THE FEASIBILITY OF CONTACT HEAT EVOKED POTENTIALS (CHEPs) IN EARLY DETECTION OF SYMPTOMATIC DIABETIC DISTAL SYMMETRIC POLYNEUROPATHY (DSP)

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The feasibility of contact heat evoked potentials (CHEPs) in early detection of symptomatic diabetic distal symmetric polyneuropathy (DSP)

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Certificate of Originality

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Abstract

Background: DSP is a common complication in diabetes, yet treatment for it has been disappointing. This may be because treatments typically target reducing pain rather than reducing nerve damage. Methods to identify types of nerve damage are available but too sophisticated and specialized. Therefore, quick, convenient, inexpensive method that can be used to identify type of nerve damage in patients suffering from DSP is needed.

Objective: To investigate the feasibility of using contact heat evoked potentials (CHEPs) as a detection tool for DSP.

Method: This study had 3 stages.

1st stage: The first stage was a systematic review of studies that have been published on the treatment effect of pain in diabetic neuropathy. Randomised controlled trials comparing topically and orally administered drugs with a placebo in adults with painful diabetic neuropathy were included. The primary outcome was dichotomous data for 50% or moderate pain reduction.

2nd stage: The second stage was a cross-sectional study testing the reliability of CHEPs. Twenty-two healthy adults were recruited. CHEPs were recorded using a 64-channel EEG cap. The peak stimulating temperature was 51℃. Two separate blocks of thermal stimulations were applied to dorsum of foot and 10cm proximal to lateral malleolus.

3rd stage: The third stage was a cross-sectional study. Thirteen healthy adults, 19 diabetic patients and 10 diabetic patients with lower limb symptoms were recruited. CHEPs were recorded at midline channels of healthy adults, and of diabetic patients with and without lower limb symptoms. The peak stimulating temperature of 51℃ was applied to dorsum of foot and 10cm proximal to lateral malleolus.

Results:

1st stage: Of the 31 relevant reports found, 25 reports were included and seven were excluded. Nearly 50% of patients with diabetic neuropathy had un-resolved pain when the treatment focused on pain intensity reduction. The effects of different classes of medications on particular damaged nerve are not known.

2nd stage: The Cronbach's alpha for first negative peak - first positive peak amplitude (N1-P1 amplitude) were 0.901 and 0.753 with stimulation of dorsum of foot and 10cm proximal to lateral malleolus respectively. The single measure intra-class coefficients for N1-P1 amplitude were 0.802 and 0.604 for stimulation of dorsum of foot and 10cm proximal to lateral malleolus respectively.

3rd stage: There was significant difference of N1-P1 amplitude among the three groups following stimulation of dorsum of foot ($p = 0.028$) and 10cm proximal to lateral malleolus ($p = 0.006$). Post hoc analysis showed that N1-P1 amplitude was significantly lower in diabetic patients with lower limb symptoms when compared to diabetic patients ($p = 0.006$) and healthy controls ($p = 0.014$) with stimulation of 10cm proximal to lateral malleolus.

Discussion: There may be loss of Aδ nerve fibres in diabetic patients with lower limb symptoms as reflected by significant reduction in the N1-P1 amplitudes of CHEPs. The results were consistent with morphological studies on nerves of diabetic patients with DSP; these studies have reported markedly reduction in intraepidermal nerve fibres density, a gold standard for diagnosing small fibre neuropathy, has been reported.

Conclusion: The treatment effects on reducing nerve damage in patients with painful DSP were not known. CHEPs are a reliable method for assessing the integrity of Aδ nerve fibres. Early identification of Aδ nerve fibres damage in DSP by CHEPs is feasible.

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List of Abbreviations

ALA	Alha-lipoic acid
CHEPs	Contace heat evoked potentials
DN	Diabetic neuropathy
DSP	Diabetic distal symmetric polyneuropathy
EEG	Electroencephalogram
IDDM	Insulin dependent diabetes mellitus
IENF	Intraepidermal nerve fibres
LEPs	Laser evoked potentials
NNT	Number needed to treat
OR	Odds Ratios
NADPH	Nicotinamide adenine dinucleotide
NCV	Nerve conduction velocity
NIDDM	Non-insulin dependent diabetes mellitus
NO	Nitrous oxide
RCT	Randomised controlled trials
SWME	Semmes-Weinstein monofilament examination
TCNS	Toronto clinical neuropathy score

Chapter 1
Introduction

1.1 Introduction

Distal symmetric polyneuropathy (DSP) is one of the most common complications of diabetes and affects 13-30% of the diabetic population (Young, Boulton, Williams, Mcleod, and Sonksen, 1993; Fedele et al., 1997; Sands, Shetterly, Franklin, and Hamman, 1997; Tapp et al., 2003). It usually progresses gradually and involves both small and large sensory fibres, with the deterioration of small-fibre function possibly being faster than that of large fibres (Smith, Ramachandran, Tripp, and Singlenton, 2001; Malik et al., 2005). Positive and negative symptoms in patients with DSP include pain, paraesthesia, numbness and loss of sensation (Partanen et al., 1995; Sorensen, Molyneaux, and Yue, 2002). These symptoms may appear intermittently when there is minimal DSP (Davies, Brophy, Williams, and Taylor, 2006), and early nerve damage may not be detectable by conventional diagnostic methods (Liu et al., 2005).

Disease-modifying therapies (Ward, Barnes, Fisher, and Jessop, 1971; Diabetes Control and Complications Trial Research Group [DCCT], 1993, 1995) and symptomatic treatments are used to stabilise DSP and can reduce pain intensity (Backonja et al., 1998; Kochar et al., 2004). However, treatment for DSP has been disappointing. This may be because treatment typically targets pain reduction rather than reduction in nerve damage. Methods to identify small nerve fibre damage such as skin biopsy are available but require a specially equipped laboratory and specially trained personnel. Therefore, a quick, convenient, inexpensive method that can be used to identify small nerve fibre damage in patients suffering from DSP is needed. The present study aimed to investigate whether there is small nerve fibre damage in diabetic patients with lower limb symptoms using contact heat evoked potentials (CHEPs).

This study consisted of three stages. In the first stage, a systematic review was conducted of studies that have been published on the treatment of pain in diabetic neuropathy. The purpose of that review was to evaluate the effect of symptomatic treatments for DSP to look further into the need for the early detection of DSP and identify types of nerve damage before the commencement of treatment. The details of this systematic review are presented in Chapter 6. In

the second stage, cross-sectional research was carried out to test the reliability of CHEPs and explore their characteristics in healthy adults. The results of this research are presented in Chapter 7. In the third stage, a cross-sectional study was conducted to determine whether there is small myelinated A-fibre damage in patients with minimal DSP using CHEPs. The study findings are given in Chapter 8.

1.2 Background to the study

DSP is a common complication of diabetes, and can have various symptoms. The annual cost of treating more than 5 million patients with symptomatic DSP in 2001 in the United States was USD 237 million (Gordois, Scuffham, Shearer, Oglesby, and Tobian, 2003). A comparison of health care costs amongst patients with no, mild, moderate and severe DSP reveals a substantial increase in costs with an increase in the severity of DSP (Currie et al., 2006).

Research conducted in the United States into the productivity of the diabetic working population with symptoms consistent with DSP has revealed that there

is a significant loss in productivity amongst symptomatic diabetic patients compared to asymptomatic ones (Candrilli, Davis, Kan, Lucero, and Rousculp, 2007; Stewart, Ricci, Chee, Hirsch, and Brandenburg, 2007). A study conducted in Europe found that reduced work time, disability and becoming unemployed or taking early retirement were significantly associated with increasing pain severity in patients suffering from DSP (Tölle, Xu, and Sadosky, 2006).

The frequency of physician visits is reported to increase with increasing pain severity amongst patients with painful DSP (Tölle, Xu, and Sadosky, 2006). Tölle, Xu and Sadosky (2006) found that more than 90% of 140 patients suffering from DSP received a medication prescription from their physician, and Gore, Brandenburg, Hoffman, Tai and Stacey (2006) revealed that the most commonly prescribed medications in such cases are opioids, NSAIDs, anticonvulsants and antidepressants. Despite the different classes of medications prescribed, it has been found that more than 50% of patients with painful DSP still suffer from moderate to severe pain (Gore, Brandenburg, Hoffman, Tai, and Stacey, 2006; Tölle, Xu, and Sadosky, 2006).

The effect of DSP-related pain on physical functioning and quality of life cannot be underestimated. Studies report that patients with painful DSP experience at least a moderate level of interference in physical function, including general activity, walking ability, enjoyment of life, normal work, mood and sleep (Tölle, Xu, and Sadosky, 2006; Hoffman, Sadosky, and Alvir, 2009) and greater interference in physical function with increasing pain severity (Hoffman, Sadosky, and Alvir, 2009). In addition, patients with painful DSP are reported to have higher levels of anxiety and depression compared to healthy controls (Gore, Brandenburg, Hoffman, Tai, and Stacey, 2006; Hoffman, Sadosky, and Alvir, 2008).

The suboptimal pain management amongst patients with symptomatic DSP, the considerable physical and psychological burden of these patients, and the huge economic costs associated with DSP indicate that there is an urgent need for better management of this condition. As there is a substantial increase in health care costs corresponding with an increase in the severity of DSP, the identification of DSP in the early stage and delay of the progression of the disease could at least minimise these costs.

1.3 Definition of relevant terms

1.3.1 Diabetes mellitus

Diabetes mellitus (DM) is related to the dysfunction of either insulin secretion or insulin action and is characterised by hyperglycaemia. Its diagnostic indicators include an abnormal plasma glucose level and symptoms of diabetes, the classic ones being polyuria, polydipsia and unexplained weight loss. Patients are diagnosed with diabetes mellitus if they fulfil one of the following criteria: diabetes symptoms and a causal plasma glucose concentration (obtained at any time of the day regardless of the last meal time) ≥ 200 mg/dl (11.1 mmol/l); a fasting plasma glucose level (no caloric intake for at least eight hours) ≥ 126 mg/dl (7.0 mmol/l); or a two-hour, post-load glucose level ≥ 200 mg/dl (11.1 mmol/l) in the oral glucose tolerance test (OGTT), which should follow the description issued by the World Health Organization (American Diabetes Association [ADA], 2005). There are two types of diabetes mellitus – insulin-dependent/Type 1 diabetes and non-insulin-dependent/Type 2 diabetes.

1.3.2 Insulin-dependent diabetes mellitus

Insulin-dependent (Type 1) diabetes is divided into immune-related and idiopathic diabetes and is usually diagnosed in juveniles. Excluding the idiopathic type of diabetes, complete insulin deficiency due to β-cell destruction is the main aetiology of insulin-dependent diabetic mellitus (ADA, 2005).

1.3.3 Non-insulin-dependent diabetes mellitus

Non-insulin-dependent (Type 2) diabetic mellitus is related to insulin resistance and relative insulin deficiency, and typically occurs in adults (ADA, 2005).

1.3.4 Diabetic distal symmetric polyneuropathy

In this study, the classification and staging of distal symmetric polyneuropathy are based on the Toronto Clinical Neuropathy Score (TCNS).

1.3.5 Painful diabetic distal symmetric polyneuropathy

Diabetics with painful DSP were taken in the study reported herein to be those who had had intermittent or persistent painful lower limb symptoms for at least three months at the time of examination.

1.4 Research problem

DSP is a worldwide problem (Young et al., 1993; Partanen et al., 1995; Fedele et al., 1997; Herman et al., 1998; Saadi et al., 2007; Pradeepa, Rema, Vignesh, Deepa, and Mohan, 2008). Neuropathic pain symptoms are reported in 3-20% of patients with DSP (Boulton, Knight, Drury, and Ward, 1985; Partanen et al., 1995; Sorensen et al., 2002; Daousi et al., 2004). Symptoms include pain paroxysms, deep aching pain (Otto, Bak, Bach, Jensen, and Sindrup, 2003), hot or burning pain, and pain that feels electric, sharp, achy, tingling, cold, dull or tight (Galer, Gianas, and Jensen, 2000). These symptoms are thought to be related to small nerve fibre damage or dysfunction. During the progression of neuropathy, they can appear intermittently or continuously (Galer et al., 2000);

hence, the alteration in nerve function might not match the symptoms.

Morphological studies show that diabetic neuropathy involves both small and large nerve fibre damage, and that the abnormal rate of the former is higher than the abnormal rate of the latter (Smith et al., 2001; Shun et al., 2004; Malik et al., 2005; Sorensen, Molyneaux, and Yue, 2006; Løseth, Stålberg, Jorde, and Mellgren, 2008). The involvement of small fibres well before large ones in the early stages of diabetes has been reported in clinical studies (Dyck et al., 2000; Sumner et al., 2003)

Various methods have been developed to examine the integrity of small nerve fibres, including laser evoked potentials (LEPs), sural nerve biopsy, skin biopsy, quantitative sensory testing (QST), the current perception threshold test and corneal confocal microscopy. However, these tests have limitations: LEPs can cause superficial burns (Bromm and Treede, 1983); small myelinated fibres cannot be distinguished from large ones with sural nerve biopsy (Malik et al., 2005); QST quantifies the severity of nerve damage but has limited ability to target the type of individual fibre that could benefit from therapeutic intervention. Thermal perception and threshold test is one of the QST and it is used to assess

the function of small myelinated and unmyelinated nerve fibres (Annonymous, 1988), the intra-individual variation of thermal threshold is low (Jamal, Hansen, Weir, & Ballantyne, 1985) and the sensitivity was 72% in patient with small fibre neuropathy (Shukla et al., 2005); however QST rely on patient subjective report and the result may be affected by distraction and tired during the procedure. Corneal confocal microscopy can only differentiate between severe and no neuropathy (Quattrini et al., 2007). Amongst these tests, quantifying intraepidermal nerve fibre density by skin biopsy is useful and can be used to assess peripheral nerve injury. Unfortunately, this requires a specific kind of laboratory that is available only in major research institutes (Sorensen et al., 2006).

In clinical settings, the management of DSP takes two main routes: disease-modifying therapies, such as glycaemic control, and symptomatic treatment. Although various treatment modalities are available, the improvement of the condition of small nerve fibres has not yet been objectively demonstrated, which may be related to the commencement of treatment in the advanced rather than the early stage of nerve fibre damage or the lack of a valid and reliable objective diagnostic test for the early detection of small nerve fibre damage and

monitoring of disease progression. Accurate and early detection of DSP is important to identify at-risk patients, anticipate deterioration, access new pharmacological and non-pharmacological therapies, promote the awareness of diabetic management and improve the quality of life of patients.

1.5 Study aim

The aim of this study was to investigate whether there is nerve damage in diabetics with lower limb symptoms.

1.6 Research questions

1.6.1 Stage 1

1) What are the effects of symptomatic treatments amongst patients with DSP?

2) Are there effective treatments for patients with the symptoms of DSP?

1.6.2 Stage 2

1) Are CHEPs a reliable method, in terms of the intraclass correlation coefficient (ICC) and Cronbach's alpha, for assessing the integrity of small myelinated fibres?
2) What is the reproducibility of CHEPs in terms of percentage at different sites in the lower extremities of healthy adults?
3) What is the relationship between pain intensity ratings and CHEP amplitudes at different sites in the lower extremities of healthy adults?
4) What is the relationship between body height and CHEP latencies at different sites in the lower extremities of healthy adults?

1.6.3 Stage 3

1) Are there differences in CHEP amplitudes and latencies amongst healthy adults and diabetic patients with and without lower limb symptoms?
2) Are there differences in CHEP amplitudes and latencies between healthy adults and diabetic patients with lower limb symptoms?
3) Are there differences in CHEP amplitudes and latencies between diabetic patients with and without lower limb symptoms?

1.7 Research hypotheses

1.7.1 Stage 1

No research hypothesis was posited in stage 1 because it was a systematic review.

1.7.2 Stage 2

1) CHEPs are a reliable method to assess the integrity of small myelinated fibres.
2) A positive relationship exists between pain intensity rating and CHEP amplitudes at different sites in the lower extremities.
3) A positive relationship exists between body height and CHEP latencies at different sites in the lower extremities.

1.7.3 Stage 3

1) CHEP amplitudes are lower amongst diabetic patients with lower limb symptoms compared to those without lower limb symptoms and healthy adults.
2) CHEP latencies are longer amongst diabetic patients with lower limb symptoms compared to those without lower limb symptoms and healthy adults.

1.8 Delimitation

Small nerve fibre damage is found in early-stage DSP (Løseth et al., 2008), and only skin biopsy, an invasive procedure, can identify such damage in patients with mild DSP (Sorensen et al., 2006). LEPs can activate small nerve fibres and assess their function; however, this method is seldom used in the diabetic population because it causes superficial burns (Bromm and Treede, 1983). Another convenient method, confocal corneal microscopy, cannot differentiate between no and mild neuropathy (Malik et al., 2003; Quattrini et al., 2007). CHEPs, however, are a non-invasive, convenient, inexpensive method that can be used to detect small nerve fibre damage, and the equipment required to carry out this assessment is commonly available in the electrodiagnostic unit of hospitals, clinics and research institutes.

Various classes of medications are used to treat symptomatic DSP; however, the evaluation of their efficacy by an objective measure of small nerve fibre function cannot be identified. CHEPs can become a surrogate outcome measure of small nerve fibre damage in pharmacological studies in clinical and academic settings. Also, early detection and intervention are crucial for many acute and chronic

diseases. Regular screening for diabetic complications is provided in many countries. CHEPs can be used as a screening tool to assess small nerve fibre damage to identify at-risk patients and thus enable early intervention.

1.9 Organisation of the thesis

In Chapter 1, the background of the study, statement of the problem, research questions, research hypotheses and delimitations of the study have been presented. The literature on diabetic neuropathy and painful DSP is reviewed in Chapters 2 and 3, respectively. The conceptual framework of the study is presented in Chapter 4. The methods and procedures, results, discussions and conclusions for the first, second, and third stages of the study are presented in Chapters 5, 6 and 7, respectively. In Chapter 8, the major findings are summarised and the conclusion is given.

Chapter 2
Literature Review on
Diabetic Distal Symmetric Polyneuropathy

2.1 Introduction

Diabetic distal symmetric neuropathy (DSP) is one of the most common complications of diabetes and represents a major health problem worldwide (Young et al., 1993; Fedele et al., 1997; Sands et al., 1997; Tapp et al., 2003). This review will introduce the classification scheme of diabetic neuropathy proposed by Thomas (1997) and staging systems for DSP. The epidemiology, natural history and pathogenesis of DSP will be explored, and the existing treatment modalities for DSP will be examined.

2.2 Epidemiology of diabetic distal symmetric polyneuropathy (DSP)

2.2.1 Prevalence

DSP is a common complication of diabetes. An Australian study of diabetes complications reported that, based on assessment that included the neuropathy deficit score, neuropathy symptom score, pressure perception test results and drop in blood pressure, 13.1% of known patients with non-insulin-dependent diabetes mellitus (NIDDM) and 7.1% of newly diagnosed with NIDDM had neuropathy (Tapp et al., 2003). A multi-centre, hospital clinic-based study of the prevalence of DSP in the United Kingdom showed that, based on assessment using the neuropathy disability score and neuropathy symptom score, 32.1% of 3949 NIDDM patients and 22.7% of 2414 insulin-dependent diabetic mellitus (IDDM) patients had DSP (Young et al., 1993). Another UK multi-centre study reported a higher prevalence, with 32.3% of 8757 diabetic patients diagnosed as having DSP using the diabetic neuropathy index (Fedele et al., 1997). A diabetic complications study in Egypt used the vibration perception threshold to define DSP and reported that 22% and 18% of known and newly diagnosed diabetic patients,

respectively, suffered from DSP (Herman et al., 1998). One study found that, based on clinical neuropathic symptoms and nerve conduction studies, 8.3% of 86 patients with newly diagnosed NIDDM had DSP (Partanen et al., 1995). Using the diabetic neuropathy score and diabetic neuropathy examination score to define DSP in their study in the United Arab Emirates, Saadi and colleagues (2007) reported that 34.7% amongst 57 diabetics had DSP.

An epidemiological study in India reported that, based on the vibration perception threshold at the distal plantar surface of bilateral great toes, 13.6% and 11.2% of known and newly diagnosed NIDDM patients, respectively, suffered from DSP (Pradeepa et al., 2008). A hospital-based study in Singapore reported that 32.6% of 135 diabetic patients of different races suffered from DSP (Lee, Tey, and Chew, 1993). DSP was found in 11.1% of 558 Chinese NIDDM patients in a Taiwanese study that used the 10 g monofilament test, a neurometer and the vibration perception test to assess DSP (Cheng et al., 1999).

Bao and colleagues explored the prevalence of DSP in 38 Hong Kong IDDM children/youth aged 4-21 years, and reported that based on the results of nerve conduction studies of 14 nerves, 68.4% had DSP (Bao, Wong, Wang, and Low, 1999). Ko and colleagues conducted an 18-month clinic-based cross-sectional study to investigate the prevalence of DSP in 150 Hong Kong diabetic patients aged below 40 years, and found that 6.7% of 45 IDDM patients and 7.6% of 105 NIDDM patients had DSP using the monofilament and vibration perception tests to detect DSP (Ko, Chan, Lau, and Cockram, 1999).

2.2.2 Incidence

The San Luis Valley Diabetes Study (Sands et al., 1997) found that 66 of 231 NIDDM patients who had no signs or symptoms of neuropathy at baseline assessment had developed distal symmetrical neuropathy by their 4.7-year follow-up visit and that the overall incidence rate of distal symmetrical neuropathy was 6.1 per 100 person years. A 10-year follow-up study in Spain showed that the incidence rate of neuropathy in NIDDM patients was 39 per 1000 person years (Mundet et al., 2008).

The prevalence of DSP is found to vary from 8% to 35%, possibly because of the variation in the criteria used to define DSP between studies. The high prevalence of DSP indicates the need to prevent its development in the diabetic population and to develop early detection and intervention methods to reduce the healthcare burden associated with this condition.

2.2.3 Risk factors

The risk of developing DSP increases with the duration of diabetes (Young et al., 1993; Partanen et al., 1995; Fedele et al., 1997; Valensi, Giroux, Seeboth-Ghalayini, and Attali, 1997; Cheng et al., 1999; Tapp et al., 2003) and poor glycaemic control (Partanen et al., 1995; Valensi et al., 1997; Herman et al., 1998). Age (Young et al., 1993; Fedele et al., 1997; Valensi et al., 1997; Herman et al., 1998; Cheng et al., 1999; Tapp et al., 2003), height (Tapp et al., 2003), high uric acid levels (Tapp et al., 2003), increased insulin consumption (Sands et al., 1997), having a history of angina pectoris and smoking (Sands et al., 1997) are also risk factors for neuropathy. Partanen and colleagues (1995) found that patients with hypoinsulinemia tended to develop polyneuropathy.

2.2.4 Clinical course

Boulton et al. (1985) found that the prevalence of DSP in IDDM patients was 10.7%, while Partanen et al. (1995) found that 8.3% of 88 newly diagnosed NIDDM patients aged between 45 and 64 had DSP, and that the prevalence of DSP was 20.9% in the same group of patients after 10 years. DSP has been confirmed amongst 8.3-18% of patients at the time of diagnosis of NIDDM, and may be associated with the prolonged period of hyperglycaemia in these patients before the presentation of NIDDM (Partanen et al., 1995; Herman et al., 1998).

2.2.5 Clinical features

DSP involves small and large sensory fibres and usually progresses gradually. Patients may experience neuropathic pain or lose the ability to sense pain or temperature. The classic symptoms show ‘glove and stocking’ distribution: in the upper extremities, they start distally in the fingertips and move up proximally to the hands and arms, while in the lower extremities, they start in the toes and progress upward (Greene, Stevens, and Feldman,

1999). However, the intensity and diversity of symptoms vary amongst diabetic patients – some experience minor tingling in one or two toes whereas others suffer from severe painful neuropathy (Tesfaye, 2007).

2.3 Classification of diabetic neuropathy

Numerous classification schemes of the various syndromes of diabetic neuropathy (DN) have been proposed in recent years, including those based on clinical patterns (Kelkar, 2005; Sinnreich, Taylor, and Dyck, 2005), disturbance of the peripheral nervous system (Thomas, 1997) and pathophysiology (Dyck, Davies, Litchy, and O'Brien, 1997; Sinnreich et al., 2005). Because the pathophysiology of DN is still unclear, it is better to classify DN based on clinical patterns or disturbance of the peripheral nervous system than on pathophysiology. Sinnreich and colleagues (2005) proposed a DN classification system based on the symmetry of the neuropathy and subdivided the resulting types into more than 10 subtypes of neuropathy. That system is useful but difficult to follow compared with the one proposed by Thomas (1997), which was, therefore, used in this review (Table 2.1).

Table 2.1 Classification of diabetic neuropathy

Hyperglycaemic neuropathy
Symmetric polyneuropathy
Sensory/autonomic polyneuropathy
Acute painful diabetic neuropathy
Focal and multifocal neuropathy
Cranial neuropathy
Thoracoabdominal neuropathy
Focal limb neuropathies
Diabetic amyotrophy
Mixed forms

Adapted from "Classification, differential diagnosis, and staging of diabetic peripheral neuropathy," by P. K. Thomas, 1997, *Diabetes*, *46*(Suppl. 2), p.S54.

2.3.1 Hyperglycaemic neuropathy

Gregersen (1968) reported an increase in peroneal motor nerve conduction velocity (NCV) after insulin treatment for 8-35 days in 13 newly diagnosed and untreated diabetes patients, none of whom had clinical symptoms of neuropathy at baseline. Terasawa and colleagues (2006) described a patient

with hyperglycaemic neuropathy: a 66-year-old woman with systemic lupus erythematosus (SLE) was admitted to hospital because of subacute bilateral leg numbness and gait disturbance, and investigation revealed hyperglycaemia and a decrease in NCV compatible with demyelinative neuropathy. NCV increased rapidly over one week of insulin treatment. This rapid improvement after good glycaemic control indicates that the structural change of the nerve was not permanent (Thomas, 1997).

2.3.2 Symmetric polyneuropathy

Acute painful DN and DSP are subclasses of symmetric polyneuropathy. Archer and colleagues (1983) described a series of patients with acute painful DN, all of whom had profound weight loss followed by distal lower limb burning pain, especially at night. Another diabetic patient developed acute painful DN after intensive insulin treatment, presenting with pain and a burning sensation in the lower limbs (Guldiken et al., 2004). Studies show that the painful neuropathic symptoms of newly diagnosed diabetics decrease after good glycaemic control (Castellanos et al., 1996; Vital et al., 1997).

In contrast to acute painful DN, the onset of DSP is insidious and the manifestations are more persistent. It is a predominantly sensory and autonomic type of symmetric polyneuropathy (Thomas, 1997), and is a common form of DN.

2.3.3 Focal and multifocal neuropathy

Cranial neuropathy. The nerves supplying the external ocular muscles are commonly involved in cranial neuropathy (Boulton, Arezzo, Malik, and Sosenko, 2004). This condition is thought to be related to microvascular infarct, and resolves spontaneously after a few months in the majority of patients (Boulton et al., 2005).

Thoracoabdominal neuropathy. Lauria and colleagues (2005) described diabetic truncal neuropathy in three patients, all of whom experienced sudden sharp or burning pain over the trunk and had an increased vibration threshold in the distal extremities. A nerve conduction study showed sensory polyneuropathy in two patients and axonal sensory-motor polyneuropathy in the other one, while skin biopsy revealed a reduction in

both epidermal and dermal nerve fibres in the related region in two patients and a reduced number of intraepidermal nerve fibres in the other one.

Focal limb neuropathies. Focal limb neuropathies are usually related to nerve entrapment and develop in more than one third of diabetics. The nerves commonly involved are the ulnar, median, peroneal and medial plantar nerves (Boulton et al., 2005).

