

Pain Catastrophizing and Mindfulness: Exploring Mechanisms of Change Associated with Participation in a Mindfulness-Based Stress Reduction Program in Diabetic Peripheral Neuropathy Patients

Amanda Lauren Simpson Carson

A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS OF ARTS

Graduate Program in Psychology York University Toronto, Ontario

August 2017

© Amanda Carson, 2017

Abstract

Diabetic peripheral neuropathy (DPN) affects up to half of those with type 2 diabetes mellitus. Chronic neuropathic pain, a common symptom of DPN, remains difficult to treat pharmacologically. Mindfulness-based stress reduction (MBSR) has demonstrated benefits in chronic pain populations and a recently completed randomized controlled trial demonstrated improved function among patients with DPN who completed the program. The present study used archival data from this recently completed trial, with 62 participants (Mean age = 59.7 years, SD = 8.8). It was predicted that improved function following MBSR training would be explained by increased mindfulness and a reduction of pain catastrophizing. Mediation analysis indicated that while mindfulness was a mediator, pain catastrophizing was not, when controlling for baseline scores. This suggests that MBSR may improve function through self-awareness and one's ability to engage in the present moment non-judgmentally, rather than through one's ability to control and reduce pain-related catastrophic cognitions.

Keywords: mindfulness, MBSR, neuropathic pain, pain catastrophizing, mediation

Dedication

To my family, who have given me all I ever needed to succeed.

Acknowledgments

To my supervisor Dr. Melody Wiseheart, I could not have done this without your guidance and expertise. All you have taught me about research methods played a role in each step of this process.

Thank you so much to each of my lab members. Tina Weston, Annalise D'Souza, Katie Matthews, Vanessa Foot and Fenote Girma, learning from each of you has been a true privilege and you have all had a hand in guiding this project forward and helping me to persevere.

To Dr. Patricia Poulin, thank you so much for being a true mentor. Your passion for research and putting patients first is inspiring and has furthered my own enthusiasm in the field tremendously. Thank you to Dr. Howard Nathan and the Ottawa Hospital Interdisciplinary Pain Research team for providing me with the data to conduct this study and supporting me throughout the project. Thank you to Canadian Diabetes Association for funding the primary study.

Thank you to my family, to whom this project is dedicated to, for supporting me through thick and thin. To my mom, Paula Simpson, thank you for always listening and providing unconditional support, encouragement and a healthy dose of honesty when it was necessary. To my dad, Dale Carson, thank you for always reminding me that I have the skills I need to succeed. To my brother, Corey Carson, thank you for helping me to always take time to enjoy life and reminding me not to take myself too seriously. To my grandfather, James Simpson, I thank you for encouraging a love of the pursuit of knowledge from a young age and for your unwavering support.

To my husband, Christopher McFaul, thank you for inspiring me to want to know more about the world, to aim to answer challenging problems, and to question everything. You have been my steadying force for over seven years and your advice and support helped make this happen.

Abstractii
Dedicationiii
Acknowledgementsiv
Table of Contentsv
List of Tablesvi
List of Figuresvii
Introduction1
Neuropathic Pain & Diabetes
The Fear-Avoidance Model of Chronic Pain
Mindfulness & the Fear-Avoidance Model7
Objectives
Hypotheses
Methods
Design12
Participants
Procedure14
Measures15
Data Screening and Analyses
Results
Descriptive Statistics
Preliminary Analysis
Correlation Analysis
Mediation Analysis
Discussion
Conclusion
References
Appendix A: CONSORT Flow Diagram
Appendix B: Questionnaires

Table of Contents

List of Tables

Table 1: Descriptive Statistics	18
Table 2: Means and Standard Deviation of Primary Variables	19
Table 3: Correlational Analysis	21

List of Figures

Figure 1. Statistical diagram showing coefficients of mediation model	23
Figure 2. Graphical representation from Schutze et al., 2010 integrating mindfulness into the	
fear-avoidance model of chronic pain	28

Introduction

Neuropathic Pain & Diabetes

Diabetes mellitus is a medical condition that impacts up to 12.9% of North Americans (Guariguata, Whiting, Weil, & Unwin, 2011) and leads to many long term complications such as retinopathy (potential loss of vision), nephropathy (leading to renal failure), foot ulcers and peripheral neuropathy (Genuth et al., 2003). Chronic neuropathic pain, a common symptom of diabetic peripheral neuropathy, is challenging to treat and it is often related to poor health outcomes and a reduced quality of life (Boulton et al., 2005). Between 26% and 50% of patients with type 2 diabetes have been diagnosed with diabetic peripheral neuropathy, while up to 25% of those patients will develop neuropathic pain as a result (Van Hecke, Austin, Khan, Smith, & Torrance, 2014; Tesfaye et al., 2011).

Neuropathic pain is typically caused by a lesion or dysfunction within the nervous system, either centrally or peripherally (Merskey & Bogduk, 1994). In the case of diabetes, poorly controlled blood glucose level can lead to nerve damage, often affecting nerve endings in the hands and feet (Adler et al., 1997). In addition to its etiology, what distinguishes neuropathic pain from other types of pain are its characteristic symptoms that can be described as burning, electric shocks, shooting pain or uncomfortable tingling/numbness (paresthesia). To provide context of what this experience is like, patients with neuropathic pain have described the sensation as 'walking barefoot on hot sand or marbles' (Tesfaye et al., 2011). Allodynia is also common; it is a painful sensation caused by seemingly innocuous stimuli such as light touch or contact with fabric. This can happen during daily activities such as putting on socks or being covered by a blanket or sheet (Lolignier, Eijkelkamp, & Wood, 2015). Clinical features such as paresthesia and allodynia are often experienced in parts of the body which may appear otherwise

normal and healthy, making diagnoses difficult (Tesfaye et al., 2011). This creates challenges in coping and in treatment that are unique to neuropathic conditions.

Neuropathic forms of pain are particularly difficult to treat as they tend to be resistant to many commonly prescribed analgesics (Gilron, Watson, Cahill, & Moulin, 2006). Evidence has shown that pharmacological treatment provides only partial relief of the pain at best, while often resulting in adverse effects that also reduce quality of life. Common side effects of tricyclic antidepressants and anticonvulsants include adverse cardiac effects, insomnia, drowsiness and dizziness. More severe risks may be associated with the prescription of opioids including possible seizures, respiratory depression and cognitive dysfunction (Gilron et al., 2006; Tesfaye et al., 2011). Additionally, the majority of recommended treatment approaches for neuropathic pain in diabetes treat the symptoms, and are not expected to improve the condition itself (Tesfaye et al., 2011).

The limited advances in the treatment of neuropathic pain, including painful diabetic peripheral neuropathy, mean that those who are affected must learn to cope with the symptoms and impairment associated with them. In reviewing the literature pertaining to neuropathic pain and health-related outcomes, Jensen, Chodroff, and Dworkin (2007) provided unequivocal evidence that neuropathic pain negatively impacts patients' quality of life. Specifically, the severity of neuropathic pain is negatively related to the magnitude of its interference with physical, emotional and social functioning, and it is often associated with sleep problems, all leading to reduced overall health-related quality of life (Jain, Jain, Raison, & Maletic, 2011). In a study of 495 patients with moderate to severe diabetic peripheral neuropathy, nearly a quarter of participants met criteria for depression at baseline, increasing to 28.4% after 18 months and those

higher in depressive symptoms were more likely to have severe restrictions in their daily activities (Vileikyte et al., 2009).

The presence of associations between neuropathic pain and all aspects of functioning suggests that a biopsychosocial approach is crucial to understanding the characteristics, development and treatment of the condition. Other forms of pain have been examined through this lens (Melzack & Katz, 2006), which has led to interdisciplinary treatment which take psychological and environmental factors into account, beyond the traditional pharmacological approach.

The Fear-Avoidance Model of Chronic Pain

Contrary to early biomedical theories that explained pain as a purely sensory event in which pain intensity was thought to provide a good proxy for tissue damage alone, it is now understood that pain is a subjective experience. The perception of pain is influenced by bidirectional neural pathways that carry sensory information. These pathways are influenced by emotional and cognitive information that can inhibit or expedite the transmission of a painful stimuli to the brain. This means that there is not a direct relationship between tissue damage or injury and the perception of pain since the signal can be influenced by psychosocial information beyond biological mechanisms (Melzack, 2001). Gaining an understanding of the subjective factors that impact the experience of pain may lead to more effective treatments. This is particularly true for those with neuropathic forms of pain, given the limited advances in treatment and the impact of the symptoms on daily life.

The well-supported fear-avoidance model of chronic pain as described by Vlaeyen and Linton (2000) explains how fear plays a role in the development of pain-related disability and other influential variables within the cycle. Pain-related fear has been conceptualized as fear of experiencing pain, fear of activities that may elicit pain, or fear of movements which may (re)injure the individual. Within this framework, confrontation and avoidance lie on opposite ends of the spectrum in terms of how one might respond to the fear of pain. Confronting painrelated fear should lead to a decrease in fear over time and more desirable health and psychological outcomes. Conversely, avoidance of pain sensations and cognitions may lead to a phobic state, in which fear-related processes, such as pain catastrophizing, negative affect and hypervigilance, contribute to further fear avoidance and consequent functional disability following disuse.

Although pain-related fear may have a purpose in situations in which the avoidance of movement serves to prevent further injury and allow time to heal, total avoidance of movement or physical activity is maladaptive over time, and will lead to impaired function, and more negative mood and psychological symptoms (Fujii, Matsudaira, & Oka, 2013; Pinto et al., 2014). This is thought to occur as pain-related fear is negatively reinforced by avoidance behaviours. In other words, although the avoidance of fearful stimuli such as moving a limb that is in pain may reduce fear in the short term, it may increase the fear response, or anticipation of pain over the long term, potentially leading to a phobic state. Therefore, a mutual reinforcement of avoidance behaviours and pain-related fear may contribute to the development of disability (Vlaeyen & Linton, 2000).

