Biomedical and Psychosocial Factors Associated with Pain and Disability after Peripheral Nerve Injury

by

Christine B. Novak

A thesis submitted in conformity with the requirements for the degree of Doctorate of Philosophy

Institute of Medical Science
University of Toronto

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Abstract

The main objective of my dissertation was to evaluate the biomedical and psychosocial factors associated with pain and disability in patients following traumatic upper extremity nerve injuries. This was approached by conducting 3 studies. The first study surveyed peripheral nerve surgeons regarding the assessment of pain in patients with nerve injury. The results showed that only 52% of surgeons always evaluate pain in patients referred for motor/sensory dysfunction. Pain assessment frequently includes verbal response and assessment of psychosocial factors is infrequent. The second study was a retrospective review to assess disability, as measured by the Disabilities of the Arm, Shoulder and Hand (DASH), in patients with chronic nerve injury. Results showed substantial disability (mean DASH 52 ± 22) and a significantly lower health status (p < 0.001) compared with well-established norms. In the regression model, the factors associated with the DASH ($R^2 = 44.5\%$) were pain, older age and nerve injured. The third study was a cross-sectional evaluation of the biomedical and psychosocial factors associated with pain and disability after upper extremity nerve injury in 158 patients. DASH scores were significantly higher in patients with workers’ compensation or litigation (p = 0.03), brachial plexus injuries (p
< 0.001) and unemployed patients (p < 0.001). In the multivariable regression analysis, the final model explained 52.7% of the variance with these predictors; pain intensity (Beta = .230, p = 0.006), nerve injured (Beta = -.220, p = 0.000), time since injury (Beta = -.198, p = 0.002), pain catastrophizing (Beta = .192, p = 0.025), age (Beta = .187, p = 0.002), work status (Beta = .179, p = 0.008), cold sensitivity (Beta = .171, p = 0.015), depression score (Beta = .133, p = 0.066), workers’ compensation/litigation (Beta = .116, p = 0.049) and gender (Beta = -.104, p = 0.09). Future investigation regarding treatments of the factors that are associated with disability and chronic pain will assist to improve health related quality of life in patients with traumatic nerve injury.
Acknowledgements

A PhD is a journey of hard work, perseverance, persistence, determination and good luck. I am extremely grateful to everyone who walked with me and helped me on this long, educational, sometimes tortuous and definitely rewarding journey.

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This dissertation is dedicated to my brother, who taught me about the virtues of perseverance, determination and tenacity, how to continue with honour in the face of adversity and most importantly to never give up.
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<td>analysis of variance</td>
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<tr>
<td>Cold Intolerance Severity Scale</td>
<td>CISS</td>
</tr>
<tr>
<td>Cold Sensitivity Scale</td>
<td>CSS</td>
</tr>
<tr>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
<td>DMS</td>
</tr>
<tr>
<td>Disabilities of the Arm, Shoulder and Hand</td>
<td>DASH</td>
</tr>
<tr>
<td>dorsal root entry zone</td>
<td>DREZ</td>
</tr>
<tr>
<td>electromyography</td>
<td>EMG</td>
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<tr>
<td>Hospital Anxiety and Depression Scale</td>
<td>HADS</td>
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<td>International Association for the Study of Pain</td>
<td>IASP</td>
</tr>
<tr>
<td>International Classification of Functioning, Disability and Health</td>
<td>ICF</td>
</tr>
<tr>
<td>magnetic resonance imaging</td>
<td>MRI</td>
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<td>McGill Pain Questionnaire</td>
<td>MPQ</td>
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<td>Medical Research Council</td>
<td>MRC</td>
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<tr>
<td>millimetre</td>
<td>mm</td>
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<tr>
<td>numeric rating scales</td>
<td>NRS</td>
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<tr>
<td>odds ratio</td>
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<tr>
<td>Pain Catastrophizing Scale</td>
<td>PCS</td>
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<td>Pain Rating Index</td>
<td>PRI</td>
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Post-traumatic Stress Disorder (PTSD)

Post-traumatic Stress Disorder Checklist - Civilian version (PCL-C)

Present Pain Intensity (PPI)

standard deviation (sd)

Short Form McGill Pain Questionnaire (SF-MPQ)

Short Form Medical Outcomes 36 (SF-36)

United States (US)

verbal rating scale (VRS)

visual analog scale (VAS)

World Health Organization (WHO)
Chapter 1
Introduction

1 Introduction

Traumatic peripheral nerve injury may result in substantial morbidity and the cost of traumatic hand and nerve injuries may be substantial to both the individual and society.

Recovery following nerve injury is variable and is thought to be primarily dependent upon the severity of the nerve injury, nerve regeneration and capacity of the motor endplates or sensory end organs to reinnervate. However, many injuries appear to be of similar severity and yet recovery and patient functional outcome is variable. Outcome studies following nerve injury typically have reported physical impairment as related to the recovery of motor fibres and sensory end organs in terms of muscle strength, touch sensation, two-point discrimination. In contrast, symptoms of cold sensitivity and pain intensity are reported less frequently. The influence of these biomedical factors related to physical impairment may account for only a portion of the functional recovery following nerve injury. Studies that have evaluated other musculoskeletal disorders have identified the importance and influences of psychosocial factors on outcome. These factors have been mostly disregarded in the assessment of patients following nerve injury.

The World Health Organization (WHO) has developed the International Classification of Functioning, Disability and Health (ICF) to provide a conceptual framework for defining health and disability. This model incorporates body structures and functions (physiological function), activity and participation in the context of life domains with consideration of the
impact of contextual (environmental and personal) factors (World Health Organization, 2001; Jette, 2009). In the context of the patient with a peripheral nerve injury, this model takes into consideration the interaction between the condition after injury (physical impairment and activity performance) and the personal and environmental factors which may affect outcome.

Multiple biomedical factors, including motor or sensory dysfunction, pain, and cold sensitivity, may be present after nerve injury. These limitations in body function or structure may be defined as physical impairments and may result in disability as defined by an activity or participation limitation. However, psychosocial factors may also be associated with the resultant disability. Previous studies of patients with distal radius fractures, osteoarthritis and nerve pathologies have shown evidence of an association between psychosocial factors (such as pain catastrophizing, anxiety and depression), pain intensity and patient satisfaction (Bailey, Vaskutas, Fox, Baum, & Mackinnon, 2009; Lozano Calderon, Paiva, & Ring, 2008a; Lozano Calderon, Souer, Jupiter, & Ring, 2008b; Souer, Lozano Calderon, & Ring, 2008). The association of the biomedical and psychosocial factors in patients with peripheral nerve injury and the relative contributions of these factors to patient disability have yet to be determined. Identification of the factors that are associated with disability and functional outcome will assist in the development of more comprehensive and efficacious treatment strategies for patients with incomplete recovery and morbidity associated with traumatic upper extremity nerve injury.

In my dissertation, I will evaluate the biomedical and psychosocial factors associated with pain and disability following traumatic upper extremity nerve injury. In Chapter 2, the review of the relevant literature and background will be presented. This chapter includes a published
Chapter 2
Review of Literature

2 Background

Traumatic peripheral nerve injury may result in morbidity associated with motor or sensory impairment and/or pain as a direct result of trauma to the nerve. The cost of traumatic hand and nerve injuries may be substantial to both the individual and society (Dias & Garcia-Elias, 2006; Rosberg, Carlsson, & Dahlin, 2005a; Rosberg et al., 2005b).

2.1 Occurrence of Upper Extremity Peripheral Nerve Injury

Peripheral nerve dysfunction may occur from various etiologies related to traumatic and non-traumatic causes. Nerve injuries resulting from trauma vary in severity and as a consequence, the requisite treatment and ultimate recovery will also vary. The prevalence of traumatic upper extremity peripheral nerve injuries appears to be relatively small compared to other trauma injuries, although the exact number of nerve injuries is difficult to determine. Midha (1997) reported 60 patients with brachial plexus injuries from a total of 4,538 trauma patients that were seen at a level 1 trauma center in Ontario, Canada over a nine year period. Noble, Munro, Prasad & Midha (1998) reported 5,777 trauma patients seen between January 1986 to November 1996 and there were 200 upper and lower extremity nerve injuries in 162 patients (2.8 %). Beghi, Kurland, Mulder & Nicolosi (1985) reviewed the available records from 1970 to 1981 at the Mayo Clinic. The authors reported 579 clinic records related to the brachial plexus and in 44 cases, brachial plexus nerve injury was the result of trauma or
compression (the total records available at the Mayo Clinic were not stated). McAllister, Gilbert, Calder & Smith (1996) evaluated the etiology and pattern of nerve injury in 813 patients with upper extremity trauma. Injuries were more prevalent in males (74.2%), in younger patients and were associated with sharp lacerations. In a study from Sweden, Ekholm et al. (2006) reported 8.5% of injuries to the humerus resulted in a radial nerve palsy. In a systematic review of the management of radial nerve palsy following humeral fracture by Shao, Harwood, Grotz, Limb & Giannoudis (2005), the prevalence of radial nerve injury was reported to be 11.8%.

Recovery following peripheral nerve injury may vary from complete restoration of motor and/or sensory function to complete residual paresis and numbness. The costs associated with peripheral nerve injuries may vary relative to the severity of nerve injury, recovery and treatment. In patients with traumatic forearm and hand injuries, Rosberg et al (2005a) reported higher disability and costs (medical and personal) in patients with more severe injuries. In another study by Rosberg et al. (2005b), substantial cost was reported for treatment of patients with median and/or ulnar nerve injuries and the cost increased with concomitant tendon injuries and in patients who changed jobs. Peripheral nerve injuries result in a substantial cost to the individual and society, although the exact cost is difficult to determine and may be influenced by a number of factors related to the injury, individual and society.

Neuropathic pain following traumatic peripheral nerve injury is variable and when present, may be severe in intensity. The International Association for the Study of Pain (IASP) defines “neuropathic pain” as pain resulting from a lesion or disease affecting the somatosensory system (Loeser & Treede, 2008). It is difficult to determine the prevalence of
neuropathic pain caused by traumatic nerve injury. In the surgical literature, those studies which have reported the prevalence of traumatic peripheral nerve injuries do not include data regarding neuropathic pain. In the pain literature, neuropathic pain associated with peripheral sensory neuropathies are more frequently reported compared to neuropathic pain as a result of traumatic peripheral nerve injuries. In a population survey from the United Kingdom, a 45% prevalence of chronic pain was reported in the general population and 8% of these individuals had neuropathic pain, although the exact origin of the pain was not stated (Torrance, Smith, Bennett, & Lee, 2006). A community based study from Austria reported a 3.3% prevalence of neuropathic pain and in the majority of cases, non-traumatic etiologies were identified as the cause of the pain (Gustorff et al., 2008). Many of these individuals from Austria reported pain related activity restriction, sleep disturbance, depression and anxiety. Hayes, Browne, Lantry & Burstal (2002) identified 51 patients with acute neuropathic pain out of a total 4,888 new patients who were seen at a 500-bed Australian hospital over a two and a half year period. Of the 51 patients with neuropathic pain, 43% involved a traumatic injury. The prevalence of peripheral nerve injuries including the brachial plexus may be small compared to the overall prevalence of traumatic injuries but the morbidity associated with these injuries may be substantial with significant cost to the individual and society at large.

2.2 Neuropathic Pain in Patients with Upper Extremity Nerve Injury
This section presents a review and critical analysis of the published literature dealing with outcomes of patients following traumatic upper extremity nerve injuries. This review of the literature has been accepted for publication in Physiotherapy Canada, (Novak, C. B. & Katz,
J. (2010). Neuropathic Pain in Patients with Upper Extremity Nerve Injury. *Physiotherapy Canada, 62*:109-201). Permission to reproduce this manuscript in my dissertation was granted by the publisher. In this literature review, I was specifically interested in the following questions: In outcome studies of patients with traumatic nerve injury, is neuropathic pain reported when present and if reported, what type of assessments, measures or questionnaires are utilized? Are valid measures of upper extremity disability, such as the Disabilities of the Arm, Shoulder and Hand (DASH), used in outcome studies of patients with upper extremity nerve injury?
2.2.1 Abstract

Purpose: The purpose of this review was to present an analysis of the literature of the outcome studies reported in patients following traumatic upper extremity nerve injuries (excluding amputation), to assess the presence of an association between neuropathic pain and outcome in patients following traumatic upper extremity nerve injuries, and to provide recommendations for inclusion of more comprehensive outcome measures by clinicians who treat these patients.

Summary of Key Points: A Medline and CINAHL literature search retrieved 48 articles. This review identified very few studies of patients with peripheral nerve injury that reported neuropathic pain. When pain was reported, visual analog or numeric rating scales were most frequently used, and standardized questionnaires measuring pain or psychosocial function were rarely administered. Recent evidence shows substantial long term disability and pain in patients following peripheral nerve injury.

Recommendation: To better understand neuropathic pain in patients following peripheral nerve injury, future outcome studies should include valid, reliable measures of physical impairment, pain, disability, health related quality of life, and psychosocial functioning.
2.2.2 Introduction

The International Association for the Study of Pain (IASP) defines neuropathic pain as pain resulting from a lesion or disease in the peripheral or central nervous system (Cruccu et al., 2004; Loeser et al., 2008; Merskey & Bogduk, 1994). Within this broad categorization, various etiologies may cause “neuropathic pain”. Neuropathic pain may occur as a result of trauma, central nervous lesions, or diseases such as diabetic peripheral neuropathy, herpetic nerve lesions, or multiple sclerosis, and each etiology has different implications with regard to assessment and treatment. Many of the studies and reviews in the literature have evaluated neuropathic pain as it relates to disease states or limb amputation, but few have included other traumatic peripheral nerve injuries. Although it is commonly believed that traumatic upper extremity nerve injury may be associated with poor outcome that is often related to pain, most studies report only physical impairment related to motor and/or sensory recovery. Few studies report neuropathic pain following nerve injury or the impact of the resultant physical impairments on the patient (Ahmed-Labib, Golan, & Jacques, 2007; Choi, Novak, Mackinnon, & Kline, 1997; Novak, Anastakis, Beaton, & Katz, 2009b).

The purpose of this review was to present an overview of the literature of the outcome studies reported in patients following traumatic upper extremity nerve injuries (excluding amputation). We were specifically interested in assessing the presence of an association between neuropathic pain and outcome in patients following traumatic upper extremity nerve injuries and in providing recommendations for inclusion of more comprehensive outcome measures by clinicians.
2.2.3 Methods

The following specific questions were investigated: In outcome studies of patients with traumatic nerve injury, is persistent pain systematically recorded? Is neuropathic pain reported when present? If it is reported, what types of assessments are used? Are valid measures of upper extremity disability, such as the Disabilities of the Arm, Shoulder and Hand (DASH), used in outcome studies of patients with upper extremity nerve injury?

2.2.3.1 Search Strategy

The literature for the present review was obtained by an electronic search of Ovid Medline databases (1950–2009), CINAHL (1979–2009), the Cochrane Database of Systematic Reviews (2005-2009), and subsequent review of the reference lists of retrieved articles. The search included both subject headings and keywords and included articles up to November 2009. It was limited to the English language and adults, and it excluded amputation injuries, case reports and abstracts.

To assess the presence of the terms “neuropathic pain” and “health related quality of life outcome” in studies of patients with traumatic nerve injury, the initial Medline search included “neuropathic pain” AND “quality of life”. The term “quality of life” was used because it is a Medline subject heading and because, particularly in the surgical literature, this is the term commonly used to refer to disability and health related quality of life. We then performed a more extensive Medline search to include broader terms. The search strategy used the following terms: “brachial plexus OR radial nerve OR median nerve OR ulnar nerve” AND “recovery of function OR treatment outcome” AND “pain”. To include all
peripheral nerves, we used the following terms: “peripheral nerve” AND “pain OR pain measurement” AND “disability OR disability evaluation” AND “arm OR arm injuries OR hand OR hand injuries OR upper extremity”. The search in the Cochrane Database of Systematic Reviews used the following terms: “nerve injury” OR “brachial plexus” OR “median nerve” OR “ulnar nerve” OR “radial nerve”.

2.2.4   Results

The initial Medline search included “neuropathic pain” AND “quality of life” and this search found 79 citations. Based on the titles and abstracts, 59 articles described neuropathic pain resulting from spinal cord injuries, amputations, low back, lower extremity, or non-injury etiologies (e.g., cancer, diabetic neuropathy, herpes, multiple sclerosis); these articles were excluded. The other 20 articles were retrieved for closer examination. None of the 20 articles reported outcomes related only to patients with traumatic upper extremity nerve injury. Eight of the 20 reported outcomes in patients with neuropathic pain resulting from various etiologies, including small samples of patients with nerve injury. The search was also performed in CINAHL, but no additional articles were retrieved.

A more extensive Medline search included broader terms: “brachial plexus OR radial nerve OR median nerve OR ulnar nerve” AND “recovery of function OR treatment outcome” AND “pain”. This search retrieved 330 citations. Review of the titles and abstracts found 31 citations that appeared to be related to traumatic upper extremity nerve injuries, and these were retrieved for closer examination. The search was also performed in CINAHL; no additional articles were retrieved.
To include all peripheral nerves, the terms were: “peripheral nerve” AND “pain OR pain measurement” AND “disability OR disability evaluation” AND “arm OR arm injuries OR hand OR hand injuries OR upper extremity”. This search retrieved 387 citations, including 24 articles related to traumatic upper extremity nerve injuries. Because the DASH (Beaton et al., 2001; Beaton, Wright, Katz, & Upper Extremity Collaborative Group, 2005; Davidson, 2004; Gummesson, Atroshi, & Ekdahl, 2003; Dias, Rajan, & Thompson, 2008; Gummesson, Ward, & Atroshi, 2006; Hudak, Amadio, & Bombardier, 1996; SooHoo, McDonald, Seiler, & McGillivary, 2008) questionnaire is commonly used to measure upper extremity outcome, a separate search was conducted using “disability” or “DASH” by using the following search terms: “arm injuries OR brachial plexus OR radial nerve OR median nerve OR ulnar nerve” AND “recovery of function OR treatment outcome” AND “disability OR DASH”. This search retrieved 108 citations. A review of the titles and abstracts yielded 16 articles that evaluated outcome following nerve injury with consideration of disability and five articles that included evaluation with the DASH. The remaining five articles were not primarily reports of nerve injury outcome but reports of various orthopaedic surgical procedures where nerve related complications were reported. The search was also performed in CINAHL; no additional articles were retrieved.

The search in the Cochrane Database of Systematic Reviews retrieved 102 citations. There was one citation relevant to the treatment of radial nerve injuries, but only the protocol was published.
The relevant articles from these searches regarding outcome following nerve injury are presented in Table 2.1.

### Table 2.1 Characteristics of Included Studies

<table>
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<th>First Author (Year)</th>
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<th>Nerve injured patients</th>
<th>Study</th>
<th>Outcomes presented</th>
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<tr>
<td>Gousheh (2009)</td>
<td>19</td>
<td>19 brachial plexus</td>
<td>Outcome following free muscle transfer</td>
<td>MRC motor grading scale, overall result</td>
</tr>
<tr>
<td>Lefaucheur (2009)</td>
<td>16</td>
<td>4 brachial plexus</td>
<td>Motor cortex stimulation for refractory peripheral neuropathic pain</td>
<td>VAS, brief pain inventory, MPQ, sickness impact profile, medication quantification scale</td>
</tr>
<tr>
<td>Novak (2009)</td>
<td>84</td>
<td>84 upper extremity</td>
<td>Outcome following traumatic nerve injury</td>
<td>SF36, DASH</td>
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<tr>
<td>Bertelli (2008b)</td>
<td>22</td>
<td>22 brachial plexus</td>
<td>Outcome following surgery</td>
<td>MRC motor grading scale,</td>
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<tr>
<td>Bertelli (2008a)</td>
<td>36</td>
<td>36 brachial plexus</td>
<td>Outcome following surgery</td>
<td>MRC motor grading scale, pain intensity</td>
</tr>
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<td>14 brachial plexus</td>
<td>Outcome following DREZ procedure</td>
<td>Pain intensity, life quality, Karnofsky Performance Scale</td>
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<td>Cold intolerance following nerve injury</td>
<td>Cold intolerance, thermography</td>
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<td>107 median or ulnar</td>
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<td>Cold Intolerance Severity Score</td>
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<td>Muscle strength, pain relief</td>
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<td>Bruyns (2003)</td>
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<td>96 median or ulnar</td>
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<td>Strength, sensibility, return to work</td>
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<td>Kim (2001)</td>
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<td>Eggers (2001)</td>
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<td>103 brachial plexus</td>
<td>Report new evaluation system</td>
<td>New classification system for flail upper limb</td>
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<td>Pain relief</td>
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<td>Geertzen (2000)</td>
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<td>Pain, muscle strength, Shoulder Disability Questionnaire</td>
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<td>Motor recovery</td>
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<td>Bentolila (1999)</td>
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<td>Outcome following surgery</td>
<td>Motor recovery, pain relief, return to work, satisfaction</td>
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<td>28 median</td>
<td>Outcome following surgery</td>
<td>Sensibility, pick-up test</td>
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<td>13 neuromas</td>
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<td>Pain relief, hand function, return to work</td>
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<td>Rath (1997)</td>
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<td>Emery (1997)</td>
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<td>Cold intolerance following injury</td>
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<td>Outcome following surgery</td>
<td>Telephone questionnaire, satisfaction, employment, life domains</td>
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<td>Pain relief</td>
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<td>Tonkin (1996)</td>
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<td>Study Description</td>
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<td>44</td>
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<td>Evans</td>
<td>1994</td>
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<td>Neuromas Outcome following surgery</td>
<td>Pain relief, return to work</td>
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<td>52</td>
<td>Neuromas Outcome following surgery</td>
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<td>1984</td>
<td>49</td>
<td>Ulnar Outcome following surgery</td>
<td>Strength, sensibility, vascular tests</td>
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<td>Rorabeck</td>
<td>1980</td>
<td>23</td>
<td>Brachial Plexus Outcome following surgery</td>
<td>Return to work</td>
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</table>

DASH = Disabilities of the Arm, Shoulder and Hand; DREZ = dorsal root entry zone; MPQ = McGill Pain Questionnaire; MRC = Medical Research Council; SF-36 = Short Form Medical Outcomes 36; RTW = return to work

2.2.5 Discussion

Our literature search revealed very few articles that evaluated neuropathic pain and/or disability in patients following peripheral nerve injury. The term “neuropathic pain” is not typically used to refer to pain following a traumatic upper extremity nerve injury. Many of the outcome studies following nerve injury or surgery included only measures of physical impairment and return to work as a measure of function (Bertelli & Ghizoni, 2008a; Bertelli & Ghizoni, 2008b; Doi et al., 2000; Eggers & Mennen, 2001; Gousheh & Arastreh, 2009; Hsu et al., 2004; Kanpolat, Tuna, Bozkurt, & Elhan, 2008; Meiners, Coert, Robinson, & Meek, 2005; Nath, Lyons, & Bietz, 2006; Ricardo, 2005; Sood & Elliot, 1998; Terzis, Vekris, & Soucacos, 1999; Terzis & Kostas, 2006; Tonkin, Eckersley, & Gschwind, 1996; Waikakul, Wongtragul, & Vanadurongwan, 1999; Wong, Coert, Robinson, & Meek, 2006), and the studies that did include the DASH (Ahmed-Labib et al., 2007; Davidson, 2004; Novak et al., 2009b) were published more recently.
The IASP defines “neuropathic pain” as resulting from a lesion or disease in the peripheral or central nervous system, and pain following a traumatic peripheral nerve injury would therefore be classified as neuropathic pain. However, traumatic peripheral nerve injuries excluding amputation injuries are not frequently included in the neuropathic pain literature, and there have been few reports of patients with peripheral nerve injuries included among other more common etiologies (Dworkin, Jensen, Gammaitoni, Olaleye, & Galer, 2007; Jensen, Chodroff, & Dworkin, 2007; Meyer-Rosberg et al., 2001b; Meyer-Rosberg et al., 2001a; Toth, Lander, & Wiebe, 2009). In a literature review by Jensen et al. (2007), neuropathic pain was negatively associated with health related quality of life and stronger associations were demonstrated when pain specific measures were compared to more generic measures. Numerous etiologies were included in the review by Jensen et al. and there was no differentiation between types of lesions. An overview of neuropathic pain by Dworkin et al. (2007) identified nine common peripheral neuropathic pain syndromes. Traumatic injury was not listed among these neuropathic pain syndromes. Meyer-Rosberg et al. (2001b) evaluated the burden of illness in patients with neuropathic pain and among their sample of patients was a small number with traumatic peripheral nerve injury. The authors reported a high level of pain with significantly lower SF-36 scores in all domains compared to normative data, but information was not presented specifically on the patients with traumatic peripheral nerve injury.

In the surgical literature, studies that report outcomes following peripheral nerve injuries rarely report information about pain (e.g., pain quality, intensity, frequency of episodes, duration). In our survey of peripheral nerve surgeons, only 52% reported formally assessing pain in patients referred primarily for motor or sensory dysfunction following nerve injury,
and in patients referred for pain, the most frequent method of assessing pain was a verbal
patient response (Novak, Anastakis, Beaton, & Katz, 2009a). This lack of detailed
assessment of neuropathic pain in patients with nerve injury parallels the underrepresentation
of pain assessment in the surgical literature following traumatic peripheral nerve injury.

The paucity of citations in the literature regarding neuropathic pain resulting from traumatic
peripheral nerve injury may be related to the relatively small number of cases of nerve injury
compared to other causes of neuropathic pain and other types of trauma. An urban population
survey from the United Kingdom reported a 45% prevalence of chronic pain, with 8% of
neuropathic origin (Torrance et al., 2006). The causes of neuropathic pain were not reported
in this study. A 3.3% prevalence of neuropathic pain was reported in a study from Austria, in
which the majority of subjects identified non-traumatic etiologies as the cause of the pain
(Gustorff et al., 2008). The exact prevalence of traumatic nerve injuries is difficult to
determine (Ekholm, Ponzer, Tornkvist, Adami, & Tidermark, 2008; Midha, 1997; Noble,
Munro, Prasad, & Midha, 1998). Midha (1997) reported that 4,538 trauma patients were seen
from January 1986 to December 1994 at a level 1 trauma center in Ontario, Canada,
including 60 patients with brachial plexus injuries. Noble et al. (1998) reported the
prevalence of upper and lower extremity peripheral nerve injuries from the same institution.
From January 1986 to November 1996, 5,777 trauma patients were seen; 200 nerve injuries
were identified in 162 patients (2.8%). An epidemiological study of humeral fractures from
Sweden reported that only 8.5% of injuries involved a radial nerve palsy (Ekholm et al.,
2006). These studies reveal a low prevalence of peripheral nerve injuries compared to the
overall prevalence of traumatic injuries; however, the morbidity associated with these
injuries may be severe, and early comprehensive assessment and intervention is essential for optimal outcomes.

2.2.5.1 Outcome Measures

Studies that have evaluated outcome following peripheral nerve injury have routinely focused on physical impairment, including sensory and motor dysfunction (Bertelli et al., 2008a; Bertelli et al., 2008b; Bruyns et al., 2003; Doi et al., 2000; Gousheh et al., 2009; Hsu et al., 2004; Mitz, Meriaux, & Vilain, 1984; Nath et al., 2006; Polatkan, Orhun, Polatkan, Nuzumlali, & Bayri, 1998; Ricardo, 2005; Rosen, Dahlin, & Lundborg, 2000a; Terzis et al., 1999; Tonkin et al., 1996; Wong et al., 2006). Outcome measures following motor nerve injury usually include manual muscle testing with the Medical Research Council (MRC) grading system, amount of weight that can be lifted or subjective grading by the researchers on scales ranging from “excellent” to “poor” (Bengtson et al., 2008). Patient functional assessment and/or pain evaluation are rarely included in outcome studies. The few studies that have reported pain predominantly included patients following brachial plexus nerve injuries (Bentolila, Nizard, Bizot, & Sedel, 1999; Berman, Birch, & Anand, 1998; Bertelli et al., 2008a; Bruxelle, Travers, & Thiebaut, 1988; Geertzen, Groothoff, Nicolai, & Rietman, 2000; Htut, Misra, Anand, Birch, & Carlstedt, 2006; Kato, Htut, Taggart, Carlstedt, & Birch, 2006; Kanpolat et al., 2008; Samii, Bear-Henney, Ludeman, Tatagiba, & Blomer, 2001; Waikakul et al., 1999). In these studies, traumatic injuries, root avulsions, and injuries proximal to the dorsal root ganglion were associated with more pain; surgical intervention and the timing of surgery relative to injury were identified as important factors in alleviating pain. These outcome studies reported pain intensity and frequency; however, validated
patient report questionnaires to assess the impact of the pain or impairment on the patient were not included.

Riess, Cogbill, Patel, Lambert & Mathiason (2007) reported significant short and long term disability following scapulothoracic dissociation compared to patients with brachial plexus nerve injuries. Outcome was evaluated by telephone interview; interviews included basic questions about upper extremity strength and work. No validated outcome measures were used in this study, and participants were not asked about pain. In another telephone survey, Choi et al. (1997) contacted 32 patients with brachial plexus injury and administered quality of life questions from the US General Social Survey. Moderately high general life satisfaction and quality of life were reported; 75% of patients reported “significant pain” and 38% were using pain medications.

Rating scales and composite scores have been introduced for the assessment of sensibility, motor function and impairment following nerve injury. In general, these rating scales and composite scores have placed very little emphasis on pain, including pain associated with cold sensitivity. The MRC scale (Medical Research Council of the U.K., 1976) is a six-point scale ranging from 0 to 5 based on the function of the muscle against gravity or with manual resistance; modifications of this scale have been described. Hight et al. and Zachary introduced a scale to categorize recovery of sensibility that was later modified by Mackinnon and Dellon (1988). This scale includes a range from “no sensibility” to “complete recovery” and considers touch, two-point discrimination, and pain response. The composite score introduced by Rosen and Lundborg (2000b) includes three domains (sensory, motor, pain/discomfort); cold intolerance and hyperaesthesia are ranked on a numeric scale, and these two parameters make up the pain/discomfort domain. Aberg et al. (2007) presented a
method for clinical evaluation following peripheral nerve injury. They investigated the applicability of a battery of clinical tests in a small sample of 15 patients with median nerve injuries and 15 control subjects. The tests in this clinical assessment were sensory recovery (two-point discrimination, cutaneous pressure thresholds, pin prick, thermal thresholds, sensory nerve conduction velocity and amplitude), motor recovery (manual muscle testing, grip and pinch strength, motor nerve conduction velocity and amplitude, needle electromyography), and functional recovery (four questions about function, pain, cold intolerance and dysaesthesia; DASH; motor performance test; Sollerman hand function test; sensorimotor test). Only one question addressed pain (present or absent) and one question addressed cold intolerance (present or absent), and the study included no quantification of their intensity, frequency, or impact on functional outcome.