Diabetic amyotrophy (lumbosacral radiculoplexus neuropathy). Diabetic amyotrophy was first reported by Bruns in 1890 in three diabetic patients, and the subsequent description of this condition was in 1953 by Garland and Taverner (cited in Davidson, Travis, and Bernier, 2003). The pathophysiology of amyotrophy may be related to an immune-mediated inflammatory response (Kelkar, Masood, and Parry, 2000). Clinically, it usually presents with asymmetrical proximal muscle weakness, decreased deep tendon reflexes and denervation. Treatment focuses on pain control, physical therapy and glycaemic control (Davidson et al., 2003).

In summary, NCV can be increased by intensive glycaemic control in

patients with hyperglycaemic neuropathy. However, intensive glycaemic control can induce acute painful neuropathy. Profound weight loss and burning pain in the lower extremities are typical symptoms of acute painful neuropathy. Focal and multifocal neuropathies are relatively less reported. DSP is a commonly reported type of diabetic neuropathy.

2.4 Diagnosis and staging of DSP

DSP is defined as progressive nerve fibre damage and loss, especially in the distal part of the sensory, autonomic and motor nerves, which proceeds proximally. At the San Antonio conference on diabetic neuropathy in 1988, the American Diabetes Association and American Academy of Neurology concluded that the diagnosis of DSP should be based on symptoms, neurological examination, sensory loss, autonomic function and electrophysiological investigation (Anonymous, 1988).

2.4.1 Rochester neuropathy scoring system

The Rochester neuropathy scoring system uses the neuropathy symptom profile, neuropathy symptom score and neuropathy disability score. Based on information obtained from a nerve conduction study, the neuropathy disability score, quantitative sensory testing (QST) and the neuropathy symptom score, DSP is staged as follows: stage 0 (no neuropathy), stage 1 (asymptomatic neuropathy), stage 2 (symptomatic neuropathy) and stage 3 (disabling neuropathy) (Dyck, 1988). The reproducibility of this staging system was confirmed by the Rochester Diabetic Neuropathy Study (Dyck et al., 1991).

2.4.2 Diabetic neuropathy score

Neuropathological assessment based on the recommendations of the San Antonio conference and Dyck (1988) is valuable; however, it is time consuming and requires much manpower in routine clinical screening. A two-step method was developed at the University of Michigan to address these problems. The first step consists of a 15-item questionnaire on foot

sensation and a brief clinical examination including foot inspection, vibration sensation assessment at the dorsum of the great toe, and grading of ankle reflexes that can be performed by a non-neurologist or nurse practitioner. The patient is referred to a neurologist if his or her score in the first step is greater than 2. The second step includes a clinical neurological examination, nerve conduction study and QST. The quantitative examination score is combined with the results of the abnormal nerve conduction test to produce the diabetic neuropathy score. It takes about 45 minutes to complete this step (Feldman et al., 1994); however, the equipment for a nerve conduction study may not be available in every clinical setting.

2.4.3 Toronto clinical neuropathy score

Another diagnostic and staging method, the Toronto Clinical Neuropathy Score (TCNS), was developed for routine screening for DSP, and comprises symptom, reflex and sensory test scores. The maximum TCNS has a value of 19 points, and a score greater than five are classified as having diabetic symmetric polyneuropathy (Perkins et al., 2001). This method has been

validated for the cross-sectional prediction of the electrophysiological and morphological severity of DSP. The TCNS showed a significant negative correlation with sural nerve fibre density (r^2 = -0.479, $p < 0.0001$), summed amplitude of nerve conduction study (r^2 = -0.386, $p < 0.0003$) and summed conduction velocity (r^2 = -0.283, $p = 0.0086$) (Bril and Perkins, 2002). It has been used as an outcome measure and diagnostic tool in various studies (Zinman et al., 2004; Bril and Buchnana, 2006; Manschot et al., 2008; O'Donnell et al., 2008).

2.4.4 Definition of distal symmetric polyneuropathy for clinical research

In 2005, the American Academy of Neurology developed a definition of DSP to guide research studies. They proposed that, to achieve the most accurate diagnosis of DSP, signs, symptoms and electrophysiological findings should be considered. They pointed out that symptoms alone have relatively poor diagnostic accuracy, whereas combinations of signs are better in predicting the presence of polyneuropathy. They also stated that a nerve conduction study is crucial in making a diagnosis because it is a sensitive, specific and validated measure, and, therefore, electrodiagnostic

studies should be part of clinical research but not a requirement for field or epidemiologic studies. Finally, they proposed that subjects should have an ordinal likelihood of ++++ and ++ for clinical research and epidemiologic studies, respectively (Table 2.2) (England et al., 2005).

Table 2.2

Estimated likelihood of distal symmetric polyneuropathy for case definition

Condition 1	Condition 2	Condition 3	Condition 4	Condition 5	Conclusion
Neuropathic symptoms	**Decreased or absent ankle reflexes**	**Decreased distal sensation**	**Distal muscle weakness or atrophy**	**Nerve conduction studies**	**Ordinal likelihood**
Present	Present	Present	Present	Abnormal	++++
Absent	Present	Present	Present	Abnormal	++++
Present	Present	Present	Absent	Abnormal	++++
Present	Present	Absent	Absent	Abnormal	++++
Present	Absent	Present	Absent	Abnormal	++++
Absent	Present	Absent	Present	Abnormal	+++
Present	Absent	Absent	Absent	Abnormal	+++
Absent	Absent	Absent	Absent	Abnormal	++
Absent	Present	Absent	Absent	Abnormal	++
Present	Present	Present	Absent	Normal	++
Present	Absent	Present	Absent	Normal	+
Present	Present	Present	Present	Normal	-

Adapted from "Distal symmetric polyneuropathy: A definition for clinical research. Report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation," by J. D. England et al., 2005, *American Academy of Neurology*, *64*, p.201.

2.5 Pathogenesis of diabetic neuropathy

2.5.1 Hyperglycaemia

The pathogenesis of DN is multifactorial; however, the primary cause of diabetic neuropathy is thought to be hyperglycaemia (Biller and Bogousslavaky, 2001). Motor and sensory NCV are reported to be slower in NIDDM patients compared with age-matched non-diabetic controls (Ward et al., 1971; Graf et al., 1981). Ward and colleagues (1971) found that 4 out of 39 newly diagnosed diabetics (10%) had clinically apparent peripheral neuropathy. A longitudinal study of patients with predominantly NIDDM from the Rochester cohort found that the duration of diabetes determined the severity of neuropathy (Dyck et al., 1993). Tight glycaemic control by intensified insulin therapy (DCCT, 1993, 1995), pancreatic transplantation (Navarro, Sutherland, and Kenedy, 1997) and islet cell transplantation (Lee et al., 2005; Warnock et al., 2008) successfully delay the onset and slow the progression of neuropathy in IDDM patients. Hyperglycaemia has been proposed to damage the peripheral nerves in several ways by increasing polyol pathway activity and contributing to the formation of advanced

glycation end products (AGE) and free radicals.

2.5.2 Polyol pathway and aldose reductase

Glucose uptake to peripheral nerves is not insulin dependent and thus is proportional to the ambient blood glucose concentration. When the level of blood glucose increases, it is channeled through the polyol pathway. Aldose reductase is one of the enzymes participating in this pathway. It is expressed by the Schwann cells and has a low affinity for glucose. When the blood glucose level is high, aldose reductase converts glucose to sorbitol, which then metabolises to fructose by sorbitol dehydrogenase. Sorbitol and fructose are relatively impermeable to the nerve membrane and accumulate within the nerve, causing nerve damage (Apfel, 1999).

2.5.3 Oxidative stress

Oxidative stress and a decrease in nitrous oxide (NO) are found to be associated with DN. Oxidative stress may be related to the depletion of glutathione and nicotinamide adenine dinucleotide (NADPH), which is a

co-factor in the regeneration of glutathione (Figueroa-Romero, Sadidi, and Feldman, 2008). Glutathione functions mainly as an antioxidant and thus protects against oxidative stress (Vincent, Russell, Low, and Feldman, 2004). The depletion of NADPH inhibits the synthesis of NO and reduces the ability of glutathione to neutralise oxygen free radicals, and thus results in nerve damage. Decreases in NO can lead to vascular insufficiency and subsequently impaired blood supply to the nerves (Yagihashi, Yamagishi, and Wada, 2007).

2.5.4 Advanced glycation end products

Advanced glycation end products (AGE) are proposed to be one of the contributing factors in DN. Hyperglycaemia increases the glycation of intracellular proteins, especially in insulin-independent tissue or nerves, resulting in nerve damage (Vlassara and Palace, 2002). The glycation of various nerve proteins can impair nerve function in different ways, such as modifying tubulin, which interferes with axonal transport. AGE can induce oxidative stress, which impairs microvascular reactivity and nerve blood flow (Sugimoto, Yasujima, and Yagihashi, 2008).

In summary, hyperglycaemia, the polyol pathway and aldose reductase, AGE and oxidative stress contribute to DN. However, no individual factor is responsible. Identifying the chain effects of each factor would increase the understanding of the aetiology of DN.

2.6 Treatment of diabetic distal symmetric polyneuropathy

Preventive measures and symptom control are commonly used to manage DN. Good glycaemic control is the mainstay of treatment to delay or prevent the onset of neuropathy, while medications including tricyclic compounds, anticonvulsants, ion channel blockers and topical agents are commonly used to control the symptoms of neuropathic pain.

2.6.1 Glycaemic control

Tight glycaemic control has been shown to be effective in slowing the progress of DN. Ward and colleagues (1971) reported that the popliteal and median motor NCV of 39 diabetics improved after six months of disease

control. In the Diabetes Control and Complications Trial, 1441 IDDM patients were randomly assigned to tight glucose and conventional insulin therapy groups. The results of clinical examination, autonomic testing and nerve conduction studies demonstrated that tight glycaemic control delayed the onset and slowed the progression of neuropathy. However, adverse effects including severe hypoglycaemia and weight gain were reported in the tight glycaemic group (DCCT, 1993, 1995). A similar study with 102 IDDM patients also found that tight glycaemic control slowed the progression of neuropathy (Reichard, Nilsson, and Rosenqvist, 1993), while Ohkubo and colleagues (1995) confirmed the positive effect of tight glycaemic control in patients with NIDDM.

2.6.2 Vascular endothelial growth factor gene transfer

A randomised, double-blind controlled trial with 43 NIDDM and 7 IDDM patients with lower limb symptoms investigated vascular endothelial growth factor gene transfer (Ropper et al., 2009). There were significant improvements in symptom scores and pain ratings in the gene transfer group, whereas the nerve conduction study, thermal threshold and vibration

threshold test results revealed no significant effect. However, although the pain intensity rating and symptom scores decreased, serious adverse events including myocardial ischemia, congestive heart failure, stroke and colorectal bleeding occurred in the treatment group (Ropper et al., 2009).

2.6.3 Islet transplantation

Islet transplantation has been shown to improve glycaemic control in IDDM patients. The procedure has also been found to stabilise or slightly improve diabetes-induced retinopathy and neuropathy based on nerve conduction studies conducted one year after the procedure (Lee et al., 2005; Warnock et al., 2008).

2.6.4 Aldose reductase inhibitors

A systematic review was conducted of 32 randomised controlled trials that investigated the effects of aldose reductase inhibitors in 879 patients with DN. All patients in these studies received the medications for six months, and no significant improvement in NCV or neuropathic symptoms was

reported. Dose-limiting adverse events such as severe hypersensitivity reactions led to the withdrawal of some patients from the studies (Chalk, Benstead, and Moore, 2007).

2.6.5 Alpha-lipoic acid

A meta-analysis was performed of four randomised controlled trials that examined the effects of alpha-lipoic acid (ALA) in 1258 diabetic patients with symptomatic polyneuropathy. All patients in these studies received a 600 mg intravenous infusion of ALA daily for three weeks. Significant improvement was found in the Total Symptom Score (TSS), individual symptoms including pain, burning and numbness, and some of the items in the neuropathy impairment score such as pinprick and touch-pressure sensation and ankle reflexes (Ziegler, Howak, Kempiert, Vargha, and Low, 2004). The effect of oral treatment with ALA has also been explored. The SYDNEY 2 trial, a dose-response, randomised, double-blind, placebo-controlled study, investigated the effect of taking 600 mg, 1200 mg, or 1800 mg of ALA for five weeks in 181 diabetic patients with symptomatic polyneuropathy. Significant improvement was found in the

TSS, individual symptoms including stabbing and burning pain, the sensory function subtest of the neuropathy impairment score, and the number, severity and change in the Neuropathy Symptoms and Change (NSC) score. The most frequent adverse event was dose-dependent nausea, which affected 13-48% of patients in the three groups (Ziegler et al., 2006). Another open label study, which was conducted in Korea, involved the oral administration of 600 mg ALA daily to 61 diabetic patients with symptomatic polyneuropathy for eight weeks, and reported similar results for the TSS (Haham, Kim, and Kim, 2004).

2.7 Summary

DSP is one of the most common complications in patients with diabetes. Compared to other composite scoring systems for grading the severity of neuropathy, the Toronto Clinical Neuropathy Score is simple, easy to use and less time consuming, and thus it was used as a screening tool in this study.

Tight glycaemic control and islet transplantation in IDDM patients are effective in stabilising DSP. Vascular endothelial growth factor gene transfer was found to

improve symptoms in IDDM and NIDDM patients, but is associated with severe adverse events including myocardial infarction. The results of the use of aldose reductase inhibitors to treat DSP are not promising. ALA, however, was found to be useful in treating symptomatic polyneuropathy.

Neuropathic symptoms are mostly related to small nerve fibre damage; however, objective outcome measures are seldom employed in clinical trials, which may be related to the lack of valid and reliable methods for examining small fibre function. Although the pathogenesis of DSP is still unclear, the involvement of small nerve fibres in the early stage of DSP has been documented, with symptoms of impairment including pain, paraesthesia and numbness, amongst others.

In the next chapter, a literature review was conducted to explore the prevalence, presentation and clinical course of symptomatic DSP, the morphological changes associated with this condition, and diagnostic tests and treatment modalities for it.

Chapter 3
Literature Review of
Symptomatic Diabetic Polyneuropathy

3.1 Introduction

Pain is the predominant symptom in patients with small and large fibre neuropathy (Periquet et al., 1999). Periquet et al. (1999) found a reduction in pinprick and light touch sensation and vibration detection in patients classified with large and small fibre neuropathy where pain was the predominant symptom. The epidemiology, potential mechanisms and treatments for painful DSP and methods for examining the pain pathway will be described in detail in this chapter.

3.2 Epidemiology of painful diabetic symmetrical polyneuropathy

3.2.1 Prevalence

Neuropathic pain symptoms are commonly reported by patients with DSP; however, the prevalence of painful DSP has not been fully investigated. Partanen and colleagues (1995) found that amongst 132 patients newly diagnosed with NIDDM, 7-13% had pain and paraesthesia. In the same patient group 10 years after diagnosis, the prevalence of pain and paraesthesia was 20% and 33%, respectively. In a study involving 2610 NIDDM patients, Sorensen and colleagues (2002) found that painful neuropathy was present in 11.4% of those who had a vibration perception threshold $\geq$ 30v and in 3.3% of those who had a vibration perception threshold < 30. A cross-sectional study conducted in the United Kingdom reported that 26.4% of 269 NIDDM patients with DSP experienced some degree of pain, and found that amongst the patients classified as having no neuropathy using the Toronto Clinical Neuropathy Scoring System, 7.4% did report pain (Davies et al., 2006).

3.2.2 Risk factors

Duration of diabetes, glycaemic control and the length of peripheral nerves are more likely to predict insensate than painful neuropathy. However, patients are likely to develop painful symptoms within the first few years after the onset of diabetes (Sorensen et al., 2002). A prospective survey showed that 61% and 56% of 105 patients with painful DN had a family history of DN and painful DN, respectively (Galer et al., 2000).

3.2.3 Natural history

Boulton and colleagues (1983) investigated 36 patients who had painful DN, and found that the pain score, ankle pressure index and peroneal nerve motor conduction velocity had not changed at the four-year follow-up. Another study investigated 132 newly diagnosed NIDDM patients and found that 7-13% of them had pain and paraesthesia. After 10 years, amongst the 86 patients who remained in this study, 20% and 33% had pain and paraesthesia, respectively, and over this period an increasing number of patients experienced an absence of Achilles tendon reflex and loss of

vibration sensation (Partanen et al., 1995). Galer and colleagues (2000) reported that amongst 104 patients, 72% experienced increasing pain, 12% a decrease in pain and 15% no change in their pain condition following the onset of painful DN.

3.2.4 Clinical features

The neuropathic pain symptoms associated with DSP include burning and shooting pain, allodynia and paraesthesia/dysaesthesia. In a prospective study of 133 patients with NIDDM, pain and paraesthesia were frequently observed in patients, and defined as neuropathy (Partanen et al., 1995). Sorensen and colleagues (2002) found that there was both significant overlap and differences in positive and negative symptoms of neuropathy. In another study, 77% of 35 patients with painful diabetic neuropathy reported pain paroxysms compared with 46% of 46 patients with non-diabetic painful neuropathy; deep aching pain was the most common pain symptom experienced by nearly 31% and 71% of patients with non-diabetic and diabetic painful neuropathy, respectively; and dynamic mechanical and thermal hypaestesia was reported by less than 40% of diabetic and

non-diabetic patients (Otto et al., 2003). The survey of Galer et al. (2000), however, revealed that 53% and 64% of patients with diabetic painful neuropathy had constant pain and hot or burning pain, respectively, while aching was reported by 50% of patients and bilateral neuropathic symptoms by more than 90%. Regarding temporal patterns of pain, Davies et al. (2006) reported that patients with mild DSP felt pain occasionally whereas those with moderate to severe DSP felt pain continuously with intermittent exacerbation.

Amongst the various symptoms of diabetic peripheral neuropathy, paraesthesia of the feet and urination difficulties were correlated in one study with the loss of light touch sensation, based on the results of the Semmes-Weinstein monofilament examination (SWME) (5.07/10 g [odds ratio (OR) 8.67, 2.23-33.62] and 4.3/2 g [OR 5.64, 1.64-19.36] monofilaments) (Kamei et al., 2005). Not all patients with burning pain in the feet have a higher thermal threshold (Smith, Ali, and Fowler, 1991). In one study, patients with painful diabetic neuropathy had a higher vibration perception threshold compared with the non-painful group (Sorensen et al., 2002). Research indicates that pain in diabetic neuropathy is always

associated with small fibre dysfunction (Lanting et al., 1989).

3.2.5 Impact on quality of life

Only a few studies have investigated the quality of life of patients living with painful DN. Galer and colleagues (2000) reported that more than 50% of 104 patients with painful DN had impaired physical mobility, working ability, sleep quality and psychosocial wellbeing. Another study found that patients with painful DN had poor sleep quality, perceived decreased physical mobility, were less energetic and had more emotional problems compared with those with asymptomatic DN (Benbow, Wallymahmed, and Macfarlane, 1998). Davies and colleagues (2006) used a recently developed neuropathy and foot ulcer-specific quality of life instrument and found that patients with painful DSPN had significantly poorer quality of life compared to those without pain.

3.3 Potential mechanism of painful diabetic symmetric polyneuropathy

3.3.1 Intraepidermal nerve fibre (IENF) density

Smith and colleagues (2001) examined eight patients with early diabetic neuropathy and found reduced IENF density and abnormality of some individual attributes of nerve conduction amongst them compared with healthy controls. Another study explored IENF density in 38 patients with painful and non-painful diabetic neuropathy, and found that it was significantly lower amongst the former group but that there were no differences in the vibration perception threshold, cold detection threshold or ankle reflex response between the two groups (Sorensen et al., 2006). Shun et al. (2004) compared symptomatic diabetic neuropathy patients with healthy controls and found a significant reduction in IENF density amongst the former, while Løseth et al. (2008) reported that IENF density was significantly reduced in diabetics with or without symptoms compared with healthy controls.

3.3.2 Myelinated and unmyelinated fibre degeneration

A qualitative analysis was conducted of the density of sural nerve fibres of two patients with DN, who presented with pain, hypaesthesia and autonomic dysfunction. The authors found that, compared with healthy controls, there was a marked reduction in total myelinated fibre density, especially small myelinated fibre density, unmyelinated fibre degeneration with regeneration and axonal loss in the DN patients. In contrast, the large myelinated fibres were only mildly affected, as reflected by the slight slowing in conduction velocity (Brown, Martin, and Asbury, 1978). Shun et al. (2004) reported a significant reduction in the number of epidermal nerves in the epidermis of symptomatic diabetic patients and the complete denervation of their skin, as well as fragmented dermal nerve fibres in the dermis. Malik and colleagues (2005) observed morphological changes in diabetic patients with minimal neuropathy for more than eight years and found no significant axonal degeneration but obvious segmental demyelination with remyelination in myelinated fibres. The increase in the thermal detection threshold demonstrated the deterioration of function in small myelinated fibres. Apart from a significant reduction in the

conduction velocity of the median and peroneal motor nerves, these patients still had no symptoms, and their neuropathy deficit score, vibration perception threshold and sural nerve amplitude and velocity did not change significantly in eight years.

In summary, the morphometric changes in dermal and epidermal innervation suggest that nerve degeneration in symptomatic diabetic patients may be related to the progression of neuropathy. Several studies show that DN involves both small and large nerve fibre neuropathy and that the abnormality of small nerve fibres is greater than that of large ones (Smith et al., 2001; Shun et al., 2004; Malik et al., 2005; Sorensen et al., 2006; Løseth et al., 2008). Therefore, in the early stage of neuropathy, the involvement of small nerve fibres may precede that of large ones in some diabetic patients.

3.4 Clinical examination of the pain pathway

The pain pathway has been explored using various modalities including cutaneous electrical stimulation (Masson and Boulton, 1991), mechanical stimulation (Sorensen et al., 2002) and thermal stimulation (Shukla, Bhatia, and Behari, 2005). Subjective self-report methods are commonly used to measure the function of the nervous system. Various methods have been developed to examine the integrity of small myelinated fibres in different diseases (American Association of Electrodiagnostic Medicine [AANEM], 1999; Valeriani, Le Pera, Niddam, Chen, and Arendt-Nielsen, 2002; Shukla et al., 2005).

3.4.1 Quantitative sensory testing (QST)

QST was developed to quantify and assess the sensory function of patients with neuropathy and neuropathic syndrome. The vibration perception, thermal perception, and light touch tests and painful stimulation are commonly used as they test specific sensory pathways. QST is a psychophysical test that relies on the cooperation of the participants. In addition, the sensitivity, specificity, reproducibility and accessibility

determine the value of individual QST. A specific QST will be illustrated below.

3.4.1.1 Vibration perception test

The vibration perception test is a procedure that is widely used in clinical and research settings to examine the function of large diameter nerve fibres (Sorensen et al., 2002). It has been used as a "gold standard" to validate other tools for assessing diabetic peripheral neuropathy. It assesses the function in Meissner and Pacinian corpuscles and their related large fibres using a frequency of 120-200 Hz (Anonymous, 1992). Hwu et al. (2002) demonstrated that age was an important factor contributing to the variability in the vibration perception threshold between healthy and diabetes mellitus Chinese populations. Gareth, Jaswinder, Aber and Mather (1988) found that the variability between the bilateral big toes was 30% in diabetics using biothesiometry. The ventral surface of the first toe has been found to have lower vibration perception compared with the dorsal surface (Dimitrakoudis and Bril, 2002). Ziegler, Mayer and Gries (1988) found no significant difference in the vibration perception threshold between metabolically

stable controls and newly diagnosed IDDM patients.

3.4.1.2 Thermal perception and thermal pain test

The thermal perception test is used to assess the function of free nerve endings and their related small myelinated and unmyelinated afferent fibres (Anonymous, 1992). Thermal perception and thermal pain are measured by a thermode that operates by the Peltier principle. The reproducibility in the foot of diabetics of the warm and cold thresholds has been found to be low (Bravenboer, van Dam, Hop, Steenhoven, and Erklens, 1992). One study reported that the sensitivity of thermal perception testing was 72% in detecting small fibre neuropathy in patients with normal NCV (Shukla et al., 2005). The diagnostic value of warm perception testing in patients with small fibre neuropathy may be higher than that of cold perception testing (Shukla et al., 2005). The warm and cold perception thresholds have been found to be high in metabolically stable newly diagnosed IDDM patients compared to normal subjects (Ziegler et al., 1988). Using the Glasgow method, the intra-individual variation in thermal perception threshold was found to be 5% (Jamal, Hansen, Weir, and Ballantyne, 1985). It has been

proposed that the thermal perception threshold is useful in detecting small fibre dysfunction in neuropathy (Bertelsmann, Heimans, Weber, van der Veen, and Schouten, 1985; Jamal et al., 1985; Lin, Chiu, Tchen, and Fu, 1990).

3.4.1.3 Light touch

The light touch test is used to examine the function of Merkel touch domes and Meissner corpuscles and their related large diameter fibres (Anonymous, 1992). The Semmes-Weinstein monofilament examination (SWME) is one of the methods used to quantify light touch response. The site for the test and the calibre of the monofilament varies. Kamei et al. (2005) discovered that the Semmes Weinstein 4.31/2 g monofilament was more sensitive in detecting diabetic peripheral neuropathy compared with the 5.07/10 g one (60% vs. 30%, respectively), whereas the specificity using the 5.07/10 g monofilament to detect diabetic peripheral neuropathy was greater than that using the 431/2 g one (92.9% vs. 73.8%, respectively). The low sensitivity of the 5.07/10 g monofilament suggests that it might be able to detect advanced diabetic peripheral neuropathy. A strong association has been

found between the 5.07/10 g monofilament and the lower limb vibration test and ankle reflex, which suggests that it may be useful in diagnosing large fibre neuropathy.

Regarding the site of light touch stimulation, the dorsum of the first toe proximal to the nail bed has been found to yield greater accuracy and fewer false positive values in diagnoses of diabetic sensorimotor neuropathy compared with the pulp of the first toe (Dimitrakoudis and Bril, 2002). Another study reported that the specificity of the 10-g SWME on the ventral surface of the first, third and fifth toe; ventral surface of the first, third and fifth metatarsal head; and ventral surface of the medial and lateral mid-foot and the heel and dorsal surface of the foot between the base of the first and second toes was similar (87.5-100%) using nerve conduction studies as a "gold standard" in detecting diabetic peripheral neuropathy, while the third metatarsal head had higher sensitivity (86.2%) compared with the other sites. In addition, testing on 10 sites together or only on the third and fifth metatarsal yielded similar sensitivities and specificities (Lee et al., 2003). The SWME is also proposed to evaluate treatment effects in diabetic peripheral neuropathy (Akahori et al., 2004).

The differences in the response at various surfaces may be due to different receptors, fibre length, skin thickness and neuropathy mechanisms. Although various testing sites and monofilament calibres have been proposed, the standardisation of the procedure is crucial in clinical and research settings. However, responses also depend on subjective reporting and may be affected by cultural and gender differences.

In summary, QST is a psychological test and requires patient cooperation during the procedure; therefore, the variation in the results may be related to the lack of concentration/inattention of patients.

3.4.2 Current perception threshold testing

Current perception testing assesses the detection threshold of the dine wave stimulation produced by a constant electric current (Anonymous, 1992). It seems that cutaneous receptors are stimulated directly as no particular receptors exist for an electric current (Anonymous, 1992). The neurometer is the sole commercially available device to test current perception. It delivers sinusoidal electrical stimulation through surface electrodes at

frequencies of 5 Hz, 200 Hz and 2000 Hz (AANEM, 1999). It is posited that different afferent pathways are stimulated with different current frequencies: 5 Hz for C-fibres, 200 Hz for A-delta fibres and 2000 Hz for A-beta fibres (AANEM, 1999). A positive correlation has been found between the current perception threshold at 2000 Hz and the vibration perception threshold, and that at 5 Hz and the log thermal threshold (Masson and Boulton, 1991). It takes only 10 to 15 minutes for a full assessment of the functional integrity of the peripheral nerve fibres (Masson and Boulton, 1991). However, similar to other psychophysical tests, subject cooperation is a major issue. The standardisation of electrode placement and applied pressure may enhance the accuracy of the test (Masson, Hunt, Gen, and Boulton, 1989).

3.4.3 Skin biopsy

The use of a skin biopsy to assess DN was first described in 1989 (Lauria et al., 2005). A significant decrease in the density of intraepidermal nerve fibres (IENF) in patients with painful sensory neuropathy has been reported (Holland et al., 1998). In 2005, the European Federation of Neurological

Societies recommended a standard method for skin biopsies by quantifying the linear IENF density and laboratory process. They concluded that for the diagnosis of small fibre neuropathy, the quantification of IENF density is more sensitive than either a sensory nerve conduction study or sural nerve biopsy (Lauria et al., 2005). Skin biopsies are useful in identifying peripherally anatomical defects in neuropathy (Holland et al., 1998). However, a special laboratory is required and may be available only in major research institutes and not in normal clinical settings.

3.4.4 Sural nerve biopsy

Sural nerve biopsy is a method to evaluate peripheral nerve disorders. The sural nerve is usually taken from midway between the lateral malleolus and Achilles tendon (Kumar and Jacob, 2004; Ruth et al., 2005). This method is useful in diagnosing systemic vasculitis, leprosy and chronic inflammatory demyelinating polyradiculoneuropathy (Gabriel et al., 2000). The results of a prospective study showed that sural nerve biopsy was particularly useful in guiding patient management in demyelinating neuropathy and multiple mononeuropathy (Gabriel et al., 2000). However, pain in the sural nerve

distribution (Flachenecker, Janka, Goldbrunner, and Toyka, 1999; Gabriel et al., 2000; Ruth et al., 2005; Dahlin et al., 2008), dysaesthesia (Flachenecker et al., 1999; Ruth et al., 2005), paraesthesia (Kumar and Jacob, 2004), persistent sensory loss (Kumar and Jacob, 2004; Ruth et al., 2005) and infection (Dahlin et al., 2008) have been reported in patients who had sural nerve biopsy. The painful symptoms declined within two years (Flachenecker et al., 1999). Microsurgical repair of sural nerves immediately after biopsy has been proposed to minimise the incidence of post-operative paraesthesia, hypesthesia and dysaethesia (Schoeller et al., 2004), but the generalisability of this method is still under discussion (Schoeller et al., 2004). In addition, it is not possible to distinguish between small and large myelinated fibres using this method. Therefore, the use of sural nerve biopsy as a diagnostic tool in DN has to be balanced against the long-lasting side effects.

3.4.5 Corneal confocal microscopy

Corneal confocal microscopy is a non-invasive technique used to study conrneal nerve morphology, especially for the quantification of the C and A-delta corneal nerve fibres (Oliveira-Soto and Efron, 2001). Two studies reported progressive reductions in corneal nerve fibre density and branch density with an increase in the severity of neuropathy in diabetic patients; however, a significant reduction was found only amongst neuropathy groups compared to healthy controls, and amongst diabetic patients with severe neuropathy, based on the neuropathy deficit score, compared to no neuropathy diabetics (Malik et al., 2003; Quattrini et al., 2007). Whilst corneal confocal microscopy allows the identification of C and A-delta nerve damage, it demonstrates a limited ability to assess the severity of neuropathy or differentiate nerve damage amongst various types of nerve fibres. Further refinement of this method for the early detection of DN is required.

3.4.6 Laser Doppler Imager Technique (LDI)

Laser Doppler Imager Technique (LDI) is a non-invasive method to assess neurogenic flare response of unymelinated C-fibre to nociceptive stimulation (Krishnan & Rayman, 2004). There are several methods to induce flare response including electrical stimulation and a 44°C thermal stimulation Electrical stimulation involved needle insertion (Krämer, Schmelz, Birklein, & Bicker, 2004) while thermal stimulation required only a skin heater to generate a flare response (; Kunkel et al., 2007; Green, Krishnan, & Rayman, 2009; Krishnan, Quattrini, Jeziorska, Malik, & Rayman, 2009). In addition, the neurogenic nature of the flare response after thermal stimulation has been confirmed (Krishnan & Rayman, 2004).

Kunket and colleagues (2004) reported that there was significant reduction in LDIflare area and LDI maximal hyperemic response (LDImax) in patient suffering from diabetes with and without clinical neuropathy. Furthermore, the LDIflare area was significantly reduced in diabetics with clinical neuropathy compared to those without neuropathy. A recent study also reported that there was significant reduction in LDIflare in patients with painful diabetic neuropathy and those with painless neuropathy, however, no significant difference was found between the two diabetic groups (Krishnan, Quattrini, Jeziorska, Malik, & Rayman, 2009). Whilst LDI allows defining C fibre damage in diabetic population, the ability of LDI to grade the level of severity of neuropathy and early detect diabetic neuropathy has not yet been confirmed. Further study on C-fibre function in diabetics with different stage of neuropathy is required.

Furthermore, there are two types of fibre transmitting nociceptive information in nerve system, they are myelinated A-delta fibre and unyelinated C-fibre (Godfrey, 2005). Diabetic patients with symptomatic neuropathy may involve not only C-fibre but A-fibre damage; therefore, method for investigating A-delta fibre function is also an integral part in examination of diabetics with symptomatic neuropathy.

3.4.7 Nerve conduction studies (NCS)

Nerve conduction study is used to evaluate the neurological disorder such as sensorimotor neuropathy and mononeuropathy by applying electrical stimulation to the nerve (Annoymous, 1988; Natly & Sabbahi, 2001). The primary aim of NCS is to assess functional status of large myelinated sensory and motor nerve fibres in lower and upper limbs (Annoymous, 1988). It is the integral part for DSP definition proposed by American Academy of Neurology, the American Association of Electrodiagnostic Medicine and the American Academy of Physical Medicine and Rehabilitation (England et al., 2005) and the key component of various diagnostic tools such as Rochester neuropathy scoring system (Dyck, 1988) and diabetic neuropathy score (Feldman et al., 1994).

Nerve conduction studies on median, ulnar and peroneal motor nerve, median, ulnar and sural sensory nerve was recommended assessment for diabetic neuropathy in the report and recommendations of the San Antonio Conference on diabetic neuropathy (Annoymous, 1998). For motor nerve testing, supramaximal stimuli were applied at distal and proximal points of the nerve. The muscle-action potential amplitude and latency at each site

of stimulation was recorded and the conduction velocity between the distal and proximal part of the nerve was calculated for each nerve. For sensory nerve testing, electrical stimulation was applied and the orthodromically sensory action potential and conduction velocity were recorded and calculated (Natly & Sabbahi, 2001).

Although NCS is a key diagnostic test in DSP, it assesses large nerve fibre function rather than small nerve fibre. In patient suffering from DSP, there may be involvement of small and large nerve fibres; therefore combination of small and large fibre assessment may provide comprehensive information of patient's neurological status.

3.4.8 Autonomic fibre measurements

Impairment of peripheral autonomic nervous system may involve in early stage of small fibre neuropathy (Low, Sandroni, Fealey, & Low, 2006). Sympathetic skin response (SSR) and quantitative sudomotor axon reflex test (QSART) are tests used to evaluate sudomotor control, which is recommended for assessment of autonomic nervous system function (Anonymous, 1988). QSART is measuring the amount of sweat volume following stimulation by acetylcholine ionophoresis (Low, Caskey, Tuck, Fealey, & Dyck, 1983). Reduction in sweat volume indicates sudomotor abnormality (Shimad et al., 2001). QSART is commonly used test but expensive specialized equipment is required to perform the test. SSR is measuring the electrodermal activity of the skin after electrical stimulation and is a surrogate measure for sudomotor function (Shahani, halperin,

Boulu, & Cohen, 1984). This test is easy to perform; however, there is great variability in SSR within subjects (Illigens & Gibbons, 2009)

3.4.9 Laser evoked potentials (LEPs)

The use of laser evoked potentials (LEPs) to investigate the integrity of the nervous system is increasing. It is possible to obtain objective responses after stimulation. LEPs have been using to investigate the pain pathway of different pain conditions including complex regional pain syndrome, migraine and trigeminal neuralgia (de Tommaso et al., 2007; Moreau, Berquin, and Plaghki, 2007; Truini and Cruccu, 2008). However, only a few studies have used it to test the peripheral nerve system in diabetes. The integrity of the pain pathway has been examined in the early stage of IDDM using LEPs, and a significant reduction in foot LEP amplitudes and prolonged latencies have been found in the patient group compared with healthy controls. The researchers proposed that there may be subclinical and selective damage of small myelinated fibres in the early stage of diabetes (Rossi et al., 2002). Agostino and colleagues (2000) investigated the diagnostic value of LEPs in 45 patients with diabetic neuropathy and various degrees of nerve damage and found that a high percentage of

patients had no response on the dorsum of the foot and hand. Amongst the responsive patients, only 18 had a significant reduction in foot amplitude. The researchers proposed that there may be axonal degeneration in those with reduced amplitudes and possible demyelination in those with no response. The limited routine use of LEPs in the diabetic population may be related to the superficial burns resulting from their application (Bromm and Treede, 1983), although no complications in diabetics have been reported.

3.4.10 Contact heat evoked potentials (CHEPs)

The development of contact heat evoked potentials (CHEPs) in recent years has improved our ability to examine the nervous system. The advantages of CHEPs compared with thermal laser stimulation are the increase in the stimulation area and the rapid increase in the temperature to allow the activation of the small unmyelinated C fibre. This is a non-invasive procedure (Arendt-Nielsen and Chen, 2003).

In conclusion, quantitative sensory tests allow the quantification of the severity of nerve damage based on subjective responses. For objective

assessment, skin biopsy and sural nerve biopsy reveal in detail morphological changes in nerve fibres but are invasive procedures. Corneal confocal microscopy is not able to differentiate amongst diabetics with no, mild and moderate neuropathy. Therefore, a non-invasive objective test that allows the accurate and early detection of neuropathy is required. A detailed description of a possible method, CHEPs, is given in the following section.

3.5 Contact heat evoked potentials

3.5.1 Background

The electroencephalogram (EEG) captures the continuous electrical activity of the brain through scalp electrodes (Connolly, Sharbrough, and Wong, 2003). Alpha and beta waves are present in EEGs without external stimulation. Alpha waves are 8-13 Hz and have a relatively large amplitude. They are related to a relaxed but awake state in human beings. Beta waves are 13-20 Hz, and their amplitude is lower than that of alpha waves. They are associated with a more alert mental state in human beings (Kellaway, 2003).

Evoked potentials are electrical signals generated in response to sensory stimulation of the nervous system. They can be obtained by time locking the recording of the EEG to the onset of an event and differentiated from background electrical activity because they are more consistent in morphological structure. However, the amplitudes are relatively small, usually ranging from 1 to 10 microvolts compared with the 10 to 100

microvolts of the background EEG. An amplifier is required when trying to obtain evoked potentials (Luck, 2005).

The signals of evoked potentials are usually recorded from the cerebral cortex, brainstem, spinal cord and peripheral nerves. Auditory, visual and somatosensory stimuli are sensory evoked potentials that are commonly used in clinical medicine to examine the function of the central nervous system (Luck, 2005). In recent years, the use of LEPs and CHEPs to examine nociceptive pathways has been proposed.

3.5.2 Contact heat evoked potentials and nociceptive pathways

Studies show that CHEPs share characteristics with LEPs, which suggests that CHEPs are mediated by nociceptive responses (Valeriani et al., 2002). Le Pera and colleagues (2002) reported that diversion of attention did not affect the amplitude, latency or topography of the major CHEP components, as represented by a stable and reproducible Cz/P730 brain evoked potential. In addition, CHEPs have been confirmed to be a valid test in clinical applications and research into nociceptive pathways and human pain (Chen,

Niddam, and Arendt-Nelsen, 2001). Chen et al. (2001) proposed that late contact heat evoked potentials contained components related to A-delta fibre activation and the initial perception of pain, and that ultra-late contact heat evoked potentials contained components related to C fibre activation. Chen et al. (2001) suggested that contact heat evoked potentials be used to assess the integrity of A-delta and C fibres. A positive correlation was found between stimulus intensity and late contact heat evoked potentials in both normal individuals (Chen et al., 2001).

3.5.3 Validity and reliability of CHEPs

Parallel dysfunction of the large and small afferent fibres in DN has been revealed using LEPs (Agostino et al., 2000). CHEPs share characteristics with LEPs; however, the former, in contrast to the latter, do not produce superficial burns after their application. The activation of myelinated A-delta fibres following the application of a 51°C thermal stimulus on hairy skin has been confirmed by various studies (e.g., Granovsky et al., 2005), but only one study has successfully activated unmyelinated C fibres using CHEPs (Granovsky et al., 2005).

The reproducibility of CHEPs at different body sites was explored by Chen and colleagues (2006): 51°C thermal stimulation was applied to the right and left volar forearm, dorsum of the right hand and foot, and peroneal area, and the baseline temperature was 32°C for each stimulation. There were 20 constant-intensity stimuli in each block, and the inter-stimulus interval was 5s. Two stimulation blocks were applied at the same body site to confirm the reproducibility of CHEPs and a 3-5 minute break was given between the blocks if there was no reproducible waveform. The percentage of reproducible CHEPs in the study was 36-62%, with the forearm having the highest percentage followed by the hand, peroneal area and foot. The unsatisfactory rate of reproducible CHEPs in the preceding study may be related to the short break between the two stimulation blocks and short inter-stimulus interval. In summary, CHEPs have been found to be a valid method to examine the integrity of myelinated A-delta fibres, but further research should be conducted to examine the reliability of this method.

3.6 Symptomatic treatment of painful diabetic neuropathy

3.6.1 Antidepressants

There are several types of antidepressants, including tricyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) (McQuary and Wiffen, 2006). TCAs inhibit pre-synaptic uptake of serotonin and noradrenaline and block some post-synaptic histamine and muscarinic receptors. Several studies have reported significant pain reduction when comparing desipramine (Max et al., 1991), citalopram (Sindrup et al., 1992), impramine (Kvinesdal, Molin, Frøland, and Gram, 1984), amitriptyline (Max et al., 1987) and mexiletine (Goldstein, Lu, Detke, Lee, and Iyengar, 2005; Raskin, D'Souza, and Wernicke, 2005; Kajdasz et al., 2007) with a placebo. The most common adverse affects of TCAs are dry mouth and sedation.

3.6.2 Anticonvulsants

Anticonvulsants are thought to work through the blockage of sodium channels, acting on subunits of calcium channels and modulating GABA synthesis and metabolism (McQuary and Wiffen, 2006). Those reported to have short-term pain reduction effects include sodium valproate (Kochar et al., 2002; Kochar et al., 2004), gabapentin (Backonja et al., 1998), lamotrigine (Eisenberg, Lurie, Braker, Daoud, and Ishay, 2001), carbamazepine (Rull, Quiberera, Gonzálze-Millán, and Castañeda, 1969) and pregabalin (Lesser, Charma, LaMoreaux, and Poole, 2004; Rosenstock, Tuchman, LaMoreaux, and Sharma, 2004; Richter et al., 2005; Arezzo, Rosenstock, Lamoreaux, and Pauer, 2008; Tolle, Freynhagen, Versavel, Trostmann, and Young, 2008). The common side effects of anticonvulsants are somnolence and dizziness and the major adverse reaction is liver derangement. Two of 100 participants withdrew from a study of sodium valporate because of liver damage (Kochar et al., 2002; Kochar et al., 2004).

3.6.3 Opioids

The use of opioids in chronic pain management is a topic of long-standing debate; however, they are increasingly being used in neuropathic pain management. Oxycodone (Gimbel, Richards, and Portenoy, 2003; Watson, has been found to be associated with significant pain reduction in patients with DN compared with a placebo. The most commonly reported adverse events related to controlled-release oxycodone are constipation, somnolence (Gimbel et al., 2003; Watson et al., 2003) and nausea.

3.6.4 Tramadol

Tramadol (Harati et al., 1998) and tramadol/acetaminophen (Freeman et al., 2007) have been found to be associated with significant pain reduction in patients with DN compared with a placebo. The most commonly reported adverse events related to tramadol are nausea, constipation, headache and somnolence (Harati et al., 1998).

3.6.5 Ion channel blockers

The results for the pain-relieving effect of mexiletine, an ion channel blocker, are mixed. Two studies reported significant pain relief in patients receiving mexiletine compared with those receiving a placebo (Dejgard, Petersen, and Kastrup, 1988; Oskarsson, Ljunggren, and Lins, 1997), whereas no statistical differences in pain reduction were reported in two other studies (Stracke, Meyer, Schumacher, and Federlin, 1992; Wright, Oki, and Graves III, 1997).

3.6.6 Topical analgesics

The effect of topical analgesics has begun to be explored in recent years, and the benefits of various topical agents including capsaicin (Capsaicin Study Group, 1991) and isosorbide dinitrate (ISAD) spray (Yuen, Baker, and Rayman, 2002) remain to be confirmed. 5% lidocaine patch has been found to be associated with significant pain reduction and minimal side effect in one open label study (Barbano et al., 2004). Future randomized controlled trials should be conducted to confirm the benefit of 5% lidocaine

patch in patients with painful DSP.

3.6.7 Non-pharmacological treatment

Transient relief of painful symptoms by transcutaneous electrostimulation in a small group of NIDDM patients presenting with painful peripheral neuropathy was reported by Kumar and Marshall (1997). A symptomatic therapy such as a bed cradle was suggested by Poncelet (2003) to decrease superficial stimulation if allodynia was present.

In summary, although different agents are used for neuropathic pain management, the problem persists, which may be related to the difference in subject selection criteria and outcome measures. A systematic review was conducted to look further into the issue.

3.7 Summary

DSP usually presents with positive or negative symptoms, which always begin in the distal lower extremities and gradually spread proximally in the course of the disease. In general, positive symptoms such as pain and paraesthesia appear in the early stage of DSP, and a strong association has been found between small nerve fibre damage and these symptoms. Morphological studies have demonstrated that small fibre damage precedes large fibre damage in patients with minimal DSP. However, no individual surrogate diagnostic test can distinguish between minimal and severe neuropathy. Various studies show that different classes of medications can effect significant pain reduction, but pain is still an unresolved problem in clinical settings. This may be related to the initiation of treatment in the advanced stage of the disease and the lack of a valid and reliable surrogate measure of small nerve fibre damage. Therefore, the development of a surrogate measure of early-stage small nerve fibre damage is needed.

Chapter 4
Conceptual Framework

4.1 Introduction

DSP affected between 6% and 35% of the world's diabetic population and accounted for more than US$200 million in health care costs in United states in 2001(Gordois et al., 2003). The aetiology of DSP remains unclear, and the outcomes of its various methods of treatment are not currently optimal. Therefore, disease prevention may represent a new direction for the management of DSP, and it thus provides the framework for this study. In this chapter, the study's conceptual framework and the definitions of a number of key terms are presented.

4.2 Development of study framework

Over the past decade, increasing emphasis has been placed on disease prevention as a means of reducing health care costs, an approach that is in line with the folk

wisdom of ‘prevention is better than cure’. In its current understanding, disease prevention has three levels: primary, secondary and tertiary. The aim of primary prevention is to prevent the onset of disease in healthy people; secondary prevention focuses on the early identification of disease and the provision of treatment as early as possible to prevent disease-related complications or other problems; and tertiary prevention involves the management of late-stage disease to minimise the degree of disease-related disability (Kennie, 1993).

Diabetes in Chinese populations is increasing (Chan and Cockram, 1997; Pan, Yang, Li and Liu, 1997), and thus the prevention of diabetic complications is becoming increasingly important. Secondary prevention has been shown to decrease the motility rate, delay the onset of complications, stabilise the disease process, increase the recovery rate and reduce the risk of recurrence in patients with Alzheimer’s disease (Buettner and Fitzsimmons, 2009; Yu et al., 2009), stroke (Rothwell et al., 2007), diabetic retinopathy (Anonymous, 1991), diabetic nephropathy (Lin et al., 2003) and pre-diabetic neuropathy (Smith et al., 2006). Secondary prevention – the early detection of and intervention in DSP – therefore, provides the framework for the present study (Figure 4.1).

Although early intervention is crucial, the accurate diagnosis of DSP in the early stage is a prerequisite. Such a diagnosis requires both a clear definition of the disease and sensitive diagnostic tools. Measures of the signs and symptoms are the major components of health assessment. Lower limb symptoms are intermittent in the early stage of DSP (Park, Baek and Park, 2007), and thus its early diagnosis can be difficult. Indeed, symptom assessment alone may not reflect the actual problems of the nervous system, especially those related to small nerve fibres.

Various objective methods for the early detection of DSP have emerged in recent years (Park, Lee, Lee and Oh, 2003; Løseth et al., 2008), although, to date, no individual test is able to distinguish between mild neuropathy and a lack thereof. In this study, the integrity of the small nerve fibres in diabetics with lower limb symptoms was examined using contact heat evoked potentials (CHEPs).

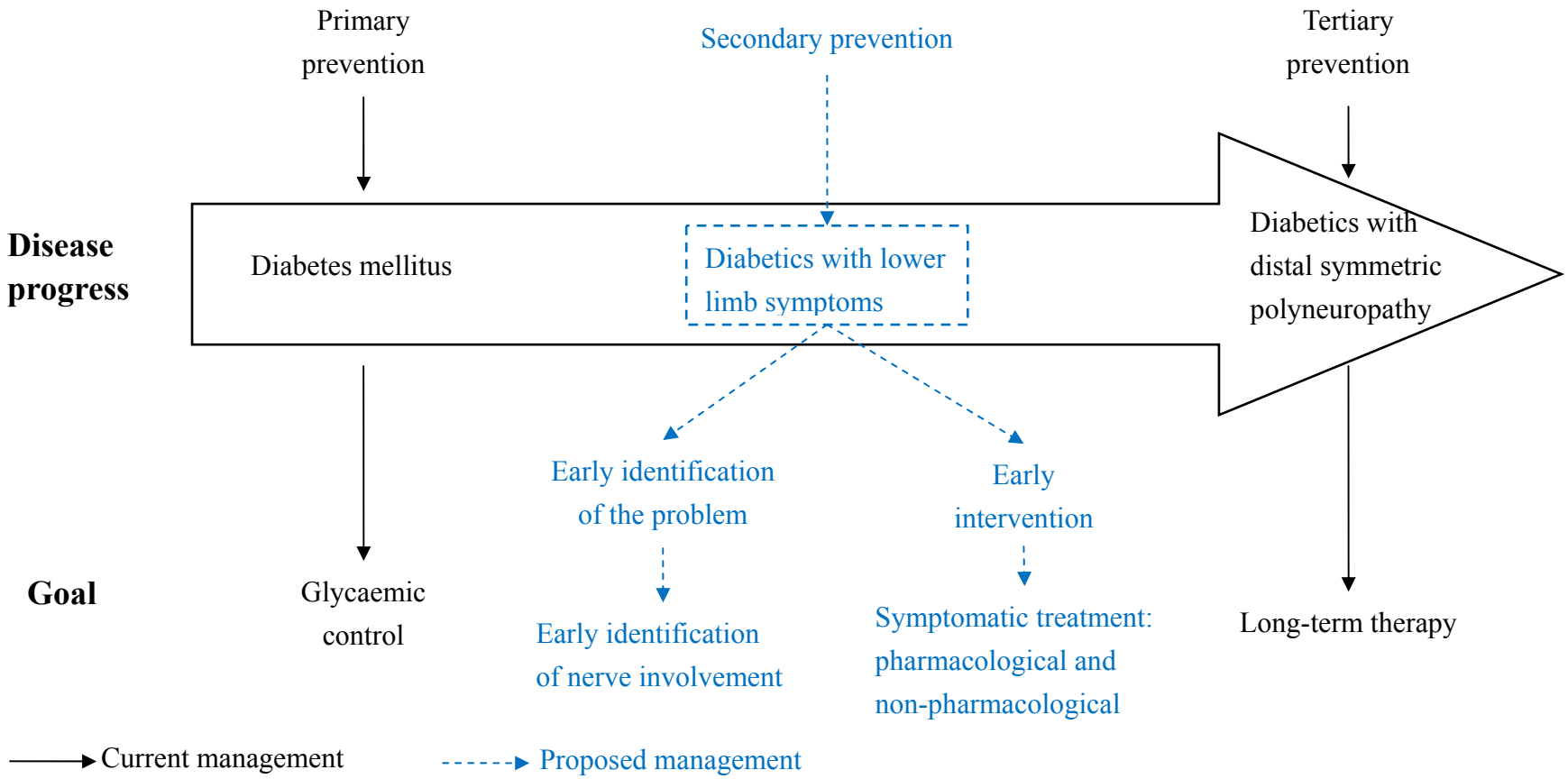

Figure 4.1. Conceptual framework for the study.

4.3 Relationships amongst variables

Patients suffering from DM may develop DSP, which is one of its most common complications (Young et al., 1993; Herman et al., 1998; Pradeepa et al., 2008). The progress of DSP development and its presentation vary amongst individuals. Diabetics may present with intermittent symptoms in the lower limbs when they are in the early stage of DSP and with persistent symptoms in the moderate to advanced stage (Galer et al., 2000). Therefore, diabetics may present with intermittent lower limb symptoms for different periods of time prior to DSP diagnosis.

The most common approach to preventing diabetic complications is maintaining normoglycaemia (DCCT, 1993, 1995). Although such control is addressed in general diabetic care, a certain proportion of diabetics are still reported to have DSP (Saadi et al., 2007; Pradeepa et al., 2008). Once DSP has been diagnosed, long-term therapy, including disease-modifying agents such as ALA and pain-reducing agents such as anticonvulsants are used to reduce symptoms.

The treatment effects of these long-term therapies determine the future management direction. The treatment strategies remain unchanged if existing therapies are optimal, whereas the management strategies may require re-formulation. To determine whether a new approach to the management of symptomatic DSP is required, in this study a systematic review of the effects of various classes of mediations for the treatment of symptomatic DSP was conducted. The results were then used to inform the need for the secondary prevention of DSP.

According to the principle of secondary prevention, early detection and intervention reduce motility (Lin et al., 2003; Smith et al., 2006). It is proposed that the identification of DSP in its early stage (diabetics presenting with lower limb symptoms) is beneficial to DSP management. However, intermittent and minimal symptoms in the early stage may be neglected by both patients and health care professionals, and hence no intervention may take place.

The presentation of symptoms indicates an imbalance in body function, and these warning signs should be addressed as early as possible to prevent

deterioration. Symptoms in patients suffering from DSP may be related to small nerve fibre damage (Malik et al., 2005; Sorensen et al., 2006), and thus subjective reports of these symptoms, e.g., pain intensity ratings, may not be sufficient to reflect the severity of the problem. Therefore, non-invasive objective assessment is needed to identify nerve involvement in diabetics with lower limb symptoms. Once such nerve damage has been identified, early intervention can take place.

CHEPs may be a valuable method of assessing small myelinated fibre integrity. However, the reliability and feasibility of this method in the detection of small nerve fibre damage should be confirmed before it is adopted in a clinical setting. The reliability and feasibility of CHEPs were thus duly tested in Stages 2 and 3 of this study.