One of the advantages of understanding the experience of pain through the fear-avoidance model is that it is a dynamic framework, constantly updated based on emerging evidence (Zale & Ditre, 2015). For example, in 2000, Vlaeyen and Linton did not consider pain intensity to be a vital component of the model. However, after several studies concluded that pain intensity is a threatening experience which drives escape and avoidance behaviours, it is considered a predictive factor of disability, and as such, has been integrated into the model (Leeuw et al., 2007). Additionally, the model has been validated and supported using rigorous methods such as structural equation modeling with a large sample size (Cook, Brawer, & Vowles, 2006), providing further evidence for its use in understanding biopsychosocial perspectives of pain.

A limitation of our current understanding of the fear-avoidance model is that although it has been tested many times in samples with musculoskeletal or mixed-pain conditions (Cook et al., 2006; Leeuw et al., 2007; Vlaeyen & Linton, 2000), few have studied how the framework applies in neuropathic conditions. A cross-sectional study by Poulin et al. (2016) confirmed that pain catastrophizing significantly predicted pain intensity, pain-related disability as well as depression in cancer survivors with neuropathic pain. de Jong et al. (2005) looked at pain-related fear and disability in a group of patients with complex regional pain syndrome, although small sample size (N = 8) and lack of longitudinal data reflect similar problems across the few studies that have assessed neuropathic conditions. It seems intuitive that there would be similarities in its application across pain conditions (Leeuw et al., 2007), but this needs to be empirically tested.

The notion that the fear of pain may become more disabling than the pain itself has led researchers to investigate which variables might present influencing roles in this process and ideally increase the likelihood of confronting pain-related fear. Of note, pain catastrophizing is considered a key variable in the fear-avoidance model based on its predictive ability in relation to other pain-related outcomes. Pain catastrophizing can be described as a negative cognitive orientation towards pain (Sullivan, Bishop, & Pivik, 1995).

A commonly used measure for pain catastrophizing is the *Pain Catastrophizing Scale* (Sullivan et al., 1995). In this scale, pain catastrophizing is conceptualized in three separate dimensions which are helplessness, rumination and magnification. It also provides a total

catastrophizing score. Support for including pain catastrophizing in the fear avoidance model includes a study by Pavlin, Sullivan, Freund & Roesen, (2005), who demonstrated that those who are more prone to pain catastrophizing were more likely to experience higher pain intensities and levels of disability in the weeks following surgery. Additionally, catastrophizing is related to the chronicity of pain, as shown by Forsythe et al. (2008), who found that within a group of arthritis patients, those who had higher tendencies to catastrophize in relation to their pain, were more likely to experience persistent pain and disability up to two years following knee-replacement surgery.

Examining pain catastrophizing in neuropathic forms of pain, in a sample of patients with fibromyalgia, catastrophizing predicted self-reported pain-related behaviours and coping strategies both before and after clinical intervention (Nicassio, Schoenfeld-Smith, Radojevic, & Schuman, 1995). Additionally, a number of studies have linked pain catastrophizing to disability, including those with neuropathic forms of pain such as sensory neuropathy (Lucey et al., 2011) and mixed neuropathic pain diagnoses (Arnow et al., 2011; Sullivan, Lynch, & Clark, 2005), with Sullivan et al. concluding that catastrophizing predicted pain-related disability more so than pain intensity. Research findings have situated pain catastrophizing as a crucial factor in understanding chronic pain and how it might impact related factors such as pain intensity and disability.

The detrimental effects of pain catastrophizing in relation to both pain and psychosocial function raises the question of which positive coping mechanisms might interrupt the negative fear-avoidance cycle and how might they be implemented. A revised model of fear-avoidance and chronic pain has proposed that the relationship between pain intensity and pain

catastrophizing can be moderated through mindfulness (Schütze, Rees, Preece, & Schütze, 2010).

Mindfulness & the Fear-Avoidance Model

Mindfulness has been described as the ability to maintain a moment-to-moment, nonjudgmental awareness of our experiences (e.g., thoughts, bodily sensations and emotions; Kabat-Zinn, 1990). Moreover, mindfulness-based interventions conceptualize mindfulness as a skill that can be learned and practiced over time. Mindfulness-based stress reduction (MBSR) was first developed by Kabat Zinn (1982) as a group program for those with chronic illness who were not responding to standard medical treatments. It focuses on improving awareness and acceptance of moment-to-moment experiences, including physical discomfort and negative emotions. These interventions have been shown to result in reduced psychological symptoms and improved health and well-being among different clinical and non-clinical groups (Carmody & Baer, 2008; Grossman, Niemann, Schmidt, & Walach, 2004; Khoury et al., 2013; Veehof, Oskam, Schreurs, & Bohlmeijer, 2011).

Although mindfulness-based interventions have been applied to many different conditions and demographics, their effectiveness has been demonstrated in many randomized trials including reducing depression (Sephton et al., 2007) and improving health-related quality of life (Schmidt et al., 2011) among women with fibromyalgia, reducing psychological distress in rheumatoid arthritis patients (Pradhan et al., 2007), as well as improving pain acceptance, function and quality of life in failed back surgery syndrome patients (Esmer, Blum, Rulf, & Pier, 2010). In a systematic review by Veehof and colleagues (2011) consisting of controlled and uncontrolled mindfulness and acceptance based interventions, moderate effect sizes were found for pain intensity, depression, anxiety, physical well-being and quality of life. In terms of an operational definition, mindfulness is considered to be a multi-faceted construct (Baer, 2006). Given its complex nature, consensus has not yet been achieved on how to operationalize and measure it. Kabat-Zinn's definition drew primarily from Buddhist and yogic teachings. Alternative operational definitions have included components of self-regulation of attention, focusing on the present moment, and maintaining curiosity, openness and acceptance of the present moment (Bishop et al., 2006).

Baer and colleagues sought to operationalize the individual facets of mindfulness. This was accomplished through examining the psychometric properties of five prominent, self-report mindfulness questionnaires which included the Mindful Attention Awareness Scale (Brown & Ryan, 2003), the Freiburg Mindfulness Inventory (Walach, Buchheld, Buttenmüller, Kleinknecht, & Schmidt, 2006), the Kentucky Inventory of Mindfulness Skills (R. A. Baer, Smith, & Allen, 2004), the Cognitive and Affective Mindfulness Scale (Feldman, Hayes, Kumar, Greeson, & Laurenceau, 2007) and the Mindfulness Questionnaire (Chadwick, Hember, Mead, Lilley & Dagnan, 2005). After evaluating the factor structure of the combined items, they compiled a comprehensive five-facet conceptualization of mindfulness. This structure includes observing, describing, acting with awareness, non-judgment and non-reactivity to experiences.

Observing refers to one's ability to notice or attend to internal or external experiences. Describing refers to one's ability to label internal experiences with words and descriptions. Acting with awareness refers to one's ability to attend to what is occurring in the present moment in contrast to automaticity or running on 'autopilot'. Non-judgment refers to approaching one's thoughts and feelings in a non-evaluative way. Finally, non-reactivity towards inner experiences refers to the tendency to allow thoughts and feelings to come and go without getting caught up in a particular experience. Many mindfulness researchers posit that the central mechanisms of action in mindfulness-based interventions is thought to be increased mindfulness itself (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006). However, it has yet to be established if increased mindfulness is the sole determinant of health improvements following the intervention (Harrison, Scott, Johns, Morris, & McCracken, 2017), or if other psychosocial factors such as a reduction in pain catastrophizing, are the mechanisms through which therapeutic effects are seen.

This first study to look at pain catastrophizing and mindfulness was conducted by Schutze et al. (2010). They examined how mindfulness related to various aspects of the fearavoidance model of chronic pain and found that it negatively predicted pain intensity, negative affect, pain catastrophizing, pain related fear, pain hypervigilance and functional disability. Additionally, they found that mindfulness moderated the relationship between pain intensity and pain catastrophizing. The authors explain this effect by describing mindfulness as a type of attention that is 'at odds' with the cognitive components associated with pain catastrophizing such as judgement, automatic, conceptual processing and rumination. By counteracting these negative thought patterns through accepting practices, mindfulness is thought to facilitate more realistic and non-judgmental cognitions related to pain.

Cassidy, Atherton, Robertson and Walsh's (2012) study of low back pain patients both supported the relationships established in Schutze et al.'s study, but also found that both mindfulness and pain catastrophizing changed significantly following a cognitive-behavioural pain management program. Although this program was not mindfulness-based, it still encourages the notion that interventions targeting unhelpful thinking styles may be able to produce comparable results for patients by increasing levels of mindfulness and reducing catastrophic thoughts regarding pain. Comparable relationships were found in a study which evaluated the use of a mindfulness-based meditation program via videoconferencing, in which both those in a live class and those in a distance education program achieved similar improvements in both mental health and pain catastrophizing (Gardner-Nix, Backman, Barbati, & Grummitt, 2008).

A limitation found in past research that has examined the relationship between mindfulness and pain catastrophizing is the use of a uni-dimensional measure of mindfulness, specifically the use of the Mindful Attention Awareness Scale (MAAS; Brown & Ryan, 2003). In the development of a multi-faceted model of mindfulness, Baer et al. (2006) found that the items from Brown and Ryan's scale loaded solely onto the acting with awareness facet.

Both Schutze et al. and Cassidy et al.'s use of the Mindful Attention Awareness Scale is limiting in the sense that it has been established that mindfulness is a complex, multi-faceted construct, and should therefore be measured as such. Additionally, the MAAS has shown to be less reliable than more comprehensive means of measurement (Park, Reilly-Spong, & Gross, 2013). Some studies, in focusing primarily on clinical outcomes, have not measured mindfulness at all (Gardner-Nix et al., 2008). These methods illustrate a gap in the research in terms of investigating the role of mindfulness in non-musculoskeletal pain, using a comprehensive measure of mindfulness.

