, 1993; Stanton et al., 2001; Terrell et al., 1999).

3.5.2.1 The Health-Related Quality of Life Scale (HRQOL)

The Health-Related Quality of Life Scale consists of three 0-10 NRS that measuring the average, worst, and least pain intensity. Very few studies have used this pain measure to examine pain intensity in cancer populations (Cleary et al., 1995). They have shown a high internal consistency (coefficient alpha of 0.89 to 0.92) in the three items.

3.5.2.2. The Rotterdam Symptom Checklist (RSCL)

The Rotterdam Symptom Checklist (RSCL) consists of a list of symptoms to assess the quality of life of cancer patients. This self-reporting measure covers four domains: physical symptom distress, psychological distress, activity level and overall global quality of life. Physical symptom distress includes pain-related symptoms such as sore muscles, low back pain, headache, and abdominal aches. Users are

asked to rate pain intensity on a 0-3 VRS. Some studies have used the RSCL to investigate cancer pain intensity (de Haes et al., 1990). Factor analysis showed that these pain items loaded onto one single pain factor in only one group of cancer patients. The study also showed good internal consistency (coefficient alpha of 0.81).

3.5.2.3 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer (EORTC QLQ-C36)

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer (EORTC QLQ-C36) contains 36 items on quality of life among cancer patients. The cancer pain intensity measure in the EORTC QLQ-C36 consists of three 1-4 NRS to assess pain intensity with movement and with rest (Sigurdardottir et al., 1993). The study demonstrated that these three items have a good internal consistency (alpha of 0.81).

3.5.2.4 The Head and Neck Quality of Life Instrument (HN QOL)

The Head and Neck Quality of Life Instrument (HN QOL) evaluates four domains in cancer patients with head and neck tumours: eating, communications, pain, and emotion. Pain items are made up of two 5-point VRS of bothersomeness of mouth, jaw, or throat pain and shoulder, or neck pain, and two 5-point VRS of pain medication consumption and physical problems. All scores are combined into a

composite score. The HN QOL has good internal consistency of 0.79 (Cronbach's alpha) and test-retest reliability of 0.81 (Terrell et al., 1999).

3.5.2.5 The Breast Cancer Treatment Outcome Scale (BCTOS)

The Breast Cancer Treatment Outcome Scale (BCTOS) assesses three pain items: breast pain, shoulder stiffness, and breast sensitivity. A study has shown that the BCTOS has internal consistency of 0.81 (Cronbach's alpha) (Stanton et al., 2001).

In summary, some of these multiple-item pain measures are cancer-specific, some have focused on the other relevant common symptoms of cancer patients, and others have tapped into how pain affects the quality of life of cancer patients. However, further studies are required to establish the validity, reliability and sensitivity of these pain measures in various cancer populations of different cultures.

3.6 Cancer pain measures for pain interference

3.6.1 Brief Pain Inventory (BPI)

The BPI was refined from the Wisconsin Brief Pain Questionnaire (WBPQ) (Cleeland & Ryan, 1994; Daut, Cleeland, & Flanery, 1983) to assess cancer pain. It contains questions to assess pain intensity and its impact on daily functions (Appendix 4). By far, the BPI Pain Intensity Scale is the most commonly used multiple-item measure in cancer research (Jensen, 2003). The patient is asked to rate

their worst, least, and average pain in the past 24 hours and current pain intensity on four 0-10 NRS for pain intensity, with “no pain” and “pain as bad as you can imagine” at the two ends.

Many studies have examined cancer pain intensity using the BPI Pain Intensity Scale (Caraceni et al., 1996; Cleeland & Ryan, 1994; Ger, Ho, Sun, Wang, & Cleeland, 1999). They have used factor analysis to demonstrate the pain intensity items loaded onto a single factor, therefore these items are valid for measuring pain intensity. The BPI Pain Intensity Scale has been shown to have high internal consistency in these studies in cancer populations from different cultures, such as Taiwanese (Ger et al., 1999) and Italian (Caraceni et al., 1996). However, among the 164 articles reviewed by Jensen (2003), no study was found to investigate the sensitivity of the BPI Pain Intensity Scale in detecting pain level changes with pain treatment.

The Brief Pain Inventory has a long and a short version. The BPI-short form (BPI-SF), containing nine questions, is more commonly used. The BPI-SF is used to assess cancer pain intensity as well as the effect of pain on multiple functions (general activity, mood, ability to walk, normal work, relationship with others, sleep and enjoyment of life) on a ‘0 to 10’ scale. In addition, patients are asked about the location of their pain, which can be indicated on a diagram, and their perception of the cause of pain and pain relief (Cleeland & Ryan, 1994).

The BPI-SF is found to be useful for both cancer and non-cancer pain because it is short and quick to administer (Caraceni et al., 2004; Coplan et al., 2004; Keller et al., 2004; Tan, Jensen, Thornby, & Shanti, 2004). It has been translated into many languages for clinical and research use, for example, Italian, Japanese, Chinese, German, Greek, Norwegian, and Spanish. Studies have demonstrated the validity and reliability of the BPI-SF in different cultures and languages (Badia et al., 2003; Caraceni et al., 1996; Klepstad et al., 2002; Mystakidou et al., 2001; Wang et al., 1999; Uki, Mendoza, Cleeland, Nakamura, & Takeda, 1998). However, the BPI-SF has been criticized for being too brief for comprehensive assessment of the multidimensions in cancer pain (Twycross, Harcourt, & Bergl, 1996).

3.7 Cancer pain measures for pain quality and pain affect

3.7.1 McGill Pain Questionnaire (MPQ)

The McGill Pain Questionnaire (MPQ) is a multidimensional pain assessment tool that was developed by Melzack (1975). The original MPQ is the long form which was later refined to a short form (SF-MPQ) (Appendix 5). The SF-MPQ is considered to be promising for cancer pain assessment as it provides qualitative data on the many other dimensions in a cancer pain experience. Also, it is one of the most commonly used tools by healthcare professionals in the oncology setting in Hong Kong. The design originated from the three dimensions that were postulated in the Gate Control Theory for pain: sensory-discriminative, motivational-affective and cognitive-evaluative (Melzack & Wall, 1965).

The SF-MPQ contains four parts: the first is a diagram on which the patient can indicate the location of pain. The second part consists of a group of 78 words primarily divided into 3 major classes - sensory, affective and evaluative - with an additional 'miscellaneous' class. These four groups of pain descriptors or words that describe pain are further grouped into 20 subclasses. Each group contains two to six words with varying intensity for the different specified qualities. Patients are asked to select the groups that best describe their pain experience and circle only one word from each subclass within any selected class. The third part comprises another group of words to describe the pattern of pain, and the final part has a scale with 5 word descriptors (mild, discomforting, distressing, horrible and excruciating) for rating the present pain intensity (PPI). It can be self-administered or administered verbally by reading each word group and asking the patients to indicate which word in the specified group that best describes their pain. However, studies have reported that the responses in oral and written formats may not be equivalent (Klepac, Dowling, Rokke, Dodge, & Schafer, 1981).

The SF-MPQ has been extensively tested to be a reliable and concurrently valid multidimensional scale (Chapman, 2001). However, the tool has been criticized for several reasons. First, it requires a longer time (5-15 minutes) to complete compared to the VAS or NRS, possibly due to the fact that patients are unfamiliar with the vocabulary. Considering the need for repeated assessment, the tool is burdensome to the patients who have a limited attention span, and also may contribute to delaying

pain treatment (McGuire, 1984). The second criticism is directed towards the vocabulary of the word descriptors. The words used are either difficult to understand and/ or not used by cancer patients to describe their pain (Deschamps, Band, & Coldman, 1988).

In a meta-analysis including nine studies with a total of 340 cancer patients, it was noted that approximately 30-40% of certain word descriptors were selected (Wilkie et al., 1990). However, as much as 60-70% of the words were either selected less frequently or failed to be selected by these patients. Also, it is still questionable as to whether the tool lacks vocabulary that might be used by patients. This may contribute to the development of the tool. Words were taken from psychological and medical literature and not from cancer patients who experienced pain, and were first tested on healthy, young and well-educated university students (Melzack & Torgerson, 1971). Thirdly, these students were from varying cultural and socioeconomic backgrounds: aspects such as their different ethnicity, sex, age or education may have influenced their choice of words. Further, ethnicity has hardly been considered in the meta-analysis of all the studies using the SF-MPQ (Wilkie et al., 1990). Thus, the validity of the SF-MPQ for use across cultures remains questionable. It is important to ensure the words that are translated into other languages are meaningful to cancer patients with different cultural and ethnic backgrounds.

Although cancer pain has been conceptualized as multidimensional (physiological, sensory, affective, cognitive, sociocultural and behavioural dimensions), the most commonly used cancer pain assessment measures in clinical oncology settings and cancer research remain restricted to measuring the sensory and affective dimensions of pain. It is important to reveal the multifaceted dimensions of cancer pain in order to foster holistic patient care at an individual level.

3.8 Cancer pain measures for total pain

3.8.1 The Chinese Cancer Pain Assessment Tool (CCPAT)

The Chinese Cancer Pain Assessment Tool (CCPAT) consists of 53 items that measure multiple dimensions of cancer pain: the functional dimension (FD), psychosocial dimension (PD), pharmacological dimension (PHD), emotional dimension (ED), pain beliefs and meanings dimension (PBMD), and overall pain intensity dimension (PID) (Appendices 6 & 7). Each dimension encompasses a number of descriptive statements depicting the influence of cancer pain on these dimensions and the patients' view and feelings towards cancer pain. The CCPAT has integrated the Chinese Pain Intensity Verbal Rating Scale (C-PIVRS) into the overall Pain Intensity Dimension (Chung et al., 2000).

Chung et al. (2001) have demonstrated that the CCPAT has an internal consistency of 0.88 (Cronbach's alpha), and an inter-rater reliability of 0.96. The tool is able to discriminate 80.8% of subjects suffering from cancer pain from other chronic pain

diagnoses (Chung et al., 2001). It has concurrent validity with the well-established McGill Pain Questionnaire.

In a study to correlate the CCPAT pain dimensions and β-end, 39 male and 9 female heterogeneous cancer patients were recruited (Chung et al., 2002). Cancer diagnoses mainly included gastrointestinal cancer, nasopharyngeal carcinoma, and lung cancer. Blood samples were taken to determine the β-end. All subjects were asked to complete the CCPAT. Pearson's correlation tests found significant correlations between β-endorphin and the weighted psychosocial (-0.24, p=0.04), the weighted emotional (-0.31, p=0.01) and the weighted sum (-0.26, p=0.03). Regression analysis showed that the weighted psychosocial, weighted emotional, weighted intensity were significant predictors of the β-endorphin level. They concluded that the importance of the psychosocial, emotional and intensity factors in cancer pain assessment was re-affirmed using β-endorphin as a biological benchmarker. The findings also suggest that the CCPAT can accurately reflect the pain experience of cancer patients and thus may guide the pain relief regime in principle.

Each tool has its limitations. The researcher argues that the CCPAT developed in the Chinese culture in Hong Kong may not be entirely valid for Chinese people in mainland China or Taiwan since there are variations within different ethnic groups. The descriptor words and terminology that are commonly used by the Hong Kong Chinese people may not necessarily be familiar to Chinese people of a different background. Despite these weaknesses, the CCPAT has the strength of having been

developed from a triangulation study including cancer patients, oncology doctors and nurses. The data collected to formulate the themes of the CCPAT were captured in a clinical setting, thus it is superior to the MPQ, in which the descriptive words for pain were taken from literature and not the experience of cancer patients. Also, it is worth bearing in mind that the validity of translated Western tools being used with patients from varying cultures and ethnicities is still questionable. With its consideration of the differences between Western and Chinese people in terms of cultural and socioeconomic backgrounds, the CCPAT has the advantage of being culturally sensitive, unique and meaningful to the Chinese people. Thus, the CCPAT was chosen for use in the current study to capture the multifaceted pain dimensions in the cancer pain experience.

3.9 Conclusion

Various tools are available for single-item to multiple-item pain measures, spanning the dimensions of the pain experience from physiological to sociocultural. Clearly, it is pertinent in any given clinical setting to use appropriate tools that provide useful information as well as a basis for multidisciplinary interventions. The lack of psychometric properties and sociocultural components in a tool will result in the loss of important information that allows healthcare professionals to make accurate pain assessments and justifiable decisions for multidisciplinary pain treatment modalities.

CHAPTER 4

REVIEW OF β-ENDORPHIN AND PAIN

4.1 Introduction

This chapter will review the current literature related to β-endorphin and pain in in vivo and in vitro studies. The review will begin with an overview of what endorphin is and its properties. The discussion will also deliberate what effects extraneous variables have on β-endorphin. These include circadian rhythm, gender, BMI, menstrual cycle, blood pressure and drugs.

4.2 β-endorphin

Endorphin derives its name from the contraction of "endogenous morphine" meaning morphine produced within the body (Levinthal, 1988), a term originally coined for morphinomimetic or morphine-like peptides (Frohman, 1980). Because endorphins, endogenous opioids, have similar dual pharmacological actions as morphine in producing both analgesic and euphoric effects, they are also referred to as "the body's own narcotics" (Carr & Goudas, 1999; Hopson & Wessells, 1990). Endogenous opioid peptides are classified into three peptide families: endorphins, enkephalins and dynorphins (Hollt, 1986; Millan, 1986). Each opioid peptide derives from three different genes encoded with distinct precursor molecules, pro-

opiomelanocortin (POMC), proencephalin (PENK) and prodynorphin (PDYN) respectively (Dubner & Hargreaves, 1989; Hollt, 1986; Millan, 1986). Of these, β-endorphins are lymphocyte-derived opioid peptide products of POMC, which belongs to the endorphin family and has intriguing analgesic properties (Cabot et al., 1997; Lyons & Blalock, 1997).

β-endorphin is a 31-residue peptide hormone which is yielded mainly from the intermediate lobe of the pituitary gland and the nucleus of the hypothalamus (Cabot et al., 1997; Lyons & Blalock, 1997) It has been suggested that corticotropin-releasing hormone (CRH), a stress hormone, produced within the hypothalamus and immune system is responsible for triggering the release of β-endorphin (Schafer et al., 1997). These opioid peptides produce potent analgesic effects by binding to specific opioid receptors, such as μ, κ, δ, and ε receptors, that are widely distributed throughout the central nervous system (CNS) (Ishii et al., 2000; Pleuvry, 1993). Glutamate is a major excitatory neurotransmitter in the brain that acts on ionotropic receptors (Ishii et al., 2000). N-methyl-D-aspartate (NMDA) and non-NMDA receptors are subtypes of ionotropic receptors. A recent study has reported that NMDA and non-NMDA receptors located supraspinally have differential sensitivities to β-endorphin and morphine (Ishii et al., 2000). Results suggested that the differential involvement of these glutamatergic receptors with μ– and ε– opioid receptors in the antinociception induced by β-endorphin and morphine in the formalin test (a pain model for moderate, persistent pain) might be due to the different coupling mechanisms at various levels of the neuraxis in the descending

pain control systems. It is important to note that β-endorphin has the most intriguing analgesic effect of all opioid peptides (Millan, 1986). Studies have found that it is 21 times more potent than morphine (Yaksh, Gross, & Li, 1982).

The half-life of β-end has been determined (Aronin, Wiesen, Liotta, Schussler, & Krieger, 1981; Iranmanesh, Lizarralde, & Veldhuis, 1993). A study investigated the half-life of endogenously generated β-endorphin in seven healthy men aged between 32-52 years by post-insulin stimulation (acute metabolic stress of hypoglycaemia) (Iranmanesh et al., 1993). Hypoglycaemic stress resulted in a 7.5-fold increase in the mean β-end. Deconvulation analysis was used to determine the locations, amplitudes and durations of β-endorphin secretory bursts, and to estimate the endogenous half-life of β-endorphin. The nadir of plasma glucose concentrations post-insulin administration was followed by secretory bursts of β-endorphin which peaked at 42 ± 2.2 minutes.

It was reported that the half-life of endogenous β-endorphin was 18-30 minutes with a mean of 22 ± 1.7 minutes. A previous study has shown the half-life of β-endorphin in three healthy subjects following exogenous injection of human synthetic β-endorphin to be longer (32-51 minutes) (Aronin et al., 1981). Several possible reasons might explain the difference. First, the variation in the assay method, immunoradiometric assay (IRMA) and radioimmunoassay (RIA). The RIA method reacts with β-lipotropin on an equimolar basis. β-lipotropin has a longer half-life than β-endorphin, therefore cross-reactivity with β-lipotropin contributes to

a longer half-life of β-endorphin (Iranmanesh et al., 1993). IRMA may contribute to the increased specificity of β-endorphin and thus a shorter half-life. Two, deconvulation analysis does not lead to prolonged duration because of β-endorphin reactivity in serum.

4.3 β-endorphin and analgesia in animal models

Numerous researchers have examined β-endorphin and analgesia in animal models (Baron & Gintzler, 1987; Barrett, Kent & Voudouris, 2000; Dalton & Widdowson, 1989; Hamra, Kamerling, Wolfsheimer & Bagwell, 1993; Ishii et al., 2000; Kulling et al., 1989; McCarthy et al., 1993; Mousa et la., 1983; Mousa et al., 2000; Owens et al., 1984; Przewlocka et al., 1988; Vaswani et al., 1988). These studies involve different methods to increase β-endorphin levels in rats (Wistar and Sprague-Dawley strains), mice (C57, DBA, DBA/2), horses (thoroughbreds), ewes, and terrestrial slugs in order to examine the relationship between these levels and pain. Broadly speaking, there are two types of methods to increase the circulation of β-endorphins: exogenous and endogenous. Early studies have used exogenous synthetic β-endorphins administered to the animals to investigate their effect on pain. Endogenous β-endorphins are elicited by methods such as stress, pregnancy, diurnal fluctuation, light-induced functional pinealectomy (LFPX), and the more advanced method of gene therapy (exogenous upregulation of the transfected β-endorphin gene).

With the raised β-endorphin levels, the animals are then subjected to pain stimuli tests such as thermal (hot-plate or radiant heat lamp exposure) and chemical (formalin or Freund's complete adjuvant (FCA) injection) (Fuller & Robinson, 1993; Hawranko, Monroe, & Smith, 1994; Ishii et al., 2000; Loh, Tseng, Wei, & Li, 1976; Mousa et al., 2000; Nakagawasai et al., 1999). The animals respond to pain by exhibiting pain behaviours including paw-lick, paw-bite, or paw-shake, foot-lift, tail-flick, jump, skin twitch or hoof withdrawal reflexes. While human laboratory research monitors pain responses by subjective reporting, animals are assessed by observing their behaviours. In animals, pain threshold and tolerance levels are measured by the latency time which is the amount of time elapsed between pain stimulation and the animal's first behavioural response, for example paw-licking. A longer latency time indicates a higher pain threshold.

4.3.1 Exogenous β-endorphin and analgesia

Early researches attempted to determine the effects of exogenous β-endorphins on pain. Mice were subjected to hot-plate tests monitored by tail-flick latencies after administration of synthetic β-endorphins by intravenous and intracerebro-ventricular routes. The studies reported profound potent antinociceptive effects of exogenous β-endorphins in these mice (Loh et al., 1976; Tseng, Loh, & Li, 1976). Another study using laboratory rats also showed total body analgesia for 4 hours after intracerebrospinal injection of β-endorphins (Bloom, Segal, Ling, & Guillemin, 1976). The analgesic effects were reversed by naloxone, suggesting opioid

involvement in analgesia. Naloxone is an opiate receptor antagonist that can bind with opioid receptors, hence blocking the analgesic effects of opioids. Despite these remarkable observations, the results only demonstrated limited evidence of the role of β-endorphins in pain modulation.