2.2.5.2 Measurement of Neuropathic Pain

Pain is a subjective experience that is best evaluated by subjective patient report. Various approaches have been described for assessing neuropathic pain, ranging from simple verbal rating scales (VRS), numeric rating scales (NRS), and visual analogue scales (VAS) to multi-item, multidimensional questionnaires that measure the quality and intensity of pain. The VAS, NRS, and VRS, which usually provide a unidimensional measure of pain intensity (or pain affect, depending on the scale anchors), are commonly used to measure pain in the clinical setting. Introduced by Melzack (1975), the McGill Pain Questionnaire (MPQ) is the most frequently used and cited pain questionnaire. However, only one outcome study used the MPQ to assess pain following treatment for neuropathic pain (Lefaucheur et al., 2009).
The MPQ, developed by Melzack (1975) to obtain quantitative and qualitative measures of the experience of pain, yields two global scores: the pain rating index (PRI) and the present pain intensity (PPI). The PRI is the sum of the rank values of the 75 words chosen from 20 sets of qualitative words, each containing two to six adjectives that describe the sensory, affective, and evaluative properties of pain. The lists of pain descriptors are read to patients, who are asked to choose the word in each category that best describes their pain at the moment. The PPI is rated on a scale of 0 (none) to 5 (excruciating). The short form MPQ (SF-MPQ) was developed by Melzack (1987) for use when time is limited and when more information is required than is provided by unidimensional measures such as the VAS. The SF-MPQ consists of 15 adjectives from the sensory (n = 11) and affective (n = 4) categories of the original MPQ. Each adjective is rated on a four-point scale.

The selection of the optimal treatment approach and/or medication may be optimized by differentiating between nociceptive and neuropathic pain (Bennett et al., 2007). A modification of the SF-MPQ has been recently published that is reliable and valid for patients with neuropathic and non-neuropathic pain (Dworkin et al., 2009). The two main differences between the SF-MPQ and the modified SF-MPQ are the addition of seven adjectives relevant to neuropathic pain and the inclusion of a 10-point numeric rating scale to rate the intensity of each descriptor. Each version of the MPQ has been shown to have at least adequate psychometric properties, and each is a reliable and valid measure of acute and chronic pain (Melzack & Katz, 2006). Other questionnaires that have been described for assessment of neuropathic pain include the Neuropathic Pain Scale (Galer & Jensen, 1997), the Pain Quality Assessment Scale (Jensen et al., 2006), and the PainDetect (Freynhagen, Baron, Gockel, & Tolle, 2006). The Neuropathic Pain Scale is a 10-item scale in which patients are
asked to rank various dimensions (intensity, quality, allodynia) of pain on an 11-point NRS. This scale was validated with a diverse group of patients that included those with peripheral nerve injury, and it has been shown to be sensitive to alterations in the quality and intensity of neuropathic pain (Galer et al., 1997; Jensen, 2004; Jensen et al., 2005). However, it was limited to those patients who attended a chronic pain clinic, and, as outlined by the authors, it may not represent all of the pain qualities that patients with neuropathic pain experience. The Pain Quality Assessment Scale is a 20-item questionnaire modified from the Neuropathic Pain Scale to include more descriptors to differentiate neuropathic and non-neuropathic pain. This scale was validated in 40 patients with carpal tunnel syndrome; this group did not include other etiologies of neuropathic pain (Jensen et al., 2006). The PainDetect is 20-item questionnaire developed to evaluate the qualities associated with neuropathic pain (Freynhagen et al., 2006). Patients are asked to rank the degree of their symptoms on a scale of 0 to 10 for different qualities of pain. A higher score indicates more pain. This questionnaire was validated in a sample of patients with chronic low back pain; and the group did not include patients with a traumatic nerve injury. The authors reported a sensitivity of 85% and specificity of 80% in classifying patients with neuropathic pain (Freynhagen et al., 2006). Although these findings indicate moderate sensitivity and specificity, this measure has not been validated for use in patients with neuropathic pain following traumatic nerve injury. None of these neuropathic pain questionnaires has been universally accepted, and none has been used exclusively in patients with traumatic peripheral nerve injury.
2.2.5.3 Assessment of Disability and Health Status

Biopsychosocial models of disablement and health linking the biomedical, social and personal perspectives have been developed by the World Health Organization (WHO) and by others including Nagi, Verbrugge and Jette (Jette, 2006; Verbrugge & Jette, 1994; World Health Organization, 2001). Based on Nagi’s model, Verbrugge and Jette (1994) described the disablement process as a pathway between active pathology, impairment, functional limitations, and disability, with consideration of other individual and risk factors (Jette & Haley, 2005). Within the framework of the International Classification of Function, Disability and Health (ICF) model developed by the WHO, body structures and functions (physiological function), activity, and participation are considered in the context of life domains with interaction between the contextual environmental and personal factors (World Health Organization, 2001; Jette, 2009). In terms of nerve injury, this model takes into consideration the interaction between the condition after injury (physical impairment and activity performance, including participation) and contextual (personal and environmental) factors.

Generic health measures such as the Short Form Medical Outcomes 36 (SF-36) were designed to assess health status. Responses to the SF-36 may be calculated in eight domains and/or summarized in a physical and a mental component score (Brazier et al., 1992; Garratt, Ruta, Abdalla, Buckingham, & Russell, 1993; Hopman et al., 2000; McHorney & Raczek, 1993; Ware & Sherbourne, 1992). Meyer-Rosberg et al. (2001a) compared scores on the SF-36 and the Nottingham Health Profile for a diverse group of patients with neuropathic pain. They found that these patients had poorer scores compared to normative values and patients with high levels of pain scored worse on both measures. In a retrospective chart review,
patients with traumatic upper extremity nerve injuries had a significantly lower health status in all SF-36 domains and component scores (Hopman et al., 2000; Novak et al., 2009b). Ahmed-Labib et al. (2007) reported significantly worse health status in all SF-36 scores except general health, vitality, and the mental component score, as well as a higher level of disability, in patients following brachial plexus injury and reconstructive surgery. Based on correlational analysis, the authors concluded that root avulsion injuries and delayed surgical repair were associated with poorer functional outcome. Kitajima, Doi, Hattori, Takka & Estrella (2006) evaluated 30 patients with brachial plexus nerve injuries with a minimum follow-up of 12 months. Compared to the Japanese normative data, the nerve injured patients had a significantly lower health status (physical function, bodily pain, role physical and physical composite score). Generic questionnaires are useful for assessing general health status, but they may be limited in the assessment of upper extremity outcome. Disease-specific questionnaires such as the DASH may be more sensitive to diagnoses and pathologies affecting the upper extremity.

The DASH is a 30-item patient report measure to assess upper extremity disability that has established psychometric properties (Beaton et al., 2001; Beaton et al., 2005; Dias, Bhowal, Wildin, & Thompson, 2001; Gummesson et al., 2003; Gummesson et al., 2006; Hudak et al., 1996; SooHoo et al., 2008). Although the DASH is the most validated measure of upper extremity disability, it was not commonly used in the outcome studies of patients with nerve injury found in our literature search. Studies that evaluated disability with nerve injury reported high DASH scores (Ahmed-Labib et al., 2007; Bushnell, McWilliams, Whitener, & Messer, 2008; Davidson, 2004; Ekholm et al., 2008; Novak et al., 2009b; Topel et al., 2009). In the evaluation of patients following an upper extremity nerve injury, substantial disability
was found, and this was predicted by pain, older age, and brachial plexus injury (Novak et al., 2009b). Davidson (2004) used the DASH to evaluate 274 patients following upper extremity traumatic injuries, including amputations and brachial plexus injuries. High levels of disability were reported, and these were significantly higher in patients with brachial plexus injuries (Davidson, 2004). Ahmed-Labib et al. (2007) evaluated 31 patients following surgery for a brachial plexus injury; assessment included the DASH and SF-36. These patients reported high levels of disability, and their scores for six of the eight SF-36 domains were significantly worse compared to normative data. Topel et al. (2009) evaluated 33 patients following upper extremity arterial trauma. Patients with concomitant nerve injury (81%) had more functional deficits, with a significantly higher DASH score and lower SF-36 physical composite score. Patients with a radial nerve palsy following humeral fractures were evaluated by Ekholm et al. (2008) using patient reported outcome, including the DASH and the SF-36; most patients reported low disability levels and good health status. Following digital nerve repair, Bushnell et al. (2008) reported low levels of disability as assessed by the QuickDASH. Wong, Fung, Cuh & Chan (2007) evaluated 146 patients following traumatic hand injuries, both before participation in a rehabilitation program and at discharge. Both DASH scores and QuickDASH scores were included in the data analysis, which showed a high correlation ($r = 0.96$) between these scores at admission and discharge. There was a significant improvement in DASH scores at discharge; patients who did not return to work reported significantly more disability at both admission and discharge ($p < 0.05$).
2.2.5.4 Considerations of Cold Sensitivity and Contextual (Psychosocial) Factors

2.2.5.4.1 Cold Sensitivity

Cold sensitivity, described as pain or discomfort, stiffness, sensory disturbance, and colour changes with exposure to cold, is frequently reported following traumatic upper extremity injuries (Graham & Schofield, 2008; Irwin, Gilbert, Terenghi, Smith, & Green, 1997; Novak et al., 2009a; Ruijs, Jaquet, Brandsma, Daanen, & Hovius, 2008; Vaksvik, Hetland, Rokkum, & Holm, 2009). The terms “cold sensitivity” and “cold intolerance” have been used interchangeably in the literature; in this review, the term “cold sensitivity” is used, except in cases where reference is made to published studies whose authors have used the term “cold intolerance”. The symptoms of cold sensitivity are often attributed to poor outcome following traumatic peripheral nerve injuries and have been reported more frequently in patients with digital amputations and replantations (Backman, Nystrom, Backman, & Bjerle, 1993; Campbell & Kay, 1998; Collins, Novak, Mackinnon, & Weisenborn, 1996; Craigen, Kleinert, Crain, & McCabe, 1999; Dabernig, Hart, Schwabegger, Dabernig, & Harpf, 2006; Graham et al., 2008; Irwin et al., 1997; Lithell, Backman, & Nystrom, 1998; McCabe, Mizgala, & Glickman, 1991; Nancarrow, Rai, Sterne, & Thomas, 1996; Nylander, Nylander, & Lassvik, 1987; Ruijs, Jaquet, Daanen, & Hovius, 2006; Ruijs, Jaquet, Van Riel, Daanen, & Hovius, 2007; Vaksvik et al., 2009). Several studies have supported the continuation of cold sensitivity symptoms in patients with hand injuries and nerve injuries and following replantation (Campbell et al., 1998; Collins et al., 1996; Nancarrow et al., 1996; Povlsen, Nylander, & Nylander, 1995a; Povlsen, Nylander, & Nylander, 1995b; Vaksvik et al., 2009). Campbell and Kay (1998) evaluated 176 patients following hand injuries, 73% of whom reported cold related symptoms; most of these were related to pain. Graham and Schofield
(2008) evaluated patients more than two years after hand injury; most of these patients (90% of trauma cases) reported cold intolerance, and only 9% reported an improvement over time. Long term cold intolerance in patients with hand injuries was evaluated by Nancarrow et al. (1996); 69% of patients reported cold intolerance, and 97% of these patients continued to have symptoms five years after injury. Collins et al. (1996) reported long term follow-up of patients after upper extremity nerve injury. Among patients who were at least five years post injury, 76% reported cold intolerance, and 87% of these patients reported moderate or severe symptoms. Dabernig et al. (2006) evaluated patients after digital replantation, with a mean follow-up time of five years. The mean DASH score was 11 (out of a total possible score of 100), and cold intolerance was reported by 87% of patients. In a diverse group of patients with neuropathic pain that included traumatic nerve injuries, cold-evoked pain was rated as the most intense pain (Meyer-Rosberg et al., 2001b).

Evaluation of cold sensitivity in the literature is variable and includes verbal scales, patient report questionnaires, and physical assessment (Carlsson, Cederlund, Hoglund, Lundborg, & Rosen, 2008; Collins et al., 1996; Craigen et al., 1999; Graham et al., 2008; Irwin et al., 1997; McCabe et al., 1991; Ruijs et al., 2006; Traynor & MacDermid, 2008). Traynor and MacDermid (2008) compared cold immersion and a patient report questionnaire in healthy control subjects; while both physical and subjective assessments were reliable, they were not significantly correlated with each other. Objective tests such as cold immersion, measurement of rewarming, or arterial pressures may adequately assess vascular status, but these types of assessments provide no indication of the pain and cold symptoms perceived by the patient (Backman et al., 1993; Nylander et al., 1987; Povlsen et al., 1995a; Povlsen et al., 1995b; Traynor et al., 2008). Patient report questionnaires such as the Cold Sensitivity
Severity Scale, introduced by McCabe et al. (1991) and the Cold Intolerance Symptom Scale (Irwin et al., 1997; Ruijs et al., 2006; Ruijs et al., 2007) introduced by Irwin et al. (1997) provide an opportunity for patients to rank their symptoms on a numeric scale. In both scales, a higher score indicates a greater degree of cold sensitivity.

2.2.5.4.2 Contextual (Psychosocial) Factors

While pain questionnaires and rating scales (verbal and numerical) can assess pain intensity, quality, and frequency and are often used in the surgical literature (Atherton, Fabre, Anand, & Elliot, 2008; Berman, Anand, Chen, Taggart, & Birch, 1996; Berman, Symonds, & Birch, 2004; Chen, Lu, & Yeh, 2003; Dellon & Mackinnon, 1986; Emery, Blondet, Mertens, & Sindou, 1997; Evans & Dellon, 1994; Hazari & Elliot, 2004; Kim, Kam, Chandika, Tiel, & Kline, 2001a; Lefaucheur et al., 2004; Mackinnon & Dellon, 1987; Rath et al., 1997; Rorabeck, 1980; Saitoh et al., 2003; Sindou, Blondet, Emery, & Mertens, 2005; Thomas & Kitchen, 1994), these types of measures do not evaluate the psychosocial factors that are often associated with neuropathic pain. The European Federation of Neurological Societies presented guidelines for the assessment of neuropathic pain (Cruccu et al., 2004). A baseline assessment can be achieved with NRS, VRS, or VAS, and more in-depth assessment can include pain descriptors, temporal factors, and functional impact (Cruccu et al., 2004; Gilron, Watson, Cahill, & Moulin, 2006). In our recent survey of peripheral nerve surgeons, 75% of surgeons reported that they quantitatively assess pain in patients referred for pain following nerve injury, but very few surgeons used a validated questionnaire to assess pain in these patients (Novak et al., 2009a). Although it is recognized that psychosocial factors may contribute to poor outcome and ongoing neuropathic pain, these factors are rarely reported in
the surgical literature following traumatic peripheral nerve injuries (Doornberg et al., 2005; Lindenhovius, Buijze, Kloen, & Ring, 2008; Lozano Calderon et al., 2008a; Novak et al., 2009b; Souer et al., 2008).

Associated contextual (psychosocial) factors have been shown to play an important role in the experience of chronic pain in other populations. In particular, the role of depression (Nicholson & Verma, 2004), fear-avoidance (Leeuw et al., 2007), pain catastrophizing (Edwards, Bingham, Bathon, & Haythornthwaite, 2006), and post-traumatic stress disorder (PTSD) symptoms (Asmundson, Coons, Taylor, & Katz, 2002), in other chronic pain populations warrants serious consideration and study in patients with traumatic peripheral nerve injuries. Given the traumatic nature of the injuries these patients have sustained, we believe that it is essential to thoroughly evaluate not only pain but also PTSD symptoms.

PTSD typically develops after exposure to an event or situation that is perceived to be threatening to the physical or emotional integrity of an individual. DSM-IV-TR diagnostic criteria (American Psychiatric Association, 2000) for PTSD cover three symptom clusters: (1) re-experiencing the traumatic event (e.g., nightmares and “flashbacks”); (2) emotional numbing (e.g., feeling detached from others) and avoidance of thoughts, feelings and activities associated with the trauma; and (3) increased arousal (e.g., insomnia, exaggerated startle reflex, hypervigilance). Recent data show that chronic pain and PTSD are strongly associated (Asmundson et al., 2002; Asmundson & Katz, 2008). One possible reason for the high co-morbidity of PTSD and chronic pain may be the substantial symptom overlap common to both disorders, including anxiety and hyperarousal, attentional biases, avoidant behaviours, emotional lability, and elevated somatic focus. The overlap in symptoms suggests that the two disorders may be mutually maintaining or may share an underlying
psychological vulnerability that places some individuals with a greater likelihood of developing one or both disorders. Anxiety sensitivity has been identified as one of the trait vulnerability factors that predispose individuals to develop chronic pain, PTSD or both (Asmundson et al., 2002). The intractability of the two disorders is not surprising when viewed in the context of mutual maintenance and shared vulnerability models. This underscores the importance of screening for both disorders when either one is present, especially in patients who have sustained a traumatic nerve injury, given the painful and traumatic nature of the precipitating event.

2.2.6 Limitations
The major limitation of this review is the paucity of literature reporting outcomes following nerve injury beyond physical impairment. Assessment following nerve injury should include measures of physical impairment such as range of motion, strength and sensibility. Pain assessment with questionnaires such as the modified MPQ to assess both neuropathic and nociceptive pain will provide valuable information beyond pain intensity. Additional patient report questionnaires such as the DASH will provide information about upper extremity disability, and questionnaires to evaluate for symptoms of depression, fear-avoidance, pain catastrophizing, and PTSD symptoms will be useful in identifying concomitant psychosocial factors that may affect outcome.
2.2.7 Future Directions

The assessment of pain in patients with neuropathic pain secondary to traumatic peripheral nerve injuries has lagged behind that of patients with neuropathic pain of other etiologies. The relative lack of information extends beyond measures of pain per se; as described in this review, there is very little information on the associated upper extremity disability, pain disability or health status in patients with traumatic peripheral nerve injuries. Assessment in future studies should include measures of physical impairment, pain, associated contextual (personal and environmental) factors, and functional outcomes, such as disability, to provide a more comprehensive patient evaluation and the opportunity to maximize patient outcome and minimize morbidity following nerve injury.
2.3 Classification of Peripheral Nerve Injury

This section reviews the commonly used systems for classifying nerve injury. Traumatic nerve injuries vary in severity of nerve injury relative to the severity of the trauma. Nerve injury will result in a number of changes at the level of the injury, the distal and proximal nerve segment, the distal sensory/motor end organ, the cell body and the central cortex. Two classification systems for nerve injury are commonly cited (Seddon, 1943; Sunderland, 1978). Seddon (1943) introduced a classification that consisted of 3 levels; neurapraxia, axonotmesis and neurotmesis. Sir Sydney Sunderland (1978) expanded the classification to include five degrees of nerve injury (I to V) and each degree reflects an increase in severity of the nerve injury. A first degree injury which is similar to Seddon’s neurapraxia is a temporary conduction block as a result of demyelination of the nerve. Once the nerve has remyelinated and the conduction block is resolved, motor and/or sensory function will return. With a first degree injury, complete recovery is expected within 12 weeks following injury. A second degree injury involves more severe trauma and injury to the nerve. It is similar to the type of injury described by Seddon as an axonotmesis. Distal and proximal axonal degeneration occur and changes are evident in the electrodiagnostic studies with indications of muscle fibre denervation. Nerve regeneration will occur at the rate of approximately one millimetre (mm) per day. With a second degree injury, complete recovery is expected since the endoneurial sheath is intact, unless the rate of muscle degeneration exceeds the rate of nerve regeneration; that is if the injury is too far proximal for muscle reinnervation to occur before complete muscle degeneration has occurred and thus reinnervation is not possible. A third degree injury involves more severe trauma and similar to a second degree injury, proximal and distal axonal degeneration will occur. However, in contrast to a second degree
injury, the endoneurial tubes are not intact with a third degree injury. Therefore the regenerating axons may not reach their original end organs and incomplete recovery is anticipated. Patients with these types of injuries will benefit from motor and sensory reeducation to maximize functional outcome. A fourth degree injury is a neuroma-in-continuity and this neuroma will preclude the axons from advancing distally beyond the level of injury. A fifth degree injury is complete nerve transection. Fourth and fifth degree injuries require surgical intervention to restore neural continuity. Nerve regeneration will then proceed similar to the recovery seen with a third degree injury at the rate of approximately one mm per day with an advancing Tinel’s sign. A sixth degree nerve injury is the term used to describe a mixed nerve injury which involves varying degrees of nerve injury (I to V) within the same nerve (Mackinnon & Dellon, 1988).

Sunderland II, III, IV and V degree injuries involve axonal degeneration proximal and distal to the site of nerve injury and denervation of the sensory end organs and muscle fibres (Mackinnon et al., 1988). Recovery of motor and sensory function is dependent upon reinnervation of the motor end plates and sensory receptors. Sensory recovery is possible for many years following nerve injury, however the quality of sensibility may be compromised with long delays prior to reinnervation of the sensory end organs (Mackinnon et al., 1988). Reinnervation of the muscle fibres requires that the motor axons reach the target muscle within a critical period of time (Fu & Gordon, 1995; Lien, Cederna, & Kuzon, 2008). The exact duration of time in which motor fibre reinnervation is possible is unknown. However in an animal model, motor recovery substantially declined when the surgical repair occurred greater than one month following injury (Kobayashi et al., 1997). However the critical time period for reinnervation is related to the type of nerve injury; shorter for transection nerve
injuries (Sunderland V degree injury) compared to in-continuity nerve lesions such as a crush injury which may result in a Sunderland II and III degree injury (Mackinnon et al., 1988). Motor recovery depends upon a viable source of regenerating motor axons and better recovery occurs with shorter durations of muscle denervation.

Reinnervation of the motor fibres and sensory end organs following nerve injury are dependent upon the degree of nerve injury, patient and injury factors. However for some patients, the recovery that occurs is less than optimal and remains a challenging problem.

2.4 Recovery Following Peripheral Nerve Injury

Traumatic peripheral nerve injury results in a number of peripheral and central nervous system responses. Recovery following nerve injury depends upon timely nerve regeneration and reinnervation of the distal sensory and motor targets and correct remapping of the cortex. Management of patients following nerve injury includes both non-operative and operative treatments and there are many reports of outcome following these treatments. Assessment following nerve injury includes patient or surgeon subjective assessment, patient reported questionnaires and/or objective measures such as brain imaging, electromyography or nerve conduction studies and there are no widely accepted standardized methods to report outcome.

2.4.1 Traumatic Injury to the Brachial Plexus

Traumatic injury to the brachial plexus may cause avulsion of multiple roots or injury to a single trunk, division, or nerve, and may result in substantial physical impairment due to loss
of motor and/or sensory function or pain. There is no standard evaluation to assess patients following brachial plexus nerve injury and there is wide variation in the methods used to report outcome and recovery. Recovery of motor function following brachial plexus nerve injury or surgery is most often reported using the MRC scale, a modification of the MRC scale or a surgeon graded outcome. In patients with no recovery following injury, surgical intervention using nerve grafts and/or nerve transfer to restore distal shoulder, elbow and in some cases hand function have been used. Reported outcomes have ranged from incomplete to complete recovery of distal shoulder, elbow and hand function. In most studies, individual surgeon assessment or a muscle grading system was used, although these muscle grading systems have not been uniformly utilized (Bentolila et al., 1999; Bertelli & Ghizoni, 2007; Bertelli et al., 2008b; Cardenas-Mejia, O'Boyle, Chen, & Chuang, 2007; Chuang, Yeh, & Wei, 1992; Chuang, Lee, Hashem, & Wei, 1995; Chuang, Epstein, Yeh, & Wei, 1993; Ferraresi, Garozzo, & Buffatti, 2004; Gousheh et al., 2009; Gu, 2007; Haninec, Samal, Tomas, Houstava, & Dubovy, 2007; Hsu et al., 2004; Htut, Misra, Anand, Birch, & Carlstedt, 2007; Jivan, Kumar, Wiberg, & Kay, 2009; Kim, Cho, Tiel, & Kline, 2003; Leechavengvongs, Witoonchart, Uerpairojkit, Thuvasethakul, & Ketmalasiri, 1998; Mackinnon, Novak, Myckatyn, & Tung, 2005; Merrell, Barrie, Katz, & Wolfe, 2001; Moiyadi, Devi, & Nair, 2007; Novak, Mackinnon, & Tung, 2003; Oberlin et al., 1994; Richardson, 1997; Riess, Cogbill, Patel, Lambert, & Mathiason, 2007; Suzuki, Doi, Hattori, & Pagsaligan, 2007; Terzis et al., 1999; Terzis et al., 2006; Tonkin et al., 1996; Tung, Novak, & Mackinnon, 2003; Waikakul et al., 1999; Zheng, Hou, Gu, Shi, & Guan, 2008). Hand sensation was reported in patients with brachial plexus avulsion injuries by Hattori et al. (2009) and the evaluation was performed using vibration and pressure thresholds and two-
point discrimination. In these studies of patients with brachial plexus nerve injuries, outcome was reported in terms of motor or sensory physical impairment.

Brachial plexus injuries which involve root avulsion may result in severe neuropathic pain (Berman et al., 1998; Berman et al., 1996; Htut et al., 2006; Kato et al., 2006). Studies which have reported operative procedures for pain management, including the dorsal root entry zone (DREZ) procedure, have reported varying degrees of success in terms of pain relief (Bertelli et al., 2008a; Bruxelle et al., 1988; Chen & Tu, 2006; Htut et al., 2006; Chen et al., 2003; Kato et al., 2006; Samii et al., 2001). Evaluation using instruments other than those that measure pain relief or pain intensity is rarely included in outcome studies of these patients.

2.4.2 Traumatic Injury to the Median, Ulnar, Radial, and/or Digital Nerves

Reports of recovery of distal wrist and hand function following injury to the median, ulnar, radial and/or digital nerves have used a variety of sensory and motor evaluation tools. Injury to the distal median nerve may result in loss of sensation to the sensory distribution of the median nerve to the hand and loss of thumb opposition. Compromise of hand sensation can result in a substantial loss of hand function (Lundborg & Rosen, 2007). Compared to patients with median nerve injuries, patients with injury to the ulnar nerve have more difficulty with fine motor function due to the loss of the intrinsic muscles and less difficulty related to hand sensibility. Injuries to the radial nerve result in motor loss to the wrist and finger extensors which may result in substantial morbidity.
The majority of studies that have reported outcome following distal nerve injuries, reconstructive surgery and/or hand therapy have evaluated hand sensibility and in some cases motor function but few have evaluated the impact of the injury on the patient. Motor recovery following radial nerve injuries have focused on the degree of wrist and finger extension (Kim et al., 2001a; Shao, Harwood, Grotz, Limb, & Giannoudis, 2005; Shergill, Bonney, Munshi, & Birch, 2001; Roganovic & Petkovic, 2004). Ekholm et al. (2008) in their review of recovery following fractures to the humerus did include patient reported disability. Low levels of disability as indicated by the DASH scores were reported but this may be indicative spontaneous recovery of the radial nerve function in the majority of patients (Ekholm et al., 2008). Long term results following tendon transfer for radial nerve palsy were reported by Altintas et al. (2009). The authors included motor recovery and reported low levels of disability as shown by low DASH scores.

Outcome studies following (1) surgery to repair or graft the median nerve and (2) postoperative therapy have reported recovery in terms of sensory recovery such as vibration and cutaneous pressure thresholds and two-point discrimination (Kato, Minami, Kobayashi, Takahara, & Ogino, 1998; Kim, Kam, Chandika, Tiel, & Kline, 2001b; Mavrogenis, Spyridonos, Antonopoulos, Soucacos, & Papagelopoulos, 2009; Meek, Coert, & Wong, 2003; Novak, Kelly, & Mackinnon, 1992; Polatkan et al., 1998; Rosen et al., 2000a; Roganovic, 2005). Outcome following ulnar nerve injuries in the upper extremity has focused on the motor recovery utilizing various grading systems (Battiston & Lanzetta, 1999; Kim, Han, Tiel, Murovic, & Kline, 2003; Terzis & Kokkalis, 2008; Roganovic, 2004). A study by Ruijs, Jaquet, Kalmijn, Giele & Hovius (2005) evaluated injuries which involved both the median and ulnar nerves and the authors focused on the predictors of motor recovery
and hand sensibility. Studies which have evaluated functional outcome included return to work as the measure of functional outcome (Bruyns et al., 2003; Jaquet et al., 2001). Jaquet et al. (2001) evaluated motor and sensory recovery in patients with median and ulnar nerve injuries and functional outcome was defined as return to work. In this study, the predictors of not returning to work were poor sensory and motor recovery. Bruyns et al. (2003) evaluated predictors of return to work in patients with median and/or ulnar nerve injuries. Return to work was related to median and ulnar nerve injuries, level of education, type of employment and compliance to therapy. In patients following median and/or ulnar nerve injuries, Taylor et al. (Taylor, Anastakis, & Davis, 2009) reported cortical changes and plasticity using brain imaging techniques. These cortical changes were associated with sensory recovery.

Following nerve injury, recovery of function is related to numerous personal, injury and treatment factors and also widely varies dependent on the specific nerve injured. The impact of this recovery in terms of quality of life, psychosocial impact, disability or health status has been reported in very few studies (Ahmed-Labib et al., 2007; Choi et al., 1997; Davidson, 2004; Kitajima, Doi, Hattori, Takka, & Estrella, 2006; Meiners et al., 2005; Nath et al., 2006; Topel et al., 2009).