Nathan and colleagues (under review) addressed these limitations and recently completed a randomized controlled trial comparing the effects of medical management alone compared to medical management combined with mindfulness-based stress reduction for patients with painful diabetic peripheral neuropathy. They demonstrated that those in the MBSR group experienced a significant decrease in pain interference (41.4%) three months following the intervention compared to the control group, as well as improvements in both pain catastrophizing and mindfulness. Using archival data from Nathan et al., the current study will explore how pain catastrophizing and mindfulness might explain how mindfulness-based interventions work in this population.

Objectives

The primary objective of this study is to explore the influencing role mindfulness and pain catastrophizing have on disability throughout a MBSR program in those with diabetic peripheral neuropathy. Of all the components illustrated in Vlaeyen's fear-avoidance model, attention is paid to pain catastrophizing, as this is understood to be the cognitive route through which the fear of pain develops (Vlaeyen, Kole-Snijders, Boeren, & van Eek, 1995). Sullivan et al. (2001) notes that much of the research examining the relationship between pain and catastrophizing has been cross-sectional. This study examines it over the course of an intervention and at follow up.

Second, much of research that has applied the fear-avoidance model has used either nonspecified (Schutze et al., 2010) or musculoskeletal chronic pain conditions (Cassidy et al., 2012). Presently, the role of pain catastrophizing and mindfulness in relation to pain-related disability has not been explored in those with painful diabetic peripheral neuropathy participating in a mindfulness-based stress reduction program. The role of the current study is to assess if these key variables may explain the impact the intervention has on pain-related disability.

Hypotheses

This current analysis is an attempt to understand why a reduction in pain interference occurs over the course of a mindfulness-based stress reduction program and through what mechanisms the intervention is effective. Studies have shown that greater pain catastrophizing is related to higher levels of disability in pain-related conditions (Forsythe et al., 2008; Pavlin, Sullivan, Freund, & Roesen, 2005), and higher mindfulness predicts lower pain catastrophizing (Cassidy et al., 2012; Schütze et al., 2010), but the effects of the two constructs on pain-related disability have not yet been compared simultaneously. It is predicted that participating in the intervention will reduce pain interference as a result of its relationship with pain catastrophizing. Through similar mechanisms, mindfulness is also expected to mediate the effects of participating in MBSR and pain interference. These hypotheses will be tested in a parallel mediation model.

Sequential analysis to determine if mindfulness influences pain catastrophizing, thereby reducing pain-related disability was not possible given the restricted number of time points variables were measured (Hayes, 2013).

Methods

Design

This study was conducted using archival data that has been previously collected at The Ottawa Hospital Pain Clinic as part of a large randomized control trial comparing mindfulnessbased stress reduction to a wait-list control among patients with painful peripheral diabetic neuropathy, referred to from this point forward as the *primary study* (Nathan et al., 2017, under review). The primary study was a registered clinical trial with the *National Institutes of Health* (Registration #NCT02127762) and was approved by the Ottawa Hospital Health Sciences Centre Research Ethics Board (Approval Number # 20120541-01H). Funding in support of this study was received from the Canadian Diabetes Association. The current archival study presents a subset of this data and was conducted after the primary analysis had been completed.

Participants

The primary study recruited patients by telephone from a database of patients attending the Ottawa Hospital Endocrine and Diabetes Centre who had consented to be contacted for research projects. Some patients were also referred to the study by diabetes healthcare team members in the Ottawa community.

The primary study enrolled men and women over 18, and included adults with Type 1 or Type 2 Diabetes Mellitus regardless of whether or not they were receiving insulin. Additionally, they had to have demonstrated good glycemic control (HbA1c 6.5-9), and had been diagnosed with diabetic peripheral neuropathy for at least one year. Patients were eligible to participate if they had experienced pain for longer than 6 months, with moderate to severe levels of pain intensity, which equates to a mean score of 4 or greater on a visual analogue scale (VAS) from zero to nine. Patients responding "yes" to 3 or more of the 7 subjective items on the neuropathic pain scale were asked to rate their pain on a VAS scale (0-9) at the same time each day for 7 consecutive days. Each day they filled out 2 VAS scales: one for pain at rest and one for pain with activity. Patients were included only if the mean score for one or other scale was 4 or greater. Patients were excluded if they had previously participated in a mindfulness-based workshop or group before.

Sample size was determined in the *primary study* to achieve 80% power to detect a minimally important absolute difference of 30% in the intervention group, compared to the control. These assumptions indicated that a sample size of 80 participants were required. The *primary study* planned to recruit 94 patients (47 patients in each group, accounting for 15% attrition). Recruitment stopped after 66 patients were enrolled due to exhaustion of funds.

Two hundred and fifty individuals were screened for eligibility. Thirty-one participants were randomized to the mindfulness-based stress reduction program, while 33 were randomized to the wait-list control group. Thirty participants from the MBSR group and thirty-two from the

wait-list control group completed the follow up questionnaire and were included in analysis (See Appendix A).

Participants' ages (years) ranged from 35-79 in both groups and the mean age was 59.7 (SD = 8.8). Half of the participants in the treatment group were retired, while the other half were generally evenly split between being either employed or on disability. Similarly, 56.3% of participants in the control were retired, while 25.0% were on disability and 12.5% were employed. Further details will be provided in the descriptive statistics section in *Results*.

Procedure

After meeting eligibility criteria and providing informed consent, participants were first offered medical management to optimize pain control, working with an interdisciplinary team at the Ottawa Hospital Pain Clinic. This phase lasted a minimum of 3 months and up to 5 months. Optimal pharmacological management was based on two consensus statements made regarding the evidence-based treatment of painful diabetic peripheral neuropathy (Bril et al., 2011; Tesfaye et al., 2011). After confirming that patients were on a stable drug regiment for at least 3 weeks, they were randomized into either the intervention group or a wait-list control group. Patients were discouraged from making any changes to their medication regimen during the time of the study. Patients in the control group were offered the ability to participate in a MBSR course following the completion of the study.

The intervention group participants were enrolled into an 8-week MBSR program consisting of weekly 2.5-hour workshops and one 6-hour session on a weekend midway through the course. The MBSR courses were offered by community practitioners with formal mindfulness training and who had at least 5 years of experience leading MBSR programs. Materials and methods used are recommended by the Center for Mindfulness, where this method was developed (University of Massachusetts).

In order to evaluate the effect of the intervention, participants in both the control and intervention arms completed a series of self-report questionnaires at four points in time: immediately after enrolment in the study (T1), after the medical optimization had occurred and before the intervention period started (T2), 2 weeks after the group intervention (T3) and 3 months following the completion of the intervention (T4).

Measures

A series of self-report questionnaires were used to collect information about participants' age, gender, employment status, pain duration and diabetes duration. Questionnaires can be seen in *Appendix B*.

The Brief Pain Inventory (BPI; Cleeland, 1991) is a 32-item questionnaire which assesses pain in terms of background characteristics, severity, medication usage and pain interference relating to functional disability. The pain interference subscale will be the outcome variable of interest. Scores on this scale range from 0 to 10, with higher scores reflecting greater levels of pain-related disability in response to seven daily activities: general activity, mood, walking ability, work, relations with other people, sleep and enjoyment of life. The average of these provides a total interference score. A one point change on the interference scale mean score has been recommended by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials guidelines as a reasonable minimal clinically significant change (Dworkin et al., 2008). The BPI has been determined to be both valid and reliable in samples with painful diabetic peripheral neuropathy (Zelman, Gore, Dukes, Tai, & Brandenburg, 2005), with a Cronbach's alpha coefficient of .94. The Pain Catastrophizing Scale (PCS; Sullivan et al., 1995) which is a well-validated 13item instrument designed to evaluate the degree to which patients have negative self-statements and catastrophizing thoughts when in pain. The measure consists of 3 subscales of rumination, magnification and helplessness but scores can also be totalled for an overall measure of pain catastrophizing. Total PCS scores range from 0 to 52 with higher scores indicating higher pain catastrophizing. The subscales have been validated in neuropathic pain patients (Sullivan et al., 2005) with Cronbach's alpha coefficients of .85 (rumination), .75 (magnification) and .86 (helplessness). With good criterion-related validity, the total PCS score has a reliability coefficient of .95.

The Five Facets Mindfulness Questionnaire (FFMQ; Baer et al., 2006) is a 39-item instrument measuring five aspects of mindfulness: Non-reactivity to inner experience; observing, describing, acting with awareness, and being non-judgmental of experiences. Cronbach's alpha for the subscales range from .75-.91. Additionally, the subscales can be added to create a total composite mindfulness score. A review by Park, Reilly-Spong and Gross (2013) demonstrated that that the FFMQ had the highest possible rating in internal consistency and construct validity when compared to several other commonly implemented instruments measuring mindfulness.

Data Screening and Analyses

Data was entered into the Statistics and Package for Social Sciences (SPSS Statistics for Windows, Version 21.0) and screened for accuracy and outliers. There was less than 1% of data missing across patients and all questionnaires. Missing data were imputed backwards or forwards from other time points depending on when the missing value occurred. For example, if the participant did not complete question 1 at T2, their T1 question 1 score would be imputed

forward. Data was not imputed across the intervention. There were no detected issues in terms of normality, linearity, and multicollinearity among the independent variables.