4.3.2 Endogenous β-endorphins and analgesia

Apart from exogenous β-endorphins, researchers have investigated how endogenous β-endorphins relate with pain. Various methods have been used to evoke β-endorphins release including stress and pregnancy. Recent studies have used the normal diurnal variations of β-endorphins as well as a manually controlled circadian rhythm known as light-induced functional pinealectomy (LFPX), and gene therapy.

4.3.2.1 Stress-induced analgesia (SIA)

For the past two decades, researchers have investigated endogenous opioid peptides and pain, using exercises as a form of stress to produce analgesia. The most often used animal stress model is cold swim stress (CWS) (Koltyn, 2000). Other stress models include forced walking stress, foot-shock stress, insulin injection, and aggressive confrontation. When animals are stimulated by stressful situations β-endorphins are released from the brain and the immune cells. As a result, stress-induced analgesia (SIA) is observed, which may be attributed to the binding of β-endorphins to the opioid receptors (Kulling et al., 1989; Millan et al., 1981; Mousa,

Miller, Jr., & Couri, 1981; Mousa et al., 1983; Nakagawasai et al., 1999; Rittner et al., 2001). It has been suggested that SIA is triggered by two endogenous opioid systems: peripheral and central (outside and within the central nervous system).

SIA was examined in a study with male rats in the cold water swim (CWS) model to evaluate the peripheral endogenous opioid system (Rittner et al., 2001). Pain responses were observed after inoculation of a chemical, Freund's complete adjuvant (FCA), into the paws of the rats. Antinociceptive effects were evaluated by paw pressure thresholds before and at 2, 6, and 96 hours after CWS stress. There was a 160% increase in SIA which paralleled the significant (3.9-fold) increase of peripheral β-endorphin content in the paw. It was concluded that increased opioid peptide-containing immune cells contribute to more profound analgesia, and that the number of these immune cells is proportional to the degree of antinociception. Studies have also shown that opioid peptides such as β-endorphin are detectable in different immune cells, including monocytes or macrophages, lymphocytes, and mast cells (Cabot et al., 1997; Przewlocki et al., 1992; Stein et al., 1990). It has been suggested that these mechanisms may have implications for patients in immunosuppressed states, such as cancer patients (Rittner et al., 2001). Cancer patients, who undergo tumour-related treatments such as whole–body irradiation, cyclosporine or chemotherapy, are often immunosuppressed (affecting the circulation of peripheral immune cells), which may abolish the endogenous pain control system (Rittner et al., 2001).

Another study investigated SIA by exposing male mice to a 6 hours' forced walking stress model to detect changes in the central endogenous opioid system. Analgesia was evaluated using the formalin test and observing paw-licking behaviour at 0, 10, and 30 minutes after formalin injection (Nakagawasai et al., 1999). A significant SIA was observed in stressed animals between 10 to 30 minutes into the formalin test compared to non-stressed animals, antagonized by β-endorphin 1-27 (an opioid receptor antagonist). The immunohistochemical distribution of β-endorphin was increased in the periaqueductal gray (PAG) matter and arcuate nucleus of the medial basal hypothalamus of the brain after stress. It was suggested that the elevation of central β-endorphin levels was associated to SIA after forced walking stress (Nakagawasai et al., 1999).

In an attempt to investigate how an animal CWS stress model influences the central and peripheral changes of opioid peptide levels, male Sprague-Dawley rats were examined using the tail-flick method. Tissue extracts of the brain, pituitary, and adrenal glands, and plasma levels were collected and assayed to determine the levels of different opioid peptides. The results showed that the SIA evoked was reversed by prior administration of naloxone. There was a 42% decrease in the pituitary β-endorphin levels, but this peptide level was significantly raised in the hypothalamus (36%) and plasma (336%). Dynorphin levels were found to be decreased in the hypothalamus and not changed in the pituitary, while enkephalin levels decreased in the adrenal glands and demonstrated no significant change in the CNS or peripheral levels (Vaswani et al., 1988). They concluded that CWS stress produces a

differential effect on both central and peripheral endogenous opioid peptides. SIA may involve other opioid peptides such as dynorphin and enkephalin (Vaswani et al., 1988). It may also trigger non-opioidernegic antinociception mechanisms (Hawranko et al., 1994; Rubinstein et al., 1996).

4.3.2.2 Pregnancy-induced analgesia

Pregnancy is considered to be another form of stress that induces analgesia. Increased tolerance to pain stimuli during pregnancy has been demonstrated in a number of studies. Pregnancy-induced analgesia was studied in rats by comparing the effects of pregnancy on various forms of noxious stimulation such as hot-plate, tail-flick, colorectal distention, and hypertonic saline-induced writhing (Iwasaki, Collins, Saito, & Kerman-Hinds, 1991; Jayaram, Singh, & Carp, 1995). In one study, analgesia was assessed by the hot-plate and tail-flick tests in pregnant mice. The animals were tested in late pregnancy on day 17 or 18 and in the postpartum period on days 2 and 8 after delivery. Hot-plate latency was significantly longer in pregnant mice than in nonpregnant controls. Naloxone significantly lowered pain sensitivity in pregnant mice, which is suggestive of endogenous opioid involvement (Jayaram et al., 1995).

Another study examined the relationship between β-end and pain threshold in labour-induced analgesia. Baron and Gintzler (1987) found that pregnant rats in their study also had an increased pain threshold as determined by jump latency time on days 12, 14 and 21 of pregnancy. They further examined the effect of hypophysectomy or

dexamethasone on the pregnant rats. The results showed that the pain threshold was not affected by hypophysectomy (removal of the pituitary gland) or dexamethasone (pharmacological suppression of pituitary function), but that β-end were significantly reduced. It was concluded that pregnancy-induced analgesia may be mediated by central rather than peripheral opioid systems. They correlated the β-end and jump threshold values on day 21 of pregnancy. However, no correlation was found between the β-end and the pain threshold.

Stress-induced analgesia has been linked to the HPA axis. It is well established that stress results in the coupled release of β-endorphins and adrenocorticotropin (ACTH) from the pituitary gland (Bergmann, 1987; Mousa et al., 1981; Mousa et al., 1983; Shutt, Fell, Connell, & Bell, 1988). Despite the findings from the study conducted by Baron and Gintzler (1987), many studies have demonstrated evidence that SIA are antagonized by hypophysectomy and dexamethasone which indicate involvement of the HPA axis (Kelly, 1982; Millan, Przewlocki, & Herz, 1980; Mousa et al., 1981; Mousa et al., 1983). Further, adrenalectomy can inhibit SIA and be reinstated by corticosterone therapy (MacLennan et al., 1982). These findings suggest that corticosteroid (the pituitary-adrenal axis) has a role in SIA modulation, and that the adrenal-pituitary axis may modulate the endogenous opiate system (Mousa et al., 1981; 1983). It is clear that stress can induce intrinsic analgesia by triggering both central and peripheral (within and outside the brain) opioid-mediated pain inhibitory mechanisms (Binder et al., 2004; Vaswani et al., 1988). These studies have clearly shown that β-endorphins play a role in pain modulation, whether peripherally or

centrally. Further, Iwasaki and Namiki have reviewed studies on pregnancy-induced analgesia and commented that it is mainly explained by the endogenous opioid system.

However, there are no straightforward answers as to how exactly β-endorphins are involved in the modulation of pain. An array of factors has been suggested to affect the endogenous SIA, which may contribute to activation of different intrinsic antinociceptive mechanisms. The contributing factors are stress models (type of stressors) (Hawranko et al., 1994; Kelly, 1982; Owens et al., 1984), duration and method of stress application (Shutt et al., 1988), types and strains of animals (Przewlocka et al., 1988), and sensitivity of opioid receptors (Przewlocka et al., 1988; Przewlocki, Lason, Majeed, & Przewlocka, 1985). In addition, an interplay between the central and peripheral mechanisms for antinociception has been postulated . It is important to note that β-endorphins may have a predictive role in pain and analgesia (Kulling et al., 1989; Matejec, Ruwoldt, Bodeker, Hempelmann, & Teschemacher, 2003). Numerous studies have suggested that β-endorphins are involved in pain modulation, but the correlation is not strongly evident. This inconsistency is possibly due to the difference in β-endorphin levels obtained as a result of different sample collection times and measurement methods, different types of stress models and animals used, and different pain tests employed. Second, the studies are diverse in attempting to correlate different sources of β-endorphin (central and peripheral). Because of variations in the triggering mechanisms and triggered systems, as well as the separate regulation of the β-endorphins in the plasma and cerebrospinal fluid

(CSF) (Matejec et al., 2003), a strong correlation is unlikely to be evident in a variety of study conditions. Third, these animal studies can only examine the sensory dimension of pain, which limits the correlation with the other possible dimensions such as the emotional and psychosocial dimensions.

4.3.2.3 Circadian rhythm of β-endorphin and analgesia

A circadian rhythm of β-endorphin exists in animals wherein the plasma level reaches its peak at the beginning of the active period, and its trough at the beginning of the inactive period (Hamra et al., 1993). This type of diurnal rhythm is found in rats, horses, and monkeys (Chen, Kuhn, Advis, & Sarkar, 2004; Hamra et al., 1993; Naber et al., 1981). Studies have used the normal and laboratory-controlled circadian rhythm to examine the relationship between β-endorphin levels and pain responses.

Eight horses were used to determine the pain threshold in accordance with the normal diurnal rhythm of β-endorphin. The β-end levels were taken six different times in a day (0600, 0900, 1200, 1500, 1800, and 2400). Pain sensitivity was measured by skin twitch reflex latency (STRL) and hoof withdrawal reflex latency (HWRL) using radiant heat lamp test. The β-end peaked at 0900 and were strongly positively correlated with STRL but not with HWRL, suggesting that β-endorphin has a role in pain modulation (Hamra et al., 1993). The researchers suggested that endogenous opioid peptides may modulate pain threshold in the horse.

Another animal model study investigated the β-end and pain threshold in rats that had undergone light-induced functional pinealectomy (LFPX). LFPX is a method used to control the diurnal rhythm by altering the light-dark cycle by means of a manually controlled illumination box. LFPX has produced significant increases in β-end levels, which are thus thought to be modulated by melatonin. Pain threshold was determined by measuring paw-lick and jump following hot-plate tests. The LFPX group had significant elevated β-end and significantly longer hot-plate latency compared to the control groups. This finding has provides evidence that a raised pain threshold is accompanied by elevated β-endorphin levels (Barrett et al., 2000). The study has also shown some evidence that melatonin mediates the circadian rhythm of β-endorphins. This melatonin-opioid axis is suggested to modulate pain threshold, however the exact underlying mechanism of melatonin on the opioid system remains unclear. It is important to note that the synthesis and secretory patterns of β-endorphins have been demonstrated that β-end is the most potent and abundantly endogenous opioid as marked by diurnal variations in in vivo and in vitro studies (Barreca et al., 1986; Kerdelhue et al., 1983). It has been suggested that β-endorphins have a functional role in pain and perhaps mechanisms other than pain as well.

4.3.2.4 Exogenous upregulation of β-endorphin and analgesia

A recent and more advanced gene therapy study has been conducted to determine changes in β-endorphin levels and relate them to pain threshold (Ishii et al., 2000).

One hundred and twenty rats were divided into four groups, the first group receiving subarachnoid transplantation of β-endorphin-producing cells and the other 3 acting as controls (transplant of cells without transfection of the β-endorphin gene, transplant with medium, and no transplantation). Pain responses were measured using hot-plate and formalin tests before and after the transplantation. The results showed that the rats that received gene therapy demonstrated significantly less nociceptive behaviour than the controls (Ishii et al., 2000). The observed prominent analgesic effects were blocked by naloxone. Other studies have transplanted (xenogeneic tumour) cells secreting β-endorphin into the cerebrospinal fluid (CSF) of Sprague-Dawley rats (Saitoh, Taki, Arita, Ohnishi, & Hayakawa, 1995a; Saitoh, Taki, Arita, Ohnishi, & Hayakawa, 1995b). Similar analgesic effects were reported when the animals were tested with three analgesiometric tests, namely the tail-pinch, hot-plate, and electrical stimulation tests (Saitoh et al., 1995b). These rats with encapsulated cells secreting β-endorphin had significantly higher pain thresholds than control rats. The induced analgesia was attenuated by naloxone, which is suggestive of opioid involvement in pain modulation.

In summary, many animal model studies have investigated the relationship between β-endorphins and pain. These studies demonstrate that β-endorphin is involved in pain modulation; however, the association between β-endorphin and pain remains unclear. One major limitation is that the studies tend to be male-dominant, leading to poor generalizability of results to the female counterparts.

4.4 β-endorphin and analgesia in human studies

4.4.1 Effects of attribute and extraneous variables on β-endorphin

Many studies have investigated the relationship between β-endorphin and pain perception involving human subjects. Before discussing these human studies, the discussion on the effects of extraneous variables on β-endorphin will be highlighted. These include circadian rhythm, gender, BMI, menstrual cycle, blood pressure and drugs.

4.4.1.1 Circadian rhythm

β-endorphin has a mode of activation of the HPA axis by the circadian rhythm which manifests itself as diurnal changes. Diurnal variation in both the plasma and cerebrospinal fluid level of β-endorphin has been demonstrated in humans, with the highest levels occurring in the early morning (Barreca et al., 1986; Naber et al., 1981; Nicolau et al., 1986; Ostrowska, Buntner, Zwirska-Korczala, Pardela, & Marek, 1997). Contrary to these findings, a recent study with 48 Chinese patients who had experienced cancer pain in the past 24 hours was recruited by convenience sampling in an oncology unit. Venous blood for β-endorphin were taken at 8 a.m. and 8 p.m. The mean plasma β-endorphin levels were 42.55 pg/ ml (SEM ± 5.47) and 42.15 pg/ ml (SEM ± 5.80) respectively. There was no significant difference between the morning (8 a.m.) and the evening (8 p.m.) β-endorphin levels in a group of cancer patients (Chung et al., 2002). There seems to be a loss of β-endorphin circadian

variation in this cancer population. Although the study did not comment or discuss on the interesting observation, other studies have found similar impairment or disruption.

Studies have also found impaired or disrupted circadian rhythm occurring in various cancer population (lung, gastrointestinal, and breast cancers) after cancer treatments (Abercrombie et al., 2004; Crippa et al., 2003; Jiang, Lu & Ji, 2004; Muc-Wierzgon et al., 2003; Mussi et al., 2003). A few earlier studies have been conducted to investigate the plasma β-endorphin levels in cancer patients and healthy control subjects (Barni et al., 1988; Lissoni et al., 1990). They have found that the mean plasma β-endorphin levels were elevated in cancer patients than controls and that β-endorphin circadian rhythm seemed to be altered.

A recent review by Sephton and Spiegel (2003) reported that circadian rhythm alterations occur in tumor tissue, tumor-bearing animals, and cancer patients. Greater disruption is seen in more advanced diseases. Rhythm alterations include diminished amplitude, phase shifts, period changes, and erratic peaks and troughs in endocrine, metabolic, immunological, and rest- activity cycles. In the review, it was stated that psychosocial factors can engender dysregulation of circadian function. Cancer-related circadian dysregulation may also be driven by genetic factors, environmental and behavioral influences, and effects of the tumor on host clock regulation. This circadian disruption might hasten tumor growth. Thus, stress-related circadian disruption may have negative implications for cancer prognosis. They concluded

that emerging data in the human and animal literature suggest circadian regulation may be an important prerequisite for the maintenance of host defenses against cancer.

4.4.1.2 Gender difference in β-endorphin

Gender plays a role in plasma β-endorphin variations. Studies have consistently found that there is a gender difference in the β-end. Females have significantly lower basal β-endorphin levels compared to males (Gianoulakis, Dai, & Brown, 2003; Goldfarb et al., 1998; Leuschen, Willett, Bolam, & Nelson, Jr., 1991; Ritter, Sonnichsen, Mohrle, Richter, & Schwandt, 1991). The difference is significant across all ages, including infants and adults (Gianoulakis et al., 2003; Leuschen et al., 1991). Researchers concluded that being male was a significant predictor of an elevated level of β-end. It has been reported that the difference was independent of the time of the women's menstrual cycle (Goldfarb et al., 1998), but suggested to be attributed to gender differences in the activity of the HPA axis under basal conditions (Gallucci et al., 1993).

Data have also shown that the pattern of organization of a variety of brain neuropeptide systems is sex-related (Matsumoto, Sekine, Murakami, & Arai, 2000). Examples of these are substance P (Malsbury & McKay, 1994), cholecystokinnin (CCK) (Micevych, Park, Akesson, & Elde, 1987), vasopressin (de Vries, Buijs, & Sluiter, 1984), and vasoactive intestinal polypeptide (VIP) (Zhou, Hofman, Gooren, & Swaab, 1995). In females, gonadotropin-releasing hormone (GnRH) neurons have

approximately twice the number of synapses as in males, which is attributed to β-endorphin immunoreactive terminals. This is attributed to a subset of β-endorphin immunoreactive neurons, which have been reported to accumulate estrogen (Morrell, McGinty, & Pfaff, 1985) and to contain immunoreactive classical estrogen receptors (ERα) (Lehman & Karsch, 1993). Evidence has shown that estrogen is responsible for stimulating growth of axons and dendrites, and for synapse formation (Toran-Allerand, 1984). Estrogen markedly enhances synaptogenesis in the arcuate nucleus (Arai & Matsumoto, 1978) and the medial amygdala (Nishizuka & Arai, 1982). A recent study has revealed the relationship between circulating estrogen and central β-endorphin, and suggested that the depletion of central β-endorphin resulted in the release of GnRH and ovulation (Yu, 2004). Endogenous peptides, for example β-endorphin and neuropeptide, which are activated by estrogen, have been implicated in regulating sexual receptivity (Mills, Sohn, & Micevych, 2004).

In addition, sex steroids are known to play a crucial role in reproductive neuroendocrine functions (Matsumoto et al., 2000). Morphological differences and gender-specific physiological responses include endocrine and behavioural functions such as the dimorphic stress response of the adrenal axis, dimorphic regulation of gonadotropin, somatostatin, growth hormone (GH) secretion, and dimorphic sexual behaviour (Ehrhardt & Meyer-Bahlburg, 1981; Jansson, Eden, & Isaksson, 1985; McCormick, Furey, Child, Sawyer, & Donohue, 1998; Murray, Simonian, Herbison, & Gillies, 1999). These responses may not be solely dependent on a differential morphological development of the CNS, but on sex-related differences of the

neurotransmitter systems. Studies have reported a sexual dimorphism in several central neurotransmitters such as adrenaline, noradrenaline, dopamine and serotonin (Simerly, Zee, Pendleton, Lubahn, & Korach, 1997; Weiss, Abney, Cook, & Ober, 2004). Sexual dimorphism in the distribution pattern of neuronal cell bodies and fibres that contain several types of neurotransmitters and neuromodulators in the hypothalamus have been demonstrated in immunohistochemical studies (Matsumoto et al., 2000).