2.5 Measurement of Outcome

Reports of outcome following nerve injury commonly include measures of physical impairment related to function of the sensory end organs or muscle fibres. In contrast, patient reported function, health related quality of life, measures of psychosocial functioning, or disability using valid and reliable questionnaires are infrequently included in published reports following peripheral nerve injury.
Assessment of only physical impairment may give an incomplete picture of the impact of the nerve injury on the patient. Functional outcome related to such factors as the impact on the patient’s quality of life and psychosocial functioning, employment issues, activities of daily living or participation in activity may be more indicative of how the patient is functioning with the residual morbidity following nerve injury. Meiners et al. (2005) reported on patient disability, employment and leisure issues in 61 patients following nerve repair in the forearm, wrist or hand. The results showed that 81% of patients returned to their pre-injury job and that 92% had returned within 12 months. The authors used a VAS to assess patient reported disabilities and pain. Significant correlations were reported between the activity restriction scale and pain, hobbies, housekeeping and job as assessed by a VAS. It should be noted that while there is a large body of empirical literature showing that a VAS is a reliable and valid instrument for pain measurement, the same cannot be said for the use of a VAS when measuring other constructs; the psychometric properties of a VAS when used to measure disability, activity restriction, and housekeeping, etc have not been evaluated. In another study, the predictors for return to work in patients who had sustained a median or ulnar nerve injury were reported by Bruyns et al. (2003). The authors reported that 59% of patients had returned to work and most to their pre-injury job. Return to work was related to education level, type of employment, compliance to hand therapy and type of injury. Jaquet et al. (2001) evaluated 220 patients after traumatic forearm or wrist injuries which included median, ulnar and/or radial nerve injury. Sensory and motor recovery were reported in addition to return to work which the authors termed “work disability”. In these patients, the nerve injuries were associated with substantial physical impairment and return to work was associated with poor motor and sensory recovery.
Choi et al. (1997) evaluated 32 patients following brachial plexus nerve surgery. Using quality of life questions from the United States (US) General Social Survey, the authors reported moderate life satisfaction in 78% of these patients and no patients reported extreme dissatisfaction. More than half of the patients were employed at the time of the survey. Nath et al. (2006) reported on 40 consecutive patients with C5-6 brachial plexus root injuries. Preoperative and postoperative assessment included motor function as graded on the MRC scale and the WHO quality of life questionnaire. Improvement was reported in the motor function of the biceps muscle and the patient’s health related quality of life. Pain was also assessed as one of the domains of this questionnaire and the authors report significant improvement in this domain in most patients, although 2 patients reported continued pain. Using standardized measures such as the DASH and the SF-36, substantial disability and decreased health status have been reported in patients with brachial plexus injuries (Ahmed-Labib et al., 2007; Davidson, 2004; Kitajima et al., 2006).

Generic questionnaires such as the SF-36 may provide an indication of health status across a broad range of health conditions. Kitajima et al. (2006) evaluated 30 patients with brachial plexus injury. Compared to Japanese age matched control subjects, the patients with brachial plexus nerve injury had significantly worse SF-36 (physical function, role physical, bodily pain, physical component score) domain scores ($p < 0.05$). General health status questionnaires were designed for assessment of a broad range of conditions that may affect health status and may be limited in their assessment of specific upper extremity pathologies. Disease specific questionnaires provide a more sensitive measure of the clinical condition or diagnosis within the upper extremity (Beaton et al., 2001; Bengtson et al., 2008). In the case
of upper extremity peripheral nerve injuries, the DASH questionnaire is the instrument of choice to assess disability.

2.5.1 Disabilities of the Arm, Shoulder and Hand (DASH)

The DASH was developed by the American Academy of Orthopedic Surgeons, the Council of Musculoskeletal Specialty Societies and the Institute of Work and Health (Hudak et al., 1996). It is a disease specific patient reported questionnaire designed to assess disability based upon physical symptoms and function. The initial version included 821 items from 13 previously published scales (Hudak et al., 1996). These items were reduced in number to 177 by three members of a collaborative group and then were further reduced to 75 items by expert opinion. These 75 items were then formatted into questions and pretested on 20 patients. The DASH was then reduced to 30 items in addition to two subscales related to work and recreation (sports/performing arts). Marx, Bombardier, Hogg-Johnson & Wright (1999) evaluated the DASH on the basis of clinical judgment and psychometric properties. They found the items on the DASH could be selected to include items, which represented both clinical importance and a single attribute. Good validity and reliability have been established for the DASH (Beaton et al., 2001; Hunsaker, Cioffi, Amadio, & Caughlin, 2002). The validity, test-retest reliability and responsiveness of the DASH were evaluated by Beaton et al. (2001). The DASH correlated strongly with the Brigham questionnaire and the Shoulder Pain and Disability Index. There was strong test-retest reliability (ICC .96) and good responsiveness in patients who were assessed before and after treatment. SooHoo et al. (2008) evaluated the construct validity of the DASH in patients with a variety of upper extremity conditions. Strong correlations were reported between the DASH scores and the
SF-36. Hunsaker et al. (2002) reported normative data which were collected from the US
general population and the authors found excellent internal consistency among the items.
Dias et al. (2008) compared the DASH, the Michigan Hand Questionnaire and the Patient
Evaluation Measure among 100 patients with a variety of hand and wrist pathologies. With
all three measures, the authors report high internal consistency and a strong correlation
between the DASH and Michigan Hand Questionnaire (r = .82).

The ability to detect change over time (responsiveness) was evaluated in the DASH and the
Michigan Hand Questionnaire in patients before and after surgery for carpal tunnel syndrome
(Gay, Amadio, & Johnson, 2003). The authors found good correlation between the DASH
and carpal tunnel functional scale and found the DASH to be responsive following carpal
tunnel surgery. In patients following wrist fractures, MacDermid, Richards, Donner, Bellany
& Roth (2000) reported good responsiveness of the DASH to detect clinical change over
time. In patients who received hand therapy for wrist and hand pathologies, the DASH also
showed good responsiveness (MacDermid & Tottenham, 2004). McMillan and Binhammer
(2009) reported good responsiveness in the DASH, Michigan Hand Questionnaire and
Patient-Specific Functional Scale in patients seeking surgery for tumor, wrist pain, carpal
tunnel syndrome and finger contracture. Horng et al. (2010) reported good responsiveness of
the DASH in patients following hand injuries and the DASH was a predictor of number of
days on disability.

Disability as assessed by the DASH has been reported in various pathologies involving the
upper extremity and in the general US population. Hunsaker et al. (2002) reported US
population based data for the DASH and indicated a mean DASH score of 10.10 ± 14.86 in
the general population. In patients with hand-arm vibration syndrome, Poole and Mason
(2005) reported a mean DASH score of 28 which increased to 38.3 in patients with concomitant carpal tunnel syndrome. The significant predictors of the DASH in the study by Poole and Mason (2005) included sensorineural stage, use of vibrating tools, and age. Few studies have used the DASH to measure disability in patients following traumatic upper extremity nerve injury (Ahmed-Labib et al., 2007; Davidson, 2004; Ekholm et al., 2008; Topel et al., 2009). Ahmed-Labib et al. (2007) administered the DASH, SF-36 and a measure of pain intensity to 31 patients following a brachial plexus nerve injury. The mean DASH score was 70 which indicated substantial disability in these patients. Patients with root avulsions had higher levels of disability, more pain and lower health status. In the study by Davidson (2004), high levels of disability were reported in patients with brachial plexus nerve injuries and amputation injuries. The mean DASH score was 72 in patients with brachial plexus nerve injuries. Topel et al. (2009) reported higher DASH scores in patients with upper extremity arterial injuries and concomitant nerve injuries. Ekholm et al. (2008) evaluated 33 patients with radial nerve injury following a fracture to the humerus and included assessment of disability using the DASH and health status using the SF-36. Most patients had spontaneous recovery of the radial nerve function and therefore low levels of disability were reported. Evaluation of the psychometric properties of the DASH has shown that this questionnaire has excellent validity, reliability and responsiveness to measure disability in patients with upper extremity pathologies.

2.5.2 Neuropathic Pain

As defined by the IASP, neuropathic pain is pain which results from a lesion or disease in the peripheral or central nervous system (Merskey et al., 1994; Cruccu et al., 2004; Loeser et al.,
Pain following a traumatic peripheral nerve injury may be intermittent or constant and may be related to allodynia, hyperalgesia or cold sensitivity. In the literature, the term “neuropathic pain” is more frequently used to describe pain resulting from sensory neuropathies, post-herpetic neuralgias, spinal cord injuries and amputation and this term is not frequently used to describe pain following a traumatic peripheral nerve injury.

As noted in our review of the published literature (Chapter 2.2), many outcome studies of patients following nerve injury do not include an assessment of pain. Therefore it is difficult to determine from the literature the degree to which pain may be a problem in patients following upper extremity nerve injury. The paucity of published reports of neuropathic pain in this patient population may mean that neuropathic pain was not present or that it was present, but was not assessed. Studies that did report pain following upper extremity nerve injury are more common in patients with brachial plexus nerve injuries, particularly avulsion type injuries where the spinal nerve roots are torn from their attachment to the spinal cord. Outcome studies have been conducted to evaluate the efficacy of the DREZ procedure in relieving neuropathic pain in patients with root avulsions (Kanpolat et al., 2008; Sindou et al., 2005; Rath et al., 1997; Chen et al., 2003; Samii et al., 2001). In these studies, assessment of pain included verbal numerical rating scales and/or general statements regarding pain relief. None of these outcome studies utilized validated patient reported questionnaires to assess the impact of the pain or recovery on the patient.

Neuromas which often develop following injury to sensory nerves may result in substantial allodynia or hyperalgesia and initially are treated non-operatively. With intractable pain, operative treatment typically performed to transpose the neuroma away from the painful region and bury it in deeper tissue (e.g., muscle) (Atherton et al., 2008; Dellon et al., 1986;
Evans et al., 1994; Hazari et al., 2004; Mackinnon et al., 1988; Mackinnon et al., 1987; Sood et al., 1998). This procedure often results in reports of reduced pain, however validated questionnaires to assess outcome are rarely used.

Because pain is a subjective experience, the gold standards for assessing pain are patient self-report instruments (e.g., NRS, VRS or VAS) which typically have been used to provide an indication of pain intensity or pain affect. These unidimensional measures do not provide information about the impact of pain on the individual or their life domains. The most utilized multi-dimensional self-report questionnaires to assess the three main dimensions of pain (sensory, affective, and evaluative) are the MPQ and the SF-MPQ (Grafton, Foster, & Wright, 2005; Melzack, 1975; Melzack, 1987; Melzack et al., 2006).

2.5.3 Measures of Pain

Measures of pain to assess the intensity and frequency dimensions of pain using numerical or Likert scales are frequently used (Katz, Finnerup, & Dworkin, 2008). VRS may be used with descriptors from least severe to most severe or with descriptors such as no pain, mild, moderate, severe, and these words can then be converted into a numeric (ordinal) scale (Katz & Melzack, 1999). One of the difficulties with interpreting the data provided from these types of scales is that since they are ordinal in nature, one cannot assume that the intervals between points (or verbal descriptors) on the scale are equal; therefore, the amount of pain between mild and moderate may be substantially different from the amount between moderate to severe. VAS involve use of a 10 centimetre, horizontal line in which the endpoints are labeled with verbal descriptors such as “no pain” and “worst possible pain”.
The patients are asked to place a vertical line on the scale which corresponds to their level of pain. The advantages of the VAS include its ease of use/administration and scoring, and its ratio scale properties (true zero and equality of intervals between points) making it amenable for use with parametric statistical techniques. However, some patients may have difficulty completing or understanding the task and careful consideration should be given to the anchor endpoint descriptors and time periods of recall to ensure valid assessment. Simple concepts such as pain intensity may be adequately assessed with the VAS. However, multidimensional aspects of the pain experience may not be interpreted uniformly by different individuals and therefore simple measures such as the VAS may be inadequate to capture and measure these qualities.

The qualities of pain and intensity may be assessed with the SF-MPQ. The SF-MPQ is composed of elements from the MPQ and consists of 15 pain adjectives (11 sensory, 4 affective), a VAS pain intensity measure and the present pain intensity (PPI) index (Melzack, 1987). From the pain adjectives, three pain scores may be calculated from the intensity reported (sensory, affective, total descriptors). The SF-MPQ also includes a 10 cm VAS and the PPI index to assess pain intensity. The validity and reliability for the SF-MPQ was reported by Melzack (1987) and others (Grafton et al., 2005). The SF-MPQ is the most widely used pain questionnaire and overall it has good to excellent psychometric properties. The SF-MPQ has been shown to be sensitive to change following treatment of neuropathic pain in patients with painful sensory neuropathies and a small sample of patients with postsurgical/posttraumatic neuropathic pain (Gilron et al., 2005; Lynch, Clark, & Sawynok, 2003).
A number of scales have purported to measure neuropathic pain, such as the PainDetect, the Neuropathic Pain Questionnaire, the Leeds Assessment of Neuropathic Symptoms and Signs, the Pain Quality Assessment Scale and the Neuropathic Pain Scale (Bennett, 2001; Bennett, Smith, Torrance, & Potter, 2005; Bennett, Smith, Torrance, & Lee, 2006; Bennett et al., 2007; Bouhassira et al., 2005; Dworkin et al., 2009; Freynhagen et al., 2006; Galer et al., 1997; Jensen et al., 2006; Krause & Backonja, 2003). More recently, a modification of the SF-MPQ to assess the qualities of neuropathic pain was introduced by Dworkin et al. (2009). This modified SF-MPQ includes 22 pain descriptors which are ranked on a numerical scale from zero to ten. In these studies which evaluated the validity of the assessment of neuropathic pain, the majority of subjects had pain originating from painful neuropathies or groups of subjects from pain clinics in which no clear delineation of the etiology was identified (Table 2.2).
<table>
<thead>
<tr>
<th>Study</th>
<th>Assessment Tool</th>
<th>Subjects (n)</th>
<th>Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dworkin et al. (2009)</td>
<td>SF-MPQ-2 22 pain descriptors 4 subscales (continuous, intermittent, neuropathic &amp; affective pain)</td>
<td>882</td>
<td>n = 349 (neuropathic pain from diabetic neuropathy, other neuropathic pain/nerve damage); n = 533 (non-neuropathic pain from fibromyalgia, migraine headache, low back pain) Painful diabetic neuropathy</td>
</tr>
<tr>
<td>Freynhagen et al. (2006)</td>
<td>PainDetect 3 sections, Gradation of pain, Pain pattern, Radiating pain</td>
<td>411</td>
<td>n = 228 (neuropathic pain from low back pain, post-herpetic, polytrauma); n = 164 (non-neuropathic pain from arthritis, low back pain, visceral origin) Low back pain</td>
</tr>
<tr>
<td>Jensen et al. (2006)</td>
<td>Pain Quality Assessment Scale 20 items</td>
<td>40</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Bouhassira et al. (2005)</td>
<td>Neuropathic Pain Symptom Inventory 12 items</td>
<td>176</td>
<td>n = 120 Peripheral origin (39 nerve trauma), n = 56 central origin</td>
</tr>
<tr>
<td>Krause &amp; Backonja (2003)</td>
<td>Neuropathic Pain Questionnaire 12 items</td>
<td>528</td>
<td>n = 149 neuropathic (etiology not stated)  n = 233 non-neuropathic</td>
</tr>
<tr>
<td>Bennett et al. (2001; 2005)</td>
<td>LANSS 5 symptom items &amp; 2 clinician evaluation items</td>
<td>60</td>
<td>n = 30 Neuropathic (8 postsurgical neuropathy, 6 post-traumatic neuropathy, 5 lumbar radiculopathy, 3 CRPS I, 2 cervical radiculopathy, 2 Peripheral neuropathy, 2 post-herpetic neuralgia, 1 phantom limb pain, 1 malignant &amp; n = 30 nociceptive pain</td>
</tr>
<tr>
<td>Bennett et al. (2006)</td>
<td>Self report LANSS 7 items</td>
<td>200</td>
<td>n = 100 Neuropathic (n = 25 Nerve entrapment, n = 8 CRPS I, n = 11 CRPS II, n = 10 Phantom limb, n = 9 Peripheral neuropathy, n = 9 Post surgical neuropathy, n = 8 Post-traumatic neuropathy, n = 7 Post herpetic neuralgia, n = 3 Cancer related brachial plexopathy, n = 2 Cancer related lumbar plexopathy, n = 3 Post stroke, n = 3 Trigeminal neuralgia, n = 2 Diabetic neuropathy) n = 100 non-neuropathic</td>
</tr>
<tr>
<td>Galer &amp; Jensen (1997)</td>
<td>Neuropathic Pain Scale</td>
<td>288</td>
<td>n = 128 post-herpetic neuralgia, n = 69 reflex sympathetic dystrophy, n = 67 traumatic peripheral nerve injury (mononeuropathy without autonomic dysregulatory signs), n = 24 diabetic neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78</td>
<td>n = 3 spinal cord injury, n = 4 causalgia, n = 32 reflex sympathetic dystrophy, n = 33 traumatic peripheral nerve injury, n = 6 diabetic neuropathy</td>
</tr>
</tbody>
</table>

LANSS = Leeds Assessment of Neuropathic Symptoms and Signs, CRPS = Complex regional pain syndrome
None of the questionnaires, outlined in Table 2.2, have been specifically validated in patients with traumatic nerve injuries. In general, the SF-MPQ is the most widely used measure to assess the qualities and intensity of pain. These measurement scales provide valuable information regarding the frequency, intensity and quality of pain but do not assess the impact of the pain on the patient. Depending on the type of pain and other associated factors (injury, personal and environmental), the impact of the pain may vary between individuals.

2.5.4 Cold Sensitivity

Cold sensitivity or intolerance has been defined as an abnormal response (pain, discomfort, sensory disturbance, stiffness and/or color changes) to cold exposure following a traumatic injury (Campbell et al., 1998). Cold sensitivity or cold intolerance has been associated with poor outcome following traumatic upper extremity injuries (Campbell et al., 1998; Collins et al., 1996; Craigen et al., 1999; Graham et al., 2008; Irwin et al., 1997; Koman, Slone, Smith, Ruch, & Poehling, 1998; Lithell et al., 1998; Povlsen et al., 1995b; Ruijs et al., 2007; Stokvis, Ruijs, van Neck, & Coert, 2009). Cold sensitivity and cold intolerance are two terms that are commonly used to describe these abnormal symptoms with exposure to cold. These terms have been used interchangeably in the literature which has added to the confusion in the field. Campbell and Kay (1998) propose the term “Trauma Induced Cold Associated Symptoms” to describe this condition. In my dissertation, I have chosen to use the term cold sensitivity except in reference to publications in which the authors have used the term cold intolerance.
The symptoms associated with cold sensitivity are often associated with poor outcome following traumatic peripheral nerve injuries and have been frequently reported in patients with replantation injuries and digital amputations (Backman et al., 1993; Campbell et al., 1998; Carlsson, Cederlund, Holmberg, & Lundborg, 2003; Collins et al., 1996; Craigen et al., 1999; Dabernig et al., 2006; Graham et al., 2008; Irwin et al., 1997; Lithell et al., 1998; McCabe et al., 1991; Nylander et al., 1987; Ruijs et al., 2006; Ruijs et al., 2007). Poor long term outcome has been associated with persistence of cold sensitivity in patients with hand injuries, nerve injuries and replantation injuries (Campbell et al., 1998; Collins et al., 1996; Nancarrow et al., 1996; Povlsen et al., 1995a; Povlsen et al., 1995b). Campbell and Kay (1998) evaluated patients following hand injuries and reported that 73% of 176 patients reported cold-related symptoms and most were associated with pain. In the study by Graham and Schofield (2008), patients who were more than 2 years following hand injury were contacted for evaluation. The response rate for trauma patients was 34%. Cold intolerance was reported by 90% of the patients with traumatic injuries and only 9% of these patients reported an improvement in their symptoms over time. In patients following hand trauma, Nijhuis et al. (2009) reported 38% of patients had abnormal cold intolerance and more severe trauma was associated with more severe cold intolerance. Nancarrow et al. (1996) assessed long term cold intolerance in 65 patients with hand injuries. Of these, 69% indicated the presence of cold intolerance and 5 years after injury, 97% continued to report these symptoms. In patients who were at least 5 years following nerve injury, Collins et al. (1996) reported that 76% of patients had cold sensitivity and 87% of these patients had moderate or severe symptoms. No difference in reported cold sensitivity was found between patients who reported normal hand sensation compared to those with abnormal sensation. Dabernig et al.
(2006) used the DASH to evaluate patients after digital replantation (mean follow-up time of 5 years). The mean DASH score in this group of patients was 11, which indicated a relatively low level of disability, but 87% of patients reported cold intolerance. In a group of patients with neuropathic pain from a variety of etiologies which included traumatic nerve injuries, the most intense pain was reported as occurring from cold provocation (Meyer-Rosberg et al., 2001b). These studies provide evidence of the negative relationship between cold sensitivity and outcome. Identification of patients with these symptoms may provide the opportunity for appropriate treatment of cold sensitivity.

2.5.5 Measures of Cold Sensitivity

A variety of self-report and physician/health care professional-administered assessment tools are available to evaluate cold sensitivity; including physical assessments, verbal rating scales and patient reported questionnaires (Carlsson et al., 2008; Collins et al., 1996; Craigen et al., 1999; Graham et al., 2008; Irwin et al., 1997; McCabe et al., 1991; Ruijs et al., 2006; Traynor et al., 2008). Objective tests which involve cold immersion and measurement of rewarming or arterial pressures are valid measures of the vascular status, but these types of objective assessments do not provide information regarding the pain and/or cold symptoms experienced by the patient (Backman et al., 1993; Nylander et al., 1987; Povlsen et al., 1995a; Povlsen et al., 1995b; Traynor et al., 2008). Questionnaires such as the Cold Sensitivity Scale (CSS) introduced by McCabe et al. (1991) and the Cold Intolerance Symptom Scale (CISS) (Irwin et al., 1997; Ruijs et al., 2006; Ruijs et al., 2007) introduced by Irwin et al. (1997) utilize patient report to rank symptoms on a numeric scale.
The McCabe CSS was developed from items reported by 35 patients who had cold exposure symptoms following a hand injury (McCabe et al., 1991). The authors reduced these items to four items to assess the severity of cold sensitivity and added three work related questions for the work exposure score. The CSS was then completed by 80 control subjects and 20 patients with nerve injury. Validity of the scale was determined by a significantly higher score in the nerve injured patients compared to the control subjects. However, the authors did not assess the validity of the specific tasks within the questionnaires by asking the subjects to perform each task. Test-retest reliability of the CSS was established in a group of 35 patients (r = 0.92) and for the work exposure subscale (r = 0.94). The CSS questionnaire was used to prospectively evaluate 123 patients with hand trauma injuries (Craigen et al., 1999). In this series of patients, the significant single predictor of long term cold sensitivity was traumatic bony injury. In contrast to other studies, the presence of cold sensitivity was not related to smoking or amputation injuries (Irwin et al., 1997). Collins et al. (1996) used the CSS questionnaire to evaluate cold sensitivity in patients following an upper extremity nerve injury and reported substantial cold sensitivity in these patients. The mean CSS score was 137 and there was a significant relationship between the CSS and patient subjective rating of cold sensitivity. The CSS is a reliable measure and possesses face validity.

The CISS includes the questions from the CSS in addition to specific questions regarding the frequency of symptoms and impact on daily activities (Irwin et al., 1997). A scoring system was developed for the CISS and the questionnaire was tested on 331 patients with cold intolerance and 67 subjects with no symptoms of cold intolerance. Cold intolerance was more likely to occur in patients who were smokers and who had crush or avulsion injuries. Complete median or ulnar nerve division and a concomitant blood vessel injury were
associated with more severe cold intolerance. The CISS was found to have good test-retest reliability \((r = .9)\) in patients who were assessed six months following the first assessment. Ruijs et al. (2006) administered the CISS to 68 healthy subjects and found that neither age nor gender was significantly associated with cold intolerance. Based upon these healthy subjects, the authors recommended that a score of 30 (95% confidence interval from the mean CISS score 12.9) be used as the threshold to identify patients with cold intolerance. However this criterion was not based upon the assessment of subjects with cold sensitivity. Carlsson et al. (2008) evaluated the reliability and validity of a Swedish translation of the CISS and the CSS. Test retest reliability was established in 100 patients and all of the ICCs were greater than 0.85. Validity was evaluated by comparison of the CISS score to the SF-36, the DASH, subjective patient assessment and VAS. Moderate correlation with the CISS was reported with correlation coefficients ranging from 0.64 (SF-36 bodily pain) to 0.81 (VAS cold intolerance).

CISS scores were evaluated by Ruijs et al. (2009) who examined digital rewarming patterns in 12 patients with median and ulnar nerve injuries and 12 control subjects following exposure to a cold water stress test. The patients with better rewarming patterns had lower CISS scores and better recovery of sensation. Stokvis et al. (2009) reported CISS scores before and after surgery for treatment of an upper extremity neuroma. The mean preoperative CISS score was 54 and there were 30 patients (91%) who had scores greater than 30 which indicated a level of abnormal cold intolerance. Postoperatively, the mean CISS score was 52 which was not significantly different from the preoperative CISS scores. The CISS scores were significantly correlated with VAS pain intensity \( (r = 0.443, p = 0.01) \) and the DASH scores \( (r = 0.438, p = 0.01) \). Carlsson et al. (2008) evaluated disability and cold intolerance in
patients following hand injury and reported moderate correlation between the DASH and cold sensitivity (CSS, $r = 0.67$ and CISS $r = 0.73$). The CISS is a reliable measure which has been shown to be a valid measure of cold sensitivity in patients with nerve injury.

To evaluate the assessment of cold sensitivity, Traynor and MacDermid (2008) compared physical assessment with cold immersion and a patient reported questionnaire, the CISS, in healthy subjects. Each subject completed the CISS and underwent cold immersion of one hand (12 degrees Celsius for 5 minutes with temperature recovery measured for 20 minutes). The authors reported strong test-retest reliability with the subjective questionnaires and the physical assessment. There were no significant correlations between the patient reported questionnaires and the objective physical assessments. These assessments were performed in healthy subjects and not patients who have cold sensitivity. The responses may differ in those patients with hand trauma or nerve injury compared to normal uninjured subjects.

Taken together, the literature indicates that cold sensitivity is associated with poor outcome following hand trauma and injury to the upper extremity peripheral nerves. Many studies have utilized the CISS and/or the CSS to assess cold sensitivity and comparison of patient and/or surgeon subjective reports of outcome. Few studies have utilized valid and reliable measures to compare disability and cold sensitivity following traumatic upper extremity injuries.

2.6 Disablement Frameworks

The concept of disability as defined by Nagi (1965) refers to a physical or mental limitation within a social context. The medical model considers disability as a characteristic of the
individual which is a direct result of the injury or disease, whereas a social model considers disability as a result of a social problem not the individual. In terms of nerve injury, disablement models may be useful to define or delineate the consequences of the nerve injury on the individual and within the context of society. The biopsychosocial model of disablement has integrated both the medical and social frameworks of disability and has integrated the biological, personal and social perspectives within one model (Jette, 2006). Nagi (1965) described a pathway of active pathology, impairment, functional limitation and disability. Active pathology may be caused by an etiology that disrupts the normal cellular processes. In the case of an injury to a motor nerve, it may represent muscle denervation. Impairment refers to an abnormality of the tissue, organ or body system, and in the case of nerve injury, this may be the resultant loss of muscle strength with an injury to a motor nerve or numbness with injury to a sensory nerve. Impairments may occur due to the initial pathology, or secondarily, due to limitations as a result of the initial pathology, such as deconditioning of the surrounding muscles from disuse in patients with nerve injury. Functional limitations are restrictions in basic physical performance, such as limitations in raising the arm overhead. In Nagi’s model (1965), disability represents the discrepancy between an individual’s capability and the specific demands of their physical and social environment. Disability would then translate into the inability to play a sport, such as baseball, that requires the capability to perform overhead arm activity involved in throwing and catching a ball. Verbrugge and Jette (1994) expanded the Nagi model to include factors which may influence the disablement pathway including predisposing risk factors (such as medical comorbidities, sociodemographics, lifestyle), intra-individual factors (such as lifestyle, activity or behavioural changes, coping skills, attitudes) and extra-individual factors
that are external to the individual (such as physical and social environment, external supports, medical care). These additional factors may affect the interrelationships between the factors within the disablement pathway.

The WHO introduced and subsequently modified the International Classification of Impairments, Disabilities and Handicap (ICF) model which comprises 3 main concepts (impairments, disabilities, handicaps) related to disease and health conditions (World Health Organization, 2001). The ICF incorporates the positive and negative influences on the health condition and factors which may influence that health condition. Functioning is considered at three levels: the body part, the entire person and the entire person in the context of their environment. Each level contains 3 domains of function related to body function and structures, activities and participation (Figure 2.1).
Figure 2.1 International Classification of Functioning, Disability and Health (ICF) Model.

This model considers the interrelationships among the health condition and body functions/structures, activity, participation and influence of the contextual factors. It can be viewed in both positive (improvement) and negative terms (degradation) ranging from health to disability. (Reprinted from: International Classification of Functioning, Disability and Health: ICF. Geneva, Switzerland: World Health Organization. 2001)

Body Functions and Structures refer to physiologic function and anatomical body parts, respectively. Impairment of these structures or functions may result due to a loss of, or deviation from, normal function. The Activity component refers to the ability of the individual to perform an action or task and this may be limited when the individual has difficulty performing their required tasks or actions. Participation refers to the involvement of the individual in life situations. The gap between the individual’s capacity to perform
actions and their environment, including personal factors reflects performance. The
Contextual factors which include environmental and personal factors include the individual’s
environment in which they live and other factors such as age, gender, medical co-morbidities,
coping styles, other psychosocial issues (Jette & Keysor, 2003; World Health Organization,
2001). The activity and participation may be termed positively or negatively and it is the
negative aspect which reflects decline and disability.

Although the models by the ICF, Nagi and Verbrugge and Jette, differ in theory and
structure, these models provide a framework to conceptualize the disablement process and its
components, to consider the individual at many levels and specify the factors that may be
interrelated. Consideration of factors beyond physical impairment such as sensory loss or
muscle weakness which occur following nerve injury provides a broader perspective to
assess the factors which influence functional loss and disability. The ICF model has been
described for use in patients with musculoskeletal pathologies such as arthritis and distal
radius fractures which represent different types of pathologies ranging from an ongoing
inflammatory process to a traumatic injury and thus different pathologies would have
different expected outcomes over the course of the disease and/or recovery process (Harris,
MacDermid, & Roth, 2005; Jette et al., 2003; Stucki & Cieza, 2004).

Dixon, Johnston, McQueen & Court-Brown (2008) evaluated the ability of the DASH to
operationalize the ICF. The authors included 24 reviewers to allocate the items of the DASH
into the various ICF constructs. They found that five items were related to impairment, 19 to
activity, three to participation and seven were related to activity and participation restrictions.
Harris et al. (2005) reviewed the ICF framework in relation to distal radius fracture. Patient
reported questionnaires for the wrist and health status were included in the evaluation and the
authors reported that the ICF model provided a useful framework for evaluation beyond physical impairment in patients following distal radius fracture.

The diversity of the ICF model lends itself to application in patients following nerve injury. The consideration of factors beyond physical impairment is essential for the assessment of the health effects and disability following nerve injury. The inclusion of contextual (personal and environmental) factors have been lacking in the assessment of patients following nerve injury and the influence of these factors on outcome.