In accordance with Preacher and Hayes' recommendations (2004), a series of regression models were constructed based on the findings of the primary study and were used to detect a mediating effect of either mindfulness or pain catastrophizing on pain-related disability. The PROCESS macro was used to conduct the analysis, which employs a bootstrap method to estimate the indirect (or mediating) effect. A test of inference was conducted using bootstrap confidence intervals. This has been shown to have additional power compared to previous methods using normal theory hypothesis testing which posits unrealistic assumptions of normality (Williams & Mackinnon, 2008). Mindfulness and pain catastrophizing were entered in a parallel mediator model as this offers additional statistical power and the ability to compare the indirect effect sizes of each mediator (Hayes, 2013). Five thousand random samples were created from the original data to calculate the indirect effects. In order to understand the impact of the intervention on the outcome, the model will include mediators at T3, immediately following the intervention. As we are interested in the outcome (pain interference) over a longer period of time, we included T4, at 3 month follow up in the mediation model.

Results

Descriptive Statistics

Baseline demographics and relevant variables were similar between groups (Table 1). Participants' ages ranged from 41-79 in the MBSR group and 35-79 in the control group. On average, patients experienced diabetes much longer than the duration of their pain. Immediately following the intervention (T3) pain catastrophizing appeared to be lower in the MBSR group, and mindfulness was higher in the MBSR group as seen in *Table 2*. Pain interference was lower at 3 month follow up (T4) in the treatment group than the control. The primary analysis confirmed the differences between groups were statistically significant between relevant measures.

Table 1. Descriptive Statistics

	All (<i>n</i> =62)	Control (<i>n</i> =32)	MBSR (<i>n</i> =30)		
Characteristic					
Age, years, mean (SD)	59.7 (8.8)	59.8 (8.7)	59.7 (9.1)		
Female, n (%)	35 (56)	20 (62.5)	15 (50)		
Diabetes Type 2, <i>n</i> (%)	48 (77)	24 (75)	24 (80)		
Severe Pain, <i>n</i> (%)	17 (27)	8 (25)	9 (30)		
Pain Duration, years, mean (SD)	7.4 (6.0)	8.0 (6.7)	6.7 (5.2)		
Post-secondary education, <i>n</i> (%)	46 (74)	23 (71.9)	23 (76.7)		
Work status, <i>n</i> (%)					
Employed	11(17.7)	4 (12.5)	7 (23.3)		
Retired	33 (53.2)	18 (56.3)	15 (50)		
Disability	15 (24.2)	8 (25)	7 (23.3)		
Other	3 (4.8)	2 (6.3)	1 (3.3)		

Preliminary Analysis

A mixed effects logistic regression analysis from Howard et al. (under review) confirmed their primary hypothesis that those in the MBSR group, the majority of patients (63.3%) experienced clinically important decrease in pain interference by 1 point or greater from the time of randomization to T4 (3 month follow up). Fewer participants in the control group saw a reduction in pain interference (21.9%) and this was a statistically significant difference (p = 0.02, 95% CI = 1.5, 63.8). Furthermore, the MBSR group also saw a 46.5% reduction in pain

catastrophizing from randomization to follow up, post-intervention (p < 0.01, CI = -17.18, -7.52).

Table 2. Means and Standard Deviations of Pain Catastrophizing (PCS, Total Score), Mindfulness (FFMQ, Total Mean Score), and Pain Interference (BPI, Interference Subscale) at various time points

		MBSR (N = 30)	Control $(N = 32)$
	Variable	Mean (SD)	Mean (SD)
	Pain Catastrophizing	23.4 (11.9)	27.6 (12.1)
T1	Mindfulness	3.3 (0.6)	3.32 (0.6)
	Pain Interference	4.9 (2.0)	4.83 (2.4)
	Pain Catastrophizing	22.0 (11.6)	23.9 (12.2)
T2	Mindfulness	3.4 (0.5)	3.4 (0.6)
	Pain Interference	4.9 (2.1)	4.6 (2.5)
	Pain Catastrophizing	14.8 (10.9)	24.6 (12.0)
T3	Mindfulness	3.6 (0.4)	3.3 (0.5)
	Pain Interference	4.0 (2.4)	5.2 (2.3)
	Pain Catastrophizing	11.3 (10.4)	25.6 (10.6)
T4	Total Mindfulness	3.7 (0.5)	3.2 (0.4)
	Pain Interference	3.2 (2.1)	5.1 (2.4)

Correlation Analysis

A series of point-biserial correlations were calculated to analyze the relationships between group (dichotomous) and relevant variables at different time points. As can be seen in *Table 3,* group assignment to either the MBSR or wait-list control group was moderately related to pain catastrophizing post-intervention, T3 ($r_{pb} = .40$, p = 0.001), total mindfulness postintervention, T3 ($r_{pb} = -.34$, p = 0.006) and pain interference at 3 month follow up, T4 ($r_{pb} = -0.39$, p = 0.002). In other words, following the intervention, being assigned to the wait-list control group meant you were more likely to be higher in pain catastrophizing, pain interference and lower mindfulness. There were no significant relationships between group assignment and baseline characteristics.

With consideration to the proposed mediation model (*Figure 1*), possible mediators were found to be correlated with the outcome measure. Bivariate Pearson correlations indicated that total mindfulness (r = -0.39, p = 0.002) and pain catastrophizing (r = 0.37, p = 0.003) immediately following the intervention period (T3) were both significantly related to pain interference at 3 month follow up (T4). These relationships provided further evidence to explore possible mediators between participating in the MBSR program and pain interference.

Measure	1	2	3	4	5	6	7	8	9
1. Intervention Arm ¹	-								
2. Pain Interference (V2)	-0.07	-							
3. Pain Interference (V3)	0.25	0.72**	-						
4. Pain Interference (V4)	0.39**	0.56**	0.77**	-					
5. Total Mindfulness (V2)	-0.01	-0.24	-0.24	-0.14	-				
6.Total Mindfulness (V3)	-0.34**	-0.22	-0.41**	-0.39**	0.72**	-			
7. Total Mindfulness (V4)	-0.46**	-0.18	-0.35**	-0.37**	0.51**	0.79**	-		
8. Pain Catastrophizing (V2)	0.08	0.45**	0.34**	0.27*	-0.18	-0.15	-0.11	-	
9. Pain Catastrophizing (V3)	0.40**	0.40**	0.41**	0.37**	-0.29*	-0.41**	-0.41**	0.67**	-
10. Pain Catastrophizing (V4)	0.57**	0.34**	0.40**	0.55**	-0.12	-0.40**	-0.51**	0.52**	0.72**

Table 3. Correlations between pain catastrophizing, total mindfulness, pain interference and intervention group at various time points (N = 62).

¹ Intervention arm, 0 = MBSR group, 1 = Wait-list control group

* *p* < .05

** *p*<.01

Mediation Analysis

The PROCESS macro (Hayes, 2013) was used to perform a mediation regression analysis and to investigate the hypothesis that pain catastrophizing and mindfulness mediated the effects of a mindfulness-based stress reduction program and pain interference. A mediation analysis was conducted using ordinary least squares path analysis showing that participating in MBSR indirectly influenced pain-related disability through its effect on mindfulness, whereas there was no indirect effect of pain catastrophizing. *Figure 1* demonstrates the relationships between intervention group, mediators and outcome.

Age, gender and baseline characteristics (T2) were controlled for within this model, which entered both mediators in parallel. The bootstrap bias-corrected confidence intervals indicate with 95% confidence that treatment group influences pain-related disability indirectly through mindfulness [unstandardized regression coefficient (*B*) = 0.55; *SE* = 0.32; 95% *CI* = 0.06, 1.35], but not pain catastrophizing (*B* = - 0.17; *SE* = 0.31; 95% *CI* = - 0.90 to 0.37) as the confidence interval contains zero.

When analyzing the individual relationships within the model, as predicted, pathways between the predictor (group), and each respective mediator were significant, as seen in *Figure 1*. In satisfying the assumptions required for mediation to occur, mindfulness significantly predicted pain interference (b₂) but pain catastrophizing was not a significant predictor (b₁). Finally, there was a significant direct effect of intervention group on pain-related disability (c' =1.68, p = 0.005). As such, the primary hypothesis that mindfulness influences the relationship between participating in MBSR and pain-related disability through a mediating effect was supported, whereas pain catastrophizing was not a significant mediator.

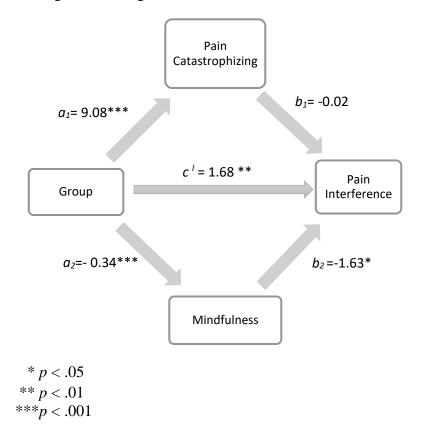


Figure 1. Statistical diagram showing coefficients of mediation model.

Discussion

Nathan and colleagues (under review) recently completed a randomized controlled trial comparing the effects of a mindfulness-based stress reduction (MBSR) program to a wait-list control group in patients with painful diabetic peripheral neuropathy. The primary goal of the present study was to further explain Nathan et al.'s *primary analyses*' finding that compared to patients who were assigned to a wait-list control condition, patients with painful peripheral diabetes neuropathy who participated in the MBSR intervention (MBSR) experienced a significantly greater reduction in pain-related disability.

To situate our findings among the existing literature, the group means were found to be comparable to other studies employing the same measures. Pain catastrophizing and pain-related disability were higher in the control group than treatment following the intervention period, but the means were comparable to previous studies which looked at similar relationships (Schütze et al., 2010) and the control group was higher in pain catastrophizing than other neuropathic samples that have been analyzed (Poulin et al., 2016). It should be noted that neither the pain catastrophizing average for the MBSR group (M = 14.8, SD = 10.9) and the control group (M = 34.6, SD = 12.4) fall within what Sullivan (1995) deems to be a clinically relevant level of catastrophizing. Mindfulness at follow up in the control group was lower than Poulin et al.'s (2016) study looking at cancer survivors with neuropathic pain (M = 3.6, SD = 0.5). At the same point in time, the MBSR group's mindfulness score was higher (M = 3.6, SD = 0.4).