4.4.1.3 Effects of BMI on β-endorphin

Differences in body mass index (BMI) may contribute to the variations in β-end. A number of studies have examined the β-end in obese and normal weight subjects. Basal β-end are significantly higher in obese subjects than normal weight controls (Baranowska et al., 2000; Giugliano et al., 1991; Nakagawa, Fuke, Irahara, & Aono, 1994; Zelissen, Koppeschaar, Erkelens et al., 1991; Zelissen, Koppescharr, Thijssen et al., 1991). The observed result was similar even in women during labour when compared to obese mothers were compared to normal weight mothers (Nakagawa et al., 1994). The difference in β-end was not influenced by weight loss or normalization of weight in obese subjects (Giugliano et al., 1991; Zelissen et al., 1991a; Zelissen et al., 1991b). They pointed out that the β-end in obesity may be affected by manipulations of the HPA axis. It has also been suggested that the mechanism may be of hypophyseal and peripheral origin (Krzyzanowska-Swiniarska, Gruszczynska, Pilarska, Widecka, & Czekalski, 1993). Similar elevated β-end have

been found in obese subjects, however these studies lack a consistent definition of obesity and normal BMI which may contribute to measurement errors. Also, some studies have not reported the gender or controlled this factor in the data analysis, possibly leading to further ascertainment errors (Baranowska et al., 2000; Giugliano et al., 1991; Krzyzanowska-Swiniarska et al., 1993; Nilsson et al., 1997).

4.4.1.4 Effects of menstrual cycle on β-endorphin

Menstrual cycle is another contributing factor for fluctuations in β-end in women. A number of studies have examined changes in the β-end across the menstrual cycle in humans but the results have been rather inconsistent. Eight healthy female subjects were recruited to investigate the β-end through three normal menstrual cycles. Fasting β-end were taken between 8 a.m. and 10 a.m. at 2- to 4-day intervals. The levels were found to be raised at three different points during the menstrual cycle. Day 0 was determined by using the LH surge. The highest β-endorphin levels were found to be at the periovulatory phase on days -1, 0, +1, slightly falling at the luteal phase on days +9 and +12. The level was significantly lower during menstruation and the premenstrual period than in the follicular phase (Chuong, Smith, & Tsong, 1989; Facchinetti, Martignoni, Fioroni, Sances, & Genazzani, 1990). By contrast, another study reported the β-end increases in the luteal phase of the menstrual cycle, followed by a rapid drop at menstruation (Laatikainen, 1991). The production of opioid peptides is found to increase during puberty and drop at menopause (Facchinetti et al., 1990). These authors also examined the β-end and cortisol

responses to corticotropin-releasing hormone in seven patients with menstrual migraine and seven healthy subjects in the follicular phase and the premenstrual period. They found that β-end and cortisol levels were significantly increased in both patients and controls, independent of the menstrual cycle phase. It was concluded that a periodal premenstrual hypothalamic dysfunction was exerted by opioids on the HPA axis, which is a fundamental adaptive mechanism involved in stress responses and in pain control.

A recent study has been conducted to examine whether changes in β-end influence pain perception in women with premenstrual dysphoric disorder (PMDD) (Straneva, Maxiner, Light, & Girdler, 2000). Twenty-seven women with PMDD and 27 controls were recruited for a pain sensitivity test and blood taking for β-end in the follicular (days 4-8) and luteal phases (3-7 days before menstruation). The pain sensitity test included using a blood pressure cuff inflated around one arm to 200 mmHg and remaining on the arm to measure the pain threshold time and pain tolerance time, or until 20 minutes had elapsed. The results showed that the PMDD women had significantly lower β-end at baseline than the controls. In addition, the PMDD women had significantly lower pain threshold and pain tolerance times, and greater affective scores in both cycles. It was suggested that the endogenous β-endorphin pain-inhibitory system may be chronically dysregulated in PMDD women.

4.4.1.5 Effects of blood pressure on β-endorphin and pain

There is increasing evidence to indicate that hypertension is associated with higher pain threshold (Fillingim & Maixner, 1996; Sheps et al., 1992), and that this may contribute to higher β-end. The relationship between blood pressure and pain perception was investigated in 10 hypertensive and 10 normotensive men (Sheps et al., 1992). These men were subjected to thermal heat tests. Pain threshold and pain tolerance were evaluated and β-end were measured at pre- and post-tests. The results showed that the mean arterial pressure of all the subjects has a significant positive correlation with both pain threshold and pain tolerance. Also, the β-end at the pre- and post-tests was significantly different in the hypertensive and normotensive men. It was concluded that there is interaction between blood pressure and endogenous opioids wherein the mechanism for cardiovascular regulatory and pain inhibitory functions is likely to be mediated by the baroreceptor system. The findings cannot be generalized due to the small sample size that only included men.

Fillingim and Maixner (1996) studied 25 male and 23 female healthy age-matched normatensive volunteers to determine the relationship between resting blood pressure and pain responses during thermal and ischemic pain tests. Pain threshold and tolerance were measured as pain responses to nociceptive stimuli. However, β-end was not taken. They reported that blood pressure, including the systolic, diastolic, and mean arterial pressures, was significantly correlated with pain responses among

males but not females, with higher blood pressure being associated with higher pain threshold and tolerance. It was concluded that the difference may be attributed to baroceptor-induced analgesia or the modulatory effect of endogenous opioids on blood pressure.

4.4.1.6 Effects of drugs on β-endorphin

Studies have shown that dexamethasone, opiates, and to a lesser extent morphine, can have inhibitory effects on the release of β-endorphin when administered as spinal anaesthesia or systemically (Janicki, Erskine, & van der Watt, 1993; Jarmukli, Ahn, Iranmanesh, & Russell, 1999; Kehlet, 1988; Leonard, Klem, Asher, Rapoff, & Leff, 1993). It is important to note the effects of drugs on the β-endorphin production because of the suppression in the plasma level.

Having seen the effect of extraneous variables on the β-endorphin, there now follows a discussion of the current literature related to β-endorphin and pain in humans. Numerous studies have examined the relationship between β-endorphin levels and pain perception (Bacigalupo, Langner, Schmidt, & Saling, 1987; Bacigalupo, Riese, Rosendahl, & Saling, 1990; Bernardini et al., 1992; Bernstein et al., 1995; Dubois et al., 1981; Guieu et al., 1995; Iranmanesh et al., 1993; Le Blanc-Louvry, Coquerel, Koning, Maillot, & Ducrotte, 2000; Rothenberg et al., 1996; Sheps et al., 1995). Subjects recruited were either normal healthy people or patients to investigate whether different levels of β-endorphin would influence how these subjects

experienced and reported pain. Similar to in vivo studies, two basic methods were used to raise the β-endorphin levels: exogenous or endogenous. In the exogenous method, β-endorphins were elevated by administration via intrathecal or epidural injection. Endogenous methods included physical stress, exercise, labour and psychological stress, as well as interventions that stimulate β-endorphin production. These elevated levels of β-endorphin were then correlated with experimental or clinical pain.

4.4.2 Exogenous β-endorphin and analgesia

Some researchers have attempted to determine the effect of the exogenous β-endorphin on pain. In a randomized single blinded trial, 14 cancer patients were recruited to enable the researchers to examine the effect of exogenous synthetic β-endorphin on intractable pain. Intrathecal injection of 3mg synthetic β-endorphin was administered (Oyama, Jin, Yamaya, Ling, & Guillemin, 1980). The results showed that profound pain relief was produced within minutes and the mean duration of analgesia was 33 hours, the longest being up to 73 hours. Epidural administration of the same amount of exogenous β-endorphin has produced a similar pain-relieving effect, but with slower onset and lesser duration of analgesia (Oyama, Fukushi, & Jin, 1982). Intrathecal administration of synthesized β-endorphin has no significant effect on pituitary-adrenocorticol function (Oyama, Yamaya, Jin, & Kudo, 1982). However these studies are limited by flaws in design. The major flaw is the lack of control groups, for example, administration of normal saline, for comparison of

results, yielding insufficient evidence to support the reported effect. The results cannot exclude the possibility of a chance or placebo effect.

4.4.3 Endogenous β-endorphin and analgesia

The findings in numerous human studies have demonstrated that endogenous β-endorphin is involved in the modulation of pain. β-end are raised by different forms of stress such as physical (exercise, labour, and trauma) and psychological stress, as well as elevated β-endorphin levels induced by interventions include transcranial electrostimulation (TCES) and octreotide infusion (Bacigalupo et al., 1990; Befon et al., 2000; Bernstein et al., 1995; Gabis et al., 2003; Iranmanesh et al., 1993; Rothenberg et al., 1996; Sheps et al., 1995). Also, a number of studies have examined the β-end variations in different pain conditions. Significant increases (approximately 2-, 3-, 7.5- and 21-fold) were demonstrated during psychological stress, following traumatic injury, in hypoglycaemia and in maternal plasma during delivery respectively. These studies attempted to investigate the correlation between β-end and pain intensity. However the results have been shown to be inconsistent. The nature of the observed correlation may be divided into three broad categories. First, an inverse (negative) relationship forms the predominant category wherein elevated β-end is correlated with reduced pain intensity. Two, a direct (positive) relationship is sometimes reported, wherein elevated β-end is correlated with increased pain intensity. Third, no significant relationship is occasionally reported, wherein β-end is not correlated with pain intensity.

4.4.3.1 Exercise-induced analgesia

Evidence from research on humans has shown that exercise as a form of stress induces analgesia; this is supported by numerous animal studies. Running and cycling are the most often used exercises in human studies (Koltyn, 2000). Pronounced but temporary analgesia is observed during maximal exertion by exercise. A recent study has demonstrated that exercise-induced analgesia is elicited in both men and women during exercise on a treadmill for 30 minutes at 75% maximal oxygen uptake (VO_2 max) (Hoffman et al., 2004). The subjects had lower VAS scores indicating a higher pain threshold and tolerance during ischemic, pressure, thermal and cold-pressor pain tests following exercises (Gurevich, Kohn, & Davis, 1994; Janal, Colt, Clark, & Glusman, 1984; Oktedalen, Solberg, Haugen, & Opstad, 2001). It has been reported that during exercise, β-end increase two-fold when at least 70% of VO_2 max is reached. Results have consistently shown that β-end increases during and post-exercise in healthy men and women, trained runners and even pregnant women (Hoffman et al., 2004; Janal et al., 1984; Oktedalen et al., 2001; Varrassi, Bazzano, & Edwards, 1989). Elevated β-end has produced analgesia and a euphoric effect that is blocked by the antagonist naloxone.

Even though there is growing evidence of endogenous opioids in analgesia during stress, some researchers however have found no correlation between the exercise-associated opioid hyperendemia (raised β-end) and hypoalgesia (reduced VAS scores). Some researchers have not included a correlational analysis for the two

variables (objective biomarker and subjective pain) (France & Urban, 1991; Hikita et al., 1993). It was suggested that exercise-induced analgesia is probably due to the activation of central pain-inhibitory mechanisms (Droste, 1992). The release of the β-endorphin that is observed under physical exercise may serve as a marker for activating central analgesia mechanisms (Droste, 1992). While animal research has shown evidence that there are multiple analgesia systems, including opioid and non-opioid systems, human research offers mixed support for the involvement of endogenous opioid system (Koltyn, 2000). The properties of the exercise stressor are an important determinant of which analgesic system will be triggered.

4.4.3.2 Labour-stress, β-endorphin and pain

Labour is another form of stress. In a clinical situation, where 38 women at term gestation who delivered 38 healthy infants vaginally were recruited to determine the correlation between β-end and pain responses at various stages (Bacigalupo et al., 1990). Blood samples were taken in the second stage of spontaneous labour, immediately postpartum, and during the early postpartum period. Pain intensities were measured by verbal rating scale (no, mild, moderate and severe pain). The β-end rose progressively with increasing pain intensity with the highest plasma level parallel to severe pain intensity. This plasma level increased 3-fold during severe pain compared to that with no pain intensity. The findings demonstrated that the β-end were positively correlated with pain intensity. It was concluded that the pain of labour is a potent stimulus to the release of β-endorphins, although other stressors such as the mother's physical exertion and anxiety may influence the level. Also,

elevated β-endorphin levels may exist to serve the function of modulating pain perception.

4.4.3.3 Physical stress, β-endorphin and pain

In another clinical situation, 28 male and 20 female patients with traumatic injury, mean age of 42.43 (SD ± 20.31), and 33 controls were recruited to investigate how trauma stress-induced β-endorphin levels correlate with pain perception (Bernstein et al., 1995). The controls were healthy volunteers who matched the trauma patients for age, gender, height, and race. Pain perception was assessed by using a VAS and β-end level was taken in a trauma centre. The results showed no correlation between the VAS score and the β-end.

4.4.3.4 Psychological stress, β-endorphin and pain

In an attempt to examine whether psychological stress alters β-end and how these levels relate to pain perception, 20 patients with coronary artery disease were subjected to psychological stress test (Sheps et al., 1995). The stress test included public speech, wherein subjects had to present 3 brief tape-recorded speeches of a real-life hassle situation. Pain threshold was assessed using a thermal test at baseline and immediately after the stress test. β-end were taken four times, immediately before the thermal pain threshold test, twice during speech presentation (8-10minutes, 13-15 minutes) and after 10 minutes' rest following the tape recording. It was

reported that psychological stress significantly increased β-end and that there was a significantly direct correlation between this plasma level and pain threshold ($r = 0.577$, $p = 0.008$).

4.4.3.5 Intervention-induced β-endorphin and pain

Various interventions have increased the β-end in patients with pain conditions to examine whether these raised plasma levels correlate with pain intensity (Befon et al., 2000; Gabis et al., 2003; Mystakidou, Befon, Hondros, Kouskouni, & Vlahos, 1999). In a randomized double-blind controlled study, 20 chronic back pain patients received 30 minutes of either transcranial electrostimulation (TCES) or placebo treatment on 8 consecutive weekdays (Gabis et al., 2003). Blood samples were taken for β-end, and pain intensity was measured by VAS before and after the first treatment. Although a significant placebo effect was observed (70-80% of the control group experienced pain relief), there were no accompanying changes in the β-end. In the intervention group, the mean β-end was increased from 32.8 to 57.1 pg/ml and the mean VAS score reduced from 6.6 to 4.5. There was an inverse correlation between β-end and pain intensity ($r = -0.5$).

Another study has examined the relationship between β-end and pain intensity in cancer patients (Befon et al., 2000). Octreotide, a synthetic analogue of somatostatin, was used to elevate the β-end in 25 advanced gastrointestinal cancer patients who had experienced pain. β-end and pain intensity (VAS) were assessed before the

infusion of octreotide, and thereafter at 12, 24, 48 hours and 7 days post-infusion. The β-end increased after 12 hours of infusion, the VAS score was reduced significantly, and a significant inverse correlation was found (r = -0.54). However, no correlation was reported on the other days. It was suggested that β-end are likely to be associated with the reduced pain level, with octreotide as an analgesic agent. However it is unclear by which mechanisms the octreotide induces analgesia.

4.4.3.6 Plasma β-endorphin level variations in pain conditions

A number of studies have demonstrated that there are variations in β-end in different pain conditions. Some studies have found that the β-end is lower in patients who have certain pain conditions than in controls. The β-end is significantly lower in painful conditions such as complex regional pain syndrome (Takahashi et al., 2000) or painful duodenal ulcer (Tonnarini, Delle, Chianelli, Mariani, & Negri, 1995), in painful inflammatory disease like rheumatoid arthritis (RA) (Elbeialy, Elbarbary, & Kamel, 1997) or Crohn's disease (Wiedermann et al., 1994), and in the acute phase of myocardial infarction (Buratti et al., 1998), where the immune system is activated. It has been suggested that lowered plasma levels are attributed to the release of the peptide from lymphocytes infiltrated into the region peripheral to the pain protect the host against pain. However, in some studies, cancer patients also have lower β-end due to immunosuppression when cyclosporine (CSA) or total body irradiation (TBI) inhibits the generation of endogenous analgesia: this may contribute to the exacerbation of pain (Przewlocki et al., 1992; Stein et al., 1990).

By contrast, some researchers have reported that higher β-end accompanies the clinical pain experience when compared to that of controls. Examples of such findings have been found in studies of chronic pelvic pain (Ahmed et al., 1991), women in labour pain (Bacigalupo et al., 1990), postoperative pain (Matejec et al., 2003) and recurrent dysmenorrhea (Marchini, Tozzi, Bakshi, Pistai, & Fedele, 1995). In these situations, it has been suggested that the increased β-end is related to the immune cells that are prepared to respond to acute painful stimuli (Marchini et al., 1995). In the laboratory setting, researchers have reported that experimental ischaemic pain is not accompanied by raised β-end (Bach, Fahrenkrug, Jensen, Dahlstrom, & Ekman, 1987; Gullner, Nicholson, Wilson, Bartter, & Orth, 1982).

A recent correlational study has further examined the link between β-end and the manifold pain dimensions in cancer patients (Chung et al., 2002). Forty-eight Chinese patients with various types of cancers were recruited to have blood samples taken to determine their β-end levels in the morning. Pain dimensions were assessed by using the culturally specific Chinese Cancer Pain Assessment Tool (CCPAT) (Chung et al., 2000; Chung et al., 2001). The pain dimensions in this tool include functional, psychosocial, pharmacological, emotional, pain beliefs and meanings, and pain intensity. They found that the β-end was significantly correlated with the psychosocial and emotional dimensions of cancer pain and concluded that the importance of psychosocial and emotional factors in pain assessment is re-affirmed by using β-endorphin as a biomarker. However, the generalizability of the study is limited due to its small sample size and the heterogeneity of the sample. Thus, the

current study was conducted with a larger sample in a homogeneous group of cancer patients. The relationship between β-end and important pain dimensions is investigated and the predictive value of the CCPAT scores is determined.

Overall, many studies have not demonstrated the correlation between β-end and pain. Some studies have shown a correlation, however the results were inconsistent. Most studies have focused on the association between β-end and the sensory dimension of pain, or pain intensity.

4.5 β-endorphin, mood and pain in animal and human studies

More recently, β-endorphin has been demonstrated to play a significant role in mood modulation in animal and human studies. Mood and emotion is a well-recognized component of pain response (Chapman, 2001).

Post-exercise euphoria in endurance athletes has been consistently reported in many studies, which have suggested that it is attributed to a marked increase in endogenous opioid peptides, wherein the β-end has been elevated 2-fold (Janal et al., 1984; Mehl, Schott, Sarkar, & Bayly, 2000; Rahkila, Hakala, Alen, Salminen, & Laatikainen, 1988). Other studies have shown that the baseline β-end were up to 3-fold higher in patients who had major depression than in control subjects (Goodwin et al., 1992). A recent study by Panerai et al. (2002) reported similar findings, namely that depressed patients had higher β-end (53.2 +/- 6.02 pmol/l) than healthy subjects (25.43 +/- 1.43

pmol/l). More recent studies have demonstrated that endorphins may relieve pain by modulating the psychological and emotional perception of pain (Amanzio & Benedetti, 1999; O'Callaghan, 1996).

Studies have consistently shown that opioid receptor blockade (including β-endorphin receptor) decreases anxiety, depressive state, and negative affect, while increased positive affect has been observed after aerobic exercise, but failed to produce effects in the absence of exercise (Jarvekulg & Viru, 2002). β-endorphin blood mononuclear cell concentrations were significantly higher in depressed patients (Panerai et al., 2002). Chronic antidepressant treatment has been shown to normalize the serotonin-induced release of β-endorphin in a rat model, wherein depressive behaviour was observed to be ameliorated (Zangen, Nakash, Roth-Deri, Overstreet, & Yadid, 2002).

In a study with a chronic stress animal model, prenatally stressed pregnant female rats were engaged in a forced swim test (Koehl et al., 1999). The stressed animals were observed to increase their defensive withdrawal behaviour and immobility, which is indicative of anxiety and depressive-like behaviours. Interestingly, these behaviours were reversed by CRH antagonists and antidepressants (Alonso, Castellano, Quintero, & Navarro, 1999; Ward, Johnson, Salm, & Birkle, 2000). Other studies have further confirmed that the administration of antidepressants attenuates the HPA axis activity or normalizes the axis dysfunction (Holsboer, 1999; Reul, Stec, Soder, & Holsboer, 1993).