2.7 Psychosocial Factors

The emphasis in outcome studies regarding patients following peripheral nerve injury has been on the physical impairments related to motor and sensory recovery. Less importance has been directed towards the influence of psychosocial factors on outcome, particularly the association between psychosocial factors and pain and disability. Jacquet et al. (2002) evaluated the psychological impact of nerve injuries in the forearm and the impact on functional outcome and return to work. Using the Impact of Event Scale, the authors reported higher psychological stress in patients with multiple nerve injuries. Functional outcome and return to work were associated with higher levels of psychological stress. Argoff (2007) reports the importance of comorbid conditions, such as depression, anxiety and sleep disturbance which may negatively affect response to treatment of patients with neuropathic pain, although in this review of the literature multiple etiologies of neuropathic pain were included. Meyer-Rosberg et al. (2001b; 2001a) found sleep disturbance and other aspects of quality of life were impaired in their patients with neuropathic pain and this in turn affected
their participation in social roles and work. Patients with traumatic nerve injuries were included in the studies by Meyer-Rosberg et al. (2001b; 2001a) as were other etiologies which resulted in neuropathic pain. Marchie and Mahoney (2008) reported an association between perceived social support and disability as measured by the QuickDASH in patients following carpal tunnel release. The negative aspects of outcome, lower rates of return to work and higher levels of psychological stress have been associated with chronic nerve injury and neuropathic pain (Argoff, 2007; Meyer-Rosberg et al., 2001b; Meyer-Rosberg et al., 2001a; Turk, Audette, Levy, Mackey, & Stanos, 2010). The importance of other psychological constructs, such as pain catastrophizing, depression and post-traumatic stress symptoms has been demonstrated through their association with higher levels of pain and poorer outcome. The relevant literature is reviewed in the following section.

2.7.1 Pain Catastrophizing

Pain catastrophizing refers to negative thinking regarding the experience of pain. Those individuals who catastrophize feel overwhelmed by pain, ruminate about it and/or feel helpless in the face of pain (Sullivan, Bishop, & Pivik, 1995; Sullivan, Lynch, & Clark, 2005). Catastrophizing about pain has been shown to negatively influence pain-related outcomes and to contribute to increased pain responses, more emotional distress and increased pain behaviour. Studies that have evaluated patients with acute postoperative pain and more chronic musculoskeletal conditions, such as osteoarthritis and fibromyalgia, show that pain catastrophizing is associated with poor outcome such as higher reported levels of pain and decreased functional outcome (Buenaver, Edwards, & Haythornthwaite, 2007; Edwards et al., 2005; Edwards et al., 2006; Edwards, Haythornthwaite, Smith, Klick, & Katz,
Patient reported questionnaires such as the Pain Catastrophizing Scale (PCS) are designed to assess the degree of pain catastrophizing (Sullivan et al., 1995; Sullivan et al., 2005). The PCS was designed to assess pain catastrophizing with an overall total score and three subscales (rumination, magnification and helplessness). The validity and reliability have been established for the PCS (Chibnall & Tait, 2005; Osman et al., 1997; Osman et al., 2000; Van Damme, Crombez, Bijttebier, Goubert, & Van Houdenhove, 2002). Osman et al. (1997) evaluated the factor structure in 288 students and showed that the three factor model relating to each subscale was the best fit. The factor structure of the PCS was also evaluated as a function of race and workers’ compensation in patients with low back pain (Chibnall et al., 2005). In these patients, a two factor structure including helplessness and magnification was the best fit for the data. Van Damme et al. (2002) evaluated the PCS in Dutch speaking patients with low back pain and fibromyalgia and in pain-free individuals. They found that the data were best represented in a three factor model which confirmed the original factor structure of the scale: rumination, magnification and helplessness.

Pain catastrophizing has been associated with acute pain following surgery (Pavlin et al., 2005; Riddle et al., 2010; Sommer et al., 2010). Sommer et al. (2010) evaluated the predictors of acute postoperative pain in patients undergoing a variety of elective surgical procedures including surgeries to the upper extremity. The significant predictors of acute
postoperative pain were pain catastrophizing, preoperative pain, expected pain and fear of surgery. Pavlin et al. (2005) evaluated the influence of catastrophizing on postoperative pain in patients undergoing anterior cruciate ligament repair and higher levels of acute postoperative pain were associated with pain catastrophizing. Similarly, Riddle et al. (2010) reported pain catastrophizing as a predictor of higher pain scores in patients following knee arthroplasty.

In patients with chronic conditions and chronic pain, catastrophizing had been negatively associated with outcome including higher pain intensity and pain disability (Severeijns et al., 2001; Sullivan et al., 2005). Sullivan et al. (2005) evaluated the specific facets of pain catastrophizing in patients with neuropathic pain. The authors included 80 patients with diabetic neuropathy, herpetic neuralgia, postsurgical and post-trauma. The authors reported significant associations between pain catastrophizing and pain intensity and pain disability. They also found a strong association between pain intensity and the PCS helplessness subscale. Severeijns et al. (2001) evaluated the relationship between pain intensity, disability and pain catastrophizing in a group of patients with chronic pain from a variety of etiologies. Higher levels of pain intensity, disability and psychological distress were reported in patients who catastrophized. However, the authors emphasized that strong associations were found but the direction of causality could not be determined with a cross sectional design. In a review article, Edwards et al. (2006) found that pain catastrophizing was an important factor in patients with rheumatologic disorders. The authors report a relationship between pain catastrophizing and higher levels of pain intensity, depression and disability. In a study of patients with scleroderma, social environments such as lower education levels were found to be associated with pain catastrophizing (Edwards et al., 2005). However, the relationship
between education level and pain intensity was not significant after controlling for pain
catastrophizing and symptoms of depression. Using brain imaging techniques, Gracely et al.
(2004) reported a relationship between pain catastrophizing and increased activation of brain
structures which were associated with pain processing and the attentional and emotional
aspects in patients with fibromyalgia.

Pain catastrophizing has been associated with negative outcomes in patients with chronic
pain, low back pain and acute knee surgery. Turner, Jensen & Romano (2000) evaluated
patients from a pain treatment program who had chronic pain from a variety of etiologies.
After controlling for age, sex and pain intensity, pain catastrophizing and beliefs were
independent predictors of depression but were not predictors of physical disability. Pain
catastrophizing has also been shown to be associated with pain intensity and outcome
following surgery. Edwards et al. (2009) evaluated patients who underwent total knee
arthroplasty using a longitudinal study design to assess patients from baseline to 12 months
following surgery. Pain catastrophizing did not change over the course of the study in
contrast to decreases in pain intensity and symptoms of depression. Catastrophizing was a
predictor of pain severity when depression scores were not included in the model. In patients
with low back pain, Picavet et al. (2002) reported an association between pain
catastrophizing and fear of movement. Buenaver et al. (2007) evaluated the association
between pain catastrophizing, pain outcomes and social responses in patients with low back
pain and upper and lower limb pain from a variety of etiologies. Pain catastrophizing was
correlated with pain intensity, severity and interference. The authors concluded that
perceived social responses did influence the relationship between pain outcomes and pain
catastrophizing. Cano, Leonard & Franz (2005) introduced an addition to the PCS to include
the consideration of the influence of catastrophizing of significant others such as spouse, partner, friends or family. The authors assessed undergraduate students from an urban university and reported an association with pain catastrophizing between patients and their partners. Higher levels of pain catastrophizing in significant others was associated with higher levels of pain intensity, depression symptoms and other psychological distress.

In patients with upper extremity pathologies, previous studies have evaluated the association between outcome and psychosocial factors including pain catastrophizing and depression (Lozano Calderon et al., 2008a; Lozano Calderon et al., 2008b; Niekel et al., 2009). In patients following carpal tunnel release, Lozano Calderon et al. (2008a) evaluated the relationship between disability, patient satisfaction and psychosocial factors. The authors reported a significant negative correlation between the DASH scores and patient satisfaction. The presence of pain catastrophizing and depressive symptoms were significant predictors of disability. In patients with a variety of hand pathologies, Niekel et al. (2009) evaluated the relationship between DASH scores and psychosocial measures including symptoms of pain catastrophizing, pain anxiety and depression. There was a small correlation between DASH scores and pain catastrophizing and a moderate correlation between the DASH scores and symptoms of depression and anxiety. In the regression analysis, pain catastrophizing and depression symptoms were predictors of the DASH.

These studies highlight the importance of pain catastrophizing in patients with musculoskeletal pathologies and the potential relationship that may exist between pain catastrophizing and disability in patients with upper extremity nerve injury. The role of pain catastrophizing and outcome has yet to be evaluated in patients following traumatic upper extremity nerve injury.
2.7.2 Depression Symptoms

Chronic pain and disability in patients with upper extremity pathologies have been associated with symptoms of depression and these symptoms may contribute to poor outcome (Lozano Calderon et al., 2008a; Lozano Calderon et al., 2008b; Ring et al., 2006). In patients with a variety of upper extremity pathologies including carpal tunnel syndrome, trigger finger, distal radius fracture, elbow pain and de Quervain’s tenosynovitis, Ring et al. (2006) reported strong correlations between the DASH score and symptoms of depression as measured by the Center for Epidemiologic Studies-Depression Scale. Similarly, in patients with trapeziometacarpal joint arthrosis, DASH scores were associated with symptoms of depression and pain catastrophizing (Lozano Calderon et al., 2008b). As a single predictor, the depression scores accounted for 50% of the variance. Patient satisfaction and DASH scores after carpal tunnel release were also associated with depression symptoms (Lozano Calderon et al., 2008a).

Patient report questionnaires such as the Hospital Anxiety and Depression Scale (HADS) may be used to identify symptoms of anxiety and depression in patients with milder symptoms (Zigmond & Snaith, 1983). The HADS is composed of 14 items which can be summarized by the anxiety and depression subscales and was shown to be more sensitive in individuals with milder symptoms of anxiety and depression (Zigmond et al., 1983). Good validity and reliability have been reported for the HADS (Aben, Verhey, Lousberg, Lodder, & Honig, 2002; Bjelland, Dahl, Haug, & Neckelmann, 2002; Hann, Winter, & Jacobsen, 1999; Lisspers, Nygren, & Oderman, 1997; Mykletun, Stordal, & Dahl, 2001; Quintana et al., 2003). With data based from the general population in Norway, Mykletun et al. (2001)
evaluated the factor structure of the HADS. The authors reported satisfactory internal consistency with both subscales and showed that the items loaded onto 2 factors although two of the items did not appear to be unique to either anxiety or depression. The factor structure was assessed in patients from a musculoskeletal pain clinic (Pallant & Bailey, 2005). The authors report a two factor structure with items loading on anxiety and depression although similar to the results reported by Mykletun et al. (2001), one item did not load onto the anxiety factor. Mykletun et al. (2001) reported high levels of anxiety and depression as measured by the HADS in patients from a musculoskeletal pain clinic. The mean value for the HADS anxiety was 9.26 and for the HADS depression was 8.14. The authors found these values in patients with musculoskeletal pain were higher compared to other reports of anxiety and depression scores from patients with breast cancer, end stage renal disease, and chronic pulmonary disease (Mykletun et al., 2001). Overall, the HADS has been shown to be useful in the assessment of symptoms of anxiety and depression in patients with non-psychiatric diagnoses.

2.7.3 Post-traumatic Stress Symptoms

Anxiety related to injury may be exhibited by patients following a traumatic injury. Post-traumatic stress disorder (PTSD) is defined as an anxiety disorder which is related to a traumatic event and this disorder is a classification within the Diagnostic and Statistical Manual of Mental Disorders - 4th edition (DMS-IV) of the American Psychiatric Association (2000). PTSD may include avoidance of stimuli related to the traumatic event, emotional numbing of general responsiveness, hyperarousal and/or re-experiencing the traumatic event in thoughts and dreams (American Psychiatric Association, 2000; Breslau, 2002). PTSD is
commonly associated with military trauma but as Breslau outlines, PTSD associated with non-military trauma is more common compared to military trauma cases (Breslau, 2002). In the general population, PTSD is reported in 7-12% of the population and the prevalence is reportedly higher in survivors of previous trauma (Asmundson et al., 2002). In a study by Breslau et al. (1998) which included an urban sample, traumatic events including serious accidents, were more prevalent in men, younger age and those in minority groups. An increased risk of developing PTSD has been associated with childhood trauma and psychiatric history of the individual and/or family (Brewin, Andrews, & Valentine, 2000). Individuals with PTSD may also be at risk for other associated disorders such as depression, anxiety and substance abuse (Breslau, 2002). PTSD and chronic pain often occur together and may share a mutual dependence (Asmundson et al., 2002; Asmundson et al., 2008). In patients with PTSD, there have been higher reports of pain and more health related problems and similarly, there have been reports of higher levels of PTSD in patients with chronic pain (Asmundson et al., 2002; Asmundson et al., 2008). As outlined by these authors, certain characteristics of chronic pain may maintain or exacerbate the symptoms of PTSD and vice versa some components of PTSD may maintain or exacerbate the symptoms related to chronic pain. Post-traumatic stress symptoms may occur as a subthreshold level and not meet the criteria of the diagnosis of PTSD. This cluster of post-traumatic stress symptoms may be distressing to the patient and may compromise recovery. Reports of low levels of post-traumatic stress symptoms have been reported in patients with traumatic hand injuries (Opsteegh et al., 2009; Opsteegh et al., 2010). Symptoms of post-traumatic stress were associated higher levels of pain and lower rates of return work. Although PTSD has been associated with other types of non-military trauma and with chronic pain, post-traumatic
stress symptoms or anxiety are not typically considered with traumatic peripheral nerve injury nor are these symptoms frequently assessed. Post-traumatic stress symptoms have not been previously assessed in patients following upper extremity nerve injury using valid, reliable measures. If present, these symptoms may be associated with higher levels of pain and poorer outcome.

The Post-traumatic Stress Disorder Checklist - Civilian version (PCL-C) is a self report questionnaire designed to assess symptoms of post-traumatic stress (Weathers, Litz, Huska, & Keane, 1994; Blanchard, Jones-Alexander, Buckley, & Forneris, 1996). Good reliability and validity have been reported with this measure (Blanchard et al., 1996; Ruggiero, Del Ben, Scotti, & Rabalais, 2003). Blanchard et al. (1996) evaluated individuals following a motor vehicle accident or sexual assault. The authors found high internal consistency for the PCL-C (Cronbach’s alpha 0.9) and strong correlation (r = 0.9) with another measure of post-traumatic stress, the Clinician Administered PTSD Scale. Ruggiero et al. (2003) reported good reliability (test-retest, internal consistency) and good validity when using the PCL-C in a group of college students. Using exploratory factor analysis, Pagé, Kleiman, Asmundson & Katz (2009) evaluated the factor structure of the PCL-C in patients who were undergoing major surgery. The authors reported in the pain-free patients two factors (re-experiencing/avoidance and emotional/numbing/hyperarousal) were the best fit of the data and in patients with pain, one factor accounted for 51.1% of the variance. In patients following motor vehicle accidents or sexual assault, Blanchard et al. (1996) reported a mean PCL-C score of 45.8 ± 16.1. Similarly, in patients undergoing major surgery, Pagé et al. (2009) reported a mean PCL-C score of 45 ± 20.6 in pain-free patients and 46.7 ± 9.7 in patients with pain. However, there has been lack of agreement regarding the criterion score
for the diagnosis of PTSD. This criterion value reportedly varies between 44, 45 and 50 and appears to be different in patients with different etiologies (Ruggiero et al., 2003). In the assessment of patients with traumatic nerve injury, post-traumatic stress is rarely considered and questionnaires such as the PCL-C are not reported.

Concurrent symptoms of both chronic pain and post-traumatic stress symptoms are not uncommon following trauma. Pain may be related to musculoskeletal origin or nerve related. While there are many reports of pain following nerve injury, assessment of anxiety or post-traumatic stress symptoms in patients with nerve injury are lacking. Aspects of both chronic pain and post-traumatic stress may share a mutual dependence to maintain the high comorbidity between the post-traumatic stress symptoms and pain in patients with nerve injury.

2.8 Summary

The above review indicates that there is wide variability in the reports of outcome in patients following upper extremity nerve injury, and standardized methods of assessment have not been universally accepted. Assessment of physical impairment is the most frequently reported outcome in the literature. Many patients sustain what appears to be a similar injury, yet outcomes vary in terms of recovery of physical impairment, pain and disability. In terms of outcome, the biomedical factors which affect nerve regeneration and reinnervation of the motor and sensory end organ targets have been examined. More recently, the influence of psychosocial factors has been considered in the outcome of patients with musculoskeletal disorders but the role of these factors in the experience of pain and disability has received
very little empirical attention in patients with upper extremity peripheral nerve injuries. The relationships among the various biomedical and psychosocial factors outlined above have yet to be evaluated in patients with traumatic peripheral nerve injury.
Chapter 3
Objectives & Hypotheses

3 Main Objective
The main objective of my dissertation is to evaluate the biomedical and psychosocial factors associated with pain and disability in patients following traumatic upper extremity nerve injuries. This main objective has been translated into specific questions and hypotheses as articulated in the following two sections.

3.1 Specific Questions
1. Do patients following peripheral nerve injury have high levels of disability?

2. Is pain present in patients following peripheral nerve injury?

3. What is the relationship between pain and disability?

4. Do peripheral nerve surgeons routinely assess pain in patients following traumatic nerve injuries?

5. Is cold sensitivity associated with higher levels of pain and disability following peripheral nerve injury?

6. Are biomedical factors such as gender, age and level of injury associated with pain and disability in patients following peripheral nerve injury?

7. Are psychosocial factors such as depression, anxiety and pain catastrophizing associated with pain and disability in patients following peripheral nerve injury?
3.2 Hypotheses

The specific hypotheses for each study are outlined. The data analyses are described in detail in the Methods of each study (Chapters 5, 6 and 7).

Study 1 (Chapter 5), Evaluation of Pain Measurement Practices and Opinions of Peripheral Nerve Surgeons

Specific hypothesis:

1. Most peripheral nerve surgeons do not routinely assess pain.

2. When pain is assessed, pain intensity rating scales are most frequently used.

Study 2 (Chapter 6), Patient Reported Outcome Following Peripheral Nerve Injury

Specific hypotheses:

1. High levels of disability will be present.

2. High levels of pain will be present.

3. Patients with brachial plexus lesions will report more pain and disability.

4. Pain will be associated with greater disability.
Study 3 (Chapter 7), Biomedical and Psychosocial Factors Associated with Pain and Disability after Peripheral Nerve Injury

Specific hypotheses:

1. High levels of disability will be present.

2. High levels of pain will be present.

3. Pain will be associated with greater disability.

4. Cold sensitivity will be associated with more pain and disability.

5. Patients with brachial plexus lesions will report more pain and disability.

6. Symptoms of depression, anxiety and pain catastrophizing will be associated with greater disability.
Chapter 4
Materials and Methods

4 Materials and Methods

The specific materials and methods for each of the studies are described in the chapters related to each individual study (Chapters 5, 6 and 7).

4.1 Research Ethics Board Approval

Studies 1, 2 and 3 (Chapters 5, 6 and 7) were approved by the Research Ethics Boards of the following institutions; University Health Network, University of Toronto and York University (Appendix A). Study 3 (Chapter 7) included patients from the Division of Plastic & Reconstructive Surgery, Washington University School of Medicine, St. Louis, Missouri and this study was also approved by the Human Studies Committee at Washington University School of Medicine in St. Louis (Appendix A). The approved consent forms for Study 3 (Chapter 7) are included in Appendix B.
Chapter 5
Study 1

The literature reviewed in the introduction of this dissertation and recently published review (Novak, C. B. & Katz, J. Neuropathic Pain in Patients with Upper Extremity Nerve Injury. *Physiotherapy Canada* (2010) 62:190-201.) revealed that most outcome studies of patients following nerve injury report motor and sensory impairments but fail to assess other relevant, non-biomedical factors that have been shown to be associated with pain and recovery in other patient samples. Few outcome studies even assess for the presence or absence of pain or pain relief, and those that do report pain have used verbal or numeric rating scales of pain intensity, leaving out other important dimensions of pain (e.g., affective, evaluative, quality, frequency, duration). The purpose of Study 1 was to ascertain the extent to which peripheral nerve surgeons assess for pain in their patients and to examine their opinions about pain in patients with upper extremity nerve injury.

Study 1, Evaluation of Pain Measurement Practices and Opinions of Peripheral Nerve Surgeons, surveyed the practices and opinions of peripheral nerve surgeons regarding pain assessment in patients following upper extremity nerve injury. This study was published in Hand 2009; 4(4):344–349, and permission to reproduce this manuscript has been obtained from the publisher. This study was presented at the American Society for Peripheral Nerve, Annual Meeting, Maui, Hawaii, January 9-11, 2009.
5 Evaluation of Pain Measurement Practices and Opinions of Peripheral Nerve Surgeons

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5.1 Abstract

Purpose: The purpose of this study was to evaluate the opinions and practices of peripheral nerve surgeons regarding assessment and treatment of pain in patients following nerve injury.

Methods: Surgeons with expertise in upper extremity peripheral nerve injuries and members of an international peripheral nerve society were sent an introductory letter and electronic survey by email (n = 146). Seventy members responded to the survey (48%) and 59 surgeons completed the survey.

Results: For patients referred for motor or sensory dysfunction, 31 surgeons (52%) indicated that they always formally assess pain. In patients referred for pain, 44 surgeons (75%) quantitatively assess pain using a verbal scale (n = 24) or verbal numeric scale (n = 36). The most frequent factors considered very important in the development of chronic neuropathic pain were psychosocial factors (64%), mechanism of injury (59%), workers’ compensation/litigation (54%) and iatrogenic injury (48%). In patients more than six months following injury, surgeons frequently see: cold sensitivity (54%), decreased motor function
(42%), paraesthesia/numbness (41%), fear of returning to work (22%), neuropathic pain (20%) and emotional/psychological distress (17%).

Conclusion: Only 52% of surgeons who responded to the survey always evaluate pain in patients referred for motor/sensory dysfunction. Pain assessment most frequently includes verbal patient response and assessment of psychosocial factors is rarely included. Predominantly patient related factors were considered important in the development of chronic neuropathic pain.

5.2 Introduction

Pain can negatively affect outcome and health related quality of life (Cocito et al., 2006). In patients following nerve injury, neuropathic pain can contribute to significant disability and has been reported following peripheral nerve injury, particularly in patients with brachial plexus injuries (Bentolila et al., 1999; Bertelli et al., 2008a; Cocito et al., 2006; Htut et al., 2006; Jensen et al., 2007; Samii et al., 2001). Many outcome studies of nerve injured patients present motor and sensory functional outcomes but do not report information regarding the absence or presence of pain (Aberg et al., 2007; Bertelli et al., 2007; Chuang et al., 1992; Chuang et al., 1995; Chuang et al., 1993; Jaquet et al., 2001; Leechavengvongs et al., 1998; Leechavengvongs, Witoonchart, Uerpairojkit, & Thuvasethakul, 2003; Mackinnon et al., 2005; Novak et al., 2003; Tung et al., 2003). In the surgical literature, many studies that report pain in nerve injured patients generally use unidimensional measures (verbal ratings or visual analog scales of pain intensity) and do not include assessment of the psychosocial
factors that may be associated with pain (Bentolila et al., 1999; Bertelli et al., 2008a; Htut et al., 2006; Kato et al., 2006; Kim et al., 2003; Nath et al., 2006; Samii et al., 2001).

The purpose of this study was to evaluate peripheral nerve surgeons’ opinions and practices regarding pain assessment and treatment in patients following nerve injury.

5.3 Methods

A survey was developed to include questions related to the assessment and treatment of pain in patients following nerve injury. A physical therapist, hand surgeon, psychologist and clinical epidemiologist developed the preliminary questionnaire. To examine the survey questions for content, clinical relevance, clarity, flow and wording, three different surgeons who operate on patients with upper extremity nerve injuries reviewed the questionnaire. Based on their feedback, the survey was modified and pilot tested on three different surgeons to ensure that the questions were understandable and clinically relevant.

The opinions of surgeons with expertise in the treatment of patients with upper extremity peripheral nerve injuries were sought for this study. Following approval by our institutional and university Research Ethics Boards, the active surgeons from an international peripheral nerve society who had a registered email address were invited to participate (n = 146). An introductory letter and anonymous electronic survey were sent by email. The non-respondents were sent two subsequent reminders by email at two weeks following the initial email and then three weeks following the first reminder. In total, 70 members responded to the survey (48%): after first mailing, n = 39, after second mailing, n = 19, after third mailing, n = 16. There were 6 surgeons who declined to participate and 5 who indicated that they do
not operate on patients with nerve injuries. In total, the sample consisted of 59 surgeons who completed the questionnaire.

There were 49 men and 10 women with a mean age of 50 years (standard deviation (sd) 9 years) and mean years in practice of 16 (sd 10 years). The majority of the surgeons were from plastic surgery (n = 37) followed by orthopedic surgery (n = 12), neurosurgery (n = 8), general surgery (n = 1) and one respondent indicated both plastic and orthopedic surgery. Thirty-nine surgeons (66%) reported that they operate on patients with brachial plexus injuries.

5.3.1 Data Analysis

Data analyses were performed using Statistical Package for the Social Sciences (version 15.0 for Windows, SPSS Inc., Chicago, IL, USA). Using chi-squared analyses for the categorical data and t-tests for the continuous data, comparisons were made of the demographics and survey responses between: 1) those surgeons who operate on brachial plexus injuries and those that do not operate on brachial plexus injuries. 2) those surgeons who quantitatively assess pain and those that do not. 3) those surgeons who “always” assess pain in patients with motor or sensory dysfunction and those that do not. 4) those surgeons who responded after the first mailing compared to the late responders (surgeons that responded to the subsequent mailings).
5.4 Results

Comparisons between the surgeons who responded to the survey early (after the first email) or late (to subsequent emails) revealed no significant differences in the demographics; male vs. female (p = .736), age (p = .483), surgical specialty (p = .588), years in practice (p = .787) or surgeons who operate on brachial plexus patients compared to those that do not (p = .409).

5.4.1 Questionnaire Responses to Pain Assessment and Treatment

In patients referred for pain resulting from a nerve injury, 44 surgeons (75%) indicated that they “quantitatively assess pain” using a verbal scale (n = 24), verbal numeric scale (n = 36), visual analog scale (n = 14) or pain questionnaire (n = 7). The specific “pain questionnaires” identified were the McGill pain questionnaire, the Disabilities of the Arm, Shoulder and Hand (DASH), the SF-36 and pain questionnaires developed by the surgeon. There were no significant differences in the demographics between surgeons who do or do not quantitatively assess pain (male vs. female, p = .306; age, p = .174; years in practice, p = .281; surgical specialty, p = .346; early vs. late mailing response, p = .796). There was a lower frequency of pain assessment in patients referred for motor or sensory dysfunction resulting from nerve injury; 31 surgeons (52%) reported that they “always formally assess pain” in these patients.

In this survey, neuropathic pain was defined as “pain resulting from a nerve injury”. When asked “when neuropathic pain becomes chronic?”, six months was the most frequent response (n = 23), however the responses ranged from three days to one year (less than six months, n = 23; greater than six months, n = 9; no answer, n = 4). The factors that were considered very important in the development of chronic neuropathic pain included
psychosocial factors (64%), mechanism of injury (59%), involvement of workers’ compensation or litigation (54%) and iatrogenic lesions from a previous surgery (48%) (Table 5.1).

Table 5.1: Factors Important in the Development of Chronic Neuropathic Pain

<table>
<thead>
<tr>
<th>Factors</th>
<th>Percentage of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosocial factors</td>
<td>64</td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td>59*</td>
</tr>
<tr>
<td>Involvement of workers’ compensation or litigation</td>
<td>54</td>
</tr>
<tr>
<td>Iatrogenic injury from previous surgery</td>
<td>48</td>
</tr>
<tr>
<td>Injury proximal to the dorsal root ganglion</td>
<td>37**</td>
</tr>
<tr>
<td>Surgical repair</td>
<td>34</td>
</tr>
<tr>
<td>Brachial plexus injury distal to the dorsal root ganglion</td>
<td>29</td>
</tr>
<tr>
<td>Age of patient</td>
<td>19</td>
</tr>
<tr>
<td>Gender</td>
<td>7</td>
</tr>
</tbody>
</table>

* Significantly more surgeons who “quantitatively assess pain” (p = .01).
** Significantly more surgeons who operate on brachial plexus injuries (p = .028)

Surgeons who quantitatively assess pain selected “mechanism of injury” more frequently (p = .01) as an important factor in the development of neuropathic pain and an injury proximal to the dorsal root ganglion was selected more frequently by surgeons who operate on patients.
with brachial plexus injuries compared to those that do not (p = .028). There was no difference in the selection of these factors between the early and late responders to the survey.

For the treatment of patients with chronic neuropathic pain, the most frequent non-operative interventions were “refer to physical or occupational therapy” (64%) and “refer to pain management” (63%) (Table 5.2).

Table 5.2: First Non-operative Interventions Used For Patients with Chronic Neuropathic Pain

<table>
<thead>
<tr>
<th>Non-operative Intervention</th>
<th>Percentage of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refer to physical or occupational therapy</td>
<td>64*</td>
</tr>
<tr>
<td>Refer to pain management</td>
<td>63</td>
</tr>
<tr>
<td>Prescribe anti-convulsants</td>
<td>58**</td>
</tr>
<tr>
<td>Prescribe anti-depressants</td>
<td>37</td>
</tr>
<tr>
<td>Prescribe topical creams</td>
<td>20</td>
</tr>
<tr>
<td>Prescribe opioids</td>
<td>20</td>
</tr>
<tr>
<td>Refer to psychologist &amp;/or psychiatrist</td>
<td>17</td>
</tr>
<tr>
<td>Refer for naturopathic treatments</td>
<td>2</td>
</tr>
</tbody>
</table>

The subcategory of surgeons who “always” assess pain more frequently “prescribe anti-convulsants” **(p=.03) and less often “refer to physical or occupational therapy” *(p=.03).
Surgeons who “always” assess pain in patients referred with motor and/or sensory dysfunction more frequently selected “prescribe anticonvulsants” (p = .03) and less frequently “refer to physical or occupational therapy” (p = .03). There were no statistical differences between surgeons who “quantitatively assess pain” and those that do not; between those surgeons who operate on brachial plexus injuries and those that do not; between early versus late responders.

In patients more than six months following nerve injury and repair, surgeons reported that they frequently see patients with cold sensitivity (54%), decreased motor function (42%) and paraesthesia/numbness (41%) (Table 5.3).