It was hypothesized that the effect of MBSR on pain-related disability would occur through two possible psychological mechanisms. Both increased mindfulness and lower pain catastrophizing were expected to explain the relationship between treatment group and painrelated disability, respectively. While mindfulness was found to be a mediator between intervention group and pain-related disability, pain catastrophizing was not. One possible explanation for failing to detect a mediating effect may be that baseline characteristics of both catastrophizing and pain interference are greater predictors of pain interference following an MBSR intervention than the intervention itself.

An alternative explanation for the absence of the mediating effect of pain catastrophizing may be due small sample size. The primary study (Nathan et al., in preparation) was not designed for the purposes of a mediation analysis. It is possible that testing the relationships with a larger sample size would allow an effect of pain catastrophizing to be seen. This is further evident through a post-hoc evaluation of the mediation analyses power. Given the mediation effect observed, based on guidelines from Fritz and MacKinnon (2007), the pain catastrophizing pathway would require a sample size of 396 to achieve 0.80 power. The effect of mindfulness was sufficiently large to be statistically detected; the sample size required to achieve 0.80 power in this case was 53. This may indicate why the study was able to detect an effect of one but not the other. Further analysis with a larger is sample size is necessary to further understand the nature of pain catastrophizing's relationship and relevance to clinical outcomes, following participation in a mindfulness-based stress reduction program. A larger sample would also allow for assessing the relative contribution of various aspects of pain catastrophizing and facets of mindfulness.

Although evidence has made comparisons between mindfulness and pain catastrophizing acting at opposite ends of the spectrum of how attention is controlled in relation to pain (Cassidy et al., 2012; Schütze et al., 2010), they are not opposing factors. While they were related to each other at baseline and following the intervention, the strength of the negative relationship observed between the two was only moderate. As such, one can have increased mindfulness and

regardless of whether they have tendencies to catastrophize about their pain, they will experience less pain-related disability following the intervention.

Smeets, Vlaeyen, Kester and Knottnerus (2006) and Turner, Holtzman and Mancl (2007) both found that pain catastrophizing mediates pain-related disability in cognitive behaviouralbased treatments for musculoskeletal chronic pain conditions. This difference in findings may highlight respective mechanisms of improvement in pain-related disability, in that MBSR improves function through increased mindfulness, impacting participants' ability to remain aware, decentered and in the present moment. Cognitive behavioural therapy, on the other hand may function through its ability to teach control over thought patterns and actively attempting to alter maladaptive thoughts that may lead to catastrophizing cognitions.

Mindfulness is related to both pain-related disability and catastrophizing, as such, it may represent a third variable that minimizes the relationship between the two when statistically accounted for. Mindfulness encourages a decentering, accepting attitude towards thoughts as they arrive. As catastrophic cognitions would be accepted in this frame of mind, those with tendencies to catastrophize may continue to do so despite increased mindfulness. The goal of MBSR programs is not to control one's thoughts, but rather become more accepting of them (Kabat-Zinn, 1982).

Contrary to catastrophizing, mindfulness was a significant mediator between participating in MBSR and pain-related disability. In other words, the relationship between participating in MBSR and pain-related disability is influenced by an individual's level of mindfulness following the intervention, while taking into account participants' baseline characteristics (mindfulness, pain catastrophizing and pain-interference), in addition to age and gender. Mindfulness has been shown to consistently increase following participation in MBSR group training (Visted, Vøllestad, Nielsen, & Nielsen, 2015), and these findings demonstrate that the same is true in a sample of those with painful diabetic peripheral neuropathy.

Additionally, the mediating effect of mindfulness on pain-related disability can be explained through the impact mindfulness has on individuals' ability to be aware in the present moment, evaluating situations (including painful ones) with non-judgmental and non-reactive acceptance. This may occur through processes which disrupt the recurring fear-avoidance cycle, such as self-regulating one's awareness, particularly in regards to their body, and through increasing their acceptance of their pain and symptoms. These findings have clinical implications, particularly for those with peripheral diabetic neuropathy. Clinicians treating those with neuropathic pain and diabetes may wish to consider mindfulness-based interventions based on their ability to reduce pain-related disability. Furthermore, understanding which factors are the most influential towards relevant outcomes can help shape the development of future interventions to ensure their effectiveness is optimized for a given population.

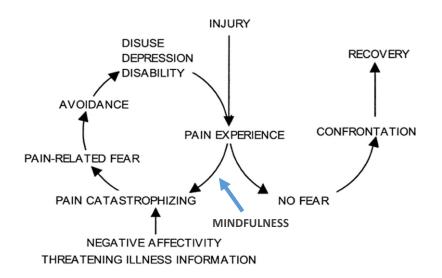
Many studies have implied that the statistically significant mediation effect of mindfulness on pain-related disability through MBSR would suggest a causal relationship between the included variables (Preacher, 2015). However, others have warned to be cautious in interpreting the results of mediation analysis (Danner, Hagemann, & Fiedler, 2015; Fiedler, Schott, & Meiser, 2011). This is due to the many relationships that have not been tested or included in the model that may also be significant. As such, the nature of the presented results suggest that increased mindfulness may be one of many possible mechanisms in which MBSR programs are effective at reducing pain-related disability.

Towards the pursuit of a more comprehensive model which may better explain why MBSR is effective at reducing pain-related disability, additional variables should be included in

27

future studies, such as pain-related fear, avoidance, and mood. The findings of this study that indicate mindfulness influences pain-related disability over the course of a MBSR program support Schutze et al.'s (2010) suggestion that mindfulness is a factor that should be considered in the context of the fear-avoidance model of chronic pain as seen in their revised model (Figure 2). However, as pain catastrophizing was not a mediator between MBSR and pain interference, it begs the question that perhaps the fear-avoidance model of chronic pain cannot be applied to neuropathic pain conditions in the same way it is to musculoskeletal conditions. Further assessment is required.

Figure 2. Graphical representation from Schutze et al., 2010 integrating mindfulness into the fear-avoidance model of chronic pain (Adapted from Vlaeyen & Linton, 2000).



Future research in this domain should aim to assess these variables at additional time points. By measuring relevant constructs at various times, sequential analysis can be conducted (Hayes, 2013). In other words, it could be determined if changes in mindfulness preceded changes in other fear-avoidance model variables, and their relationship with outcomes like painrelated disability. Although possible with Hayes' mediation analysis (2013), moving towards more sophisticated and robust methods such as structural equation modeling, more complex models can be represented and tested (Cook et al., 2006). This would provide a comprehensive understanding of the factors involved in pain-related disability over the course of a mindfulness-based interventions.

Additionally, using structural equation modelling would allow future studies to include individual facets of mindfulness simultaneously when looking at different outcomes during MBSR. Recently, Poulin et al. (2016) found that being non-judgmental and acting with awareness were most consistently related to pain-related outcomes. Day, Smitherman, Ward and Thorn (2015) investigated the relationships between mindfulness and catastrophizing. They concluded that the two constructs were moderately related and that each facet was a predictor of catastrophizing, although this was not the case when 'worry' was controlled for. This further highlights the complex nature of the relationship between mindfulness, pain catastrophizing and the fear-avoidance model, encouraging researchers to determine which factors are most influential and helpful to patients in reducing disability and improving quality of life. Additionally, examining these relationships in a temporal perspective may prove useful for intervention development to determine the aspects of an intervention that are effective at different points in time.

Conclusion

The present study investigated two possible mediators which may explain why MBSR is effective at reducing pain-related disability. Although the results must be interpreted with consideration to small sample size and a limited number of time points preventing the use of more sophisticated analytical methods, the current study found that mindfulness was a significant mediator of MBSR effects on pain-related disability while pain catastrophizing was not. This study represents a step forward in the literature through its use of data from a randomized control trial design and as well as recommended mediation analysis methodology that increases power (Preacher and Hayes, 2004; Hayes, 2013) compared to previous traditional methods (Baron & Kenny, 1986). Additionally, we have looked at these mediating relationships in a previously untested population of those with painful peripheral diabetic neuropathy. Understanding how pain and its' effect on disability can be impacted by MBSR and mindfulness can have implications for those with neuropathic forms of pain. Further research is warranted to determine how MBSR impacts different variables within the fear-avoidance model which may influence disability.