4.4 Definitions of the research variables

4.4.1 Contact heat evoked potentials

Contact heat evoked potentials (CHEPS) are electrical potentials recorded from an individual's scalp following the contact heat stimulation of the hairy skin.

4.4.2 Pain intensity rating

A pain intensity rating requires an individual to rate his or her degree of pain on a numerical scale that ranges from 0 to 10, where 0 is no pain and 10 is pain as severe as can be imagined.

4.4.3 Symptoms

Symptoms are subjective evidence of disease that can be perceived only by the patient. Structured interviews were conducted with all of the participants in the present study to identify such distal lower limb symptoms as

numbness, paraesthesia, allodynia, pain and hyperalgaesia.

4.5 Assumptions

1) The early detection of diabetic complications is important in diabetic patient care.
2) Pain and symptoms are subjective experiences that may indicate imbalance and dysfunction of the body.

4.6 Summary

A conceptual framework with a management pathway for painful DSP based on the concept of disease prevention has been proposed in this chapter. This framework guides the inquiry process of this thesis.

Chapter 5

Stage 1 – The Effects of Symptomatic Treatments for Patients with Painful Diabetic Neuropathy: A Systematic Review

5.1 Introduction

Various classes of medications are used to manage the pain associated with diabetic neuropathy, and it is expedient to compare their effects by conducting a systematic review. In this chapter, the systematic review will be described in detail, the treatment efficacy in terms of the odds ratio (OR) and number needed to treat (NNT) will be calculated for each class of medication, and the implications of the results will be discussed.

5.2 Research objective

A systematic review was conducted to evaluate the effect of symptomatic treatment of DSP to look further into the need for the early detection of DSP and identify types of nerve damage before the commencement of treatment.

5.3 Research questions

1) What are the effects of symptomatic treatments amongst patients with diabetic neuropathy?

2) Are there effective symptomatic treatments for patients with symptomatic DSP?

5.4 Method

5.4.1 Search strategy to identify studies

Several methods were used to identify the studies to be included. Randomised trials that studied the analgesics used to treat DN were identified using Medline(R) without revision from 1966 to October 2006, Embase from 1980 to October 2006, EMB reviews-ACP Journal Club from 1991 to Sept/Oct 2006, and the Cochrane Library 3rd Quarter 2006 issue from the Cochrane Central Register of Control Trials. Additional reports were identified from the reference lists of the retrieved papers.

The key search terms were anticonvulsant, non-steroidal anti-inflammatory drugs, ion channel blocker and neuropathy, antiepileptic/anticonvulsant and neuropathy, antidepressant or antidepressive agents and neuropathy, tramadol and neuropathy, opioid and neuropathy, pregabalin and neuropathy, duloxetine and neuropathy, capsaicin and neuropathy, antidepressant or antidepressive agents and diabetic neuropathies or diabetic peripheral neuropathy, and antidepressant or antidepressive agents and peripheral

neuropathy.

5.4.2 Inclusion criteria

1) Participants in the studies were adults aged 18 years or above with diabetic neuropathy.
2) The interventions involved the administration of an oral or a topical analgesic.
3) The classes of drugs included paracetamol, antidepressants, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), N-methyl D-aspartate (NMDA) antagonists, tramadol, capsaicin and anticonvulsants.
4) The comparison was a placebo.
5) The primary and secondary outcomes of the studies included subjective reports of pain relief or pain intensity.
6) Randomised controlled trials (RCTs) that investigated the analgesic effects of pain-relieving drugs for patients with diabetic neuropathy.
7) Full-text reports published in English.

5.4.3 Exclusion criteria

1) Studies comparing different classes of analgesics such as anticonvulsants versus antidepressants.
2) Non-randomised trials, case reports, clinical observations and studies of intravenous analgesics, intramuscular analgesics or Chinese herbal medicine.
3) Studies without randomisation and blinding.
4) Trials with a sample size less than 10.
5) Trials with a Jadad score less than or equal to 2.

5.4.4 Methodological quality assessment

The Jadad score is a validated tool that is used to assess the quality of RCTs (Jadad et al., 1996), and it has been used in many systematic reviews (Nickel, Sander, and Moon, 2008; Ferreira, Lemos, Figueiroa, and de Souza, 2009; Vavken, Arrich, Schuhfried, and Dorotka, 2009). It consists of three items that cover randomisation, double blinding and a description of withdrawing from trials. The total score ranges between 0 and 5, and a trial with a score of less than 3 is classified as a poor-quality one (Table 5.1).

Table 5.1 Jadad score calculation

Item	Score
Was the study described as randomised?	1
Was the method used to generate the sequence of randomisation described and appropriate (random numbers, computer generated, etc.)?	1
Deduct one point if the method used to generate the sequence of randomisation was described but inappropriate (allocated alternately, or according to date of birth, or hospital number).	-1
Was the study described as double blinded?	1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?	1
Deduct one point if the study was described as double blinded but the method of blinding was inappropriate.	-1
Was there a description of withdrawals and dropouts?	1

There may be selection bias during subject recruitment and the allocation of study groups in clinical trials. The inappropriate handling of withdrawals and dropouts may also bias the results. Allocation concealment and intention to treat analysis (ITT) can reduce these biases. Therefore, the use of concealment and ITT were also assessed. Quality assessment was made by two reviewers and disputes were settled by consensus.

5.4.5 Data extraction

Studies were selected for retrieval from the library by reviewing the information from the titles and abstracts against the inclusion criteria. Based on the titles, studies identified from the reference list of the available articles were retrieved. Full reports of the studies were compared with the inclusion criteria to determine their relevance to the systematic review. Two reviewers extracted data independently to examine the study and patient characteristics, efficacy and side effects.

Twenty-five letters were sent to the authors for further information on their published reports including the method of randomisation, concealment, double blinding, outcome measures and reason for withdrawal. Two of them replied (Sindrup et al., 1992; Watson et al., 2003).

5.4.6 Outcomes

Pain intensity rating is a commonly used outcome measure in clinical trials. Thirty per cent (Farrar, Young, LaMoreaux, Werth, and Poole, 2001) and 50% (McQuay, Carroll, Jadad, Wiffen, and Moore, 1995) pain reduction from the baseline are defined as clinically important and relevant outcomes, respectively, and the latter is commonly used. In the present review, clinical success was defined as an approximately 50% reduction in pain. This was the number of patients with either ‘moderate’, ‘good’, or ‘notable’ improvement on the global assessment of treatment or at least moderate pain relief on a suitable categorical scale. Secondary outcomes were a 30% reduction in pain and the number of patient withdrawals due to adverse events.

5.5 Data management and analysis

The results were combined and expressed as the odds ratio (OR) with the 95% confidence intervals (CIs), using a random effects model for studies with sufficient data. An OR equal to 1 indicates no difference in treatment efficacy between the treatment and the control group. An OR greater than 1 indicates that the medication used in the treatment group is more likely to have a pain reduction effect than the one used in the control group (Smyth, 2002). There are different statistical models for conducting meta-analysis, which include the random effects model, which is a conservative method that allows heterogeneity between studies, and the fixed effects model, which assumes that there is no variation between studies (Lipsey and Wilson, 2000).

The NNT and 95% CIs were calculated based on the reciprocal of the absolute risk reduction (ARR) (Equation 5.1) and 95% CI of the ARR, respectively (Equation 5.2) (Badenoch and Heneghan, 2002). The NNT was defined as the average number of patients who would need to be treated to have 30%, 50%, or moderate pain reduction/improvement in one patient.

	Control	Experimental
Event	a	b
No Event	c	d

Control event rate (CER) $= \frac{a}{a+c}$.

Experimental event rate (EER) = $\frac{b}{b+d}$.

ARR = CER – EER.

NNT = $\frac{1}{ARR}$. (5.1)

95% CI of the ARR = ARR $\pm 1.96 \times \sqrt{\frac{CER \times (1-CER)}{a+c} + \frac{EER \times (1-EER)}{b+d}}$.

95% CI of an NNT = 1/95% CI of the ARR. (5.2)

The results may vary between studies and this inconsistency can be quantified with the I^2 statistic, which is a statistical test of heterogeneity. This test is used to assess whether the variation across studies is due to heterogeneity or chance. The value of I^2 is between 0 and 100%, with a value of 0% representing no observed

heterogeneity and a larger value indicating a higher level of heterogeneity (Higgins, Thompson, Deeks, and Altman, 2003). The I^2 was calculated for studies with sufficient data, while homogeneity was assessed visually for those studies without sufficient data.

Different classes of medications are used for the treatment of painful DN; therefore, a subgroup analysis was conducted based on different classes of drugs. All statistical calculations were performed using Review Manager 4.2, and the QUOROM guidelines were followed (Moher et al., 1999).

5.6 Results

5.6.1 Description of the studies

One thousand two hundred and thirty one citations were screened for eligibility. No eligible study on NSAIDs was identified, and 32 full-text articles published in English were retrieved. Amongst the 32 studies, mixed patient groups were used in three (Sindrup, Andersen et al., 1999; Sindrup, Madsen, Brøsen, and Jesen, 1999; Freynhagen, Strojek, Griesing, Whalen, and Balkenohl, 2005), randomisation was not employed in two (Ertas, Sagduyu, Arac, Uludag, and Ertekin, 1998; Erdemoglu and Varlibas, 2006), and the Jadad score was less than or equal to 2 in two (Stracke et al., 1992; Gorson, Schott, Herman, Ropper, and Rand, 1999); hence, these studies were excluded. In total, 25 articles that met the inclusion criteria were included, and 17 of them were used in the meta-analysis (Figure 5.1). Amongst the included studies, four investigated antidepressants; ten, anticonvulsants; two, serotonin noradrenaline reuptake inhibitors (SNRIs); four, an ion channel blocker; two, opioids; one, tramadol; one, an N-methyl-D-asprate (NMDA) antagonist; and two, topical agents. Table 5.2

shows the characteristics and methodological quality of the studies.

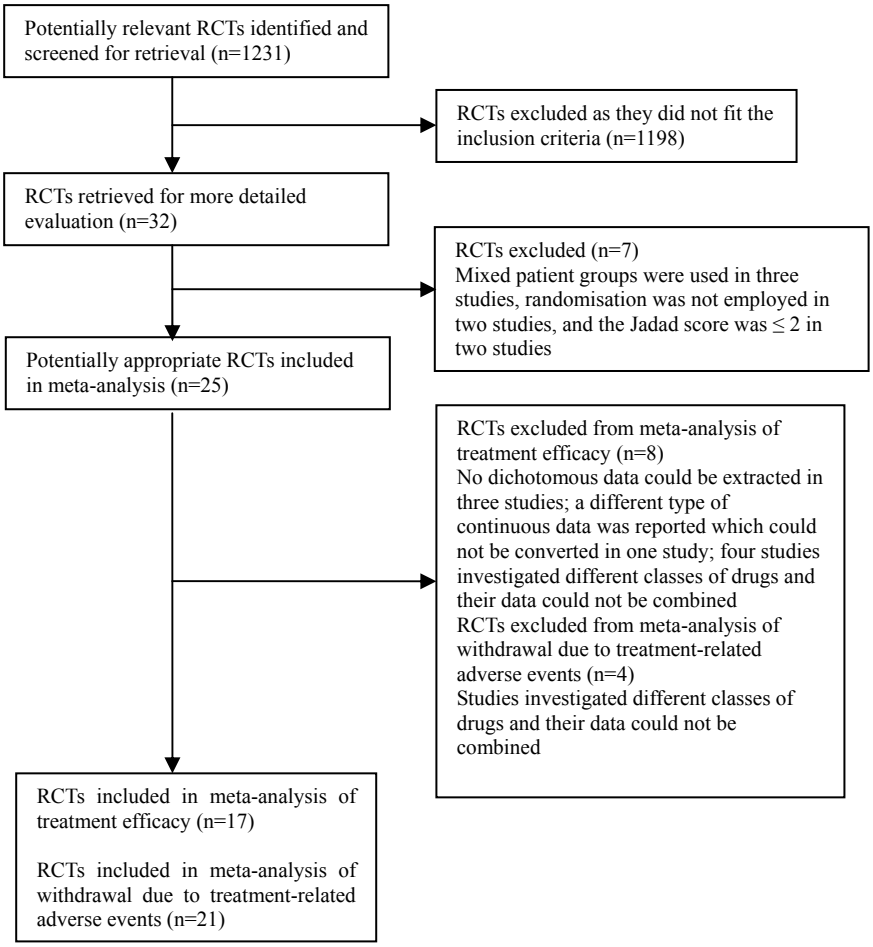

Figure 5.1. Identification and inclusion of studies.

Table 5.2 Characteristics of included studies

Drug class	Trial	Active drug	Daily dose (mg)	N	Age (mean)	Design	Jadad score	Concealment	ITT*	Treatment period	Follow-up (efficacy of treatment)
Topical Treatment											
Capsaicin	Capsaicin study group, 1991	0.075% capsaicin cream	Apply four times daily	277	60	Parallel	4	NM	Yes(for PGE)	8 weeks	Upon completing treatment
Isosorbide Dinitrate Spray	Yuen, 2002	Isosorbide Dinitrate (ISDN) Spray 30mg	Spray both feet with 30mg before bedtime	24	63.7	Crossover, 2-week washout	4	NM	No	4 weeks	Upon completing treatment
Oral treatment											
Anticonvulsant	Rull, 1969	Carbamazepine	200-600	30	54.2	Crossover, no washout	4	NM	No	2 weeks	Upon completing treatment
	Backonja, 1998	Gabapentin	3600	165	53	Parallel	5	NM	Yes	8 weeks	Upon completing treatment
	Eisenberg, 2001	Lamotrigine	25-400	59	55	Parallel	3	NM	No	10 weeks	Upon completing treatment
	Dogra, 2005	Oxcarbazepine	1445 (mean)	146	60	Parallel	5	Yes	Yes	16 weeks	Upon completing treatment
	Beydoun, 2006	Oxcarbazepine	600/1200/ 1800	347	60	Parallel	5	Yes	Yes	16 weeks	Upon completing treatment
	Rosenstock, 2004	Pregabalin	300	146	59.7	Parallel	5	Yes	No	8 weeks	Upon completing treatment
	Richter, 2005	Pregabalin	150/600	246	57	Parallel	5	NM	Yes	6 weeks	Upon completing treatment
	Lesser, 2004	Pregabalin	75/300/600	337	59.9	Parallel	5	Yes	Yes	5 weeks	5 weeks for double blind period
	Kochar, 2002	Sodium valporate	1200	57	56	Parallel	3	Yes	Yes	4 weeks	Upon completing treatment
	Kochar, 2004	Sodium valporate	1000	43	55	Parallel	5	NM	No	3 months	Upon completing treatment

Table 5.2 (cont'd) Characteristics of included studies

Drug class	Trial	Active drug	Daily dose (mg)	N	Age (mean)	Design	Jadad score	Concealment	ITT*	Treatment period	Follow-up (efficacy of treatment)
Antidepressant											
TCA	Max, 1987	Amitriptyline	25-100	37	57 (median)	Crossover, no washout	4	NM	No	6 weeks	Upon completing treatment
	Max, 1991	Desipramine	Mean 201	24	62 (median)	Crossover, no washout	4	NM	No	6 weeks	Upon completing treatment
	Kvinesdal, 1984	Imipramine	100	15	54	Crossover, no washout	4	NM	No	5 weeks	Upon completing treatment
SSRI	Sindrup, 1992	Citalopram	40	18	56 (median)	Crossover, 1-week washout	4	NM	No	3 weeks	Upon completing treatment
SNRI	Goldstein, 2005	Duloxetine	20/60/120	457	60	Parallel	4	Yes	Yes	12 weeks	Upon completing treatment
	Raskin, 2005	Duloxetine	60/120	348	58.8	Parallel	5	Yes	Yes	12 weeks	Upon completing treatment
Ion channel blocker	Dejgard, 1998	Mexiletine	10mg/kg	16	50 (median)	Crossover, 4-week washout	3	NM	No	10 weeks	Upon completing treatment
	Oskarsson, 1997	Mexiletine	225/450/675	126	53.5	Parallel	3	NM	No	3 weeks	Upon completing treatment
	Wright, 1997	Mexiletine	600	31	50	Parallel	3	NM	Yes	3 weeks	Upon completing treatment
NMDA antagonist	Nelson, 1997	Dextromethorphan	Mean 381	14	54 (median)	Crossover, 1-week washout	5	NM	No	6 weeks	Upon completing treatment
Opioid	Gimbel, 2003	Controlled-release oxycodone	10-120	159	59	Parallel	5	Yes	Yes	42 days	Upon completing treatment
	Watson, 2003	Controlled-release oxycodone	10-80	45	63	Crossover, no washout	5	Yes	Yes	4 weeks	Upon completing treatment
Tramadol	Harati, 1999	Tramadol	200-400	125	59	Parallel	5	Yes	Yes	42 days	Upon completing treatment

ITT = Intention to treat analysis; NM = Not mentioned; NMDA = N-methyl D-aspartate; PGE = Physician's global evaluation; TCA = Tricyclic antidepressant; SSRI = Selective serotonin reuptake inhibitor; SNRI = serotonin noradrenaline reuptake inhibitor.

5.6.2 Anticonvulsants

Ten trials, with a total of 1270 patients, investigated traditional and newer generation anticonvulsants including sodium valporate (Kochar et al., 2002; Kochar et al., 2004), gabapentin (Backonja et al., 1998), lamotrigine (Eisenberg et al., 2001), carbamazepine (Rull et al., 1969), pregabalin (Lesser et al., 2004; Rosenstock et al., 2004; Richter et al., 2005) and oxcarbazepine (Dogra, Beydoun, Mazzola, Hopwood, and Wan, 2005; Beydoun, Shaibani, Hopwood, and Wan, 2006). A crossover design was used in the carbamazepine trial. Two of the pregabalin studies (Lesser et al., 2004; Richter et al., 2005) and one of the oxcarbazepine studies (Beydoun et al., 2006) were dose response trials. The treatment period was from two weeks to three months. No efficacy data were extracted from the study of Kochar et al. of sodium valporate (Kochar et al., 2004). Data on 300 mg pregabalin (Lesser et al., 2004; Rosenstock et al., 2004), 1200 mg oxcarbazepine (Beydoun et al., 2006) and the first treatment period for the carbamazepine trial were extracted for meta-analysis. Data on 600 mg pregabalin (Lesser et al., 2004; Richter et al., 2005) were analysed separately. Anticonvulsants were categorised into two groups, traditional and newer generation ones.

5.6.2.1 Traditional anticonvulsants

The pooled OR for the treatment efficacy of traditional anticonvulsants was 7.59 (95% CI 2.16-26.58) with little variation between studies and no significant heterogeneity (I^2 = 14.7%, p = 0.31) (Figure 5.2). The pooled OR for adverse events leading to

withdrawal for traditional anticonvulsants was 1.51 (95% CI 0.33-6.96) with no heterogeneity detected between studies (I^2 = 0%, p = 0.74) (Figure 5.3). The NNT for a 50% reduction in pain for traditional anticonvulsants was 2.88 (95% CI 1.98-5.27).

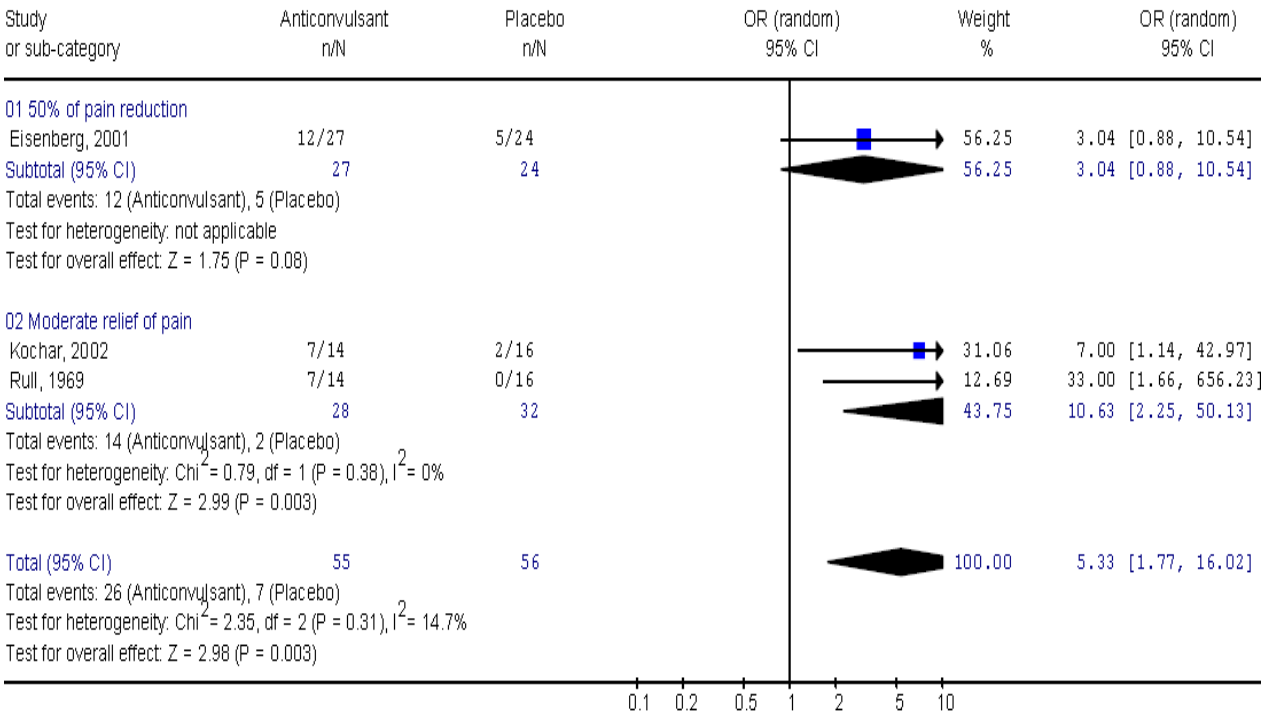

Figure 5.2. Treatment efficacy of traditional anticonvulsants versus a placebo.

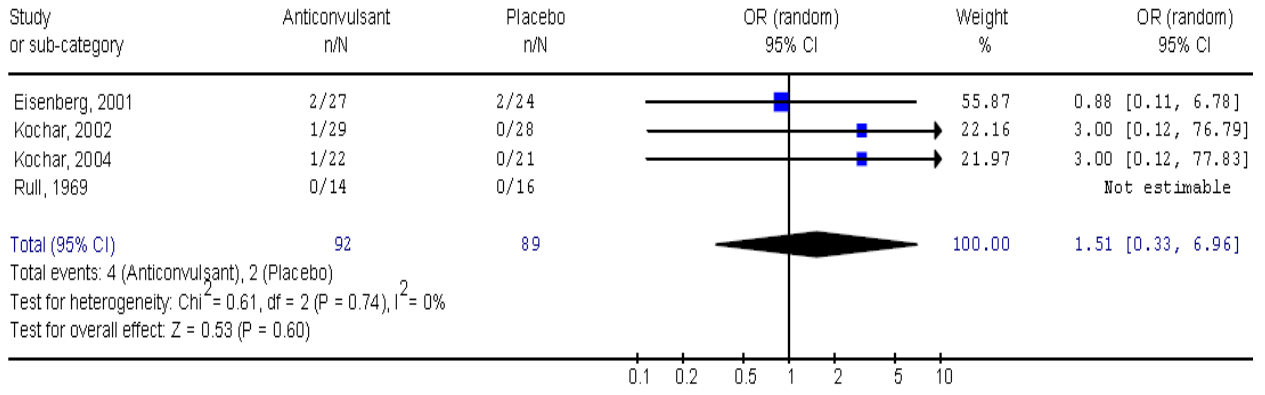

Figure 5.3. Withdrawal due to adverse events related to traditional anticonvulsants versus a placebo.

5.6.2.2 Newer generation anticonvulsants

The pooled OR for the treatment efficacy of newer generation anticonvulsants was 3.25 (95% CI 2.27-4.66) with no heterogeneity detected between studies (I^2 = 0%, p = 0.75) (Figure 5.4). The pooled OR for adverse events leading to withdrawal for traditional anticonvulsants was 2.98 (95% CI 1.75-5.07) with slight variation between studies and no significant heterogeneity (I^2 = 0.8%, p = 0.4) (Figure 5.5). The NNT for a 50% reduction in pain for newer generation anticonvulsants was 4.05 (95% CI 3.14-5.7).

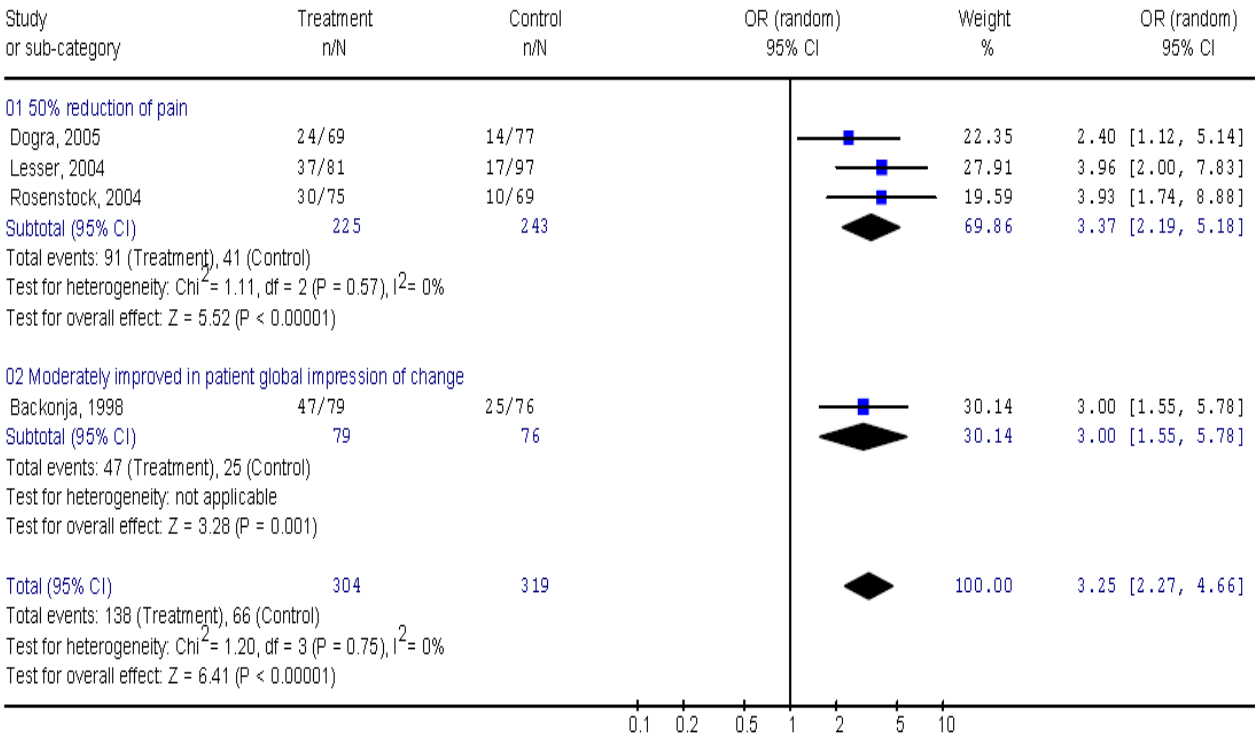

Figure 5.4. Treatment efficacy of newer generation anticonvulsants versus a placebo.