Table 5.3: Patient Characteristics Frequently Seen More Than Six Months Following Nerve Injury

<table>
<thead>
<tr>
<th>Factors</th>
<th>Percentage of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold sensitivity</td>
<td>54</td>
</tr>
<tr>
<td>Decreased motor function</td>
<td>42*</td>
</tr>
<tr>
<td>Paraesthesia or numbness</td>
<td>41</td>
</tr>
<tr>
<td>Fear of using extremity</td>
<td>22**</td>
</tr>
<tr>
<td>Fear of returning to work</td>
<td>22**</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>20</td>
</tr>
<tr>
<td>Emotional or psychological distress</td>
<td>17</td>
</tr>
</tbody>
</table>

* Significantly more surgeons who operate on brachial plexus injuries selected decreased motor function (p = .02). ** Surgeons who responded later to the survey compared to the early respondents selected “fear of using the extremity” (p = .006) and “fear of returning to work” (p = .045) more frequently.
Surgeons who operate on patients with brachial plexus injuries did select “decreased motor function” more frequently compared to surgeons who do not operate on the brachial plexus (p = .024). Surgeons who responded later to the survey compared to the early respondents selected “fear of using the extremity” (p = .006) and “fear of returning to work” (p = .045) more frequently. There were no statistical differences between those surgeons who quantitatively assess pain and those that do not.

5.5 Discussion

Neuropathic pain is defined by the International Association for the Study of Pain as pain resulting from dysfunction or a lesion in the peripheral or central nervous system (Cruccu et al., 2004; Merskey et al., 1994). Chronic neuropathic pain is usually defined as pain after six months from onset and in our survey, many surgeons (39%) defined the onset of “chronic” at six months following nerve injury. However, there were more surgeons who defined it by periods of time more than or less than six months following injury which points to inconsistency in the definition of “chronic neuropathic pain” among peripheral nerve surgeons. In the surgeons’ general comments submitted in the survey, “chronic neuropathic pain” was often attributed to neuropathic pain, which was uncontrolled and non-responsive to treatment.

Neuropathic pain and cold sensitivity are frequently reported as contributing to poor outcome following nerve injury (Berman et al., 1998; Bruxelle et al., 1988; Collins et al., 1996; Craigen et al., 1999; Freedlander, 1986; Graham et al., 2008; Htut et al., 2006; Irwin et al., 1997; Kato et al., 2006). However few outcome studies provide details regarding these
patient symptoms and most studies of nerve injured patients report only motor and sensory function. Graham and Schofield (2008) reported the prevalence of cold intolerance symptoms in patients greater than two years following hand injuries. The questionnaire was returned by 25% of patients and cold intolerance was reported by most of these patients (90% in trauma cases). Only 9% of patients with cold intolerance reported an improvement over time. Collins et al. (1996) evaluated 85 patients who were at least five years following nerve injury and 76% reported cold intolerance, which did not appear to decrease over time. In our survey, 54% of surgeons reported that six months following nerve injury, cold sensitivity was a frequent symptom. However, there was no indication of a specific outcome measure used to quantify the degree of pain or disability related to cold sensitivity. Many of the respondents to our survey indicated that referral to pain management and/or physical or occupational therapy is one of the first non-operative interventions utilized for patients with neuropathic pain. Therefore, many of the surgeons may assume that these facets of outcome regarding pain and disability are assessed and addressed by other sub-specialties.

Many questionnaires, which evaluate pain, disability, cold sensitivity and psychosocial factors, are time consuming to complete and analyze and therefore may be difficult to include in clinical practice. The European Federation of Neurological Societies recently outlined their neuropathic pain assessment guidelines (Cruccu et al., 2004). Visual analog scales, numerical rating scales or verbal rating scales, which are simple to use, can provide a quantitative assessment of pain intensity and may be used to provide a baseline assessment (Cruccu et al., 2004). Others have advocated assessment of pain intensity in addition to sensory descriptors, temporal variation and functional impact (Gilron et al., 2006). Based upon simple assessment, patients who indicate the presence of neuropathic pain can be
referred to pain specialists for more in depth evaluation and prompt treatment of the pain and associated sequelae.

The response rate for our survey was 48%. To minimize the likelihood of non-response bias and to increase the generalizability, a higher response rate is desirable but when compared to the response rate for physician questionnaires, this rate is similar to those previously reported (Asch, Jedrziewski, & Christakis, 1997; Braithwaite, Emery, de Lusignan, & Sutton, 2003; Cull, O'Connor, Sharp, & Tang, 2005; Cummings, Savitz, & Konrad, 2001; Drummond, Sharp, Carsin, Kelleher, & Comber, 2008; Kellerman & Herold, 2001). Many of the studies that have evaluated physician survey response rates used postal mail surveys and in a study comparing electronic and postal mail surveys, there was a shorter response time with electronic surveys but no difference in response rate or data quality (Akl, Maroun, Klocke, Montori, & Schunemann, 2005). We utilized several of the methods recommended to increase the response rate, which included a short questionnaire, personalized email, survey began with the demographic data and each subsequent email to non-respondents had a link to the questionnaire (Akl et al., 2005; Braithwaite et al., 2003; Drummond et al., 2008; Kellerman et al., 2001). Monetary and non-monetary incentives have been used to increase response rates and in a recent systematic review, VanGeest, Johnson & Welch (2007) found that monetary incentives improved the response rate. In our study, no incentives were given to complete the survey.

The most significant limitation associated with a low response rate is the presence of non-response bias. The comparison of early and late respondents to the survey has been introduced as one method to address this issue. Previous studies have suggested that respondents to later mailings may by classified as “proxies” for the non-respondents and
these late responders may represent qualities similar to the non-respondents (Kellerman et al., 2001; Sobal & Ferentz, 1989). The validity of this conclusion has been challenged. Blalock and Dial (1990) hypothesized that these similarities may not be present in the unevaluated responses or demographics. In our survey, there were no differences in the demographics between the early and late responders but the late responders did more frequently report patients with “fear of using the extremity” and “fear of returning to work”. There were no differences in the factors considered important in the development of chronic neuropathic pain.

Leslie (1972) proposed that individuals with a group identity share similar traits concerning attitudes and opinions towards group issues and therefore response bias is less likely in studies that use a homogeneous group. Peripheral nerve surgeons represent a relatively homogeneous group regarding knowledge and training compared to other physicians or the general population. Therefore the differences between respondents and non-respondents in surveys involving peripheral nerve surgeons may have less significance in the attitude towards pain following nerve injury. However, the relatively low response rate in our study does limit the assumptions that one can make regarding the practices and beliefs of the non-respondents. Based on the surgeons who did complete our survey and the results reported in outcome studies, there appears to be many surgeons who do not quantitatively assess pain or the associated factors in patients following nerve injury and yet many recognize the presence of cold sensitivity, pain and psychological sequelae following nerve injury.

Significant disability, related to cold sensitivity and/or neuropathic pain, may result following nerve injury and early treatment is advocated (Ahmed-Labib et al., 2007; Birch, Bonney, & Wynn Parry, 1998; Carlsson et al., 2003; Carlsson et al., 2008; Collins et al.,
1996; Craigen et al., 1999; Htut et al., 2006; Irwin et al., 1997; Kato et al., 2006). However, in our study, few surgeons reported using valid, reliable questionnaires to assess pain, cold sensitivity or disability following nerve injury and in those patients not specifically referred for a pain problem only 52% of surgeons “formally assess pain”. Therefore these symptoms with respect to frequency, intensity and disability may be under represented in the reports of outcome in patients following nerve injury. Early recognition of neuropathic pain and prompt intervention may provide the opportunity for more efficacious treatment.
Chapter 6
Study 2

This study evaluated patient reported pain and disability and the factors associated with disability in patients following an upper extremity traumatic nerve injury. I hypothesized that in these patients high levels of disability would be reported and that pain would be a significant predictor of disability. Study 2, Patient Reported Outcome Following Peripheral Nerve Injury, was published in the Journal of Hand Surgery 2009; 34A(2):281-287 and permission to reproduce this manuscript was granted by the publisher. This study was presented at the American Association for Hand Surgery, Annual Meeting, Maui, Hawaii, January 7-10, 2009 and the Canadian Pain Society, Annual Meeting, Quebec City, Quebec, May 27-30, 2009.
6 Patient Reported Outcome Following Peripheral Nerve Injury

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6.1 Abstract

Purpose: This study evaluated patient reported outcome and the factors associated with disability following an upper extremity traumatic nerve injury. We hypothesized that patients at least 6 months following injury would report significant disability and that pain would be the strongest predictor of the DASH.

Methods: Following Research Ethics Board approval, the medical charts were reviewed of patients with these inclusion criteria: adults; presenting to a nerve surgeon; six months or greater after traumatic nerve injury. Patients completed the DASH and the SF-36 as a routine part of the initial evaluation. These data were reviewed retrospectively to determine the predictors of the DASH score.

Results: There were 84 patients (mean age 38 years, sd 14 yrs), which included brachial plexus (n = 27) and peripheral nerve (n = 57) injuries. The mean time following injury was 38 months (sd 47). For all SF-36 domains, the mean values of the nerve injured patients were significantly lower than the normative data (p < 0.001), indicating a lower health status. The
mean DASH score was 52 (sd 22)/100. Significantly more disability was associated with more SF-36 bodily pain ($r = -0.59$, $p < 0.0001$) and with brachial plexus injuries ($p = 0.023$). In the final regression model, SF-36 bodily pain ($\beta = -0.475$, $p < 0.001$), age ($\beta = 0.360$, $p = 0.014$) and nerve injured ($\beta = -0.40$, $p = 0.023$) were significant predictors of the DASH ($R^2 = 44.5\%$). SF-36 bodily pain ($\beta = -0.523$, $p < 0.001$) accounted for 35% of the variance.

Conclusion: Substantial long term disability (high DASH scores) was found in patients following nerve injury that was predicted by higher pain, older age and brachial plexus injury. Further investigation of this pain and the associated factors may provide the opportunity for improved health related quality of life.

6.2 Introduction

Outcome following peripheral nerve injury frequently includes only measurement of nerve impairment such as sensory and motor function (Chuang et al., 1992; Chuang et al., 1995; Chuang et al., 1993; Leechavengvongs et al., 1998; Leechavengvongs et al., 2003; Mackinnon et al., 2005; Nakamichi & Tachibana, 1998; Novak & Mackinnon, 2002a; Novak & Mackinnon, 2002b; Novak et al., 2003; Novak & Mackinnon, 2004; Oberlin et al., 1994; Richardson, 1997; Samardzic, Grujicic, & Antunovic, 1992; Tung et al., 2003). Patient reported outcome and disability using valid and reliable measurement tools are rarely included in published reports and few studies have evaluated functional outcome or health related quality of life following peripheral nerve injury (Ahmed-Labib et al., 2007; Choi et al., 1997; Kitajima et al., 2006).
Chronic neuropathic pain which may occur following a peripheral nerve injury is often severe and directly impacts patient outcome and previous studies have reported the presence of severe chronic neuropathic pain in patients with brachial plexus injuries (Berman et al., 1998; Bertelli et al., 2008a; Bruxelle et al., 1988; Htut et al., 2006; Kato et al., 2006). Studies of patients with elbow and wrist injuries have identified pain as a significant contributor to upper extremity disability (Doornberg et al., 2005; Souer et al., 2008). Our clinical impression is that the presence of chronic neuropathic pain following peripheral nerve injury is a dominant predictor of disability and poor functional outcome.

The objective of this study was to evaluate patient reported outcome and the factors associated with disability in patients following an upper extremity traumatic nerve injury. We hypothesized that in select patients who sought a medical assessment at least six months following an upper extremity nerve injury, high levels of disability as measured by the DASH would be reported and that pain as assessed by the SF-36 would be a significant predictor of disability.

6.3 Material & Methods

This study used an existing clinical database from a single surgeon to identify eligible patients that were seen in a specialty clinic for patients with nerve related diagnoses from January 1997 to March 2007. A chart review of the medical records was then performed. The database included the records of 791 patients with nerve related diagnoses (such as nerve compression, nerve injury, tumors, congenital anomalies) to the upper and lower extremities. For this study, the inclusion criteria included patients with an upper extremity traumatic
peripheral nerve injury and who, at their initial consult visit, were at least six months following injury. Six months was chosen as the lower threshold to allow us to look at longer term outcomes in patients who sought medical assessment at least six months following nerve injury. Following approval from the institutional and university Research Ethics Boards, the database was reviewed to obtain the names of patients who met the inclusion criteria. The medical charts were then reviewed. At the initial patient consult, each patient was asked to complete two questionnaires, the Disabilities of the Arm, Shoulder, and Hand (DASH) and the SF-36. Patients who were unable to understand the questionnaires due to language barriers and did not have a translator, did not complete the questionnaires and were excluded. Demographic data, the DASH and the SF-36 from the initial consult visit were extracted from the chart.

There were 65 men and 19 women with a mean age of 39 years (standard deviation (sd) 14 years). The mean ± sd time from injury to initial consult was 38 ± 47 months (range 6 to 239 months). The dominant hand was involved in 44 cases and workers’ compensation or litigation was involved in 20 cases. All cases involved traumatic nerve injury and the most frequent site of injury was the brachial plexus (n = 27). The other nerves injured included the median (n = 18), ulnar (n = 16), median and ulnar (n = 5), radial (n = 8), ulnar and radial (n = 1), accessory (n = 2), axillary (n = 3), long thoracic (n = 3) and suprascapular (n = 1).

6.3.1 Measures
The SF-36, Version 2, is a generic health status questionnaire with established validity and reliability (Brazier et al., 1992; Garratt et al., 1993; Jenkinson, Wright, & Coulter, 1994;
McHorney et al., 1993; Ware et al., 1992). There are eight domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health), which can be reported separately or a normalized composite score for the physical and mental components can be calculated. A higher score indicates a better health status.

The DASH is a 30-item self-reported questionnaire to assess disease specific upper extremity outcome and disability. It was developed to measure physical function and symptoms in patients with upper limb musculoskeletal disorders and good reliability and validity have been reported (Beaton et al., 2001; Dias et al., 2008; Gummesson et al., 2003; Hudak et al., 1996; SooHoo et al., 2008). Each item is ranked on a 5-point Likert scale ranging from “no difficulty” to “unable”. A composite score is calculated from the completed responses and the score cannot be calculated if more than three items are missing. A higher DASH score reflects a greater degree of disability.

6.3.2 Data Analysis

Data were entered in a spreadsheet and the statistical analyses were performed with Statistical Package for the Social Sciences (version 15.0 for Windows, SPSS Inc., Chicago, IL, USA). Means and standard deviations were calculated for continuous data which were tested for normality and collinearity before analysis. Frequency counts were calculated for categorical data. One-sample t-tests were used to compare the SF-36 scores from the present sample with the published Canadian normative values (Hopman et al., 2000) on the eight domains and the physical and mental component scores. Non-parametric Spearman correlations were used to evaluate the association between the DASH and the SF-36 bodily
pain and the time since injury. T-tests were used to compare the DASH scores between the following independent variables; workers’ compensation or litigation involvement status (yes vs. no), dominant hand affected (yes vs. no) and gender (male vs. female). A one-way ANOVA was used to compare the DASH scores of patients with brachial plexus injuries, single shoulder nerve injuries and distal nerve injuries (median, ulnar and radial). If a significant F-test (main effect) was found (p < .05), paired linear contrasts between each of the pairs was completed.

Multiple linear regression using manual backward elimination was used to evaluate the variables that predicted outcome as measured by the DASH (Harrell, 2001). The initial model included the following seven independent variables; gender, involvement of workers’ compensation or litigation, dominant hand injured, time since injury, age, nerve injured and SF-36 bodily pain. Collinearity between the variables was checked by the appropriate correlation coefficient. Correlations greater than 0.8 were deemed to be collinear and one of the pair was eliminated from the model based on clinical sensibility. Subsequent models were derived by manual backward elimination using a criterion p-value associated with the beta coefficient of 0.1 or greater to remove a variable. The variable with the largest p-value was eliminated from the model first and the subsequent regression model was fitted with the remaining variables. This process was repeated until only variables with a p-value less than 0.1 remained in the final model. To investigate the influence of each variable included in the final model, a forward entry multiple regression was used in which the variable with the smallest p-value was entered first followed by the next until all significant variables had been entered.
6.4 Results

The independent and dependent continuous variables were tested for normality. The only variable with a non-normal distribution was time since injury (skewness 2.3) which was positively skewed with a mean of 38 months, median 18 months and mode seven months. Time since injury was transformed using a log 10 tranformation which corrected the non-normality. Regression analyses performed using the untransformed data and log 10 transformed data did not differ and therefore the untransformed data were used for the regression model analyses.

The means and standard deviations for the DASH and SF-36 are shown in Table 6.1.

Table 6.1: Mean Values for the DASH Scores and SF-36 Domains and Composite Scores

<table>
<thead>
<tr>
<th></th>
<th>Mean score</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DASH</td>
<td>52</td>
<td>22</td>
</tr>
<tr>
<td>SF-36 Bodily Pain</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>SF-36 Physical Function</td>
<td>60</td>
<td>23</td>
</tr>
<tr>
<td>SF-36 Role Physical</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td>SF-36 General Health</td>
<td>61</td>
<td>24</td>
</tr>
<tr>
<td>SF-36 Vitality</td>
<td>49</td>
<td>24</td>
</tr>
<tr>
<td>SF-36 Social Function</td>
<td>57</td>
<td>30</td>
</tr>
<tr>
<td>SF-36 Mental Health</td>
<td>58</td>
<td>23</td>
</tr>
<tr>
<td>SF-36 Role Emotional</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>SF-36 Physical Component</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>SF-36 Mental Component</td>
<td>42</td>
<td>13</td>
</tr>
</tbody>
</table>

The domains of the SF-36 were compared to the Canadian normative values, which were derived from a prospective cohort of 9423 adult men and women (Hopman et al., 2000). For all eight domains and the physical and mental component scale, the mean values of the nerve
injured patients were significantly lower than the normative values \((p < 0.001)\) which indicated a lower health status in the patients with nerve injury (Figure 6.1).

Figure 6.1: Comparison of SF-36 domains and the physical and mental component scores between nerve injured patients and Canadian normative data. The scores of the nerve injured patients were significantly lower in all domains \((p < 0.001)\) which indicated a decrease in health status compared to the Canadian normative data.

High SF-36 bodily pain was defined as an SF-36 bodily pain score that was lower than two standard deviations \((sd 23)\) from the normative \((\text{Hopman et al., 2000})\) mean value of 75.6. An
SF-36 bodily pain score less than 30 was considered different from the normative data and based on this criterion, there were 27 nerve injured patients with more bodily pain.

6.4.1 Univariate Variables Associated with DASH

There was a significant negative correlation between the DASH score and the SF-36 bodily pain score ($r = -0.602$, $p < 0.0001$) indicating a higher level of disability in those patients with more pain as measured by the SF-36 and no correlational relationship was found between the DASH and time since injury ($r = -0.009$, $p = 0.844$). There were no significant differences in DASH scores between patients with or without workers’ compensation or litigation ($p = 0.37$), with or without the dominant hand affected ($p = 0.22$) and between males and females ($p = 0.095$). The one-way ANOVA comparing the DASH score between nerve groups was significant ($p = 0.048$) and the planned contrasts indicated that DASH scores were significantly higher ($p = 0.023$) in patients with brachial plexus injuries ($60 \pm 20$) compared to patients with more distal nerve injuries ($48 \pm 23$) and single shoulder nerve injuries ($46 \pm 18$) (Figure 6.2).
Figure 6.2: Comparison of level of nerve injury and the outcome of the DASH. There were significantly higher levels of disability reported in patients with brachial plexus injuries *(p = 0.023).
6.4.2 Multivariable Regression

Multiple linear regression was used to evaluate the factors that predicted outcome as measured by the DASH. Multicollinearity was not evident as indicated by low correlation coefficients among the independent variables (Table 6.2).

Table 6.2: Evaluation of Correlational Relationships Between the Predictor Factors and the DASH

<table>
<thead>
<tr>
<th></th>
<th>DASH</th>
<th>Bodily Pain</th>
<th>Nerve Injured</th>
<th>Age</th>
<th>Time since Injury</th>
<th>Gender</th>
<th>WC/Lit*</th>
<th>Dominant Hand Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>DASH</td>
<td>1.000</td>
<td>-.590 (.000)</td>
<td>-.244 (.013)</td>
<td>.290 (.004)</td>
<td>-.022 (.422)</td>
<td>-.185 (.046)</td>
<td>.103 (.176)</td>
<td>.136 (.110)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>-.590 (.000)</td>
<td>1.000</td>
<td>.137 (.106)</td>
<td>-.080 (.235)</td>
<td>.046 (.340)</td>
<td>-.028 (.400)</td>
<td>-.240 (.014)</td>
<td>-.072 (.259)</td>
</tr>
<tr>
<td>Nerve Injured</td>
<td>-.244 (.013)</td>
<td>.137 (.106)</td>
<td>1.000</td>
<td>.095 (.194)</td>
<td>.006 (.478)</td>
<td>-.008 (.472)</td>
<td>.123 (.133)</td>
<td>.052 (.318)</td>
</tr>
<tr>
<td>Age</td>
<td>.290 (.004)</td>
<td>-.080 (.235)</td>
<td>.095 (.194)</td>
<td>1.000</td>
<td>.067 (.271)</td>
<td>-.302 (.003)</td>
<td>-.086 (.217)</td>
<td>.052 (.320)</td>
</tr>
<tr>
<td>Time since Injury</td>
<td>-.022 (.422)</td>
<td>.046 (.340)</td>
<td>.006 (.478)</td>
<td>.067 (.271)</td>
<td>1.000</td>
<td>.020 (.430)</td>
<td>-.198 (.035)</td>
<td>.191 (.041)</td>
</tr>
<tr>
<td>Gender</td>
<td>-.185 (.046)</td>
<td>-.028 (.400)</td>
<td>-.008 (.472)</td>
<td>-.302 (.003)</td>
<td>.020 (.430)</td>
<td>1.000</td>
<td>.102 (.178)</td>
<td>-.060 (.295)</td>
</tr>
<tr>
<td>WC/Lit*</td>
<td>.103 (.176)</td>
<td>-.240 (.014)</td>
<td>.123 (.133)</td>
<td>-.086 (.217)</td>
<td>-.198 (.035)</td>
<td>.102 (.178)</td>
<td>1.000</td>
<td>.085 (.220)</td>
</tr>
<tr>
<td>Dominant Hand Involved</td>
<td>.136 (.110)</td>
<td>-.072 (.259)</td>
<td>.052 (.318)</td>
<td>.052 (.320)</td>
<td>.191 (.041)</td>
<td>-.060 (.295)</td>
<td>.085 (.220)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

* WC/Lit = Workers’ compensation or litigation involvement
Manual backward elimination was used to fit the final regression model (Tables 6.3 & 6.4).

Table 6.3: Preliminary Multivariable Regression Model with Seven Predictor Variables (Dependent Variable: DASH)

<table>
<thead>
<tr>
<th>Model</th>
<th>$R^2$</th>
<th>Predictor Variables</th>
<th>Standardized Coefficients</th>
<th>$t$-value</th>
<th>Level of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.470</td>
<td>(Constant)</td>
<td></td>
<td>7.617</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bodily Pain</td>
<td>-.536</td>
<td>-6.076</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nerve involved</td>
<td>-.200</td>
<td>-2.317</td>
<td>.023</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age</td>
<td>.225</td>
<td>2.523</td>
<td>.014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time since injury</td>
<td>-.022</td>
<td>-.253</td>
<td>.801</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender</td>
<td>-.130</td>
<td>-1.470</td>
<td>.146</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WC/lit*</td>
<td>.020</td>
<td>.216</td>
<td>.829</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dominant hand involved</td>
<td>.091</td>
<td>1.051</td>
<td>.297</td>
</tr>
</tbody>
</table>

* WC/lit = Workers’ compensation or litigation involvement

Table 6.4: Final Multivariable Regression Model Using Manual Backward Elimination (Dependent Variable: DASH)

<table>
<thead>
<tr>
<th>Model</th>
<th>$R^2$</th>
<th>Predictor Variables</th>
<th>Standardized Coefficients</th>
<th>$t$-value</th>
<th>Level of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final</td>
<td>.445</td>
<td>(Constant)</td>
<td></td>
<td>8.927</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bodily Pain</td>
<td>-.542</td>
<td>-6.420</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nerve involved</td>
<td>-.195</td>
<td>-2.304</td>
<td>.024</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age</td>
<td>.265</td>
<td>3.151</td>
<td>.002</td>
</tr>
</tbody>
</table>
In the preliminary regression model which included all seven independent variables (gender, workers’ compensation or litigation involvement, dominant hand injured, time since injury, age, nerve injured and SF-36 bodily pain), the significant predictors were SF-36 bodily pain (beta = -.475, p < 0.001), age (beta = .360, p = 0.014) and nerve injured (beta = -4.804, p = 0.023) and explained 47% of the variance in the DASH scores. Using manual backward elimination and 0.1 level of significance for removal, the final model contained the predictor variables SF-36 bodily pain (beta = -4.81, p < 0.001), age (beta = .424, p = 0.002) and nerve injured (beta = -4.683, p = 0.024) and 45% of the variance was explained with this model (Appendix C). To evaluate the influence of each predictor in the final model, these three significant variables were then entered into the regression model in three steps beginning with SF-36 bodily pain (step 1), age (step 2) and nerve involved (step 3). The model with only the SF-36 bodily pain (beta = -.523, p < 0.001) explained 35% of the variance (R² = .35, p < .0001) (Appendix C). After controlling for the other variables, age (R² = .059, p = .006) explained 6% of the variance and nerve involved 4% of the variance (R² = .037, p = .024).

6.5 Discussion
Outcome following a peripheral nerve injury may vary dependent upon multiple injury and patient factors. Previous studies of patients following nerve injury and reconstructive surgery have predominately included measures of motor and sensory recovery (Bertelli et al., 2007; Chuang et al., 1992; Chuang et al., 1995; Chuang et al., 1993; Leechavengvongs et al., 1998; Leechavengvongs et al., 2003; Mackinnon et al., 2005; Moiyadi et al., 2007; Nakamichi et al., 1998; Novak et al., 2002a; Novak et al., 2002b; Novak et al., 2003; Novak et al., 2004; Oberlin et al., 1994; Richardson, 1997; Samardzic et al., 1992; Tung et al., 2003). More
recently, the trends in outcomes research following nerve injury have been directed towards more functional results and patient reported outcomes (Ahmed-Labib et al., 2007; Choi et al., 1997; Kitajima et al., 2006). High levels of disability and decreased health status in patients following brachial plexus injury and reconstructive surgery have been reported (Ahmed-Labib et al., 2007; Kitajima et al., 2006). In our select patients, who were at least six months following nerve injury and sought medical assessment, there was a high level of disability and a significantly lower health status in all SF-36 domains.

In our present study, the high level of disability as measured by the DASH was predicted by SF-36 bodily pain, older age and brachial plexus injuries. The final regression model showed SF-36 bodily pain to be a strong predictor of disability and accounted for 35% of the explained variance. Chronic neuropathic pain has been associated with a poor outcome in patients following nerve injury (Berman et al., 1998; Htut et al., 2006; Kitajima et al., 2006; Cocito et al., 2006). Choi et al. (1997) reported a moderately high quality of life in patients with brachial plexus injuries, although 75% of the patients had significant pain and 38% continued to use pain medications. Higher pain intensity has been associated with brachial plexus patients who did not undergo surgical repair, had more roots avulsed and had a long delay between injury and surgery (Htut et al., 2006; Kato et al., 2006). Previous studies have established an association between injury and patient demographic variables and outcome and our study used multivariable regression analysis to evaluate the predictors of disability. In our study, the SF-36 bodily pain score was the most significant predictor of disability, however only 44.5% of the variance was explained by the injury and demographic variables included in our analysis. Psychosocial factors such as depression, pain catastrophizing, anxiety have been associated with outcome or satisfaction in patients with carpal tunnel
syndrome, distal radius fractures and elbow fractures (Doornberg et al., 2005; Lozano Calderon et al., 2008a; Souer et al., 2008). The unexplained variance in our study may be associated with other biomedical or psychosocial factors, which remain to be identified.

This retrospective study only included patients who were at least six months following nerve injury and who had been referred to a specialty nerve clinic. There are patients following nerve injury who do not have chronic neuropathic pain or who have low levels of pain and are managing well (low disability) but there are others who have significant neuropathic pain and disability. We chose to look at patients who were at least six months following nerve injury because these are likely the patients who do have a higher level of chronic neuropathic pain and associated disability. While we do not know what percentage of nerve injured patients this group would comprise, our clinical impression is that these patients are the most difficult to manage. In this preliminary investigation, we have shown that patients who seek medical assessment at least six months following nerve injury report a significant level of disability and this is in part associated with chronic neuropathic pain. However, in our regression model, 55.5% of the variance was unexplained and this variance may be related to other biomedical and psychosocial factors.

Further investigation into chronic neuropathic pain following peripheral nerve injury may provide a better understanding of the underlying mechanisms, relevant biomedical and psychosocial factors associated with pain and disability and, ultimately, more effective treatments and improved health related quality of life.
In Study 2 (Chapter 6), substantial disability was reported by patients with upper extremity nerve injury and the significant variables associated with the DASH were pain, older age and brachial plexus nerve injury. A cross sectional study of prospectively collected data provided the opportunity to confirm these findings and to evaluate the association between the DASH and additional biomedical and psychosocial factors in patients with long standing nerve injury. This study was partially funded by a Research Grant Award from the American Association of Hand Surgery. This study has been submitted for publication and it is presently under peer review. This study was presented at the Canadian Physiotherapy Association annual meeting, St. John’s, Newfoundland, July 24, 2010 and will be the American Society for Surgery of the Hand annual meeting, Boston, Massachusetts, October 9, 2010.
Biomedical and Psychosocial Factors Associated with Pain and Disability after Peripheral Nerve Injury


7.1 Abstract

Background: The purpose of this study was to evaluate the biomedical and psychosocial factors associated with pain and disability more than six months following upper extremity nerve injury.

Methods: This cross sectional study included patients between six months and 15 years following an upper extremity nerve injury. Assessment included a series of patient self-report questionnaires. Disabilities of the Arm, Shoulder and Hand (DASH) scores were compared using independent samples t-tests, analysis of variance or correlations. Multivariable linear regression was used to evaluate the predictors of the DASH scores.

Results: The sample included 158 patients with a mean age of $41 \pm 16$ years and median time from injury was 14 months (range 6-167). DASH scores were significantly higher in patients with workers’ compensation or litigation ($p = 0.02$), brachial plexus nerve injuries ($p < 0.001$) and in those unemployed ($p < 0.001$). There was a significant positive correlation between DASH scores and pain intensity ($r = .51$, $p < 0.001$). In the multivariable regression
analysis for the predictors of the DASH, the final model explained 52.7% of the variance with the following predictors; pain intensity (Beta = .230, p = 0.006), brachial plexus nerve injury (Beta = -.220, p = 0.000), time since injury (Beta = -.198, p = 0.002), pain catastrophizing score (Beta = .192, p = 0.025), age (Beta = .187, p = 0.002), work status (Beta = .179, p = 0.008), cold sensitivity (Beta = .171, p = 0.015), depression score (Beta = .133, p = 0.066), workers’ compensation or litigation (Beta = .116, p = 0.049) and gender (Beta = -.104, p = 0.09).