References

- Adler, A. I., Boyko, E. J., Ahroni, J. H., Stensel, V., Forsberg, R. C., & Smith, D. G. (1997).
 Risk factors for diabetic peripheral sensory neuropathy. Results of the Seattle Prospective Diabetic Foot Study. *Diabetes Care*, 20(7), 1162–7.
- Arnow, B. A., Blasey, C. M., Constantino, M. J., Robinson, R., Hunkeler, E., Lee, J., ...
 Hayward, C. (2011). Catastrophizing, depression and pain-related disability. *General Hospital Psychiatry*, 33(2), 150–156. https://doi.org/10.1016/j.genhosppsych.2010.12.008
- Baer, R. A. (2006). Using Self-Report Assessment Methods to Explore Facets of Mindfulness. *Assessment*, 13(1), 27–45. https://doi.org/10.1177/1073191105283504
- Baer, R. A., Smith, G. T., & Allen, K. B. (2004). Assessment of Mindfulness by Self-Report: The Kentucky Inventory of Mindfulness Skills. *Assessment*, 11(3), 191–206. https://doi.org/10.1177/1073191104268029
- Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*, 51(6), 1173–82. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3806354
- Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., & Devins, G. (2006). Mindfulness: A Proposed Operational Definition. *Clinical Psychology: Science and Practice*, 11(3), 230–241. https://doi.org/10.1093/clipsy.bph077
- Boulton, A. J. M., Vinik, A. I., Arezzo, J. C., Bril, V., Feldman, E. L., Freeman, R., American Diabetes Association. (2005). Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care*, 28(4), 956–62. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15793206

- Bril, V., England, J., Franklin, G. M., Backonja, M., Cohen, J., Del Toro, D., ... American Academy of Physical Medicine and Rehabilitation. (2011). Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*, *76*(20), 1758– 1765. https://doi.org/10.1212/WNL.0b013e3182166ebe
- Brown, K. W., & Ryan, R. M. (2003). The benefits of being present: mindfulness and its role in psychological well-being. *Journal of Personality and Social Psychology*, 84(4), 822–48.
 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12703651
- Carmody, J., & Baer, R. A. (2008). Relationships between mindfulness practice and levels of mindfulness, medical and psychological symptoms and well-being in a mindfulness-based stress reduction program. *Journal of Behavioral Medicine*, *31*(1), 23–33. https://doi.org/10.1007/s10865-007-9130-7
- Cassidy, E. L., Atherton, R. J., Robertson, N., Walsh, D. A., & Gillett, R. (2012). Mindfulness, functioning and catastrophizing after multidisciplinary pain management for chronic low back pain. *Pain*, *153*(3), 644–650. https://doi.org/10.1016/j.pain.2011.11.027
- Chadwick,P., Hember, M., Mead,S., Lilley, B., & Dagnan,D. (2005). Responding mindfully to unpleasant thoughts and images: Reliability and validity of the Mindfulness Questionnaire. Unpublished manuscript.

Cleeland, C. (1991). Brief pain inventory (short form). Pain Research Group [Viitattu, 9–10.]

Cook, A. J., Brawer, P. A., & Vowles, K. E. (2006). The fear-avoidance model of chronic pain:
Validation and age analysis using structural equation modeling. *Pain*, *121*(3), 195–206.
https://doi.org/10.1016/j.pain.2005.11.018

- Danner, D., Hagemann, D., & Fiedler, K. (2015). Mediation analysis with structural equation models: Combining theory, design, and statistics. *European Journal of Social Psychology*, 45(4), 460–481. https://doi.org/10.1002/ejsp.2106
- Day, M. A., Smitherman, A., Ward, L. C., & Thorn, B. E. (2015). An Investigation of the Associations Between Measures of Mindfulness and Pain Catastrophizing. *The Clinical Journal of Pain*, 31(3), 222–228. https://doi.org/10.1097/AJP.000000000000102
- De Jong, J. R., Vlaeyen, J. W. S., Onghena, P., Cuypers, C., Den Hollander, M., & Ruijgrok, J. (2005). Reduction of pain-related fear in complex regional pain syndrome type I: The application of graded exposure in vivo. *Pain*, *116*(3), 264–275. https://doi.org/10.1016/j.pain.2005.04.019
- Dworkin, R. H., Turk, D. C., Wyrwich, K. W., Beaton, D., Cleeland, C. S., Farrar, J. T., ... Zavisic, S. (2008). Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *The Journal of Pain*, 9(2), 105–121. https://doi.org/10.1016/j.jpain.2007.09.005
- Esmer, G., Blum, J., Rulf, J., & Pier, J. (2010). Mindfulness-based stress reduction for failed back surgery syndrome: a randomized controlled trial. *The Journal of the American Osteopathic Association*, *110*(11), 646–52. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21135196
- Feldman, G., Hayes, A., Kumar, S., Greeson, J., & Laurenceau, J.-P. (2007). Mindfulness and Emotion Regulation: The Development and Initial Validation of the Cognitive and Affective Mindfulness Scale-Revised (CAMS-R). *Journal of Psychopathology and Behavioral Assessment*, 29(3), 177–190. https://doi.org/10.1007/s10862-006-9035-8

Fiedler, K., Schott, M., & Meiser, T. (2011). What mediation analysis can (not) do. Journal of

Experimental Social Psychology, 47(6), 1231–1236.

https://doi.org/10.1016/j.jesp.2011.05.007

- Forsythe, M. E., Dunbar, M. J., Hennigar, A. W., Sullivan, M. J. L., & Gross, M. (2008). Prospective relation between catastrophizing and residual pain following knee arthroplasty: two-year follow-up. *Pain Research & Management*, *13*(4), 335–41. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18719716
- Fujii, T., Matsudaira, K., Oka, H. (2013). Factors associated with fear-avoidance beliefs about low back pain. J Orthop Sci, 18(6), 909-915. doi:10.1007/s00776-013-0448-4.
- Fritz, M. S., & Mackinnon, D. P. (2007). Required sample size to detect the mediated effect. *Psychological Science*, 18(3), 233–9. https://doi.org/10.1111/j.1467-9280.2007.01882.x
- Gardner-Nix, J., Backman, S., Barbati, J., & Grummitt, J. (2008). Evaluating distance education of a mindfulness-based meditation programme for chronic pain management. *Journal of Telemedicine and Telecare*, 14(2), 88–92. https://doi.org/10.1258/jtt.2007.070811
- Genuth, S., Alberti, K. G., Bennett, P., Buse, J., Defronzo, R., Kahn, R. & Nathan, D. (2003). Follow-up Report on the Diagnosis of Diabetes Mellitus. *Diabetes Care*, 26(11). Retrieved from http://care.diabetesjournals.org/content/26/11/3160
- Gilron, I., Watson, C. P. N., Cahill, C. M., & Moulin, D. E. (2006). Review Neuropathic pain : a practical guide for the clinician.
- Grossman, P., Niemann, L., Schmidt, S., & Walach, H. (2004). Mindfulness-based stress reduction and health benefits. *Journal of Psychosomatic Research*, 57(1), 35–43. https://doi.org/10.1016/S0022-3999(03)00573-7
- Guariguata, L., Whiting, D., Weil, C., & Unwin, N. (2011). The International Diabetes Federation diabetes atlas methodology for estimating global and national prevalence of

diabetes in adults. *Diabetes Research and Clinical Practice*, 94(3), 322–332. https://doi.org/10.1016/j.diabres.2011.10.040

- Harrison, A. M., Scott, W., Johns, L. C., Morris, E. M. J., & McCracken, L. M. (2017). Are We Speaking the Same Language? Finding Theoretical Coherence and Precision in "Mindfulness-Based Mechanisms" in Chronic Pain. *Pain Medicine*, pnw310. https://doi.org/10.1093/pm/pnw310
- Hayes, A. F. (2013). Introduction to mediation, moderation, and conditional process analysis : a regression-based approach. Retrieved from https://www.researchgate.net/publication/289066201_Introduction_to_Mediation_Moderati on_and_Conditional_Process_Analysis_A_Regression-Based_Approach
- Jain, R., Jain, S., Raison, C. L., & Maletic, V. (2011). Painful Diabetic Neuropathy is More than Pain Alone: Examining the Role of Anxiety and Depression as Mediators and Complicators. *Current Diabetes Reports*, 11(4), 275–284. https://doi.org/10.1007/s11892-011-0202-2
- Jensen, M. P., Chodroff, M. J., & Dworkin, R. H. (2007). The impact of neuropathic pain on health-related quality of life: Review and implications. *Neurology*, 68(15), 1178–1182. https://doi.org/10.1212/01.wnl.0000259085.61898.9e
- Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *General Hospital Psychiatry*, 4(1), 33–47. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7042457
- Kabat-Zinn J. (1990) Full catastrophe living: Using the wisdom of your body and mind to face stress, pain, and illness. New York: Delacourt, 1990.

Khoury, B., Lecomte, T., Fortin, G., Masse, M., Therien, P., Bouchard, V., ... Hofmann, S. G.

(2013). Mindfulness-based therapy: A comprehensive meta-analysis. *Clinical Psychology Review*, *33*(6), 763–771. https://doi.org/10.1016/j.cpr.2013.05.005

- Leeuw, M., Goossens, M. E. J. B., Linton, S. J., Crombez, G., Boersma, K., & Vlaeyen, J. W. S. (2007). The Fear-Avoidance Model of Musculoskeletal Pain: Current State of Scientific Evidence. *Journal of Behavioral Medicine*, *30*(1), 77–94. https://doi.org/10.1007/s10865-006-9085-0
- Lolignier, S., Eijkelkamp, N., & Wood, J. N. (2015). Mechanical allodynia. *Pflugers Archiv : European Journal of Physiology*, 467(1), 133–9. https://doi.org/10.1007/s00424-014-1532-0
- Lucey, B. P., Clifford, D. B., Creighton, J., Edwards, R. R., McArthur, J. C., & Haythornthwaite,
 J. (2011). Relationship of depression and catastrophizing to pain, disability, and medication
 adherence in patients with HIV-associated sensory neuropathy. *AIDS Care*, 23(8), 921–8.
 https://doi.org/10.1080/09540121.2010.543883
- Melzack, R. (2001). Pain and the neuromatrix in the brain. *Journal of Dental Education*, 65(12), 1378–82. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11780656
- Melzack, R., & Katz, J. (2006). Pain in the 21st Century: The Neuromatrix and Beyond. In *Psychological Knowledge in Court* (pp. 129–148). Boston: Kluwer Academic Publishers. https://doi.org/10.1007/0-387-25610-5_7
- Merskey, H., & Bogduk, N. (1994). *Classification of Chronic Pain. IASP Pain Terminology*. https://doi.org/10.1002/ana.20394
- Nathan, H., Poulin, P., Wozny, D., Taljaard, M., Smyth, C., Gilron, I., Sorisky, A., Lochnan, H. and Shergill, Y. (2017) RCT of Mindfulness Based Stress Reduction for Painful Diabetic Peripheral Neuropathy. *Pain*. Under revision.