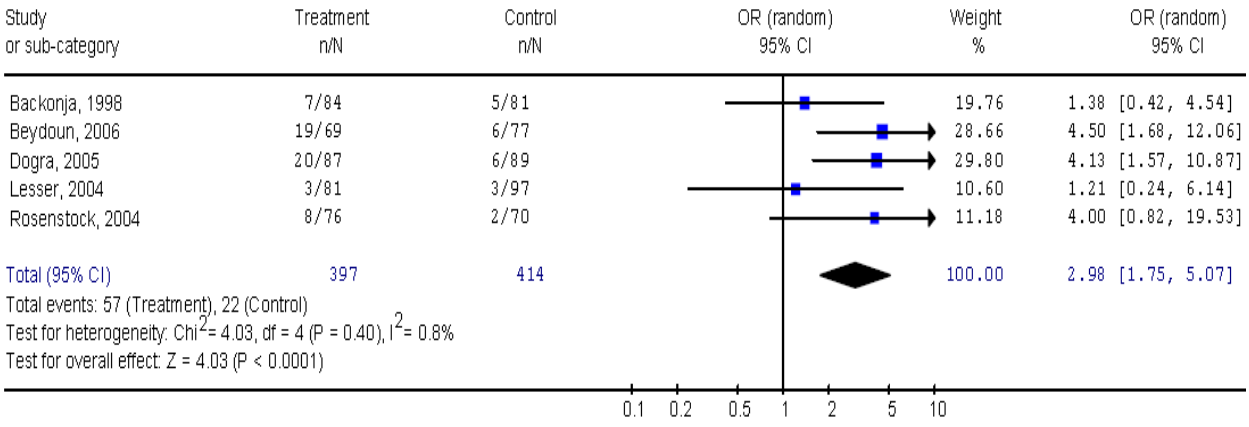

Figure 5.5. Withdrawal due to adverse events related to newer generation anticonvulsants versus a placebo.

The ORs in terms of 50% pain relief for pregabalin 600 mg daily (Lesser et al., 2004; Richter et al., 2005) and pregabalin 300 mg daily (Lesser et al., 2004; Rosenstock et al., 2004) were 3.96 (95% CI 2.5-5.55) and 3.95 (95% CI 2.34-6.66), respectively. The ORs in terms of 30% pain relief for pregabalin 300 mg and 600 mg daily were 3.28 and 3.84, respectively (Lesser et al., 2004). The OR in terms of 30% pain relief for oxcarbazepine 1445 mg was 2.04 (Dogra et al., 2005). The OR in terms of adverse effects leading to withdrawal was 2.81 (95% CI 1.13-7.04) for pregabalin 600 mg daily (Lesser et al., 2004; Richter et al., 2005) and 2.23 (95% CI 0.68 -7.26) for pregabalin 300 mg daily (Lesser et al., 2004; Rosenstock et al., 2004).

The NNT for pregabalin 600 mg daily (Lesser et al., 2004; Richter et al., 2005) and 300 mg daily (Lesser et al., 2004; Rosenstock et al., 2004) for a 50% reduction in pain

were 3.69 (95% CI 2.75-5.63) and 3.75 (95% CI 2.76-5.85), respectively. The NNT for pregabalin 600 mg and 300 mg daily for a 30% reduction in pain were 3.08 (95% CI 2.16-5.41) and 3.48 (95% CI 2.33-6.84), respectively (Lesser et al., 2004). The NNT for oxcarbazepine 1445 mg for a 30% reduction in pain was 6.11 (95% CI 3.14-113.9) (Dogra et al., 2005).

Common side effects from anticonvulsant use included somnolence and dizziness and the major adverse reaction was liver derangement. Two participants withdrew from a study because of liver derangement (Kochar et al., 2002; Kochar et al., 2004).

5.6.3 Antidepressants

Four trials with a total of 94 patients investigated desipramine (Max et al., 1991), citalopram (Sindrup et al., 1992), impramine (Kvinesdal et al., 1984) and amitriptyline (Max et al., 1987). Three studied tricyclic antidepressants (TCAs) and one investigated serotonin reuptake inhibitors (SSRIs). All of them were crossover studies with treatment periods from three to six weeks. Only one study had a one-week washout period: the data from the first treatment period of this study were extracted and analysed (Sindrup et al., 1992).

5.6.3.1 Serotonin reuptake inhibitors (SSRIs)

The OR for citalopram for 50% pain relief was 3.5 (95% CI 0.3-38.2), and that for adverse events leading to withdrawal was 5.6 (95% CI 0.3-125.5) (Sindrup et al., 1992). The NNT for citalopram for 50% pain relief was 7.5 (95% CI -9.5-2.69) (Sindrup et al., 1992).

5.6.3.2 Tricyclic antidepressants (TCAs)

The pooled OR for the treatment efficacy of TCAs was 22.24 (95% CI 5.83-84.75) with slight variation between studies and no significant heterogeneity (I^2 = 1.5%, p = 0.36) (Figure 5.6). The NNT for TCAs to yield notable improvement in the global assessment and moderate pain relief was 1.74 (95% CI 1.42-2.26). The pooled OR for adverse effects leading to withdrawal for TCAs was 2.32 (95% CI 0.59-9.9) with no heterogeneity detected (I^2 = 0%, p = 0.77) (Figure 5.7). The adverse effects most frequently leading to withdrawal were dry mouth and sedation.

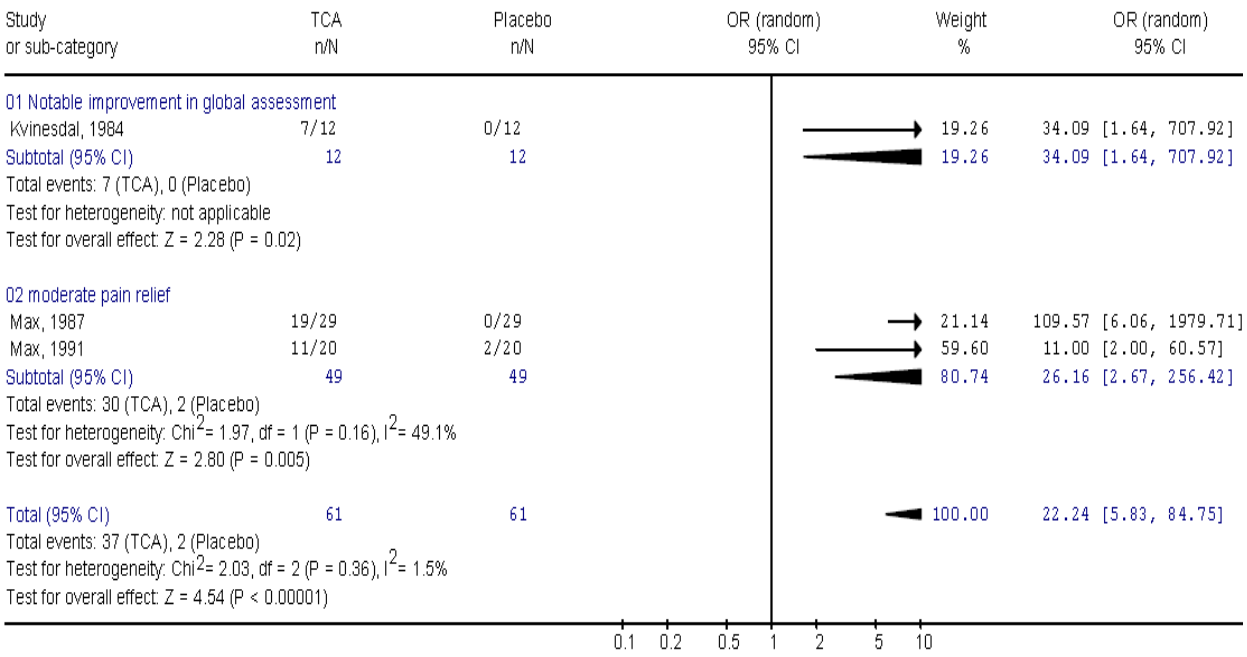

Figure 5.6. Treatment efficacy of TCAs versus a placebo.

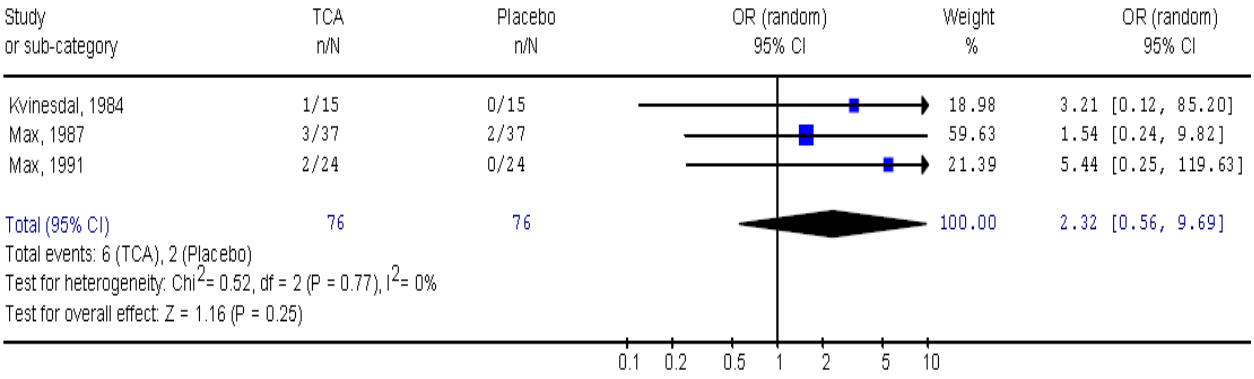

Figure 5.7. Withdrawal due to adverse events related to TCAs versus a placebo.

5.6.4 Serotonin noradrenaline reuptake inhibitor (SNRI)

Two trials with a total of 445 patients investigated duloxetine (Goldstein et al., 2005; Raskin et al., 2005). Both used a 12-week, parallel-group design and were dose response trials. The pooled OR in terms of 50% pain relief for duloxetine 60 mg was 2.55 (95% CI 1.73-3.77) with no significant heterogeneity detected (I^2 = 0%, p = 0.7) (Figure 5.8), and that of duloxetine 120 mg was 2.1 (95% CI 1.03-4.27) with significant heterogeneity detected (I^2 = 69.5%, p = 0.07) (Figure 5.9).

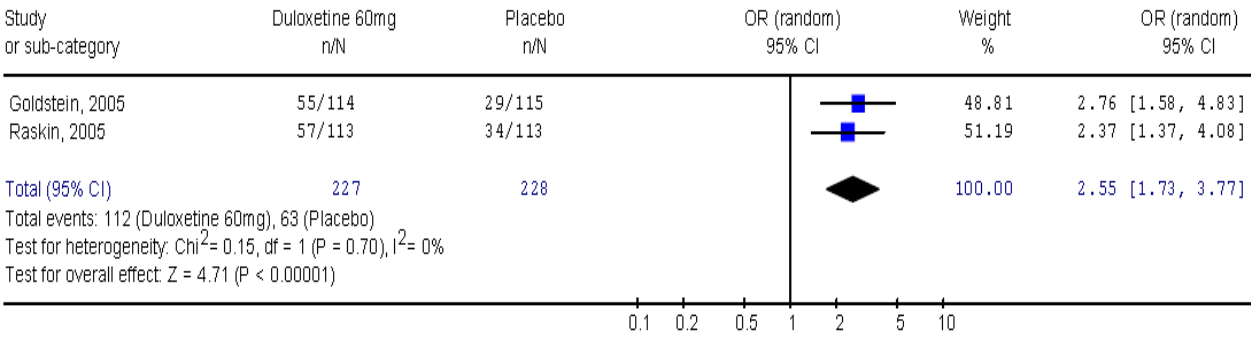

Figure 5.8. Treatment efficacy of duloxetine 60 mg versus a placebo.

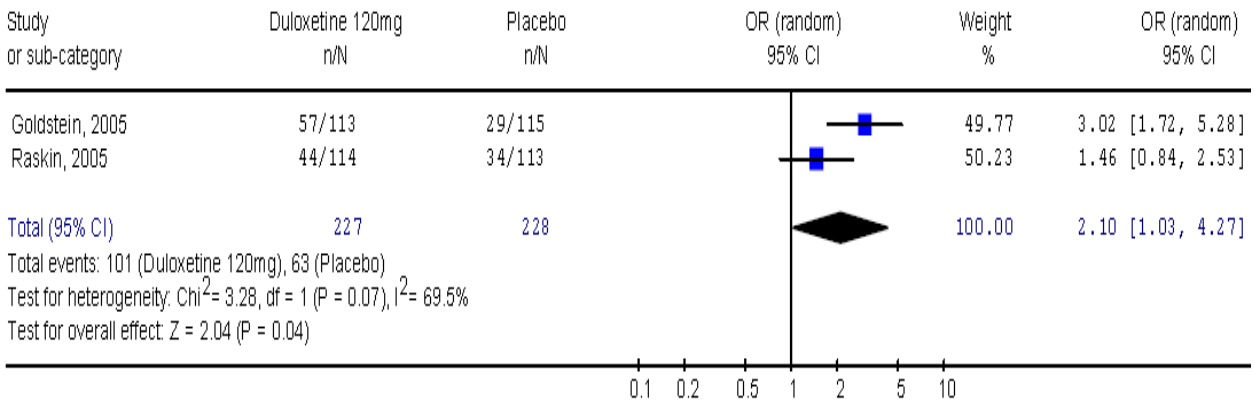

Figure 5.9. Treatment efficacy of duloxetine 120 mg versus a placebo.

The NNT for duloxetine 60 mg for 50% pain relief was 4.61 (95% CI 3.29-7.7), and that of duloxetine 120 mg was 5.93 (95% CI 3.91-12.23). The NNT for duloxetine 60 mg and 120 mg for 30% pain relief were 5.38 (95% CI 3.19-17.26) and 4.84 (95% CI 3-12.53), respectively.

The pooled OR for adverse events leading to withdrawal from duloxetine 60 mg was 2.36 (95% CI 1.05-5.35) with no significant heterogeneity detected (I^2 = 0%, p = 0.59) (Figure 5.10), and that for duloxetine 120 mg was 4.65 (95% CI 2.18-9.94) with no significant heterogeneity detected (I^2 = 0%, p = 0.84) (Figure 5.11). The most frequently reported adverse events were nausea, somnolence, dizziness and constipation.

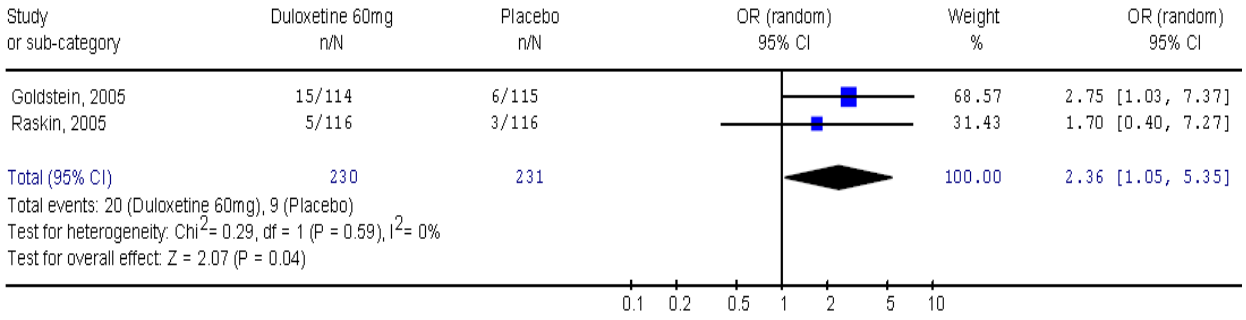

Figure 5.10. Withdrawal due to adverse events related to duloxetine 60 mg versus a placebo.

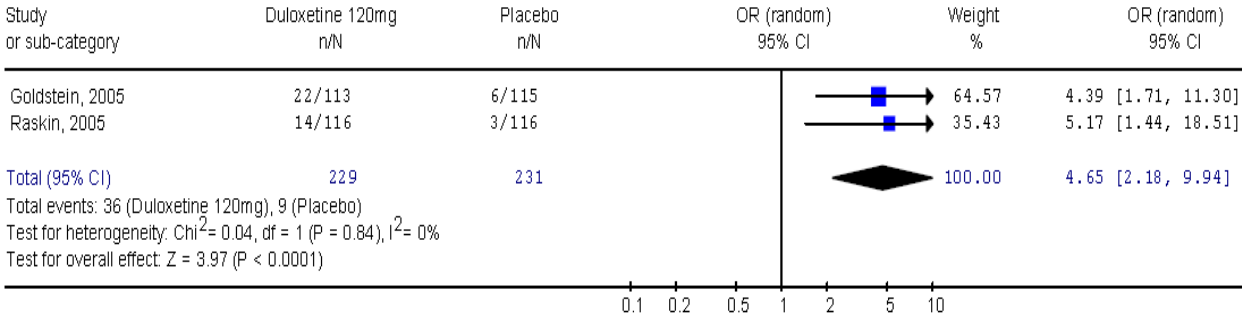

Figure 5.11. Withdrawal due to adverse events related to duloxetine 120 mg versus a placebo.

5.6.5 Ion channel blocker

Three trials investigated mexiletine in a total of 173 patients. One used a crossover design (Dejgard et al., 1988), and another was a dose-response study (Oskarsson et al., 1997). The pooled weighted mean difference of the mean visual analogue scale for pain intensity for mexiletine 600-720 mg and a placebo was -1.07 (95% CI -2.64 to -1.11) with no heterogeneity detected (I^2 = 0%, p = 0.88) (Figure 5.12). One study reported no statistical differences between mexiletine 600-675 mg and a placebo over a

three-week treatment period (Wright et al., 1997). The pooled OR for adverse effects leading to withdrawal for mexiletine was 1.08 (95% CI 0.13-8.8) (Figure 5.13). Adverse effects leading to withdrawal included itching, pain, headache, nausea and vomiting (Wright et al., 1997).

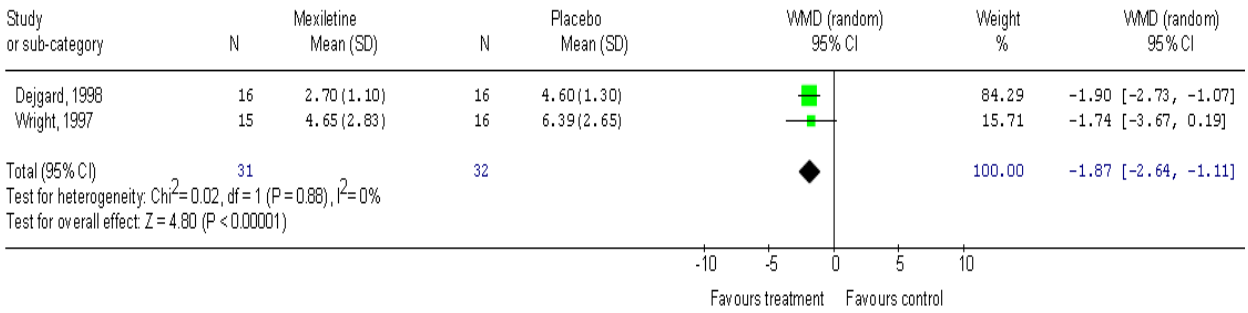

Figure 5.12. Weighted mean differences (WMD) of the mean visual analogue scale for pain intensity.

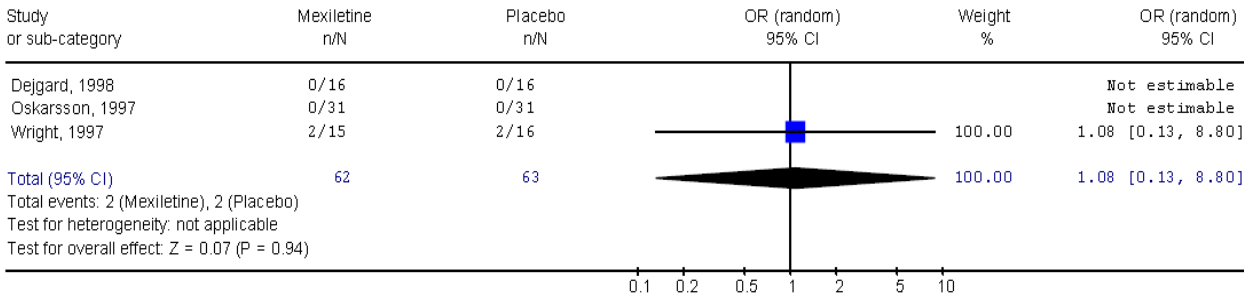

Figure 5.13.Withdrawal due to adverse events related to mexiletine versus a placebo.

5.6.6 NMDA antagonist

One trial, with 14 patients, investigated dextromethorphan (Nelson, Park, Robinovitz, Tsigos, and Max, 1997). It used a crossover design with a six-week treatment period and one-week washout. The data for the first treatment period could not be extracted; therefore, the calculation was based on the data of the whole treatment period. The OR in terms of 50% pain relief for dextromethorphan (381 mg mean daily dose) was 31.2 (95% CI 1.5-633.1), and the NNT in terms of 50% pain relief for dextromethorphan (381 mg mean daily dose) was 1.71 (95% CI 1.24-3.74). In the published data, there are no extractable dichotomous data on adverse events leading to withdrawal.

5.6.7 Opioids

Two trials with a total of 159 patients investigated controlled-release oxycodone (Gimbel et al., 2003; Watson et al., 2003). One of the oxycodone trials used a crossover design (Watson et al., 2003) and the other reported that a 37 mg average daily dose of controlled-release oxycodone had a superior analgesic effect compared with a placebo (Gimbel et al., 2003). The OR for the treatment efficacy of oxycodone was 5.25 (95% CI 1.83-15.03. The NNT for oxycodone for 50% pain relief was 2.62 (95% CI 1.67-6.04).

The pooled OR for adverse events leading to withdrawal for oxycodone was 2.87 (95% CI 1.01-8.18) with considerable variation between studies, but there was no

statistically significant heterogeneity (I^2 = 35.6%, p = 0.21) (Figure 5.14). The most common adverse events related to controlled-release oxycodone use were constipation, somnolence and nausea.

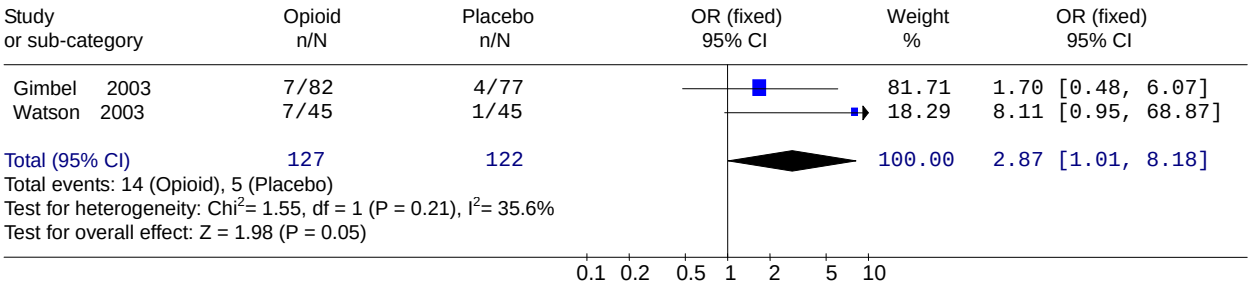

Figure 5.14. Withdrawal due to adverse events related to opioids versus a placebo.

5.6.8 Tramadol

One trial with 127 patients investigated tramadol (Harati et al., 1998). Although no necessary data could be extracted from the published report on tramadol, those previously obtained in another study were used and published in this study (Sindrup and Jensen, 1999). The OR for 50% pain relief was 3.8 (95% CI 1.8-8) for tramadol with an average daily dose of 210+/-113mg. The NNT for tramadol 210+/-113mg daily for 50% pain relief was 3.09 (95% CI 2.05-6.3).

The OR for adverse events leading to withdrawal for tramadol was 10.5 (95% CI 1.29-85.55). The withdrawal-related adverse events for tramadol were dyspepsia and nausea. Common adverse events related to tramadol use were nausea, constipation,

headache and somnolence.

5.6.9 Topical agents

5.6.9.1 Isosorbide dinitrate spray

One trial with a total of 22 patients investigated isosorbide dinitrate spray (Yuen et al., 2002). It used a crossover design with a four-week treatment period and two-week washout. However, no dichotomous data could be extracted from the published reports. The author reported that there was significant relief from burning sensation in the treatment group.

5.6.9.2 Capsacin

One trial with a total of 277 patients investigated 0.075% capsaicin cream (Capsaicin Study Group, 1991). It used an eight-week parallel-group design and the capsaicin cream was applied to the skin four times daily. The OR in terms of 50% pain relief was 2.37 (95% CI 1.32-4.26) and that of adverse events leading to withdrawal was 4.02 (95% CI 1.45-11.16). The most common adverse events were a burning sensation on the site of application, coughing or sneezing, accidental irritation to other body parts and rashes. The NNT in terms of 50% pain relief was 4.64 (95% CI 2.93-11.19).

5.7 Discussion

5.7.1 Clinical symptoms, nerve damage and outcome measure

Painful symptoms are frequently reported by patients suffering from DN. Neuropathic pain symptoms are reported in 3-20% (Boulton et al., 1985; Partanen et al., 1995; Sorensen et al., 2002; Daousi et al., 2004) and closely related to small nerve fibre damage. In clinical settings, DN management takes two main routes: disease-modifying therapies, such as glycaemic control, and pain intensity reduction therapies, which involve various kinds of analgesics. Although pain intensity may not be sufficient to reflect the outcome of treatment, it is a common outcome criterion in clinical research. Only a few studies have reported treatment efficacy with regard to different qualities of pain including allodynia (Richter et al., 2005) and burning pain (Yuen et al., 2002; Goldstein et al., 2005), or the improvement of nerve function (Arezzo et al., 2008).

The results of this review reveal that some patients cannot tolerate the adverse effects of these medications, as the OR for adverse events leading to withdrawal was between 1.08 and 4.65, and even 10.5 for individual medications. In addition, treatments focusing on pain intensity reduction did not yield satisfactory results for all patients, as reflected by the NNT of different classes of medications. Small nerve fibre damage may precede large nerve fibre damage in the early stage of DN (Smith et al., 2001; Malik et al., 2005; Løseth et al., 2008). Treatments that target a particular damaged nerve with a specific class of medication can enhance the treatment effect and reduce

patient suffering. Furthermore, the use of a lower dose of medication in the early stage of disease could increase medication tolerance and optimise treatment effect.

5.7.2 Early diagnosis of DSP

DSP is often not diagnosed until patients present with clinical symptoms and the disease is moderately advanced. The Glycemic Optimization with Algorithm and Labs at Point of Care (GOALA1C) trial in the United States found that 19% of 7892 patients with clinical signs were not diagnosed as having DN (Herman and Kennedy, 2005). Electrophysiology studies can detect large fibre dysfunction in DSP; however, there is a discrepancy between clinical manifestations and electrophysiological study findings of DPN. Liu and colleagues (2005) investigated clinical symptoms and electrophysiological features of 700 Chinese diabetic patients and reported normal electrophysiological findings in patients presenting with neuropathy and abnormal electrophysiological results in patients without clinical symptoms. The diagnosis of DSP is challenging because of the variation in clinical presentation and changes in physiological status. Despite these obstacles, early diagnosis would allow a better understanding of DN-related problems or complications, and thus they could be addressed. It is postulated that definite interventions will not be offered until DSP can be accurately diagnosed in the early stage.

5.7.3 The benefit and obstacle of early DSP intervention

Effective early intervention approaches are those that prevent problems or complications in the early stage of disease. Several lines of evidence show that such approaches yield better outcomes in acute and chronic diseases. Cognitive training and participation in health promotion courses in the early stage of Alzheimer's disease improves cognition (Buettner and Fitzsimmons, 2009), activities of daily living and decision making (Yu et al., 2009). The early implementation of stroke treatment after a transient ischemic attack or minor stroke was found to significantly reduce the risk of early recurrent stroke in 1278 patients (Rothwell et al., 2007). The Early Treatment Diabetic Retinopathy Study Research Group assessed the effects of early photocoagulation on diabetic macular oedema and found that early photocoagulation reduced visual loss in NIDDM patients, while 5-year follow-up revealed improvement in visual acuity (Anonymous, 1991). It is believed that early intervention in painful DSP can also yield better outcomes.