Conclusions: Patients with peripheral nerve injury reported substantial disability, pain and cold sensitivity. Disability as measured by the DASH score was predicted by brachial plexus nerve injury, older age, pain intensity, work status, time since injury, cold sensitivity and pain catastrophizing.

7.2 Introduction

Recovery following upper extremity peripheral nerve injury is variable and may result in ongoing significant morbidity. Outcome studies of patients following upper extremity nerve injury frequently include measures of physical impairment such as range of motion, strength and sensation (Bertelli et al., 2007; Chuang et al., 1995; Chuang et al., 1993; Haninec et al., 2007; Htut et al., 2006; Htut et al., 2007; Mackinnon et al., 2005; Merrell et al., 2001; Nath, Lyons, & Bietz, 2007; Novak & Katz, 2010; Terzis et al., 2006; Tung et al., 2003). Measures which evaluate the impact of the physical impairment on the patient and validated measures of disability are not commonly included in the surgical literature.
Although few studies have evaluated disability after peripheral nerve injury, the evidence points to high levels of disability in these patients (Ahmed-Labib et al., 2007; Bengtson et al., 2008; Novak et al., 2009b). Disability following nerve injury may be related to biomedical factors including motor or sensory dysfunction, pain, and cold sensitivity. However, psychosocial factors may also be associated with disability in patients with nerve injury. Previous studies have shown evidence of an association between psychosocial factors (such as anxiety, depression and pain catastrophizing) and pain intensity, patient satisfaction and disability in patients with distal radius fractures, osteoarthritis and nerve pathologies (Bailey et al., 2009; Lozano Calderon et al., 2008a; Lozano Calderon et al., 2008b; Souer et al., 2008). The relative contribution to, and association of the biomedical and psychosocial factors with, reported disability has yet to be determined in patients with peripheral nerve injury. Identification of the factors that are associated with functional outcome and disability will assist in the development of more comprehensive treatment strategies for patients with nerve injury.

The main objective of this cross sectional study was to evaluate the biomedical and psychosocial factors associated with disability and pain in patients following upper extremity nerve injury. We hypothesized that; 1) patients with peripheral nerve injury would present with high levels of disability; 2) pain would be significantly associated with disability; 3) patients with brachial plexus lesions would report higher levels of pain and disability than those with more distal nerve injuries; 4) cold sensitivity would be associated with increased pain and greater disability; 5) higher levels of psychosocial distress (depression, post-traumatic stress and pain catastrophizing) would be associated with more disability.
7.3 Methods

This cross sectional study was approved by our institutional and university Research Ethics Boards.

7.3.1 Subjects

Adult patients were included in the study if they were between six months and 15 years following traumatic upper extremity peripheral nerve injury. The lower criterion of six months was chosen to include patients who would be classified as having chronic pain following a peripheral nerve injury. In this sample, all patients were adults at the time of injury. Those patients with a previous upper motor neuron lesion, an amputation, a self-inflicted injury or who were unable to understand the questionnaires were excluded from the study. Between September 2007 and August 2009, patients were recruited when the study coordinator was present at the clinic (University of Toronto Hand Program, Toronto, Ontario, Canada and the Division of Plastic & Reconstructive Surgery, Washington University School of Medicine, St. Louis, Missouri, USA). One hundred and sixty-four patients were invited to participate in the study (six patients declined); 158 patients participated including 77 patients from the University of Toronto Hand Program, Toronto, Ontario, Canada and 81 from the Division of Plastic & Reconstructive Surgery, Washington University School of Medicine, St. Louis, Missouri, USA.
7.3.2 Testing Protocol

Following signed informed consent, all testing was completed at one visit (approximately 30 minutes). The assessment included a series of questionnaires; Cold Intolerance Severity Scale (CISS), Short Form McGill Pain Questionnaire (SF-MPQ), Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, Hospital Anxiety and Depression Scale (HADS), Post-traumatic Stress Disorder Checklist - Civilian version (PCL-C), Pain Catastrophizing Scale (PCS), co-morbidity index. The order of questionnaire administration was randomly determined for each patient. The questionnaires were numbered and computer software was used to generate a randomization schedule for the administration order of the questionnaires for each patient.

7.3.2.1 Disabilities of the Arm, Shoulder and Hand (DASH) Questionnaire

The DASH was designed to assess disability in patients with upper extremity musculoskeletal disorders (Beaton et al., 2001; Hudak et al., 1996). There are 30 items related to symptoms and physical function, which are ranked on a five-point Likert scale and the DASH score is calculated from the responses. A higher DASH score indicates greater level of disability. As recommended by the questionnaire developers, missing items were replaced with the mean value of all subjects for that item (Beaton et al., 2001). As well, the developers state that the total score should not be calculated (i.e., estimated) if more than three items are missing; however, in the present study no patient had more than two missing responses. Good validity and reliability have been reported for the DASH (Beaton et al., 2001; Gummesson et al., 2003; Hudak et al., 1996; SooHoo et al., 2008).
7.3.2.2 Short Form McGill Pain Questionnaire (SF-MPQ)

The McGill Pain Questionnaire (MPQ) was developed to assess quantitative and qualitative measures of the pain experience (Melzack, 1975). The SF-MPQ consists of 15 adjectives from the sensory (n = 11) and affective (n = 4) categories of the original MPQ (Melzack, 1987). Each descriptor is rated on a four-point rating scale and a pain rating index is calculated. Pain intensity was assessed on a 10 cm visual analog scale (VAS) with the anchors “no pain” and “worst possible pain”. Good validity and reliability have been shown for the SF-MPQ (Grafton et al., 2005; Melzack, 1987).

7.3.2.3 Cold Intolerance Symptom Scale (CISS)

The CISS was designed to evaluate the sensitivity of exposure to cold with questions regarding the frequency, duration, severity and impact of cold sensitivity (Irwin et al., 1997; Ruijs et al., 2006). The scores for each item are summed to give a total score ranging from 0 to 100; the higher the score, the greater the cold sensitivity. There is evidence of good validity and reliability for the CISS in patients following upper extremity trauma (Carlsson et al., 2008; Irwin et al., 1997; Ruijs et al., 2006). The CISS includes questions regarding cold sensitivity while performing certain physical tasks. Some patients with peripheral nerve injury are physically unable to perform these tasks and therefore are unable to answer these questions. A validated method to control for missing data in the CISS scoring has not been published. Therefore we performed a sensitivity analysis using four different methods to replace the missing values (mean, median, linear trend, linear interpolation). There were no
statistical differences between the mean values calculated with each method and strong correlation coefficients \((r = .99, p < 0.001)\) were found between all methods. Therefore we chose to impute missing data for the CISS using linear trend regression analysis for each item (Norman & Streiner, 2000).

### 7.3.2.4 Hospital Anxiety and Depression Scale (HADS)

The HADS was used to measure symptoms of anxiety and depression (Zigmond et al., 1983). In total, there are 14 items in the HADS, which include seven items for anxiety and seven items for depression. Each item is ranked by the patient on a scale from 0 to 3 and the sum score is calculated for each subscale. A higher score indicates a higher degree of anxiety or depressive symptoms. The validity and reliability of the HADS has been established (Aben et al., 2002; Bjelland et al., 2002; Hann et al., 1999; Lisspers et al., 1997; Mykletun et al., 2001; Quintana et al., 2003).

### 7.3.2.5 Post-traumatic Stress Disorder Checklist – Civilian Version (PCL-C)

The PCL-C is a 17-item questionnaire designed to evaluate post-traumatic stress symptoms. The patient indicates on a scale of 1 (not at all) to 5 (extremely) how much they are bothered by each item. A higher score indicates more symptoms of post-traumatic stress. Validity, internal consistency and reliability have been shown for this measure of post-traumatic stress symptoms (Blanchard et al., 1996; Pagé, Kleiman, Asmundson, & Katz, 2009; Ruggiero et al., 2003).
7.3.2.6   Pain Catastrophizing Scale (PCS)

The PCS was designed to measure the degree of exaggerated negative thinking relative to the pain experience (Sullivan et al., 2005). This questionnaire includes 13 items and patients are asked to indicate the degree on a scale from 0 (not at all) to 4 (all the time) that they feel each thought or feeling when they experience pain (Sullivan et al., 1995). There are three subscales (rumination, magnification, helplessness) and a total score which may be calculated. A higher score indicates a higher degree of pain catastrophizing. Validity and reliability have been established for the PCS (Chibnall et al., 2005; Gracely et al., 2004; Osman et al., 1997; Osman et al., 2000; Van Damme et al., 2002).

7.3.2.7   Co-morbidity Index

The co-morbidity index is a patient reported questionnaire to assess medical co-morbidities. The validity of this self-reported co-morbidity questionnaire has been established with comparison to the review of medical charts (Sangha, Stucki, Liang, Fossel, & Katz, 2003). The patient is asked to indicate if a particular medical condition is present, being treated and limits activities and each medical condition may score up to 3 points (score range 0 to 45). A higher co-morbidity score indicates more medical co-morbidities.

7.3.3   Statistical Methods

For continuous data, means and standard deviations or medians and ranges were calculated and for categorical data, frequency counts were calculated. Continuous data were tested for normality and collinearity before analysis. The DASH scores were compared using unpaired
t-tests for the following independent variables; gender (male vs. female), workers’
compensation or litigation involvement (yes vs. no), dominant limb affected (yes vs. no),
marital status (married or living with partner vs. single, widowed, separated, divorced),
education (college or higher vs. high school graduate or lower), geographic location (Toronto
vs. St. Louis). Correlation coefficients were used to evaluate the association between DASH
scores and age and time since injury. A one-way analysis of variance (ANOVA) was used to
compare DASH scores and nerve injured (brachial plexus nerve injuries, single shoulder
nerve injuries defined as a single nerve injury to the shoulder region (axillary, suprascapular,
long thoracic), distal nerve injuries defined as an injury to the median, ulnar, radial or digital
nerves), to compare the DASH scores and work status (working, homemaker/student/retired,
unemployed) and to compare the DASH scores between income groups. A significant (p <
.05) F-test (main effect) was followed up with Tukey’s post hoc analysis.

To evaluate the variables that were associated with disability as measured by the DASH
(dependent variable), multivariable linear regression with manual backward elimination was
used (Harrell, 2001). Based upon the univariate statistical analysis, the preliminary regression
model included the predictor variables with a p-value of 0.2 or smaller (Hosmer &
Lemeshow, 1989). Collinearity between the predictors that were entered into the
multivariable linear regression was assessed with the appropriate correlation coefficient and
if correlations were greater than 0.8, one of the pair was eliminated from the model based on
the authors’ clinical experience. Regression models were derived by manual backward
elimination using a beta coefficient criterion p-value of 0.1 or greater to remove a variable.
The predictor variable with the largest p-value was eliminated and the subsequent regression
model was fitted with the remaining variables. The final model included only those predictors with a beta coefficient p-value less than 0.1.

Based on the regression analysis for the final model, a total of 158 patients provided sufficient power (0.8) for this analysis. This was based upon one main dependent outcome variable (DASH) and 10 patients per predictor variable (restricting the number of variables in the model to fewer than 16) (Norman et al., 2000).

### 7.4 Results

Patient demographics are presented in Table 7.1. There were 158 patients (53 women, 105 men) included in this study. The mean ± standard deviation (sd) age was 41 ± 16 years. The time from injury to recruitment was positively skewed (median 14 months; range 6 to 167 months). The dominant hand was involved in 95 cases. The level of injury in the upper extremity was the brachial plexus in 61 cases, single shoulder nerve in 14 cases (axillary (6), suprascapular (3), long thoracic (5)) and distal nerve in 83 cases (median (17), ulnar (19), radial (28), digital (8), median & ulnar (10), median & radial (1)). Workers’ compensation or litigation was involved in 50 cases and there was no difference between nerve injured groups (p = .875). At the time of the study, 81 patients reported working full or part-time, 21 were retired, students or homemakers and 56 patients were unemployed (including those on disability or workers’ compensation).

There were 94 patients who reported being married or living with a partner; 64 were single, separated, divorced or widowed. There were 106 patients who reported having college or
university education or higher. Annual household income was reported as being less than $20,000 by 30 patients (Table 7.1).

Table 7.1  Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>105</td>
<td>66.5</td>
</tr>
<tr>
<td>Female</td>
<td>53</td>
<td>33.5</td>
</tr>
<tr>
<td><strong>Dominant hand affected</strong></td>
<td>95</td>
<td>60.1</td>
</tr>
<tr>
<td><strong>Nerves Injured</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>61</td>
<td>38.6</td>
</tr>
<tr>
<td>Single shoulder nerve</td>
<td>14</td>
<td>8.9</td>
</tr>
<tr>
<td>Distal nerve</td>
<td>83</td>
<td>52.5</td>
</tr>
<tr>
<td><strong>Work Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working (full or part time)</td>
<td>81</td>
<td>51.6</td>
</tr>
<tr>
<td>Unemployed</td>
<td>56</td>
<td>35.4</td>
</tr>
<tr>
<td>Homemaker, student, retired</td>
<td>21</td>
<td>13.4</td>
</tr>
<tr>
<td><strong>Workers’ compensation &amp;/or litigation involvement</strong></td>
<td>50</td>
<td>31.6</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married or living with partner</td>
<td>94</td>
<td>59.5</td>
</tr>
<tr>
<td>Single, separated, divorced or widowed</td>
<td>64</td>
<td>40.5</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some college/university or higher*</td>
<td>106</td>
<td>67.1</td>
</tr>
<tr>
<td><strong>Income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than $19,999</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>$20,000 to $49,000</td>
<td>27</td>
<td>17.1</td>
</tr>
<tr>
<td>$50,000 to $79,000</td>
<td>50</td>
<td>31.6</td>
</tr>
<tr>
<td>Greater than $80,000</td>
<td>33</td>
<td>20.9</td>
</tr>
<tr>
<td>Missing data</td>
<td>18</td>
<td>11.4</td>
</tr>
</tbody>
</table>

*one patient did not answer this question
The mean scores $\pm$ sd for each questionnaire are presented in Table 7.2.

**Table 7.2  Summary of Questionnaire Scores**

<table>
<thead>
<tr>
<th>Questionnaire Score</th>
<th>Mean score $\pm$ standard deviation</th>
<th>Scale Range</th>
<th>Cronbach’s Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>DASH Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work module</td>
<td>44 $\pm$ 22</td>
<td>0-100</td>
<td>.96</td>
</tr>
<tr>
<td>Sports/Performing Arts module</td>
<td>60 $\pm$ 35</td>
<td>0-100</td>
<td>.97</td>
</tr>
<tr>
<td></td>
<td>70 $\pm$ 32</td>
<td></td>
<td>.94</td>
</tr>
<tr>
<td>Hospital Anxiety Depression Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety subscale</td>
<td>7 $\pm$ 4</td>
<td>0-21</td>
<td>.83</td>
</tr>
<tr>
<td>Depression subscale</td>
<td>5 $\pm$ 4</td>
<td>0-21</td>
<td>.82</td>
</tr>
<tr>
<td>Pain Catastrophizing Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>16 $\pm$ 15</td>
<td>0-52</td>
<td>.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rumination subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 $\pm$ 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Magnification subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 $\pm$ 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Helplessness subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 $\pm$ 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-traumatic Stress Disorder Checklist – Civilian Version</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>33 $\pm$ 14</td>
<td>17-85</td>
<td>.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reexperiencing subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 $\pm$ 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Avoidance subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 $\pm$ 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emotional numbing subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 $\pm$ 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperarousal subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 $\pm$ 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold Intolerance Symptom Scale</td>
<td>33 $\pm$ 26</td>
<td>0-100</td>
<td>.95*</td>
</tr>
<tr>
<td>Comorbidity Index</td>
<td>Total number indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 $\pm$ 1</td>
<td>0-15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total score</td>
<td>2.8 $\pm$ 3.1</td>
<td>0-45</td>
</tr>
</tbody>
</table>

* standardized item alpha
The mean DASH score was 44 ± 22 indicating a substantial level of disability. Eighty seven patients (55%) scored higher than 39.46 on the DASH, a score that corresponds to two sds above the mean normative value reported by Hunsaker et al (2002). A significant positive association was found between brachial plexus injury and a high DASH score (p < 0.001). The mean VAS pain intensity score was 4.2 ± 3.0 and the mean total SF-MPQ Pain Rating Index was 13.0 ± 10.8 (sensory 10.5 ± 8.3, affective 2.5 ± 3.1). The mean CISS score was 33 ± 26 indicating a high level of cold sensitivity. There were 81 patients (51%) who were classified with abnormal cold sensitivity (CISS score greater than 30, per Ruijs et al (2006)).

In patients with upper extremity nerve injury, excellent internal consistency was found for the DASH (Cronbach’s alpha = .96), PCS (Cronbach’s alpha = .96), PCL-C (Cronbach’s alpha = .93) and the CISS (standardized item alpha = .95) and good internal consistency for the HADS anxiety and depression subscales (Cronbach’s alpha = .83 and .82, respectively).

7.4.1 Univariate Statistical Analyses

Patients receiving workers’ compensation or engaged in litigation had significantly higher DASH scores than those who were not (p = 0.02) (Table 7.3). Statistically significant differences in the DASH scores were not found for the other independent variables; gender (p = 0.06), dominant limb injured (p = 0.30), marital status (p = 0.65), education level (p = 0.06) or geographic location (p = 0.23). The one-way ANOVA comparing the DASH score among nerve injury groups was statistically significant (p < 0.05). Post hoc analysis revealed that DASH scores in patients with brachial plexus injuries were significantly higher than in patients with distal nerve injuries (p < 0.001). The one-way ANOVA comparing DASH scores between work status groups was statistically significant (p < 0.05). Post hoc analysis
revealed that the DASH scores in patients who were unemployed were significantly higher than those working ($p < 0.001$). There was no significant difference in DASH scores as a function of level of income ($p = 0.284$).
Table 7.3 Univariate Statistical Analyses Between DASH, Pain Intensity, Cold Sensitivity and Independent Variables

<table>
<thead>
<tr>
<th></th>
<th>DASH Mean ± sd (p-value)</th>
<th>Pain Intensity Mean ± sd (p-value)</th>
<th>Cold Sensitivity Mean ± sd (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 ± 21</td>
<td>4.0 ± 3.0</td>
<td>32 ± 27</td>
</tr>
<tr>
<td>Female</td>
<td>49 ± 22</td>
<td>4.7 ± 2.9</td>
<td>44 ± 28</td>
</tr>
<tr>
<td>(p = .06)</td>
<td></td>
<td>(p = .18)</td>
<td>(p = .01)</td>
</tr>
<tr>
<td><strong>Workers’ compensation or litigation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50 ± 21</td>
<td>4.6 ± 3.1</td>
<td>39 ± 26</td>
</tr>
<tr>
<td>No</td>
<td>42 ± 21</td>
<td>4.1 ± 3.1</td>
<td>29 ± 25</td>
</tr>
<tr>
<td>(p = .02)</td>
<td></td>
<td>(p = .36)</td>
<td>(p = .03)</td>
</tr>
<tr>
<td><strong>Dominant Hand Injured</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46 ± 21</td>
<td>4.2 ± 3.1</td>
<td>31 ± 26</td>
</tr>
<tr>
<td>No</td>
<td>42 ± 23</td>
<td>4.3 ± 3.0</td>
<td>35 ± 25</td>
</tr>
<tr>
<td>(p = .30)</td>
<td></td>
<td>(p = .79)</td>
<td>(p = .38)</td>
</tr>
<tr>
<td><strong>Nerve Injured</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>52 ± 19</td>
<td>4.4 ± 3.2</td>
<td>34 ± 26</td>
</tr>
<tr>
<td>Single shoulder</td>
<td>40 ± 21</td>
<td>3.8 ± 3.2</td>
<td>17 ± 24</td>
</tr>
<tr>
<td>Distal Nerve</td>
<td>39 ± 22</td>
<td>4.2 ± 2.9</td>
<td>34 ± 25</td>
</tr>
<tr>
<td>(p = .001)</td>
<td></td>
<td>(p = .80)</td>
<td>(p = .05)</td>
</tr>
<tr>
<td><strong>Work status</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Working (full or part time)</td>
<td>38 ± 20</td>
<td>3.7 ± 2.7</td>
<td>30 ± 22</td>
</tr>
<tr>
<td>Unemployed</td>
<td>54 ± 20</td>
<td>5.2 ± 3.2</td>
<td>36 ± 28</td>
</tr>
<tr>
<td>Homemaker, retired or student</td>
<td>43 ± 21</td>
<td>3.6 ± 2.8</td>
<td>33 ± 29</td>
</tr>
<tr>
<td>(p &lt; .001)</td>
<td></td>
<td>(p = .01)</td>
<td>(p = .39)</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
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</tr>
<tr>
<td>Single, widowed</td>
<td>43 ± 22</td>
<td>4.2 ± 3.1</td>
<td>28 ± 25</td>
</tr>
<tr>
<td>Married, living with partner</td>
<td>45 ± 21</td>
<td>4.2 ± 3.0</td>
<td>35 ± 25</td>
</tr>
<tr>
<td>(p = .65)</td>
<td></td>
<td>(p = .10)</td>
<td>(p = .99)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>College or higher</td>
<td>42 ± 21</td>
<td>3.8 ± 2.8</td>
<td>32 ± 24</td>
</tr>
<tr>
<td>High school or lower</td>
<td>49 ± 20</td>
<td>5.0 ± 3.1</td>
<td>34 ± 29</td>
</tr>
<tr>
<td>(p = .06)</td>
<td></td>
<td>(p = .01)</td>
<td>(p = .53)</td>
</tr>
</tbody>
</table>
DASH scores and VAS pain intensity scores were positively correlated \( (r = .51, p < 0.001) \).

There was a weak positive correlation between DASH scores and age \( (r = .16, p = 0.02) \).

VAS pain intensity was strongly positively correlated with the CISS score \( (r = .50, p < 0.001) \), the PCS total score \( (r = .66, p < 0.001) \) and the PCS subscales; rumination \( (r = .66, p < 0.001) \), magnification \( (r = .57, p < 0.001) \) helplessness \( (r = .65, p < 0.001) \). There was a moderate positive correlation between VAS pain intensity scores and PCL total score \( (r = .47, p < 0.001) \), HADS anxiety score \( (r = .32, p < 0.001) \) and HADS depression score \( (r = .41, p < 0.001) \) (Table 7.4).
Table 7.4 Correlational Relationship Between the DASH Scores and Other Questionnaires

<table>
<thead>
<tr>
<th></th>
<th>Pearson Correlation Coefficient</th>
<th>Level of Significance</th>
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<tr>
<td>Hospital Anxiety Depression Score</td>
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<tr>
<td>Total Score</td>
<td>.41</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>.28</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Depression</td>
<td>.47</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 cm Visual Analog Scale</td>
<td>.51</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Pain Catastrophizing Scale</td>
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<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>.46</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Rumination</td>
<td>.44</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Magnification</td>
<td>.40</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Helplessness</td>
<td>.45</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Post-traumatic Stress Disorder Checklist – Civilian Version</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>.43</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Reexperiencing</td>
<td>.35</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Avoidance</td>
<td>.28</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Emotional numbing</td>
<td>.42</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Hyperarousal</td>
<td>.39</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Cold Intolerance Symptom Scale</td>
<td>.38</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Comorbidity Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number indicated</td>
<td>.24</td>
<td>.002</td>
</tr>
<tr>
<td>Total score</td>
<td>.25</td>
<td>.002</td>
</tr>
</tbody>
</table>
7.4.2 Multivariable Regression Analysis

Multivariable linear regression with manual backward elimination was used to evaluate the factors that statistically predicted disability as measured by the DASH. Our criterion for multicollinearity was $r = 0.8$ and the correlation coefficient between the HADS anxiety score and the PCL-C was $r = 0.76$. To control for the potential multicollinearity between these two closely related variables, the HADS anxiety score was not included in the regression model. Both the HADS anxiety and PCL-C assess anxiety related symptoms and this likely accounts for the high correlation coefficient. Because this study assessed patients following a traumatic nerve injury and the PCL-C was designed to assess symptoms of post-traumatic stress, we chose to include the PCL-C in the regression model and not the HADS anxiety score as the former measure is more closely related to the nature of the injury than is the latter. The correlation coefficients between the variables in the regression analysis are presented in Table 7.5.
Table 7.5 Correlation Coefficients* Between Variables in the Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>DASH</th>
<th>Gender</th>
<th>Age</th>
<th>Education</th>
<th>Work</th>
<th>Work</th>
<th>WC/Lit</th>
<th>Single</th>
<th>Distal</th>
<th>Comorb</th>
<th>PCL</th>
<th>Pain</th>
<th>CISS</th>
<th>PCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DASH</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>-15</td>
<td>-13</td>
<td>-16</td>
<td>-06</td>
<td>-20</td>
<td>-20</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.16</td>
<td>0.02</td>
<td>0.16</td>
<td>0.06</td>
<td>0.16</td>
<td>0.16</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Education</td>
<td>-0.15</td>
<td>-0.08</td>
<td>-0.16</td>
<td>0.02</td>
<td>-0.20</td>
<td>-0.20</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Work Status Unemp</td>
<td>0.34</td>
<td>0.22</td>
<td>0.23</td>
<td>0.16</td>
<td>0.23</td>
<td>0.16</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work Status H/R/S</td>
<td>0.02</td>
<td>0.11</td>
<td>0.07</td>
<td>0.07</td>
<td>0.07</td>
<td>0.07</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WC/lit</td>
<td>0.19</td>
<td>0.01</td>
<td>0.01</td>
<td>0.00</td>
<td>0.12</td>
<td>0.07</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since injury</td>
<td>-0.04</td>
<td>-0.11</td>
<td>-0.07</td>
<td>-0.06</td>
<td>-0.07</td>
<td>-0.08</td>
<td>0.09</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single shoulder</td>
<td>-0.06</td>
<td>0.06</td>
<td>0.06</td>
<td>0.06</td>
<td>0.03</td>
<td>0.06</td>
<td>0.03</td>
<td>0.07</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal nerve</td>
<td>-0.26</td>
<td>0.06</td>
<td>0.06</td>
<td>0.10</td>
<td>0.25</td>
<td>0.08</td>
<td>0.02</td>
<td>0.08</td>
<td>-0.33</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorb index</td>
<td>0.25</td>
<td>0.08</td>
<td>0.44</td>
<td>0.03</td>
<td>0.09</td>
<td>0.02</td>
<td>-0.02</td>
<td>-0.02</td>
<td>-0.02</td>
<td>-0.01</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCL score</td>
<td>0.43</td>
<td>0.03</td>
<td>0.13</td>
<td>0.19</td>
<td>0.32</td>
<td>0.17</td>
<td>0.21</td>
<td>0.15</td>
<td>0.04</td>
<td>0.16</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain intensity</td>
<td>0.51</td>
<td>-0.11</td>
<td>-0.01</td>
<td>-0.20</td>
<td>0.24</td>
<td>0.08</td>
<td>0.07</td>
<td>0.27</td>
<td>-0.05</td>
<td>-0.01</td>
<td>0.18</td>
<td>0.47</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CISS</td>
<td>0.38</td>
<td>-0.21</td>
<td>-0.21</td>
<td>-0.05</td>
<td>0.10</td>
<td>0.01</td>
<td>0.18</td>
<td>0.31</td>
<td>-0.19</td>
<td>0.07</td>
<td>0.09</td>
<td>0.38</td>
<td>0.50</td>
<td>1</td>
</tr>
<tr>
<td>PCS</td>
<td>0.48</td>
<td>-0.12</td>
<td>-0.12</td>
<td>-0.23</td>
<td>-0.03</td>
<td>-0.06</td>
<td>0.27</td>
<td>-0.05</td>
<td>-0.04</td>
<td>0.12</td>
<td>0.64</td>
<td>0.66</td>
<td>0.29</td>
<td>1</td>
</tr>
<tr>
<td>HADS depression</td>
<td>0.47</td>
<td>-0.07</td>
<td>-0.07</td>
<td>-0.12</td>
<td>-0.30</td>
<td>-0.07</td>
<td>0.10</td>
<td>0.11</td>
<td>-0.12</td>
<td>-0.15</td>
<td>0.26</td>
<td>0.70</td>
<td>0.41</td>
<td>0.26</td>
</tr>
</tbody>
</table>

*Pearson correlation coefficient (1-tailed level of significance); DASH = Disabilities of the Arm, Shoulder and Hand, WC/Lit = workers' compensation or litigation, PCL = Post-traumatic Stress Disorder Checklist - Civilian version, CISS = Cold Intolerance Severity Scale, PCS = Pain Catastrophizing Scale, HADS = Hospital Anxiety and Depression Scale, Unempl = unemployed, H/S/R = homemaker, student or retired, Comorb = comorbidity
The distribution of time from injury was positively skewed (skewness = 2.8). The non-normality was corrected using a log10 transformation and these transformed data were used in the regression analysis (Norman et al., 2000). Based upon the univariate statistical analyses (p-value less than 0.2), the preliminary regression model included the following independent variables; gender, age, education, work status, time since injury, workers’ compensation or litigation involvement, nerve injured, comorbidity index, HADS depression score, PCL-C score, VAS pain intensity, CISS score, PCS total score. Using manual backward elimination and 0.1 level of significance for removal (Table 7.6), the final model accounted for 52.7% of the variance and contained 10 predictor variables (Table 7.7); pain intensity (Beta = .230, p = 0.006), nerve injured (Beta = -.220, p < 0.001), time since injury (Beta = -.198, p = 0.002), pain catastrophizing score (Beta = .192, p = 0.025), age (Beta = .187, p = 0.002), work status (Beta = .179, p = 0.008), cold sensitivity (Beta = .171, p = 0.015), depression score (Beta = .133, p = 0.066), workers’ compensation or litigation (Beta = .116, p = 0.049) and gender (Beta = -.104, p = 0.09).
<table>
<thead>
<tr>
<th>Model</th>
<th>R Square</th>
<th>R Square Change</th>
<th>Predictors Included</th>
<th>Predictors Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.535</td>
<td>.535</td>
<td>(Constant), PCS score, work status, nerve injured, Workers’ compensation/Litigation, comorbidity index, gender, education, time since injury, cold sensitivity, age, HADS depression, pain intensity, PCL total score</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>.535</td>
<td>.000</td>
<td>PCL score</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>.534</td>
<td>-.001</td>
<td>PCL score, education</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>.532</td>
<td>-.001</td>
<td>PCL score, education, work status (homemaker, student, retired)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>.530</td>
<td>-.003</td>
<td>PCL score, education, work status (homemaker, student, retired), comorbidity index</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>.527</td>
<td>-.003</td>
<td>PCL score, education, work status (homemaker, student, retired), comorbidity index, nerve injured (single shoulder)</td>
<td></td>
</tr>
</tbody>
</table>

HADS = Hospital Anxiety and Depression Scale, PCL = Post-traumatic Stress Disorder Checklist - Civilian version, PCS = Pain Catastrophizing Scale
Table 7.7 Final Multivariable Regression Model Using Manual Backward Elimination
(Dependent Variable: DASH)

<table>
<thead>
<tr>
<th>Model</th>
<th>$R^2$</th>
<th>Predictor Variables</th>
<th>Unstandardized Coefficients B</th>
<th>Standardized Coefficients Beta</th>
<th>t-value</th>
<th>Level of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final</td>
<td>.527</td>
<td>(Constant)</td>
<td></td>
<td></td>
<td></td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain intensity</td>
<td>1.652</td>
<td>.230</td>
<td>2.772</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nerve injured</td>
<td>-9.505</td>
<td>-.220</td>
<td>-3.668</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time since injury</td>
<td>-12.205</td>
<td>-.198</td>
<td>-3.195</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain catastrophizing</td>
<td>.284</td>
<td>.192</td>
<td>2.258</td>
<td>.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age</td>
<td>.259</td>
<td>.187</td>
<td>3.138</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Work status</td>
<td>8.035</td>
<td>.179</td>
<td>2.676</td>
<td>.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cold sensitivity</td>
<td>.145</td>
<td>.171</td>
<td>2.467</td>
<td>.015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depression score</td>
<td>.735</td>
<td>.133</td>
<td>1.849</td>
<td>.066</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Workers’ compensation or litigation</td>
<td>5.375</td>
<td>.116</td>
<td>1.984</td>
<td>.049</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender</td>
<td>-4.728</td>
<td>-.104</td>
<td>-1.709</td>
<td>.090</td>
</tr>
</tbody>
</table>

Based upon the standardized Beta coefficients in the final regression model, pain intensity, brachial plexus nerve injury, time since injury and pain catastrophizing resulted in higher DASH scores.
7.5 Discussion

The results of the present study indicate that patients with a peripheral nerve injury reported substantial disability which was predicted by a combination of biomedical and psychosocial factors (pain intensity, brachial plexus nerve injury, pain catastrophizing, older age, work status, time since injury and cold sensitivity). Previous studies of patients following traumatic peripheral nerve injuries tend to report only measures of physical impairment (Bengtson et al., 2008; Novak et al., 2010). Assessments of motor and sensory recovery provide data regarding nerve remyelination and/or regeneration and reinnervation of the motor fibres and/or sensory end organs but do not provide insight into the overall impact of the injury on the patient. More recently studies have recognized the importance of patient self report questionnaires, disability and health related quality of life (Ahmed-Labib et al., 2007; Bailey et al., 2009; Bengtson et al., 2008; Choi et al., 1997; Novak et al., 2009b).