- Nicassio, P. M., Schoenfeld-Smith, K., Radojevic, V., & Schuman, C. (1995). Pain coping mechanisms in fibromyalgia: relationship to pain and functional outcomes. *The Journal of Rheumatology*, 22(8), 1552–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7473482
- Park, T., Reilly-Spong, M., & Gross, C. R. (2013). Mindfulness: a systematic review of instruments to measure an emergent patient-reported outcome (PRO). *Quality of Life Research : An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, 22(10), 2639–59. https://doi.org/10.1007/s11136-013-0395-8
- Pavlin, D. J., Sullivan, M. J. L., Freund, P. R., & Roesen, K. (2005). Catastrophizing: a risk factor for postsurgical pain. *The Clinical Journal of Pain*, 21(1), 83–90. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15599135
- Pinto, R. Z., Ferreira, P. H., Kongsted, A., Ferreira, M.L., Maher, C.G., Kent, P., Self-reported moderate-to-vigorous leisure time physical activity predicts less pain and disability over 12 months in chronic and persistent low back pain. *Eur J Pain*. 2014;18(8):1190-1198. doi:10.1002/j.1532-2149.2014.00468.x.
- Poulin, P. A., Romanow, H. C., Rahbari, N., Small, R., Smyth, C. E., Hatchard, T., ... Wilson,
 K. G. (2016). The relationship between mindfulness, pain intensity, pain catastrophizing,
 depression, and quality of life among cancer survivors living with chronic neuropathic pain. *Supportive Care in Cancer*, 24(10), 4167–4175. https://doi.org/10.1007/s00520-016-3243-x
- Pradhan, E. K., Baumgarten, M., Langenberg, P., Handwerger, B., Gilpin, A. K., Magyari, T., ... Berman, B. M. (2007). Effect of Mindfulness-Based stress reduction in rheumatoid arthritis patients. *Arthritis & Rheumatism*, 57(7), 1134–1142. https://doi.org/10.1002/art.23010

Preacher, K. J. (2015). Advances in Mediation Analysis: A Survey and Synthesis of New

Developments. *Annual Review of Psychology*, 66(1), 825–852. https://doi.org/10.1146/annurev-psych-010814-015258

- Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments, & Computers*, 36(4), 717–731. https://doi.org/10.3758/BF03206553
- Schmidt, S., Grossman, P., Schwarzer, B., Jena, S., Naumann, J., & Walach, H. (2011). Treating fibromyalgia with mindfulness-based stress reduction: Results from a 3-armed randomized controlled trial☆. *Pain*, 152(2), 361–369. https://doi.org/10.1016/j.pain.2010.10.043
- Schütze, R., Rees, C., Preece, M., & Schütze, M. (2010). Low mindfulness predicts pain catastrophizing in a fear-avoidance model of chronic pain. *Pain*, 148(1), 120–127. https://doi.org/10.1016/j.pain.2009.10.030
- Sephton, S. E., Salmon, P., Weissbecker, I., Ulmer, C., Floyd, A., Hoover, K., & Studts, J. L. (2007). Mindfulness meditation alleviates depressive symptoms in women with fibromyalgia: Results of a randomized clinical trial. *Arthritis & Rheumatism*, 57(1), 77–85. https://doi.org/10.1002/art.22478
- Smeets, R. J. E. M., Vlaeyen, J. W. S., Kester, A. D. M., & Knottnerus, J. A. (2006). Reduction of Pain Catastrophizing Mediates the Outcome of Both Physical and Cognitive-Behavioral Treatment in Chronic Low Back Pain. *Journal of Pain*, 7(4), 261–271. https://doi.org/10.1016/j.jpain.2005.10.011
- Sullivan, M., Bishop, S., & Pivik, J. (1995). The pain catastrophizing scale: development and validation. *Psychological Assessment*, 7(4), 524–532. https://doi.org/10.1037/1040-3590.7.4.524

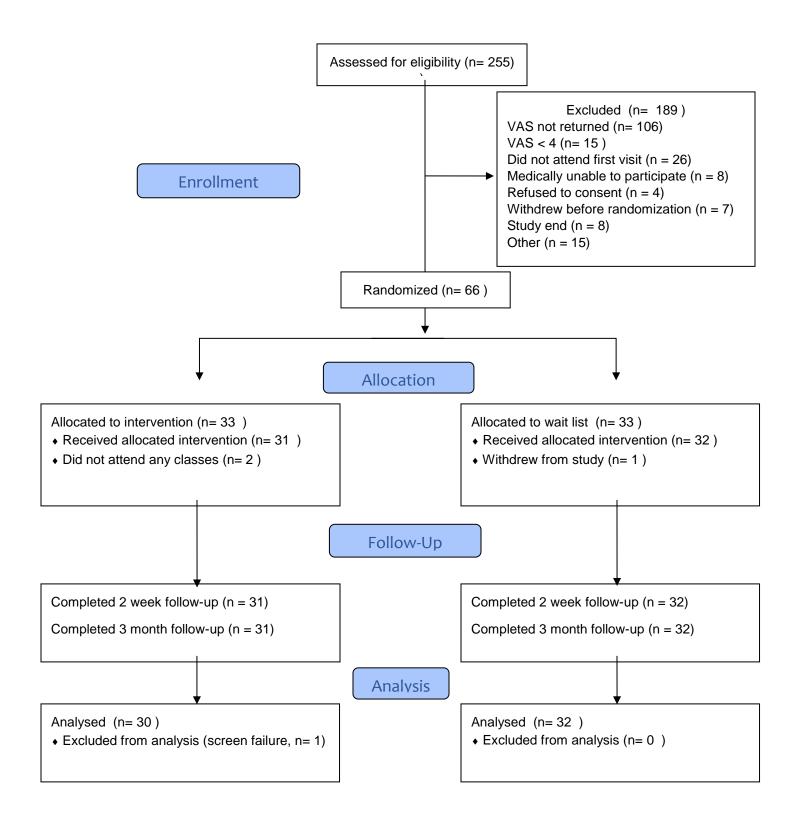
Sullivan, M. J. L., Lynch, M. E., & Clark, A. J. (2005). Dimensions of catastrophic thinking

associated with pain experience and disability in patients with neuropathic pain conditions. *Pain*, *113*(3), 310–315. https://doi.org/10.1016/j.pain.2004.11.003

- Sullivan, M. J. L., Thorn, B., Haythornthwaite, J. A., Keefe, F., Martin, M., Bradley, L. A., & Lefebvre, J. C. (2001). Theoretical Perspectives on the Relation Between Catastrophizing and Pain. *The Clinical Journal of Pain*, *17*(1), 52–64. https://doi.org/10.1097/00002508-200103000-00008
- Tesfaye, S., Vileikyte, L., Rayman, G., Sindrup, S. H., Perkins, B. A., Baconja, M., ... Boulton,
 A. J. M. (2011). Painful diabetic peripheral neuropathy: consensus recommendations on
 diagnosis, assessment and management. *Diabetes/Metabolism Research and Reviews*, 27(7),
 629–638. https://doi.org/10.1002/dmrr.1225
- Turner, J. A., Holtzman, S., & Mancl, L. (2007). Mediators, moderators, and predictors of therapeutic change in cognitive-behavioral therapy for chronic pain. *Pain*, 127(3), 276–286. https://doi.org/10.1016/j.pain.2006.09.005
- Van Hecke, O., Austin, S. K., Khan, R. A., Smith, B. H., & Torrance, N. (2014). Neuropathic pain in the general population: A systematic review of epidemiological studies. *Pain*, 155(4), 654–662. https://doi.org/10.1016/j.pain.2013.11.013
- Veehof, M. M., Oskam, M.-J., Schreurs, K. M. G., & Bohlmeijer, E. T. (2011). Acceptancebased interventions for the treatment of chronic pain: A systematic review and metaanalysis. *Pain*, 152(3), 533–542. https://doi.org/10.1016/j.pain.2010.11.002
- Vileikyte, L., Peyrot, M., Gonzalez, J. S., Rubin, R. R., Garrow, A. P., Stickings, D., ... Boulton,
 A. J. M. (2009). Predictors of depressive symptoms in persons with diabetic peripheral neuropathy: a longitudinal study. *Diabetologia*, 52(7), 1265–1273.
 https://doi.org/10.1007/s00125-009-1363-2

- Visted, E., Vøllestad, J., Nielsen, M. B., & Nielsen, G. H. (2015). The Impact of Group-Based Mindfulness Training on Self-Reported Mindfulness: a Systematic Review and Metaanalysis. *Mindfulness*, 6(3), 501–522. https://doi.org/10.1007/s12671-014-0283-5
- Vlaeyen, J. W., Kole-Snijders, A. M., Boeren, R. G., & van Eek, H. (1995). Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain*, 62(3), 363–72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8657437
- Vlaeyen, J. W., & Linton, S. J. (2000). Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*, 85(3), 317–32. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10781906
- Walach, H., Buchheld, N., Buttenmüller, V., Kleinknecht, N., & Schmidt, S. (2006). Measuring mindfulness—the Freiburg Mindfulness Inventory (FMI). *Personality and Individual Differences*, 40(8), 1543–1555. https://doi.org/10.1016/j.paid.2005.11.025
- Williams, J., & Mackinnon, D. P. (2008). Resampling and Distribution of the Product Methods for Testing Indirect Effects in Complex Models. *Structural Equation Modeling : A Multidisciplinary Journal*, 15(1), 23–51. https://doi.org/10.1080/10705510701758166
- Zale, E. L., & Ditre, J. W. (2015). Pain-Related Fear, Disability, and the Fear-Avoidance Model of Chronic Pain. *Current Opinion in Psychology*, *5*, 24–30. https://doi.org/10.1016/j.copsyc.2015.03.014
- Zelman, D. C., Gore, M., Dukes, E., Tai, K.-S., & Brandenburg, N. (2005). Validation of a Modified Version of the Brief Pain Inventory for Painful Diabetic Peripheral Neuropathy. *Journal of Pain and Symptom Management*, 29(4), 401–410. https://doi.org/10.1016/j.jpainsymman.2004.06.018

Appendix A: CONSORT Flow Diagram



Appendix B: Questionnaires

Coping with Chronic Pain Survey

To help us understand your current situation, please complete the following as fully as possible.

Where do you experience the most pain? Please check ($\sqrt{}$) only one. 1.

 [] Head, face, mouth [] Neck (cervical) region [] Shoulders [] Arms, hands [] Chest [] Abdominal region [] Upper back 	 [] Lower back, lumbar spine [] Legs, feet [] Pelvic region [] Genital region (private parts) [] Joints [] All over body [] Other (<i>please specify</i>)
--	---

How long have you had pain? ______ (approximate start date) 2.

Please tell us a little about yourself:

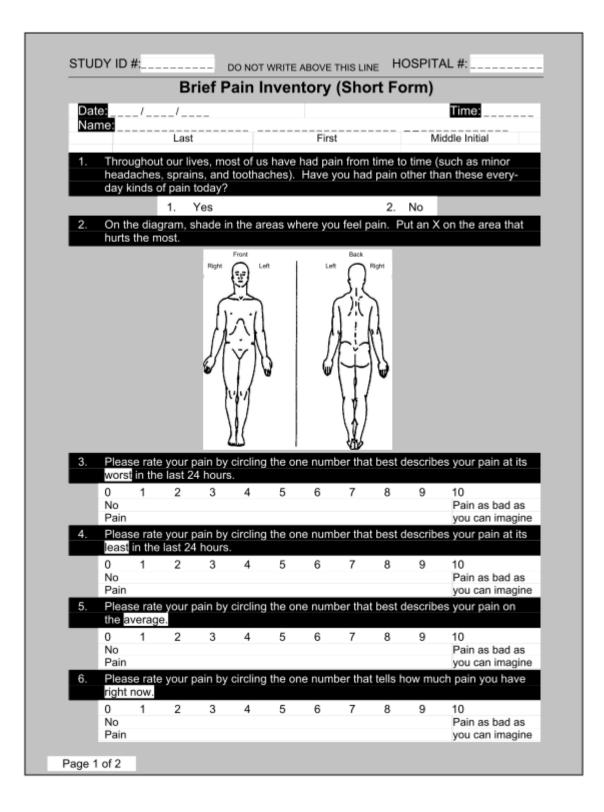
- What is your age? _____
 4. What is your gender? [] male [] female

 3.
- 5. What is your current marital or relationship status?
 - [] Single (include separated, divorced or widowed)
 - [] Married or [] Living with partner; How long? _____ (years)
- What is your **current** employment status? (please check the single most representative) 6.
 - ____ Full-time ____ Other (please specify) _____ _____ Part-time ____ Unemployed Student
- 7. In broad terms, how would you categorize your ethnic background?
 - [] Caucasian origin
 - [] First Nations origin

- [] African origin

[] Asian origin

[] Other (please specify)



Dat											Time:
Nar	ne:		Last				F	irst			Middle Initial
7.	What	treatm	ente o	r med	ications	are voi	, receiv	ing for y	our ps	ain2	
1.	what	ucau		i meu	Ications	are you	receiv	ing ior y	our pe	21012	
8.	In the	e last 2	4 hour	s, how	/ much r	elief ha	ve pain	treatme	ents or	medi	cations
		ded? F ave re			the one	percen	tage th	at most	shows	s how	much relief
	900 T	10%			40%	50%	60%	70%	80%	90%	100%
	No		2070	0070	4070	5070	0070	1070	0070	50 /	Complete
	Relief										Relief
9.		e the or ered w			nat descr	ribes ho	ow, duri	ing the p	bast 24	hour	s, pain has
	A. 0	Gene 1	ral Acti 2	3	4	5	6	7	8	9	10
	Does			-		-	-		-		Completely
	Interf	010								_	Interferes
	В. 0	Mood 1	2	3	4	5	6	7	8	9	10
	Does		2	5	4	5	0	'	0	_	Completely
	Interf	ere		_							Interferes
	C.		ng Abi			-		-			40
	0 Does	1 not	2	3	4	5	6	7	8	9	10 Completely
	Interf										Interferes
	D.										sework)
	0 Does	1 not	2	3	4	5	6	7	8	9	10 Completely
	Interfe										Interferes
	E.	Relati	ons wi	th oth	er peopl	е					
	0	1	2	3	4	5	6	7	8	9	10
	Does										Completely Interferes
	F.	Sleep									
	0	1	2	3	4	5	6	7	8	9	10
	Does										Completely
	Interfe G.		ment c	flife							Interferes
	0	Enjoy 1	2	3	4	5	6	7	8	9	10
	Does										Completely
	Interf	ere									Interferes

FFMQ

Please rate each of the following statements using the scale provided. Circle the number that best describes *your own opinion* of what is *generally true for you*.

Plea	se indicate below	Never or rarely true				Very often/ always true
1.	I perceive my feelings and emotions without having to react to them.	1	2	3	4	5
2.	When I'm walking, I deliberately notice the sensation of my body moving.	1	2	3	4	5
3.	I find it difficult to stay focused on what's happening in the present.	1	2	3	4	5
4.	I'm good at finding the words to describe my feelings.	1	2	3	4	5
5.	I criticize myself for having irrational or inappropriate emotions.	1	2	3	4	5
6.	I watch my feeling without getting lost in them.	1	2	3	4	5
7.	I notice how foods and drinks affect my thoughts, bodily sensations, and emotions.	1	2	3	4	5
8.	I pay attention to how my emotions affect my thoughts and behaviours.	1	2	3	4	5
9.	When I take a shower or a bath, I stay alert to the sensations of water on my body.	1	2	3	4	5
10.	It seems I am "running on automatic" without much awareness of what I'm doing.	1	2	3	4	5
11.	I can easily put my beliefs, opinions, and expectations into words.	1	2	3	4	5
12.	I tell myself that I shouldn't be feeling the say I'm feeling.	1	2	3	4	5
13.	In difficult situations, I can pause without immediately reacting.	1	2	3	4	5
14.	I pay attention to sensations, such as the wind in my hair or sun on my face.	1	2	3	4	5
15.	I rush through activities without being really attentive to them.	1	2	3	4	5
16.	It's hard for me to find words to describe what I'm thinking.	1	2	3	4	5
17.	I believe some of my thoughts are abnormal or bad and I shouldn't think them.	1	2	3	4	5
18.	When I have distressing thoughts or images, I am able to just notice them without reacting.	1	2	3	4	5
19.	I pay attention to sounds, such as clocks ticking, birds chirping, or cars passing.	1	2	3	4	5
20.	I do jobs or tasks automatically, without being aware of what I'm doing.	1	2	3	4	5
21.	I have trouble thinking of the right words to express how I feel about things.	1	2	3	4	5

		Never or rarely true				Very often/ always true
22.	I make judgements about whether my thoughts are good or bad.	1	2	3	4	5
23.	When I have distressing thoughts or images, I feel calm soon after.	1	2	3	4	5
24.	I find myself doing things without paying attention.	1	2	3	4	5
25.	When I have a sensation in my body, it's hard for me to describe it because I can't find the right words.	1	2	3	4	5
26.	I tell myself I shouldn't be thinking the way I'm thinking.	1	2	3	4	5
27.	When I have distressing thoughts or images, I "step back" and am aware of the thought or image without getting taken over by it.	1	2	3	4	5
28.	I notice the smells and aromas of things.	1	2	3	4	5
29.	When I do things, my mind wanders off and I'm easily distracted.	1	2	3	4	5
30.	Even when I'm feeling terribly upset, I can find a way to put it into words.	1	2	3	4	5
31.	I think some of my emotions are bad or inappropriate and I shouldn't feel them.	1	2	3	4	5
32.	Usually when I have distressing thoughts or images, I just notice them and let them go.	1	2	3	4	5
33.	I can usually describe how I feel at the moment in considerable detail.	1	2	3	4	5
34.	I don't pay attention to what I'm doing because I'm daydreaming, worrying or otherwise distracted.	1	2	3	4	5
35.	I disapprove of myself when I have irrational ideas.	1	2	3	4	5
36.	I notice visual elements in art or nature, such as colors, shapes, textures, or patterns of light and shadow.	1	2	3	4	5
37.	I am easily distracted.	1	2	3	4	5
38.	My natural tendency is to put my experiences into words.	1	2	3	4	5
39.	Usually when I have distressing thoughts or images, I judge myself as good or bad, depending on what the thought/image is about.	1	2	3	4	5

PCS Scale
Using the following scale, please indicate the degree to which you have these thoughts and feelings when you
are experiencing pain. "When I'm in pain"

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worry all the time about whether the pain will end.	0	1	2	3	4
I feel I can't go on.	0	1	2	3	4
It's terrible and I think it's never going to get any better.	0	1	2	3	4
It's awful and I feel that it overwhelms me.	0	1	2	3	4
I feel I can't stand it anymore.	0	1	2	3	4
I become afraid that the pain will get worse.	0	1	2	3	4
I think of other painful events.	0	1	2	3	4
I anxiously want the pain to go away.	0	1	2	3	4
I can't seem to keep it out of my mind.	0	1	2	3	4
I keep thinking about how much it hurts.	0	1	2	3	4
I keep thinking about how badly I want the pain to stop.	0	1	2	3	4
There is nothing I can do to reduce the intensity of the pain.	0	1	2	3	4
I wonder whether something serious may happen.	0	1	2	3	4