Early intervention relies on accurate diagnosis in the early stage of disease, however, an easy and convenient method for detecting early-stage small nerve fibre damage in patients with diabetic neuropathy is not yet available. To achieve better outcomes, such a method is required.

5.8 Limitations of the study

This systematic review did not include studies that have been published in languages other than English; hence, the results from these studies have been ignored. The participants in the included studies had moderate to severe pain; therefore, the results of the present review may not reflect the treatment effect in patients with mild pain. Only a few studies examined the use of topical medications in the treatment of painful DN, and thus no meta-analysis of these medications could be conducted.

5.9 Conclusion and recommendations

Although the effect of different kinds of drugs on pain intensity reduction is the focus of an increasing number of trials, pain management is still a problem in clinical settings. Further research into the efficacy of treatment targeting damaged nerves rather than pain intensity reduction is necessary. Indeed, a surrogate method is needed to identify the change in small nerve fibres after treatment. The reliability of CHEPs, a potential surrogate method for detecting small nerve fibre damage, will be tested in the next stage.

Chapter 6

Stage 2 – The Characteristics and Reliability of Contact Heat Evoked Potentials in Healthy Adults

6.1 Introduction

The unsatisfactory results of symptomatic treatment amongst some patients with painful DN may be due to treatment that focuses on pain reduction rather than the individual type of nerve damage. Indeed, the lack of a surrogate method for identifying mild neuropathy in patients with DSP is a problem. CHEPs have been proposed to be a potential method for examining the integrity of small myelinated nerve fibres; however, its reliability has not yet been tested. This chapter will present the details of the research method to investigate the reliability of CHEPs and the study findings and conclude with a discussion of these findings.

6.2 Research objectives

1) To test the reproducibility of CHEPs at different stimulation sites in the lower extremities of healthy adults.
2) To explore the relationship between body height and CHEP latencies at different sites in the lower extremities of healthy adults.
3) To explore the relationship between pain intensity ratings and CHEP amplitudes at different sites in the lower extremities of healthy adults.
4) To test the reliability of CHEPs at different stimulation sites in the lower extremities of healthy adults.

6.3 Research questions

1) What is the reproducibility of CHEPs in terms of percentage at different sites in the lower extremities of healthy adults?
2) What is the relationship between body height and CHEP latencies at different sites in the lower extremities of healthy adults?
3) What is the relationship between pain intensity ratings and CHEP amplitudes at different sites in the lower extremities of healthy adults?
4) Are CHEPs a reliable method, in terms of the intraclass correlation coefficient (ICC) and Cronbach's alpha, for assessing the integrity of small myelinated fibres?

6.4 Research hypotheses

1) There is a positive relationship between body height and CHEP latencies at different sites in the lower extremities of healthy adults.
2) There is a positive relationship between pain intensity ratings and CHEP amplitudes at different sites in the lower extremities of healthy adults.
3) CHEPs are a reliable method for assessing the integrity of small myelinated fibres.

6.5 Study design

This was a cross-sectional study with one group of healthy adults. The reliability of CHEPs was tested and CHEP characteristics in healthy adults were explored.

6.5.1 Sampling

Participants were recruited using convenience sampling. Potential participants were identified amongst friends, colleagues and relatives. Eligible subjects based on the following inclusion and exclusion criteria were invited to participate in the study, which lasted 3-4 hours. A $100 supermarket coupon was given to subjects as a token of appreciation for their participation.

6.5.1.1 Inclusion criteria

1) Aged between 18 and 60
2) Mentally alert

6.5.1.2 Exclusion criteria

1) Known history of DM
2) Known history of lumbar discogenic disease or nerve root compression
3) Known history of neurological disease such as neuropathy
4) Known history of peripheral vascular disease
5) Known history of central nervous system disease such as brain tumour
6) Known history of chronic pain syndrome such as trigeminal neuralgia

6.5.2 Instrument

6.5.2.1 Contact heat stimulation

CHEP stimulation was performed using the Pathway ATS/CHEPS (Medoc, Ramat Yishai, Israel) (Figure 6.1), which is a computer-controlled device capable of generating and recording the objective response of A-delta fibres using rapid heat-induced pain. The thermode consists of an external fast-heating foil with a heating rate of 70ºC/s and a Peltier device that allows a cooling rate of 40ºC/s. The round

activation area of the thermode is 573 mm^2 (27 mm in diameter). Cooling begins immediately following the attainment of the target heat pulse temperature, which is set using software provided by the manufacturer. The skin temperature is monitored by two thermocouples at the surface of the thermode. The system automatically switches off if the heat exchange between the thermode and the skin is not optimal.

Figure 6.1. Pathway (ATS/CHEPs) device for thermal heat stimulation.

6.5.2.2 Numerical pain rating scale

The numerical pain rating scale (NPRS) is a horizontal line with the numbers 0 through 10 evenly distributed along the line (Figure 6.2). Zero, located at one end of the line, indicates no pain; 10, located at the other end, represents the worst pain that one can imagine. The number chosen represents the participant's pain intensity rating, and can be treated as ratio data (Jensen, Karoly, and Braver, 1986; Jensen and Karoly, 1992). The validity and reliability of the NPRS have been confirmed in a number of studies (e.g., Ferraz et al., 1990; Wilkie, Lovejoy, Dodd, and Tesler, 1990; Jensen and Karoly, 1992; Puntillo and Neighbor, 1997; Berthier, Potel, Lecoute, Tonze, and Baron, 1998).

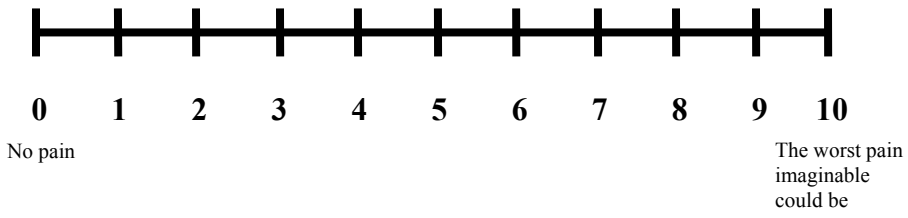

Figure 6.2. Numerical Pain Rating Scale.

6.5.3 Ethical considerations

The nature and purpose of the study were explained to all participants and a written information sheet was given to them for their reference (Appendix A). All of the participants signed the consent form before data collection was undertaken (Appendix B). They were assured that their participation was voluntary and that they could withdraw from the study at any time without prejudice. The study involved the application of thermal stimulation; therefore, the procedure could cause additional pain to subjects. Their condition was observed throughout the procedure to detect any signs of discomfort, such as fatigue or an impending attack of pain. Care was taken to ensure that the thermal pain would not induce tissue damage, such as redness, or a scalding sensation. The study was discontinued if any of the above occurred. Personal information and data remained confidential and anonymous. The ethical guidelines endorsed by the International Association for the Study of Pain (IASP) were followed, and ethical approval was obtained from Hong Kong Polytechnic University.

6.6 Data collection

6.6.1 Screening and data collection forms

A screening form, which contained a list of the inclusion and exclusion criteria, was used to recruit suitable participants (Appendix C). A data collection form was used to collect demographic data, including body height and weight, medical and surgical history, and medication history (Appendix D).

6.6.2 Contact heat evoked potentials

On the day of the study, subjects sat in a reclining chair with their eyes closed, in a quiet room with an ambient temperature around 22-23ºC. The procedure was modified from that of Granovsky and colleagues (2005). The heat stimuli were delivered at the dorsum of the foot and 10 cm proximal to the lateral malleolus of the non-dominant side of all subjects at a peak temperature of 51ºC. The baseline temperature was 35ºC for all stimuli. The time from onset to peak temperature was 250 ms.

Each stimulus block consisted of 16 constant-intensity stimuli. The inter-stimulus interval was 10-15 s, and the duration of each stimulus was 0.2 s. Subjects were allowed to withdraw from the stimulation if it became intolerable. The thermode was moved slightly between stimuli to avoid potential sensitisation, desensitisation, or fatigue of the receptors. Before beginning evoked potential recording, several stimuli

were applied to prevent expectation effects and reduce novelty ones. Different body sites were stimulated in a pseudorandom order. Two identical blocks of stimulation were applied to the same body site to test the reliability, and a 15-minute break was given between the two blocks of thermal stimuli at the same body site. Participants rated the perception of each stimulus 3 s after stimulus onset using the NPRS (Appendix E).

6.6.3 Contact heat evoked potential recording

The CHEPs were recorded using 64-channel surface recording electrodes, which were placed on the scalp according to the standard 10-20 system (Figure 6.3). The reference was at bilateral earlobes. The EEG was recorded within a 0.01 to 100 Hz bandpass and digitised at a sampling rate of 1000 Hz by Neuroscan 4.4. The scalp-electrode impedance was less than 5 kΩ. An ocular artefact was obtained by vertical electro-oculography of the left eye and horizontal electro-oculography of both eyes. A 10-second baseline before stimulus onset was included in each recording epoch. A trigger signal was given at the beginning of the temperature increase.

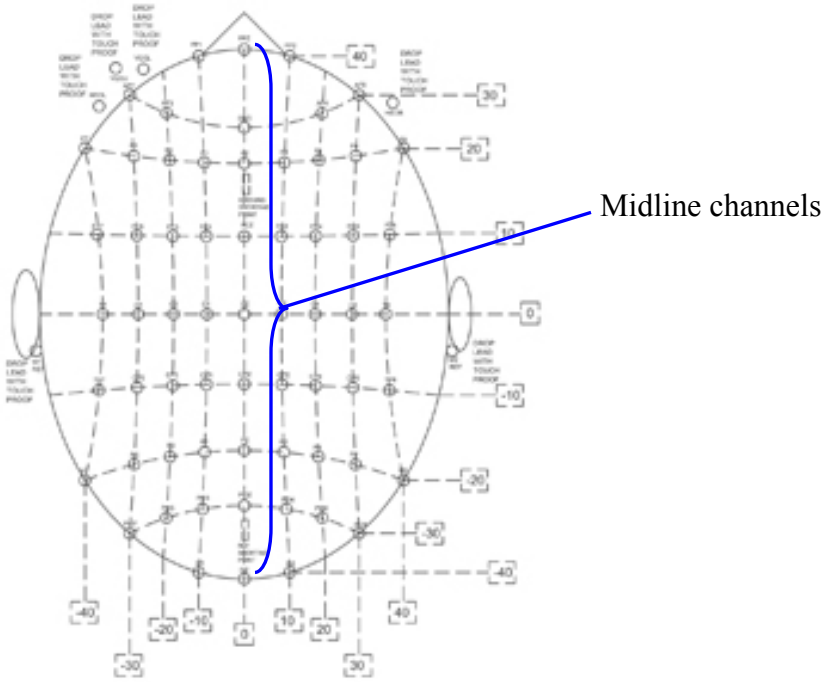

Figure 6.3. 64-channel EEG electrode layout.

6.7 Data management and analysis

Descriptive data including demographic information, body height and skin temperature at the stimulation site were input and analysed using Statistical Package for the Social Sciences (SPSS) version 13.0. All raw data entered in the computer were checked for errors by double checking with the data collection form. The descriptive statistics were used to analyse these data.

EEG data were recorded and digital EEG data were analysed using Neuroscan 4.4. Peri-stimulus epochs contaminated by artefacts were discarded and excluded from signal

averaging. The remaining sweeps for each stimulation site were averaged separately. At least two sets of averaged waveforms were obtained from the same stimulation site to calculate the percentage of reproducibility and reliability coefficients. The peak amplitudes and latencies of the major negative (N1) and subsequent positive (P1) peaks of evoked potentials, and the negative to positive amplitude (N1-P1 amplitudes) were identified from the averaged waveform of each electrode. The latencies and amplitudes were presented as the mean values +/- standard deviation.

The averaged waveforms of all 64 channels were assessed and the maximal responsive channels were identified. Data from the maximal responsive channels were used for data analysis. The relationship between body height and peak latencies, and pain intensity ratings and N1-P1 amplitudes were analysed using Pearson's product-moment correlation coefficient. T-test was used to analyse the differences between the two sets of CHEP parameters of each stimulation site, the differences between the two sets of pain intensity ratings at each stimulation site, and the pain intensity ratings between the two stimulation sites. The reproducibility of CHEPs at each stimulation site was calculated as a percentage. The reliability of CHEPs at each stimulation site was analysed and represented by the single measure intraclass correlation (ICC) and Cronbach's alpha.

6.8 Results

6.8.1 Characteristics of participants

The participants consisted of 21 healthy adults (10 males and 11 females) aged between 28 and 56 years (mean age 45.1 ± 7.83) with a mean body height of 164.8 (± 7.6) cm and a mean body mass index of 22.96 (± 4.92). Two of them were smokers and one of them was a moderate consumer of alcohol. All of them were right handed. None had a known surgical history. Two had hypertension and are taking oral anti-hypertensive medicine. All of them had no allodynia, paresthesia, loss of sensation on bilateral lower limb and scored 0 point in TCNS. All of them had negative results in straight leg raise test. All of them completed the data collection procedure. There was no significant difference in skin temperature between the two stimulation sites ($t = 1.212$, $p = 0.24$).

6.8.2 Preliminary analysis of CHEPs

Stimulation of the dorsum of the foot and 10 cm above the lateral malleolus at a peak temperature of 51ºC evoked well-defined potentials in all 21 participants. When stimulating these two sites, 70-80% of the maximal responses appeared in the midline channels, mostly in the Cz one, followed by the FCz and CPz channels. Therefore, the amplitude and latency of the Cz channel was used for data analysis.

6.8.3 Reproducibility of CHEPs at each stimulation site

Table 6.1 shows the reproducibility of CHEPs at each stimulation site of the lower limbs. All of the stimulations at the dorsum of the foot were reproducible, and the stimulation 10 cm proximal to the lateral malleolus was not reproduced in one subject.

Table 6.1

Percentage of reproducible CHEPs at different stimulation sites of the lower limbs (N = 21)

Stimulus and sites	N	Number of reproducible CHEPs	Percentage of reproducible CHEPs
Dorsum of foot, 51ºC	21	21	100%
10 cm proximal to lateral malleolus, 51ºC	21	20	95.2%

6.8.4 The characteristics of contact heat evoked potentials (CHEPs) in healthy adults

Figure 6.4 shows the waveforms evoked in the Cz channel in one representative subject following stimulation of the dorsum of the foot and 10 cm above the lateral malleolus. The 51ºC thermal stimulation generated a negative peak response followed by a positive peak response in all but one of the subjects at the two different sites of the lower limbs. There was no identifiable evoked response following thermal stimulation 10 cm proximal to the left lateral malleolus at time 2 in the one subject.

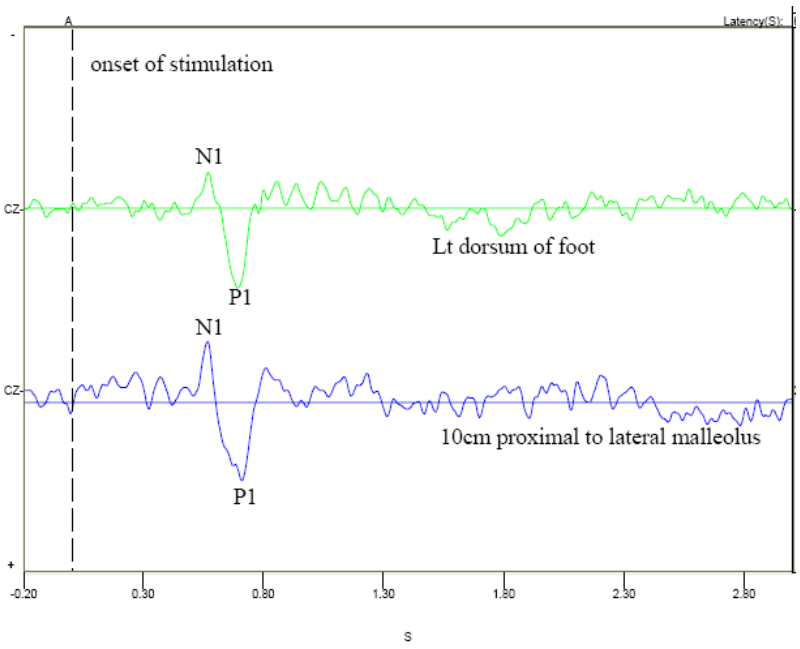

Figure 6.4. CHEPs of the dorsum of the left foot and 10 cm proximal to the left lateral malleolus.

Table 6.2 shows the CHEPs in normal healthy adults. The mean N1 and P1 latencies of the foot were longer than those 10 cm proximal to the lateral malleolus, and the mean N1 amplitude, P1 amplitude and N1-P1 amplitude of the foot were lower than those 10 cm proximal to the lateral malleolus.

Table 6.2 CHEPs in normal healthy adults (N = 21)

Stimulus and sites	N	N1 latency (s)	N1 amplitude (μV)	P1 latency (s)	P1 amplitude (μV)	N1-P1 amplitude (μV)
Dorsum of foot, 51ºC	21	0.585(0.032)	-10.21(5.69)	0.691(0.045)	17.21(8.2)	29.87(14.64)
10 cm proximal to left lateral malleolus, 51ºC	21	0.574(0.033)	-10.91(4.14)	0.69(0.042)	17.94(7.19)	30.93(11.57)

6.8.5 Relationship between body height and CHEP latencies at different body sites

There were significant correlations between the N1 latency 10 cm proximal to the lateral malleolus and body height ($r = 0.433$, $p = 0.05$) (Figure 6.5), but not between the N1 latency of the foot and body height ($r = 0.422$, $p = 0.056$) (Figure 6.6), P1 latency of the foot and body height ($r = 0.403$, $p = 0.07$) (Figure 6.7) or P1 latency 10 cm proximal to the lateral malleolus ($r = 0.349$, $p = 0.121$) (Figure 6.8). Hence, the hypothesis that there will be a positive relationship between body height and N1 latency of CHEPs 10cm proximal to the lateral malleolus is supported. However, the hypothesis that there will be a positive relationship between body height and P1 latency of CHEPs at 10cm proximal to the lateral malleolus and the dorsum of the foot is rejected. The hypothesis that there will be a positive relationship between body height and N1 latency of CHEPs at the dorsum of the foot is also rejected.

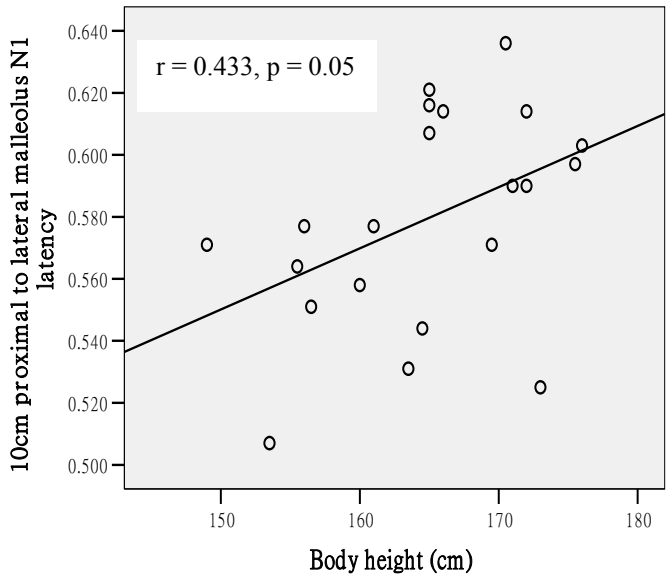

Figure 6.5. Correlation between body height and N1 latency following stimulation 10 cm proximal to the left lateral malleolus (N = 21).

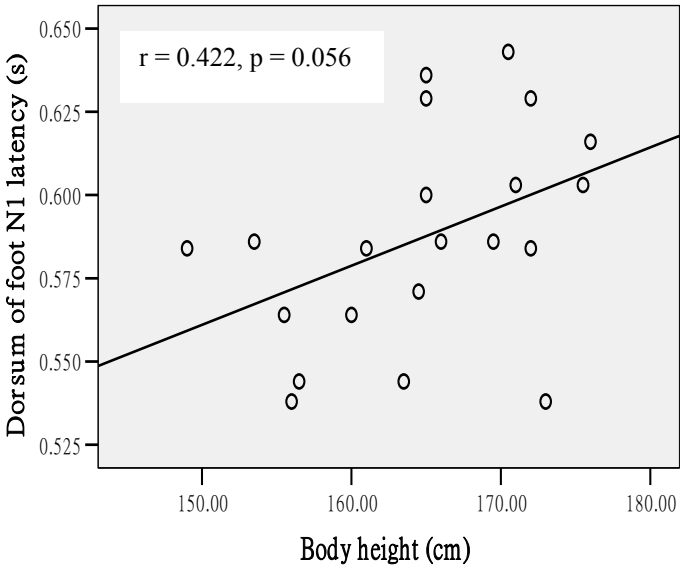

Figure 6.6. Correlation between body height and N1 latency following stimulation of the dorsum of the left foot (N = 21).

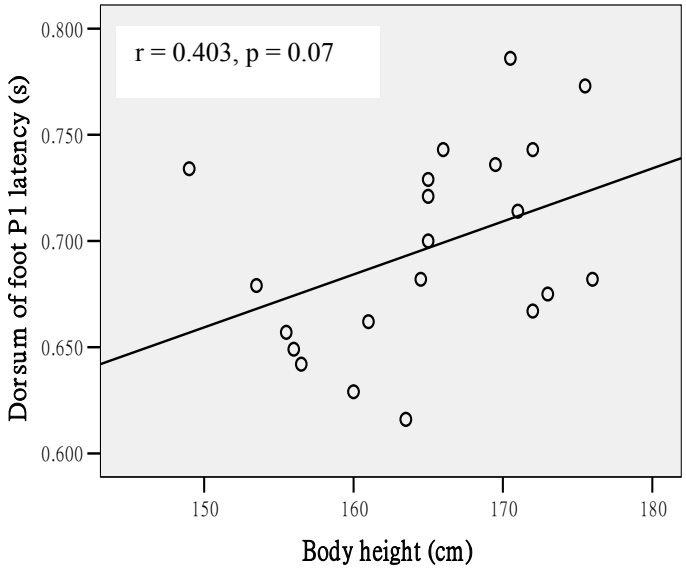

Figure 6.7. Correlation between body height and P1 latency following stimulation of the dorsum of the left foot (N = 21).

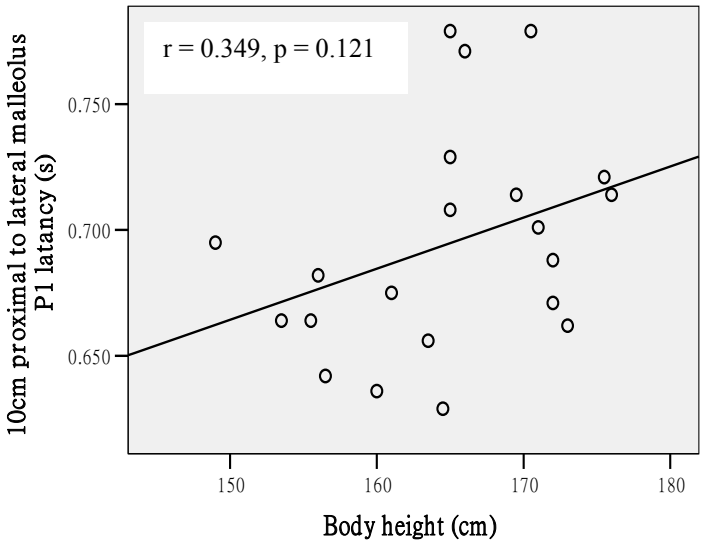

Figure 6.8. Correlation between body height and P1 latency following stimulation 10 cm proximal to the left lateral malleolus (N = 21).

6.8.6 Relationship between pain intensity ratings and N1-P1 peak amplitudes at different sites

There were no significant correlations between pain intensity ratings and N1-P1 amplitudes at the dorsum of the foot ($r = 0.004$, $p = 0.986$) or 10 cm proximal to the lateral malleolus ($r = -0.198$, $p = 0.403$). Hence, the hypothesis that there will be a positive relationship between pain rating intensity and amplitudes of CHEPs at different sites in the lower extremities is rejected.

6.8.7 Relationship of pain intensity ratings between time 1 [T1] and time 2 [T2] at different sites

Table 6.3 shows the pain intensity ratings at different body sites following thermal stimulation at different time points. There were no significant differences in the pain intensity ratings at the two time points of each stimulation site ($p > 0.05$). The pain intensity ratings were significantly correlated following stimulation of the dorsum of the foot and 10 cm proximal to the left lateral malleolus at the two time points ($r = 0.865$, $p < 0.001$; $r = 0.923$, $p < 0.001$, respectively).

No significant differences were found between the pain intensity ratings of the two different sites at times 1 and 2 ($t = 1.025$, $p = 0.318$; $t = 0.35$, $p = 0.73$, respectively). When comparing males and females, there were no significant differences in the pain intensity ratings following stimulation of the dorsum of the foot and 10 cm proximal to the left lateral malleolus ($p > 0.05$).

Table 6.3

Pain intensity ratings at different sites of the lower limbs at different time points

Stimulus and sites	N	Pain intensity rating	
		Mean(SD)	Range
Dorsum of left foot, 51ºC (T1)	21	4.3(2.3)	0.7-9
Dorsum of left foot, 51ºC (T2)	20	4(2.3)	0-8.5
10 cm proximal to left lateral malleolus (T1)	21	3.9(2.3)	0-8.7
10 cm proximal to left lateral malleolus (T2)	20	3.9(2.3)	0-7.93

6.8.8 Relationship of CHEPs between time 1 [T1] and time 2 [T2] at different sites

There were no significant differences in the N1 and P1 latencies, N1 and P1 amplitudes, or N1-P1 amplitudes between the two time points for the dorsum of the left foot (Table 6.4). There were strong correlations between the two time points for the dorsum of the left foot for the N1-P1 amplitude ($r = 0.831$, $p < 0.001$), followed by the P1 amplitude, N1 latency, P1 latency and N1 amplitude (Table 6.4)

Table 6.4

Correlations and differences between CHEPs at time 1 [T1] and time 2 [T2] at the dorsum of the left foot

Stimulus and site	CHEPs	N	Mean (SD)	Correlation		Difference	
				r	p	t	p
Dorsum of foot, 51ºC	N1 latency (s) [T1] N1 latency (s) [T2]	19	0.585(0.032) 0.571(0.046)	0.56	<0.001	2.084	0.052
	N1 amplitude (μV) [T1] N1 amplitude (μV) [T2]	19	-10.21(5.69) -10.03(5.19)	0.619	0.005	-0.16	0.875
	P1 latency (s) [T1] P1 latency (s) [T2]	19	0.691(0.045) 0.683(0.037)	0.715	0.001	1.043	0.311
	P1 amplitude (μV) [T1] P1 amplitude (μV) [T2]	20	17.21(8.2) 15.22(6.97)	0.798	<0.001	1.798	0.088
	N1-P1 amplitude ((μV) [T1] N1-P1 amplitude ((μV) [T2]	21	29.87(14.64) 26.71(12.39)	0.831	<0.001	1.779	0.09

There were no significant differences in the N1 and P1 latencies, N1 and P1 amplitudes, or N1-P1 amplitudes between the two time points at 10 cm proximal to the left lateral malleolus (Table 6.5). There were strong correlations between the two time points at 10 cm proximal to the left lateral malleolus for the P1 amplitude ($r = 0.722$, $p < 0.001$), followed by the P1 latency, N1-P1 amplitude and N1 latency, but not for the N1 amplitude ($r = 0.159$, $p = 0.543$) (Table 6.5).

Table 6.5

Correlations and differences between CHEPs at time 1 [T1] and time 2 [T2] at 10 cm proximal to the left lateral malleolus

Stimulus and site	CHEPs	N	Mean (SD)	Correlation		Difference	
				r	p	t	p
10 cm proximal To left lateral malleolus, 51ºC	N1 latency (s) [T1]	19	0.574(0.033)	0.507	0.027	0.249	0.806
	N1 latency (s) [T2]		0.573(0.022)				
	N1 amplitude (μV) [T1]	17	-10.91(4.14)	0.159	0.543	-1.009	0.328
	N1 amplitude (μV) [T2]		-9.64(3.84)				
	P1 latency (s) [T1]	20	0.69(0.042)	0.656	0.002	0.903	0.378
	P1 latency (s) [T2]		0.684(0.037)				
	P1 amplitude (μV) [T1]	19	17.94(7.19)	0.722	<0.001	1.93	0.07
	P1 amplitude (μV) [T2]		15.74(5.25)				
	N1-P1 amplitude (μV) [T1]	20	30.93(11.57)	0.625	0.003	1.946	0.067
	N1-P1 amplitude (μV) [T2]		26.93(8.92)				

6.8.9 Reliability of CHEPs at different sites of the lower limbs

For the stimulation of the dorsum of the foot, all of the CHEP parameters had a moderate to strong ICC and Cronbach's alpha coefficient, with the N1-P1 amplitude scoring the highest, followed by the P1 amplitude, N1 latency, P1 latency and N1 amplitude (Table 6.6). Hence, the hypothesis that CHEPs will be a reliable method to assess the integrity of small myelinated fibres is supported.

Table 6.6

Reliability of CHEPs at the dorsum of the left foot

Stimulus and site	CHEPs	N	Mean (SD)	Cronbach's alpha	ICC	p
Dorsum of left foot, 51ºC	N1 latency (s) [T1] N1 latency (s) [T2]	19	0.585(0.032) 0.571(0.046)	0.829	0.708	<0.001
	N1 amplitude (μV) [T1] N1 amplitude (μV) [T2]	19	-10.21(5.69) -10.03(5.19)	0.762	0.616	0.002
	P1 latency (s) [T1] P1 latency (s) [T2]	19	0.691(0.045) 0.683(0.037)	0.824	0.701	<0.001
	P1 amplitude (μV) [T1] P1 amplitude (μV) [T2]	20	17.21(8.2) 15.22(6.97)	0.881	0.788	<0.001
	N1-P1 amplitude ((μV) [T1] N1-P1 amplitude ((μV) [T2]	21	29.87(14.64) 26.71(12.39)	0.901	0.820	<0.001

ICC = intraclass correlation coefficients

For stimulation 10 cm proximal to the left lateral malleolus, the P1 amplitude had a moderate ICC and Cronbach's alpha coefficient, whereas the N1 amplitude had weak ones (Table 6.7). Comparing each CHEP parameter between the two stimulation sites, the CHEP latencies and amplitudes at the foot produced higher ICCs and Cronbach's alpha coefficients than did those at 10 cm proximal to the lateral malleolus.

Table 6.7

Reliability of CHEPs at 10 cm proximal to the left lateral malleolus

Stimulus and site	CHEPs	N	Mean (SD)	Cronbach's alpha	ICC	P
10 cm proximal To left lateral malleolus, 51ºC	N1 latency (s) [T1]	19	0.574(0.033)	0.637	0.467	0.019
	N1 latency (s) [T2]		0.573(0.022)			
	N1 amplitude (μV) [T1]	17	-10.91(4.14)	0.273	0.158	0.265
	N1 amplitude (μV) [T2]		-9.64(3.84)			
	P1 latency (s) [T1]	20	0.69(0.042)	0.789	0.651	0.001
	P1 latency (s) [T2]		0.684(0.037)			
	P1 amplitude (μV) [T1]	19	17.94(7.19)	0.815	0.688	<0.001
	P1 amplitude (μV) [T2]		15.74(5.25)			
	N1-P1 amplitude ((μV) [T1]	20	30.93(11.57)	0.753	0.604	0.002
	N1-P1 amplitude ((μV) [T2]		26.93(8.92)			

ICC = intraclass correlation coefficients

6.9 Discussion

6.9.1 Pain intensity ratings and CHEP amplitudes

No significant relationship was found between pain intensity ratings and N1-P1 peak amplitudes. The results are similar to those of a previous study that also used a Chinese population (Chen et al., 2006). Pain is a personal and subjective experience, and its perception is affected by psychological status (Johnson, Breakwell, Douglas, and Humphries, 1998), cultural background and gender (Sheffield, Biles, Orom, Maxiner, and Sheps, 2000). Biological differences in hormonal distribution, opioid activity and baroreceptor regulation between the sexes are thought to affect pain perception

(Sheffield et al., 2000). Research shows that distraction increases pain threshold and tolerance and decreases pain ratings (Johnson et al., 1998). Therefore, physiological responses may not represent a person's perception of pain intensity. CHEPs may be an appropriate objective measure of nerve damage but is not a substitute for subjective pain intensity rating in clinical and academic research.

6.9.2 The reproducibility and reliability of CHEPs

The percentage of reproducibility of this study was higher than that of a previous study (Chen et al., 2006), although the CHEPs were not reproduced in one subject at 10 cm proximal to the left lateral malleolus. The higher reproducibility may be due to the use of a higher adapting temperature (35ºC) and longer break between the two blocks of thermal stimulation (15 minutes) in the present study compared to the previous one, in which an adapting temperature of 32ºC and 5-minute break were used (Chen et al., 2006). Chao and colleagues (2007) repeated the same CHEP stimulation procedure in 15 subjects one month after the first examination. They reported 100% reproducibility and found that CHEP latency and amplitude were significantly correlated between the two time points ($r = 0.95$, $p < 0.0001$ for latency; $r = 0.84$, $p < 0.0001$ for amplitude; values that are even higher than those of the present study). In their study, the adapting temperature was 35ºC. These findings suggest that a 5- or even a 15-minute break between stimulation blocks at the same stimulation site after thermal stimulation may not be enough time for the nervous system to fully recover.

The study result showed lower reproducibility & reliability at 10cm proximal to lateral malleolus. Chen and colleagues (2006) also reported that the reproducibility of CHEPs in peroneal area was lower than the dorsum of foot. Skin temperature and skin or subcutaneous fat thickness may affect the response of CHEPs (Nelson et al., 2004; Petrofsky et al., 2009). There was no significant different in skin temperature between the two stimulation sites in the present study. Therefore, the relationship between skin or subcutaneous fat thickness and CHEPs should be explored in future study.

The present study found that the Cronbach's alpha and ICC of the CHEP parameters of the dorsum of the foot were higher than those at 10 cm above the lateral malleolus. These findings indicate that the CHEP parameters of the dorsum of the foot following thermal stimulation may be the more preferable ones for use in future clinical and research application. Hence, in the next stage, thermal stimulation was applied at this site.

6.10 Limitations of the study

The round activation area of the thermode is 573mm^2; therefore, a flat surface should be chosen when applying the thermode in order to increase the contact area. It is difficult to apply the thermode to patients with small feet or thin patients with a prominent bony area on the dorsum of the foot. In addition, the age range of the

participants was from 28 to 54; hence, the results of this study may not be generalisable to younger or older age groups.

6.11 Implications for the next stage

This study established a highly reproducible thermal stimulation protocol for CHEPs. In this protocol, the baseline temperature was 35°C, the inter-stimulus interval was 10-15 s, and the duration of each stimulus was 0.2 s, in contrast to the protocol reported by Chen and colleagues (2006), in which study the reproducibility of CHEPs was around 36-62%. The current protocol can be used in future studies to identify small A-delta fibre damage. In addition, the strong reliability of CHEPS following stimulation of the dorsum of the foot suggests that this site is preferable for examining small A-delta fibres in future research.

6.12 Conclusion and recommendations

CHEPs are a reliable tool to examine the integrity of small myelinated A-delta fibres. However, the N1-P1 peak amplitudes may not reflect the subjective pain intensity ratings and perceptions of individuals. Future studies should explore the feasibility of using CHEPs for examining the integrity of small myelinated A-delta fibres in patients with specific diseases.

Chapter 7

Stage 3 - The Feasibility of CHEPs for the Early Detection of Symptomatic DSP

7.1 Introduction

The involvement of small myelinated fibres in the early stage of DN has been proposed but there are few objective methods that can identify minimal neuropathy. The validity and reliability of CHEPs for assessing the integrity of small myelinated A-delta fibres have been demonstrated, which indicates the potential for using CHEPs to detect early DN. This chapter will present the details of the research method to explore the feasibility of using CHEPs for the early detection of DSP in diabetics with lower limb symptoms and the study findings, and conclude with a discussion of these findings.

7.2 Research objective

This study aimed to explore whether there are differences in CHEP parameters amongst healthy adults and diabetics with and those without lower limb symptoms.

7.3 Research questions

1) Are there differences in CHEP amplitudes and latencies amongst healthy adults and diabetics with and those without lower limb symptoms?

2) Are there differences in CHEP amplitudes and latencies between healthy adults and diabetic patients with lower limb symptoms?

3) Are there differences in CHEP amplitudes and latencies between diabetic patients with and those without lower limb symptoms?

7.4 Research hypotheses

1) Diabetic patients with lower limb symptoms will have lower CHEP amplitudes compared to those without lower limb symptoms and healthy adults.

2) Diabetic patients with lower limb symptoms will have longer CHEP latencies compared to those without lower limb symptoms and healthy adults.

7.5 Study design

This was a cross-sectional study that included three groups: healthy adults and diabetic patients with and those without lower limb symptoms.

7.5.1 Sampling

Participants were recruited by convenience sampling using newspaper advertisements and invitation letters to different community diabetes self-help groups, and amongst friends, colleagues and relatives. Participants in the different groups were matched by age. Eligible subjects who met the following inclusion and exclusion criteria were invited to participate in the study, which lasted for 3-4 hours. A $100 supermarket coupon was given to subjects as a token of appreciation for their participation. Age-matched healthy controls and diabetic patients who had no known history of neurological disease and a score of zero on the TCNS were also recruited.

7.5.1.1 Inclusion criteria

1) Aged between 18 and 60
2) Mentally alert
3) Confirmed to have type 2 DM according to the criteria of the American Diabetic Association
4) Stable metabolic control of blood glucose level with HbA1c $\leq$ 7.5% within the last three

months

5) Intermittent or persistent lower limb symptoms
6) Toronto Clinical Neuropathy Score less than or equal to 5 points

7.5.1.2 Exclusion criteria

1) Known history of lumbar discogenic disease or nerve root compression exclusive of neuropathy related to spinal problems
2) Known history of inherited or alcoholic neuropathy
3) Known history of renal impairment such as diabetic nephropathy or chronic renal failure
4) Known history of neurological disease such as tarsal tunnel syndrome
5) Known history of peripheral vascular disease
6) Known history of central nervous system disease such as brain tumour
7) Known history of chronic pain syndrome other than painful DSP

7.5.2 Instrument

7.5.2.1 Contact heat stimulation

CHEP stimulation was performed using the Pathway ATS/CHEPS (Medoc, Ramat Yishai, Israel). This device is the same one that was used in stage 2 of this study, and a detailed description of it is given in the previous chapter.

7.5.2.2 Numerical pain rating scale

The numerical pain rating scale (NPRS) was used to rate the pain intensity 3 seconds after each thermal stimulation. This scale is the same one that was used in stage 2 of this study, and a detailed description of it is given in the previous chapter.

7.5.2.3 Toronto Clinical Neuropathy Score (TCNS)

The TCNS was developed for routine screening for DSP by Perkins et al. (2001). It consists of symptom, reflex and sensory scores. The symptom scores cover six items including pain, numbness, tingling and weakness of the feet, upper limb symptoms and ataxia. One point is given for each item if there is a matching symptom. The reflex scores of both the ankle and knee are graded as absent, reduced, or normal. Two points are given for the absence of a reflex, one point for a reduced reflex and no points for a normal reflex. The sensory scores, rated as normal or abnormal, cover five sensory modalities: pinprick, temperature, light touch, vibration and position sensation. Getting five or more incorrect responses for each item indicates abnormality and one point is then given. The maximum sensory score is 19 points and participants with a score greater than five are classified as having neuropathy.

The cross-sectional prediction of the electrophysiological and morphological severity of DSP has been validated (Bril and Perkins, 2002). It shows a significant negative correlation with sural nerve fibre density, summed amplitude nerve conduction studies

and summed conduction velocity (Bril and Perkins, 2002).

7.5.3 Ethical considerations

The nature and purpose of the study were explained to all participants and a written information sheet was given to them for their reference (Appendix A). All of the subjects signed the consent form before participating in the research study (Appendix B). They were assured that their participation was voluntary and that they could withdraw from the study at any time without prejudice. The study involved the application of thermal stimulation; therefore, the procedure could cause additional pain to subjects. Their condition was observed throughout the procedure to detect any signs of discomfort such as fatigue or an impending attack of pain. Care was taken to ensure that the thermal pain would not induce tissue damage, such as redness or a scalding sensation. The study was discontinued if any of the above occurred. Personal information and data remained confidential and anonymous. The ethical guidelines endorsed by the IASP were followed, and ethical approval was obtained from Hong Kong Polytechnic University.

7.6 Data collection

A screening form, which contained a list of the inclusion and exclusion criteria, was used to recruit suitable participants (Appendices C and F). A data collection form was used to collect basic demographic data including body height and weight, medical and surgical history, and medication history. A structured interview was conducted to collect information on the history of painful diabetic neuropathy including the time since the onset of neuropathy symptoms and pain. The participants were asked to describe their pain in detail, including its location(s) and duration, the pain intensity using the NPRS, and the quality of the pain. Information on covariates of pain including history of smoking and level of blood sugar control was also solicited (Appendix D). A venous blood sample was taken and sent to a laboratory for blood glucose analysis (HbA1c).

7.6.1 Classification of diabetic distal symmetric polyneuropathy

The TCNS was used to assess the severity of DSP. It comprises symptom, reflex and sensory scores (Table 7.1).

Table 7.1 Toronto Clinical Neuropathy Score

Symptom scores	**Present (1)**	**Absent (0)**	
Foot pain			
Numbness			
Tingling			
Weakness			
Ataxia			
Upper limb symptoms			
Reflex scores	**Absent (2)**	**Reduced (1)**	**Normal (0)**
Knee reflexes			
Ankle reflexes			
Sensory test scores	**Abnormal (1)**	**Normal (0)**	
Pinprick			
Temperature			
Light touch			
Vibration			
Position sense			
Total score			

Scored ≤ 5 **No neuropathy**

Scored 6-8 **Mild neuropathy**

Scored 9-11 **Moderate neuropathy**

Scored ≥ 12 **Severe neuropathy**

7.6.1.1 Symptom scores

The participants were asked about the presence or absence of the following symptoms: pain, numbness, tingling and weakness in both feet, the presence or absence of upper limb symptoms and the presence or absence of ataxia. One point was given for the presence of symptoms.

7.6.1.2 Reflex scores

Ankle reflexes were examined bilaterally with the use of a tendon hammer. They were elicited in the sitting position with the participant relaxed and the foot dorsiflexed slightly to obtain optimal stretch of the muscle. The Achilles tendon was struck directly. If the reflex was absent, then a reinforcement technique (the Jendrassik manoeuvre) was used. Reflexes elicited using the Jendrassik manoeuvre were considered to be reduced and one point was given. If a reflex was not elicited even with the Jendrassik manoeuvre, then the reflex was documented as absent and two points were given.

Knee reflexes were examined with the use of a tendon hammer. They were elicited in the sitting position with the participant relaxed and one leg crossed. The patellar tendon was stuck directly. If the reflex was absent, then a reinforcement technique (the Jendrassik manoeuvre) was used. Reflexes elicited using the Jendrassik manoeuvre were considered to be reduced and one point was given. If a reflex was not elicited even with the Jendrassik manoeuvre, then the reflex was documented as absent and

two points were given.

7.6.1.3 Sensory test scores

Before each sensory test, a reference stimulation was applied to the sternum and the participant was asked about the nature of the perceived sensation. If the perceived sensation was accurate, then the sensation test was performed with the participant keeping his or her eyes closed.

7.6.1.3.1 Vibration sensation test

Vibration sensation testing by the on-off method was conducted bilaterally using a 128 Hz tuning fork. The tuning fork was placed over the bony prominence at the dorsum of the great toe just proximal to the nail bed. The participants were asked to report the perception of the start of the vibration sensation and the termination of vibration on damping. The test was repeated twice on each toe. The participant was asked to say ‘yes’ if he or she felt the application of the tuning fork and the damping of the vibration. Five or more incorrect responses given for the eight possible stimuli indicated abnormality and one point was given.

7.6.1.3.2 Light touch test

A 10 g monofilament was applied to a non-calloused site on the dorsum of the great toe just proximal to the nail. The test was repeated four times on each toe. The participant was asked to say ‘yes’ if he or she felt the application of the monofilament. Five or more incorrect responses given for the eight possible stimuli indicated abnormality and one point was given.

7.6.1.3.3 Superficial pain sensation

A neurotip was applied to a non-callused site on the dorsum of the great toe just proximal to the nail. The test was repeated four times on each toe. The participant was asked to say ‘yes’ if he or she felt the application of the neurotip. Five or more incorrect responses given for the eight possible stimuli indicated abnormality and one point was given.

7.6.1.3.4 Temperature test

A cold tuning fork was applied to a non-callused site on the dorsum of the great toe just proximal to the nail. The test was repeated four times on each toe. The participant was asked to say ‘yes’ if he or she felt the application of the tunning fork. Five or more incorrect responses given for the eight possible stimuli indicated abnormality and one point was given.

7.6.1.3.5 Position sense test

Each great toe was held with one hand by the researcher. The researcher moved the distal phalanx up or down with the fingers of the other hand, which was positioned at the medial and lateral aspects of the toe. The test was repeated four times on each toe. The participant was asked to choose up or down following the toe movement. Five or more incorrect responses given for the eight movement indicated abnormality and one point was given.

A TCNS $\leq$ 5 indicated no neuropathy; 6-8, mild neuropathy; 9-11, moderate neuropathy; and $\geq$ 12, severe neuropathy. Participants with a score of six or more points were excluded from the study.

7.6.2 Contact heat evoked potentials

On the day of the study, the subjects sat in a reclining chair with their eyes closed, in a quiet room with an ambient temperature around 22-23ºC. The procedure was modified from that of Granovsky and colleagues (2005). The heat stimuli were delivered at the dorsum of the foot and 10 cm proximal to the lateral malleolus of the non-dominant side of all subjects at a peak temperature of 51ºC. The baseline temperature was 35ºC for all stimuli. The time from onset to peak temperature was 250 ms.

Each stimulus block consisted of 16 constant-intensity stimuli. The inter-stimulus

interval was 10-15 s, and the duration of each stimulus was 0.2 s. Subjects were allowed to withdraw from the stimulation if it became intolerable. The thermode was moved slightly between stimuli to avoid potential sensitisation, desensitisation, or fatigue of the receptors. Before beginning evoked potential recording, several stimuli were applied to prevent expectation effects and reduce novelty ones. Different body sites were stimulated in a pseudorandom order. Participants rated the perception of each stimulus 3 s after stimulus onset using the NPRS.

7.6.3 Contact heat evoked potentials recording

The CHEPs were recorded from midline electrodes of a 64-channel surface recording cap, which was placed on the scalp according to the standard 10-20 system (Figure 7.1). The reference was at bilateral earlobes. The EEG was recorded within a 0.01 to 100 Hz bandpass and digitised at a sampling rate of 1000 Hz using Neuroscan 4.4. The scalp-electrode impedance was less than 5 kΩ. An ocular artefact was obtained by vertical electro-oculography of the left eye and horizontal electro-oculography of both eyes. A trigger signal was given at the beginning of the temperature increase, and a 10-second baseline before stimulus onset was included in each recording epoch.

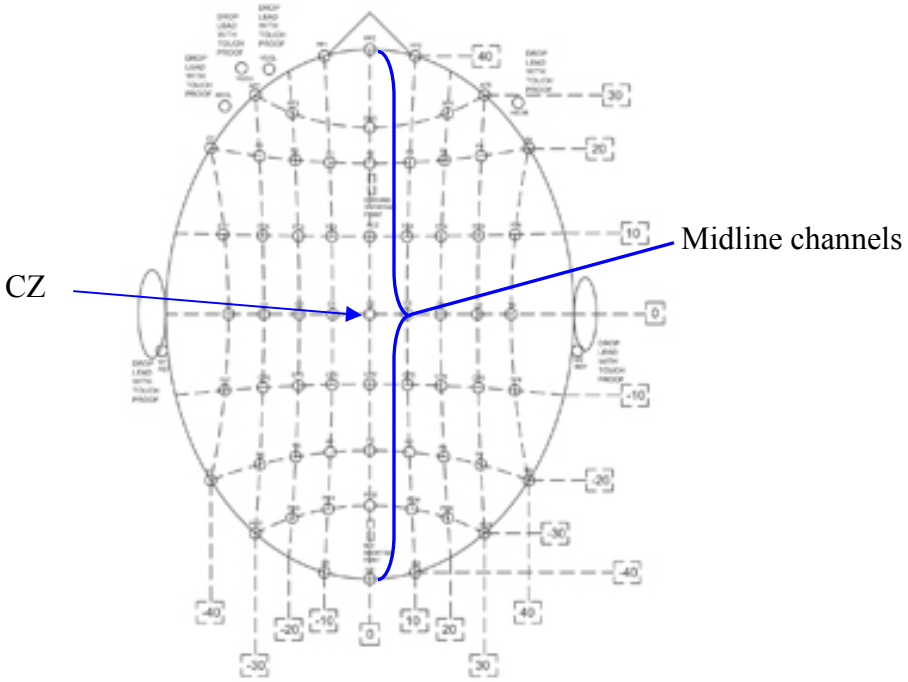

Figure 7.1. 64-channel EEG electrode layout with the Cz channel indicated.

7.7 Data management and analysis

Descriptive data including demographic information, body height and skin temperature at the stimulation site were input and analysed using SPSS 13.0. All raw data entered in the computer were checked for errors by double checking with the data collection form. The descriptive statistics were used to analyse these data.

EEG data were recorded and digital EEG data were analysed using Neuroscan 4.4. Peri-stimulus epochs contaminated by artefacts were discarded and excluded from signal

averaging. The remaining sweeps for each stimulation site were averaged separately. The peak amplitudes and latencies of the first negative (N1) and subsequent positive (P1) peaks of evoked potentials, and the negative to positive amplitude (N1-P1 amplitude) were identified from the averaged waveform of each electrode. The latencies and amplitudes were presented as the mean values +/- standard deviation.

Data from the Cz channel were used for further data analysis. The differences in CHEP amplitudes and latencies and pain intensity ratings amongst the three groups were analysed using one-way analysis of variance (ANOVA). Post hoc analysis was used to analyse the differences in CHEP amplitudes and latencies between healthy adults and diabetic patients with lower limb symptoms, and between diabetic patients with and those without lower limb symptoms. The interaction effects between glycaemic control (HbA1c $\leq$ 6, HbA1c 6.1-7, HbA1c 7.1-7.5) and the two diabetic groups, and duration of diabetes (diabetic duration $\leq$ 5 years, > 5 years and $\leq$ 10 years, > 10 years) and the two diabetic groups were analysed using two-way ANOVA. Log or square root transformed data were used for data analysis if the data were not normally distributed and there was unequal variance between groups. A non-parametric test was used if the transformed data were not normally distributed and there was unequal variance between groups. Post hoc analysis was not conducted for the non-parametric data.

7.8 Results

7.8.1 Characteristics of participants

The participants included 13 healthy adults, 19 diabetics (without lower limb symptoms), and 10 diabetics with lower limb symptoms. Table 7.2 shows the demographic characteristics of the study population. There were no significant differences in age, body height, body weight, body mass index or skin temperature at either stimulation site amongst the three groups. All participants were right handed. None of them had a known history of lumbar discogenic disease or spinal surgery, or was taking analgesics. None of the diabetic patients had a known history of foot ulcers.

All healthy subjects and diabetic s without lower limb symptoms had no allodynia, paresthesia, loss of sensation on bilateral lower limb and scored 0 point in TCNS. All of them had negative results in straight leg raise test. All diabetics with lower limb symptoms had negative results in straight leg raise test and had no lower limb sensation loss, allodynia, paresthesia or numbness that compatible to peripheral and spinal nerve distribution.

There were no significant differences in duration of diabetes or HbA1c level between the two diabetic groups. Intermittent symptoms in the feet and toes for more than three months including numbness, a frozen feeling, a crawling sensation, aching, tiredness, ‘撩撩吓’ and pricking were reported by diabetics with lower limb symptoms. The

mean duration of symptoms was 1.49 years (range 0.33 – 6 years, SD 1.75) and one of them had a pain score of 3 out of 10 on the day of procedure. Two diabetic patients withdrew from the study, one from the diabetic group and one from the diabetic with lower limb symptoms group. The reasons for withdrawal were pain intolerance following thermal stimulation and fear of pain respectively. One diabetic with lower limb symptom had no evoked response following thermal stimulation of both sites and one diabetic with lower limb symptom had no evoked response following thermal stimulation at 10cm proximal to lateral malleolus.

Table 7.2 Demographic characteristics of the study population

	Healthy adults (N=13)	Diabetics (N=19)	Diabetics with lower limb symptoms (N=10)	P
Sex				
Male (n)	6	5	6	/
Female (n)	7	14	4	/
Mean age (SD)	51.4(4.2)	52.2(5.3)	55.1(4.6)	0.176
Smoker (n)	2	1	0	/
Drinker (n)	0	0	0	/
Mean height (cm) (SD)	163.2(10.8)	164.3(8.3)	163.5(5)	0.705
Mean weight (kg) (SD)	61.8(14.2)	64.6(11.2)	64.1(10.9)	0.812
Mean BMI	22.8(4.5)	23.9(3.6)	24(4.3)	0.697
Medical history				
Carpal tunnel syndrome	0	1	0	/
Cataract	0	1	0	/
Chronic rhinitis	1	0	0	/
Congestive heart failure	0	0	1	/
Degenerative knee	0	0	2	/
Diabetes mellitus				
IDDM	0	0	0	/
NIDDM	0	19	10	/
Hepatitis B carrier	0	0	1	/
Hypertension	2	9	5	/
Hyperlipaemia	0	4	2	/
Osteoporosis	0	0	1	/
Tennis elbow	0	0	1	/
Trigger finger	0	0	1	/
Foot ulcer	0	0	0	/
Surgical history				
Cardiac catherization	0	0	1	/
Spinal surgeries	0	0	0	/
Lower limb surgeries				
Medial thigh excision	0	0	1	/

Table 7.2 (cont'd) Demographic characteristics of the study population

	Healthy adults (N=13)	Diabetics (N=19)	Diabetics with lower limb symptoms (N=10)	P
Current analgesic prescription	0	0	0	/
Past analgesic prescription				
NSAID	0	0	1	/
Concurrent medications				
Antihistamines	2	1	0	/
Anti-hypertensive drugs	0	9	4	/
Antiplatelet drugs	0	2	2	/
Beta-adrenoceptor blocking drugs	0	1	1	/
Calcium-channel blockers	0	1	0	/
Diuretics	0	1	0	/
Lipid-regulating drugs	0	6	5	/
Nitrates	0	1	0	/
Reported to have pain on the day of procedure	0	0	1	/
Mean HbA1c (%) (SD)	NA	6.39(0.7)	6.45(0.5)	0.812
Mean length of DM (years) (SD)	NA	4.5(3.8)	6.6(7.7)	0.907*
Mean TCNS (SD)	0	0	2.3(1.6)	/
Diabetic control measures				
Diet	NA	1	2	/
Oral anti-diabetic medicines	NA	18	6	/
Insulin	NA	0	1	/
Oral anti-diabetic medicines and insulin	NA	0	1	/
Lt dorsum of foot skin temperature (ºC) (SD)	30.3 (2.15)	31.2(2.57)	29.1(2.27)	0.084
10 cm proximal to Lt lateral malleolus skin temperature (ºC) (SD)	29.9(1.55)	31(1.69)	29.8(1.11)	0.433

BMI = body mass index; IDDM = insulin dependent diabetes mellitus; NA = not applicable; NIDDM = non-insulin dependent diabetes mellitus; *log transformation; TCNS = Toronto Clinical Neuropathy Score

7.8.2 Pain intensity ratings of healthy adults, diabetics and diabetics with lower limb symptoms

Post hoc analysis showed no significant differences in pain intensity ratings during thermal stimulation between healthy adults and diabetics, healthy adults and diabetics with lower limb symptoms, and diabetics and diabetics with lower limb symptoms (Table 7.3).

Table 7.3

Pain intensity ratings of healthy adults and diabetic patients with and without lower limb (LL) symptoms at different sites

		n	Mean NPRS (SD)	F	p	Partial Eta Squared	Post hoc analysis (p)		
Dorsum of foot	Healthy adults (N=13)	13	4.9(2.9)	1.4	0.26	0.159	0.255*	0.938**	0.566***
	Diabetics without LL symptoms (N=19)	17	3.5(2)						
	Diabetics with LL symptoms (N=10)	9	4.04(2.6)						
10 cm proximal to lateral malleolus	Healthy adults (N=13)	13	4.6(2.7)	1.2	0.325	0.233	0.472*	0.344**	0.895***
	Diabetics without LL symptoms (N=19)	18	3.5(2.7)						
	Diabetics with LL symptoms (N=10)	9	3.1(2.1)						

NPRS = Numerical pain rating scale; *Healthy adults vs. diabetics without lower limb symptoms; **Healthy adults vs. diabetics with lower limb symptoms; ***Diabetics without lower limb symptoms vs. diabetics with lower limb symptoms.

7.8.3 CHEPs of healthy adults and diabetic patients with and those without lower limb symptoms

There were significant differences in the N1 latency and amplitude and N1-P1 amplitude amongst the three groups when thermal stimulation was applied to the dorsum of the left foot (Table 7.4). Post hoc analysis showed that diabetic patients with lower limb symptoms had significantly lower N1-P1 amplitudes compared with diabetic patients without such symptoms. However, there was no significant difference in N1 latencies between healthy adults, diabetic patients with and without lower limb symptoms (Table 7.4). Hence, the hypothesis that diabetic patients with lower limb symptoms will have lower CHEP amplitudes is supported. However, the hypothesis that diabetic patients with lower limb symptoms will have longer CHEP latencies is rejected.

Thermal simulation 10 cm proximal to the left lateral malleolus resulted in significant differences in N1 amplitude and N1-P1 amplitude amongst the three groups (Table 7.5). Post hoc analysis showed that diabetic patients with lower limb symptoms had significantly lower N1-P1 amplitudes compared with healthy adults and diabetic patients without lower limb symptoms (Table 7.5). Hence, the hypothesis that diabetic patients with lower limb symptoms will have lower CHEP amplitudes is supported. However, the hypothesis that diabetic patients with lower limb symptoms will have longer CHEP latencies is rejected.

Table 7.4

CHEPs of healthy adults and diabetic patients with and without lower limb symptoms following stimulation of the dorsum of the left foot

	Healthy adults	Mean (SD)	Diabetics	Mean (SD)	Diabetics with LL symptoms	Mean (SD)	F	p	Partial Eta Squared	Post hoc analysis (p)		
N1 latency (s)	N=13	0.59 (0.042)	N=17	0.593 (0.018)	N=8	0.625 (0.037)	3.306	0.048	0.159	0.975*	0.059**	0.069***
N1 amplitude (μV)	N=13	-10.35 (5.19)	N=16	-8.33 (3.86)	N=7	-3.94 (3.4)	5.019	0.013	0.233	0.432*	0.009**	0.079***
P1 latency (s)	N=13	0.7 (0.048)	N=18	0.711 (0.035)	N=8	0.722 (0.033)	0.837	0.441	0.044	0.706*	0.419**	0.787***
P1 amplitude (μV)	N=12	15.3 (5.57)	N=18	15.9 (7.07)	N=8	11.69 (6.4)	1.21	0.31	0.065	0.967*	0.451**	0.292***
N1-P1 amplitude (μV)	N=12	25.08 (8.55)	N=18	25.62 (10.47)	N=7	14.66 (4.57)	4.001	0.028	0.191	0.986*	0.054**	0027***

LL = Lower limb; *Healthy adults vs. diabetics without lower limb symptoms; **Healthy adults vs. diabetics with lower limb symptoms; ***Diabetics without lower limb symptoms vs. diabetics with lower limb symptoms.

Table 7.5

CHEPs of healthy adults and diabetic patients with and without lower limb symptoms following stimulation 10 cm proximal to the left lateral malleolus

	Healthy adults	Mean (SD)	Diabetics	Mean (SD)	Diabetics with LL symptoms	Mean (SD)	F	p	Partial Eta Squared	Post hoc analysis (p)		
N1 latency (s)	N=12	0.0597 (0.028)	N=17	0.609 (0.023)	N=6	0.599 (0.018)	1.108	0.343	0.065	0.346*	0.977**	0.641***
N1 amplitude (μV)^	N=12	-10.69 (5.98)	N=18	-9.46 (3.28)	N=6	-3.39 (1.97)	12.105 (X^2)	0.002	/	/	/	/
P1 latency (s)^	N=13	0.7 (0.055)	N=16	0.718 (0.026)	N=6	0.74 (0.03)	3.854 (X^2)	0.146	/	/	/	/
P1 amplitude (μV)^	N=13	17.66 (11.15)	N=18	14.17 (4.46)	N=7	10.7 (5.36)	2.967 (X^2)	0.227	/	/	/	/
N1-P1 amplitude (μV)	N=11	23.23 (8.57)	N=18	23.63 (6.09)	N=6	12.84 (5.13)	6.031	0.006	0.274	0.987*	0.014**	0.006***

LL = Lower limb; ^Kruskal-Wallis test; *Healthy adults vs. diabetics without lower limb symptoms; **Healthy adults vs. diabetics with lower limb symptoms; ***Diabetics without lower limb symptoms vs. diabetics with lower limb symptoms.

7.8.4 Interaction effect of HbA1c and N1-P1 peak amplitude of CHEPs

7.8.4.1 Dorsum of the left foot

There was a significant main effect of the different DM groups on the N1-P1 peak amplitude of the dorsum of the foot ($F(1, 20) = 7.48$, $p = 0.013$), and diabetic patients with lower limb symptoms had lower N1-P1 amplitudes. There was no significant main effect of HbA1c level on the N1-P1 peak amplitude of the dorsum of the foot ($F(2, 20) = 0.788$, $p = 0.468$). There was no significant interaction between HbA1C and DM with or without symptoms on the N1 latency of the dorsum of the foot ($F(1, 20) = 0.191$, $p = 0.666$).

7.8.4.2 10 cm proximal to the left lateral malleolus

There was a significant main effect of the different DM groups on the N1-P1 peak amplitude 10 cm proximal to the lateral malleolus ($F(1, 19) = 7.91$, $p = 0.001$), and diabetic patients with lower limb symptoms had lower N1-P1 peak amplitudes. There was no significant main effect of HbA1c

level on the N1-P1 peak amplitude 10 cm proximal to the lateral malleolus ($F(2, 19) = 0.213$, $p = 0.81$). There was no significant interaction between HbA1C and DM with or without symptoms on the N1 latency 10 cm proximal to the lateral malleolus ($F(1, 19) = 1.337$, $p = 0.262$).

7.8.5 Interaction effect of duration of DM and N1-P1 peak amplitude of CHEPs

7.8.5.1 Dorsum of the left foot

There was a significant main effect of the different DM groups on the N1-P1 peak amplitude of the dorsum of the foot ($F(1, 20) = 5.769$, $p = 0.026$), and diabetic patients with lower limb symptoms had lower N1-P1 amplitudes. There was no significant main effect of duration of diabetes on the N1-P1 peak amplitude of the dorsum of the foot ($F(2, 20) = 0.005$, $p = 0.995$). There was no significant interaction between the duration of diabetes and DM with or without symptoms on the N1 latency of the dorsum of the foot ($F(1, 20) = 0.146$, $p = 0.706$).

7.8.5.2 10 cm proximal to left lateral malleolus

There was a significant main effect of the different DM groups on the N1-P1 peak amplitude 10 cm proximal to the lateral malleolus ($F(1, 19) = 4.613$, $p = 0.045$), and diabetic patients with lower limb symptoms had lower N1-P1 peak amplitudes. There was no significant main effect of duration of diabetes on the N1-P1 peak amplitude 10 cm proximal to the lateral malleolus ($F(2, 19) = 2.229$, $p = 0.135$). There was no significant interaction between the duration of diabetes and DM with or without symptoms on the N1 latency 10 cm proximal to the lateral malleolus ($F(1, 19) = 1.738$, $p = 0.203$).

7.8.6 Power of the study

The power of the study was calculated using the statistical software Power Analysis and Sample Size (PASS) 2008. The power was calculated based on the unequal sample sizes of each group in the power calculations for one-way ANOVA. The relevant values for each dependent variable including the alpha, number of groups, sample size multiplier, group sample size pattern, mean of each group and standard deviation of subjects were entered.

For the dorsum of the left foot following thermal stimulation, the powers of the negative peak amplitude and N1-P1 amplitude were 0.78 and 0.68, respectively. At 10 cm proximal to the left lateral malleolus, the powers of the negative peak amplitude and N1-P1 amplitude were 0.87 and 0.85, respectively. The overall power of the study was 0.80, and the alpha was 0.05.

7.9 Discussion

7.9.1 CHEP characteristics in diabetic patient with lower limb symptoms

The N1-P1 amplitude of CHEPs was significantly lower in the diabetic patients with lower limb symptoms compared to those without lower limb symptoms and healthy adults. The results indicate that there may be a loss of myelinated Aδ fibres. Chao and colleagues (2008) investigated the relationship of the CHEP parameter IENF density in neuropathy patients with skin denervation and found a positive correlation between IENF density and negative-positive amplitude. They concluded that skin

denervation was a major factor correlated to CHEP amplitude. In addition, the results of the present study are consistent with those of morphological studies of marked reduction in IENF density, a gold standard for diagnosing small fibre neuropathy in symptomatic diabetic patients (Løseth, Stålberg, Jorde, and Mellgren, 2008).

7.9.2 Duration of diabetes and DSP

Various studies report that diabetic patients with a longer duration of diabetes tend to develop DSP (Young et al., 1993; Partanen et al., 1995; Fedele et al., 1997; Valensi et al., 1997; Cheng et al., 1999; Tapp et al., 2003). However, an interaction effect between duration of diabetes and diabetic patients with or without lower limb symptoms was not found in the present study. This may be because there was only a slightly longer mean duration of diabetes in patients with lower limb symptoms, the mean duration of diabetes in both groups was less than seven years, and the small number of subjects in both groups.

7.9.3 Glycaemic control and DSP

Tight glycaemic control has been reported to delay the onset and progression of DSP in IDDM patients (DCCT 1993, 1995; Reichard et al., 1993). However, no significant interaction effect was found between HbA1c and diabetic patients with or without lower limb symptoms in the present study. This may be due to the non-significant difference in HbA1c level between the two diabetic groups and small number of subjects in both groups.

Although the mean HbA1c level was below 7.5 for all diabetic participants, 10 out of 29 of them reported having intermittent lower limb symptoms, which is a risk factor for developing DSP, other than hyperglycaemia, that should not be ignored during patient education. Age (Cheng et al., 1999; Tapp et al., 2003), height (Tap et al., 2003), high uric acid levels (Tapp et al., 2003), increased insulin consumption (Sands et al., 1997) and smoking (Sand et al., 1997) are other risk factors for developing DSP. Smith and colleagues (2006) reported a significant improvement in IENF density in patients with pre-diabetic neuropathy after their participation in a lifestyle

modification programme. Therefore, the control of (controllable) risk factors and regular screening should be included in diabetes management.

7.9.4 Feasibility of using CHEPs for the early detection of DSP

Following stimulation 10 cm proximal to the left lateral malleolus, the N1-P1 peak amplitude of CHEPs was significantly lower in diabetics with lower limb symptoms and a TCNS score between 1 and 5 compared to healthy adults and diabetics without lower limb symptoms. In addition, the N1-P1 peak amplitudes of diabetics with lower limb symptoms in the present study were similar to those of six diabetic patients who were diagnosed as having small fibre neuropathy in the study of Chao and colleagues (2008). Thus, the decrease in N1-P1 peak amplitudes may reflect early-stage small nerve fibre neuropathy, and can be identified by CHEPs. As the sample size was small in this study, a large cohort of diabetics with border spectrum of DSP is required to test the reliability of CHEPs in early detection of DSP in future studies. Finally, this method is not simple and time consuming, therefore, the procedure should be simplified in future studies.

7.10 Limitations of the study

One participant from the diabetic group and one participants from the diabetic with lower limb symptoms group withdrew from the study because of pain intolerance and fear of pain, which indicates that this method may not be suitable for patients who cannot physically or psychologically tolerate thermal stimulation. All of the diabetic participants in this study suffered from NIDDM and were between 40 and 60 years of age; hence, the results may not be generalisable to patients with IDDM, the elderly, or the young. Finally, all of the participants in the present study were mentally alert and cooperative. The feasibility of applying CHEPs in mentally incapable populations is unknown.

7.11 Implications of the study

The results of this study demonstrate the feasibility of using CHEPs to detect early-stage small nerve fibre damage. CHEP stimulation is a simple procedure and can be conducted in any institute with an electrodiagnostic unit. Therefore, there is great potential for the application of CHEPs in routine screening for diabetic complications, the evaluation of pharmacological and non-pharmacological treatment effects and monitoring of the progress of DSP. Finally, the development of a home-based self-monitoring device based on the principle of CHEPs could be explored in future research.

7.12 Conclusion and recommendations

The results demonstrate that CHEP stimulation elicits a corresponding electrophysiological response in diabetic patients with lower limb symptoms. The feasibility of using CHEPs as a surrogate method for DSP screening remains to be established in future research. The integration of

nerve conduction studies and CHEPs may provide a comprehensive view of the involvement of large and small nerve fibres in diabetics with lower limb symptoms. Finally, the use of CHEPs for detecting early-stage DSP is demonstrated to be feasible. Future studies should investigate the reliability, sensitivity and specificity of CHEPs in early detection of DSP.

Chapter 8
Conclusion

8.1 Introduction

DSP is a common complication of diabetes. Patients suffering from this condition can have various symptoms, with neuropathic pain commonly reported symptom. Although various medications are available for treating pain related to DSP, many patients are disappointed with the treatment outcomes. This substandard pain management may be due to the focus of treatment of symptoms rather than cause, and the lack of a surrogate objective method to distinguish between mild and severe DSP. The purpose of this study was to investigate whether there is small nerve damage in diabetics with lower limb symptoms. The study involved three stages. The first stage was a systematic review of studies of the effect of the pharmacological treatment of painful DN to explore the need for the early detection of DSP and identify types of nerve damage before the commencement of treatment. The second stage was a cross-sectional study to test the reliability of CHEPs and explore CHEP characteristics in healthy adults. The third stage was a cross-sectional study exploring the feasibility of using CHEPs

to detect early-stage DSP. The major findings of these studies will be summarised in this chapter.

8.2 Summary of the major findings

8.2.1 Stage 1

The ORs in terms of 50% reduction in pain for antidepressants and traditional anticonvulsants were higher than those for newer generation anticonvulsants, opioids and an ion channel blocker. The NNT in terms of 50% reduction in pain amongst the different classes of medications were between 1.74 and 5.38. The OR in terms of withdrawal due to adverse events was between 1.08 and 10.5 for individual medications. These results indicate that substantial numbers of patients suffering from painful DSP may not benefit from pharmacological treatments because of intolerable adverse events. Low-dosage treatment in the early stage of DSP may increase drug tolerance. Finally, matching individual classes of medications with different types of nerve damage may also enhance treatment effects.

8.2.2 Stage 2

There were 100% reproducible CHEPs following stimulation of the dorsum of the left foot and 95.2% reproducible CHEPs following stimulation 10 cm proximal to the left lateral malleolus. Regarding stimulation of the dorsum of the foot, the N1-P1 amplitude had the highest Cronbach's alpha (0.901) and ICC (0.820), followed by the P1 amplitude, N1 amplitude, P1 latency and N1 latency. Regarding stimulation 10 cm proximal to the left lateral malleolus, the P1 amplitude had the highest ICC (0.815) and Cronbach's alpha (0.688), followed by the P1 latency, N1-P1 amplitude and N1 latency.

8.2.3 Stage 3

There was a significant difference in N1-P1 amplitude amongst the three groups following stimulation of the dorsum of the foot ($p = 0.028$) and 10 cm proximal to the lateral malleolus ($p = 0.006$). Post hoc analysis showed that diabetics with lower limb symptoms had significantly lower N1-P1 amplitudes following stimulation of the dorsum of the left foot compared to diabetic patients without lower limb symptoms ($p = 0.027$).

Regarding stimulation 10 cm proximal to the left lateral malleolus, post hoc

analysis showed that diabetics with lower limb symptoms had significantly lower N1-P1 amplitudes compared with healthy adults ($p = 0.014$) and diabetics without lower limb symptoms ($p = 0.006$).

There were no significant interaction effects between HbA1c and DM with or without symptoms, and duration of diabetes and DM with or without symptoms at the two stimulation sites.

8.3 Findings that have not been reported

Oral TCAs and traditional anticonvulsants appear to offer better short-term pain relief than newer generation anticonvulsants. Some patients with painful DSP may not benefit from existing pharmacological treatments. CHEPs is a reliable method for detecting A-delta fibre damage as reflected by the moderate to strong ICC and Cronbach's alpha coefficients of the CHEP parameters. Finally, CHEPs is able to detect A-delta fibre damage in patients with minimal symptomatic DSP.

8.4 Conclusion

Various classes of medications are used to treat painful DSP; however, some patients are disappointed with the treatment outcomes. Treatment targeting the early stage of nerve damage rather than pain intensity reduction could improve treatment results. There exists a surrogate method to detect early-stage small fibre damage, CHEPS. The results for CHEP stimulation of the dorsum of the left foot and 10 cm proximal to the left lateral malleolus in healthy adults indicate that this method has moderate to strong reliability. Hence, it is feasible to use CHEPs to detect early A-delta fibre damage in diabetic patients with minimal neuropathy.

Appendix A

Information Sheet

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學
護理學院
School of Nursing

香港 九龍 紅磡
Hung Hom Kowloon Hong Kong

有 關 資 料

探討糖尿病性周圍神經疾病引起的疼痛與 A 神經纖維及 C 神經纖維的功能之關係

誠邀閣下參加由香港理工大學護理學院研究黃敏蓁負責執 ，鍾慧儀教授監督的研計劃。

這項研究的目的是找出糖尿病性周圍神經疾病引起的疼痛與 A 神經纖維及 C 神經纖維的功能之關係。

糖尿病於近年有上升的趨勢，而當中患有糖尿病性周圍神經疾病約佔二至三成。根據統計資料顯示，約有二成患者出現被疼痛困擾的情況。A 神經纖維及 C 神經纖維是主要傳遞疼痛信息的纖維，而它們與糖尿病性周圍神經疾病引起的疼痛之關係尚未清楚。因此了解它們之關係有助於增加對此疾病的認識，對日後預防及治療能夠提供重要的線索。

研究中所涉及到的問卷及實驗約需二至 三小時。在這研究中，研究員將在你的腳背、及小腿外側用 Pathway-Pain and Sensory Evaluation System 產生不同的溫度刺激。在腳趾底部用 TSA-II NeuroSensory Analyzer 產生不同的震動刺激。 並使用腦電描記述將閣下對溫度刺激的反應轉換成腦電圖。希望這些資料能有助於了解糖尿病性周圍神經疾病引起的疼痛與 A 神經纖維及 C 神經纖維的功能之關係，爲未來的醫療發展奠下重要的基礎。

閣下享有充分的權利在研究開始之前或之後決定退出這項研究，而不會受到任何對閣下不正常的代遇或責任追究 。凡有關閣下的資料均會保密，一切資料的編碼只有研究人員知道。

如果閣下有任何對這項研究的不滿，請隨時與香港理工大學人事倫理委員會秘書

親自或寫信聯絡(地址:香港理工大學人力資源辦公室 M1303 室轉交)。

如果閣下想獲得更多有關這項研究的資料，請與黃敏蓁聯絡，電話 9208　或接觸她 的導師鍾慧儀教授，電話 27666548。

為表謝意 ，閣下於完成檢查後會獲贈價值 HK$100 的購物禮券。此外，我們會向您解釋檢查報告的內容及把報告的副本交給您以作保存。

研究員:博士研究生黃敏蓁資深護師

Appendix B

Consent form

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學
護理學院
School of Nursing

香港 九龍 紅磡
Hung Hom Kowloon Hong Kong

有 關 資 料

參 與 研 究 同 意 書

研究名稱: 探討利用中文疼痛強度敘駭述比擬量度表之效度及信度

本 人 _____ 同 意 參 加 由_____ 負 責 執 行 的 研 究 項 目 。

我 理 解 此 研 究 所 獲 得 的 資 料 可 用 於 未 來 的 研 究 和 學 術 交 流 。然 而 我 有 權 保 護 自 己 的 隱 私 , 我 的 個 人 資 料 將 不 能 洩 漏 。

我 對 所 附 資 料 的 有 關 步 驟 已 經 得 到 充 分 的 解 釋 。我 理 解 可 能 會 出 現 的 風 險 。我 是 自 願 參 與 這 項 研 究 。

我 理 解 我 有 權 在 研 究 過 程 中 提 出 問 題, 并 在 任 何 時 候 決 定 退 出 研 究 而 不 會 受 到 任 何 不 正 常 的 待 遇 或 責 任 追 究 。

參 加 者 姓 名 _____.

參 加 者 簽 名_____

研 究 人員 姓 名 _____.

研 究 人員 簽 字 _____.

日 期 _____.

Appendix C

Screening form for healthy adult

Subject no: _____

Date of visit: _____

Eligibility		
Inclusion criteria: √ one box for each question:	**Yes**	**No**
1. Subject is a male or female between 18 and 60 years at the time of the screening visit	☐	☐
2. Subject is mentally alert	☐	☐
Exclusion criteria: √ one box for each question:		
1. Subject has known history of diabetic mellitus	☐	☐
2. Subject has known history of lumber discogenic disease or nerve root compression	☐	☐
3. Subject has known history neurological disease such as neuropathy	☐	☐
4. Subject has known history of peripheral vascular disease	☐	☐
5. Subject has known history of central nerve system disease such as brain tumour	☐	☐
6. Subject has known history of chronic pain such as trigeminal neuralgia	☐	☐

Did the subject meet all the entry criteria?

☐ Yes ☐ No

Appendix D

Data collection form (completed by researcher)

Subject no: _____ Date of visit: _____

I. Demography

1. Date of birth: _____
2. Sex: □ Male □ Female
3. Are you smoking: □ No □ Yes
4. Are you drinking alcohol: □ No □ Yes
5. Height: _____ cm; Body weight: _____ kg
6. BMI: _____
7. Dominant hand: □ Rt □ Lt

II. Medical conditions

	√ only one response for each condition	
	No medical condition	Current or past condition, please specify the condition
1. Blood and lymphatic system disorders	☐	☐, _____
2. Cardiac disorders	☐	☐, _____
3. Ear and labyrinth disorder	☐	☐, _____
4. Endocrine disorders	☐	☐, _____
5. Eye disorders	☐	☐, _____
6. Gastrointestinal disorders	☐	☐, _____
7. Hepatobiliary disorders	☐	☐, _____
8. Immune system disorders	☐	☐, _____
9. Metabolism and nutrition disorders	☐	☐, _____
10. Musculoskeletal and connective tissue disorders	☐	☐, _____
11. Neoplasms benign, malignant and unspecified (including cysts and polyps)	☐	☐, _____
12. Nervous system disorders	☐	☐, _____

Medical Conditions (continuous)

13. Psychiatric disorders	☐	☐, _____
14. Renal and urinary disorders	☐	☐, _____
15. Reproductive system and breast disorders	☐	☐, _____
16. Respiratory, thoracic and mediastinal disorders	☐	☐, _____
17. Skin and subcutaneous tissue disorders	☐	☐, _____
18. Vascular disorders	☐	☐, _____

III. Surgical procedure

1. Has the subject had any spinal surgeries?

☐ No

☐ Yes, please record below:

2. Has the subjects had any lower limb surgeries?

☐ No

☐ Yes, please record below:

IV. Concurrent medications

Type	Generic name	Dose	Duration of use

V. Painful and nonpainful DSP and analgesic history (for diabetic participant)

1. Types of diabetic mellitus: IDDM / NIDDM (delete the inappropriate one)
2. Length of time had diabetic mellitus _____ weeks/months/years (delete the inappropriate one)
3. Length of time had painful lower limb symptoms _____weeks/months/years (delete the inappropriate one)
4. Describe the quality of the pain _____
5. Indicate the location of the pain _____
6. The present pain intensity (C-PIVRS): _____
7. Current analgesic prescription for this painful condition:

   _____
8. Past analgesic prescription for this painful condition:

   _____
9. Has the subject had history of foot ulcer? □ No □ Yes, site_____, duration _____

Subject no: _____

Date of visit: _____

Appendix E
Pain intensity rating after each stimulation

Stimulation site	Sequence	Temp.																			
( ) Dorsum of foot		51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃
		51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃
( ) Dorsum of foot		51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃
		51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃
( ) 10cm proximal to lateral malleolus		51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃
		51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃
( ) 10cm proximal to lateral malleolus		51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃
		51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃	51℃

Appendix F

Screening form for diabetic patient

Subject no: _____

Date of visit: _____

Eligibility		
Inclusion criteria: √ one box for each question:	**Yes**	**No**
1. Subject is a male or female between 18 and 60 years at the time of the screening visit	☐	☐
2. Subject is mentally alert	☐	☐
3. Subject is confirmed to have diabetic mellitus according to American Diabetic Association	☐	☐
4. Subject has stable metabolic control of blood glucose with HbA1c equal or less than 7.5% within 3 months	☐	☐
5. Subject has intermittent or persistent lower limb symptoms	☐	☐
6. Subject scores ≤ 5 points in Toronto clinical neuropathy score	☐	☐
Inclusion criteria: √ one box for each question:		
1. Subject has known history of lumbar discogenic disease or nerve root compression	☐	☐
2. Subject has known history of inherited neuropathy	☐	☐
3. Subject has known history of alcoholic neuropathy	☐	☐
4. Subject has known history of renal impairment such as diabetic nephropathy, chronic renal failure	☐	☐
5. Subject has known history of neurological disease such as tarsal tunnel syndrome	☐	☐
6. Subject has known history of peripheral vascular disease	☐	☐
7. Subject has known history of central nerve system disease such as brain tumour	☐	☐
8. Subject has known history of chronic pain other than painful DSP	☐	☐

Did the subject meet all the entry criteria?

☐ Yes ☐ No

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