The World Health Organization (WHO) and others have presented biopsychosocial models for disability and function which link together the biomedical, personal and social perspectives (Jette, 2006; Verbrugge et al., 1994; World Health Organization, 2001; Jette et al., 2005). The WHO has proposed the International Classification of Function, Disability and Health (ICF) model and within this framework, body structures and functions (physiological function), activity and participation are considered in the context of life domains in addition to the impact of environmental and personal factors (World Health Organization, 2001; Jette, 2009). In terms of nerve injury, this model captures the interaction between the condition after injury (physical impairment and activity performance) and the personal and environmental factors.
Disability is considered a limitation in tasks, activities or performance of daily activities and in the case of nerve injury, due to physical impairment. The DASH was designed to assess disability in patients with upper extremity musculoskeletal disorders based upon physical function and symptoms (Beaton et al., 2001; Gummesson et al., 2003; Hudak et al., 1996; SooHoo et al., 2008). Few studies have reported disability as measured by the DASH in patients with peripheral nerve injury (Ahmed-Labib et al., 2007; Novak et al., 2009b; Topel et al., 2009). In a previous retrospective chart review of patients with upper extremity nerve injury, we found substantial disability as measured by the DASH which was associated with pain, older age and brachial plexus nerve injuries (Novak et al., 2009b). The results of the present study confirm these initial findings, showing that high levels of disability were reported by patients with an upper extremity nerve injury. Other studies have reported high levels of disability in patients with brachial plexus injuries (Ahmed-Labib et al., 2007; Davidson, 2004). Using the DASH and the SF-36, Ahmed-Labib et al. (2007) reported a correlation between poor functional outcome and root avulsion injuries and delayed surgical repair. Topel et al. (2009) evaluated 33 patients with upper extremity arterial injuries and reported more severe functional deficits in patients with a concomitant peripheral nerve injury although no statistically significant differences were noted. In the present study, we found high levels of disability in patients with an upper extremity nerve injury and a significant predictor of higher disability scores was brachial plexus nerve injury.

Poor outcome associated with neuropathic pain following traumatic nerve injuries has been reported (Campbell & Meyer, 2006; Dworkin et al., 2007; Htut et al., 2006; Kato et al., 2006; Novak et al., 2009b). Brachial plexus nerve injury is often associated with more severe pain and is a significant predictor of disability. Choi et al. (1997) evaluated a group of patients
following brachial plexus injury and surgery. These patients reported a moderately high general quality of life, although 75% reported significant pain. In a sample of patients with nerve compression and nerve injury, Bailey et al. (2009) reported moderate pain which was associated with lower quality of life and higher depression scores. In patients with brachial plexus nerve injury, Htut et al. (2006) found that surgical repair was associated with pain relief and pain intensity was highest among patients who did not undergo surgical repair. Kato et al. (2006) investigated the impact of operative delay on pain relief in 148 patients with brachial plexus injuries. Significant positive correlations were observed between pain intensity and number of avulsed nerve roots and a longer interval between injury and surgery. In the present study, we did not examine root avulsions specifically but did find that patients with brachial plexus injuries had more pain and disability compared to patients with more distal nerve injuries. Pain intensity was a significant predictor of disability and was also strongly correlated with cold sensitivity. In our previous retrospective chart review study, more bodily pain, as assessed by the SF-36, was reported in patients with an upper extremity nerve injury (Novak et al., 2009b). Pain intensity has also been associated with disability in other musculoskeletal disorders. Souer et al. (2008) evaluated patients following distal radius fracture and pain was a significant positive predictor of the DASH scores. Patients with intra-articular elbow fractures were evaluated using physician based rating scales and patient reported questionnaires (DASH, SF-36) (Doornberg et al., 2005). The predictors of the DASH included pain and range of motion and as a single predictor pain explained 36% of the variance in the regression model. In another study following elbow trauma, Lindenhovius et al. (2008) reported that the strongest predictor of the DASH was pain and accounted for 41% of the variance. Consistent with these findings, the results of the present study of patients
with a traumatic peripheral nerve injury, show that pain intensity is a significant predictor of
disability (Beta = .230, p = 0.006). These data highlight the importance of the relationship
between pain intensity and patient reported disability and emphasize the need for good long
term pain management and a comprehensive treatment approach to these patients.

Pain may also be associated with cold sensitivity; symptoms of pain, stiffness, sensory
disturbance and color changes with exposure to cold (Graham et al., 2008; Novak et al.,
2009a; Vaksvik et al., 2009). When present, cold sensitivity is often associated with high
morbidity and poor outcome (Backman et al., 1993; Campbell et al., 1998; Collins et al.,
1996; Craigen et al., 1999; Dabernig et al., 2006; Graham et al., 2008; Irwin et al., 1997;
McCabe et al., 1991; Nancarrow et al., 1996; Nylander et al., 1987; Povlsen et al., 1995a;
Povlsen et al., 1995b; Ruijs et al., 2006; Ruijs et al., 2007; Stokvis et al., 2009; Vaksvik et
al., 2009). The present study found high levels of cold sensitivity and disability in patients
with upper extremity nerve injury and disability was predicted by both pain and cold
sensitivity. Dabernig et al. (2006) reported a relatively low mean DASH score (11/100) in
patients after digit replantation, although 87% of patients reported cold intolerance.

Following traumatic hand injury, many studies have reported long standing and unresolved
cold sensitivity with high levels of pain (Campbell et al., 1998; Collins et al., 1996; Graham
et al., 2008; Meyer-Rosberg et al., 2001b; Nancarrow et al., 1996; Stokvis et al., 2009). Cold
sensitivity remains a substantial challenge following trauma and nerve injury particularly for
patients who reside or work in cold environments.

Historically, in the surgical literature, biomedical factors associated with outcome have been
emphasized over other potentially important variables. More recently the importance of the
relationship between psychosocial factors and outcome has been recognized. In the present
sample of patients with an upper extremity nerve injury, depression scores were moderately positively correlated with DASH scores and pain catastrophizing was a significant positive predictor of the DASH (Beta = .192, p = .025). Previous studies have evaluated the relationship between psychosocial factors such as pain catastrophizing and depression in patients with various hand pathologies, including trapeziometacarpal arthrosis and after carpal tunnel release (Lozano Calderon et al., 2008a; Lozano Calderon et al., 2008b; Niekel et al., 2009). Lozano Calderon et al. (2008a) reported a significant negative correlation between the DASH scores and patient satisfaction in patients after carpal tunnel release and pain catastrophizing and depressive symptoms were predictors of disability. Niekel et al. (2009) evaluated the relationship between DASH scores and psychosocial measures including pain catastrophizing, pain anxiety and symptoms of depression in patients with a variety of hand pathologies. The authors found a small positive correlation between DASH scores and pain catastrophizing and a moderate positive correlation between the DASH scores and symptoms of depression and anxiety. Both pain catastrophizing and depression symptoms were predictors of higher DASH scores.

Pain catastrophizing is a maladaptive cognitive style that involves negative thinking regarding the pain experience (Sullivan et al., 1995; Sullivan et al., 2005). Patients who catastrophize feel overwhelmed by pain, ruminate about it, and feel helpless in the face of pain. In a group of patients with chronic pain from a variety of etiologies, Severeijns et al. (2001) reported higher pain intensity, disability and psychological distress in patients who catastrophized. In the present study, patients following traumatic nerve injury exhibited high levels of pain catastrophizing and disability. However, disability is a multidimensional construct, which is influenced by physical impairment, activity and participation and also by
environmental and personal factors and as such requires a multi-disciplinary treatment approach (Jette, 2009; World Health Organization, 2001).

The limitations of this study include the unique patient sample, cross sectional study design, inclusion of nerve injuries six months after injury, and possibility of low statistical power for detecting certain relationships. In this investigation, we evaluated patients who were at least six months following a traumatic peripheral nerve injury. This presents a unique group of patients who continue to seek medical or surgical assessment and treatment and may not be representative of all patients following nerve injury. There are patients following nerve injury who have complete recovery and no apparent morbidity. However, patients who remain with physical impairments, pain and disability are often the most difficult to treat, overwhelm the available resources and have persistent, diminished health related quality of life. As well, inclusion of patients with nerve injuries who have not achieved full recovery may have biased the results in the direction of finding more pain and greater disability in these patients.

The primary aim of this study was to evaluate the predictors of the DASH using a multivariable regression model and a sample size of 158 was sufficient to support the inclusion of the all of the factors in the preliminary regression model. The t-tests comparing DASH scores on the dependent variables were performed, in part, to select the factors to be included in the regression model and may not have had sufficient power to detect a significant difference in all cases. Finally, given the cross sectional design used in the present study, conclusions about the direction of causality cannot be made. The present study provides the preliminary data for a comprehensive longitudinal study to evaluate the specific risk factors for persistent pain and disability following nerve injury and also to describe the nature of treatment and the relationship between measures of impairment and disability.
In summary, patients with a peripheral nerve injury reported substantial disability and pain. Disability, as measured by the DASH, was predicted by a combination of biomedical and psychosocial factors including pain intensity, brachial plexus nerve injury, pain catastrophizing, older age, work status, time since injury and cold sensitivity. Future investigation regarding efficacious treatments of the factors that are associated with disability and chronic neuropathic pain will hopefully help to improve health related quality of life in patients with traumatic nerve injury.
Chapter 8
General Discussion

8 General Discussion

This general discussion is organized into the following specific sections relating the findings of the three studies of my dissertation to the existing literature on: disability, neuropathic pain, cold sensitivity, psychosocial factors followed by limitations and directions for future research. My dissertation is the first to evaluate the association between biomedical and psychosocial factors and disability in patients with traumatic upper extremity nerve injury. The inclusion of both biomedical and psychosocial factors in the regression models and patients with a wide variety of traumatic upper extremity nerve injuries added to the strength of my dissertation. Studies 2 and 3 (Chapters 6 and 7) found high levels of disability and neuropathic pain in patients with chronic nerve injury. In Study 3 (Chapter 7), disability as measured by the DASH was predicted by biomedical and psychosocial factors including pain intensity, nerve injured, time since injury, pain catastrophizing score, age, work status, cold sensitivity, depression score, workers’ compensation or litigation and gender. This final regression model accounted for 52.7% of the variance.

Many of the previous studies which have evaluated patient outcome following traumatic peripheral nerve injuries reported only measures of physical impairment and even when using these measures, there are large variations in the types of assessments and the standards applied (Bengtson et al., 2008). While reports of motor and sensory recovery provide insight regarding neural regeneration and reinnervation of the motor fibres and/or sensory end organs, these outcome measures do not indicate the functional impact of these impairments.
on the patient. More recent studies have recognized the importance of patient self report of domains such as disability and health related quality of life in the assessment of outcome following nerve injury (Ahmed-Labib et al., 2007; Bailey et al., 2009; Bengtson et al., 2008; Choi et al., 1997; Kitajima et al., 2006). Ahmed-Labib et al. (2007) reported significantly higher DASH and SF-36 physical domain scores in patients who underwent reconstructive surgery for a brachial plexus nerve injury. Kitajama et al. (2006) reported significantly lower health status (SF-36 scores) in patients with a brachial plexus nerve injury who underwent surgery compared to the Japanese normative data. Using a telephone survey with questions adapted from the US General Social Survey, Choi et al. (1997) reported moderately high levels of quality of life and overall life satisfaction in patients following brachial plexus nerve surgery. In a sample of patients with nerve compression or nerve injury, Bailey et al. (2009) reported lower quality of life compared to normative data and overall quality of life was predicted by participation in activity and depressive symptoms. The results of Study 3 (Chapter 7) of the present dissertation are in general agreement with the above literature. In Study 3, high levels of disability were reported by patients following traumatic nerve injury and disability was associated with factors other than physical impairment. Motor and sensory recovery following nerve injury may directly impact physical impairments however assessment of this physical impairment on the patient’s life domains and activities will more accurately reflect the morbidity associated with upper extremity peripheral nerve injury. In Study 3, high levels of disability were reported by patients following traumatic nerve injury and disability was associated with factors beyond physical impairment.
8.1 Disability

Disability is a multidimensional construct and as defined by Nagi (1965), disability represents a mental or physical limitation within a social context. The biopsychosocial model for disability provides a framework for the integration of the biological, personal and social perspectives (Jette, 2006; Verbrugge et al., 1994). The ICF model, which was developed by the WHO, includes the consideration of contextual factors in activity and participation as key elements within the framework (World Health Organization, 2001). In the surgical literature regarding patients following nerve injury, the studies that have evaluated outcome do not frequently include the assessment of the impact of the injury on the patient or other types of patient reported outcome. However, in those studies that have included functional outcomes, the DASH is the most commonly used questionnaire to assess disability in patients with upper extremity injury. In Study 3 (Chapter 7), high levels of disability as measured by the DASH were reported in patients who were at least 6 months following nerve injury. Multivariable regression analysis indicated that the DASH scores were associated with pain intensity, nerve injured, time since injury, pain catastrophizing score, age, work status, cold sensitivity, scores on the depression questionnaire, workers’ compensation or litigation and gender.

The DASH is a self report questionnaire. Based upon physical functioning and symptoms, it was designed to assess disability in patients with upper extremity musculoskeletal disorders (Beaton et al., 2001; Hudak et al., 1996). Good validity, reliability and responsiveness have been reported for the DASH in a variety of upper extremity musculoskeletal pathologies (Beaton et al., 2001; Gummesson et al., 2003; Hudak et al., 1996; SooHoo et al., 2008). To date, studies have not evaluated the internal consistency or validity of the DASH in a sample
of patients with nerve injury. Indeed, there are very few outcome studies of patients with peripheral nerve injury which have reported disability (Ahmed-Labib et al., 2007; Davidson, 2004; Novak et al., 2010; Topel et al., 2009). In Study 3 (Chapter 7), the DASH showed high internal consistency which supports the use of the DASH in patients with traumatic upper extremity nerve injury. In my retrospective chart review (Study 2, Chapter 6) and prospective study of patients with chronic upper extremity nerve injury (Study 3, Chapter 7), high levels of disability as measured by the DASH were reported with mean values of $52 \pm 22$ and $44 \pm 22$, respectively, in a normal distribution. In both studies, higher DASH scores were associated with higher pain intensity, older age and brachial plexus nerve injuries. Other studies have also reported high levels of disability in patients with brachial plexus injuries (Ahmed-Labib et al., 2007; Davidson, 2004; Topel et al., 2009). Using the DASH and the SF-36, Ahmed-Labib et al. (2007) reported poor functional outcome which was correlated with root avulsion injuries and delayed surgical repair. Davidson (2004) evaluated patients with a variety of upper extremity pathologies which included amputation injuries and brachial plexus nerve injuries and reported higher DASH scores in patients with brachial plexus nerve injury. In a study of patients following traumatic arterial injuries, Topel et al. (2009) reported more severe functional deficits in those patients with arterial and concomitant nerve injuries although in this study there were no statistical differences reported. In patients with median or ulnar nerve injuries, Vordemvenne, Langer, Ochman, Raschke & Schult (2007) reported an overall mean DASH score of 22. In patients with radial nerve palsy following humeral fractures, Ekholm et al. (2008) reported relatively low DASH scores and this likely represents the high number of patients who had recovery of radial nerve function. In my dissertation studies (Chapters 6 & 7), high levels of disability in patients with
chronic upper extremity nerve injury were found and consistent with the existing literature (Ahmed-Labib et al., 2007), a significant factor associated with higher disability scores was brachial plexus nerve injury. In my studies, I recruited patients who were at least six months following upper extremity nerve injury and who had sought medical assessment. These patients represent a wide variation of recovery and many patients particularly those with brachial plexus nerve injuries had not attained maximal recovery.

The DASH questionnaire contains two additional modules regarding work and recreation (sports/performing arts). Each separate module contains four questions regarding the impact of the upper extremity pathology on the patient’s work or sports/performing arts (such as athletes and musicians). In accordance with the ICF model (World Health Organization, 2001), these separate subsections stress the importance of activity and participation in the context of disability and provide the opportunity to assess these parameters. Activity is incorporated in the items of the DASH and participation restriction may be captured in the work and sports/performing arts modules. In my studies (Chapters 6 & 7), patients with long standing nerve injury had substantial disability reported in the work and recreation modules of the DASH. This restriction in participation of life roles may impact the relations of the individual in these social roles. Disability as related to activity and participation may be present in patients with long standing traumatic nerve injury and identification of these limitations may be useful in recognizing the negative impact on these patients.
8.2 Neuropathic Pain

My dissertation demonstrated a high prevalence of neuropathic pain in patients who sought medical assessment and/or treatment following an upper extremity nerve injury. In Study 3 (Chapter 7), patients with long standing nerve injury reported high levels of pain intensity and this was significantly associated with disability. As a single predictor in a regression model, pain intensity accounted for 26% of the variance. In Study 2 (Chapter 6), significantly more pain, as assessed by the SF-36 bodily pain domain, was reported in patients with long standing nerve injury compared to the published Canadian normative values. Chronic neuropathic pain is frequently associated with poor outcome independent of the originating etiology (Bennett, 2003; Campbell et al., 2006; Dworkin et al., 2007). Bailey et al. (2009) reported moderate pain in a group of patients with nerve compression or nerve injury and pain was strongly correlated with a lower quality of life and higher scores of depression. In the regression model, participation in activity and depression scores were associated with overall quality of life although pain was not retained in the final regression model. Following traumatic nerve injury, severe neuropathic pain has been reported particularly in patients with brachial plexus nerve injuries (Bertelli et al., 2008a; Choi et al., 1997; Htut et al., 2007; Kato et al., 2006). In a group of patients following brachial plexus reconstructive surgery, Choi et al. (1997) found 75% of patients reported “significant pain”. Htut et al. (2006) found that surgical repair following brachial plexus nerve injury was associated with pain relief and that pain intensity was highest among patients who did not have surgery; consistent with theory of nerve repair. Kato et al. (2006) reported significant positive correlations between pain intensity and nerve root avulsion in patients with brachial plexus nerve injuries. In Studies 2 and 3 (Chapters 6 and 7), nerve root avulsion was not specifically evaluated but patients with
brachial plexus injuries had significantly higher levels of disability compared to more distal nerve injuries. The mean pain intensity was $4.4 \pm 3.2$ and there was no statistically significant difference in pain intensity between brachial plexus and distal nerve injuries. Pain intensity was a significant predictor of disability and it was also strongly correlated with cold sensitivity. Consistent with previous reports in the literature, the results of my dissertation indicate that pain intensity is strongly related to reported disability in patients with traumatic upper extremity nerve injury.

Pain has also been identified as a significant predictor of disability in other musculoskeletal pathologies (Doornberg et al., 2005; Lindenhovius et al., 2008; Souer et al., 2008). In patients following distal radius fracture, Souer et al. (2008) reported that pain was a significant positive predictor of the DASH scores. In patients with intra-articular elbow fractures, the predictors of the DASH included pain and range of motion and as a single predictor in the regression model, pain explained 36% of the variance (Doornberg et al., 2005). In a study following elbow trauma, Lindenhovius et al. (2008) reported that the strongest predictor of the DASH was pain which explained 41% of the variance. These studies highlight the importance of the relationship between pain intensity and higher levels of disability in patients with upper extremity pathologies and the need for comprehensive multidisciplinary pain management approaches.

In Study 1 (Chapter 5) of my dissertation, many nerve surgeons reported that they do not evaluate pain in patients with a nerve injury who were not specifically referred for pain. As well, among patients with nerve injury, few surgeons reported using valid, reliable questionnaires to assess pain, cold sensitivity or disability following nerve injury. Therefore patient symptoms related to pain with respect to frequency, intensity and disability may be
under represented in the reports of outcome following nerve injury. The results of Study 1 (Chapter 5) are consistent with the review of the literature in which assessment of pain is less frequently reported in outcome studies of patients after nerve injury compared to recovery related to sensory and/or motor function. When pain was evaluated, pain intensity was most frequently reported and the inclusion of measures to evaluate the impact of the pain on the patient were rare (Atherton et al., 2008; Bentolila et al., 1999; Berman et al., 1998; Bertelli et al., 2008a; Chen et al., 2006; Emery et al., 1997; Evans et al., 1994; Geertzen et al., 2000; Hazari et al., 2004; Kanpolat et al., 2008; Kim et al., 2001a; Lefaucheur et al., 2004; Mackinnon et al., 1987; Rath et al., 1997; Ricardo, 2005; Saitoh et al., 2003; Samii et al., 2001; Sindou et al., 2005; Sood et al., 1998; Thomas et al., 1994; Waikakul et al., 1999).

To evaluate the unique qualities of neuropathic pain, a modification of the SF-MPQ was introduced by Dworkin et al. (2009) which includes pain descriptors that are specific to neuropathic pain. In the original SF-MPQ each descriptor was ranked on a scale from none, mild, moderate or severe. However, in the modification of the SF-MPQ, each pain descriptor is ranked on a scale from zero to ten. The exploratory factor analysis resulted in a three factor solution and these three sub-scales were identified as continuous pain descriptors (6 items), intermittent pain descriptors (6 items) and neuropathic pain descriptors (4 items). A fourth subscale included the affective descriptors (4 items) from the SF-MPQ. Good validity and reliability for this modification of the SF-MPQ were shown in a group of patients with various chronic pain diagnoses (Dworkin et al., 2009). This modification of the SF-MPQ may assist in the assessment of neuropathic pain following nerve injury, although this questionnaire has not been validated in patients with traumatic nerve injury. Utilization of questionnaires to differentiate neuropathic pain from nociceptive pain may assist in
identifying patients with neuropathic pain that may be more amenable to treatment strategies specific for neuropathic pain.

8.3 Cold Sensitivity

Pain following nerve injury may be constant, intermittent and/or associated with exposure to cold temperatures. The results of Study 3 (Chapter 7) showed substantial cold sensitivity among patients with long standing nerve injury and cold sensitivity was significantly associated with higher disability. Sensitivity to cold is a common sequela of upper extremity trauma that is accompanied by one or more of the following symptoms: pain, sensory disturbance, stiffness and colour changes (Graham et al., 2008; Vaksvik et al., 2009). When cold sensitivity is present, it is often associated with high morbidity and poor outcome (Backman et al., 1993; Campbell et al., 1998; Collins et al., 1996; Craigen et al., 1999; Dabernig et al., 2006; Graham et al., 2008; Irwin et al., 1997; McCabe et al., 1991; Nancarrow et al., 1996; Nylander et al., 1987; Povlsen et al., 1995a; Povlsen et al., 1995b; Ruijs et al., 2006; Ruijs et al., 2007; Stokvis et al., 2009; Vaksvik et al., 2009). As seen in Study 3 (Chapter 7), cold sensitivity may contribute to higher levels of disability which is consistent with the poor outcome previously reported in the literature. Interventions to minimize cold sensitivity in the patients with ongoing symptoms may positively impact outcome and decrease disability following nerve injury.

In the surgical literature, patient self report questionnaires are more frequently used to assess cold sensitivity compared to objective measures of vascular status. The CISS and CSS are the two most frequently used questionnaires to assess cold sensitivity (Irwin et al., 1997;
McCabe et al., 1991). These types of questionnaires provide the opportunity to assess the severity of cold sensitivity and the impact of the symptoms with cold exposure on the patient and their activities. In Study 3 (Chapter 7), the CISS questionnaire showed good internal consistency (standardized item alpha = .95) in patients with nerve injuries at various levels in the upper extremity. Using the criteria established by Ruijs et al. (2006), in my study (Chapter 7), there were 81 patients (51%) who were classified as having abnormal cold sensitivity. The mean CISS was 33 ± 26 which is consistent with reports in the literature of patients with upper extremity nerve injury (Carlsson et al., 2008; Irwin et al., 1997; Ruijs et al., 2007). In the study by Dabernig et al. (2006), 87% of patients reported cold intolerance following digit replantation, however, the mean DASH score was relatively low at 11/100. This is in contrast to the high mean DASH score (44 ± 22) found in my study (Study 3, Chapter 7) in patients with nerve injury. The lower scores reported by Dabernig et al. (2006) may reflect the capacity of patients to better adapt following digital replantation compared to traumatic upper extremity nerve injuries or a weakness of the DASH in capturing subtle disabilities following digit replantation. Meyer-Rosberg et al. (2001b) reported that cold evoked pain was ranked as the most intense pain in patients with neuropathic pain. Campbell and Kay (1998) found that 73% of patients with traumatic hand injuries reported cold related symptoms and most complaints were pain related. The unresolved continuing symptoms of cold sensitivity with exposure to cold temperatures have been reported in many patients following traumatic upper extremity symptoms. Graham and Schofield (2008) reported cold intolerance in 90% of patients with traumatic injuries and less than 10% of these patients reported an improvement in their symptoms over time. Nancarrow et al. (1996) reported 69% of patients with hand injuries had continuing symptoms of cold intolerance and 97%
remained with symptoms five years following injury. Collins et al. (1996) reported 76% of patients following nerve injury reported continued cold intolerance more than five years following trauma. Cold sensitivity remains a cause of morbidity following trauma and nerve injury and this is particularly problematic for patients who reside and/or work in cold environments. The high rate of cold sensitivity found in my study (Chapter 7) is consistent with the reports in the literature of high levels of cold sensitivity following traumatic injuries. There was a positive correlation between cold sensitivity scores and time since injury which is consistent with the literature reports of unresolved symptoms following traumatic injury. Cold sensitivity is related to higher levels of pain intensity and in my study (Chapter 7) was associated with high levels of disability in patients with long standing nerve injury. Strategies to treat this cold sensitivity may help to minimize the morbidity and disability associated with upper extremity traumatic nerve injury.

8.4 Psychosocial Factors

In my study (Study 3, Chapter 7), high levels of anxiety, depression and pain catastrophizing symptoms were reported in patients with traumatic upper extremity nerve injuries. In the final regression model, pain catastrophizing and depression scores were associated with disability, as measured by the DASH. Post-traumatic stress and anxiety related to the injury was assessed using the PCL-C but this variable was not retained in the final regression model. There is wide variability in patient outcome which is reported following upper extremity nerve injury. Many patients sustain what appears to be a similar injury and outcome may vary in terms of physical impairment, pain and disability. The mechanisms by which this occurs are unclear and it may be related to the complex relationships among
multiple biomedical and psychosocial factors. Review of the surgical literature has revealed
an emphasis on the biomedical factors associated with outcome following nerve injury
compared to other potentially important variables, such as personal or psychosocial factors.
However, more recently the importance of the influence of psychosocial factors on outcome
in patients with upper extremity pathologies has been more reported (Bailey et al., 2009;
Lozano Calderon et al., 2008a; Lozano Calderon et al., 2008b; Niekel et al., 2009; Ring et al.,
2006; Souer et al., 2008; Vranceanu, Barsky, & Ring, 2009). My dissertation is the first to
show the association between disability and psychosocial factors, particularly symptoms of
depression, pain catastrophizing, in a sample of patients with long standing upper extremity
nerve injury.

8.4.1 Pain Catastrophizing
Pain catastrophizing involves exaggerated negative thinking regarding the experience of pain
(Sullivan et al., 1995; Sullivan et al., 2001; Sullivan et al., 2005). Individuals who
catastrophize feel overwhelmed by pain, feel helpless in the face of pain and ruminate about
the pain. The PCS was designed to assess the degree of pain catastrophizing and comprises
three subscales (rumination, magnification, helplessness) (Sullivan et al., 1995). In my study
of patients with long standing upper extremity nerve injury (Chapter 7), high internal
consistency was found with the PCS. Strong correlations were found between pain intensity
and the PCS total score and the PCS subscales; rumination, magnification and helplessness.
Pain catastrophizing was a significant predictor of disability as measured by the DASH
scores.
In patients following traumatic injury who exhibit high levels of pain catastrophizing, high levels of disability have also been reported. In a group of patients with chronic pain resulting from different etiologies, Severeijns et al. (2001) reported higher levels of pain intensity, disability and psychological distress in patients who catastrophize. Strong associations among these factors were reported but no conclusions were presented regarding the direction of causality. Pain catastrophizing has also been reported in patients with a variety of hand diagnoses. In a group of patients with different hand pathologies, Niekel et al. (2009) evaluated the relationship between DASH scores and psychosocial measures (symptoms of depression, pain catastrophizing and pain anxiety) and reported a weak correlation between DASH scores and pain catastrophizing. In patients who were attending a pain treatment program, pain catastrophizing was significantly associated with depression scores but not disability as assessed by the Roland Scale of disability (Turner, Jensen, & Romano, 2000).