Another chronic stress model involved maternal separation wherein newborn rats were separated from their mothers for 6 hours everyday from post-delivery up to 3 weeks of life (Plotsky & Meaney, 1993). They found that there was an increase in basal corticosterone/ cortisol and hypothalamic CRH expression, and an increase in basal and stress-induced plasma adrenocorticotropic hormone (ACTH) levels. In human studies, highly similar results with increased expression of CRH/mRNA and level of basal corticosterone/ cortisol have been observed in depressed patients and those with depressive illness associated with early life traumatic experience (Blackburn-Munro & Blackburn-Munro, 2001; Gold & Chrousos, 2002). Thus, it was suggested that emotions such as anxiety and depressive state are potentially linked to the HPA axis (Blackburn-Munro & Blackburn-Munro, 2001; Holsboer, 1999).

Clinically, these maladaptive changes in HPA axis function (hyper- or hypofunction) have correlated with anxiety, depressive states and chronic pain (Clauw & Chrousos, 1997; Gold & Chrousos, 2002). The efficacy of antidepressants in chronic pain treatment has been shown in animal and human studies (Holsboer & Barden, 1996; Reul et al., 1993) by attenuation of the HPA axis. Therefore, it has been inferred that chronic pain and depression may share a common underlying mechanism (Briley, 2003; Fishbain et al., 1997), but it has also been suggested that the analgesia mediating effect may be independent of mood status. However, other human studies have shown that psychological and emotional modulation contributes to analgesia

accompanied by the release of endorphins (Amanzio & Benedetti, 1999; O'Callaghan, 1996).

The HPA axis modulation in response to acute stress is well-established in vitro and vivo studies as part of the fight or flight response. Chronic pain has been known to be a stressor and therefore also activates the HPA axis. Strikingly, these recent clinical studies of depressive patients have demonstrated key changes in the HPA axis, which are remarkably similar to the results of chronic stress studies in animals and humans (Blackburn-Munro & Blackburn-Munro, 2001).

4.6 Conclusion

In summary, while many studies fail to report how β-end is correlated with pain and how strongly they are correlated with each other. Those studies that have found a correlation have provided inconsistent results. A vast number of studies have concentrated solely on how β-end is associated with the sensory dimension of pain (pain intensity), neglecting the affective and cognitive dimensions which could have a strong connection to the release of β-endorphin levels. The functional role of β-endorphin in pain assessment or modulation, has yet to be elucidated.

Chapter 5

METHOD AND PROCEDURES

5.1 Introduction

This chapter describes the method and procedures of the main study. β-endorphin level was measured in the blood samples of cancer patients and the pain dimensions were assessed by a newly-developed pain questionnaire, the Chinese Cancer Pain Assessment Tool (CCPAT). The aim of the study is delineated in this chapter and the research questions and hypotheses posed for testing are outlined. The method, the instrument (CCPAT), and measurement of the β-end level are discussed in detail. The procedure for the study, ethical issues, and the data analysis methods employed will be addressed.

5.2 Aim of study

The aim of the study is to attempt to identify the relationship between plasma β-endorphin level (objective variable) and the CCPAT pain dimensions (subjective variables). Thus, a cross-sectional correlational design is used.

5.2.1 Research questions:

i. What is the correlation between plasma β-endorphin level and the functional dimension (FD), psychosocial dimension (PD), pharmacological dimension (PHD), emotional dimension (ED), pain beliefs and meanings dimension (PBMD) and pain intensity dimension (PID) in the Chinese Cancer Pain Assessment Tool (CCPAT)?

ii. Are the weighted scores of the FD, PD, PHD, ED, PBMD, and PID in the CCPAT (independent variables) significant predictors of plasma β-endorphin level (dependent variable)?

iii. Is the plasma β-endorphin level significantly different between the pain group and the no pain group?

5.2.2 Research hypotheses

The following research hypotheses are formulated based on previous research findings. In a previous study by Chung and colleagues (2002), the results showed that β-end is inversely correlated with weighted scores of the pain dimensions including FD, PD, PHD, ED, PID and sum in a group of heterogeneous cancer patients. To reduce extraneous variables and increase research rigor, this study has recruited a larger sample of homogeneous group of liver cancer patients to further determine the correlation. The rationale for the hypotheses is as follows: as patient exhibit lower levels of β-endorphin, it may be a lack of endogenous opiotergic

activity which impact negatively on pain and mood perception. In turn, these negative impacts would affect the pain dimensions as reflected by higher pain dimensions scores.

Hypothesis 1: There is a negative/ inverse relationship between β-end and the functional dimension (FD).

Hypothesis 2: There is a negative/ inverse relationship between β-end and the psychosocial dimension (PD).

Hypothesis 3: There is a negative/ inverse relationship between β-end and the pharmacological dimension (PHD).

Hypothesis 4: There is a negative/ inverse relationship between β-end and the emotional dimension (ED).

Hypothesis 5: There is a negative/ inverse relationship between β-end and the pain beliefs and meanings dimension (PBMD).

Hypothesis 6: There is a negative/ inverse relationship between β-end and the pain intensity dimension (PID).

5.3 Method

5.3.1 Sampling

Primary liver cancer is one of the most common malignancies in China (Parkin, 2001), hence two hepatobiliary oncology units in the Sun Yat-Sen University of Medical Sciences in Guangzhou, China, were chosen as the setting for this study. Subjects were recruited by consecutive sampling according to the selection criteria as in a previous study by Chung and colleagues (2002).

5.3.2 Inclusion criteria

i. Adults aged 18 to 80. The upper limit was set to avoid changes of self-perception due to older age.

ii. All subjects were of Chinese ethnic origin to minimize cultural deviation.

iii. All subjects were alert and orientated individuals who were able to speak and read Chinese.

iv. All subjects were fully aware of their diagnosis to minimize emotional arousal and to avoid any unauthorized release of medical information.

v. The subjects had a diagnosis of Stage I or II liver cancer (+/- metastasis) and had been admitted for active treatment. This was to standardize the stage and treatment protocol, and to minimize the effects on immune cells due to the infiltration of anti-cancer drugs.

5.3.3 Exclusion criteria

i. Subjects who had had a surgery in the past week.

ii. Subjects who were suffering from diseases or pathology with manifestations of neurological signs and symptoms.

iii. Subjects who had participated in any form of exercise or physical activity in the six hours prior to sample collection.

There are rationales for the selection criteria. The CCPAT is a culturally specific tool, thus inclusion criteria included Chinese ethnic origin subjects only. Chinese families sometimes hide the diagnosis of "cancer" from patients to protect them from emotional disturbance. Therefore, only patients who were fully aware of their diagnosis were included to minimize emotional arousal. This is to reduce a potential extraneous variable in the ED measurement. The subjects who had had surgery were excluded because the studied variable of cancer pain was caused by cancer and not its treatment as defined in the clarification of terms.

5.3.4 Sample size

Since the purpose of the study was to identify the relationship between the β-end and the CCPAT pain dimensions, a correlation coefficient was employed in the sample size calculation. The calculation was done by the software SAMSIZE 2.0 (Machin, Campbell, Fayers, & Pinol, 1997). The effect size of the study was set at 0.3, which

is the usual medium effect in a linear relationship (Cohen, 1988). The power of the study was set at 0.8 and the significance level at 0.05 (2-tailed). The calculated sample size was 112 subjects.

5.4 Instrument

The Chinese Cancer Pain Assessment Tool (CCPAT) is a 53-item self-administered questionnaire. The pain dimensions assessed were: functional dimension (FD), psychosocial dimension (PD), pharmacological dimension (PHD), emotional dimension (ED), pain beliefs and meanings dimension (PBMD), and overall pain intensity dimension (PID). Each dimension comprises a varying number of statements describing how an individual's pain experience affects these dimensions.

Subjects were requested to choose a score that best described their pain experience on a 5-point Likert scale (1= strongly disagree to 5= strongly agree). The PID consists of a vertical numerical scale with Chinese pain descriptors alongside the numbers. Pain intensity ranges from 0 (no pain) at the bottom to 10 (crucified pain) at the top. Subjects can select either the numeric or the Chinese descriptors for pain. It is important to note that the vertical scale arrangement is designed specifically for Chinese people who are oriented to reading from top to bottom (Chung, Wong, Yang, & Wong, 1999).

It is a summated rating scale. Weights are allocated to each dimension by magnitude scaling to obtain composite scores. Allocation of weights to FD, PD, PHD, ED, PBMD and PID are 1.0, 1.0, 1.1, 1.1, 1.2 and 1.2 respectively. The composite scores obtained indicate the overall impact of cancer pain.

5.4.1 Validity and reliability

The CCPAT has an internal consistency of 0.88, an inter-rater reliability of 0.96 and the ability to discriminate 80.8% of subjects suffering from cancer pain from other chronic pain diagnoses (Chung et al., 2001). It has concurrent validity with the well-established McGill Pain Questionnaire.

5.5 Measurement of plasma β-endorphin

The measurement of β-end was conducted according to a previous study (Chung et al., 2002). β-end was measured by the standardized radioimmunoassay (RIA) method. Plasma samples were thawed and extracted on Seppak columns (Jessop, Eckland, Todd, & Lightman, 1989). Eluates were dried by vacuum centrifugation and residues were then reconstituted in a phosphate buffer and subjected to RIA as previously described (Jessop, Lightman, & Chowdrey, 1994). The β-endorphin tracer was synthetic β-endorphin labelled with I^{125} by the chloramine T method, and antiserum produced from rabbits (final titer 1: 48000) was used. The bound tracer was separated from the unbound using sheep anti-rabbit serum. No cross-reactivity

occurred with other POMC peptide products ά –melanocyte-stimulating hormone (ά –MSH) or ACTH, or with methionine-enkephalin. The detection limit for this assay was 0.485pg/ ml. The measurement was performed in the Endorphin Laboratory of the University of Bristol, U.K.

5.6 Procedure

5.6.1 Ethical issues

The Hong Kong Polytechnic University granted ethics approval. Permission was sought from the Cancer Centre for subjects' participation in the study. Explicit and detailed explanations of the purpose and procedure of the research, and on how to complete the CCPAT, were given to participating subjects. Written informed consent was sought from all subjects whenever possible. Subjects participated on a voluntary basis. To ensure confidentiality and anonymity, codes were used for identification.

5.6.2 Procedures

Subjects were approached consecutively by the researcher to screen and recruit individuals. Demographic data were collected from medical records, including sex, age, marital status, education, religion, and diagnoses. Data collection also included a brief pain history, analgesic consumption, and alternative pain relieving methods.

Subjects were asked to complete a CCPAT questionnaire at 8 a.m. A venous blood sample (4mls) was taken to measure β-end. The procedure was repeated at 8 p.m. of the same day to examine the diurnal rhythm. However, due to the initial high refusal rate, blood samples were only collected once in the morning, therefore diurnal rhythm was not examined in this study. The decision that was made on not taking an evening sample for β-endorphin was based on two reasons. Firstly, because of it was extremely difficult to recruit Chinese patients to have blood taken for a research. Secondly, because there was no diurnal variation in the heterogeneous sample of cancer types, and this homogeneous sample of PLC was at the first stage of a series of research, therefore future longitudinal studies will include the samples for diurnal rhythm.

The serum samples were collected into heparinized plastic bottles which were immediately placed into ice. Samples were centrifuged at 4ºC at 2500rpm for 15 minutes. Plasma samples were then stored at -30ºC in polypropylene test tubes.

5.7 Data analysis

Descriptive and inferential statistics were employed in data analyses. Descriptive statistics and ANOVA were performed to reveal associations among the demographic and clinical data including the CCPAT dimensions and the levels of β-end. Their interactions on mean β-endorphin level were also examined. Spearman's

correlation and stepwise regression was then performed to examine the relationships between β-end and the pain dimensions of the CCPAT.

5.8 Conclusion

This chapter described the examination of the relationship between β-end and the CCPAT pain dimensions by means of a cross-sectional correlation study. The aim of the study, research questions and hypotheses that posed to guide the study were outlined. Details of the method and procedures employed to conduct the study were also included.

CHAPTER 6

THE PILOT STUDY

6.1 Introduction

The goal of the pilot study is to test the feasibility of the data collection process in the main study. This chapter will clearly depict the method used to approach subjects in order to recruit and ensure that they understand the research purposes and procedures. A description of the characteristics and responses of the subjects is presented. Suggestions are formulated for the main study.

6.2 Method

Potential subjects were identified by nurses in the hepatobiliary oncology units in the Sun Yat-Sen University of Medical Sciences in Guangzhou, China, according to the selection criteria, and then introduced to the researcher. This approach helped to build a rapport, since the researcher was not familiar with the subjects, the culture, or the daily routine of the unit. Also, the researcher wore a different uniform to that of the medical staff on the unit, which may have aroused suspicion among the patients. The method of recruitment further enhanced the bridging of the security gap, because hospitals in Guangzhou have encountered strangers pretending to be medical staff or selling Chinese herbal remedies to patients.

Explicit and detailed explanations of the research purposes and how to complete the CCPAT were provided. Verbal consent was sought from all subjects prior to data collection. All data were kept confidential and the subjects were informed of their right to withdraw at any time. Subjects were asked to complete the CCPAT at their own pace. The researcher would stand by to assist the subjects for the first few questions, then return occasionally to allow the subjects to clarify any wording that might not be fully understood. Since the CCPAT was a new instrument to the subjects, therefore attention was paid to any possible misinterpretation.

Upon completion of the CCPAT, the researcher would screen the CCPAT for any questionable answers, for example, where two answers were selected instead of one, or no answers were circled, then the researcher would seek clarifications from the subjects. Blood taking was not included in the pilot study, since samples were to be collected by qualified nurses with venepuncture training.

6.3 Results and implications for the main study

Seven subjects were recruited for the pilot study, 5 (71.4%) male and 2 (28.6%) female patients with mean age 45.9 (S.D. $\pm$ 10.5) ranging between 34-65. All the subjects were literate. Most of the patients understood how to complete the CCPAT, therefore minimal assistance was required. Although several of them showed reservations about research, due encouragement from the nursing staff facilitated the recruitment and data collection process. In addition, two subjects further enquired

about the purpose of the questions in the emotional dimension (ED) and pain beliefs and meanings dimension (PBMD). They seemed to feel uncomfortable about disclosing such personal information. The researcher reassured the subjects that all data were kept confidential and that the questionnaires did not contain the subject's name and only had special codes. These codes could only be accessed by the researcher. No subjects were emotionally aroused as a result of the data collection process. There was no direct verbal feedback or comment given by any subject about the research or its process.

Several suggestions were formulated for the main study in the current setting. First, no major amendments were required for the procedure of the study. Two, the questionnaire's format was rearranged to improve readability. Third, it was suggested that the researcher needed to build a better rapport with patients prior to data collection, the goal being to gain the subjects' confidence, bridge the gap, and to ensure better cooperation during the research process. To achieve this, a clear self-introduction and explanation of the confidentiality of the study data should be reinforced. Fourth, on topics such as death or enquiries regarding personal feelings and views, the researcher should stay overt and pose those questions using a similar attitude and tone of voice as with any ordinary questions to avoid bias by the researcher or the subject. However, the researcher should be aware that the topic of death is taboo in the Chinese culture, and even more so in the situation of an individual diagnosed with cancer. Fifth, the researcher should acknowledge and

reinforce the rights of subjects in circumstances where they refuse to answer or even wish to withdraw from the study.

6.4 Conclusion

With the implications for the main study taken into account, and the data collection approach and procedure tested and deemed satisfactory, it was decided that the main study could proceed.

CHAPTER 7

THE MAIN STUDY RESULTS

7.1 Introduction

This chapter will present the results of the main study following the data analysis procedures that were described in chapter 5. The study sample will be depicted. The background of the subjects, including their demographic profile and clinical data, will be presented. The results will focus on the formulated hypotheses and research questions to elucidate the relationship between β-end and the CCPAT pain dimensions, the predictability of CCPAT scores, and β-end variations in pain and no pain groups. The **e**ffects of attribute and extraneous variables on β-end are highlighted in the final section.

Data analyses included all the values obtained in the plasma β-endorphin assays as determined by I^{125} RIA since no anomalous distribution or missing data were observed. A level of confidence of $p<0.05$ was adopted for statistical significance. Data are expressed as untransformed mean ± SEM levels in pg/ ml.

7.2 Study sample

The study sample was collected in the hepatobiliary oncology units of the Sun Yat-Sen University of Medical Sciences in Guangzhou, China. The data collection

period lasted for six months, from January to March, and then July to September of the same year. The subjects had a diagnosis of stage I or II primary liver cancer (PLC) (+/- metastasis) and had been admitted for active treatment.

The total number of subjects approached was 174. Among them, 27 refused to participate for various reasons. The most common responses were unwillingness to participate (22.2%) and feeling too tired or unwell (22.2%); other responses included too troublesome (18.5%), unwilling to have blood taken (14.8%), straight refusal with no particular reason (14.8%), or experiencing little or no pain (7.4%).

Further, 71 blood samples were discarded due to unexpected electricity failure and faulty storage. Hence, the remaining 76 subjects were included in the final study sample for analysis. Due to time constraints, no more subjects were recruited for further analysis.

7.2.1 Missing data

A total of 71 subjects were not included in the final data analysis due to loss of blood samples. Descriptive and inferential statistical tests were conducted to examine the differences between these subjects with missing data (n=71) (missing group) and the subjects in the final analysis (n=76) (thesis group). Descriptive analysis showed that the demographic data were highly comparable with 71 men (85.9%) and 10 women (10.5%), mean age was 46.31 $\pm$ 12.2. Other demographic characteristics are

highlighted as follows: 94.4% were married; 88.7% had secondary or tertiary education; 33.8% had higher-ranking positions (managerial, administrative, or professionals); 33.8% were manual workers, and 26.7% were unemployed (including housewives or retirees); 69% were atheists, 18.3% were ancestor worshippers and 8.5% were Buddhists. Clinical data showed that 53 (74.7%) patients were suffering from varying degrees of pain. Of those, 44 (83%) reported mild pain, 6 (11.3%) moderate pain, and 3 (5.7%) severe pain.

T-tests were conducted to examine the differences in the mean weighted scores of the CCPAT in the two groups (missing group and thesis group) by pain severity. Patients who experienced moderate and severe pain were not included in the t-tests because of the lack of subjects (moderate = 0; severe = 1) in the respective groups to carry out such analysis. In the remaining patients with mild or no pain, the missing and the thesis groups did not show significant differences between the mean weighted scores of the CCPAT except for FD and PD. Among those who experienced mild pain, the FD scores were significantly different in the missing and the thesis groups respectively (37.9 ± 8.4 and 32.8 ± 10.8) ($p=0.033$). Also, among those who did not experience pain, the PD scores were significantly different in the missing and the thesis groups respectively (16.1 ± 2.0 and 14.8 ± 1.9) ($p=0.02$). However, these differences in FD and PD scores would not have made significant differences in the correlational matrix because only weak correlations were demonstrated.

7.3 Demographic characteristics

In the final study sample, 68 men (89.5%) and 8 women (10.5%) were included. The mean age was 49.8 (S.D.± 12.2) ranging from 29-76. The profile of demographic characteristics is shown in Table 7.1. Most of the subjects were married (94.7%) and had secondary or tertiary education (88.2%). As for occupation, the highest percentage (40.8%) had higher-ranking positions such as in managerial, administrative, professional or business fields. About one third (30.2%) were manual workers working in, for example, the servicing industry or crafts, or as operators and in rural-related positions, while the others were unemployed (26.3%), including those who were retired or housewives. With regard to social status, almost all of the subjects (97.3%) were living with their family, children or spouse. The majority (73.7%) had a caregiver at home attending to the subject's daily needs, whereas a quarter (25%) of them were independent. Religious beliefs included ancestor worship (27.6%), which was one of the most popular religious activities among Chinese, Buddhists (5.3%), Christians (1.3%) and others (3.9%). However, many of them were atheists (60.5%).

T-tests and ANOVA were employed to examine the difference in the β-end for different demographic variables. No significant difference was found for gender, different age or BMI groups, educational levels, marital or social status: the only exception was for religion. The mean β-end was significantly higher in the subjects

who were atheists (303.0 ± SEM 14.5) than in those who had a religion (222.7 ± SEM 14.7) (p≤0.000) (Figure 7.1).

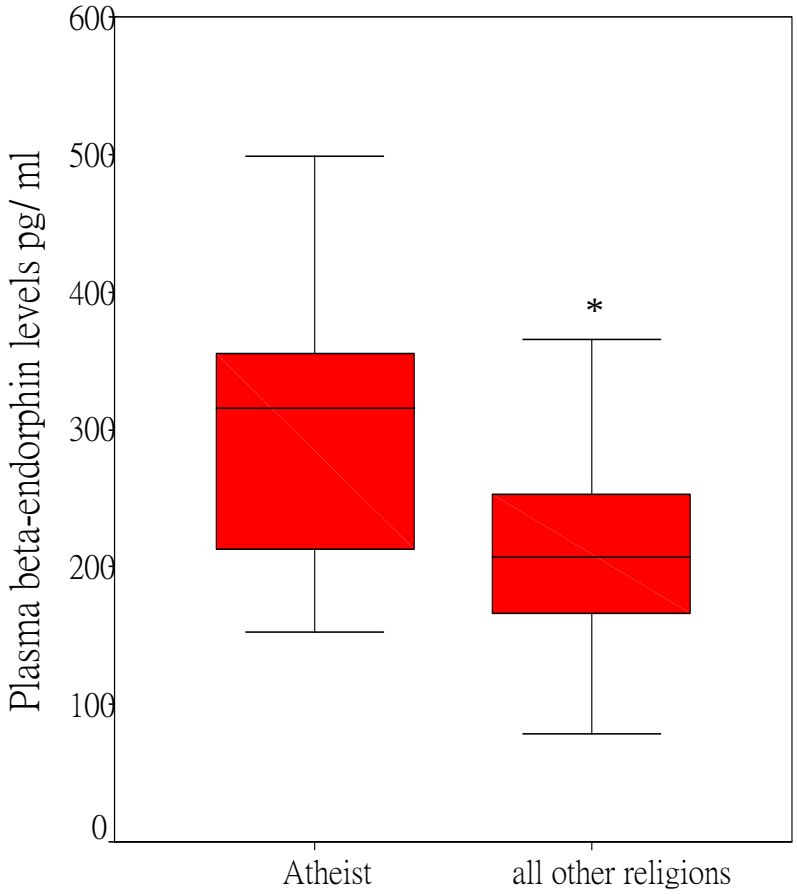


Figure 7.1 Comparison of mean plasma β-endorphin levels (pg/ml) between religious (n=46) & non-religious (n=29) groups (p≤0.000)

* p≤0.000

Table 7.1 Demographic Characteristics

Variables	n	(%)
Male	68	(89.5)
Female	8	(10.5)
Age		
29-40	17	(22.4)
41-50	26	(34.2)
51-60	16	(21.1)
>60	17	(22.4)
Marital status		
Single	2	(2.6)
Married	72	(94.7)
Divorced	1	(1.3)
Widowed	1	(1.3)
Education background*		
No formal education	1	(1.3)
Primary	6	(7.9)
Secondary	56	(73.7)
Tertiary or above	11	(14.5)
Occupation*		
Managers and administrators	11	(14.5)
Professionals/ associate professionals	16	(21.0)
Business	4	(5.3)
Service/shop sales workers	8	(10.5)
Craft and related workers	1	(1.3)
Plant/machine operators and assemblers	5	(6.6)
Skilled agricultural and fishery workers/occupation not classifiable	9	(11.8)
Unemployed	20	(26.3)
Social status*		
Living alone	1	(1.3)
Living with spouse	2	(2.6)
Living with family or children	72	(94.7)
Main caregiver at home*		
Self	19	(25.0)
Spouse	42	(55.3)
Family or children	9	(11.8)
Relatives	5	(6.6)
Religious belief*		
Atheist	46	(60.5)
Ancestor worshipper	21	(27.6)
Buddhist	4	(5.3)
Christian	1	(1.3)
Others	3	(3.9)

* 1-2 missing data

7.4 Clinical data – pain and disease history

Thirty-two (42.1%) patients were currently suffering varying degrees of pain during data collection (Table 7.2). Of those, almost all of them (96.9%) reported mild pain (1-4), only one (3.1%) reported severe pain (7-10) and none had moderate pain (5-6). As expected, the most common site of pain reported was in the abdomen (81.3%) and the back region (15.7%). Pain was observed to radiate to referred sites (25%). The most frequent sites were either in the shoulders, back or upper arm. Among those who had pain, 41% reported pain in at least two locations.

For pain relief, almost all the patients were experiencing mild pain or not having any pain at all, therefore not many patients were receiving medications or seeking methods for pain relief. Only one subject had taken a non-steroidal anti-inflammatory drug (NSAID) prior to blood sample collection. However, since the medication was taken 15 hours before the venepuncture, its effect on the level of β-endorphin would not be significant. Chinese people tend to use alternative methods for pain relief (Table 7.3). Among these Chinese PLC patients, a small number of them (14.1%) were currently using alternative methods including local application (ointments or oils) (5.6%), massage (5.6%), Chinese herbs (4.2%), Gigong (2.8%), physical activity (4.2%), relaxation (1.4%) and listening to music (2.8%). T-tests showed that there was no significant difference in the β-endorphin levels and the composite scores in the pain dimensions for the patients who were using and not using alternative pain relief methods.

None of the patients had received radiotherapy for pain relief. T-tests demonstrated no significant difference in the β-end between different stages of disease. An earlier report showed that 18-49% of cancer patients had had pain as an early symptom of the disease (Daut & Cleeland, 1982) while more recent studies reported that 35%-38% of newly diagnosed patients had experienced pain in the previous two weeks (Ger et al., 1998; Vuorinen, 1993).

Table 7.2 Clinical data

Pain/ Disease History	n	(%)
Has varying degrees of pain		
Yes	32	(42.1)
No	44	(57.9)
Pain intensity		
Mild (1-4)	31	(96.9)
Moderate (5-6)	0	(0.0)
Severe (7-10)	1	(3.1)
Site of pain*		
R upper quadrant	18	(56.3)
R lower quadrant	4	(12.5)
Epigastrum	4	(12.5)
R upper back	1	(3.1)
R mid back	2	(6.3)
L mid back	2	(6.3)
Total	30	(93.9)
Pain radiation*		
Yes	8	(25.0)
No	16	(50.0)
Site of referred pain		
R shoulder	4	(50.0)
L shoulder	1	(12.5)
Mid back	1	(12.5)
R back	1	(12.5)
L upper arm	1	(12.5)
Stage of disease		
Stage 1	21	(27.6)
Stage 2	55	(72.4)
Metastasis		
Yes	0	(0.0)
No	76	(100.0)

* missing data

Table 7.3 Alternative pain relief methods

Alternative pain relief methods	n	(%)
Current use*		
Yes	10	(13.2)
No	61	(80.3)
Local application	4	(5.3)
Massage	4	(5.3)
Chinese herbs	3	(3.9)
Acupuncture	0	(0.0)
Gigong	2	(2.6)
Religious activities	0	(0.0)
Physical activities	3	(3.9)
Relaxation	1	(1.3)
Listening to music	2	(2.6)
Others	0	(0.0)

* missing data

7.5 Mean plasma β-endorphin level

Descriptive statistics were used to reveal the mean β-end (Figure 7.2). The mean β-end was 270.4 ± SEM 11.4 pg/ml ranging from 78.9 to 498.7 pg/ml.

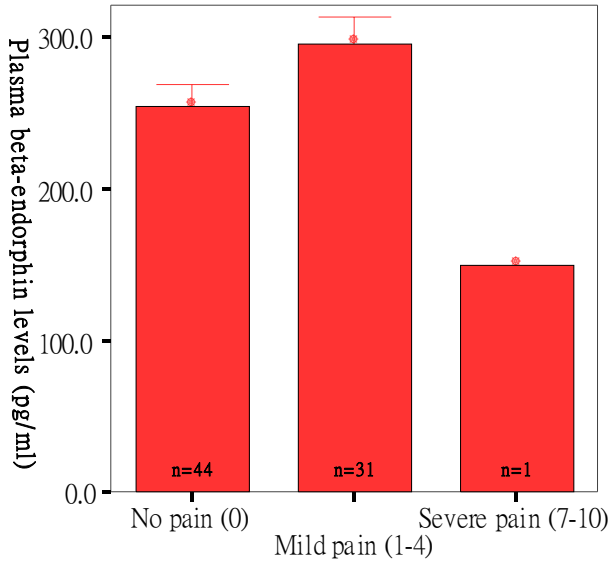


Figure 7.2 Mean plasma β-endorphin ± (SEM) levels in pg/ml in varying pain intensity (n=76).

7.6 The CCPAT pain dimensions scores

The mean weighted scores of the CCPAT were highest for all pain dimensions (FD, PD, PHD, PBMD and Sum) except the ED in the severe pain group. The subjects in the mild pain group had greater mean CCPAT scores than the no pain group in almost all pain dimensions, but slightly lower scores in the PD (Table 7.4).

Table 7.4 Mean weighted scores of CCPAT pain dimensions in varying pain intensity (n=76)

	FD	PD	PHD	ED	PBMD	Sum
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)
No pain (0)	24.1(4.8)	14.8(1.9)	17.9(4.2)	22.2(6.1)	69.2(8.8)	145.1(23.1)
Mild (1-4)	32.8(10.8)	14.3(2.3)	20.5(3.5)	24.5(6.8)	71.0(7.7)	164.8(21.7)
Severe (7-10)	36.0(0.0)	16.0(0.0)	24.2(0.0)	20.9(0.0)	78.0(0.0)	183.5(0.0)
Total	27.8(8.9)	14.6(2.1)	19.0(4.1)	23.1(6.4)	70.1(8.3)	153.6(24.6)

7.7 Correlation between plasma β-endorphin level and the CCPAT pain dimensions

The following section will address the first two research questions and hypotheses:

1. What is the correlation between plasma β-endorphin level and the weighted scores of:
   i. functional dimension (FD),
   ii. psychosocial dimension (PD),
   iii. pharmacological dimension (PHD),
   iv. emotional dimension (ED),
   v. pain beliefs and meanings dimension (PBMD),
   vi. pain intensity dimension (PID),
   vii. sum
2. Can the weighted CCPAT pain dimension scores (independent variables) predict the plasma β-endorphin level (dependent variable)?

The following research hypotheses are posed:

Hypothesis 1: There is an inverse relationship between β-end and FD score.

Hypothesis 2: There is an inverse relationship between β-end and PD score.

Hypothesis 3: There is an inverse relationship between β-end and PHD score.

Hypothesis 4: There is an inverse relationship between β-end and ED score.

Hypothesis 5: There is an inverse relationship between β-end and PBMD score.

Hypothesis 6: There is an inverse relationship between β-end and PID score.

7.7.1 Correlation between plasma β-endorphin level and pain dimensions

To address the first research question, Spearman's rho correlation demonstrated a significant but correlation between β-end and PD (r = -0.25, p=0.028) (n = 76) (Table 7.5). The correlations with FD, PHD, ED, PBMD, PID, and Sum were weak and insignificant. Inverse correlations between β-end and the weighted scores of FD, PD, PHD, ED, and Sum were observed but direct correlation with PBMD and PID (Table 7.5). These findings are in agreement with the hypotheses 1-4 in this thesis.

Table 7.5 Spearman's rho correlation coefficients (2-tailed) for plasma β-endorphin level (β-end) and the CCPAT pain dimensions (n=76)

	FD	PD	PHD	ED	PBMD	PID	Sum	Mean	SD
β-end	-.14	-.25*	-.20	-.06	.04	.10	-.10	270.4	11.4
P value	0.24	0.03	0.08	0.59	0.77	0.37	0.37		

* P< 0.05 β-end level is expressed in untransformed mean ± (SEM) levels in pg/ml.

The correlations between the β-end and the weighted FD, PD, PHD, ED, PBMD, PID and Sum scores are shown in Figures 7.3 to 7.9.

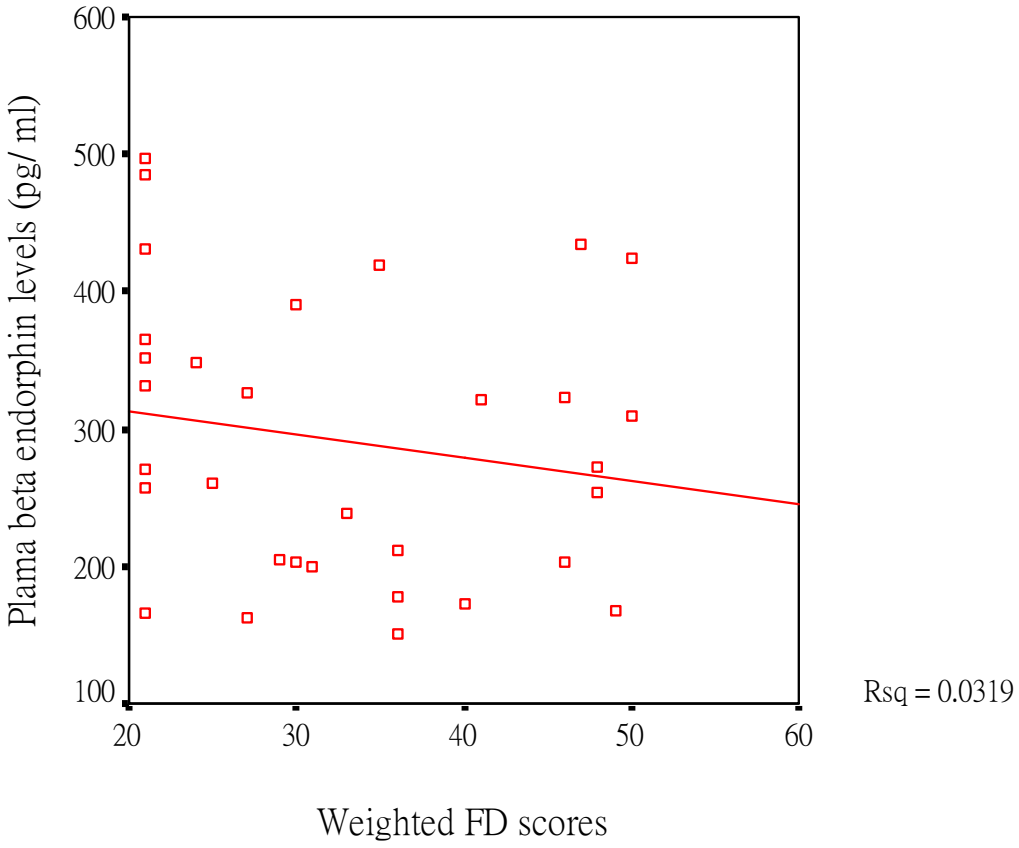


Figure 7.3 The correlation between plasma β-endorphin level and the weighted FD scores

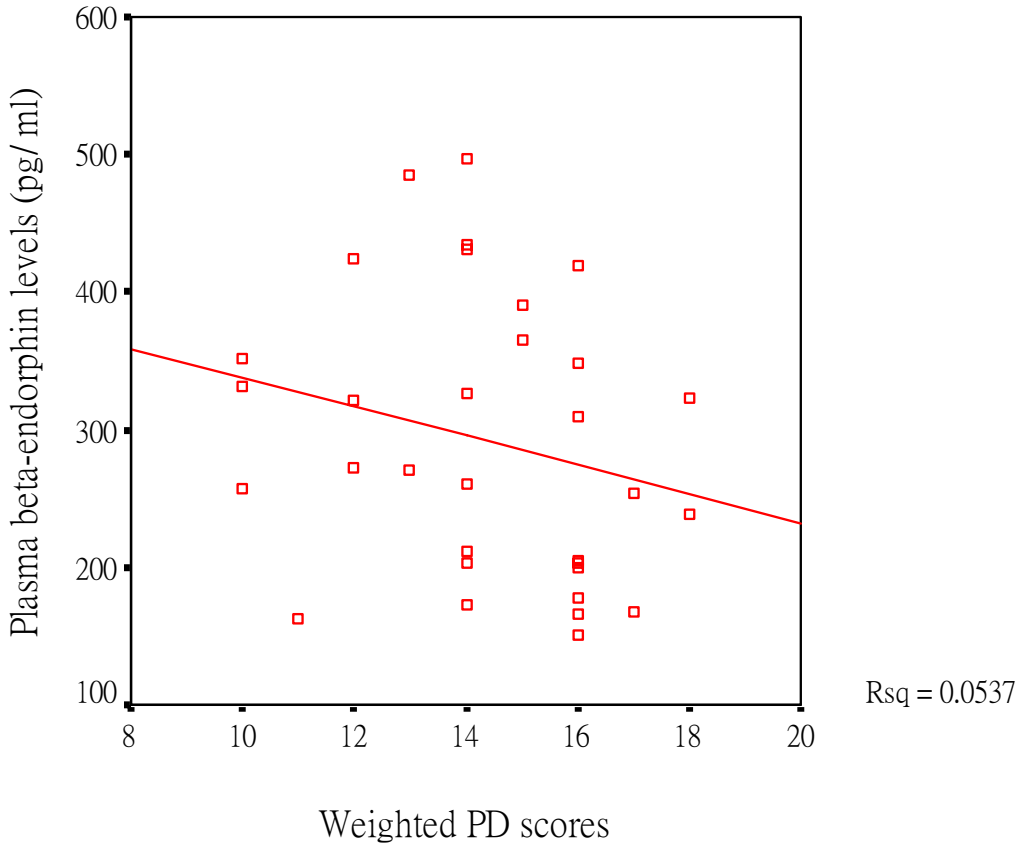


Figure 7.4 The correlation between plasma β-endorphin level and the weighted PD scores

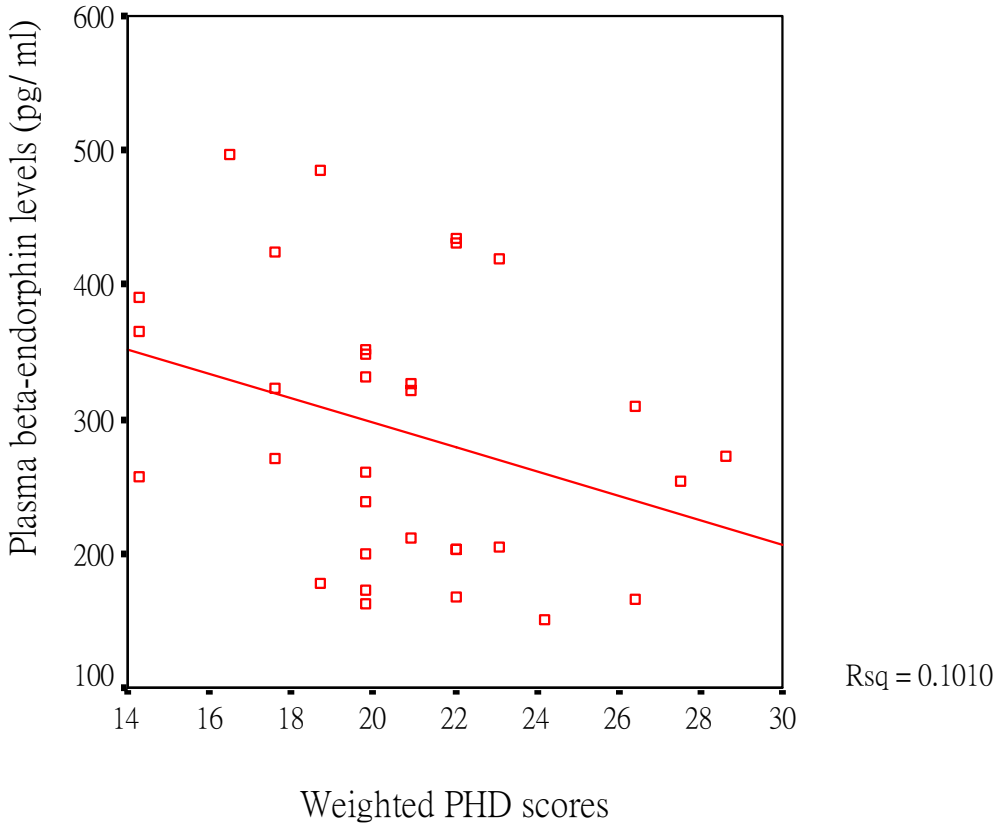


Figure 7.5 The correlation between plasma β-endorphin level and the weighted PHD scores

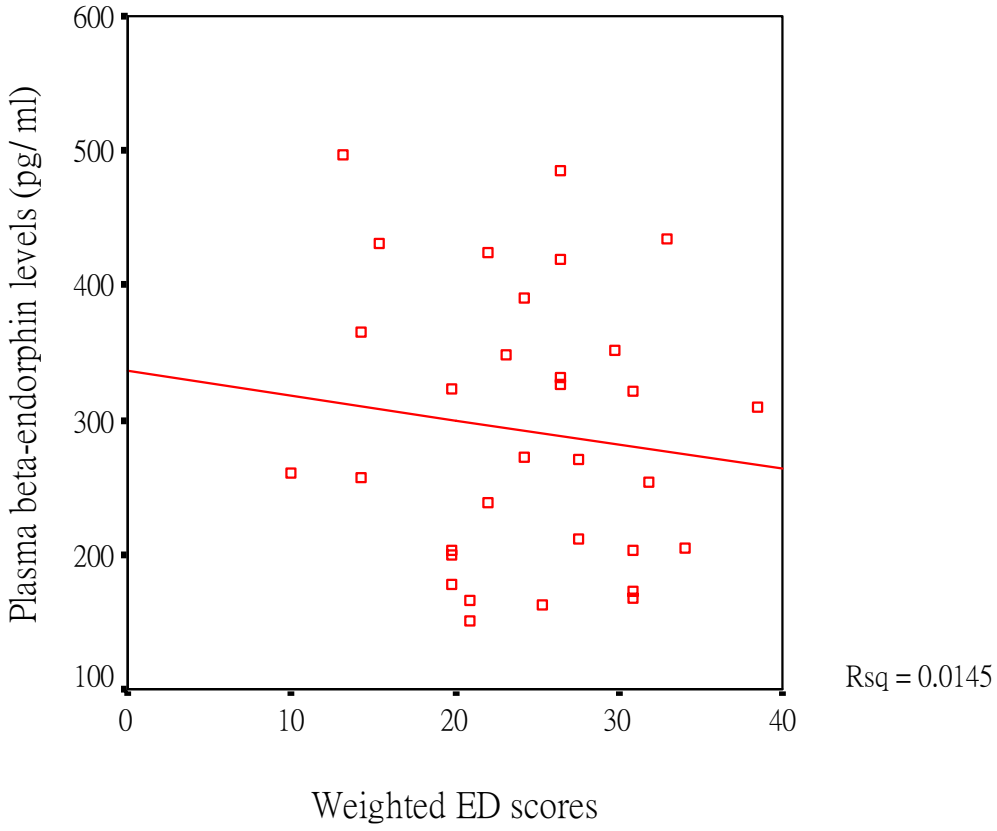


Figure 7.6 The correlation between plasma β-endorphin level and the weighted ED scores

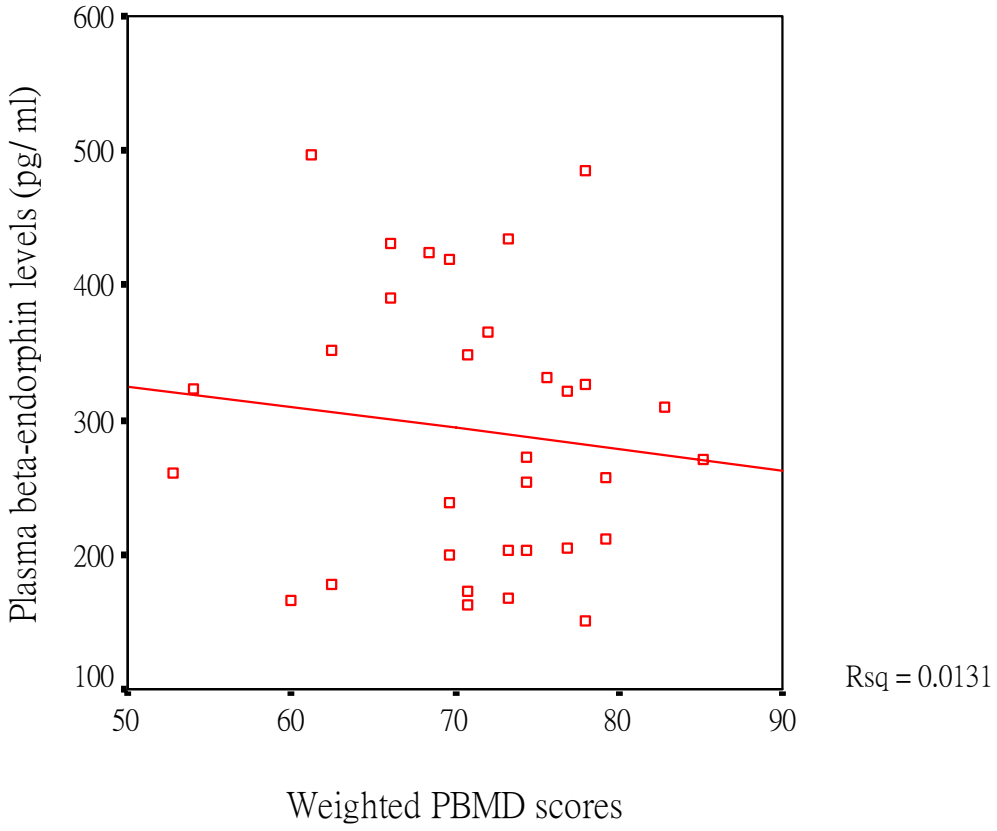


Figure 7.7 The correlation between plasma β-endorphin level and the weighted PBMD scores

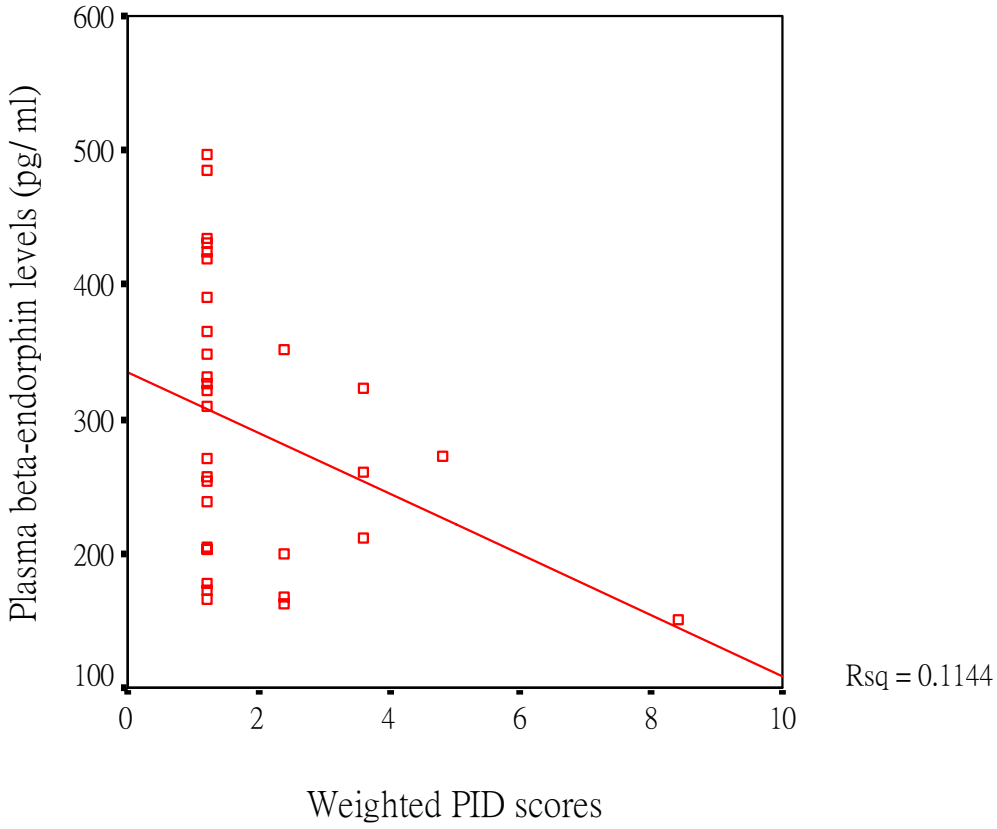


Figure 7.8 The correlation between plasma β-endorphin level and the weighted PID scores

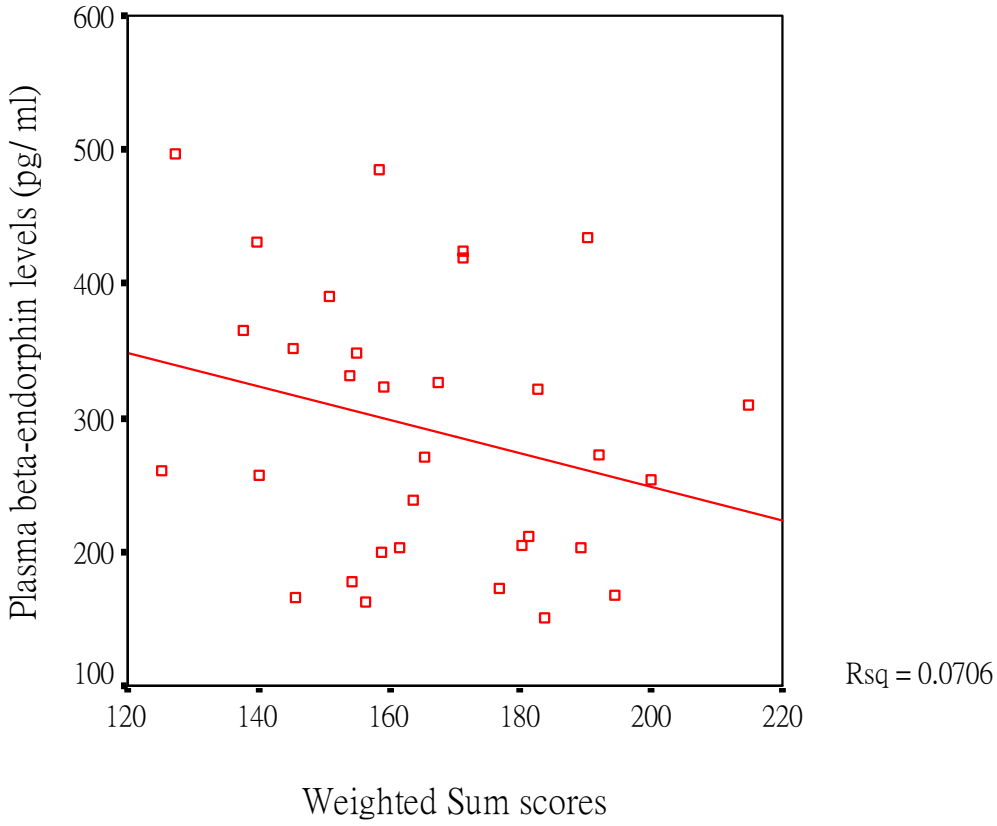


Figure 7.9 The correlation between plasma β-endorphin level and the weighted Sum scores

To avoid type I error, the correlational matrix was α-corrected by Bonferroni adjustment. The Bonferroni method is based on a very simple and general relationship. The probability that at least one of several events will occur cannot exceed the sum of individual probabilities. Therefore, the p value of 0.05 was divided by the number of tests, i.e. 0.05/ 6 = 0.0083. Thus, null hypothesis cannot be rejected.

7.7.2 Predictability of the CCPAT pain dimensions

To address the second research question, regression analysis was employed to investigate the predictability of the weighted CCPAT pain dimension scores (independent variables) for the β-end (dependent variable). β-end was entered as the dependent variable in stepwise regression analysis, but the model was not significant. None of the weighted CCPAT pain dimension scores were predictive for the β-end. Thus, the results have shown a non-linear relationship between β-end and the CCPAT pain dimensions.

7.8 Plasma β-endorphin levels and pain

The following section will address the third research question:

3. Is the plasma β-endorphin level significantly different between the pain group and the no pain group?

The β-end was not significantly different between the pain and no pain groups ($p>0.05$), however the mean β-end was higher in the pain group (291.6 ± SEM 18.0 pg/ml) than the no pain group (255.0 ± SEM 14.5 pg/ml) (Figure 7.10). Similarly, no significant difference was detected between the mild pain and no pain groups ($p>0.05$), however the mean β-end of the mild pain group was higher than that of the

no pain group (296.1 ± SEM 18.0 and 255.0 ± SEM 14.5 respectively) (Figure 7.11). Because there is only one case in the severe pain group, statistical analyses were not performed to examine the difference between the different pain intensity groups (severe, mild and no pain groups). The results demonstrate β-end variations in the pain and no pain groups.

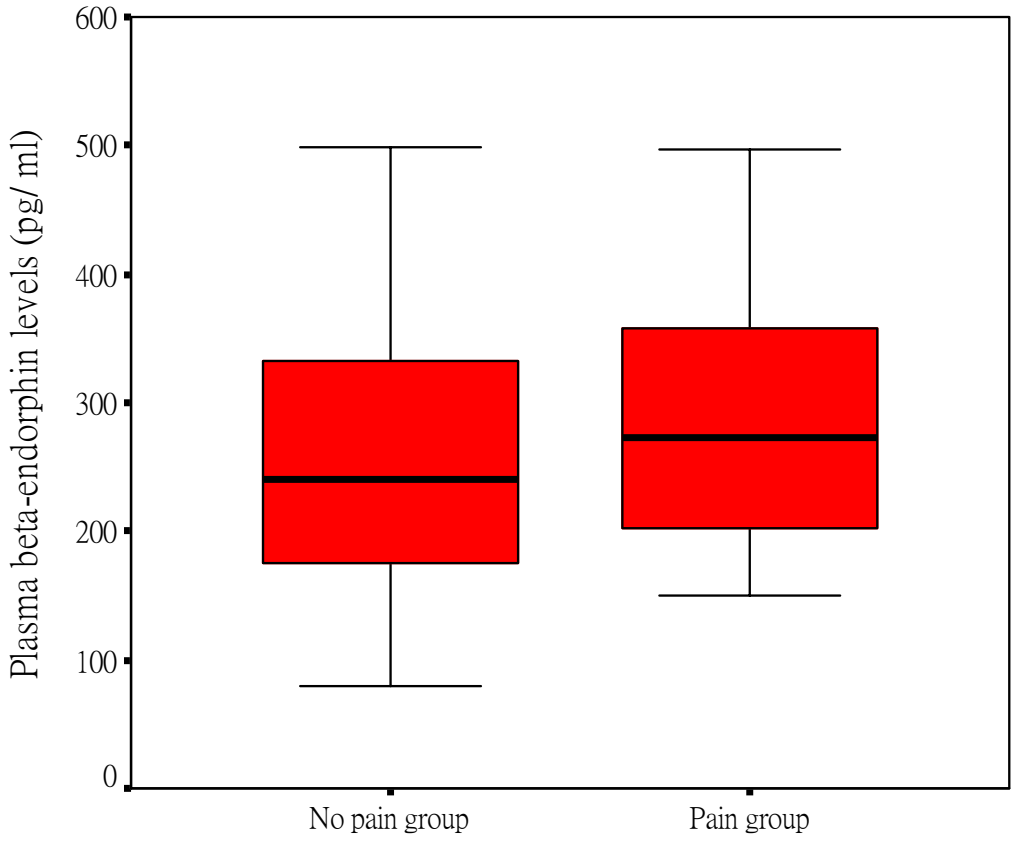


Figure 7.10 Plasma β-endorphin levels (pg/ml) in Chinese PLC patients. Comparison of mean plasma level between the pain (n=32) and no pain (n=44) groups (p=0.11).

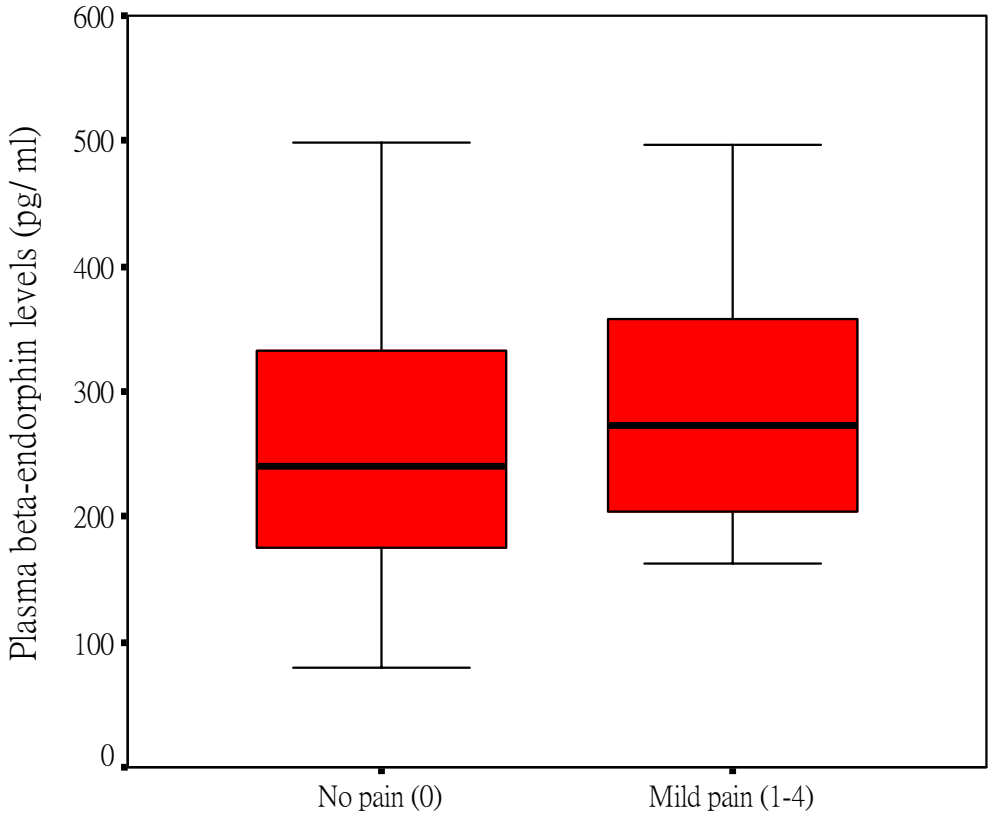


Figure 7.11 Comparison of mean plasma β-endorphin level (pg/ml) between the mild pain (n=31) and no pain (n=44) groups (p=0.08).

Despite there is no significant difference between the pain and no pain groups, Spearman's correlation in the pain group showed a significant inverse correlation (r=-0.35) between β-endorphin and pain intensity (p=0.05).

7.9 Effects of attribute and extraneous variables on plasma β-endorphin

Different attribute and extraneous variables in the pain and no pain groups are shown in Table 7.6.

Table 7.6 Attribute and extraneous variables

	No Pain		**Pain**	
	n	(%)	n	(%)
Gender				
Male	40	(52.6)	28	(36.8)
Female	4	(5.3)	4	(5.3)
BMI				
Normal (<25kg/m^2)	36	(47.4)	26	(34.2)
Obese (>/=25kg/$m^{2)}$	8	(10.5)	6	(7.9)
Regular Exercise*				
Yes	24	(31.6)	20	(26.3)
No	19	(25)	11	(14.5)
Weekly Exercise*				
<90 minutes	2	(4.5)	1	(2.3)
>/=90 minutes	22	(50)	18	(40.9)

* Missing data

As revealed in the literature, attribute and extraneous variables may contribute to the plasma level variations. T-tests were conducted to examine whether the β-end were affected by these variables.

The basal mean β-end was significantly higher in males (264.0 ± SEM 14.7) than females (165.5 ± SEM 42.5) ($p<0.05$). Higher levels of β-end was noted in pain group than no pain group regardless of gender. However, t-tests showed no significant difference ($p>0.05$) between pain and no pain, or mild pain and no pain groups by gender (Tables 7.7 and 7.8). Since the results showed the mean plasma level was not significantly different in the pain group or mild pain group by gender. Therefore, the level variation in different gender is not a concern in the correlational analysis.

The results demonstrated no significant difference between the pain and no pain groups in different BMI or exercises groups ($p>0.05$) (Tables 7.9, 7.10 and 7.11). If there were a difference, the plasma β-end levels can be controlled by analysis of covariance (ANCOVA) to statistically eliminate the extraneous variable by controlling for the differences on the extraneous variable to reduce confounding effects.

Table 7.7 Mean plasma β-endorphin level (± SEM) variations in the pain and no pain groups by gender (n=76)

	No Pain	**Pain**	
	Mean (SEM)	Mean (SEM)	*P*
Male	264.0 (14.7)	292.4 (19.1)	NS(0.24)
Female	165.5 (42.5)	285.8 (60.0)	NS(0.15)
P	0.049*	NS(0.91)	

* P< 0.05 β-end level is expressed in untransformed mean ± (SEM) levels in pg/ml.

Table 7.8 Mean plasma β-endorphin level (± SEM) variations in the mild pain and no pain groups by gender (n=75)

	No Pain	**Mild Pain**	
	Mean (SEM)	Mean (SEM)	*P*
Male	264.0 (14.7)	297.7 (19.1)	NS(0.16)
Female	165.5 (42.5)	285.8 (60.0)	NS(0.15)
P	0.049*	NS(0.83)	

* P< 0.05 β-end level is expressed in untransformed mean ± (SEM) levels in pg/ml.

Table 7.9 Mean plasma β-endorphin level (± SEM) variations in the pain (n=32) and no pain (n=44) groups by BMI category (normal <25kg/m^2, obesity >/=25kg/m^2)

	No Pain	**Pain**	
	Mean (SEM)	Mean (SEM)	*P*
Normal	249.0 (16.8)	284.5 (20.5)	NS(0.18)
Obese	282.0 (24.5)	322.2 (37.0)	NS(0.36)
P	NS(0.39)	NS(0.42)	

* P< 0.05 β-end level is expressed in untransformed mean ± (SEM) levels in pg/ml.

Table 7.10 Mean plasma β-endorphin level (± SEM) variations in the pain (n=31) and no pain (n=43) groups by looking at exercise pattern

	No Pain		**Pain**		
Regular Exercises	Mean	(SEM)	Mean	(SEM)	*P*
Yes	251.8	(19.4)	293.4	(23.4)	NS(0.18)
No	262.4	(23.2)	285.5	(31.8)	NS(0.56)
P	NS(0.73)		NS(0.84)		

* P< 0.05 β-end level is expressed in untransformed mean ± (SEM) levels in pg/ml.

Table 7.11 Mean plasma β-endorphin level (± SEM) variations in the pain (n=19) and no pain (n=24) groups by looking at weekly exercise pattern (<90 minutes and >/=90 minutes)

	No Pain		**Pain**		
	Mean	(SEM)	Mean	(SEM)	*P*
<90 mins	366.3	(10.6)	497.5	(0.0)	NS(0.89)
>/=90 mins	241.4	(19.6)	287.0	(22.7)	NS(0.14)
P	NS(0.07)		0.048*		

* P< 0.05 β-end level is expressed in untransformed mean ± (SEM) levels in pg/ml.

7.10 Conclusion

Data from the study sample are analysed using descriptive and inferential statistics. The results of the main study are presented. The demographic and clinical data of the study sample are depicted. The findings in this chapter are in agreement with the hypotheses formulated that β-end is inversely correlated with the weighted scores of FD, PD, PHD and ED in the CCPAT but directly correlated with PBMD and PID. However, the correlations were weak and non-significant after α-correction. Thus, null hypothesis cannot be rejected. One interesting finding is the significant difference in β-end between those with religious belief and atheists ($p<0.000$).

CHAPTER 8

DISCUSSION ON THE RELATIONSHIP BETWEEN PLASMA β-ENDORPHINS AND THE CCPAT PAIN DIMENSIONS

8.1 Introduction

This chapter will discuss the results of the main study that were described in chapter 7. The following discussion will be divided into three sections in accordance with the research questions. The first section will discuss the correlation between β-end and the CCPAT pain dimensions. The second section will focus on the predictability of the CCPAT scores (independent variables) for the β-end (dependent variable). The final section will highlight the β-end variations in different pain groups. Discussions will make reference to recent literature.

8.2 Demographic characteristics

8.2.1 Gender

In this cancer population, there were 68 men (89.5%) and 8 women (10.5%) approximately 8.5 times as many men as of women. The global incidence of liver cancer is approximately 3 times as many in males as in females (Rivera & Abbruzzese, 1995). In high incidence regions, such as China, the incidence rate for males is $\geq$ 20 in 100,000 every year. It is observed that many more males were recruited than females. This may attributed to a higher number of males diagnosed

and admitted to the Cancer Centre in Guangzhou for cancer treatment. There are two possible explanations for this interesting phenomenon. Firstly, Guangzhou runs an annual screening program (ultrasound examination to detect liver abnormalities) for working citizens. Males who were working accounted for 77.3% whereas only half of that percentage (37.5%) of females was working. Therefore, males are more likely to be early diagnosed with the disease. Secondly, the cost for hospitalization and treatment is very high in Guangzhou; often it is not affordable by low income earning family. Looking at the demographic data, it is evidenced by a significant percentage (40.8%) of patients in higher income jobs including managerial and administrative (government officials), professional or business. In addition, in the Chinese culture, males are predominant than females. Families who have financial constraints would consider having a male member of the family as to a female member in the priority of receiving expensive medical care.

The basal β-end was significantly higher in males than females. The finding is consistent with previous studies (Gianoulakis et al., 2003; Leuschen et al., 1991; Ritter et al., 1991). It has been suggested that the gender differences is attributed to the activity of HPA axis under basal conditions (Gallucci et al., 1993). However, the mean plasma β-end was not significantly different between the pain and no pain groups. Animal studies tend to be male-dominant thus the results cannot be compared with this study. Human studies have included both genders, however many have not reported the plasma β-end separately in male and female subjects.

8.2.2 Religious belief

It is interesting to observe the b-end variations in the two broadly categorized groups. A recent review (Breitbart, 2002) suggests measures of spirituality deal with two of its main components: faith/religious beliefs and meaning/spiritual well-being. Adequate supportive care expand beyond a focus on pain and physical symptom control, existential and spiritual issues such as meaning, hope and spirituality in general have received increased attention.

Since the use of a single item to measure religious coping is not a reliable measure of this construct (Dunn & Horgas, 2004), there are measures of spirituality to determine the different levels of spirituality in terms of their spiritual well-being (Lin & Bauer-Wu, 2003; Ramondetta & Sills, 2004). Thus, it is difficult to draw any conclusion to this variation between the two groups for two reasons: One is that spirituality was not measured in this sample therefore the level of spirituality cannot be determined in the present study. Two is that in China, religion is a taboo, so there may some patients who would not be verbally admitting to a certain religion for the fear of getting into trouble.

8.3 Correlation between plasma β-endorphin level and CCPAT pain dimensions

The findings below result from correlational analyses that were performed to examine the direction and strength of the association. In this thesis, six hypotheses were formulated that β-end is inversely correlated with the CCPAT pain dimensions.

8.3.1 Inverse correlations

The results of statistical analyses undertaken to test these hypotheses demonstrated statistical support for most of the hypotheses. The results show that the β-end has an inverse relationship with the weighted scores of FD, PD, PHD, and ED but a direct relationship with PBMD and PID. Similar findings have been shown in a recent study (Chung et al., 2002) reporting inverse correlations between the β-end and all the weighted CCPAT pain dimension scores in a heterogeneous group of cancer patients.

8.3.2 Plasma β-endorphin level and CCPAT pain dimensions

Plasma β-end was not significantly correlated with the CCPAT pain dimensions except PD. However, the relationship was demonstrated to be weak. Furthermore, α-corrected correlational matrix showed that all relationships were non-significant.

Therefore it is concluded that no relationship is assumed to exist between the studied variables because the statistical evidence is too weak to substantiate the relationships.

8.4 Predictability of CCPAT scores for the plasma β-endorphin level

The results show that the CCPAT scores were not able to predict the β-end. A non-linear relationship is demonstrated between the studied variables.

The above findings regarding the correlations are inconsistent with the previous study. Chung et al. (2002) showed that there were significant and weak correlations between β-end and various pain dimensions which include PD, ED, and Sum. In the same study, they reported that the weighted scores of PD, ED, and PID were significant predictors for β-end. They suggest that the importance of including psychological, emotional and intensity dimensions in pain assessment is reaffirmed using plasma β-endorphin as a biomarker.

The discrepancies in the findings have three possible explanations related to the difference in the study population. The previous study consisted of cancer patients with more advanced disease compared to this sample of newly diagnosed cancer patients.

Firstly, the cancer patients who were newly diagnosed may be experiencing varying degree of psychological distress such as worry and anxiety which may be related to

the diagnosis, uncertain about the disease, and less so with the pain. Also, the pain level would be different in the two samples. As an individual is viewed holistically, it is extremely difficult to tease out the emotional response whether it is attributed to the pain or the diagnosis.

Secondly, the release of b-end may be different in more advanced disease than to newly diagnosed patients. This may be attributed to patients with mild pain may trigger a different endogenous pain-inhibitory mechanism (central vs peripheral) involving a spectrum of opioids, because the level in the plasma is different to the level in CNS.

Thirdly, acute and chronic stress situations, and the level of stress may trigger different opiotergic systems eliciting different b-end levels. The chronicity of pain in more advanced disease would contribute to the chronic stress condition.

8.5 Plasma β-endorphin level variations and pain

It was shown that the mean β-end is higher in the pain group when compared to the no pain group, but the difference is not significant. The cancer population that suffers from pain exhibits higher levels of β-end. It may be explained that pain pathways stimulate endogenous opiotergic systems, including the circulating β-end. Similar variations of β-end are observed in other studies (Bacigalupo et al., 1990; Bernstein et al., 1995; Sheps et al., 1995). In these studies, pain, anxiety and stress

are potent stimuli which can induce the release of β-endorphin. The authors concluded that elevated β-endorphin levels may exist to serve a functional role of modulating pain perception.

However, in the pain group, the result demonstrated a significant inverse correlation between plasma β-endorphin level and pain intensity. The finding is consistent with previous studies (Takahashi et al., 2000; Tonnarini et al., 1995; Buratti et al., 1998).

In this cancer population, among those who were experiencing pain, those who suffer from more pain exhibit lower levels of β-endorphin. Although the issue of causality is apparent in correlational studies, there are some possible explanations for this inverse correlation. Some studies have argued that lack of activity in opiotergic systems, which may be related to immunosuppression during cancer treatment, exacerbates pain pathways (Przewlocki et al., 1992; Stein et al., 1990). Also, it has been suggested that a failure of opiotergic response may lead to a higher degree of pain signalling from the periphery (Rittner et al., 2001).

Alternatively, patients who exhibit higher levels of β-endorphin experience less pain. β-endorphin has intriguing analgesic properties (Cabot et al., 1997; Lyons & Blalock, 1997). Many vivo and vitro studies have demonstrated its potent analgesic effect by modulating pain perception (Barrett et al., 2000; Gabis et al., 2003).

8.6 Conclusion

In conclusion, the findings partially support the research hypotheses that there are inverse correlations between β-end and FD, PD, PHD and ED. It has shown that there are no relationships between β-end and the CCPAT pain dimensions and that the CCPAT pain scores were not predictive of β-end in a homogeneous group of primary liver cancer patients. These findings are inconsistent with the previous study. The β-end variations in the pain and no pain groups are suggestive of a functional role of β-endorphin in cancer pain modulation. The study also provides evidence that underpins the concept of multidimensionality in the cancer pain experience.

CHAPTER 9

CONCLUSIONS

9.1 Introduction

This chapter will conclude by summarizing the study. The research questions are revisited. The methods used to conduct the research investigating the relationship between β-end and the CCPAT pain dimensions are presented. The implications of the results for clinical practice, knowledge base and future research involving plasma β-endorphin and cancer pain will be discussed.

9.2 Research questions

The research questions are as follows:

i. What is the correlation between plasma β-endorphin level and the pain dimensions in the Chinese Cancer Pain Assessment Tool (CCPAT)?

ii. Can the weighted scores of the pain dimensions in the CCPAT (independent variables) predict the plasma β-endorphin level (dependent variable)?

iii. Is the plasma β-endorphin level significantly different between the pain and no pain groups?

9.3 Summary of method

A cross-sectional correlational study design was employed to investigate the relationship between the studied variables, namely β-end and the CCPAT pain dimensions. Blood samples were taken from a homogeneous group of primary liver cancer patients, and β-end (dependent variable) was determined by standardized RIA method. Weighted pain scores were obtained by assessing the patients' pain with the culturally specific Chinese Cancer Pain Assessment Tool (CCPAT) (independent variables). The data obtained were analysed to answer the above research questions.

9.4 Summary of findings

From the results, the answers to the research questions are revealed:

i. There is no correlation between β-end and the CCPAT pain dimensions.

ii. The CCPAT pain dimension scores are not predictive of β-end.

iii. The mean β-end of the mild pain group was higher than that of the no pain group (296.1 ± SEM 18.0 and 255.0 ± SEM 14.5 respectively).

In addition, there are several important and interesting findings as follows:

iv. The mean β-end was significantly higher in the subjects who were atheists (303.0 ± SEM 14.5) than in those who had a religion (222.7 ± SEM 14.7) ($p<0.000$).

v. The mean β-end has a significant inverse correlation with PID ($r = -0.35$) in the pain group ($p<0.05$).

vi. The basal β-end was significantly higher in males (264.0 ± SEM 14.7) than females (165.5 ± SEM 42.5) ($p<0.05$).

vii. The findings provide evidence to underpin the concept of multidimensionality in the cancer pain experience.

9.5 Implications of the results

The results of statistically significant weak correlation and the relative small sample size need to be carefully considered for clinical implications or generalizing in cancer patients. The findings of the present study have limited implications for clinical relevance but they may serve as a baseline reference to future larger sample and longitudinal design studies. This study has further supported and added to the knowledge base that cancer pain is conceptualized as multidimensional, and that β-endorphin plays an important role in cancer pain modulation.

9.6 Limitations

The limitation of this study is that the sample size is relatively small (due to unexpected damage of blood samples) which would reduce the power of the study. Also, by including a homogenous group of primary liver cancer patients, the findings may not be generalizable to all cancer patients. Interpretation of causality is always difficult in this kind of correlational study design.

9.7 Future research

Future research may include a larger sample to increase the rigor. A longitudinal design may reveal with the changes in plasma β-end level and pain dimensions in cancer patients may be more informative for the relationship. Future study will include morning and evening samples to reveal (the loss of) diurnal variations in cancer population. To increase the generazability of the results, different homogenous cancer types with more advanced disease from various Cancer Centers may be recruited.

9.8 Conclusion

This study attempted to examine the relationship between β-end and the pain dimensions in a homogenous group of Chinese patients with primary liver cancer

using the culturally specific Chinese Cancer Pain Assessment Tool (CCPAT). Future research is required to shed light on the bio-psycho-social-cultural link in the context of cancer pain experience which will enhance accuracy in the assessment of pain, contributing to better outcome in pain management. Culturally specific cancer pain assessment tool is able to tap into important pain dimensions that will enrich the concept of multidimensionality in cancer pain experience.

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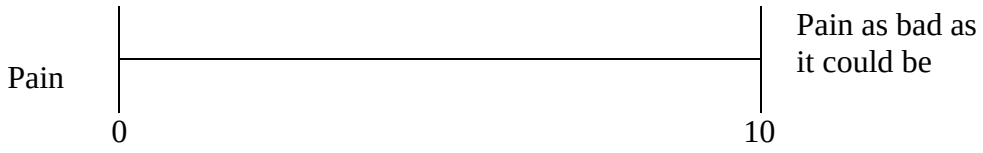
APPENDIX 1

Visual Analogue Scale (VAS)

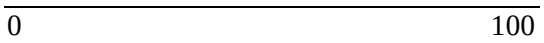


Numerical Rating Scale a) BS-11, b) NRS-101

a) The 11-point box scale (BS-11)

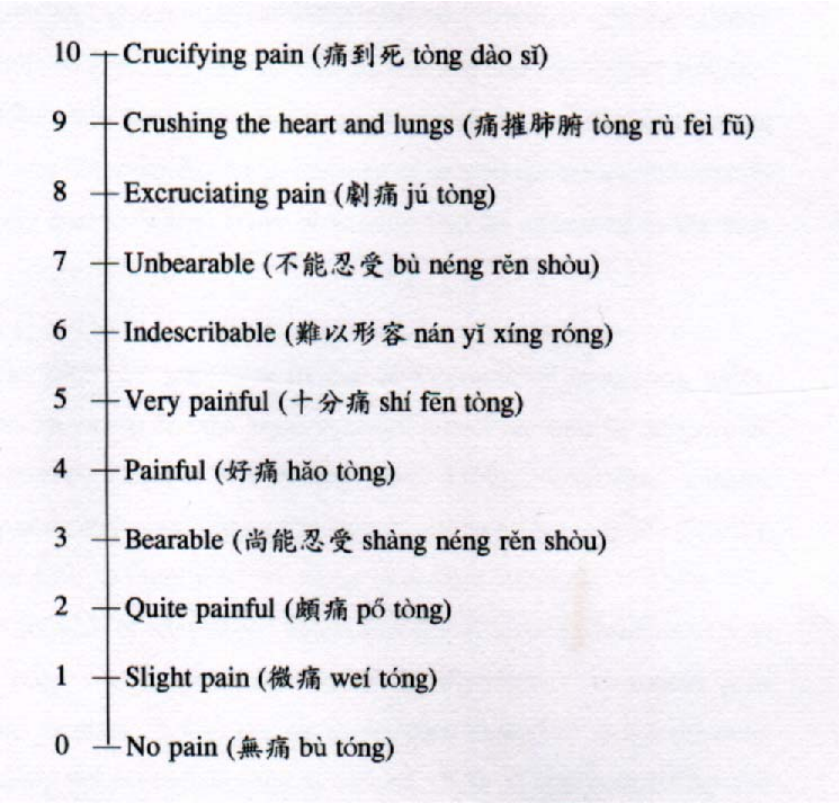
0	1	2	3	4	5	6	7	8	9	10

b) The 101-point numerical rating scale (NRS-101)



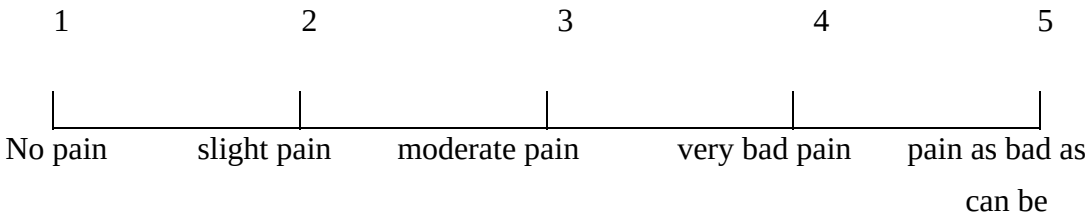
APPENDIX 2

Chinese Pain Intensity Verbal Rating Scale (C-PIVRS)



APPENDIX 3

Graphic Rating Scale (GRS)



Face Scale (FS)

APPENDIX 4

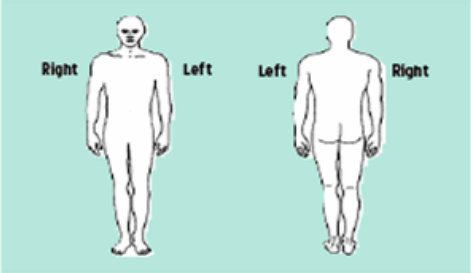
Brief Pain Inventory-Short Form (BPI-SF)

Brief Pain Inventory (Short Form)

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. yes 2. no

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its **WORST** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its **LEAST** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on the **AVERAGE**.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6) Please rate your pain by circling the one number that tell how much pain you have **RIGHT NOW**.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

8) In the past 24 hours, how much **RELIEF** have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
No Relief — Complete Relief

9) Circle the one number that describes how, during the past 24 hours. **PAIN HAS INTERFERED** with your:

A. General Activity:

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

D. Normal work (Includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

E. Relation with other people

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

G. Enjoyment of life

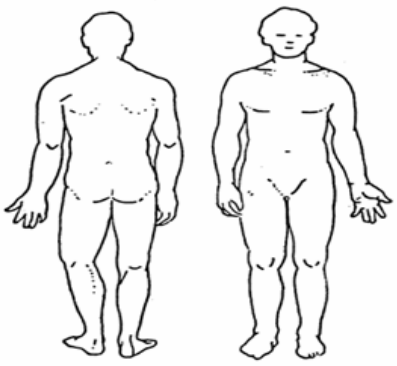
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

APPENDIX 5

Short Form -McGill Pain Questionnaire (SF-MPQ)

MC GILL PAIN QUESTIONNAIRE (MPQ)

1. WHERE IS YOUR PAIN?
Please mark, on the drawings below, the areas where you feel pain. Put E if external, or I if internal, near the areas which you mark. Put EI if both external and internal.



2. WHAT DOES YOUR PAIN FEEL LIKE?

Some of the words below describe your *present* pain. Circle *ONLY* those words that best describe it. Leave out any category that is not suitable. Use only a single word in each appropriate category—the one that applies best.

Sensory: 1–8 *Evaluative*: 16
Affective: 9–15 *Miscellaneous*: 17–20

1	2	3	4
Flickering	Jumping	Pricking	Sharp
Quivering	Flashing	Boring	Cutting
Pulsing	Shooting	Drilling	Lacerating
Throbbing		Stabbing	
Beating		Lancinating	
Pounding			
5	**6**	**7**	**8**
Pinching	Tugging	Hot	Tingling
Pressing	Pulling	Burning	Itchy
Gnawing	Wrenching	Scalding	Smarting
Cramping		Searing	Stinging
Crushing			
9	**10**	**11**	**12**
Dull	Tender	Tiring	Sickening
Sore	Taut	Exhausting	Suffocating
Hurting	Rasping		
Aching	Splitting		
Heavy			
13	**14**	**15**	**16**
Fearful	Punishing	Wretched	Annoying
Frightful	Gruelling	Blinding	Troublesome
Terrifying	Cruel		Miserable
	Vicious		Intense
	Killing		Unbearable
17	**18**	**19**	**20**
Spreading	Tight	Cool	Nagging
Radiating	Numb	Cold	Nauseating
Penetrating	Drawing	Freezing	Agonizing
Piercing	Squeezing		Dreadful
	Tearing		Torturing

3. HOW DOES YOUR PAIN CHANGE WITH TIME?
a. Which word or words would you use to describe the *pattern* of your pain?

1	2	3
Continuous	Rhythmic	Brief
Steady	Periodic	Momentary
Constant	Intermittent	Transient

b. What kind of things *relieve* your pain?

c. What kind of things *increase* your pain?

4. HOW STRONG IS YOUR PAIN?
People agree that the following 5 words represent pain of increasing intensity. They are:

1	2	3	4	5
Mild	Discomforting	Distressing	Horrible	Excruciating

To answer each question below, write the number of the most appropriate word in the space beside the question.

1. Which word describes your pain right now? _____
2. Which word describes it at its worst? _____
3. Which word describes it when it is least? _____
4. Which word describes the worst toothache you ever had? _____
5. Which word describes the worst headache you ever had? _____
6. Which word describes the worst stomach-ache you ever had? _____

APPENDIX 6

Chinese Cancer Pain Assessment Tool (CCPAT) (English version)

Pain Assessment Tool

In order to enable nurses to better understand your pain and to administer pain relief method, please circle the following answer which can best describe your experiences and feelings.

I. Functional Dimension

Please circle the appropriate number.

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1.	My eating habit is different from the past.	1	2	3	4	5
2.	I ate less than before.	1	2	3	4	5
3.	My daily activities are easily affected by pain, for example, shopping.	1	2	3	4	5
4.	Pain affects my household work.	1	2	3	4	5
5.	Pain affects me from taking bath.	1	2	3	4	5
6.	Pain affects entertainment, for example, watching television, playing mahjong, doing exercise.	1	2	3	4	5
7.	Pain affects me when I am charting.	1	2	3	4	5
8.	Pain makes me lying on the bed all day.	1	2	3	4	5
9.	Pain interrupts my sleep, for example, difficult to get asleep, waking up by pain.	1	2	3	4	5
10	I can go to toilet myself.	1	2	3	4	5
11.	I can still take short walk on my own.	1	2	3	4	5
12.	I can wash myself.	1	2	3	4	5
13.	I can change my clothes by myself.	1	2	3	4	5

Part I Score ☐

II. Psychosocial Dimension

Please circle the appropriate number.

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1.	My pain has psychosocial components, e.g. affected by events and people around.	1	2	3	4	5
2.	I want people to be aware of my pain.	1	2	3	4	5
3.	I don't want people to know my pain.	1	2	3	4	5
4.	I think that verbalize of my pin will be discriminated against by the public.	1	2	3	4	5
5.	Living with my family will make my situation better.	1	2	3	4	5

Part II Score ☐

III. Pharmacological Dimension

Please circle the appropriate number.

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1.	I am dependent on analgesic	1	2	3	4	5
2.	I have no pain after taking analgesic.	1	2	3	4	5
3.	I take analgesic regularly because it can lessen my pains.	1	2	3	4	5
4.	After taking the analgesic, I found myself getting better.	1	2	3	4	5
5.	I am afraid that analgesic does not work after my body gets used to its effect.	1	2	3	4	5

6.	I really feel comfortable after using the analgesic. Maybe it really works.	1	2	3	4	5
7.	If doctors tell me to take analgesics, I will take them.	1	2	3	4	5

Part III Score ☐

IV. Emotional Dimension

Please circle the appropriate number.

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1.	I believe that death can solve the pain problem.	1	2	3	4	5
2.	I am not interested in anything.	1	2	3	4	5
3.	I feel worried.	1	2	3	4	5
4.	I feel frustrated	1	2	3	4	5
5.	I feel anxious.	1	2	3	4	5
6.	I feel that I need to depend on someone.	1	2	3	4	5
7.	My pain makes troubles for my family.	1	2	3	4	5
8.	I feel that I can calm down.	1	2	3	4	5

Part IV Score ☐

V. Pain Beliefs and Meanings Dimension

Please circle the appropriate number.

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1.	Pain is a physical torture.	1	2	3	4	5
2.	Pain is a mental torture.	1	2	3	4	5
3.	Pain means let nature take its course.	1	2	3	4	5
4.	Pain is a challenge.	1	2	3	4	5
5.	When in pain, it gives me a chance to think about the meaning of life.	1	2	3	4	5
6.	Pain becomes part of my life.	1	2	3	4	5
7.	Having pain means analgesic is ineffective.	1	2	3	4	5
8.	Pain is arranged by God.	1	2	3	4	5
9.	Pain reminds me to accept the reality.	1	2	3	4	5
10.	Having pain means I still have sensation.	1	2	3	4	5
11.	Pain takes away the quality of life.	1	2	3	4	5
12.	Pain reminds me to treasure health.	1	2	3	4	5
13.	Pain makes people feel regretful.	1	2	3	4	5
14.	Pain makes people feel uncomfortable.	1	2	3	4	5
15.	Pain is due to the blockage of collaterals and channels.	1	2	3	4	5
16.	The basic reason for pain is problem in body function.	1	2	3	4	5
17.	Acupuncture can sooth the pains.	1	2	3	4	5
18.	Even though the cancer itself is not painful, it is a suffering.	1	2	3	4	5
19.	I cannot find a word to describe my pain.	1	2	3	4	5

Part V Score ☐

VI. Pain Intensity Dimension

As a whole, your extent of pain is:

10 crucify pain
9 crushing the heart and lungs
8 excruciating pain
7 unbearable
6 undescribable
5 very painful
4 painful
3 bearable
2 quite painful
1 slight pain
0 no pain

Part VI Score ☐

APPENDIX 7

中國癌痛評估工具 (Chinese version)

疼痛評估表

為了讓醫護人員可以更加了解你的疼痛和更有效地提供舒緩方法，請你在下列的問題中圈上最能表達你個人疼痛經驗和感受的數字。

第一部份 日常生活功能

	極之不同意	不同意	無意見	同意	極之同意
1. 飲食的胃口變了。	1	2	3	4	5
2. 食量少了。	1	2	3	4	5
3. 日常的活動受到疼痛的影響〈如上街購物〉。	1	2	3	4	5
4. 疼痛影響做家務。	1	2	3	4	5
5. 疼痛影響我自己洗澡。	1	2	3	4	5
6. 疼痛影響我的娛樂〈如看電視、看書閱報、打麻雀、做運動〉。	1	2	3	4	5
7. 疼痛影響我跟別人聊天。	1	2	3	4	5
8. 疼痛令我日間臥在床上。	1	2	3	4	5
9. 疼痛令我的睡眠受到打擾〈如不能入睡、痛醒〉。	1	2	3	4	5
10. 我可以自行到洗手間如廁。	1	2	3	4	5
11. 我現在仍然可以行一小段路。	1	2	3	4	5
12. 我能自行梳洗。	1	2	3	4	5
13. 我能自行更衣。	1	2	3	4	5

第一部份得分 ☐

第二部份 社會心理

	極之不同意	不同意	無意見	同意	極之同意
1. 四周的環境影響我的疼痛〈如人物、事物〉。	1	2	3	4	5
2. 我想別人注意我的疼痛。	1	2	3	4	5
3. 我不想別人知道我的疼痛。	1	2	3	4	5
4. 我認為疼痛是一個烙印，受到社會的歧視。	1	2	3	4	5
5. 跟家人同住，我的情況會比較好些。	1	2	3	4	5

第二部份得分 ____

第三部份 對止痛藥的看法

	極之不同意	不同意	無意見	同意	極之同意
1. 我需要依賴止痛藥。	1	2	3	4	5
2. 食了止痛藥便沒有疼痛。	1	2	3	4	5
3. 我會按時服用止痛藥，因為它能舒緩疼痛。	1	2	3	4	5
4. 吃了止痛藥後，總會好些。	1	2	3	4	5
5. 止痛藥吃多了，便對疼痛起不了作用。	1	2	3	4	5
6. 不管有沒有用，吃了止痛藥使我心安。	1	2	3	4	5
7. 醫生叫我吃〈止痛藥〉，我就吃。	1	2	3	4	5

第三部份得分 ____

第四部份 情緒

	極之不同意	不同意	無意見	同意	極之同意
1. 死是解決疼痛的方法。	1	2	3	4	5
2. 我對任何事物也提不起興趣。	1	2	3	4	5
3. 我感到擔心。	1	2	3	4	5
4. 我感到沮喪。	1	2	3	4	5
5. 我感到焦慮。	1	2	3	4	5
6. 我感到現在是需要依賴別人。	1	2	3	4	5
7. 我的疼痛為家人帶來麻煩。	1	2	3	4	5
8. 我感到可以平靜下來。	1	2	3	4	5

第四部份得分 ____

第五部份 疼痛的意義和信念

	極之不同意	不同意	無意見	同意	極之同意
1. 疼痛是肉體上的折磨。	1	2	3	4	5
2. 疼痛是精神上的折磨。	1	2	3	4	5
3. 疼痛時要順其自然。	1	2	3	4	5
4. 對付疼痛是一種挑戰。	1	2	3	4	5
5. 在疼痛的過程中，它給我一個機會去反省人生的意義。	1	2	3	4	5
6. 疼痛會成為我的一部份。	1	2	3	4	5
7. 有疼痛就代表了止痛藥無效。	1	2	3	4	5
8. 疼痛是上天的安排。	1	2	3	4	5
9. 疼痛就是提醒我要接受現實。	1	2	3	4	5
10. 有疼痛表示我仍有感覺。	1	2	3	4	5

11. 疼痛令我生活消沉。	1	2	3	4	5
12. 疼痛提醒我要保重身體。	1	2	3	4	5
13. 疼痛令人感到遺憾。	1	2	3	4	5
14. 疼痛令人感到不適。	1	2	3	4	5
15. 疼痛是因為經絡不通。	1	2	3	4	5
16. 疼痛的基本原因是身體機能有問題。	1	2	3	4	5
17. 針灸可舒緩疼痛。	1	2	3	4	5
18. 即使癌症不痛也是十分痛苦的。	1	2	3	4	5
19. 我的疼痛是無法用筆墨形容的。	1	2	3	4	5

第五部份得分 ____

第六部份 疼痛的強度

總括來說，你疼痛的強度是多少？

10	痛到死
9	劇痛
8	入心入肺
7	不能忍受
6	難以形容
5	十分痛
4	好痛
3	尚能忍受
2	頗痛
1	微痛
0	無痛

第六部份得分 ____

APPENDIX 8

INFORMATION SHEET

The Relationship of Plasma β-endorphin level and Pain Dimensions in Chinese Cancer Pain Assessment Tool (CCPAT)

You are invited to participate in a study conducted by the School of Nursing in The Hong Kong Polytechnic University. The aim of this study is to explore the role of plasma beta-endorphin in pain assessment among patients with cancer pain. The study will involve completing questionnaires about your demographic data and pain assessment. You will then have a blood sample taken (4ml) to test the plasma beta endorphin level at 8 a.m. The testing should not result in any undue discomfort. The above procedures will take approximately 20 minutes. This procedure will be repeated at 8 p.m. on the same day.

All information related to you will remain confidential, and will be identifiable by codes only known to the researcher. All data collected will be used solely for this study. You have every right to withdraw from the study before or during the research without penalty of any kind. If you have any complaints about the conduct of this research study, please do not hesitate to contact Mr. Eric Chan, Secretary of the Human Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University in person or in writing (c/o Human Resources Office of the University). If you would like more information about this study, please contact Dr. Joanne Chung by calling telephone number 2766 6548.

It is hoped that this information will help scholars and healthcare workers to understand what role β-endorphin plays in pain assessment for patients suffering cancer pain, and thus facilitate more accurate assessment and management of cancer pain.

Thank you for your interest in participating in this study.

Dr. Joanne Chung
Principal Investigator / Chief Investigator

APPENDIX 9

CONSENT TO PARTICIPATE IN RESEARCH

The Relationship of Plasma β-endorphin level and Pain Dimensions in Chinese Cancer Pain Assessment Tool (CCPAT)

I _____ hereby consent to participate in the captioned research conducted by the School of Nursing, The Hong Kong Polytechnic University.

I understand that information obtained from this research may be used in future research and published. However, my right to privacy will be retained, i.e. my personal details will not be revealed.

The procedure as set out in the attached information sheet has been fully explained. I understand the benefit and risks involved. My participation in the project is voluntary.

I acknowledge that I have the right to question any part of the procedure and can withdraw from the study at any time without penalty of any kind.

Name of participant _____

Signature of participant _____

Name of researcher _____

Signature of researcher _____

Date _____

APPENDIX 10

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

School of Nursing 護理學院

有 關 資 料

血漿腦內啡呔在癌病疼痛中所扮演的角色

你好，我們謹代表香港理工大學護理學院誠邀你參與這項研究計劃。 這項研究的目的在於發掘腦內啡呔在華人癌症患者的疼痛評估中所扮演的角色。研究進行時,我們會要求你進行一項有關你的個人資料及疼痛評估的問卷調查;然後在上午八時正我們會為你抽取血液樣本（四毫升），以量度血漿腦內啡呔的濃度。在抽取血液樣本時你只會感到輕微而短暫的不適。整個程序須時大約二十分鐘，然後在下午八時正會再重複一次。

在研究中所有有關你的個人資料將會被保密處理，並會被編成只有研究人員才能理解的編碼保存，而且所有資料只會在這項研究中使會，不會外洩。你有絕對的權利在研究開始前或進行時要求退出，退出研究後你絕不會受到任何懲罰。

如果閣下對這項研究有任何投訴或意見，歡迎以書面或親身與香港理工大學人事倫理委員會秘書陳先生聯絡（請郵寄至以下地址轉交：香港理工大學 AG426 室，人力資源辦公室）。如果閣下希望獲得更多有關這項研究計劃的資料，歡迎於辦公時間內與鍾慧儀博士（電話：2766 6548）聯絡。
多謝閣下的參與！

鍾慧儀博士

研究主管 / 首席研究員

APPENDIX 11

參與研究同意書

血漿腦內啡呔在癌病疼痛中所扮演的角色

本人_____同意參加這項由香港理工大學護理學院負責執行的研究項目。

本人明白由這項研究所獲得的資料可能會被應用於未來的研究或學術交流，然而本人的個人資料將不會被洩漏，以確保本人的個人隱私。

本人已對所附資料的有關研究步驟有充分的理解，並清楚明白在研究過程中可能會出現風險，但本人是自願參與這項研究。

本人理解在研究過程中有權提出問題，並在任何時候決定退出研究，而不會受到任何不正常的對待或被追究責任。

參加者姓名：_____

參加者簽署：_____

研究人員姓名：_____

研究人員簽署：_____

日期：_____