Karels et al. (2007) evaluated patients in a physical therapy practice with complaints of shoulder and neck pain and reported that persistent complaints were significantly associated with pain catastrophizing.

The studies which have reported relationships between pain catastrophizing and pain intensity and disability in patients with upper extremity pathologies have been cross-sectional study designs and/or the evaluation of catastrophizing has been assessed post-injury (Karels et al., 2007; Niekel et al., 2009; Severeijns et al., 2001; Turner et al., 2000). As such, it is not possible to establish causality to pain catastrophizing. In a longitudinal study, Sullivan et al. (2002) evaluated catastrophizing as a predictor of activity intolerance in a group of uninjured individuals. After controlling for pain and negative mood, pain catastrophizing was found to be a significant predictor of reduced activity. However as outlined by the authors, young
healthy volunteers were included in this study and this may introduce a selection bias. The relationships may differ in patients with pain related pathologies and higher pain intensities and warrants further investigation.

8.4.2 Symptoms of Depression

In my study (Chapter 7) of patients with chronic upper extremity nerve injury, depression scores were moderately correlated with the DASH scores and the HADS score was a factor in the final regression model. Validity, reliability and internal consistency have been presented for the English version of the HADS, in addition to several language translations (Bjelland et al., 2002; Golden, Conroy, & O'Dwyer, 2007; Herrmann, 1997; Lisspers et al., 1997; Mykletun et al., 2001; Pallant et al., 2005; Quintana et al., 2003; Spinhoven et al., 1997; Zigmond et al., 1983). Previous studies which evaluated the internal consistency of the HADS reported Cronbach’s alpha coefficients which ranged from .68 to .93 for the anxiety subscale and from .67 to .90 for the depression subscale (Bjelland et al., 2002). The internal consistency of the HADS has not been previously assessed in a sample of patients with nerve injury. In Study 3 (Chapter 7), good internal consistency was found in the anxiety and depression subscales in patients with traumatic upper extremity nerve injury supporting the use of this measure in these patients.

The relationships between psychosocial factors including depression have been reported in patients with various hand pathologies, such as trapeziometacarpal arthrosis and after carpal tunnel release (Bailey et al., 2009; Lozano Calderon et al., 2008a; Lozano Calderon et al., 2008b; Nickel et al., 2009; Ring et al., 2006). In patients following carpal tunnel release,
Lozano Calderon et al. (2008a) reported a significant negative correlation between the DASH scores and patient satisfaction, which indicated that higher levels of disability were associated with higher levels of dissatisfaction. This study also reported that the symptoms of depression and pain catastrophizing were predictors of disability, as measured by the DASH. In a group of patients with various hand pathologies, Nickel et al. (2009) reported a moderate positive correlation between the DASH scores and symptoms of depression and anxiety; in addition pain catastrophizing and depression symptoms were predictors of the DASH. Similarly in patients with trapeziometacarpal arthrosis, symptoms of depression and pain catastrophizing were associated with disability as measured by the DASH (Lozano Calderon et al., 2008b). In patients with a variety of hand pathologies, Ring et al. (2006) reported a moderate correlation between the DASH scores and symptoms of depression. Similar to other studies, depression was reported to be a significant predictor of the DASH. Bailey et al. (2009) reported high levels of depressive symptoms (as measured by the Center for Epidemiological Studies Depression Scale) and 39% of these patients had scores which may be indicative of clinical depression. The final regression model explained 61% of the variance and quality of life was predicted by depression scores and participation in activity.

In Study 3 (Chapter 7), pain catastrophizing and pain intensity were significantly associated with disability in patients who were at least six months following nerve injury. The reasons for this relationship cannot be determined with this cross sectional study design. Previous studies have concluded that those patients who catastrophize report higher levels of pain intensity. However, it may be that patients with high levels of pain intensity catastrophize because they have intense pain rather than pain catastrophizing resulting in high pain intensity. These complex relationships between pain intensity, pain catastrophizing,
depression and disability warrant further investigation to assist in appropriate assessment and treatment of these patients following traumatic nerve injury.

8.4.3 Post-traumatic Stress Symptoms

Patients with chronic nerve injury resulting from trauma do show evidence of post-traumatic stress. In Study 3 (Chapter 7), there were moderate levels of post-traumatic stress symptoms (mean PCL-C score of 33 ± 14) in patients who were at least 6 months following traumatic upper extremity nerve injury. There was a moderate correlation found between pain intensity and the PCL-C score and the DASH and the PCL-C score. The PCL-C score was not retained in the final regression model. Other studies of surgical patients and trauma victims have reported higher levels of post-traumatic stress symptoms compared to our findings in patients with traumatic nerve injury (Blanchard et al., 1996; Pagé et al., 2009).

In a meta-analysis of the risk factors associated with post-traumatic stress, Brewin et al. (2000) highlight the differences between military and civilian trauma and the importance of the relationship between post-traumatic stress symptoms and the responses following trauma. Post-traumatic stress symptoms have been associated with increased difficulties with physical and mental health (Asmundson et al., 2002). These symptoms have been related to three clusters; 1) reexperiencing the event, 2) avoidance and emotional numbing, 3) hyperarousal. An increased reporting of pain has also been associated with post-traumatic stress symptoms. Although the level of post-traumatic stress symptoms following hand trauma injury was relatively low in a study by Opsteegh et al. (2010), the authors found
higher levels of pain in patients with more symptoms of post-traumatic stress, as assessed by the Self-Rating Scale PTSD.

With evidence of post-traumatic stress in patients with chronic nerve injury, more in-depth investigation in the relationships of these factors and the role of these symptoms in disability and pain is necessary. High levels of chronic pain and post-traumatic stress symptoms in patients following traumatic nerve injury may suggest an overlap of symptoms and as such certain patients may be more likely to develop these disorders as has been documented following other traumatic events (Asmundson et al., 2002; Asmundson et al., 2008; Sharp & Harvey, 2001). Sharp and Harvey (2001) hypothesized that post-traumatic stress, pain, distress and disability may affect and be affected by attentional biases, anxiety sensitivity, trauma reminders, symptoms of depression, reduced activity levels, anxiety and pain perception and limitation of adaptation. The level of post-traumatic stress symptoms found in patients following nerve injury was not as high as those reported with other non-military traumatic events. However, these symptoms were higher than reported in the general population and merit further investigation, particularly regarding the influence that these symptoms may have on other factors such as reported pain intensity, symptoms of depression, participation in activity and disability. Also the interrelationships between pain catastrophizing, depression and post-traumatic stress may contribute to prolonged disability.

8.5 Strengths & Limitations

There are several strengths and limitations to the present series of studies. My dissertation is the first to examine the biomedical and psychosocial factors associated with pain and
disability after peripheral nerve injury. This dissertation includes the opinions of peripheral nerve surgeons regarding pain assessment and outlines the limitations in the assessment and reporting of neuropathic pain including the associated factors in medical practice and in the literature. In Studies 2 and 3 (Chapters 6 and 7), the levels of pain and disability were evaluated in patients following traumatic upper extremity nerve injury and the factors associated with disability were investigated. With evidence of high levels of disability and pain in patients with long standing nerve injury, the inclusion of biomedical and psychosocial factors in the regression models and patients with a wide variety of traumatic upper extremity nerve injuries added to the strength of Study 3 (Chapter 7).

Five limitations associated with the studies in the present dissertation are outlined; unique patient sample, inclusion of nerve injuries six months after injury, cross sectional study design, possibility of low statistical power for detecting certain relationships and low response rate to the surgeon survey. These limitations are described in the following paragraphs.

In Studies 2 and 3 (Chapters 6 and 7), patients who were at least six months following nerve injury and who had sought medical assessment and/or treatment were included. These patients who continue to seek medical or surgical assessment and treatment may represent unique characteristics that are coincident with ongoing need for care, either physical or psychosocial, and these factors may influence the relationships that were observed. Generalization of these results to all patients with nerve injury may be limited. Many patients following nerve injury have complete recovery with no residual morbidity. However, as shown in our studies and in other outcome studies, there are patients following traumatic injury who remain with physical impairment, pain and disability. It is these patients who
often present with treatment challenges, overwhelm the available resources and have persistent, diminished health related quality of life.

In Studies 2 and 3 (Chapters 6 and 7), patients who were at least six months following traumatic upper extremity nerve injury were recruited and these patients reported high levels of disability and pain. The primary aim of these studies was to evaluate the factors associated with pain and disability after nerve injury and therefore patients with a variety of levels of nerve injury and time since injury were included in these studies. However, inclusion of patients with nerve injuries who have not achieved full recovery may have biased the results in the direction of finding more pain and greater disability in these patients.

In Studies 2 and 3 (Chapters 6 and 7), strong relationships among the biomedical and psychosocial factors and disability were found in patients with chronic nerve injury. A cross sectional study design was utilized and one cannot conclude the direction of the relationships or causality. Based upon the selection criteria in the univariate analyses, the power associated with the sample size and the original hypotheses, a limited number of variables were included in the multivariable regression analyses. There may be other variables which are associated with disability and pain following peripheral nerve injury which were not included in these studies, may be important in the context of disability and merit investigation in future studies.

In Studies 2 and 3 (Chapters 6 and 7), the main aim of these studies was to evaluate the factors associated with the DASH and this was investigated using a multivariable regression model. Sample sizes of 84 in Study 2 (Chapter 6) and 158 in Study 3 (Chapter 7) were sufficient to support the inclusion of all of the factors which were included in the preliminary
regression models. The univariate statistical analyses to compare the DASH scores on the dependent variables were performed, in part, to select the factors to be included in the regression model and may not have had sufficient power to detect a significant difference in all cases.

In Study 1 (Chapter 5), 48% of the invited surgeons responded to the survey and this introduces the possibility of response bias. However, peripheral nerve surgeons represent a relatively homogeneous group regarding knowledge and training and therefore may share similar attitudes and opinions towards assessment of pain. Although these differences in opinions between respondents and non-respondents may be small, the relatively low response rate does limit the generalizations regarding the practices and beliefs of all surgeons.

8.6 Future Directions

High levels of disability and chronic neuropathic pain were found in patients with longstanding nerve injury. Disability as measured by the DASH was predicted by multiple biomedical and psychosocial factors emphasizing the importance of consideration of these factors which are associated with patient outcome. In Study 3 (Chapter 7), the final regression model accounted for 52.7% of the variance and therefore 47.3% of the variance remains unexplained. While physical impairment associated with motor and/or sensory impairment may account for some of this variance, other biomedical and psychosocial factors may be associated with disability. Other studies which evaluated the psychosocial factors after trauma have documented associations between pain catastrophizing, depression, post-
traumatic stress, pain intensity and disability. The interaction of the factors may also be important in patients with nerve injury and merits future investigation.

The influence of pain in outcome and disability has been documented and when assessed by peripheral nerve surgeons, pain intensity is most frequently reported. This dissertation emphasizes the importance of the impact of injury and resultant physical impairments on the patient and these constructs are not captured by the assessment of pain intensity. Cold sensitivity was frequently reported and it was a significant predictor of disability. Longitudinal studies to evaluate the treatment strategies to address the morbidity associated with cold sensitivity would be very beneficial to patients following traumatic nerve injury, particularly for those who reside or work in cold climates.

Symptoms of depression and pain catastrophizing were associated with greater disability. The mechanisms by which these psychosocial factors interact and the inter-relationships between pain catastrophizing, depression and post-traumatic stress in patients following traumatic nerve injury require further investigation. A longitudinal, prospective study of the risk factors for disability would permit the identification of which factors occur first and then which factors may be modified with appropriate treatment. Following the identification of the specific psychosocial factors which are most important, investigations regarding efficacious treatments could be implemented to determine the best methods and approaches to treatment.

In Studies 2 and 3 (Chapters 6 and 7), patients with chronic upper extremity peripheral nerve injury reported high levels of disability and pain. Disability, which was measured by the DASH, was predicted by biomedical and psychosocial factors which included brachial plexus
nerve injury, older age, pain, work status, time since injury, cold sensitivity and pain catastrophizing. Disability is a multidimensional construct. Previous studies have identified numerous biomedical and psychosocial factors which are associated with disability following traumatic injury and as such suggests that a multi-facet treatment approach is required. This dissertation provides evidence of the relationships between the biomedical and psychosocial factors which are associated with pain and disability in patients with traumatic upper extremity nerve injury. Future investigation regarding efficacious treatments of these factors that are associated with disability and chronic neuropathic pain will assist to improve health related quality of life in patients with traumatic nerve injury. A comprehensive longitudinal study to evaluate the specific risk factors for persistent pain and disability following nerve injury will help to provide further data to assist these patients achieve optimal outcome.

Morbidity resulting from long term nerve injury may have a clinically significant impact that is associated with modifiable factors which have not been previously addressed. My dissertation has contributed to a new understanding of outcome following nerve injury and might lead to new interventions to minimize disability and improve health related quality of life in these patients.
References


Appendix A

Notification of REB Initial Approval

Date: January 23, 2008

To: Dr. Dimitrios Anastakis
TWH 4-140

Re: 07-0730-AE
Evaluation Of Pain Measures Used By Upper Extremity Surgeons

REB Review Type: Expedited
REB Initial Approval Date: January 22, 2008
REB Expiry Date: January 22, 2009

Documents Approved:
- Protocol (received October 31, 2007)
- Questionnaire v.1 (dated October 31, 2007)
- Introductory Letter v.1 (dated January 21, 2008)
- Follow-up Letter v.1 (dated January 21, 2008)
- Follow-up Email v.1 (dated January 21, 2008)

The above named study has been reviewed and approved by the University Health Network Research Ethics Board. If, during the course of the research, there are any serious adverse events, confidentiality concerns, changes in the approved project, or any new information that must be considered with respect to the project, these should be brought to the immediate attention of the REB. In the event of a privacy breach, you are responsible for reporting the breach to the UHN REB and the UHN Corporate Privacy Office (in accordance with Ontario health privacy legislation – Personal Health Information Protection Act, 2004). Additionally, the UHN REB requires reports of inappropriate/unauthorized use of the information.

If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval. The REB must be notified of the completion or termination of this study and a final report provided. As the Principal Investigator, you are responsible for the ethical conduct of this study.


Sincerely,

Ronald Hesler, Ph.D.
Chair, University Health Network Research Ethics Board

There's always an answer. We'll find it.
Notification of REB Approval for Access to Retrospective Data for Research Purposes

Date: April 20, 2007

To: Dr. Dimitrios Anastakis
4-140, TWH

Re: 07-0206-AE
Outcome Following Peripheral Nerve Injury (Chart Review)

REB Review Type: Expedited
REB Initial Approval Date: April 14, 2007
REB Expiry Date: April 14, 2008

We wish to remind you that access to personal health records for research purposes without patient consent is a privilege granted by the REB. Please be sure to adhere at all times to the UHN Policy on Information and Data Security as noted in the Confidentiality Agreement signed as part of this submission.

If, during the course of the research, there are any confidentiality concerns, changes in the approved project, or any new information that must be considered with respect to the project, these should be brought to the immediate attention of the REB. In the event of a privacy breach, you are responsible for reporting the breach to the UHN REB and the UHN Corporate Privacy Office (in accordance with Ontario health privacy legislation – Personal Health Information Protection Act, 2004). Additionally, the UHN REB requires reports of inappropriate/unauthorized use of the information.

Please note that approval for this study will expire on this date unless the UHN REB is otherwise notified.


Sincerely,

Ronald Heslegrave, Ph.D.
Chair, University Health Network Research Ethics Board

RH/tt
Notification of REB Initial Approval

Date: July 18, 2007

To: Dr. Dimitrios Anastakis
TWH 4-140

Re: 07-0384-AE
Biomedical and Psychosocial Factors Associated With Pain and Disability After Peripheral Nerve Injury

REB Review Type: Expedited
REB Initial Approval Date: 17 July, 2007
REB Expiry Date: 17 July, 2008

Documents Approved:
Protocol (received June 5, 2007)
Informed Consent Form Version #3 (dated July 12, 2007)
Study Questionnaires (received June 5, 2007)

The above named study has been reviewed and approved by the University Health Network Research Ethics Board. If, during the course of the research, there are any serious adverse events, any confidentiality concerns, changes in the approved protocol or consent form, or any new information that must be considered with respect to the project, these should be brought to the immediate attention of the REB. In the event of a privacy breach, you are responsible for reporting the breach to the UHN REB and the UHN Corporate Privacy Office (in accordance with Ontario health privacy legislation – Personal Health Information Protection Act, 2004). Additionally, the UHN REB requires reports of inappropriate/unauthorized use of the information.

If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval. The REB must be notified of the completion or termination of this study and a final report provided. As the Principal Investigator, you are responsible for the ethical conduct of this study.


Sincerely,

Ronald Hesegave, Ph.D.
Chair, University Health Network Research Ethics Board

Rh/rp
Notification of REB Continued Approval

Date: July 7th, 2008
To: Dr. Dimitri Anastakis
    EW-2, TWH

Re: 07-0384-AE
    Biomedical and Psychosocial Factors Associated With Pain and Disability After Peripheral Nerve Injury

REB Review Type: Expedited
REB Initial Approval Date: July 17th, 2007
REB Expiry Date: July 17th, 2009

Consent Form(s) Currently Approved for Use:

Consent Form
Version date: July 12th, 2007 Number: 3

The above-named study has received continued approval from the University Health Network Research Ethics Board until the expiry date noted above. If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval. The REB must also be notified of the completion or termination of this study and a final report provided.

If, during the course of the research, there are any serious adverse events, confidentiality concerns, changes in the approved project, or any new information that must be considered with respect to the project, these should be brought to the immediate attention of the REB. In the event of a privacy breach, you are responsible for reporting the breach to the UHN REB and the UHN Corporate Privacy Office (in accordance with Ontario health privacy legislation Personal Health Information Protection Act, 2004). Additionally, the UHN REB requires reports of inappropriate/unauthorized use of the information. As the Principal Investigator, you are responsible for the ethical conduct of this study.

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement, ICH/GCP Guidelines, the Ontario Personal Health Information Protection Act (2004), and Part C, Division 5 of the Food and Drug Regulations of Health Canada.

Sincerely,

Alex Kerr
Research Ethics Coordinator

For: Ronald Heslegrave, Ph.D.
Chair, University Health Network Research Ethics Board
University of Toronto
Office of the Vice-President, Research
Office of Research Ethics

PROTOCOL REFERENCE #22070
February 26, 2008

Dr. Joel Katz
Anesthesia
200 Elizabeth St.
Toronto, ON M5G 2C4

Ms. Christina Novak
Institute of Medical Science
200 Elizabeth St.
Toronto, ON M5G 2C4

Dear Dr. Katz and Ms. Novak:

Re: Your research protocol entitled “Evaluation of Pain Measures Used by Hand Surgeons”

<table>
<thead>
<tr>
<th>ETHICS APPROVAL</th>
<th>Original Approval Date: February 26, 2008</th>
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</thead>
<tbody>
<tr>
<td>Expiry Date:</td>
<td>February 25, 2009</td>
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We are writing to advise you that a member of the Health Sciences Research Ethics Board has granted approval to the above-named research study, for a period of one year, under the REB’s expedited review process. Ongoing projects must be renewed prior to the expiry date.

The following consent documents (received January 30, 2008) have been approved for use in this study: Initial introductory letter, Follow-up email to non-respondents with an active email address and Follow-up letter to non-respondents with no email address.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events should be reported to the Office of Research Ethics as soon as possible.

Best wishes for the successful completion of your project.

Yours sincerely,

Jenny Pelo
Research Ethics Coordinator
Memo

To: Professor Joel Katz et al, Department of Psychology
    jkatz@yorku.ca

From: Alison M. Collins-Mrakas, Manager, Research Ethics

Date: Monday February 25th, 2008

Re: Ethics Approval

Evaluation of Pain Measures Used by Upper Extremity Surgeons

I am writing to inform you that the Human Participants Review Sub-Committee has reviewed and approved the above project.

Should you have any questions, please feel free to contact me at: 416-736-5914 or via email at: acollins@yorku.ca.

Yours sincerely,

Alison M. Collins-Mrakas M.Sc., LLM
Manager, Office of Research Ethics
Memo

To: Professor Joel Katz et al, Department of Psychology
   jkatz@yorku.ca

From: Alison M. Collins-Mrakas, Manager, Research Ethics

Date: Monday February 25th, 2008

Re: Ethics Approval
   
   Biomedical and Psychosocial Factors Associated with Pain and Disability
   After Peripheral Nerve Injury

I am writing to inform you that the Human Participants Review Sub-Committee has
reviewed and approved the above project.

Should you have any questions, please feel free to contact me at: 416-736-5914 or
via email at: acollins@yorku.ca.

Yours sincerely,

Alison M. Collins-Mrakas M.Sc., LLM
Manager, Office of Research Ethics
January 25, 2008

Susan E. Mackinnon
Plastic & Reconstructive Surgery
Campus Box 8238

R.E.: Project Title: "Biomedical and Psychosocial Factors Associated with Pain and Disability After Peripheral Nerve Injury"
HRPO Number: B08-13
Funding Source: Department Funded

The above-referenced project was reviewed and approved by the Washington University Human Research Protection Office (HRPO) according to the terms and conditions described below.

Project Approval Date: January 22, 2008
Project Expiration Date: January 21, 2009
Type of Review: New (Expedited)
Expedited Category: 7

HRPO complies with federal regulations contained in 45 CFR 46, which allows an IRB to use expedited review for research which presents no more than minimal risk to human participants and involves one or more of the categories approved for expedited review. All actions and recommendations approved under expedited review are reported to a convened IRB as required by federal regulations.

You are reminded that by receiving approval to conduct this research, you are expected to comply with the HRPO Project Director’s Statement of Responsibility (located at http://hrpo.wustl.edu/).

Changes in research procedures or the consent document must be approved prior to implementation of the changes. Please allow 4 weeks review of any changes.

According to federal regulations, this project requires continuing review by the IRB. Prior to the project expiration date indicated above, you are required to complete either a Continuation Request or Final Report. Forms are on the HRPO web site URL provided above. Please include the HRPO number and project title in all future correspondence.

If you have any questions, please contact the HRPO at 633-7400 or eIRB@wustl.edu.

Sincerely,

[Signatures]

Philip A. Ludbrook, M.D.
Associate Dean & Executive Chair, HRPO

Sandra S. Hale, Ph.D.
Chair, Behavioral Minimal Risk Subcommittee
Appendix B

University Health Network
Toronto General Hospital Toronto Western Hospital Princess Margaret Hospital

Informed Consent Form for Participation in a Research Study

TITLE: Biomedical and Psychosocial Factors Associated with Pain and Disability After Peripheral Nerve Injury

INVESTIGATOR: Dr. D. Anastakis (Tel: 416-603-5800, ext 5790)

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing this document.

Background
Injury to a nerve may affect movement, feeling to the skin or may cause pain. Outcome following a nerve injury and repair may be related to many factors including muscle function, sensation, pain and/or cold sensitivity and psychosocial factors. How important these factors are has not been assessed.

Purpose
You have been asked to participate in a study because you have had an injury to a nerve in your hand or arm. This study is designed to investigate the physical and psychosocial factors that are related to outcome following nerve injury and repair. This information will help other health care professionals to understand the relationship between pain, nerve injury and outcome in patients following nerve injury.

Procedures
The study will involve one visit to complete a series of questionnaires. You will not be asked to come in for any other visits or undergo any testing. However, if you agree to join the study, we also will collect some information about your diagnosis, type and date of your initial surgery, if you have had other surgeries for this nerve injury by examining your hospital chart. This information will allow us to compare how different types of nerve injuries might be associated with different responses.

Risks
There are no known risks to completing the questionnaires.
Benefits
You will not receive any medical benefit from your participation in this study. Information learned from this study may benefit other patients in the future with your injury.

Confidentiality
All information obtained during the study will be held in strict confidence. You will be identified with a study number only. No names or identifying information will be used in any publication or presentations. No information identifying you will be transferred outside the investigators in this study or this hospital.
Members of the University Health Network Research Ethics Board may look at your medical record or the study records to see that the study has been conducted properly and according to applicable laws and guidelines.

Participation
Your participation in this study is voluntary. You can choose not to participate or you may withdraw at any time without affecting your medical care.

Questions
If you have any general questions about the study, please call the doctor in charge of this study, Dr Dimitri Anastakis at (416-603-5800, ext 5790).

If you have any questions about your rights as a research participant, please call Dr. R. Heslegrave, Chair of the University Health Network Research Ethics Board at (416) 340-4557. This person is not involved with the research project in any way and calling him will not affect your participation in the study.

Consent
I have had the opportunity to discuss this study and my questions have been answered to my satisfaction. I consent to take part in the study with the understanding I may withdraw at any time without affecting my medical care. I have received a signed copy of this consent form. I voluntarily consent to participate in this study.

Study Participant’s Name (Please Print) Study Participant’s Signature Date

I confirm that I have explained the nature and purpose of the study to the subject named above. I have answered all questions.

Name of Person Signature Date

 Obtaining Consent
INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Participant 

HRPO Approval Number  

Principal Investigator Mackinnon Susan MD  

Pl's Phone Number (314) 362-4586  

Title of Project: Biomedical and Psychosocial Factors Associated with Pain and Disability After Peripheral Nerve Injury  

You are invited to take part in a research study by Dr. Mackinnon and/or colleagues.

Please ask for an explanation of any words you do not understand.

You may want to talk about the study with your family or friends before you decide to be in it.

1. **Why is this study being done?**
   Injury to a nerve may affect movement, feeling to the skin or may cause pain. Outcome following a nerve injury and repair may be related to many factors including muscle function, sensation, pain and/or cold sensitivity and psychosocial factors. How important these factors are has not been assessed.

2. **What am I being asked to do?**
   You have been asked to participate in a study because you have had an injury to a nerve in your hand or arm. This study is designed to look at the factors that are related to outcome following nerve injury and repair. This information will help other health care professionals to understand the relationship between pain, nerve injury and outcome in patients following nerve injury.

   **How long will I be in the study?**
   You will be in the study one time for about 30 minutes to complete the questionnaires. The questions will be about your nerve injury, social life, work, sex life, home life, and other things. Your answers to the questions will be kept private.

3. **What are the Costs?**
   There are no additional costs to participate in this study.

4. **What are the Risks?**
   There are no known risks to completing the questionnaires. You may refuse to answer any question for any reason. The information you give us will be given a code number. A master list linking the code number and your identity will be kept separate from the research data. Only the PI and people helping her will be able to see the list. We will protect your information, but there is a chance somebody might see it.

   **What happens if I am injured because I took part in this study?**
   Washington University investigators and their staffs will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the Investigator and/or the Human Research Protection Office Chairperson from Item 8. Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University.
5. **Are there Benefits to taking part in the study?**
   You will not receive any medical benefit from your participation in this study. Information learned from this study may benefit others in the future with your injury.

6. **What other Options are there?** Taking part in this research study is voluntary. You may choose not to take part in this research study or you may withdraw your consent at any time. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled. Other than not taking part in the research, you may choose not to complete the questionnaires.

7. **What about Confidentiality?**
   Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study explained in this consent form.

   In addition to health information that may be created by the study, the research team may access the following sources of your health information to conduct the study: your medical chart.

   **The research team will follow state and federal laws and may share your information with:**
   - Government representatives, to complete federal or state responsibilities
   - Hospital or University representatives, to complete Hospital or University responsibilities
   - Your primary care physician if a medical condition that needs urgent attention is discovered

   Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

   The research team will only use and share your information as talked about in this form. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer, at 1-866-747-4975.

   **If you decide not to sign this form, it will not affect**
   - your treatment or the care given by your health provider.
   - your insurance payment or enrollment in any health plans.
   - any benefits to which you are entitled.

   However, it will not be possible for you to take part in the study.

   **If you sign this form:**
   - You authorize the use of your PHI for this research
   - Your signature and this form will not expire as long as you wish to participate.
   - You may later change your mind and not let the research team use or share your information (you may revoke your authorization).

   To revoke your authorization, complete the withdrawal letter, found in the HIPAA section of the Human Research Protection Office website at http://hrpo.wustl.edu, or you may request that the Investigator send you a copy of the letter.

   - **If you revoke your authorization:**
     - The research team may only use and share information already collected for the study.
     - Your information may still be used and shared if necessary for safety reasons.
8. Who do I call if I have Questions or Problems?
If you have any questions, concerns or complaints about the study, or feel that you are injured because of the study call Dr Mackinnon at (314) 362-4556. If you wish to talk to someone else, or have questions or concerns about your rights as a research subject, call Dr. Philip Ludbrook, Chairman of the University’s Human Research Protection Office, at (314) 632-7400 or (800) 438-0445.

9. The Principal Investigator (PI) may withdraw you from the study without your consent if considered appropriate. For safety, it may be in your best interest to allow follow-up outside the study. The PI will share any new information that could change how you feel about continuing in the study.

10. Being in a research study does not take the place of routine physical exams or visits to your own doctor and should not be relied on to diagnose or treat medical problems.

I have read this consent form and have been given the chance to ask questions. I will also be given a signed copy of this consent form for my records. I give my permission to participate in the research described above, titled: Biomedical and Psychosocial Factors Associated with Pain and Disability After Peripheral Nerve Injury.

Participant’s Signature ___________________________ Date __________
Signature of person providing Informed Consent ___________________________ Date __________

Thank you for your important contribution to research studies that are trying to improve medical care.

This form is valid only if the Human Research Protection Office’s current stamp of approval is shown below.

Federal Regulations permit no grace period.

Washington University
Hillside Human Studies Committee
APPROVED ____________
APPROVAL EXPIRES ____________

Form 2 Page 3 of 3
## Appendix C

Chapter 6 Study 2 - Coefficients for preliminary model and each model with manual backwards elimination (Dependent Variable: DASH)

<table>
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<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>t-value</th>
<th>Level of Significance</th>
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* WC/lit = Workers’ compensation or litigation involvement
Chapter 6 Study 2 - Summary for 3 step forward entry regression models using significant predictors

(Dependent Variable: DASH)

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Model 1 Predictors: (Constant), Bodily pain
Model 2 Predictors: (Constant), Bodily pain, Age
Model 3 Predictors: (Constant), Bodily pain, Age, Nerve injured
Copyright Acknowledgements

The following manuscripts, which are located in Chapters 2, 5, 6 and 7 of this dissertation, have been published or are under peer review and permission to reproduce the published manuscripts was granted for use in this dissertation:


