DEVELOPMENT OF NEUROPATHIC PAIN SCREENING TOOL IN ISIZULU.

TEMITOPE RICHARD FAGBOHUN

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy.

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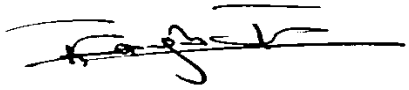
2021

DECLARATION

I, Fagbohun Temitope Richard, declare that “Development of neuropathic pain screening tool in isiZulu” hereby submitted to the University of the Witwatersrand, for the degree of doctor of philosophy, has not previously been submitted by me for a degree at this or any other University; that it is my work in design and execution, and that all material contained herein has been duly acknowledged.



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Fagbohun Temitope Richard

Signed on __29___ day of _____April_____, 2021 in PARKTOWN.

I certify that the studies included in this thesis have the approval of the Human Research Ethics Screening Committee of the University of the Witwatersrand, Johannesburg. The ethics clearance number is M150245.

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Temitope Richard Fagbohun

Signed on __29___ day of ___April__ _____, 2021 in PARKTOW

DEDICATION

I would like to thank God of Israel for taking me through this long-awaited journey and giving me the strength and courage to make this thesis a living document. This thesis is dedicated to God my creator. Secondly, I would like to dedicate this work to my late father Ademakinwa Matthew Fagbohun and my late mother Mrs Florence Mosunmola Fagbohun who passed on during my journey toward this degree in South Africa. Thank you for bringing us up in the way of the Lord. May your good soul continue to rest in the bosom of your creator. In addition, I dedicate this work to my wife Olajumoke Jessica Fagbohun, and my children Oluwafisayomi Samuel, Oluwatobiloba Eunice and Oluwapelumi David. Lastly, all my brothers (Bro.Peter, Dr Abiodun, Bro. Wumi, Yemi and Femi) in the Fagbohun family.

ABSTRACT

Neuropathic pain is a subjective experience that affects the mechanism of the somatosensory system positively (paresthesias, spontaneous pain, increased sensation of pain) or negatively. It has a debilitating effect on the cognitive, emotional, and physical function of the patients. There has not been an effective diagnosis of this type of pain, hence poor prognosis by pain experts. Indeed, there is a need for an effective diagnostic tool for neuropathic pain quality that will differentiate it from non-neuropathic pain. Several neuropathic pain screening tools (Neuropathic Pain Scale (NPS), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique en 4 Questions (DN4), PainDETECT Questionnaire (PDQ)) has been developed and validated in the description of pain symptoms and clinical signs; and translated in different languages. Neuropathic pain has been a challenging type of pain managed by pain experts and has created a burden to the patients, family of the patients and government. Several neuropathic pain diagnoses procedures have been suggested in the past, but this has not been effective in management of this type of pain.

Recently, the combination of verbal and clinical testing of the patient has brought up a good diagnosis prognosis and improved the management of neuropathic pain. This has led to development and validation of several translated tools (NPS, LANSS, ID Pain, DN4) in different local languages applicable to the test populations. None of these tools have been developed in African languages to be applicable in Africa to diagnose neuropathic pain. Therefore, in this study, neuropathic pain screening tool was conducted in IsiZulu (an official language in South Africa) speaking population attending the University of Witwatersrand hospitals (Rahima Moosa Mother and Child Hospital, Helen Joseph Hospital, Chris Hani Baragwanath Hospital and Charlotte Maxeke Academic Hospital Johannesburg, South Africa) between April 2015 and July 2019.

Firstly, we conducted a systematic review on the psychometric properties, reliability, and validity of translated version of DN4, LANSS and Pain DETECT. The outcome

showed that all the translated versions of the screening tools had a good sensitivity, specificity, reliability and validity ranging from 70%-100%.
Secondly, a neuropathic pain screening tool in isiZulu was developed from the translated DN4 version. In a sample population of 122 participants (neuropathic n = 61; nociceptive n = 61), patients were asked to describe their pain in isiZulu and the triggers thereof. Neuropathic pain was distinguished from nociceptive by location of the origin and aetiology of the patients' pain. This was recorded and transcribed to English language by professional translators. 'Burning' symptom (29%) was frequently described spontaneously by neuropathic pain patients followed by cramping (25%) and sharp pain (17%) symptoms. However, stabbing (2%) was less frequently described during the spontaneous description. Furthermore, a published copy of prompt neuropathic pain symptoms in isiZulu was read to them to identify the symptoms they were experiencing. Tingling was never mentioned as a symptom during the spontaneous description. Nevertheless, it was only after the prompt symptoms were read out in isiZulu language that the patients were able to identify tingling (61%) as a more frequent symptom they were experiencing.

Lastly, the isiZulu neuropathic pain screening tool was developed to identify patients with neuropathic pain describing their pain as 'pulling', 'cramping' and 'cutting', symptoms in conjunction with clinical signs (Hypoesthesia to pin-prick, brush and touch). This new tool was translated by the professional translator directly to isiZulu language. A pilot study was conducted at chronic pain clinics (rheumatoid arthritis clinic and orthopaedic clinic). Only participants with pure nociceptive (n=23) or neuropathic pain (n=23) were included in this study. Patients with mixed pain were excluded in the study. Two clinicians rated the pain of the patients independently. The result shows that the new tool had an accuracy of 89.0%, sensitivity 83%, specificity of 94.0%, positive predictive value 90.0% and negative predictive value 88.0% compared to the original DN4 English version. This clearly indicates the new neuropathic pain screening tool in isiZulu is reliable to distinguish neuropathic from non-neuropathic pain patients.

In conclusion, the data presented has projected insight on the importance of a translated version of screening tools to be useful in the clinical settings for distinguishing neuropathic from non-neuropathic pain in isiZulu speaking population

in South Africa. All these have added new and unique knowledge in the clinical frontiers.

PRESENTATIONS

The following presentations have arisen from this work.

Oral presentation:

Presented at Brain Research Function group, University of the Witwatersrand, Parktown, Johannesburg. BFRG DAY June, 2015 **:** Systematic review of translated version of DN4, LANSS and PDQ.

Presented at Brain Research Function group, University of the Witwatersrand, Parktown, Johannesburg**.** BFRG DAY August, 2018: isiZulu terms in description of nociceptive and neuropathic pain.

Poster presentation:

Presented a research poster at the Pain SA conference Johannesburg. 6 August 2018. Poster title: Systematic review of translated and validated neuropathic pain screening tool (DN4, LANSS, and PDQ) between 2001 and 2010.

Award

Best poster presentation PainSA Conference 2018.

PUBLICATION

Under review: International Journal of medicine and medical research

Title: Systematic review on the psychometric, reliability and validity of neuropathic pain screening tools (DN4, LANSS and PDQ) 1 January2005-19 July 2019

Temitope Fagbohun MSc, Antonia Wadley Ph.D and [1]Peter Kamerman Ph.D. School of Physiology, ,Brain Research Function Group, Faculty of Health Sciences, University of the Witwatersrand.

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- Prof P.H Karmerman. Supervised the design and planning of the study and intellectual input and frequent advice.
- Dr A. Wadley. Supervised the design and planning of the protocol and intellectual input on the final writing of the thesis. (Chapter 1,2,3)
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- Dr Sean Chatty, Co-supervisor Data collection, intellectual input on clinical content (Chapter 2)
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TABLE OF CONTENT

DECLARATION i
DEDICATION ii
ABSTRACT iii
PRESENTATIONS vi
ACKNOWLEDGEMENTS vii
TABLE OF CONTENT viii
LIST OF FIGURES xii
LIST OF TABLES xiii
LIST OF ABBREVIATIONS xv
CHAPTER 1- GENERAL INTRODUCTION 1
1.1 Introduction 2
1.2 Epidemiology of neuropathic pain 4
1.3 Classification of Pain 6
1.3.1 Acute vs chronic 6
1.3.2 Nociceptive, inflammatory, and neuropathic pain 7
1.4 Pain scales 9
1.4.1 Diagnosis of pain type based on symptoms. 10
1.4.2 Diagnosis of neuropathic pain using screening tools. 12
1.4.3 Neuropathic pain scale (NPS) 15
1.4.4 Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) 17
1.4.5 Neuropathic pain Questionnaire (NPQ) 21
1.4.6 Douleur Neuropathique en 4 Questions (DN4) 23
1.4.7 ID pain 27
1.4.8 PainDetect (PD-Q) 31
1.4.9 The need to assess neuropathy conditions in South Africa 33
1.4.10 Assessing neuropathic pain in South Africa 34
1.5 Overall conclusion 36
1.6 Aims: 37
1.6.1 Objectives 37
CHAPTER 2-GENERAL METHODOLOGY 38
2.1. Introduction 39
2.2 Study 1 – Systematic review on the psychometric, reliability, validity properties of translated version of dn4, lanss and pdq questionnaires 40
2.2.1 Study question 40
2.2.2 Study Inclusion Criteria 41

2.2.3 Search Strategy 41
2.2.4 Data handling 44
2.2.5 Screening 44
2.2.6 Data extraction 44
2.2.7 Measures of Reliability 45
2.2.8 Measures of diagnostic performance 45
2.3 Study 2: Development of a neuropathic pain screening tools in isizulu 46
2.3.1 Ethics clearance 46
2.3.2 Participants 46
2.3.3 Inclusion Criteria 47
2.3.4 Determination of pain of neuropathic origin 47
2.3.5 Neurological testing procedure 48
2.4 Study 3- Assessment of a new isizulu neuropathic pain screening tool compared to isizulu version of DN4 51
2.4.1. Protocol (The Interview) 51
2.5 Statistical analysis 53
CHAPTER 3-SYSTEMATIC REVIEW ON THE PSYCHOMETRIC, RELIABILITY, VALIDITY PROPERTIES OF TRANSLATED VERSION OF DN4, LANSS AND PDQ QUESTIONNAIRES 54
3.1 Introduction 55
3.2 Method 56
3.2.1 Study Inclusion Criteria 56
3.2.2 Search strategy 56
3.2.3 Data management 57
3.3 Results 58
3.3.1Summary of the articles included: 60
3.3.2 Description of the included studies 60
3.3.3 DN4 65
3.3.4 DN4-interview 72
3.3.5 LANSS 74
3.3.6 Self-LANSS 79
3.3.7 PainDETECT 84
3.4 Discussion 88
3.5 Conclusion 92
3.6 Recommendation 93
CHAPTER 4-DEVELOPMENT OF A NEUROPATHIC PAIN SCREENING TOOLS IN ISIZULU 94
4.1 Introduction 95

4.2 Method 97
4.2.1 Participants' inclusion criteria 97
4.2.2 Pain descriptive interview 98
4.2.3 Participants Pain Rating 99
4.2.4 Interview 99
4.2.5 Prompted response. 100
4.2.6 Statistical analysis 100
4.3 Results 100
4.3.1 Demographic and clinical characteristics 100
4.3.2 Distribution of participants according to underlying cause of pain 101
4.3.3 Pain Intensity 102
4.3.4 Spontaneous description of pain symptoms in isiZulu: 105
4.3.5 Common spontaneous descriptive symptoms pain patients 106
4.3.6 Percentage of descriptive symptoms in IsiZulu spontaneously 111
4.3.7 English symptoms selected by the neuropathic pain and nociceptive pain participants from prompted isiZulu symptoms list. 111
4.3.8 Determination of the symptom that best discriminate between nociceptive and neuropathic pain 113
4.4 CART model 114
4.4.1 Model with all variables 116
4.4.2 Model with variables selected through variable selection method (stepwise regression) 118
4.5 Discussion 122
4.6 Conclusion 124
CHAPTER 5 -ASSESSMENT OF A NEW ISIZULU NEUROPATHIC PAIN SCREENING TOOL COMPARED TO ISIZULU VERSION OF DN4 126
5.1 Introduction 127
5.2 Methodology 128
5.2.1 Inclusion criteria 128
5.2.2 Protocol 128
5.2.3 Statistical analysis 129
5.3 Results 129
5.3.1 Assessment of reliability and validity of isiZulu-DN4: 132
5.4 Discussion 135
5.5 Conclusion 135
CHAPTER 6 -GENERAL DISCUSSION AND CONCLUTION 136
6.1 Introduction 137

6.2 Systematic review on the psychometric, reliability and validity of neuropathic pain screening tools (DN4, LANSS and PDQ) between 01 January 2001 and 19th July 2019. 137
6.3 Development of neuropathic pain screening tools in isizulu 138
6.4 Pilot study of the screening tool 139
6.5 Limitations 139
6.6 Conclusion 140
6.7 Implications of the study 141
6.8 Scientific contribution of the study 141
6.9 Publications 142
6.10 My role in this research 142
APPENDIX 1 143
APPENDIX 2 146
APPENDIX 3 153
APPENDIX 4 157
APPENDIX 5 160
APPENDIX 6 163
APPENDIX 8 165
Appendix 9 167
APPENDIX 10 170
REFERENCES 177

LIST OF FIGURES

Figure 1.1: Combined 11-point numerical pain rating scale and in verbal descriptor scale……10
Figure 1.2: Diagnosis of neuropathic pain flow chart……...15
Figure 13: Phase 1 ID pain tool development process……..…29
Figure 2.1: Participant's recruitment sites summary…….....47
Figure 2.2: Vibration sensory testing…….……...….49
Figure 2.3: Ankle reflex testing……..…….50
Figure 2.4: Pinprick sensation demonstration……..51
Figure 3.1 Summary of data inclusion…… ….……59
Figure 4.1: South African 11 languages with percentage of speakers in the population…….97
Figure 4.2: pain scale rating a week before interview……..103
Figure 4.3: Worse pain time……..103
Figure 4.4: Pain rating at interview……..……104
Figure 4.5 Neuropathic and nociceptive pain symptoms……107
Figure 4.6: Spontaneous description of isiZulu pain symptom……..……111
Figure 4.7: CART analysis flow chart……..114
Figure 4.8: ROC curve for specificity and sensitivity of the logistic regression model in prediction of neuropathic and nociceptive quality of pain…….....117
Figure 4.9: ROC Curve for specificity and sensitivity of stepwise regression model in prediction of neuropathic and nociceptive quality of pain…….....120
Figure 5.1:DN4 -English version screening tool……....130
Figure 5.2: Translated DN4 in isiZulu……....131
Figure 5.3: New Neuropathic pain screening tool……....132

LIST OF TABLES

Table 1.1: Prevalence of pain with neuropathic characteristics in the general population.....5
Table 1.2: Comparison of subjective items in 5 diagnostic neuropathic pain questionnaires……...13
Table 1.3: Clinical signs in DN4 & LANSS……14
Table 1.4: ID pain neuropathic pain assessment tool and scoring system.....30
Table 2.1: PICO method used to define study method……..40
Table 2.2 Selection criteria for included articles……..41
Table 2.3 Search strategy used for e-resources.....41
Table 2.4 The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.....42
Table 3.1 Description of the included studies……..62
Table 3.2 Measure of validity of translated version of DN4.....67
Table 3.3 Measure of reliability of translated DN4 instrument……..70
Table 3.4 Measure of validity of translated of translated LANSS……76
Table 3.5 Measure of reliability of translated LANSS……78
Table 3.6 Development of translated version of s-LANSS.....80
Table 3.7 Measure of sure of reliability of translated version od s-LANSS.....81
Table 3.8 Measure of validity of tranlated versions of of the s-LANSS.....83
Table 3.9 Development of translated version of painDETECT Questionnaire.....85
Table 3.10 Measures of validity for translated versions of the PainDETECT.....86
Table 3.11 Measures of reliability for translated versions of the PainDETECT…….87
Table 4.1: Demographic and clinical characteristics according to pain type.....101
Table 4.2: Distribition of patients according to clinics……..…..102
Table 4.3: Participants worse pain site according to the Wisconsin brief pain questionnaire……..……....105
Table 4.4: Example of patients description of pain.in isiZulu translated by professional translators to English language……106
Table 4.5: Percentage of participants of IsiZulu description of prompt symptoms translated to English language.....108

Table 4.6: IsiZulu symptom spontaneous responses by nociceptive pain vs neuropathic pain patients……..109

Table 4.7: Percentages of participants (nociceptive pain patients and neuropathic pain patients) indicating the symptoms listed on the published DN4 English version prompt response……112

Table 4.8: In sample prediction (training data)……..114

Table 4.9 Out of sample prediction (test data)……..114

Table 4.10: Test of accuracy, sensitivity, and specificity of test data……115

Table 4.11: Regression analysis table……116

Table 4.12: Model Summary……116

Table 4.13: Hosmer and Lemeshow test……117

Table 4.14: Confusion matrix……117

Table 4.15: Out of sample prediction……..118

Table 4.16: Stepwise regression analysis……..119

Table 4.17: Model summary……119

Table 4.18: Hosmer and Lemeshow test……119

Table 4.19: In sample prediction……..120

Table 4.20: Out of sample prediction……..121

Table 4.21: Accuracy, sensitivity, and specificity rates for in sample prediction…..121

Table 5.1:Demongraphic and clinical characteristics according to pain type……129

Table 5.2:Test of validity of isiZulu translated DN4……..133

Table 5.3: Test of validity of new isiZulu neuropathic pain screening tool among isiZulu chronic Nociceptive and neuropathic pain patients……..134

LIST OF ABBREVIATIONS

AUC	Area under curve
CRTA	Correlation regression tree analysis
DN4	Douleur Neuropathique en 4 Questions
DSP	Distal sensory polyneuropathy
HIV-SN	HIV associated sensory neuropathy.
ICC	Intraclass Correlation Coefficient
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
MPQ	McGill Pain Questionnaire
NeuP	Neuropathic pain
NPQ	Neuropathic Pain Questionnaire
NPS	Neuropathic Pain Scale
NPSI	Neuropathic pain scale inventory
PD-Q	PainDETECT Quetionnaire
QST	Quantitative sensory testing
ROC	Receiver operating characteristic
S-LANSS	self-completed LANSS

CHAPTER 1- GENERAL INTRODUCTION

Current knowledge about chronic neuropathic and nociceptive pain and the literary in the different screening tools used to diagnosing it.

1.1 Introduction

Pain is a process of early alarm and warning about any change in the normal physiological state of the body that may cause damage (Woolf and Ma, 2007). Pain is thus a protective phenomenon, and is useful to detect, and reduce contact with noxious stimuli in order to prevent tissue injury and damage (Serrie and Servière, 2014). The redefinition of pain as suggested by the International association of study of pain (IASP, 2020) states that pain is *"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage '* (Raja,2020). Consequently, in a pathological state, like chronic pain (neurophathic), the protective function of pain is lost and may become maladaptive (Walters, 2019). Indeed, these maladaptive pain states, may interfere with a person's ability to complete activities of daily living, affect their mental health, relationships and ability to work (Dueñas *et al.*, 2016).

Neuropathic pain is generally a stressful pain condition that is associated with great suffering due to the intensity of the pain experienced by the patients and long duration of the condition (Meyer-Rosberg *et al.*, 2001; Torta, Ieraci and Zizzi, 2017). This results in low quality of life and increased burden on the individual. The increase in the prevalence of patients with neuropathic pain is associated with increase in burden on health care facilities and government expenditure in managing pain (McCarberg and Billington, 2006).

Neuropathic pain can affect individuals' quality of life negatively (Dueñas *et al.*, 2016). Moreover, the presence of neuropathic pain is associated with worse health, negative repercussion at work place, on the family, the societal environment and diminished general physical body function (e.g walking, exercise, recreational function and productivity) (Brod *et al.*, 2015; Dueñas *et al.*, 2016). A report indicates that 17% of people with this pain rate their quality of life as being worse than death (Torrance *et al.*, 2014). Furthermore, neuropathic pain results in higher degree of mood disruption (depression and anxiety), reduced mobility, fatigue due to sleep disturbances (Quattrini and Tesfaye, 2003) and increase work impairment (Sadosky *et al.*, 2014) compared with patients with non-neuropathic chronic pain (Lantheaume, 2018).

Due to the type of damage or the underlying pathological mechanisms in neuropathic pain, the disorders are differentiated based on the origin. In common diseases, injuries and their interventions, lesions to the peripheral or central somatosensory nerves may lead to neuropathy. Painful peripheral neuropathies are caused by diabetes and other metabolic conditions e.g. diabetic polyneuropathy, neurotropic viral disease (e.g. herpes zoster infection, HIV-related neuropathies), nutritional deficiencies, neurotoxicity (e.g. by chemotherapy of cancer, HIV, and tuberculosis) immune mediated disorders (e.g.Guillain–Barré syndrome chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy) and physical trauma to a nerve trunk (Szczudlik *et al*., 2014). Peripheral neuropathy develops in about one third of individuals with diabetes and about half of these will have a painful neuropathy (Timmerman *et al.*, 2013; Jensen *et al.*, 2006).

Of note, diabetes mellitus currently affects about 1.8 million South Africans with an estimated 69% of undiagnosed diabetes among diabetics and is expected to increase globally by 2045 (Sahadew and Singarem, 2019). There are few data on neuropathic pain prevalence in developing countries including South Africa; however, given the high rates of diseases and conditions that predispose towards the development of neuropathic pain in developing countries (e.g., diabetes mellitus, HIV, trauma), it is expected that the prevalence of neuropathic pain is similar or greater than it is in developed countries.

In South Africa, an estimated 35 to 60% of HIV-positive outpatients previously had a peripheral neuropathy, with three-quarters of these patients having a painful neuropathy (Maritz *et al*., 2010; Wadley *et al*., 2011; Pillay *et al*., 2015a; Moketla *et al*., 2018; Pillay *et al*., 2019b). A report published by UNAIDS 2019 data reported that approximately 7.7 million South Africans were infected with HIV (United Nations Joint Programme on HIV/AIDS (UNAIDS), 2019), which means that between 2.7 and 4.6 million people could have painful HIV-associated sensory neuropathy (HIV-SN). Moreover, HIV-SN showed good prognosis data for neuropathic pain in South Africa. This is due to the changes in the regimen rollout of new ARVs with a reduced neurotoxicity compared to the previous regimens (Starr, 2011; Pillay *et al.*, 2015). When focusing on two potential causes of neuropathic pain (diabetes and HIV-related), it is clear that the occurrence of neuropathic pain is potentially high in South

Africa. Moreover, this pain is difficult to treat and has social and economic impact on the patients (Dueñas *et al.*, 2016). Therefore, proper assessment and treatment is essential.

1.2 Epidemiology of neuropathic pain

Neuropathic pain is common in the general population, Van Hecke *et al* ., 2014 reported 7 to 8%; Breviek *et al*., 2006; van Hecke *et al*., 2013 reported 10-30%, depending on the population studied. Studies conducted in the European general population (table 1.1) reported that the prevalence of neuropathic pain was 7% while 4% of participants had chronic pain associated to nerve dysfunction (Bouhassira *et al*., 2008). A 2012 analytic review included data from the US reported 6–8%, a proportion that is likely to increase in the future (Smith and Torrance, 2012). A systematic review of the epidemiology of neuropathic pain studies globally reported a prevalence between 6.9% and 10% in general population (Van Hecke *et al*., 2014).

Table 1.1: Prevalence of pain with neuropathic characteristics in the general population

Study	Sample size/location	Definition	Prevalence
(Bouhassira *et al.*, 2008)	23,712/France	"Chronic pain with neuropathic characteristics"	6.9%
(Dieleman *et al.*, 2008)	9,311/Netherlands	"Neuropathic pain"	0.8%[a]
(Gustorff *et al.*, 2008)	7,707/Austria	"Neuropathic pain"	3.3%
(Torrance *et al.*, 2006)	3,002/United Kingdom	"Pain of predominantly neuropathic origin"	8.2%
(Toth, Lander and Wiebe, 2009)	1,207/Canada	"Chronic pain with neuropathic pain symptoms"	17.9%
(Yawn *et al.*, 2009)	3,575/United States	*NeuP	Clinical examination: 9.8%
			S-LANSS: 8.8%
			Berger criteria: 3.0%
			Self-reported: 12.4%

**NeuP - neuropathic pain; (Dieleman et al., 2008) give incidence, not the prevalence*

1.3 Classification of Pain

1.3.1 Acute vs chronic

Classifying pain may assist clinicians in the treatment of pain. There are many ways to classify pain and classifications may overlap (Woolf *et al.*, 1998; Nicholas *et al.*, 2019). Based on the duration of pain, pain can be classified as acute pain or chronic pain. Acute pain is the normal physiological and behavioural response to noxious stimuli and involves activation of the nociceptors (A-δ and C primary afferent nerve fibres) by noxious chemical, thermal or mechanical stimuli associated with surgery, trauma and acute illness (Chichorro, Porreca and Sessle, 2017). Alternatively, it may result from the nociceptive cascade triggered by tissue injury (Carr and Goudas, 1999). It is typically self-limiting and resolves with tissue healing. However, chronic pain lasts longer than the usual duration of healing from an insult or injury to the body (Merskey, 1994; Carr and Goudas, 1999). Pain lasting longer than three months is generally classified as chronic (Franz *et al.*, 2017; Nicholas *et al.*, 2019).

Consequently, chronic pain no longer serves as a protective function and is a debilitating disease in itself (Woolf, 2004, 2011). It is also difficult to manage and treat it compared to acute pain (Chandler, 2018). In addition, it is often associated with long-term illnesses such as osteoarthritis and fibromyalgia (Finnerup and Jensen, 2006). The classification of chronic pain can be nociceptive, resulting from the activation of nociceptors (e.g., chronic inflammatory diseases such as rheumatoid arthritis) or neuropathic resulting from damage to peripheral or central somatosensory pathways (e.g., trauma, diabetes mellitus, HIV) or nociplastic, resulting from altered sensory processing, with no apparent injury (e.g., fibromyalgia, irritable bowel syndrome) (Costigan, Scholz and Woolf, 2009). The prevalence of chronic pain in adults has been reported between 14% to 30% (Algudairi, Aleisa and Al-Badr, 2019; Dhanju *et al.*, 2019; Umeda and Kim, 2019). A recent study reported one out of five South African adults have chronic pain (Kamerman *et al.*, 2020).

Chronic pain is associated with persistent pain hypersensitivity, which may present itself as spontaneous pain, hyperalgesia (increased response to noxious stimuli) and/or allodynia (normally non-painful stimuli perceived as being painful) (Latremoliere and Woolf, 2009). The mechanisms involved in this hypersensitivity may involve

autonomous amplification of nociceptive signals in the central nervous system (Staud and Rodriguez, 2006; Arendt-Nielsen *et al.*, 2018), with a disturbed balance of excitation and inhibition in central circuits (Bennett, 1999; Bayot, Viadel and de Julián, 2005)

For chronic nociceptive pain and neuropathic pain, the mechanisms underlying the hypersensitivity involve changes in the peripheral (if peripheral injury has occurred) and central nervous systems (Finnerup, and Jensen 2021) .These hypersensitivity, hyperalgesia, allodynia and temporal summation especially those in the central nervous system, are postulated to “maintain” the pain (Woolf, 2011; Yang and Chang, 2019).

1.3.2 Nociceptive, inflammatory, and neuropathic pain

Nociceptive pain

Nociceptive pain represents the normal response to noxious insult or injury to tissues such as skin, muscles, visceral organs, joints, tendons, or bones, caused by a potentially harmful stimulus (extreme hot or cold, pressure, pinching and chemical) being detected by sensory receptors called nociceptors in a process called nociception (Gold and Gebhart, 2010). The International Association for the Study of Pain (IASP) defined nociception as “the neural processes of encoding and processing noxious stimuli” (Loeser and Treede, 2008).

Stimulation of a nociceptor by a noxious stimulus generates action potential (transduction) at the periphery at the end of the sensory nerve cell whose terminals are sensitive to this type of activation. The sensory impulse generated is transmitted from the periphery to the central nervous system through primary sensory neurons (C and A-delta fibres) which have their cell bodies in the dorsal root ganglia of the spinal cord (Torsney and MacDermott, 2006). Moreover, C-fibres are type II unmyelinated, small diameter (1.2-1.5 micrometer), low conducting velocity neurons (2m/s) which constitute the neuronal component of the peripheral nervous system (Somatic and autonomic nervous system) (Herdman and Jensen, 1997) .They transmit burning, warm, cramp sensory impulses to the other somatosensory pathway through the dorsal root of the spinal cord (Dubin and Patapoutian, 2010; Harding *et al*., 2020).

Therefore, damage to this fibre results in neuropathic pain. Furthermore, A-delta fibres are type II slightly myelinated, bigger axon diameter (1-5 micrometer) and the conduction velocity is higher than the C-fibres (3-30m/s) (Firmin *et al.*, 2014).They function as afferent nerve fibres in transmission of cold, pressure and pain sensation from the peripheral mechanothermal-specific nociceptor to central nervous system in a localized fashion (Yam *et al.*, 2018).

Inflammatory Pain

Inflammatory pain is a type of nociceptive pain that results from tissue damage by a noxious stimulus, infection or autoimmune disease. In the case of inflammatory pain, intact primary afferent nociceptive fibers become sensitized through the release of inflammatory mediators such as prostaglandin, bradykinin, protons, adenosine triphosphate, potassium ions by the injured tissue or infiltrating immune cells (Gilron, Baron and Jensen, 2015)(Schaible, Ebersberger and Natura, 2011). In addition, Kinins exert a number of proinflammatory effects including the release of prostanoids, cytokines and free radicals from a variety of cells (Dray, 1995). Particularly, cytokines such as IL1β, exert an important contribution to hyperalgesia which is indirectly mediated via the release of prostaglandins (Ren and Torres, 2009). These mediators either directly stimulate nociceptors (e.g., bradykinin), or sensitize the fibres by increasing receptor density and sensitivity (e.g., prostaglandins). Increased activity in primary afferent nociceptors leads to short-term and long-term use-dependent changes in the spinal cord (central sensitization), including changes in neurotransmitter release, and increases in receptor density and sensitivity in the dorsal horn of the spinal cord. These changes augment the transmission of nociceptive input to higher centres, leading to chronic inflammatory pain (Staud and Smitherman, 2002)

Neuropathic pain

Neuropathic pain is a type of chronic pain arising from the consequences of pathology affecting the somatosensory system (Loeser and Treede, 2008). Neuropathic pain may result from damage or diseases of the peripheral or the central somatosensory nervous system (Woolf and Mannion, 2009). Thus, neuropathic pain may be divided into peripheral and central neuropathic pain, or combination of nociceptive and neuropathic pain (Baron *et al*., 2017).

The development of neuropathic pain shares some features of peripheral and central sensitization that occur with inflammatory pain, nevertheless, also exhibit unique features. In the periphery, nerve injury is associated with increased excitability of the neurons brought about by changes in receptor expression and sensitivity that result in ectopic activity in the nerves and phenotypic switching of non-nociceptive fibres to express receptors and ion channels typically associated with nociceptors. Secondary changes in the central nervous system include activation of microglia, which release inflammatory mediators that sensitize nociceptive pathways, and allow non-nociceptive input to “gain access” to nociceptive pathways. Moreover, there is also reduced local and descending inhibition of nociceptive circuits (Woolf, 2011). Therefore, chronic neuropathic and nociceptive (inflammatory) pain differs in the mechanisms underlying their development and maintenance. Nociceptive-inflammatory pain is associated with activation of peripheral receptive terminals of primary afferent neurons in response to noxious chemical (inflammatory), mechanical or ischemic stimuli (Campbell *et al*., 2006). The mechanisms include hyperexcitability and abnormal impulse generation resulting in increased sensitivity to mechanical, thermal and chemical stimuli (Colloca *et al*., 2017). Moreover, nociceptive pain ultimately results in healing and resolution of inflammation processes (Baral *et al*., 2019). However; neuropathic pain does not frequently show such reversal and persists with evidence of resolution to the injury sensation observed in soft tissue resolution. Therefore resulting in somatosensory pathway damages (Xu and Yaksh, 2011).

1.4 Pain scales

Assessment of pain can be determined by the measurement of the characteristics and types of pain individual’s experience (Dansie and Turk, 2013), and depending on the extent of the characterisation, pain may be measured by uni-dimensional or multi-dimensional scales (Clark *et al.*, 2002). Uni-dimensional scales are the most basic method of assessing pain and as the name implies, they measure one aspect of the pain that is experienced. Typically, this aspect of pain is its intensity. Commonly used uni-dimensional pain intensity scales include instruments such as the numerical pain rating scale, which typically includes either 11 or 101 point scales, anchored at 0 (no pain) and 10 (worst pain imaginable) and 0 (no pain) and 100 (worst pain imaginable), respectively. Alternatives include visual analogue scales anchored at no pain and

worst pain imaginable, and verbal descriptor scales, where patients are asked to use one word (mild, moderate or severe) (Haefeli and Elfering, 2006; Younger, McCue and Mackey, 2009; Voepel-Lewis *et al.*, 2011; Ham *et al.*, 2015). Figure 1.1 shows a combined 11-point numerical pain rating scale and in verbal descriptor scale.

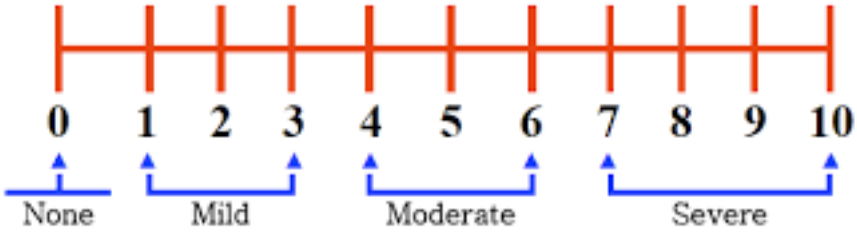

Figure 1.1: Combined 11-point numerical pain rating scale and in verbal descriptor scale.

While single features of pain can be assessed using uni-dimensional scales (as long as they have clear anchor points), they can only characterise individual features of an existing pain. However, they cannot provide nor indicate for the aetiology and type of pain. On contrary, multi-dimensional scales offer a broader assessment of a pain. For example, the widely used Brief Pain Inventory (Cleeland and Ryan, 1994) offers a more holistic measure of pain, measuring the history, location, and intensity of pain, as well as pain relief and the interference of pain on activities of daily living. Yet, the Brief Pain Inventory still only characterises the pain and its effect, and not the aetiology of the pain. Indeed, even when multiple tools are used together, unless they are designed to differentiate potential sources of pain, they are of little value when it comes to determining whether, for example, a pain is neuropathic or nociceptive. In addition, given that these two types of pain respond to different treatments, differentiation of the type of pain is essential to proper management of a pain.

1.4.1 Diagnosis of pain type based on symptoms.

Using symptoms to diagnose the underlying cause of a pain is not a new concept. In 1971, in the development of the McGill Pain Questionnaire (MPQ), Melzack and Torgensen (Melzack & Torgerson, 1976) noted the following, “the words consisted of a wordlist focussing on multiple dimensions of pain that can serve as the basis of a questionnaire, to determine the properties and nature of particular kinds of pain in

individual patients. Such a questionnaire may not only provide an aid to diagnosis and prognosis, however may also become a valuable experimental tool for studies of analgesic drugs". Thus, symptoms can aid in the diagnosis of types of pain. In 1976, Agnew and Merskey (Agnew and Merskey, 1976) attempted to differentiate pain of "organic" origin from pain of "psychiatric" origin using patients description of their pain. They found no difference in the number of words used but did report that individuals with "organic" pain used thermal words (e.g., hot, burning) more often that those individuals with "psychiatric" pain. In support of this finding, Dubuisson and Melzack,1976 using the MPQ, could differentiate between eight pain types using symptoms, with 77% of patients been correctly classified using symptom only. When combining symptoms with information on patient sex, age, and location of pain, Dubuisson and Melzack,1976 classified 100% of patients correctly. However, there were dissenters. Atkinson and colleagues (Atkinson, Kremer and Ignelzi, 1982) dismissed the notion that symptoms could be used to discriminate between kinds of pain, finding that the language of pain was too imprecise and unsystematic to be used for diagnosis.

All these early studies were, however, dogged by poor definitions of "caseness", which would have reduced the sensitivity of the analyses. When the relationship between pain type and symptoms was studied in better defined cohorts, symptoms consistently were found to differentiate between pain aetiologies. Melzack *et al.*, 1986 were able to distinguish between difficult to diagnose cases of trigeminal neuralgia and atypical facial pain, such that the type of pain could be corrected predicted in 90% of patients using just seven words from the MPQ. Masson *et al*., 1989 also using the MPQ, managed to differentiate between neuropathic pain (painful diabetic polyneuropathy in the legs) and non-neuropathic (non-neuropathic pain of the legs and feet) pain; 91% of patients were correctly identified. When summing up their findings, Masson *et al.,* 1989 noted that what was important was not individual words, but combinations of words that were important in making the diagnosis. Finally, Boureau and colleagues (Boureau *et al.,* 1990)using the French version of the MPQ, predicted the diagnostic category (neuropathic vs non-neuropathic pain) in 66% of cases. Thus, at least in the case of neuropathic pain versus non-neuropathic pain, the use of combinations of pain symptoms may be a useful means of differentiating between the two types of pain.

Indeed, when it comes to neuropathic pain, the symptomatology of the pain has been used to differentiate between different causes of neuropathic pain. For example, the Neuropathic Pain Scale, which was developed by Galer and Jensen,1997 and contained a list of 11 items (2 items assessed global features of intensity and unpleasantness, 8 items assessed sensory features, and 1 item assessed temporal pattern of pain) chosen based on clinical experience. The scale was able to differentiate between individuals with post-herpetic neuralgia as compared to other types of neuropathic pain.

1.4.2 Diagnosis of neuropathic pain using screening tools.

There are clusters of signs and symptoms in neuropathic pain that are thought to arise from the unique changes that occur in the somatosensory nerve system following nerve injury (Baron and Tölle, 2008). It is these unique features of neuropathic pain that allow the clinician to use medical history, clinical examination and diagnostic tests for evidence of nerve lesions to differentiate neuropathic from non-neuropathic pain (Finnerup *et al* 2016).

Screening tools have been developed to assist in the differential diagnosis of neuropathic versus nociceptive pain in the clinical and research setting. The three most commonly used tools are the Douleur Neuropathique en 4 Questions (DN4, Bouhasirra *et al*., 2005, originally development in French, 136 published articles based on title/abstract search for “Douleur Neuropathique 4” on PubMed), the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS, Bennett 2001, originally development in English, 190 published articles based on title/abstract search for “Leeds Assessment of Neuropathic Symptoms and Signs” on PubMed), and the PainDETECT (PD-Q, Freyenhagen *et al*., 2006), originally development in German, 285 published articles based on title/abstract search for “PainDETECT” on PubMed). Other, less commonly used screening tools include the ID Pain questionnaire (ID Pain, Portenoy 2006, originally development in English, 17 published articles based on title/abstract search for “ID Pain” on PubMed), and the Neuropathic Pain Questionnaire (NPQ, Krause and Backonja *et al;* 2003, originally development in English, 20 published articles based on title/abstract search for “Neuropathic Pain Questionnaire” on Pubmed).

Table 1.2: Comparison of subjective items in 5 diagnostic neuropathic pain questionnaires*.

	LANSS	DN4	PD-Q	NPQ	ID Pain
Pricking, tingling, pins, needles**	•	•	•	•	•
Electric shocks or shooting**	•	•	•	•	•
Hot or burning**	•	•	•	•	•
Numbness***		•	•	•	•
Pain evoked by light touching***	•		•	•	•
Painful cold or freezing pain***		•		•	
Pain evoked by mild pressure			•		
Pain evoked by cold			•		
Pain evoked by changes in weather				•	
Itching		•			

Modified from Bennett et al., 2007[*], (Dark shaded boxes highlight common symptoms experienced by pain patients shared among the screening tools. Light shaded features indicate clinical signs shared by two or more tools). LANSS: Leeds Assessment of Neuropathic Symptoms and Signs, DN4: Douleur Neuropathique en 4 Questions, NPQ: Neuropathic Pain Questionnaire, PD-Q: PainDETECT Quetionnaire, ID Pain: ID pain Questionnaire

All these questionnaires include a qualitative component that assesses symptoms shown to be core features of the quality of the pain in neuropathic pain states (see table 1.2). The similarity in the qualitative components of these tools, which were developed in English (ID Pain, LANSS), French (DN4) and German (painDETECT), indicates conservation of neuropathic pain symptoms across language groups. However, all these languages form part of the Indo-European language group and

validation studies were conducted in their respective national populations, using first-language speakers. Direct translations of these questionnaires into other languages (including non-Indo-European languages) have been undertaken, and for the most part, the direct translations of the original terms into the new language have been found and the new versions of the questionnaires validated (see chapter 2 for a systematic review of the translation and validation of these questionnaires). The commonality of terms used to describe neuropathic pain was brought to the fore for African languages in a unique study where isiZulu speakers (a language of the Niger-Congo, Southern Bantu group) with pain, and a medical history and clinical signs consistent with neuropathic pain were asked to describe their pain in their own language. The isiZulu terms they used broadly overlapped with the terms used by Indo-European group languages such as English, French and German (Shaikh *et al*., 2013). Only two of these screening tools (LANSS and DN4) include assessment of clinical signs of nerve damage (Table 1.3).

Table 1.3: Clinical signs in DN4 & LANSS

Signs	LANSS	DN4
Hypoesthesia to touch	•	•
Hypoesthesia to prick	•	•
Brushing		•

Because they assess for clinical signs in addition to neuropathic pain symptomatology, these two questionnaires are the only two that fit the criteria required for the diagnosis of probable neuropathic pain in patients with a relevant medical history, as described by Finnerup *et al*.,,2016 (Figure1. 2).

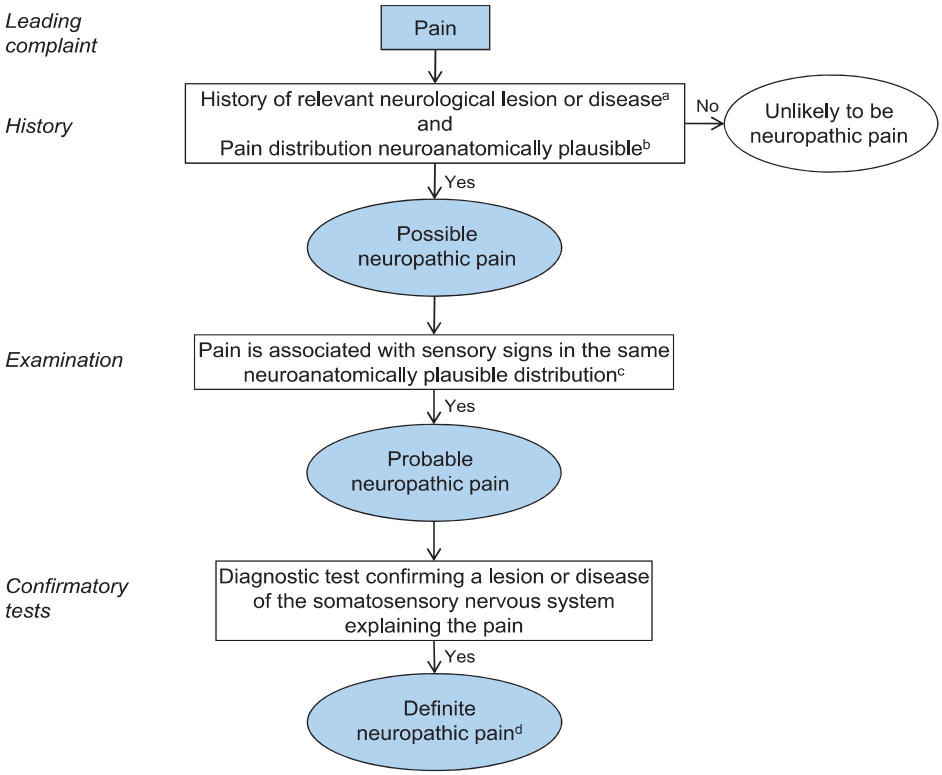

Figure 1.2: Diagnosis of neuropathic pain flow chart (Finnerup *et al*.,2016).

In the following sections I will describe the development and characteristics of the LANSS (and S-LANSS), NPQ, DN4 (and DN4 interview), ID Pain, and PD-Q, in more detail.

1.4.3 Neuropathic pain scale (NPS)

The neuropathic pain scale is a pain assessment tool developed in English in the United States of America by Galer and Jensen, 1997, However, NPS was constructed to assess the different symptoms of neuropathic pain qualities experienced by neuropathic pain patients in the designated pain clinic. This assessment tool was specific for neuropathic pain assessment and not the signs, hence, It is not a neuropathic pain diagnostic tool when used alone but a good tool to identify the sensory characteristic of neuropathic pain in chronic pain patients (Galer and Jensen, 1997)

The construction of the NPS scale was subjectively based on the author's clinical experience in the determination of correct words commonly used by the chronic pain

In a study conducted by Galer and Jensen,1897, patient with neuropathy in the description of the symptoms of pain. Eight (8) items (sharp, dull, cold, hot, itchy, sensitivity, surface pain, and deep pain) relating to neuropathic pain were selected unanimously, one item measuring the pain intensity in neuropathy and one item describing how unpleasant their experienced pain quality (Galer and Jensen, 1997) resulting into ten (10) items in total.

Patients were asked to rate whether they have the pain and their pain quality on the scale and the intensity of their pain on an 11-point pain rating numerical scale. The validation study of NPS was carried out in two phases. The first phase was conducted in a cohort study among two hundred and eighty-eight (288) pain patients with neuropathic pain of mixed origin. Patents were asked to identify their neuropathic pain symptoms on the questionnaire and rate the severity on 11 points numerical scale. Statistical analysis (Pearson's correlation coefficient) was conducted on the outcome of 10 descriptors to determine the relevancy of the items to neuropathic pain symptoms determination. Furthermore, different variance analysis was conducted on the outcome descriptors on NPS to determine the ability to identify patients with different neuropathy.
The outcome showed that items 'cold, sharp, sensitivity, and itchy' could differentiate 'Post hepatic neuralgia' from other neuropathy only but could not further differentiate other neuropathic with a mixed origin.

The second phase of the validity study was constructed to determine the sensitivity of the 10 items on the NPS questionnaire to neuropathic pain treatment (lidocaine administration and phentolamine infusion) (Galer and Jensen, 1997). Seventy-eight (78) pain patients with neuropathic pain of mixed origin that is, reflex sympathetic dystrophy, diabetic neuropathy, causalgia, and spinal cord injury, traumatic peripheral nerve injury were recruited from the chronic pain clinic. They were treated with lidocaine administration and phentolamine infusion.

It was reported that the neuropathic pain symptoms on the NPS scale decrease after the treatment. The outcome further showed that treatment with lidocaine showed a better decrease in the symptoms (deep and unpleasant pain) than phentolamine on

the NPS questionnaire (Galer and Jensen, 1997). The authors concluded that NPS focussed on neuropathic pain symptoms and treatment sensitivity only (Galer and Jensen, 1997). This validation study indicated that the NPS questionnaire is effective in the assessment of neuropathic pain symptoms quality and sensitivity of the symptoms to the treatment of neuropathic pain. NPS items on the questionnaire only showed 10 items that do not cover the whole symptoms of neuropathic pain, hence, NPS cannot be useful in the diagnosis of neuropathic pain (Galer and Jensen, 1997). This outcome could be an opening to further research on the discovery of more neuropathic pain symptoms.

1.4.4 Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)

The LANSS was the first diagnostic tool for neuropathic pain to be developed. In addition to assessing five symptom items, it also included two clinical tests for signs of peripheral nerve damage (Bennett, 2001) , The LANSS scale was developed for chronic pain patients with neuropathic pain dominating their pain experience. It was developed as an improved tool over the Neuropathic Pain Scale (NPS), which could not adequately differentiate neuropathic pain from non-neuropathic pain (Roy and Ghosh, 2013)

The construction of the LANSS scale was in two parts: first, the pain scale was constructed using one cohort and then secondly, the validity and reliability of the developed scale were tested on an independent cohort. For the first part, the construction of the tool involved identifying pain descriptors sourced from patient surveys and published data. Interestingly, the qualitative part of the questionnaire was not constructed as a checklist of symptoms, but rather, a series of questions about the nature of the sensation, with supporting adjectives indicating how the sensation may be experienced when appropriate for the question. The questions were designed to cover six domains: i) ongoing superficial pain with thermal qualities, ii) ongoing superficial pain with dysesthesia-like qualities, iii) continuous deep pain, iv) paroxysmal pain, v) stimulus-dependent pain, and vi) autonomic dysfunction.

The assessment of signs of nerve fibre dysfunction consisted of two tests: i) pin-prick sensitivity, and ii) mechanical allodynia. The assessment of pin-prick

sensitivity used graded pin-prick applicators (a series of weighted needles that were applied to the skin), while the assessment of mechanical allodynia required the stroking of the skin with a piece of cotton wool. In all cases, the stimuli were applied at the site of the pain and at a reference site located adjacent to the pain site or on the contralateral body part.

The constructed questionnaire was then administered to 60 patients with pain (30 with neuropathic pain and 30 with nociceptive pain, no patients with mixed pain were included) and logistic regression modelling was used to select the most discriminant combination of symptoms and signs. The question related to “ongoing deep pain” was selected both by patients with neuropathic and patients with nociceptive pain and was therefore removed from the final constructed scale version. The scoring of the instrument was based on the odds ratios for the questions and physical assessments generated by the final logistic regression model. That is, questions were weighted by their “importance”, with more discriminatory questions been given greater weighting. Finally, a cut-off score for differentiating between nociceptive and neuropathic pain was derived from the optimum balance between positive and negative predictive values.

The newly developed scale was then tested in a second group of patients (20 with neuropathic pain, 20 with nociceptive pain, no patients with mixed pain were included). In this second study, the questionnaire was administered twice to each patient, once by the investigator and then again, at most 30 minutes later, by another clinician. The other clinician was blinded to the score of the investigator. Item scores were then assessed for agreement between ratters and internal consistency. In addition, discriminant properties were compared between the questionnaire and clinical judgement.

When assessed against clinical judgement, the questionnaire, using a cut-off score of 12, had a sensitivity of 85% and a specificity of 80%. The positive predictive value was 81% and the negative predictive value was 84%. All items on the questionnaire were significantly associated with having neuropathic, there was good internal consistency (Cronbach alpha = 0.74), and high inter-rater agreement across all items [Cohen’s Kappa range: 0.6 (dysesthesia) to 0.88 (autonomic)].

Overall, the study, with its two-study method, was well designed and carried out. However, there were limitations. The most patently clear limitation, and one that the author raises in the discussion, is the lack of a gold-standard case definition for neuropathic pain. Therefore, all comparisons are made against an imperfect reference standard, namely, clinical judgement. In addition, while it is clear that clinical judgement was the reference standard for the second study, no mention is made of the basis for selecting the cohort for the first study, presumably it was also clinical judgement. Also, it is unclear what the involvement was of the author in the original diagnosis of the patients. If the author had been involved in the initial diagnosis, there may have been some bias introduced. The second limitation is the use of positive and negative predictive values to select the cut-off score used to differentiate between neuropathic and nociceptive pain. While positive and negative predictive values are informative for a clinician, they are heavily influenced by the prevalence of the condition that is being assessed, such that positive predictive values increase, and negative predictive values decrease as prevalence of the disease increases. In the case of this tool development, the prevalence of neuropathic pain was set at 50%, which is greater than what would be found in a general chronic pain population (Van Hecke *et al.*, 2014). This over estimation becomes even greater when the tool is used in a general adult population (see S-LANSS below). Thirdly, the questionnaire was optimized to detect large effect sizes. That is, an estimated difference of about 6.5 points (50% of the mean difference in score between neuropathic and nociceptive groups from the first study) was used when calculating the sample size for study 2. This value represents about a quarter of the span of the scale (24 points). Moreover, no patients with mixed pain were included in the study sample, so the scoring was based on the assessment of two very disparate groups, which would have maximized the differences in scores. In a real-world setting, where the source of the pain is unclear, and could include purely neuropathic, purely nociceptive, and mixed pain, the performance of the instrument may fall appreciably. Lastly, and a minor issue, was the scoring. The authors used the odds ratios from the logistic regression model, rounding the number to make scoring easier. However, they did not round the values to the nearest integer, rather they used a floor method of rounding. So, for example, the odds ratio for the dysaesthesia question was 5.24, and the odds ratio for the autonomic question was

5.91, but both were rounded to a score of 5. It is unclear why this method of rounding was used if the original objective was to differentiate the weighting of the questions using the odds ratios. Also, the confidence interval for the odds ratios are never provided, so the precision of the estimates is unknown and therefore the utility of the point estimate is unclear.

In 2005, Bennett and colleagues developed a self-report version of the LANSS, which could be completed by individuals without the aid of a clinician. The self-report version of the scale was called the S-LANSS. In order to make the questionnaire more readily self-administered, the wording of the questions were changed slightly to make them simpler, but without changing the essence of the question. Also, the assessment of signs of neuropathy were changed to facilitate self-investigation. Instead of assessing dynamic allodynia in response to a cotton whisp, individuals were instructed to gently rub the pain sites and a non-painful site with their finger and note any positive differences in sensation at the pain site (e.g., burning, pins-and-needles). Instead of pin-prick sensitivity, individuals were instructed to gently press with a finger on the pain site and a non-painful site and to note any differences in sensation at the pain site compared to the non-painful site (tenderness or numbness). As such, the second test changed from an assessment of punctate mechanical stimulus to the assessment of a blunt mechanical stimulus. Overall, the weighted scoring of the instrument was left unchanged.

The authors then assessed the questionnaire under two circumstances, firstly in a patient population attending a chronic pain clinic, and secondly a postal survey. Like the validation of the LANSS, the reference standard in the patient-based study was the clinical diagnosis of neuropathic or nociceptive pain. Patients (n = 100 per group, nociceptive vs neuropathic) also completed the S-LANSS by themselves and using an interview format by the investigator. For the self-complete, the optimum cut-off score was 12, yielding a sensitivity of 74% and a specificity of 76% (overall classification was 75%). When used in an interview format, the optimum cut-off of the S-LANSS score was 10, yielding a sensitivity of 80%, and a specificity of 80% (overall classification was 80%). The questionnaire (administered unaided and aided) had good construct and convergent validity (measured against the Neuropathic Pain Scale). Also, it had good reliability (Cronbach alpha was 0.71 for the unaided completion, and 0.81 for the interview completion).

For the postal survey, the S-LANSS was posted to two separate groups. The first group consisted of 160 randomly chosen people from a general practice population of 6841 adults, and the second group consisted of 150 consecutively sampled individuals from a waiting list for a chronic pain clinic. The survey was distributed with the Neuropathic Pain Scale in order to assess convergent validity. In total, the response rate was 56% (89/160 general practice cohort, 85/150 pain clinic cohort), with 12% (11/89) of the general practice cohort, and 55% (47/85) of the pain clinic cohort scoring 12 or more on the scale, indicating pain of predominantly neuropathic origin. When compared to the Neuropathic Pain Scale, there was good convergent validity, and there also was good internal consistency (Cronbach alpha = 0.79 for the general practice sample, and 0.72 for the pain clinic sample).

Using these two approaches (clinic study and postal survey) the S-LANSS was therefore shown to be the first validated tool for the self-identification of pain of predominately neuropathic origin, with utility for population-based studies of neuropathic pain. The authors did, however, note that there are several issues with the study. As with the validation of the LANSS, the clinical study was validated against an imperfect reference standard (clinical diagnosis of neuropathic pain), and the postal survey did not include any comparison to a reference standard. Moreover, they used the Neuropathic Pain Scale as a comparator for the S-LANSS, yet the Neuropathic Pain Scale was not designed to discriminate neuropathic and nociceptive pain. Finally, they did not assess inter-rater reliability or test-retest reliability.

1.4.5 Neuropathic pain Questionnaire (NPQ)

Neuropathic Pain Questionnaire was developed by Krause and Backonja, 2003 to provide a general assessment tool for neuropathic pain, and for this assessment to aid in the discrimination of neuropathic pain from nociceptive pain. The development involved the recruitment of 528 patients from several clinics (it is unclear how many clinics and whether these were specialist pain clinics). These patients were classified as having nociceptive, neuropathic, or other pain based on medical chart review. The final sample size consisted of 149 patients judged to have had strictly nociceptive pain and who were willing to take part in the study, and 233 patients judged to have had

strictly neuropathic pain and who were willing to take part in the study (total sample size = 382). In an attempt to quantify the veracity of this record-based classification, 32 patient records were randomly chosen and were reviewed by an independent physician. Raw agreement (not controlling for chance agreement) showed that the two physicians failed to agree in 16% of cases, agreed somewhat in 38% of cases (same primary pain diagnosis, but with one physician adding on a secondary source of pain), and fully agreed in 47% of cases. Thus, the record-based group ascertainment is a serious limitation to the study.

The 382 patients taking part in the study were given a 32-item questionnaire to complete by themselves or assisted by a research assistant (when physical disability did not allow self-completion). The items covered 18 sensory aspects, 8 affective aspects, and 6 sensitivity aspects of a person's pain. For each item, participants had to rate their pain on a 0 to 100 visual analogue scale, and thus the scale assessed not only the presence of a feature of the pain, but the intensity of that feature. Using exploratory factor analysis, they generated a six-factor solution (based on Kaiser criterion), which they termed: affect, hyperaesthesia/allodynia, sensitivity, sensory I and II, and negative sensory. Interestingly, four items that are present in the final 12-item questionnaire did not load onto any of the six factors, namely, burning pain, numbness, electric pain, and freezing pain. The inclusion of these items appears to have been determined by another, poorly described, assessment. In this other analysis, it appears that the authors compared the scores given for each of the 32-items by the nociceptive and neuropathic groups, and it was this analysis (although poorly described) that was the main determinant of whether items from the 32-item questionnaire made it onto the final 12-item questionnaire.

Once they had generated the 12-item questionnaire, they used discriminant analysis to assess the ability of the questionnaire to differentiate between patients with neuropathic pain and nociceptive pain. They used a two-step analysis to assess the discriminant ability of the questionnaire. Three-quarters of the sample was used in the initial discriminant analysis, and the remaining quarter of patients' data were set aside as a hold-out group on which the tool could be assessed. For the first group, scores from each item were entered all at once into a discriminant analysis, which was used to generate a total discriminant function score (scores ≥ 0 indicating neuropathic pain).

The resulting discriminant function successfully classified 76% of cases (sensitivity: 74.7%, specificity: 77.6%). When the discriminant function was applied to the hold-out group, it successfully classified 71% of cases (sensitivity: 66.6%, specificity: 74.4%).

There are several issues with the tool and its development, some of which have been mentioned already. In terms of the development process, there are issues with the "caseness" of participants, and there is a major issue with the same sample of patients being used to develop the 12-item questionnaire and to test it. Even the hold-out group is not a true hold-out group for this reason. Also, the process used to select items from the 32-item list is poorly reported, which is odd given the detail provided for the factor analysis, which was only peripherally used for item selection. In terms of the tool itself, the discriminant function score is calculated by multiplying the discriminant function coefficient for each item by the score for that item, and then adding all the resulting scores together. This scoring method is required to generate the overall discriminant function score, but it does slow down the use of the instrument as a quick screening tool. Secondly, the tool does not assess physical signs of neuropathy, and as such, even when combined with a suitable medical history, its diagnostic certainty is one of possible neuropathic pain (Finnerup *et al.*, 2015). Lastly, and most importantly, the tool does not perform well in terms of sensitivity or specificity, and so there will be many false positives and negative results.

1.4.6 Douleur Neuropathique en 4 Questions (DN4)

In 2005, Bouhassira and colleague's developed questionnaire to differentiate patients with chronic pain associated with neuropathic pain to patients with nociceptive pain. This French language questionnaire was called the douleur neuropathique 4 question (DN4).

The starting instrument consisted of four themes (questions). The first question assessed the quality of the pain (5 items), and the second question dealt with the quality of paraesthesia/dysesthesias (4 items). Questions three and four involved physical examination to assess signs of neuropathy. In particular, question three consisted of four assessments of hypofunction, while question four consisted of four tests of hyperfunction of the somatosensory nervous system. For all items covered within the four questions, the answers were dichotomous, being either present

("yes") or absent ("no"). All the items on this provisional questionnaire were chosen for being associated with neuropathic pain based on expert opinion and a search of the literature.

One-hundred and sixty-seven (167) patients with chronic pain of at least moderate intensity, and who were attending 1 of 14 possible pain centres in France, were each assessed by two investigator, three days apart and with no treatment initiated in that time. At each visit patients underwent a comprehensive clinical examination by a doctor. This examination formed the basis for a diagnosis of neuropathic or somatic pain (i.e., the reference standard to which the outcome of the questionnaire was to be compared to). After the clinical examination, the doctor administered the provisional questionnaire to the patient. The two doctors were unaware of the others diagnosis or questionnaire score. For a patient's data to be included in the analysis, the diagnosis the two doctors gave based on the clinical examination needed to match. Based on this criterion, data from seven patients was excluded from the analysis. Thus, in total, data from 160 patients were analysed, and based on the clinical examination, 89 (56%) of the participants had neuropathic pain and 71 (44%) had non-neuropathic pain. Importantly, none of the participants had mixed pain, diffuse pain, or pain of unclear origin. That is, the pain was deemed to be neuropathic or nociceptive in origin.

Overall, patients and doctors found that the wording of the items was clear and that the questions were relevant. Based on this assessment, the investigators deemed the questionnaire to have good face validity. Confirming the investigators selection of adjectives to describe the positive symptoms of neuropathic pain, seven of the terms were chosen significantly more often by individuals with neuropathic compared to nociceptive pain. The exceptions were "squeezing" and "lancinating". Similarly, the selection of which signs to assess was largely confirmed by the predominance of all signs assessed (except for pressure allodynia) in individuals with neuropathic pain.

The use of two investigators to assess each patient had two benefits, one is that the diagnosis of the type of pain was more firmly established (no one with discordant clinical diagnoses was included in the analysis), and two, it allowed inter-rater

agreement to be assessed. With regards to inter-rater agreement, item-based analysis found high Cohen's kappa values for all items except for the "pain evoked by contact with cold" from question 3, indicating good agreement. Further analysis of the psychometric properties of the questionnaire using factor analysis showed that there was a nine-factor solution. Each of the symptoms loaded onto an individual factor, except factor 6, which saw "tingling" and "pins-and-needles" loading on the same factor. With regards to clinical signs, there was a high degree of correlation between the items that constituted the sensory loss assessment (all four tests loaded on factor 1), and a high degree of correlation between items that constituted sensory gain (all items, except for pain increased by pressure, loaded on factor 2).

The investigators then generated a logistic regression model to determine the discriminant properties of the instrument. Before generating the model, they excluded seven items based on the analyses they had performed. Dropped items included pain symptom items, "lancinating" and "squeezing" (see above, no differentiation between neuropathic and non-neuropathic groups), evoked pain items: "pain evoked or increased by pressure" (see above, no differentiation between neuropathic and non-neuropathic groups), and "pain increased by heat" and "pain increased by cold" (see above, highly correlated with each other), and pain hypoesthesia items: "hypoesthesia to heat " and "hypoesthesia to cold" (see above, highly correlated with each other). Thus, the final questionnaire/model included 4 questions and a total of 10 items (3 for symptoms of pain, 4 for symptoms of paraesthesia/dysesthesias, 2 for signs of loss of function, and 1 for signs of hyperfunction. The modelling process involved calculating a score for the question and regressing that against the reference standard of whether the pain was neuropathic or non-neuropathic in origin. The score was calculated by simply assigning a score of "1" to all "yes" answers and a score of "0" to all "no" answers, and then summing across the 10 items. The modelling process showed that at a cut-off score of 4, yielded the highest percentage of correctly identified patients (diagnostic accuracy = 86%, sensitivity = 82.9%, specificity = 89.9%, Youden index = 0.73).

The investigators also calculated a cut-off score when only using the seven symptom items (the DN4-interview questionnaire) and found that at a cut-off of 3 they could achieve a sensitivity of 78.0%, a specificity of 81.2%, at a Youden index of 0.59. Finally, they translated the questionnaire into English using a forward and backward translation method. Although this English version was published alongside the French version, they did not validate the English version.

As already mentioned, the scoring of the questionnaire involved the simple addition of the equally weighted items. This approach makes for simple scoring, which contrasts with the weighed scoring of the NPS and the LANSS/S-LANSS. But this ease of scoring comes at the cost of treating each item as equally discriminatory and based on the validations of the NPS and LANSS/S-LANSS, this is not so. A more nuanced approach to scoring may have yielded better diagnostic accuracy. The other limitation to the study, and one that is common to all validations of diagnostic/screening tools for neuropathic pain, is the lack of a gold standard case definition. The authors appear to have tried to overcome this issue by using two independent clinical experts (experienced neurologists) to assess each participant. There is however an issue with the how the two investigators went about the process of clinically characterising the participants and then administering the questionnaire. Because the clinical diagnosis was arrived at before the questionnaire was administered, we do not know whether there was any bias in the way that the clinician applied the questionnaire. A better approach would have been to have a third and fourth investigator to administer the questionnaire; this does however would have made the study more logistically difficult to run. The last issue I have with the development process is how items were dropped from the analysis, especially those that were dropped (or not dropped) based on the factor analysis. For example, “electric shocks” and “numbness” do not load on any factor, but they both are retained in the questionnaire. Indeed, the general approach for selecting items for a questionnaire follows the process of an exploratory factor analysis, dropping items that do not load, followed by a test of internal consistency (Cronbach alpha), using drop-one analysis to identify any additional items that can be dropped.

1.4.7 ID pain

The ID Pain questionnaire was developed by the ID Pain Steering Committee (consisting of neurologists, anaesthesiologists, rheumatologists, primary care givers, and expert in questionnaire development) as a very simple and easily self-administered pain assessment tool to differentiate neuropathic pain from nociceptive pain at primary health care facilities (Portenoy, 2006b). The authors felt that the development of a new neuropathic pain screening tool was warranted because published screening tools (LANSS, S-LANSS, DN4, NPQ) were not used at the primary health care settings (no evidence was provided to support this claim).

The first step in the development of the tool was to establish a large selection of items (n = 120) that a sub-committee extracted from existing tools and the experience of the sub-committee's members. This list of 120 items was the reduced to 89 items after review by the sub-committee, and the clarity and meaning of the items had been tested on a cohort of patients who had had non-headache related pain for at least 30 days (no details were provided on this cohort of patients). The 89-item tool then entered a two-phase development process.

The primary goal of phase 1 was item reduction. Of the 588 patients recruited from 29 primary cate sites, 586 met the inclusion criteria (non-headache related pain from the same site for more than 30 days, and willing to have a follow-up assessment by a pain specialist) and took part in this phase of the study. These patients were asked to complete the 89 items questionnaire and then, within 14 days, were assessed by a pain specialist. The pain specialists were blind to the results of the questionnaire and were required to diagnose participants as having nociceptive (n = 403), neuropathic (n = 85), or mixed pain (n = 98). For analysis purposes, the mixed pain and neuropathic pian groups were collapsed into a "non-nociceptive" group (the reason for this decision was not provided). Pain specialists were briefed beforehand on the criteria used to define patients' pain condition and were provided with examples of typical conditions within each pain category. The data obtained was then subjected to a complicated data reduction strategy involving two separate processes, each with multiple steps, the results of which were then amalgamated into a final six-item scale.

Process one consisted of an exploratory factor analysis followed by stepwise multivariable logistic regression and best subset logistic regression. The factor analysis reduced the number of items to 65. These 65 items were then subjected to the modelling component, which generated 16 unique items.

Process two consisted of generating a series of 89 univariate logistic regression models (one for each item). This process identified 65 items that statistically differentiated between nociceptive and non-nociceptive pain (55 of these items were shared with the factor analysis conducted under process one). These 65 items then underwent stepwise logistic regression and best subset selection procedures, yielding 18 unique items that were significantly associated with having non-nociceptive pain.

Combining the results of process one and process two yielded 23 unique items associated with having non-nociceptive pain. After reviewing the results of the statistical analyses, and using their clinical expertise, the steering committee generated four candidate screening tools, which were then analysed using receiver operating characteristic curves (ROC) to assess the candidate tool's ability to differentiate nociceptive, mixed and neuropathic pain types. The ROC analysis was used to select the final set of items and generate scoring rules. The final solution was a four-question tool, which the steering committee thought also needed questions on numbness and touch sensitivity, thus yielding a six-item questionnaire, which also included a body map that did not factor into the scoring (figure 1.3). The selection of scoring cut-points was designed to reduce the chance of false negatives, with scores of 4 or 5 indicating pain very likely to be non-nociceptive, scores of 2 or 3 indicating pain likely to be non-nociceptive, scores of 1 indicating pain that was possibly non-nociceptive, and scores of 0 or -1 indicating pain that was unlikely to be non-nociceptive.

In the second phase, the new tool was tested in an independent sample of 353 patients with non-headache pain that had lasted greater than 30 days. All participants had been treated by a pain specialist for less than one month at the time of the study. All participants completed the new six-item screening tool, and 5 to 10 days later they completed the questionnaire again so that test-retest reliability could be established. Because of possible breaches of study protocol at one study site, 45 participants' data was discarded and so the analysis set consisted of 308 participants (105 had been

diagnosed by a pain specialist as having neuropathic pain, 104 diagnosed with mixed pain, and 98 diagnosed with nociceptive pain). When examining the scoring profiles, the mode score was 1 for the nociceptive group, 2 for mixed pain group, and 3 for the neuropathic pain group. Receiver operating characteristic analysis showed that the tool had a concordance *c* statistic of 0.69, and no details on sensitivity and specificity of the tool were provided. The *c* statistic can be interpreted as the probability that a randomly chosen person with a condition will have higher probability of the outcome than the probability that a randomly chosen person without the condition. Test-retest reliability was assessed in 225 participants with two assessments using the tool and was moderate to substantial [intraclass correlation coefficient: 0.742 (95% CI: 0.677 to 0.795), Cohen's Kappa: 0.527 (limited to joints) to 0.742 (numb)].

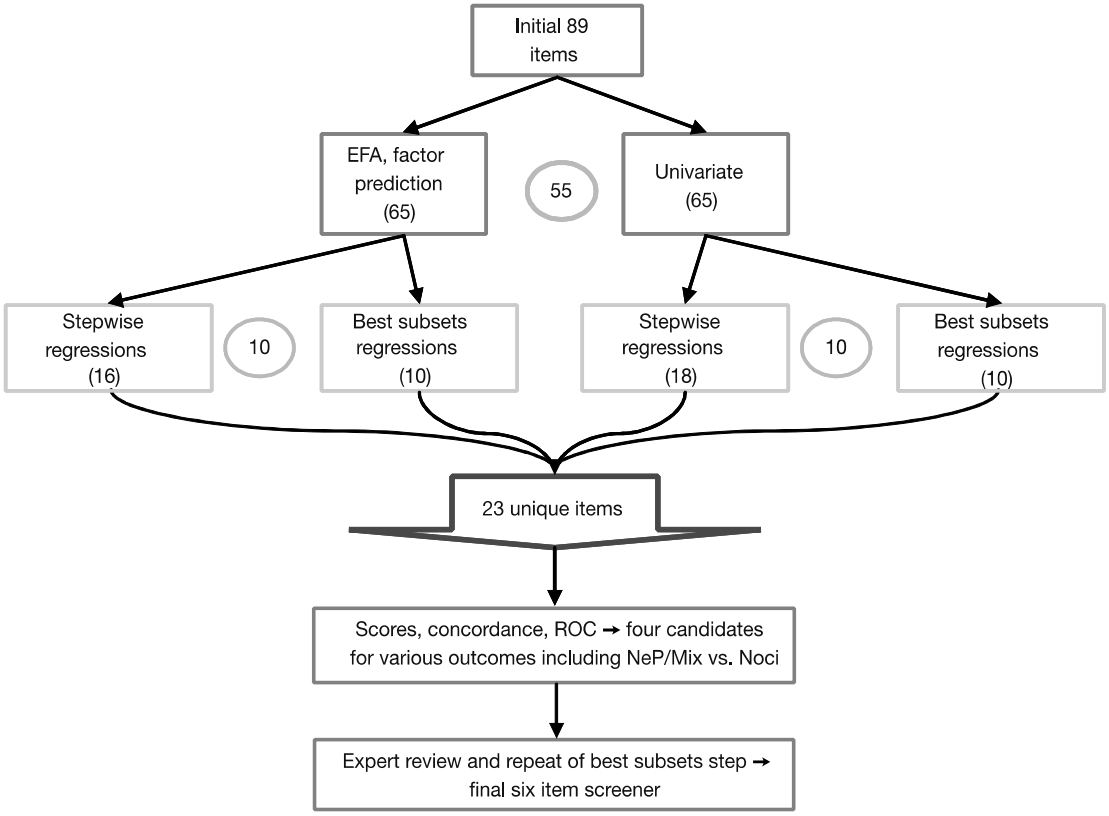

Figure 1.3: Phase 1 ID pain tool development process. EFA = explorative factor analysis,ROC = Receiver operator characteristic; NeP = Neuropathic pain (Portenoy, 2006)

Table 1.4: ID pain neuropathic pain assessment tool and scoring system (Portenoy, 2006)

Question	Score	
	Yes	No
1. Did the pain feel like pins and needles?	1	0
2. Did the pain feel hot/burning?	1	0
3. Did the pain feel numb?	1	0
4. Did the pain feel like electrical shocks?	1	0
5. Is the pain made worse with the touch of clothing or bed sheets?	1	0
6. Is the pain limited to your joints?	–1	0

There are several limitations to the design of this tool. Firstly, there is no physical examination included as part of the tool, so, even with an appropriate history, the diagnostic certainty is limited to possible neuropathic pain (Finnerup *et al.*, 2015). Secondly, from a methodological perspective the mechanism by which factor analysis was used to reduce the data set was not described, but it does not appear to have been based on items not loading onto any of the factors. Also, why use a two-pronged method of item reduction, both using stepwise and best selection in the second part of the two analytical processes. In addition, while the item reduction methodology is described, the 23 common items generated from the process are never presented. Nor do they present the 4 candidate tools, or the results of the ROC analysis for these tools, even though these analyses formed the basis of the selection of two-thirds of the items in the final tool and the scoring of the tool. The last deficiencies are related to the second phase of the development of the tool (assessment of tool validity and reliability). The *c* statistic was used to assess the diagnostic accuracy of the tool (a function the *c* statistic was not designed for), but only the point estimate is provided; a value that in itself was low. Since no confidence interval was provided, we do not know the interval included the 0.5 value, which would indicate that the test was worthless. Also, the tool developed in phase 1 was designed to differentiate nociceptive from non-nociceptive (neuropathic and mixed) pain, yet in phase 2, the tool was used to differentiate all three categories of pain (nociceptive, neuropathic, and mixed) (table 1.4). It is unclear how this change in use was accomplished.

1.4.8 PainDetect (PD-Q)

The developers of the PD-Q identified three unmet needs with regards to neuropathic pain:

1) Having a tool that could differentiate neuropathic and nociceptive components of chronic low back pain in large surveys.
2) Collecting data on the prevalence of low back pain with neuropathic features in the general population.
3) Establishing whether having neuropathic features to low back pain impacted more on life than low back pain that was primarily nociceptive in origin.

In this summary and critique of the PD-Q, I will deal with the first unmet need only, namely development of a validated screening tool to differentiate neuropathic and nociceptive components of chronic low back pain. With that aim in mind, the PD-Q was developed as a simple, quick to administer, questionnaire, which had no physical examination component, to distinguish neuropathic from non-neuropathic pain, particularly with regards to low back pain. By excluding a physical examination, the developers aimed to make the questionnaire easy to self-administer, thus making the tool appropriate for large, population-based studies.

The tool includes seven pain descriptors, which are rated on a 0 to 5 scale (0: never, 5: very strongly), one question on temporality of the pain (with four patterns provided), and one binary question on whether the pain was radiating or not (scored as +2 if the answer was “yes”). When summed the total score for the components could range from -1 to 38. The first seven items included on the scale were based on systematic review of the literature, expert opinion, and mining the records of the Deutscher Forschungsverbund Neuropathischer Schmerz (DFNS) patient database. The temporal patterns of the pain and the question about radiating pain were decided on primarily based on patient descriptions of their pain.

The performance of the scale was evaluated in a validation study. The study had 411 pain patients recruited to the study, from across 10 specialised pain care centres. Each patient was classified as either having pain of predominately neuropathic, predominately nociceptive, or unclear origin based on the assessment of two

independent pain specialists. Of the 411-patient recruited to the validation study, 392 (228 with neuropathic pain, 164 with nociceptive pain) met the inclusion criteria of: i) the two specialists concurred on the diagnosis, ii) the pain diagnosis was not “unclear” or of mixed pain, iii) the patient had at least 40/100 pain intensity on a 0 to 100 visual analogue scale, iv) the patient was sufficiently fluent in German to complete the questionnaire. Importantly, despite the study aim being to design a questionnaire for low back pain, the validation cohort included patients with a variety of causes of neuropathic pain (e.g., post-herpetic neuralgia, polyneuropathy, nerve trauma, radiculopathy).

The description and reporting of the analyses completed for the validation study are poor. The authors completed an exploratory factor analysis (principal component method), and they assessed the internal consistency of the tool using Cronbach’s alpha, but few details are provided in the statistical section of the methods, and the results are inadequately presented. From the data that are provided, it appears that there was a four-factor solution (using Kaiser criterion, eigenvalue > 1.0) to the exploratory factor analysis, with the first factor including all seven pain quality items, the second factor included one of the temporal patterns and the radiating pain item. No mention was made on what was included in the remaining factors, but it presumably was the remaining three temporal items.

Overall, the internal consistency, as measured using Cronbach’s alpha, was 0.83, an acceptable level of reliability. The logistic regression method to establish the sensitivity and specificity of the tool was sufficiently described. However, the ROC analysis, which was used to establish the questionnaire score cut-off points for neuropathic and nociceptive pain was never described except for a single sensitivity versus 1-specificity, which had little information on it. Having this information is key to understand how the cut-offs were determined, and the compromise the cut-offs had on the sensitivity and specificity of the tool. All we know is that somehow two cut-off scores were determined, and these were two cut-offs were associated with only a single set of sensitivity and specificity values. The cut-points that were established were: scores ≤ 12 indicating pain predominantly of nociceptive origin, while scores ≥ 19 indicated pain predominantly of neuropathic origin. According to the paper, the sensitivity, specificity, and probability of correct assignment was 84%. How these values relate to the cut-off points is unclear.

Additionally, in the validation study, the questionnaire appeared to be answered on a personal digital device and using a paper-and-pencil format (empirical analysis). However, it is unclear whether the same people completed the questionnaire in both formats. If the whole cohort of 392 did use both methods, the finding that the performance of the two methods was not exactly the same (sensitivity: 84% and 85%, specificity: 84% vs 80%, probability of correct assignment: 84% vs 83%) indicates that there were some minor discrepancies in the reporting by participants or there were minor errors when transcribing the data from the paper-and-pencil format. What is apparent is that of the participants that completed the questionnaire as a digital form, the majority coped well (only 10% had minor problems, and 10% required assistance).

Over and above the issues already raised, PD-Q was developed in German, with an English translation used in the final print version of the article. No information is provided on how that English version was generated. That is, which translation procedures were used. Moreover, no indication is provided how the scoring was determined. For example, why for the radiating pain item, which is a binary yes/no outcome, is a yes scored +2 and a no scored as 0, while pain quality items (it could be argued that “radiating pain” is a measure of pain quality too) are rated on 0 to 5 scales, and the temporal items are scored in a range from -1 to 1.

1.4.9 The need to assess neuropathy conditions in South Africa

Is there a problem using English-based neuropathic pain questionnaires in South Africa? Firstly, In South Africa, an estimated 35 to 60% of HIV-positive outpatients previously had a peripheral neuropathy, with three-quarters of these patients having a painful neuropathy (Maritz *et al.*, 2010; Wadley *et al.*, 2011). A report published by UNAIDS 2019 data reported that approximately 7.7 million South Africans were infected with HIV (United Nations Joint Programme on HIV/AIDS (UNAIDS), 2019), which means that between 2.7 and 4.6 million people could have painful HIV-associated sensory neuropathy (HIV-SN). Moreover, HIV-SN showed good prognosis data for neuropathic pain. This is due to the changes in the regimen rollout of new ARVs with a reduced neurotoxicity compared to the previous regimens (Starr, 2011; Pillay *et al.*, 2015). When focusing on two potential causes

of neuropathic pain (diabetes and HIV-related), it is clear that the occurrence of neuropathic pain is potentially high in South Africa. Moreover, this pain is difficult to treat and has social and economic impact on the patients (Dueñas *et al.*, 2016). Therefore, its identification and treatment is essential.

Patients with HIV-SN present with painful feet, often described as “burning” or ”aching” and some patients may present with pins-and-needles or numbness and the management of HIV-SN is centred on treating these symptoms (Ferrari *et al*., 2006; Arasho *et al*., 2008; Wadley *et al*., 2011).

Secondly, neuropathic pain is not limited to individuals with HIV and in South Africa, Peripheral neuropathy develops in about one third of individuals with diabetes and about half of these will have a painful neuropathy (Timmerman *et al.*, 2013)(Jensen *et al.*, 2006). Diabetes mellitus currently affects about 1.8 million South Africans with an estimated 69% of undiagnosed diabetes among diabetics and is expected to increase globally by 2045 (Sahadew and Singarem, 2019). There are few data on neuropathic pain prevalence in developing countries including South Africa; however, given the high rates of diseases and conditions that predispose towards the development of neuropathic pain in developing countries (e.g., diabetes mellitus, HIV, trauma), it is expected that the prevalence of neuropathic pain is similar or greater than it is in developed countries.

Diabetic sensory polyneuropathy (DSP) affects the lower limbs and feet. It is present in diabetic patients(50%) (Boulton *et al*., 2005). Pain symptoms described by DSP patients is associated with “burning, , sharp pain, electric-like or shooting pain”, aching and “numbness” (Bh adada *et al*., 2001; Boulton *et al*., 2004; Boulton *et al*., 2005).

1.4.10 Assessing neuropathic pain in South Africa

Presently, the increasing number of HIV infected and diabetic individuals and other conditions (e.g cancer) leading to neuropathy deems urgent effective screening tools in early detection of neuropathic pain.

Indeed, early detection of peripheral neuropathy from the patient whose first language is not English, to complete a standard questionnaire may have a challenges of language barrier. In addition, previous investigators on neuropathic

pain studies in South Africa may have experienced challenges of language communication. There is a need for a study that will develop a screening tool for neuropathic pain that is adaptable to a local language in this regard, IsiZulu.

As previously highlighted, cultural and ethnic differences affect pain perception, experience and management. It is relevant in a South African setting, with 11 official languages and cultural diversity to measure and assess neuropathic pain. The literary describing these cultural and ethnic differences in pain perception and expression is extensive, thus in the remainder of this section, illustrative examples of these differences will be provided.

Of note, Gianola *et al*., 2020 reported on the effects of language context and cultural identity on the pain experience of Spanish-English bilinguals. They found that the participants experienced slightly higher pain unpleasantness in Spanish compared with English. In addition, they found lower pain ratings in English for Hispanic dominant (Spanish preferring) participants. Moreover, the intensity ratings differed across language conditions (English and Spanish) for participants with stronger and language specific preferences for a single culture (Spanish). The study concluded that Hispanics portrayed less overall satisfaction with health care as their pain experience was not fully communicated due to the language barriers.

Indeed, language is a strong modulator of pain expression. Similar to the aforementioned study, Nortje and Albertyn, 2015 investigated conditions of how symbolic linguistic representations interact with perceptual mechanisms during language comprehension in the context of pain perception. Language was found to modulate the perception of pain prompted by noxious stimuli. Furthermore, they postulated that previous history of chronic pain may mediate the interplay between language comprehension and pain perception.

In addition, these findings are in conjunction with a study conducted in Finnish and Swedish speaking populations. Mustajoki *et al*., 2015 reported a discrepancy in language proficiency between the pain physician and the patient. In this regard, patients reported a lower level pain description if they discovered the physician's language skills is different to the patient's preferred language. Moreover Swedish

participants were significantly less likely to report their pain perception due to language barriers.

South Africa has a unique in cultural diversity, moreover, there is great language diversity. It has 11 official spoken languages. These languages include isiZulu, isiXhosa, Afrikaans, Northern Sotho (Sepedi), English, Setswana, Sesotho, Xitsonga, SiSwati, Tshivenda and isiNdebele. Accordingly, IsiZulu (23.82%) is the most spoken local language followed by IsiXhosa (17.6%). Although IsiZulu is mostly spoken in Kwazulu natal province, due to migration of the Zulu nation to other provinces such as Gauteng (Egoli the city of Gold), this language has become the most adaptable language in communities, including taxi rank, malls and health facilities.

1.5 Overall conclusion

Currently, effective assessment of pain in a developing country such as South Africa, is limited by the language communication between the pain physician and the patient. Furthermore, it is imperative to establish a standard of communication between the health practitioner and the patient in terms of expressing pain symptoms. Of note, the translatability of diagnostic pain screening tools to the local spoken language in a clinical setting is essential. Several translations of the DN4, LANSS, and PD-Q screening tools have been developed to assist in diagnosing neuropathic pain, but they all were developed in Asian, Arabic and European languages. None of these have been developed and validated in an African Language. Shaikh *et al*. 2013, found similarities in isiZulu speakers with regards to the terminology used in other languages screening tools to describe pain symptoms but with poor understanding of English Language terms used in developed questionnaires. This poor understanding means that the sensitivity and specificity of these screening tools will be compromised when they are used in their English form, which has implications for the effective management of a patient's pain. Hence, this study is imperative in developing neuropathic pain screening tools adapting DN4 questionnaire in IsiZulu. We have adopted DN4 due to its high sensitivity, specificity and simple pain descriptive questions to understand, we also selected isiZulu because it is a common well understood or spoken language (Alexander, 2004; Ngyende, 2011).

In the work described in this thesis, our first objective was to investigate the psychometric, reliability and validity properties of translated versions of the DN4, LANSS, and PD-Q. in published articles between 01 January 2005 to 19 July 2019.The second objective was to characterise the terminology used by isiZulu speakers to describe nociceptive and neuropathic pain, with aim of extracting terms that helped differentiate nociceptive and neuropathic pain. Finally, we aimed to test a newly developed isiZulu screening tool, which included the distinguishing terms extracted from the second aim and combined them with the physical assessment of the DN4, to screen for neuropathic pain.

1.6 Aims:

To develop a neuropathic pain screening tool in isiZulu.

1.6.1 Objectives

(i) To conduct a systematic review of the psychometric properties of translated versions of the DN4, LANSS and PD-Q (Chapter 3).

(ii) To determine which isiZulu terms are used to describe nociceptive and neuropathic pain (Chapter 4).

(iii) To determine which pain symptoms, offer the best discriminative properties between nociceptive and neuropathic pains (Chapter 4).

(iv) Assess the performance of a new isiZulu neuropathic pain screening tool compared to an isiZulu version of the DN4, generated by direct translation of the English version of the DN4 into isiZulu (Chapter 5).

CHAPTER 2-GENERAL METHODOLOGY

2.1. Introduction

In this chapter, I provide the details of the materials and methodologies used throughout this thesis. Generalized information concerning statistical analysis performed throughout this thesis is also provided in this chapter. However, specific details concerning statistical analysis performed in each chapter are given in respective chapters. In study 1, a systematic review on the psychometric properties, reliability, and validity of translated version of DN4, LANSS and Pain DETECT. The methodology is fully outlined in the general methodology and in chapter 3 methodology section. In study 2, a neuropathic pain screening tool in isiZulu was developed from the translated DN4 version. a neuropathic pain screening tool in isiZulu was developed from the translated DN4 version. In a sample population of 122 participants (neuropathic n = 61; nociceptive n = 61), patients were asked to describe their pain in isiZulu and the triggers thereof. In study 3, A pilot study was conducted at chronic pain clinics (rheumatoid arthritis clinic and orthopaedic clinic). Only participants with pure nociceptive (n=23) or neuropathic pain (n=23) were included in this study. Patients with mixed pain were excluded in the study. The methodology for study 2 and 3 are the same however, only two clinics were used in study 3 to test the newly developed screening tool.

2.2 Study 1 – Systematic review on the psychometric, reliability, validity properties of translated version of dn4, lanss and pdq questionnaires

A systematic review of the psychometric properties of translated versions of the Douleur Neuropathique en 4 Questionnaire (DN4), Leeds Assessments of Neuropathic Symptoms (LANSS) and the PainDETECT Questionnaire (PD-Q) was undertaken. The review was registered on PROSPERO: CRD42015016752.

2.2.1 Study question

The study question was what the reliability and diagnostic properties of translated versions of three neuropathic screening tools are (DN4, LANSS, PD-Q)

We used the PICO method to define our study question: This gave the direction to the designing and reporting of this systematic review (Eriksen and Frandsen, 2018. Luijendijk, 2021)

Table 2.1: PICO method used to define study method

P (patient or population)	Patients with chronic pain
I (intervention)	Diagnostic screening tool
C (comparator)	None
O (outcome)	Psychometric and diagnostic properties of neuropathic pain screening tools: DN4*†, LANSS*†, and PD*

** DN4: Douleur Neuropathigue4, LANSS: Leeds Assessment of Neuropathic symptom and sign, PD: PainDETECT† Includes the DN4-interview and S-LANSS*

2.2.2 Study Inclusion Criteria

The following article selection were used:

Table 2.2: Selection criteria for included articles

The language of publication	No restriction
Geographic location	No restriction
Publication date	1 January 2005 to 31 July 2019
Publication type	Original articles, reviews, and abstracts

2.2.3 Search Strategy

Our search strategy was as follows:

Table2.3: Search strategy used for e-resources

Databases	PubMed, Scopus, Web of Science
Hand searching	Reference lists of selected publications were checked.
Search terms	(“Douleur Neuropathique” OR DN4 OR DN-4 OR “Leeds Assessment of Neuropathic Signs and Symptoms” OR LANSS OR PainDetect OR “Pain Detect” OR PDQ or PD-Q) AND pain AND (neuropathy OR neuropathic OR neuralgia OR neuritis OR central OR stroke OR spinal) AND (translation OR adaptation OR validation OR reliability OR validity)

The following table was used as a checklist and guideline for the included articles according to PRISMA (Page *et al*., 2021).

Table 2.4: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for	

Section and Topic	Item #	Checklist item	Location where item is reported
		each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

2.2.4 Data handling

To manage references, search results were transferred to Mendeley Desktop Reference Manager (Elsevier), where all references retrieved were combined and duplicates were removed.

2.2.5 Screening

Initial screening of the included articles was done by title and abstract and was performed by T Fagbohun and checked by P Kamerman. The excluded articles were removed and the reason for their exclusion was recorded. The full text of all retained studies was then screened by T Fagbohun and P Kamerman, and a consensus list of studies was generated to include in the review.

2.2.6 Data extraction

The following data were extracted:

1. Bibliographic information
2. Study characteristics:
    a. Name of translated questionnaire
    b. Language of translation
    c. Setting (study population)

d. Study methods

e. Measures of reliability

f. Diagnostic properties.

2.2.7 Measures of Reliability

Reliability of the screening tools were determined by the following measures: Test-retest reliability (intraclass correlation coefficient “ICC”; Pearson’s correction and Spearman’s correlation), inter-rater reliability (Cohen’s Kappa lowest and highest score, and internal consistency (Cronbach’s alpha)

2.2.8 Measures of diagnostic performance

Diagnostic performance was assessed by measures of sensitivity, specificity, positive likelihood, negative likelihood, positive predictive value, and negative predictive value.

Sensitivity: is a measure of its ability to establish that such a difference is significant. Sensitivity Analysis (SA) is a method to determine the robustness of an assessment by examining the extent to which results are affected by changes in methods, models, values of unmeasured variables, or assumptions with the aim of identifying “results that are most dependent on questionable or unsupported. In other words, it is the ability of a test or instrument to yield a positive result for a subject that has that disease (Eusebi., 2013.; Trevethan, 2017; Shreffler and Huecker., 2020).

Specificity: Specificity refers to a test's accuracy at identifying those who do not have a condition or characteristic. It is the proportion of truly not at-risk or without condition (e.g., trait, disease, classification, and label) that are correctly identified as such through a diagnostic tool. In other words, it is the ability of the test or instrument to obtain normal range or negative results for a person who does not have a disease (Eusebi., 2013.; Trevethan, 2017; Shreffler and Huecker., 2020).

Positive likelihood: is the measure of probability that a positive test would be expected in a participant divided by the probability that a positive test would be expected in a participant without a disease (Eusebi., 2013.; Trevethan, 2017; Shreffler and Huecker., 2020).

Negative likelihood: The negative likelihood ratio gives the change in the odds of having a diagnosis in patients with a negative test. The change is in the form of a ratio, usually less than 1. For example, a -LR of 0.1 would indicate a 10-fold decrease in the

odds of having a condition in a patient with a negative test result (Eusebi., 2013.; Trevethan, 2017; Shreffler and Huecker., 2020).

The more the likelihood ratio for a positive test (LR+) is greater than 1, the more likely the disease or outcome. The more a likelihood ratio for a negative test is less than 1, the less likely the disease or outcome. Thus, LRs correspond nicely to the clinical concepts of ruling in and ruling out disease Eusebi., 2013.; Trevethan, 2017; Shreffler and Huecker., 2020).

Positive and Negative predictive values: PPVs determine, out of all of the positive findings, how many true positives are; NPVs determine, out of all of the negative findings, how many are true negatives. As the value increases toward 100, it approaches a ‘gold standard (Eusebi., 2013.; Trevethan, 2017; Shreffler and Huecker., 2020).

2.3 Study 2: Development of a neuropathic pain screening tools in isizulu

2.3.1 Ethics clearance

Ethical approval was granted by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg, South Africa (clearance number: M150245) (Appendix 1). Written informed consent was obtained from all participants (Appendix 4).

2.3.2 Participants

Male and female participants with pain conditions thought to be predominantly nociceptive or neuropathic were recruited from the diabetic clinics, HIV clinics, orthopaedics wards, obstetrics wards, and rheumatology clinics (Figure 2.1) at four academic teaching hospitals in Johannesburg, South Africa:

- Charlotte Maxeke Johannesburg Academic Hospital
- Chris Hani Baragwanath Academic Hospital
- Hellen Joseph Hospital
- Rahima Moosa Mother and Child Hospital

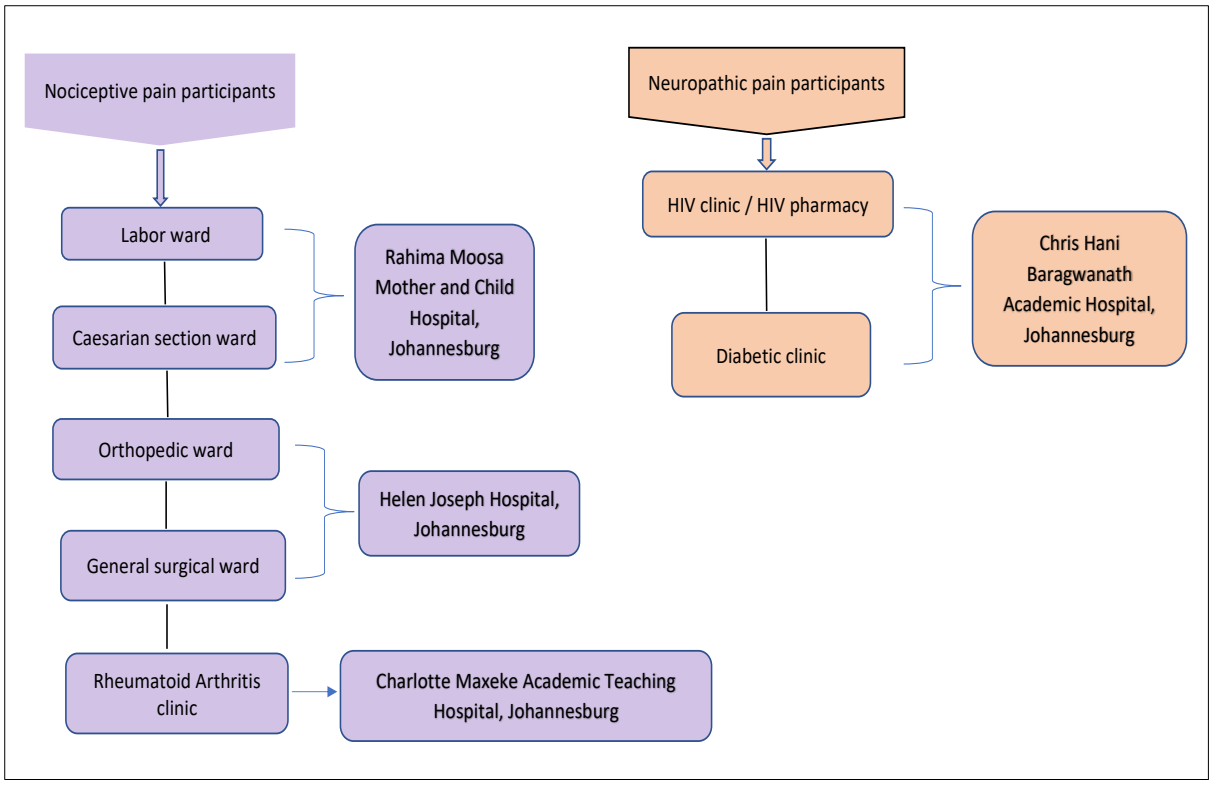

Figure 2.1: Participant's recruitment sites summary

2.3.3 Inclusion Criteria

Participants were 18 years or older, isiZulu was their primary language (i.e., the language of communication with family and friends), and had a pain condition that is thought to be predominantly nociceptive (labour pain, acute postoperative pain, pain from rheumatoid arthritis) or neuropathic (painful HIV and diabetic peripheral neuropathies). The sample size was determined according to the inclusion criteria. The confidence internal CI of 95% and margin of error +/-1% (. 01), using the standard deviation of (.05) were used to test the statistical power of the participants that met the inclusion criteria requirements.

2.3.4 Determination of pain of neuropathic origin

In participants with suspected painful HIV or diabetic polyneuropathy, the presence of a nerve lesion fitting with the anatomical distribution of the pain was confirmed through participant medical history (confirmed HIV infection or diabetes), and by the bilateral presence of at least two of the following neurological signs was assessed by the investigator (T. Fagbohun)

i) absent deep-tendon ankle reflexes

ii) reduced vibration sense at the interphalangeal joint of the big toe (<10 s)

iii) altered sensitivity to pin-prick in the feet

No patients with suspected central neuropathic pain syndromes (e.g., multiple sclerosis, post-stroke pain, below-level spinal cord injury pain) were recruited. Nor were patients with pain of unclear origin (e.g., low-back pain with radicular features) included.

2.3.5 Neurological testing procedure

2.3.5.1 Vibration senses protocol

A brief introduction was carried out by the investigator and translated by the interpreter on the use of turning fork (128Hz) to check the vibration sensation. In addition, patients were familiarised with the sensation of the tuning fork by activating the tuning fork and then placing it on the metacarpophalangeal joint of the participant middle finger. All participants identified that they experienced the sensation in their finger, and thus no other body sites were used. During this practise phase, patients were asked to describe the type of sensation they felt and to state when the sensation stopped by saying ‘stop’. After this familiarization, the participants were informed that the procedure was going to be repeated on their great toe (distal interphalangeal joint, Figure 2.2). The time interval from when the tuning fork was struck on the investigator palm to when the participant said “stop”, indicating that they could no longer feel the vibration, was timed with a stopwatch. Recordings of 10 seconds or less were tagged as abnormal sensation (Cherry *et al*., 2005).

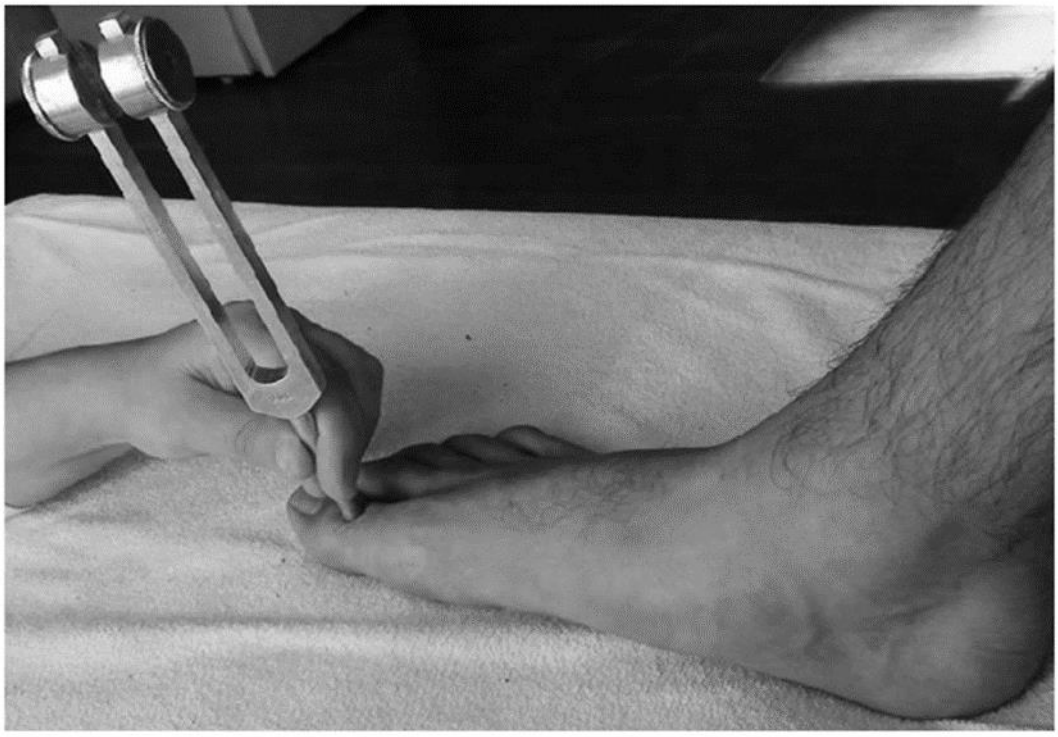

Figure 2.2: Vibration sensory testing

2.3.5.2 Ankle reflex testing procedure

In a comfortable seated position, with the upper leg supported by the seat, the investigator placed his hand beneath the participants foot supporting the ball of the foot in a slight dorsiflexed position. A rubber reflex hammer was used by the investigator to strike the Achilles tendon firmly to elicit the reflex response (movement of the foot in the direction of the plantar surface of the foot, Figure 2.3). Movement of the foot indicated a positive ankle reflex, and the procedure was carried three times. In an absence of the reflex the patient was demonstrated the Jendrassik manoeuvre, which was then performed while the reflex was re-tested. In the event of recorded as being absent.

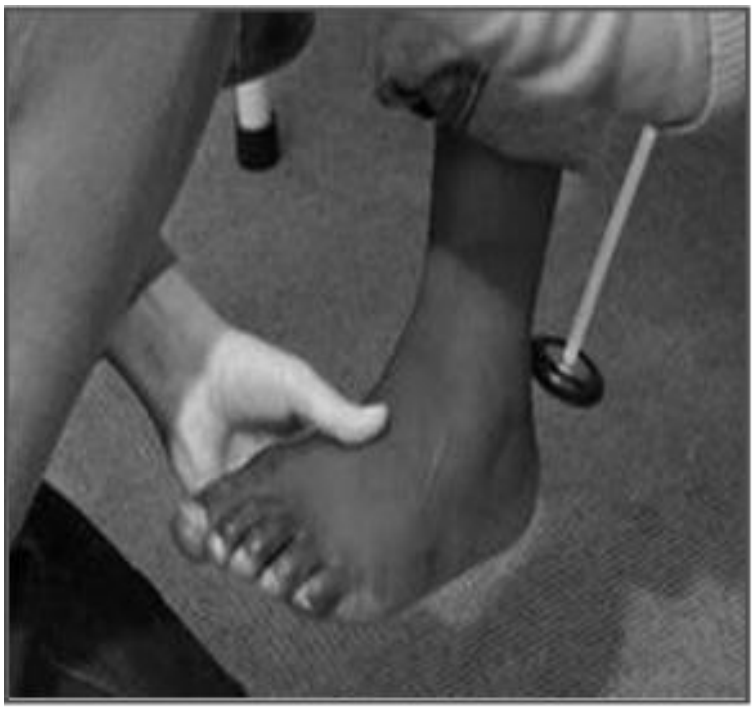

Figure 2.3: Ankle reflex testing

2.3.5.3 Pin-prick sensitivity

This was performed by the investigator using the size 4 single use safety pin. Prior to testing, the safety pin was brought out to show the participants confirming that the safety pin was a new pin, and that there was a blunt and sharp end; and both ends would be applied to the skin of the participants for him/her to differentiate the two ends (Lees and Hurwitz., 2019). Ahead of this measurement, the investigator demonstrated the pin-prick sensation on the dorsal side of his left hand while the participant was observing the procedure to identify the ‘sharp’ end and the ‘blunt’ end of the safety pin. This procedure was carried out on the dorsal side of the participants hand to identify the ‘sharp’ end from the ‘blunt’ end while eyes were closed (Figure 2.4). From there on, immediately the patients are comfortable with the procedure, the real measurement was carried out as follows: The participants were required to identify which of the edge the investigator was using to pick the big toe down to the small toes while eyes were closed. When he/she felt ‘sharp’ sensation, he/she reported ‘sharp’ or ‘blunt’ sensation(,Blackmore,and Siddiqi, 2016; Lees, and Hurwitz, 2019)

If the participants could not correctly identify the sharp edge from blunt end, it was an indication of abnormal sensation and pin-prick marked ‘absent’ on the questionnaire. The investigator extended the pin-prick sensation investigation up to medial and lateral part of the foot and progressed proximally in order to check the extent or border of nerve dysfunction up to the knees.

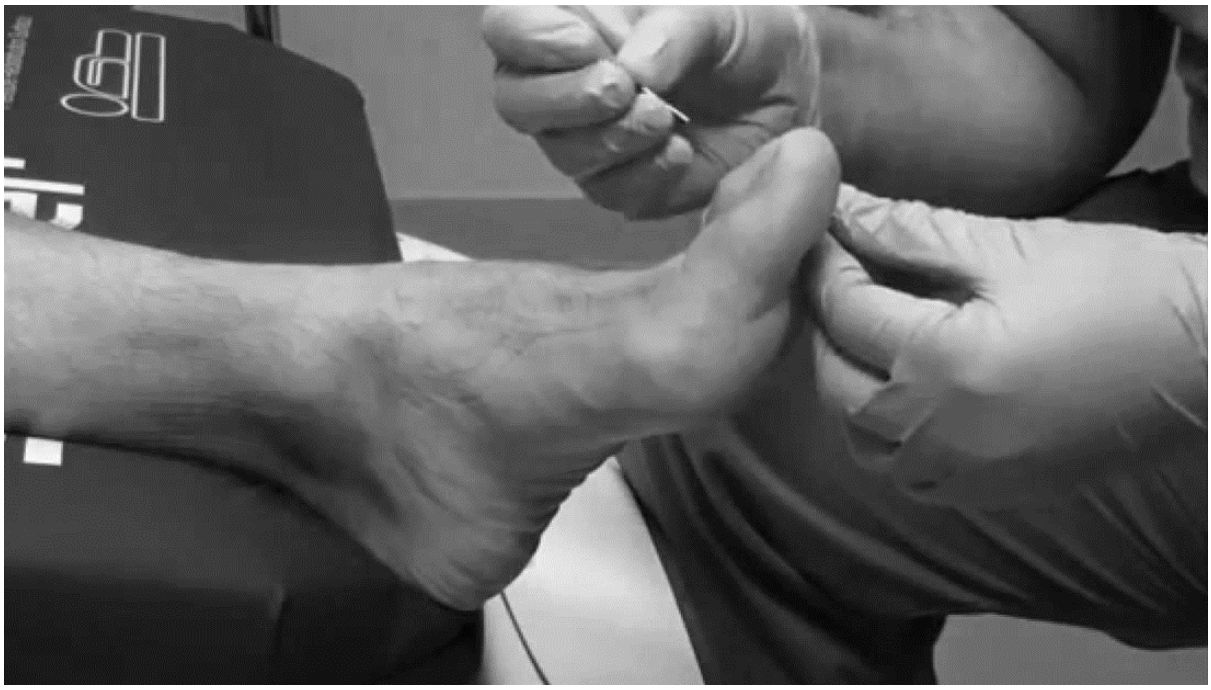

Figure 2.4: Pinprick sensation demonstration

2.4 Study 3- Assessment of a new isizulu neuropathic pain screening tool compared to isizulu version of DN4

2.4.1. Protocol (The Interview)

The method explained in study 2 was used for study 3 as a pilot study to test the validity of the newly developed neuropathic screening tool. Only male and female participants with pain conditions thought to be predominantly nociceptive or neuropathic were recruited from the chronic pain clinic at Hellen Joseph hospital and rheumatoid arthritis clinic at Charlotte Maxeke were used for the pilot study. Participants: forty-three (n = 43) participants (male and females) with chronic condition (nociceptive or neuropathic pain). Neuropathic (n = 20) and Nociceptive pain (n = 23) origin were recruited for this study.

Convenience sampling was used, and volunteers that met the inclusion criteria and consented to participation in the study were interviewed at a prepared place for the interview at the clinic. The interview was conducted by the investigator (T.Fagbohun) and interpreter (Florence Mtsweni), and was recorded using a digital voice recorder (Philips HQ stereo voice tracer). The interview consisted of three parts:

- **General and pain-related information**

  Basic demographic information (age, sex, self-identified ethnicity, primary language of communication, other languages spoken, years of education), and pain (primary pain type, primary pain location, the intensity of the primary pain, duration of primary pain, temporal characteristics of the main pain, pain medications, pain interference) data were collected. Information on the pain intensity and interference with quality of life were collected using the Wisconsin Brief Pain Questionnaire , which has been validated in isiZulu (Mphahlele *et al*.,2008). Information on the type of pain, conditions/procedures that may have given rise to the pain, and pain medications were supplemented with data from the patients' medical records.
- **Measurement of pain intensity:** The measurement of pain intensity was measure by participant indicating the intensity of their pain using the numerical rating and the location of the pain by Wisconsin Brief pain Questionnaire .
- **Pain Rating**: Using the scale in front of you marked which best describes your pain at its **worst** in the last week (A rating of 10 would indicate pain so severe as to prohibit all activity; the worst pain you can imagine).
- **Self-reported symptoms**

  Each participant was asked to give a spontaneous description, in isiZulu, of their painful, unpleasant, or unusual symptoms and sensations at the site of primary pain. The participants were also asked what triggered the primary pain.
- **Prompted symptoms.**

  To assist in adapting the DN4 questionnaire into isiZulu (see study 2-chapter 4), participants were read a list of symptoms taken from the DN4 that had been translated into isiZulu using dual forward and backward translation procedures. Participants were asked whether they: i) knew each term, ii) understood each term, iii) could provide a synonym or alternate description of the term in isiZulu

(if a synonym was given, they were asked whether they were more familiar with the term read to them, or the synonym they provided), and iv) whether they could provide an English translation of the term.

2.5 Statistical analysis

Descriptive statistics are presented as mean (SD) for parametric data, median (interquartile range, IQR) for non-parametric data, and percentages for frequency data. Univariate analyses comparing Neuropathic participants and nociceptive participants was done. All data were analyzed using the R studio software version 3.1 with the boot package through audio-recorded data from the interview transcribed and then translated into English by two independent translators. The translated transcriptions were compared and where differences occurred, a third translator arbitrated. Content analysis was used to extract self-reported pain symptoms and symptoms triggers from the translated text and then, working with the translators, the identified words, statements were matched with the isiZulu terms the participants used. Classifications and regression tree analysis (CART) was used to determine the symptoms that provide the best discrimination between individual with nociceptive and neuropathic pain. Briefly, the data were divided into a training set and test set using a random 80:20 split of data. The training set was used to generate the model, while the test set was used to access the predictive value of the model. The training of the model used 8-folder cross validation, repeated 5 times, with area under the Receiver Operator Curve (ROC) used to select the optimum model. The performance of the final model was assessed using the test data, using accuracy as the outcome measure.

CHAPTER 3-SYSTEMATIC REVIEW ON THE PSYCHOMETRIC, RELIABILITY, VALIDITY PROPERTIES OF TRANSLATED VERSION OF DN4, LANSS AND PDQ QUESTIONNAIRES

A modified version of this chapter has been accepted for publication in the

International Journal of Medicine and Medical Research

Temitope Richard Fagbohun,. Systematic review on the psychometric, reliability and validity property of translated neuropathic pain screening tools (DN4, LANSS and PDQ) between 01 January 2005 and 19th July 2019. *International Journal of Medicine and Medical Research*

3.1 Introduction

Neuropathic pain (Np) is classified as one of the worse pains reported by chronic pain patients (Scholz *et al*., 2019). An estimated 1 out of 10 chronic pain patients develop neuropathic pain, depending on the population study (Colloca *et al*., 2017). The prevalence may be as high as 51.9 % in patients being managed for chronic pain clinic (Reinhart *et al*., 2012). Evidence indicates that neuropathic pain affects both physical and emotional state of the patients (Torta *et al*., 2017). This type of pain decreases the quality of life of the patients (Torta *et al*., 2017; Rienstra *et al*., 2019) and negatively affects the patients' interaction with society (Dueñas *et al*., 2016). Neuropathic pain is associated with lesion or disease of the somatosensory pathway that leads to abnormality observed at the peripheral and central region of the system function (hyperalgesia or allodynia) (Costigan *et al*., 2009). The common symptoms associated with neuropathic pain are – sharp, burning, pins and needles, tingling, painful cold, numb and shooting (Colloca *et al*., 2017).

Diagnosing standards among pain physicians and researchers of neuropathic pain in chronic pain patients have been a challenge (Mathieson *et al*., 2015). The five Np screening tools are LANSS (Bennett, 2001), Neuropathic Pain Questionnaire (Krause and Backonja, 2003), Douleur Neuropathique 4 'DN4' (Bouhassira *et al*., 2005), ID pain (Portenoy and Committee, 2006) and PainDETECT (Freynhagen *et al*., 2006). These instruments have been validated and adapted in different languages from different countries.

Among these instruments, DN4, LANSS and PainDETECT are the most commonly used tools in the assessment of the quality of neuropathic pain in chronic pain patients due to their high sensitivity and specificity, short duration of the assessment, easy understanding of the terms and application by the pain experts (Unal-Cevik *et al*., 2010; Gudala *et al*., 2017). Translation of this tool from the language of origin to local languages is essential for good communication and effective assessment of pain quality between the researcher or pain expert and the patients.

Critically appraising the data measurement of these instruments may be valuable for the clinician and researchers in decision making based on evidence extracted from peer-reviewed articles that adopted these instruments in their studies. Therefore, the aim of this study was to conduct a systematic review on the translated version of the

Douleur Neuropathique en 4 Questionnaire (DN4), Leeds Assessments of Neuropathic Symptoms and Signs (LANSS) and the PainDETECT Questionnaire (PD-Q) tools with the objective to evaluate their psychometric, reliability and validity properties.

3.2 Method

Study design: systematic review of studies was conducted according to PRISMA guidelines (Moher *et al*., 2015). The systematic review was conducted using a developed protocol registered on PROSPERO (CRD42015016752) by the authors. PICO method (Eriksen and Frandsen., 2018), was adopted to define our study question:

P (Patient or population): Patients with chronic pain
I (Intervention): Diagnostic screening tool
C (Comparator): None
O (Outcome): Psychometric and diagnostic properties of neuropathic pain screening tools: DN4*, LANSS**, and PD-Q (* Includes the DN4-interview, ** Includes the self-complete (S)-LANSS)

3.2.1 Study Inclusion Criteria

The following article selection criteria were used:

- **Language of publication:** No restriction
- **Geographic location:** No restriction
- **Publication date:** 1 January 2005 to 31 July 2019
- **Publication type**: Original articles and abstracts

3.2.2 Search strategy

The search strategy was as follows:

Databases: PubMed, Scopus, Web of Science
Secondary search: Reference lists of selected publications were checked.
Search terms: (“Douleur Neuropathique” OR DN4 OR DN-4 OR “Leeds Assessment of Neuropathic Signs and Symptoms” OR LANSS OR PainDetect OR “Pain Detect” OR PDQ or PD-Q) AND pain AND (neuropathy OR neuropathic OR neuralgia OR

neuritis OR central OR stroke OR spinal) AND (translation OR adaptation OR validation OR reliability OR validity).

3.2.3 Data management

Search results were transferred to Mendeley Desktop Reference Manager (Elsevier), where all references retrieved were combined, and duplicates were removed.

Screening

Initial screening of the included articles was done by title and abstract and was performed by T Fagbohun and cross checked by P Kamerman. The excluded articles were removed, and the reason for their exclusion was recorded. The full text of all retained studies was then screened by T Fagbohun and P Kamerman, and a consensus list of studies was generated to include in the review.

Data extraction

The following data were extracted:

1. Bibliographic information
2. Study characteristics:
    a. Name of the translated questionnaire
    b. Language of translation
    c. Setting (study population)
    d. Study methods
    e. Measures of reliability (Reliability of the screening tools was determined by the following measures: Test-retest reliability (intraclass correlation coefficient, Pearson's or Spearman's correlation coefficient), inter-rater reliability (Cohen's Kappa lowest and highest score), and internal consistency (Cronbach's alpha))

    f. Diagnostic properties (Measures of diagnostic performance: Diagnostic performance was assessed by measures of sensitivity, specificity, positive likelihood, negative likelihood, positive predictive value, and negative predictive value:

3.3 Results

A total of 1,493 articles were obtained from the initial electronic databases search and 27 articles were finally included in the final review. The details of the study identification and selection process in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (Moher *et al*., 2015) are described in figure 3.1. One hundred and twenty-two (122) articles were excluded due to duplications. The abstract and the title of one thousand three hundred and seventy-one (1,371) articles were screened, one thousand three hundred and thirty-seven articles (1,337) articles were excluded due to not meeting the inclusion criteria of this study. Thirty-four (34) articles were further screened for full-text inclusion, and three articles were excluded for not applying DN4, LANSS or PainDETECT instrument neuropathic pain screening tools. The remaining thirty (30) articles were screened to check whether validity tests were conducted, five (5) articles were further excluded due to no validity test. Twenty-six articles were included in this review.

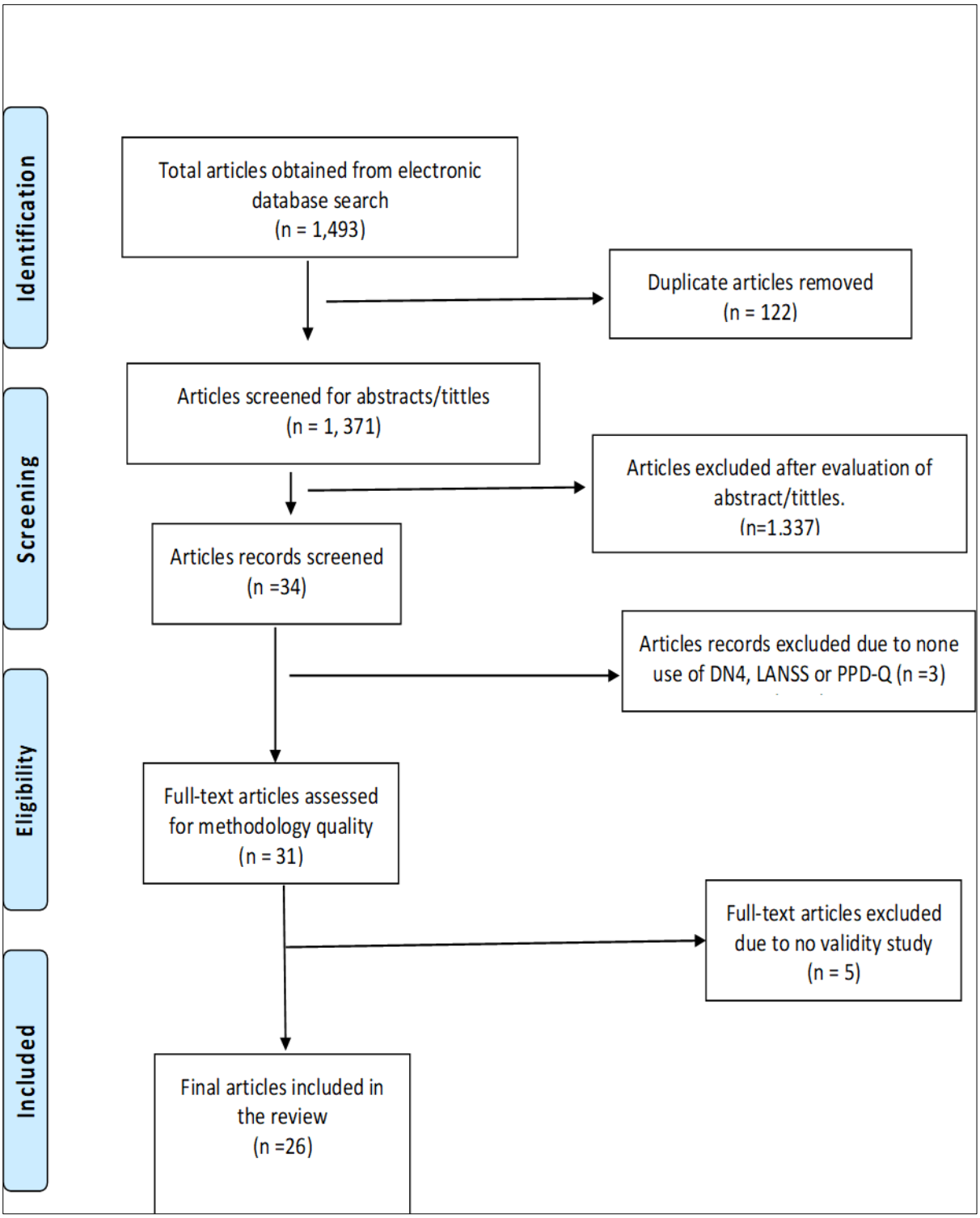

Figure 3.1 **Summary of data inclusion**

3.3.1Summary of the articles included:

A total of twenty six articles where included in this review: Eleven **DN4** articles (Matsuki *et al*. (2018) “Japanese language”;Chatila *et al*.(2017) “Arabic ”; Terkawi *et al*. (2017) Arabic” ;Kim *et al*. (2016) “Korean ”; Park *et al*. (2015) “Korean ”; Sykioti *et al*. (2015) Greek ”; Madani *et al*. (2014) “Farsi ”; Hamdan *et al*. (2014) “Spanish ”; Spallone *et al*. (2012) ‘Italian ”; Santos *et al*. (2010) ‘ Brazilian -Portuguese”; Perez *et al*. (2007) “Spanish”

LANSS: Eight articles were included using **LANSS**: Batistaki *et al*. (2016) “Greek language”; Park *et al*. (2015) “Korean” Spanos *et al*. (2015) “Greek” Barbosa *et al*. (2014) “Portuguese”; Hamdan *et al*. (2014) “Spanish” Türkel *et al*. (2014) “Turkish”; Schestatsky *et al*. (2011) “Brazilian Portuguese” Yucel *et al*. (2004) “Turkish ”

PD-Q: Four articles were included using **PD-Q**: Gudala *et al*. (2017) “Hindi language” Matsubayashi *et al*. (2013) “Japanese”; Alkan *et al*. (2013) “Turkish”; De Andrés *et al*. (2012) “Spanish”.

S-LANSS: Three articles were included following our inclusion criterial: 1. López-de-Uralde-Villanueva *et al*. (2018)” Spanish language”; Batistaki *et al*. (2016) “Spanish language”;Koc and Erdemoglu (2010) “Turkish”

3.3.2 Description of the included studies

Thirteen studies were included in the DN4 screening tool in this review (table 3.1). The DN4 was translated to eight different languages which includes: Arabic language (n=4) (Chatila *et al*., 2017; Terkawi *et al*., 2017), Brazilian Portuguese (n=1) (Santos *et al*., 2010), Korean (n=2) (Kim *et al*., 2016; Park *et al*., 2015), Spanish (n=2) (Hamdan *et al*., 2014; Perez *et al*., 2007), Farsi (n=1) (Madani *et al.*, 2014), Greek (n=1) (Sykioti *et al*., 2015), Italian (n=1) (Spallone *et al*., 2012) and Japanese (n=1) (Matsuki *et al*., 2018).

The total sample size reported was 1666. Out of this, 880 was diagnosed with neuropathic pain, 731 nociceptive pain and 55 were patients with mixed pain. Eighty-two (82) participants had mixed pain included in the neuropathic pain participants

(Hamdan *et al*., 2014). All the included articles that used DN4 instruments were published between 2007 and 2018 (table 3.1).

Table 3.1: Description of the included studies

			Sample size									
Author	**Np Tool**	**Language**	**Total**	**Neuropathic**	**Nociceptive**	**Mixed sample**	**Forward translation**	**No of forward translations**	**Backward translation**	**No of backward translations**	**Expert assessment**	**Pilot test**
Matsuki *et al*. (2018)	DN4	Japanese	187	100	87	0	Yes	1	Yes	1	Yes	No
Chatila *et al*. (2017)	DN4	Arabic	195	99	96	0	Yes	3	Yes	NS	Yes	Yes
Terkawi *et al*. (2017)	DN4	Arabic	124	77	47	0	Yes	5	Yes	2	Yes	Yes
Kim *et al*. (2016)	DN4	Korean	83	43	40	0	Yes	-	Yes	-	-	-
Park *et al*. (2015)	DN4	Korean	83	40	43	0	-	-	-	-	-	-
Sykioti *et al*. (2015)	DN4	Greek	237	123	59	55	Yes	NS	Yes	NS	Yes	-
Madani *et al*. (2014)	DN4	Farsi	175	86	89	0	Yes	5	Yes	3	Yes	Yes
Hamdan *et al*. (2014)	DN4	Spanish	212	121	91	*See footnote	-	-	-	-	-	-
Spallone *et al*. (2012)	DN4	Italian	111	50	61	0	NS	NS	NS	NS	NS	NS
Santos *et al*. (2010)	DN4	Brazilian Portuguese	101	42	59	0	Yes	2	Yes	2	Yes	Yes
Perez *et al*. (2007)	DN4	Spanish	158	99	59	0	Yes	2	Yes	2	Yes	NS

Batistaki *et al*. (2016)	LANSS	Greek	100	58	42	0	Yes	2	Yes	2	Yes	Yes
Park *et al*. (2015)	LANSS	Korean	213	113	100	0	Yes	2	Yes	2	Yes	Yes
Spanos *et al*. (2015)	LANSS	Greek	70	35	35	0	NS	NS	NS	NS	NS	NS
Barbosa *et al*. (2014)	LANSS	Portuguese	167	103	64	0	Yes	2	Yes	1	Yes	Yes
Hamdan *et al*. (2014)	LANSS	Spanish	212	121	91	*See footnote	-	-	-	-	-	-
Türkel *et al*. (2014)	LANSS	Turkish	148	99	49	0	Yes	NS	Yes	1	Yes	Yes
Schestatsky *et al*. (2011)	LANSS	Brazilian Portuguese	90	34	44	12	Yes	2	Yes	1	Yes	NS
Yucel *et al*. (2004)	LANSS	Turkish	101	49	52	0	Yes	1	Yes	1	Yes	No
Gudala *et al*. (2017)	PainDETECT	Hindi	160	80	80	0	Yes	2	Yes	2	Yes	Yes
Matsubayashi *et al*. (2013)	PainDETECT	Japanese	113	60	53	0	Yes	2	Yes	2	Yes	No
Alkan *et al*. (2013)	PainDETECT	Turkish	240	80	80	80	Yes	2	Yes	2	Yes	No
De Andrés *et al*. (2012)	PainDETECT	Spanish	221	71	71	79	Yes	2	Yes	2	Yes	NS
López-de-Uralde-Villanueva *et al*. (2018)	S-LANSS	Spanish	182	71	111	0	Yes	2	Yes	2	Yes	Yes

Batistaki *et al*. (2016)	S-LANSS	Greek	100	54	46	0	Yes	2	Yes	2	Yes	Yes
Koc and Erdemoglu (2010)	S-LANSS	Turkish	244	137	107	0	Yes	2	Yes	NS	Yes	Yes

*82 (42%) had mixed pain, but were included in the neuropathic pain group

NS – Not specified

3.3.3 DN4

Description of the DN4 articles

Eleven studies were included in the DN4 screening tool in this review (table 3.1). Two studies (Chatila *et al*., 2017; Terkawu *et al*., 2017) further evaluated the reliability and validity properties of the tools at different cut-offs. The DN4 was translated to eight different languages which includes: Arabic language (n=2) (Chatila *et al*., 2017; Terkawi *et al*., 2017), Brazilian Portuguese (n=1) (Santos *et al*., 2010), Korean (n=2) (Kim *et al*., 2016; Park *et al*., 2015), Spanish (n=2) (Hamdan *et al*., 2014; Perez *et al*., 2007), Farsi (n=1) (Madani *et al*., 2014), Greek (n=1) (Sykioti *et al*., 2015), Italian (n=1) (Spallone *et al*., 2012) and Japanese (n=1) (Matsuki *et al*., 2018). The total sample size reported n = 1,756. Out of this, n = 880 was diagnosed with neuropathic pain, n = 731 nociceptive pain and n = 55 were patients with mixed pain. Eighty-two (82) participants had mixed pain included in the neuropathic pain participants (Hamdan *et al*., 2014). All the included articles that used DN4 instruments were published between 2007 and 2018 (Table 3.1).

Forward translation was reported in eight (8) studies (Matsuki *et al*. (2018); Chatila *et al*. (2017); Terkawi *et al*. (2017); Kim *et al*. (2016); Sykioti *et al*. (2015); Madani *et al*. (2014); Hamdan *et al*. (2014);Spallone *et al*. (2012);Santos *et al*. (2010); Perez *et al*. (2007)) with the translation conducted in two studies Terkawi *et al*. (2017); Madani *et al*. (2014) in 5-times, one study Madani *et al*. (2014), 3-times , two studies in 2-times (Perez *et al*., 2007; Santos *et al*., 2010), one study in 1-time (Matsuki *et al*., 2018). Similarly, backward translation was reported in eight studies (Matsuki *et al*. (2018); Chatila *et al*. (2017); Terkawi *et al*. (2017); Kim *et al*. (2016); Sykioti *et al*. (2015); Madani *et al*. (2014); Santos *et al*. (2010); Perez *et al*. (2007)) with one study Madani *et al*. (2014) conducted in 3-times, three studies Terkawi *et al*. (2017); Santos *et al*. (2010); Perez *et al*. (2007) conducted in 2-times, three studies were not specific on the number of times backward translation was done, and three studies did not report on the backward translation (Table 3.1). Expert assessment was involved in seven (7) studies Matsuki *et al*. (2018); Chatila *et al*. (2017); Terkawi *et al*. (2017); Sykioti *et al*. (2015); Madani *et al*. (2014); Santos *et al*. (2010); Perez *et al*. (2007), and four (4) studies Chatila *et al*. (2017); Terkawi *et al*. (2017); Madani *et al*. (2014) Santos *et al*. (2010) ; conducted a pilot test while seven did not or were not specific on the conduction of pilot study (Table 3.1).

Validity and reliability of the DN4 instrument

Internal validity was reported in nine (9) studies Chatila *et al*. (2017); Terkawi *et al*. (2017); Santos *et al*. (2010); Madani *et al*. (2014); Sykioti *et al*. (2015); Matsuki *et al*. (2018); Park *et al*. (2015); Kim *et al*. (2016); Perez *et al*. (2007) of the included eleven studies (Table 3.2). Cronbach α was reported in eight (8) studies Chatila *et al*. (2017); Terkawi *et al*. (2017); Santos *et al*. (2010); Madani *et al*. (2014); Sykioti *et al*. (2015); Park *et al*. (2015); Kim *et al*. (2016); Perez *et al*. (2007) with a range of 0.55 and 0.93. Findings on test-retest validity were reported in seven studies Terkawi *et al*. (2017); Madani *et al*. (2014); Sykioti *et al*. (2015); Matsuki *et al*. (2018); Park *et al*. (2015); Kim *et al*. (2016); Perez *et al*. (2007) with ICC values between 0.81 and 0.957. One study reported the coefficients of correlation spearman value 0.81 (Terkawi *et al*., 2017).

The inter-rated reliability was conducted in seven (7) studies Chatila *et al*. (2017); Santos *et al*. (2010); Madani *et al*. (2014); Sykioti *et al*. (2015); Park *et al*. (2015); Kim *et al*. (2016); Perez *et al*. (2007) in translated DN4, Cohen's kappa lowest scored values of 0.92 were reported for brushing in one study (Chatila *et al*., 2017), while total score values of 0.818 and 0.92 were reported in two studies (Santos *et al*., 2010; Sykioti *et al*., 2015), scored values of 0.823 was reported for itching in two studies (Kim *et al*., 2016; Park *et al*., 2015) (Table 3.2)

Cohens kappa high values of 1.0, 0.826-0.946 and 0.9 were reported for hypoesthesia to brushing and hypoesthesia to pinprick in two studies (Chatila *et al*., 2017; Terkawi *et al*., 2017) and numbness (Kim *et al*., 2016; Madani *et al*., 2014; Park *et al*., 2015). Also, total Cohens kappa highest score values of 0.818 and 0.92 (total score) were reported in two studies (Santos *et al*., 2010; Sykioti *et al*., 2015).

Table 3.2: Measures of validity for translated versions of the DN4

Author	Assessed Internal validity	Cronbach alpha	Assessed Test-retest reliability	ICC*	Correlation coefficient	Assessed Inter-rater reliability	Cohen's Kappa (lowest score)	Cohen's Kappa (Highest score)	Correlation Coefficient	ICC
Chatila *et al*. (2017)	Yes	0.55 to 93	No	-	-	Yes	0.92 (brushing)	1.0 (hypoesthesia to brushing, hypoesthesia to pinprick)	-	0.99
Chatila *et al*. (2017)	Yes	0.86**	No	-	-	Yes	0.92 (brushing)	1.0 (hypoaesthesia for touch, hypoaesthesia for pinprick)	-	0.99
Terkawi *et al*. (2017)	Yes	0.7	Yes	-	-	-	-	-	-	-
Terkawi *et al*. (2017)	Yes	0.67	Yes	0.81	0.81 (Spearman)	No		-	-	-
Santos *et al*. (2010)	Yes	0.76	No	-	-	Yes	0.92 (total score)	0.92 (total score)	-	-
Madani *et al*. (2014)	Yes	0.862	Yes	0.957	-	Yes	0.416 (electric shocks)	0.826 (numbness)	-	0.957
Sykioti *et al*. (2015)	Yes	0.65	Yes	0.956	-	Yes	0.818 (total score)	0.818 (total score)	-	-
Spallone *et al*. (2012)	No	-	No	-	-	No	-	-	-	-
Matsuki *et al*. (2018)	Yes	-	Yes	0.827	-	-	-	-	-	-

Park *et al*. (2015)	Yes	0.819	Yes	0.813	-	Yes	0.823 (itching)	0.946 (numbness)	-	-
Kim *et al*. (2016)	Yes	0.819	Yes	0.813	-	Yes	0.823 (itching)	0.946 (numbness)	-	-
Perez *et al*. (2007)	Yes	0.7	Yes	0.949	-	Yes	0.68 (Not specified)	0.79 (Not specified)	-	0.926
Hamdan *et al*. (2014)	No	-	-	-	-	No	-	-	-	-

***** *Intra-class correlation coefficient;* ** *Only provided internal consistency for the entire questionnaire (used Kuder-Richdson formular)*

Sensitivity, specificity, negative and positive likelihood

Different cut-offs were adopted to differentiate the neuropathic pain from nociceptive pain in this instrument (Table 3.3). Studies included at cut off 3 showed sensitivity between 93.3-100%, specificity between 3-100%, Positive Likelihood between 5.2-5.5, Negative Likelihood between 0-3, PPV ranges between 84.3-85.6% and NPV of 72.1-97.5% in three studies.

At cut-off 4, sensitivity reported ranges between 80-96% while the specificity was between 6.8-95%, Positive likelihood 8.4- 20.2 reported in three studies, Negative Likelihood range between 0.1-0.2; PPV was between 63.9-95% and the NPV was between 69-95.5% reported in eight studies. At cut-off of 5, sensitivity reported ranges between 75-91% in four studies, specificity was between 51-99%, Positive likelihood ranged between 5-150, Negative Likelihood was between 0.1-0.2, the PPV was between 84.3-93.7% and NPV was between 53.2-92.9%. Youden index values with cut-off of three ranges between 0.46 - 0.92, cut off 4, was between 0.6-0.932 and cut-off of 5 ranges between 0.6-0.89 (Table 3.3).

Table 3.3: Measure of reliability for translated of the DN4 instrument

Author	ROC*	Cut-off used	Sensitivity (%)	Specificity (%)	Positive Likelihood	Negative Likelihood	PPV** (%)	NPV*** (%)	Youden Index
Chatila *et al*. (2017)	Yes	3	98	81.3	5.2	0	84.3	97.5	0.79
		4	96	89	8.4	0.1	89.6	95.5	0.85
		5	93	96	22	0.1	85.8	92.8	0.89
Chatila *et al*. (2017)	Yes	5	93	95.8	22	0.1	95.8	92.9	0.89
		4	96	89	8.4	0.1	98.5	95.5	0.85
Terkawi *et al*. (2017)		-	-	-	-	-	-	-	-
Terkawi *et al*. (2017)	Yes	4	88.3	75.4	-	-	-	-	-
Santos *et al*. (2010)	Yes	3	1	37.3	-	-	85	80	0.627
		4	1	6.8	-	-	-	-	0.932
		5	91	5.1	-	-	-	-	0.854
Madani *et al*. (2014)	Yes	3	95	88	8.5	0	89	95	83
		4	90	95	20.2	0.1	95	91	85
		5	83	99	150	0.2	99	86	82
Sykioti *et al*. (2015)	Yes	3	93.3	52.5	-	-	85.6	72.1	0.46
		4	89	78	-	-	92.4	69.7	0.67
		5	75	85	-	-	93.7	53.2	0.6
Spallone *et al*. (2012)	Yes	4	80	91.7	9.6	0.2	81.6	90.8	-
Matsuki *et al*. (2018)		-	-	-	-	-	-	-	-
Park *et al*. (2015)	Yes	3	100	88.2	-	-	-	-	0.882
		4	87	94	-	-	-	-	-
Kim *et al*. (2016)	Yes	3	100	88.2	-	-	-	-	0.882
		4	87	94	-	-	-	-	0.812

Perez *et al*. (2007)	Yes	4	79.8	78	-	-	85.9	69	0.58
		4	82	78	-	-	79	80.7	0.6
		4	82	78	-	-	63.9	90.2	0.6
Hamdan *et al*. (2014)	Yes	4	95	97.2	-	-	-	-	0.92
	Yes	3	97	82.3	5.5	0	85	96.3	0.79

3.3.4 DN4-interview

Two studies were included in this review instrument (Chatila *et al*., 2017; Spallone *et al*., 2012) conducted in Arabic and Italian languages respectively (table 3.1) and reported between 2012 and 2017 were participants in Arabic, and Italian population with a total sample size was 611. Patients with Neuropathic pain (NP) were 248. The number of nociceptive pain patients' range was 253 patients, and none had mixed pain (MP). Forward translation was conducted in two studies thrice (3-times), and out of the three studies that adopted this DN4-interview, one (1) study was not specific on the conduct and the number of times it was conducted. Similarly, backward translation was conducted in two studies out of the three (3) studies adopted in DN4-interview, but the number of times conducted was not specific. Expert assessment involved, and a pilot study was conducted in two studies included.

Measurement of the validity of DN4-interview instrument:

Internal validity was assessed in two studies with Cronbach alpha value between 0.55-93 and 0.86 (using Kuder- Richardson formula to assess the internal consistency of the whole questionnaire). In two studies Cohens Kappa lowest score value of 0.92 (brushing) and Cohen's Kappa Highest score values of 0.9 (electric shocks) and 1.0 (Hypoesthesia to brushing, hypoesthesia to pinprick).

Measurement of reliability of DN4-Interview

ROC was conducted in two studies included using this instrument (table 3.3). At cut off 2, the sensitivity was 99%, Specificity value of 58.3%, Positive Likelihood value 2.4, PPV of 71%, NPV of 98.2%. Two studies employ cut off 3 with sensitivity of 97%, Specificity value of between 82-82.3, Positive Likelihood value of 5.5., Negative Likelihood of 0, PPV of 85% and NPV of 96.3%. One study reported cut off value of 4 with sensitivity value of 84%, Specificity value of 90%. Positive Likelihood value of 8.1, and Negative Likelihood of 0.2, PPV 89.2% and NPV of 84.3%. Youden index value at cut off 2 was 0.56, cut off 3 was 0.79 and cut off 4 was 0.37.

3.3.5 LANSS

Description of the LANSS articles

Demographic characteristic of eight studies included using LANSS instrument in assessment of neuropathic pain (table 3.4). Eight (8) studies (Batistaki *et al*., 2016; Spanos *et al*., 2015; Park *et al*., 2015; Schestatsky *et al*., 2011; Barbosa *et al*., 2014; Hamdan *et al*., 2014; Türkel *et al*., 2014; Yucel *et al*., 2004) were included in this review. Two studies each were reported in Greek (Batistaki *et al*., 2016; Spanos *et al*., 2015) and Turkish languages (Türkel *et al*., 2014; Yucel *et al*., 2004). Each of the following languages reported one study - Brazilian Portuguese (Schestatsky *et al*., 2011), Korean (Park *et al*., 2015), Spanish (Hamdan *et al*., 2014) and Portuguese (Barbosa *et al*., 2014).

Total sample size reported was 1,081. Out of this, 612 was diagnosed with neuropathic pain while 477 was classified to have nociceptive pain. One study reported 42% of the neuropathic pain participants also had mixed pain (Hamdan *et al*., 2014). Forward translation was conducted in four studies twice and one study once. Backward translation was conducted twice in two studies. Four studies conducted backward translation one time. Six studies involved expert assessment while four studies conducted pilot studies.

LANSS measurement of validity:

Internal validity assessment was

conducted in six studies, with Cronbach alpha ranging between 0.65-0.9612 and Test-retest reliability conducted in four studies (table 3.5). One study reported intra class coefficient value of 0.77 (Batistaki *et al*., 2016) with Pearson correlation coefficient was reported in two studies (0.912-0.990 and 0.940). Inter-rated reliability was reported in two studies Schestatsky *et al*. (2011); Batistaki *et al*. (2016) with Pearson value of 0.87 in one study (Batistaki *et al*., 2016).

Table 3.4: Measures of validity for translated versions of the LANSS

Author	Assessed Internal validity	Cronbach alpha	Assessed Test-retest reliability	ICC	Correlation coefficient	Assessed Inter-rater reliability	Correlation coefficient	ICC
Schestatsky *et al*. (2011)	Yes	0.67	No	-	-	Yes	-	0.97
Spanos *et al*. (2015)	Yes	0.895	Yes	-	0.912 to 0.990* (Pearson)	No	-	-
Batistaki *et al*. (2016)	Yes	0.65	Yes	-	0.940 (Pearson)	Yes	0.87 (Pearson)	-
Park *et al*. (2015)	Yes	0.815	No	-	-	No	-	-
Barbosa *et al*. (2014)	Yes	0.77	Yes	0.77	-	No	-	-
Hamdan *et al*. (2014)	No	-	-	-	-	No	-	-
Yucel *et al*. (2004)	No	-	No	-	-	No	-	-
Türkel *et al*. (2014)	Yes	0.9612	Yes	-	0.952 (Spearman)	[#]see footnotes	-	-

* range of r coefficients for each item: [#]Difficult to interpret test-retest, and inter-rater reliability because of the manner of reporting.

Measure of reliability of LANSS instrument

Table 3.5 indicates measure of reliability of LANSS. Five studies conducted ROC at cut-off of 12. Six (6) cut off values were reported to different neuropathic pain from nociceptive pain. Cut off 2, two studies reported 80.2 and 89.8% respectively., Specificity was 100% and 94.2%, One study reported PPV 93.6% and NPV of 90.74. while one study reported the Youden index value of 0.8. Two studies reported cut off 2, sensitivity was 80.2 and 89.9, specificity was 94.2 and 100, NPV was 93.6. PPV was 90.74 with Youden index value 0.8. One study reported cut off 7 with sensitivity of 91.2%, Specificity value of 83%, Positive Likelihood 5.4, Negative Likelihood value 0.1, PPV 86% and NPV 89% with Youden index value of 0.742 (Table 3.5).

Cut off 10.5 was reported in one study with sensitivity of 88%,Specificity 95%, One study reported the use of Cut off 11 with sensitivity of 100%, specificity of 95.9%,PPV of 93.6 and NPV of 100.Four studies used cut off 12 with sensitivity ranging from 72.6-98%, specificity ranges between 74-98%, Negative likelihood was reported in two studies., NPV, at cut of 7 with value 5.4 and cut off 12 with value 36.3, Negative likelihood value 0.1 at cut off 7 and 0.3 at cut off 12, the sensitivity ranges from 72.6-98, specificity ranges from 74- 98%,Posititive likelihood was reported in a study with value of 36.3 and Negative Likelihood 0.3. Positive Predictive Value ranges between 85-99%, Negative Predictive Value of 76-96%. One study applied cut off 13, with sensitivity of 95%, specificity of 98%, PPV of 99 and Negative Predictive v=Value of 90.57. In addition, one study reported the use of cut off 14 with Sensitivity 84, Specificity 82.8, PPV 88.7 and NPV 76.8.

Table 3.5: Measures of reliability for translated versions of the LANSS

Author	*ROC*	Cut off used	Sensitivity (%)	Specificity (%)	Positive likelihood	Negative Likelihood	PPV** (%)	NPV** (%)	Youden index
Schestatsky *et al*. (2011)	No	-	-	-	-	-	-	-	-
Spanos *et al*. (2015)	No	-	-	-	-	-	-	-	-
Batistaki *et al*. (2016)	Yes	12	82.8	95.2	-	-	96	80	-
		10.5	88	95	-	-	-	-	-
Park *et al*. (2015)	Yes	12	72.6	98	36.3	0.3	98	76	Not specified
		7	91.2	83	5.4	0.1	86	89	0.742
Barbosa *et al*. (2014)		12	89	74	-	-	85	81	-
		14	84	82.8	-	-	88.7	76.8	-
Hamdan *et al*. (2014)	Yes	2	80.2	100	-	-	-	-	0.8
Yucel *et al*. (2004)	Yes	2	89.9	94.2	-	-	93.6	90.74	-
Türkel *et al*. (2014)	Yes	11	100	95.9	-	-	98	100	-
		12	98	98	-	-	99	96	-
		13	95	98	-	-	99	90.57	-

* Receiver operating characteristic, **Positive predictive value, ***Negative predictive value

3.3.6 Self-LANSS

Description

Three (3) included studies adopted LANSS-self between 2010 – 2016, one study in the Greek language (Batistaki *et al*., 2016), one study in Spanish language (López-de-Uralde-Villanueva *et al*., 2018) and one study in Turkish language (Koc and Erdemoglu, 2010) (table 3.6). Internal validity was reported in the three (3) studies with Cronbach alpha between 0.67-0.74. Test-retest validity was reported in two (2) studies with r-coefficient 964-Spearman, 0.97-Pearson, respectively. One study reported inter-rater reliability and second r-coefficient. ROC was conducted in the three (3) studies. Batistaki *et al*. (2016); López-de-Uralde-Villanueva *et al*. (2018). Koc and Erdemoglu (2010)

Table 3.6: Development of translated versions of the S-LANSS

Author	Language	Sample size	Neuropathy sample size	Nociceptive sample size	Mixed sample size	Forward translation	Number of forward translations	Backward translation	Number of backward translations	Expert assessment	Pilot test
Batistaki *et al*. (2016)	Greek	100	54	46	0	Yes	2	Yes	2	Yes	Yes
López-de-Uralde-Villanueva *et al*. (2018)	Spanish	182	71	111	0	Yes	2	Yes	2	Yes	Yes
Koc and Erdemoglu (2010)	Turkish	154	137	107	0	Yes	2	Yes	Not specified	Yes	Yes

Three (3) different cut-offs were used in this study labelled cut-off 1, cut-off 2, cut-off 3, to distinguish neuropathic pain from Nociceptive pain.

Table 3.7: Measures of reliability for translated versions of the S-LANSS

Author	Assessed Internal validity	Cronbach alpha	Assessed Test-retest reliability	ICC	Correlation coefficient	Assessed Inter rater reliability	Cohens Kappa (lowest score)	Cohens Kappa (highest score)	Correlation coefficient	ICC
Batistaki *et al*. (2016)	Yes	0.67	Yes	-	964 (Spearman)	Yes	-	-	0.54 (Pearson)	-
López-de-Uralde-Villanueva *et al*. (2018)	Yes	0.71	No	-	-	No	-	--	-	-
Koc and Erdemoglu (2010)	Yes	0.74	Yes	-	0.97 (Pearson)	No	-	-	-	-

Measurement of reliability of S-LANSS Instrument

ROC was conducted in the three studies (table 3.8) with three different cuts off. One study reported cut-off 10 with sensitivity 78.8%, Specificity 76.6%, PPV 81.2%,NPV 73.9 %.One study adopted Cut off 10.5, Sensitivity 87%, Specificity 88%, Cut of 11, Sensitivity 90.1%, Specificity 72.1 %, Positive Likelihood value of 3.23, Negative Likelihood value of 0.2, PPV 67.4 and NPV 91.0% with Youden index value of 0.62. Three studies adopted cut off 12 with sensitivity ranging between 72.3 -88.7%, specificity ranging between 78.8-95.2%, Positive likelihood value of 3.8 and Positive likelihood value 0.2 was recorded by one study (López-de-Uralde-Villanueva *et al*., 2018); PPV ranging between 70.8-96.2%, NPV between 69.4-91.4% with Youden index value 0.61 reported in one study. Cut off 13 showed sensitivity of 81.7%. Specificity 79.3%.. Positive likelihood value of 4, Negative likelihood value of 0.2, PPV of 71.6%, Negative Predictive value 87.1 with Youden index value of 0.61.

Table 3.8: Measures of reliability for translated versions of the S-LANSS

Author	ROC*	Cut off used	Sensitivity (%)	Specificity (%)	Positive Likelihood	Negative Likelihood	PPV**(%)	NPV***(%)	Youden
Batistaki *et al*. (2016)	Yes	12	86.2	95.2	-	-	96.2	83.33	-
		10.5	87	88		-	-	-	-
López-de-Uralde-Villanueva *et al*. (2018)	Yes	11	90.1	72.1	3.23	0.1	67.4	91.9	0.62
		12	88.7	76.6	3.8	0.2	70.8	91.4	0.65
		13	81.7	79.3	4	0.2	71.6	87.1	0.61
Koc and Erdemoglu (2010)	Yes	12	72.3	80.4	-	-	82.5	69.4	--
		10	78.8	76.6	-	-	81.2	73.9	-

Receiver operating characteristic, **Positive predictive value, ***Negative predictive value

3.3.7 PainDETECT

Description

Four (4) studies were included in translated PainDETECT 2012 to 2017 in population with local language Hindi (Gudala *et al*., 2017), Japanese (Matsubayashi *et al*., 2013), Spanish (De Andrés *et al*., 2012) and Turkish (Alkan *et al*., 2013). Total sample size reported (n = 974,) out of this, 371 participants had neuropathy, 364 and 239 participants were diagnosed with nociceptive and mixed pain respectively, Five (5) studies included reported forward translation, the translation was reported twice in the five (5) studies. Backward translation was reported in the five (5) studies conducted twice in the five studies. Expert assessment was conducted in the five studies. Pilot study was conducted in one study (Gudala *et al*., 2017).

PainDETECT validity characteristic

Internal validity of the terms was reported in the five (5) studies extracted with Cronbach alpha reported ranges from 0.78-0.86. Test-retest validity was reported in five (5) studies and ICC reported ranges from 0.934-0.98 in five (5) studies included. Four (4) studies reported. ROC (Alkan *et al*., 2013; De Andrés *et al*., 2012; Matsubayashi *et al*., 2013; Gudala *et al*., 2017).

PainDETECT Reliability characteristic

Table 8.3: Four cut offs were reported in the studies included using PainDETECT instrument. Cut off 12, the sensitivity was between 84-93%,, Specificity 66-68%, two studies reported PL 2.7 and 2.9; NL 0.1 and 0.2; PPV was reported by four studies ranging between 73-87%, NPV 65-88% and Youden index value of 0.575 and 0.519 reported in two studies (table 3.11).

Two studies made use of cut off 17, Sensitivity 81%, Specificity 80 and 81%; Positive Likelihood 4.1 and 4.3;Negative predictive value 65 and 81 with Youden index values of 0.613 and o.624.One study reported cut off of 18, Sensitivity 83%, Specificity 91%, PPV 90% and NPV 84%.Three study adopted cut off of 19, specificity between 71-79%, Specificity 83-93 %, Positive likelihood reported in two studies with values of 4 and 4.4, Negative likelihood 0.3 and 0.4, PPV reported in three studies ranging between 82-90%, NPV between 55-79% with Youden index reported in two studies values 0.531 and 0.613 (table 3.11).

Table 3.9: Development of translated versions of the PainDETECT

Author	**Language**	**Sample size**	**Neuropathy sample size**	**Nociceptive sample size**	**Mixed sample size**	**Forward translation**	**Number of forward translations**	**Backward translation**	**Number of backward translations**	**Expert assessment**	Pilot test
Gudala *et al*. (2017)	Hindi	160	80	80	0	Yes	2	Yes	2	Yes	Yes
Matsubayashi *et al*. (2013)	Japanese	113	60	53	0	Yes	2	Yes	2	Yes	No
De Andrés *et al*. (2012)	Spanish	221	71	71	79	Yes	2	Yes	2	Yes	Not specified
Alkan *et al*. (2013)	Turkish	240	80	80	80	Yes	2	Yes	2	Yes	No
Alkan *et al*. (2013)	Turkish	240	80	80	80	Yes	2	Yes	2	Yes	No

Table 3.10: Measures of validity for translated versions of the PainDETECT

Author	Assessed Internal validity	Cronbach alpha	Assessed Test-retest reliability	ICC	Correlation coefficient	Assessed Inter--rater reliability	Cohens Kappa (lowest score)	Cohen's Kappa (Highest score)	Correlation coefficient
Gudala *et al*. (2017)	Yes	0.83	Yes	0.94	-	No	-	-	-
Matsubayashi *et al*. (2013)	Yes	0.78	Yes	0.94	-	No	-	-	-
De Andrés *et al*. (2012)	Yes	0.86	Yes	0.934	-	No	-	-	-
Alkan *et al*. (2013)	Yes	0.81	Yes	0.98	-	-	-	-	-
Alkan *et al*. (2013)	Yes	0.81	Yes	0.98	-	-	-	-	-

Table 3.11: Measures of reliability for translated versions of the PainDETECT

Author	**ROC***	**Cut off used**	**Sensitivity (%)**	**Specificity (%)**	**Positive Likelihood**	**Negative Likelihood**	**PPV**(%)**	**NPV***(%)**	Youden
Gudala *et al*. (2017)	Yes	19	79	93	-	-	91	81	-
		12	90	66	-	-	73	87	-
		18	83	91	-	-	90	84	-
Matsubayashi *et al*. (2013)	-	-	-	-	-	-	-	-	-
De Andrés *et al*. (2012)	Yes	12	93	68	2.9	0.1	87	80	0.609
		19	75	84	4.7	0.3	92	60	0.595
		17	81	81	4.3	0.2	91	65	0.624
Alkan *et al*. (2013)	Yes	12	90	68	2.8	0.2	73	87	0.575
		19	78	83	4.4	0.3	82	79	0.6
		17	81	80	4.1	0.2	80	81	0.613
Alkan *et al*. (2013)	Yes	12	84	68	2.7	0.2	86	65	0.519
		19	71	83	4	0.4	90	55	0.531

* Receiver operating characteristic, **Positive predictive value, ***Negative predictive value

3.4 Discussion

The aim of the study was to conduct a qualitative systematic review to determine the psychometric property, reliability, and validity of translated, neuropathic pain screening tools (LANSS, DN4 and PD-Q). These tools were developed in different languages to test their capacity in diagnosing patients with neuropathic pain quality from non-neuropathic pain. However, the internal consistency of the item (Cronbach α) and test-retest reliability were evaluated to determine the reliability of the instrument. The outcome of sensitivity, specificity, positive predictive values, negative predictive values range were determined, cross examined with the original version of the screening tools to determine the validity of the instruments.

DN4 instrument

The participants' average sample size was above 30 in all the included studies Chartila *et al*.,(2017); Spallone *et al*. (2012) using DN4-interview instrument, and this indicated that all the included studies had the sample size sufficient to represent the population and achieve the aim of the study. Furthermore the studies included reported that the data were normally distributed. Forward and backward translation were conducted in 90% of the included studies from local languages (Arabic, Brazillian-Portuguese, Farsi, Greek, Italian, Japanese, Korean and Spanish) to English language and from English language back to local languages in the included studies. Tsang *et al*. (2017) reported that this process is an important step in translation research, the greater number of forward and backward translation the better the reliability of the study to avoid the error of bias. The reported Cronbach alpha value were higher than 0.6 which indicated an acceptable internal consistency among the items in the questionnaire. The involvement of expert assessment in over 80% of the included studies was in agreement with the set-out guidelines for the process of good translation (Tsang *et al*., 2017). Furthermore, a pilot study was conducted in most of the studies included which is an essential step in the determination of the reliability of the items involved in the questionnaire and the validity of the test instrument. The value of Cohen’s Kappa low and high score reported by the pain expert was higher than normal values indicating, a profound agreement among the pain expert. The average high sensitivity values, specificity values, positive likelihood value, negative likelihood value, compared to the original DN4 French version (Bouhassira *et al*. (2005) sensitivity 83%,specificity 94% showed that translated version of DN4 across the cultural and language set-up is a

reliable and valid instrument in differentiating neuropathic pain from non-neuropathic pain groups.

DN4-interview

The participants sample size in this review (n = 416) was greater than 30 in all the included studies Chartila *et al*.,(2017); Spallone *et al*. (2012) using DN4-interview instrument, this indicated that all the studies were statistically adequate, and the sample mean is on normal distribution. Forward and backward translation were conducted (67%) from local languages (Arabic and Italian) to English Language and from English Language to local languages at least (three times) which were reported as important steps in translation process, as mentioned previously, the more times the translation the better chances of avoiding the error of bias. Tsang *et al*. (2017) recommended a minimum of twice forward and backward translation for a good translation procedure. There was no specification on the number of times backward translation was conducted which could lead to a possible limitation when using this instrument. The reviewed studies Cronbach alpha value using this instrument (0.55-98) was averagely higher than 0.6 (the minimum Cronbach alpha value for a good internal consistency) which indicated an acceptable internal consistence among the items in this questionnaire , a general internal consistency measured (dichotomized measurement of reliability) by Kuder-Richardson formula (0.86) which is close to the 1 as recommended for a good reliability (Kuder and Richardson, 1937) with exception of one study (Chatila *et al*., 2017).

Moreover, expert assessment reported in over 80% of the included studies was also in agreement with the set-out guidelines for the process of good translation (Tsang *et al*., 2017). Inter-rated reliability reviewed showed a close point 0.9 to 1 in brushing at low Cohen Kappa and 1 in hypoesthesia to brushing and pinprick. This indicates there was a good agreement among the raters using this instrument (inter-rated reliability) in measuring neuropathic pain quality. This also showed that this instrument was considered as a good instrument and is consistent among the pain-experts. Therefore, this instrument could be used to distinguish neuropathic pain from non-neuropathic pain.

Pilot studies were conducted in most of the (67%) included studies, this is an essential step in determining validity of the questionnaire. The optimum sensitivity (84-99%) and specificity (58-90%) reported in the instrument indicated that this instrument (DN4-interview) was highly sensitive and specific in distinguishing neuropathic pain quality from non-neuropathic pain. Comparing the optimum value of test scores value of translated DN4-interview instrument in the included studies with the original DN4-interview test score values, the performances of the translated was not as good as the original version (Harifi *et al*., 2011; Spallone, V. *et al*. 2012)

LANSS

Our review on the psychometric, reliability and validity properties using LANSS instrument showed that test-retest reliability was conducted in 55% of the studies within the pain-experts. Only one study evaluated the intra-class correlation coefficient (0.77) This is contrary to the expectation from the original version, which showed that the included studies reported Cronbach alpha (0.67-0.9612) higher than 0.6, indicating a good internal consistency among the items. Forward and backward translation were conducted given the instrument good translation procedures in 75% of the included studies. Fifty percent (50%) complied with minimum of two time forward translation while twenty percent complied with minimum of two backward translation. This shows there were gaps in translation procedures in 70% of the included studies (Barbosa *et al*., 2014; Hamdan *et al*., 2014; Schestatsky *et al*., 2011; Türkel *et al*., 2014; Yucel *et al*., 2004). Inter-rated reliability was conducted in 20% of the included studies, which were considered as an important step in measurement of reliability in instrument testing and the validity of the instrument as compared with original LANSS translation procedure. This is in contrary to the procedure for a good neuropathic pain instrument.

The average sensitivity value (85%) and specificity values (92%) observed using this instrument indicated that LANSS is a very sensitive instrument and specific to measure the neuropathic components of a pain patient across all languages. Average Positive Predictive value (93.7%) showed that the instrument is an effective instrument in the determination of components of LANSS questionnaire that mark out neuropathic pain components. This agrees with the Bennett study in the development of LANSS neuropathic pain screening tool (Bennett, 2001). Despite the differences in the sample

size of the included articles, all tools were good instruments of measurement of reliability in measuring neuropathic pain

S-LANSS

This is a modification of the original LANSS instrument without the clinical examinations that was developed by Bennett and colleague 2005 (Bennett *et al*.,2005) Our review indicated that the internal consistence measured by Cronbach alpha (0.67-0.74) showed high internal consistency among the items Forward and backward translations were conducted in all the studies (two times) which was the minimum number of times it should be carried out; pilot study was conducted with involvement of expert assessment in all the included studies. This review showed Cronbach alpha range (0.67-0.74) which was above 0.6 recommended for a good internal consistency in translation research (Taber, 2018). However, the test–retest reliability was conducted (90%) of the included articles, which is an important translation procedure. Our review on this instrument shows an average sensitivity value (83.02%) and specificity (80.3%). These values indicated that the instrument is sensitive in determination of the neuropathic component of a pain patient.

PD-Q

All the included studies conducted forward and backward translation twice in agreement with the recommended standard of translation research. However, most of the studies did not conduct pilot studies. This is contrary to the guideline for translation procedures which is an important step in validity studies. The internal consistency of the items measured by evaluating the Cronbach alpha values (0.78-0.86) showed a high internal consistency among the items listed in the instrument. Our review showed that Test-retest reliability was conducted in all the included studies with the average value of interclass correlation coefficient (0.95), suggesting a high validity of the instrument in all the translated version. The studies showed an average sensitivity value (82.3%) and specificity (80.5%), that indicated that PDQ is a sensitive instrument in the determination of neuropathic pain component, and the items are very specific in the determination of the symptoms of neuropathic pain.

3.5 Conclusion

The original DN4 and LANSS had the most evidence for their psychometric, reliability and validity properties in peer-reviewed articles. PDQ has a high sensitivity and specificity as well but more specific in measuring neuropathic pain quality in low back pain elderly patients. It is clear in PDQ translated instrument that there was no inter-

rated reliability conducted in most of the included studies; for those that were assessed, not all of them effectively measured the reliability variables. Moreover, these findings were supported by low or very low level of evidence. In conclusion, DN4, LANSS and PDQ neuropathic pain screening tool questionnaires may provide evidence of neuropathic pain quality for effective diagnosis in their test population. However, they cannot replace a clinical assessment. Therefore, we recommend that both the clinical assessment and neuropathic pain-screening tool are essential in the diagnosis of neuropathic pain component in pain patient in clinical settings.

3.6 Recommendation

These three neuropathic pain screening tools (DN4, LANSS and PDQ) translated version performed ultimately well in other local languages at their test population, however none of these has been developed in African Language, it will be valuable to also evaluate the performance of these tools by determine the reliability and validity.

CHAPTER 4-DEVELOPMENT OF A NEUROPATHIC PAIN SCREENING TOOLS IN ISIZULU

4.1 Introduction

Neuropathic pain is a debilitating disease associated with an increased frequency in visitation to health care experts and drug usage (Colloca *et al*., 2017; Terkawi *et al*., 2017). It is expressed as different distinct symptoms such as electric-like sensations, burning and pain resulting from non-painful stimulations (hypoesthesia to light brushing, light touch). In addition, the symptoms mostly persist and become chronic; and less responsive to pain medications. Subsequently, this impairs the quality of life (sleep disturbance, anxiety, depression) (Torta,, Ieraci, and Zizzi, 2017)). Despite years of ineffective efforts in clinical management of pain, there are advances in recent research in understanding the pathophysiology of neuropathic pain. This involves the development of neuropathic pain diagnostic tools that assess the qualities and characteristics of the neuropathic pain symptoms and signs, as described by the patients. This tool has been proven to have high sensitivity, high specificity in their translated version in different countries outside the original language in which they were developed. The performance of these tools has both qualitatively and quantitatively increased the epidemiology of neuropathic pain patient's data in different countries (United Kingdom, United States, France, and Brazil) and offered new evidence on the general prevalence of chronic neuropathic pain (Torrance *et al*., 2006). A systematic review on translated version of developed and validated DN4, LANSS and PD-Q, measuring the reliability and sensitivity of these instruments across the various language versions has just been completed as part of this project that showed these instruments were good in determination of neuropathic pain quality for different populations. The reports showed that none of the existing tools were developed in an African language, indicating neuropathic pain diagnosis may not be adequate; moreover, there is a gap in epidemiological data on the prevalence of neuropathic pain in African populations. Therefore, development, and validation of more than one neuropathic pain screening tool that can assess symptoms and signs of pain patients is essential. Several brief screening and diagnostic tools (DN4, LANSS, PDQ, PainID, NPS) have been developed. The most frequently used tools are the Douleur Neuropathique en 4 Questions (DN4; original development in French; 2005), the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS; original development in English; 2005), and the PainDETECT (PD-Q; original development in German; 2006). All these questionnaires include a semantic component that assesses symptoms shown to be core features of neuropathic pain, which needs to be translated

into local languages for the instruments to be used in populations that do not speak the language in which the tool was originally developed as part of their official language. Importantly, translating a screening tool is not sufficient for its use in a new language population, and the development process should involve forward and backward translation of the original tool, and then measurement of reliability and validity of the translated instrument.

DN4 neuropathic pain screening tool was originally developed in 2005 by a group of French neuropathic pain research excerpts (French Neuropathic Pain Group). It comprises of four groups of questions which are made up of ten questions in total. Seven sensory descriptors symptoms (burning, electric shock, tinging, pins-needles, itching and painful cold) while three measures the sign related to sensory physical examination of the painful area (Hypesthesia to touch, hypoesthesia to pinprick and Allodynia developed in French language (Bouhasirra *et al*., 2005), Several authors have adopted this tools in their local population in their local languages Japanese (Matsuki *et al.,* 2018), Arabic-Language (Chatila *et al*., 2017); Terkawi *et al*., 2017), Korean (Kim *et al*., 2016 ; Park *et al.*, 2015), Greek (Sykioti *et al*., 2015), Farsi (Madani *et al*., 2014), Spanish (Hamdan *et al*., 2014), Italian (Spallone *et al*., 2012), Brazilian Portuguese (Santos *et al*., 2010). The Spanish (Perez *et al*., 2017) demonstrated high reliability, high sensitivity, and high specificity, easy to understand and less time consuming during the application. This instrument was adopted in IsiZulu (African Nguni-Language) in this study because out of the 11 official languages spoken by South Africans, IsiZulu is spoken by 22.7% of the population (Figure 4.1) (*Baron, Davies, and Lund, 2017).*

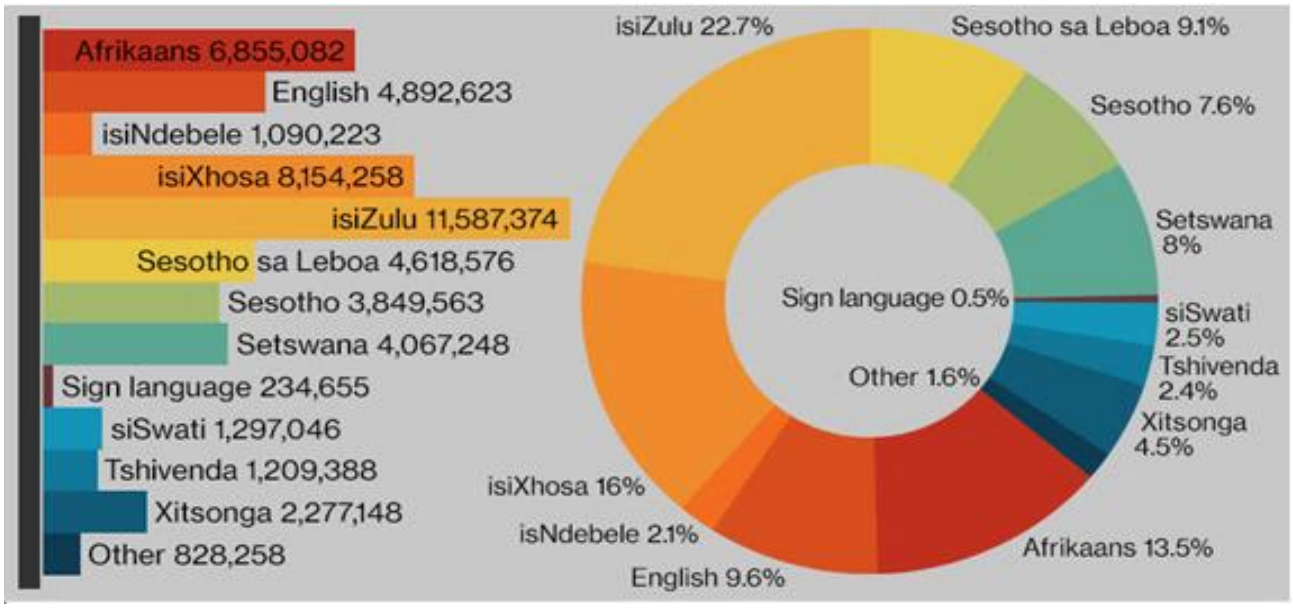

Figure 4.1: South African 11 languages with percentage of speakers in the population (Baron, Davies, and Lund, 2017).

In addition, translated isiZulu-DN4 neuropathic pain screening tool and development of semantic components of new isiZulu neuropathic pain screening tool is essential for proper neuropathic pain management (Shaikh *et al*., 2013), being cognizant of local language and cultural practices.,

Thus, this study aimed to develop a neuropathic pain screening tool in isiZulu to differentiate nociceptive and neuropathic pain among isiZulu-speaking population in Johannesburg, South Africa.

4.2 Method

An ethical approval was granted by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg, South Africa (clearance number: M150245) (Appendix 1). Written informed consent was obtained from all participants.

4.2.1 Participants' inclusion criteria

Both males and females' participants with pain conditions predominantly nociceptive or neuropathic were recruited from the diabetic clinics, HIV clinics, orthopedics wards,

obstetrics wards, and rheumatology clinics at four Wits University academic teaching hospitals in Johannesburg, South Africa (Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital, Hellen Joseph Hospital, Rahima Moosa Mother and Child Hospital).

All included participants were 18 years or older, isiZulu was their primary language (i.e., the language of communication with family and friends), and had a pain condition that is perceived to be predominantly nociceptive (labor pain, acute postoperative pain, pain from rheumatoid arthritis) (Vermelis *et al*., 2010; Brinck *et al*., 2018) or neuropathic (painful HIV and diabetic peripheral neuropathies) (Finnerup., 2013; Liampas *et al*.,2021). All participants with suspected painful HIV or diabetic polyneuropathy, the presence of a nerve lesion fitting with the anatomical distribution of the pain was confirmed through participant medical history (confirmed HIV infection or diabetes), and by the bilateral presence of at least two of the following neurological signs was assessed by the investigator (T. Fagbohun) refer to methodology section 2.2.4. The somatosensory distal nerve function was assessed in the leg of the participants using (i), vibration stimulation (using turning fork of 128Hz frequency and stopwatch) of the toes as described in Chapter 2, to determine the duration of travel of stimulus from receptors to the perceptive center in the brain, (ii), Ankle tendon reflex stimulation, (iii), pin-prick stimulation.

4.2.2 Pain descriptive interview

Wisconsin Brief Pain Questionnaire (WBPQ) was adopted to enquire on any pain the participants might be experiencing and to indicate the origin of the pain.

For example

Do you have pain? *'Yes' or 'NO'*

Have you had pain in the past months '*Yes' or 'NO'*

On the listed area provided on the questionnaire (Appendix 2) participants were asked to indicate where they had pain and if the pain was surface pain or deep pain. They were further encouraged to indicate whether the pain was caused by recent injury by accident, self-inflicted burnt or falling.

The participants were also asked to indicate the part of the body where the pain was worse.

This aspect of interview was conducted by the principal investigator Fagbohun T and interpreted to the participants in isiZulu by Florence M.

4.2.3 Participants Pain Rating

Three different pain scales were provided to the patients to describe their pain. The classification of pain was done after pain assessment.

I. **Worst pain last week** (on a scale of 0 – 10, '0' means no pain, '10'means worse pain, classified into 'mild', 'moderate' and 'severe'
II. **What time of day is your pain at its <u>worst</u>**? Using the scale, "in the morning', 'at noon', 'in the evening', 'all the time"
III. **How much pain you have <u>right now</u>:** on the scale 'mild', 'moderate'**,**' severe'

4.2.4 Interview

Nociceptive vs Neuropathic pain interview description.

The interview was conducted at the bed side of the participants in the hospital ward or dedicated site provided by the health facility. The interview was in two phases, firstly, participants were asked to describe how they perceive their pain and the trigger of their pain at the pain site (Spontaneous response) in isiZulu. At this stage, participants were not given pain description (not prompted) but where encouraged to express in full their pain description either in single words or phrase.

For example

*'**Interviewer ' ""**explain to me in isiZulu, how is the pain at your feet and how it feels like?*

***'Participants**; 'when sleeping, when I get up in the morning they hurt, it pulls, I can barely walk. I limp. The pain is from the feet to the knee. Thank you. '*

All the symptoms described by the participants were pulled out after the transcription and translated as mentioned in chapter 2 for analysis in both nociceptive pain patients and neuropathic pain patients.

4.2.5 Prompted response.

A list of neuropathic pain symptoms (‘hot/burning’, ‘numbness’, ‘painful/sore’ ’itching’, ‘tingling’, ‘electric shock’, ‘painful -cold’, ‘pins and needles’) from original DN4 questionnaire was read to the participant in isiZulu-Language and were asked to give the English language meaning. This was adapted from a similar study conducted in South Africa (Ashima *et al*., 2013). Subsequently participants were asked if they have the symptom (‘YES ‘ or ‘NO ‘ or ‘UNSURE ‘). They were also asked if they were familiar with the words/terms (‘YES ‘ or “NO”). They were further asked to provide a better isizulu word of the symptom.

4.2.6 Statistical analysis

Content analysis was used to extract self-reported pain symptoms and symptoms triggers from the translated text and then, working with the translators, the identified words, statements were matched with the isiZulu terms the participants used. Classifications and regression tree analysis (CART) was used to determine the symptoms that provide the best discrimination between individual with nociceptive and neuropathic pain. Classification And Regression Tree (CART), is a predictive model, which explains how an outcome variable's values can be predicted based on other values. A CART output is a decision tree where each fork is a split in a predictor variable and each end node contains a prediction for the outcome variable (Lewis, 2000).

4.3 Results

4.3.1 Demographic and clinical characteristics

Table 4.1 summarizes demographic and general clinical characteristics of the participants in the present study, these characteristics include age, alcohol use, gender, arthritis, diabetes, HIV, and surgery between nociceptive and neuropathic pain. The study comprised of males and females classified according to type of pain (nociceptive and neuropathic) with a mean age of 36.3 ± 18.3 SD and 50.4 ± 15.2 SD. Among the participants that gave consent to partake in the study 122 individuals had all the relevant clinical data for nociceptive and neuropathic pain screening completed. The percentage of history alcohol use was 88% and 77% in nociceptive and neuropathic pain patients respectively. In addition, these are the percentages for

arthritis (3.3 and 41%), diabetes (1.6 and 42.6), HIV (19.7 and 57.4 %) and surgery (54.1 and 42.6) between nociceptive and neuropathic pain patients respectively.

Table 4.1 Demographic and clinical characteristics according to pain type.

	Nociceptive	Neuropathic
Number	61	61
Age (years) SD	36.3 ± 18.3	50.4±15.2
Alcohol use (%)	88.5	77.0
Females (%)	77.0	88.5
Males (%)	11.5	23
Arthritis (%)	3.3	41.0
Diabetes (%)	1.6	42.6
HIV (%)	19.7	57.4
Surgery (%)	54.1	42.6

Data is presented as mean ± SD or percentage.

4.3.2 Distribution of participants according to underlying cause of pain

Table 4.2 shows 13 pain origins identified in our participants from different clinics and wards. Majority of the nociceptive pain patient's cause of pain was arthritis (osteoarthritic) 17.9%, cesarean section 17.8% and accident (16.3%). However, the least number of patients were from surgical ward (surgery 0.8%, Infection 0.8% and gun shot 0.8%). In addition, the source of neuropathic pain was HIV-SN (15.4%), neuropathy in the presence of both HIV-SN and diabetes (8.9%) and Diabetes (8.1%).

Table 4.2: Distribution of patients according to clinic

Clinic	N	Percentage
Arthritis	22	17.9
Cesarean section	22	17.8
Accident	20	16.3
HIV	19	15.4
HIV/Diabetes	11	8.9
Labour pain	11	8.9
Diabetes	10	8.1
Kidney failure	3	2.4
Cancer	1	0.8
Epigastric pain	1	0.8
Gunshot	1	0.8
Infection	1	0.8
Surgery	1	0.8

4.3.3 Pain Intensity

The pain intensity of all the participants were measured using 0-10 numerical pain scale that was divided into mild, moderate, and severe pain. Figure 4.2 shows results of pain intensity data pertaining to questions regarding pain before a week before the interview and during the interview. In neuropathic patients the percentage of severe pain was 73.8% and 63.9% of nociceptive pain patients reported that their pain was severe a week before the interview.

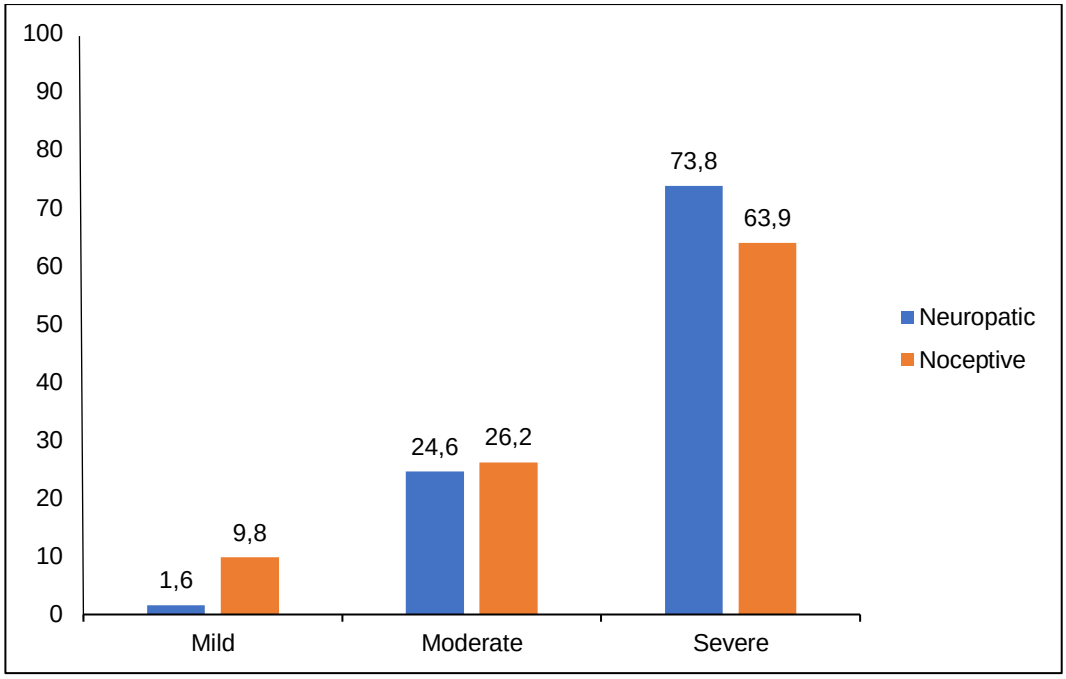

Figure 4.2: **pain scale rating a week before interview.**

4.3.5.1 Worse pain time

All neuropathic pain patients reported their pain as severe and 83.6% nociceptive pain patients reported their pain as severe all the time.

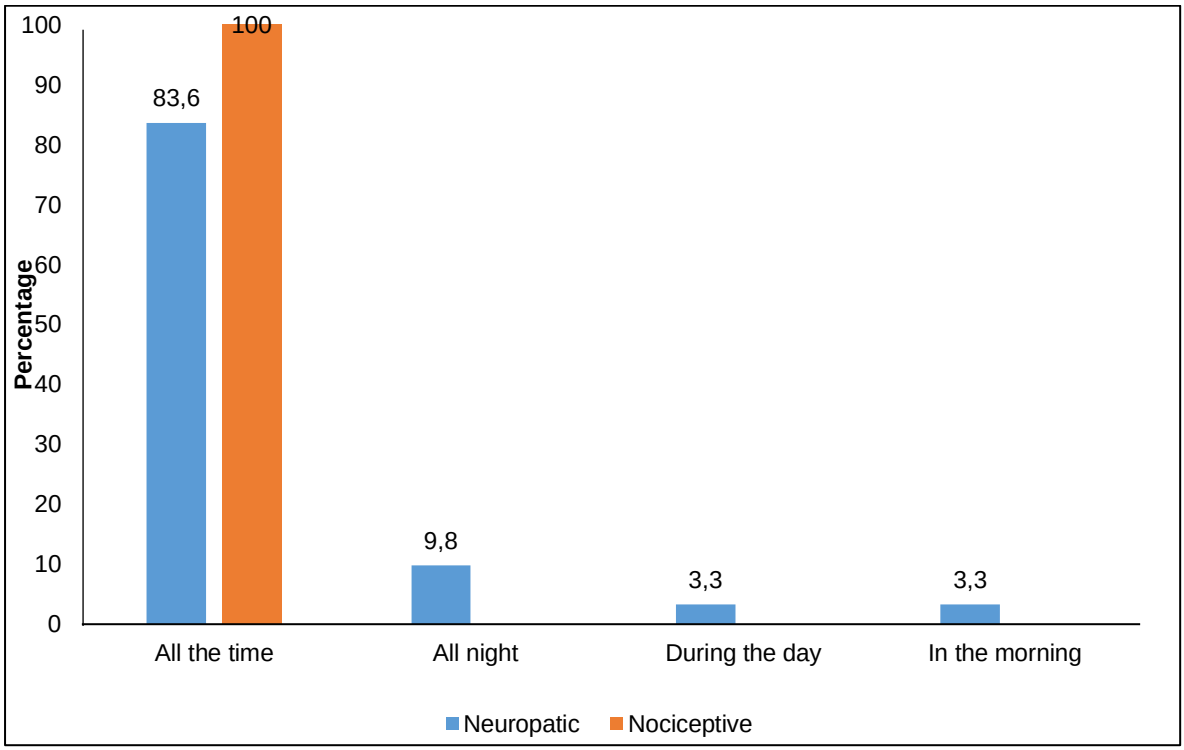

Figure 4.3: **Worse pain time**

4.3.5.2 Pain rating at interview.

At the point of the interview, 60.7% of the neuropathic pain patients reported their pain to be moderate while 57.4% of nociceptive pain reported their pain to be moderate. This indicated that all the patients were having pains rated between severe and moderate to be able to describe how their pain was perceived in isiZulu language.

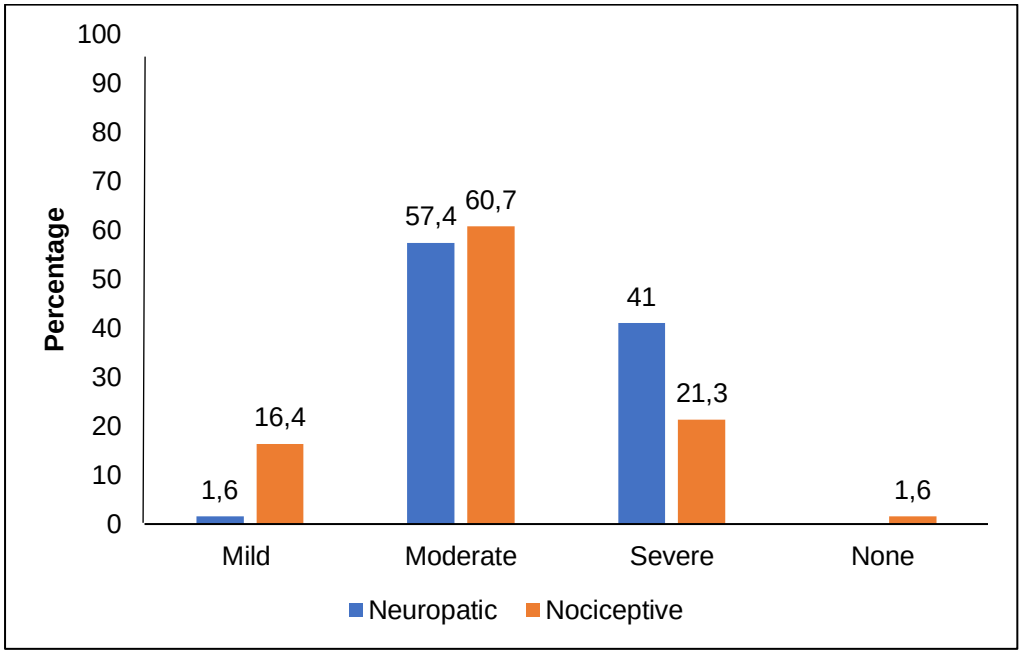

Figure 4.4: **Pain rating at interview**

4.3.5.3 Wisconsin brief pain questionnaire

Table 4.3 indicates participants' worse pain site according to the Wisconsin brief pain questionnaire. The pain location and the part of the body where the worse pain site was originating from were assessed.

Table 4.3: Participants worse pain site according to the Wisconsin brief pain questionnaire

	Description	Neuropathic (%)		Nociceptive (%)	
Worse pain site	Feet	39	63.9	12	19.7
	Hand	1	1.6	1	1.6
	Head	1	1.6		
	Joint	10	16.4	1	1.6
	Legs	3	4.9	12	19.7
	Legs/feet	1	1.6	2	3.3
	Low back	5	8.2	3	4.9
	Shoulder	1	1.6	1	1.6
	Abdomen			26	42.6
	Back			3	4.9

4.3.4 Spontaneous description of pain symptoms in isiZulu:

Several symptoms were used by our participants to describe their pain in isiZulu language that were translated back to English by the professional translators (the translation world (Pty) LTD, Sandton Johannesburg) (table 4.5). The isiZulu language descriptive terms spontaneously provided by participants when describing their pain symptoms at the pain location is detailed in table 4.6. In addition, some participants also provided examples what triggered their sensations at pain location using phrases (table 4.4).

The terms ‘pulling’, ‘sharp’, ‘cutting’ and ‘burning’ were the most common terms spontaneously used to describe the symptoms of nociceptive while ‘cramping’, ‘burning’, ‘pins’ & needles’, ‘sharp’ and ‘numb’ were common neuropathic pain symptoms used to describe their pain by the neuropathic pain participants. Some of the symptoms were extracted in the description of the event used in their pain description for example.

Table 4.4: Example of participant description of pain translated by professional translators back to English

isiZulu	English translation
'*Ama labour pain bekungathi kuyashisa, kubengazuthi kuyasika like kunomese okhathayo. Then bese kuba like azohamba, maybe azo hamba for 30 minutes. For example, lapho eqale khona kumina, izolo, ngo Friday ebusuku, kuqale like, I felt like ngazuthi kuyashisa and then kuyahamba. Kuphinde futhi ama pain akhona ayahamba for 30 minutes aphinde abuye futhi maybe after 30 minutes noma i awa aphinde abuye futhi. It's like ayashisa phansi kwesibeletho then aze ngasemhlane ama pain okuteta noma ama pain okuzala umntwana, uma umntwana ezofika usuke uzoteta. Then it was painful. Bekubuhlungu! Kungama pain abuhlungu*. '.	**'***The labour pains felt like some* ***hot (burning),*** *like a* **cut** *with a cutting knife. Then felt like the pains will go away, maybe will go away for 30 minutes. For example, when they started with me, yesterday on Friday night, it started like, I felt like it is hot and then it goes away. Again the pains would go away for 30 minutes and come again maybe after 30 minutes or an hour before coming back again. It's like hot under the womb then come to the back like labour pains or delivery pains, when the baby is about to come before you deliver. Then it was painful. It was very sore! It was* ***very painful '****.'*

IsiZulu Symptoms Extracted: '*kuyashisa***',** *'kuyasika' and 'bekubuhlungu'*
English Translation: 'burring/Hot', 'cutting' 'very painful'

4.3.5 Common spontaneous descriptive symptoms pain patients

The spontaneous description by neuropathic and nociceptive pain patients frequently used 'pulling' *Ukudonsa*) 42,3% as the most common symptom to describe their pain symptoms when not prompted with the English pain symptoms, followed by the terms 'sharp' (*Kuyasika*), 39.0%.,'burning' (*Kuyashisa)* symptom 30.9%.,'*(Kuyaluma*)

‘itching’((1.6%) and ’stabbing’ (*Ukugwaza*) (5.7%) ‘was generally less frequently used. (Figure 4.5).

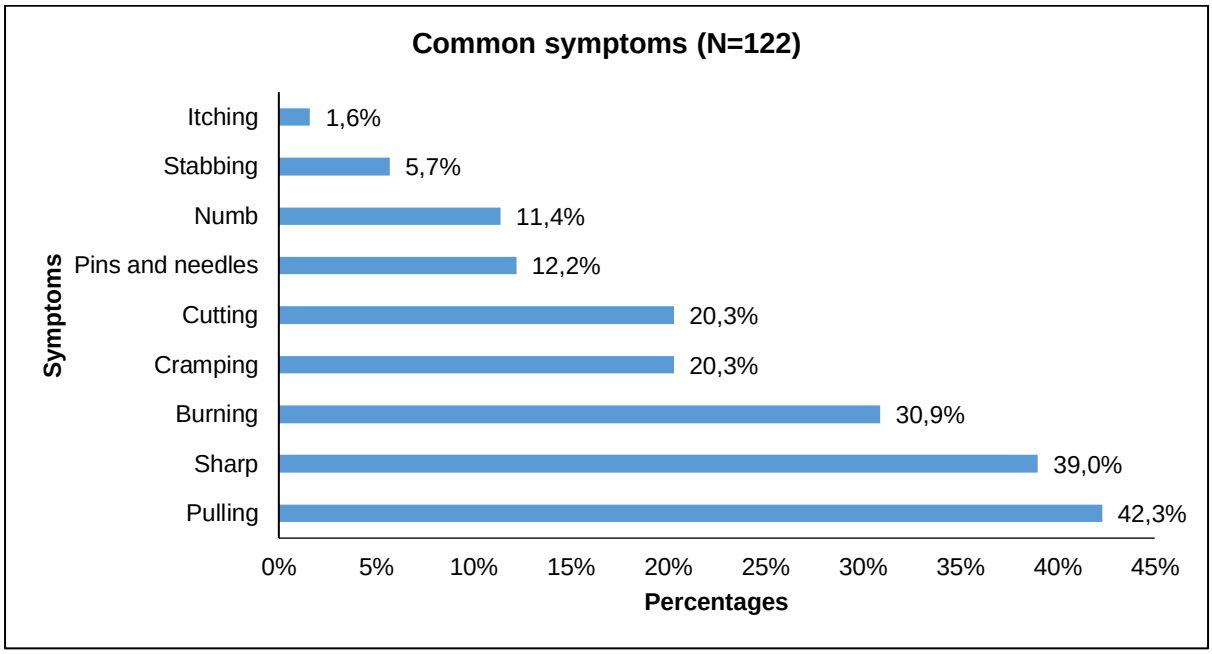

Figure 4.5 **Neuropathic and nociceptive pain symptoms**

Table 4.5: Percentage of participants of IsiZulu description of prompt symptoms translated to English language

English Symptoms descriptor	IsiZulu symptom descriptors by participants spontaneously	Accepted single term. by professional translators	Percentage of participant that used the term spontaneously
Pulling	Uyadonseka, Uyadonsa, Buyabudonsa, Ukudonsa Iyadonsa, Engathi iyatsala, Uyadonseka, Udonseka	Ukudonsa	42.3%
Sharp	Kuyasika. ,Engathi usikwe,	Kuyasika	39.0%
Burning	Bekungathi kuyashisa, Ayashisa, Kuyashisa	Kuyashisa	30.9%
Cramping	Ijaqaba, Namacramps, Amajaqamba , Amajaqaba	Amajaqamba	20.3%
Cutting	Ukusiskwa	Ukusiskwa	20.3%
Pins & Needles	Umsiko, ukugwaza, kuyahlaba	kuyahlaba	12.2%
Numb	Bekundikindiki, Indikindiki	Kundikindiki	11.4%
Stabbing	Ezihlabaya, ziyahlaba	Ukugwaza	5.7%
Itching	Iyaluma, Kuyaluma, Ziyaluma,	Kuyaluma	1.6%

Table 4.6: IsiZulu symptom spontaneous responses by nociceptive pain vs neuropathic pain patients

English Symptoms descriptor	IsiZulu symptom descriptors by participants spontaneously	Accepted single term. by professional translators	Percentage (Nociceptive pain) participant that used the term spontaneously	Percentage of participant (Neuropathic pain) that used the term spontaneously
Burning	Bekungathi Kuyashisa, Ayashisa, Kuyashisa	Kuyashisa	9.0%	29.0%
Sharp	Kuyasika. ,Engathi usikwe,	Kuyasika	31.0%	17.0%
Numb	Bekundikindiki, Indikindiki	Indikindiki	3.0.0%	%11.0
Pulling	Uyadonseka, Uyadonsa, Buyabudonsa,Ukudonsa Iyaidonsa, Engathi iyatsala, Uyaudonseka, Udonseka	Ukudonsa	41.0%	11%
Itching	Iyaluma, Kuyaluma, Ziyaluma,	Kuyaluma	2,0%	0.0%
Cramping	Ijaqaba, Namacramps, Amajaqamba , Amajaqaba	Amajaqamba	0.0%	25.0%

Pins & Needles	Umsiko, ukugwaza, kuyahlaba	kuyahlaba	1.0%	14.0%
Painful	Ibuhlungu, Ebuhlungu, Kubuhlungu, Ubuhlungu, Ubuhlungu, Kakhulu Kubuhlungu, Ekubuhlngu, Ibuhlungu ,Ubuhlungu,Ibuhlungu,Ubuhlung, Kubuhlungu,, Ubuhlungu, Izinhlungu, Ubuhlugu,Kubuhlungu ,Izinhlungu,Kubuhlungu	Kubuhlungu	100%	100.0%
Cutting	Ukusiskwa	Ukusiskwa	21.0%	4.0%
Stabbing	Ezihlabaya, Nziyahlaba	Ukugwaza	5.07%	2.0%

4.3.6 Percentage of descriptive symptoms in IsiZulu spontaneously

The percentage of the patients in figure 4.6 shows that 'pulling', sharp and cutting were frequent in spontaneous description by nociceptive patients. However, burning, cramping and sharp pain were frequent in neuropathic pain patients.

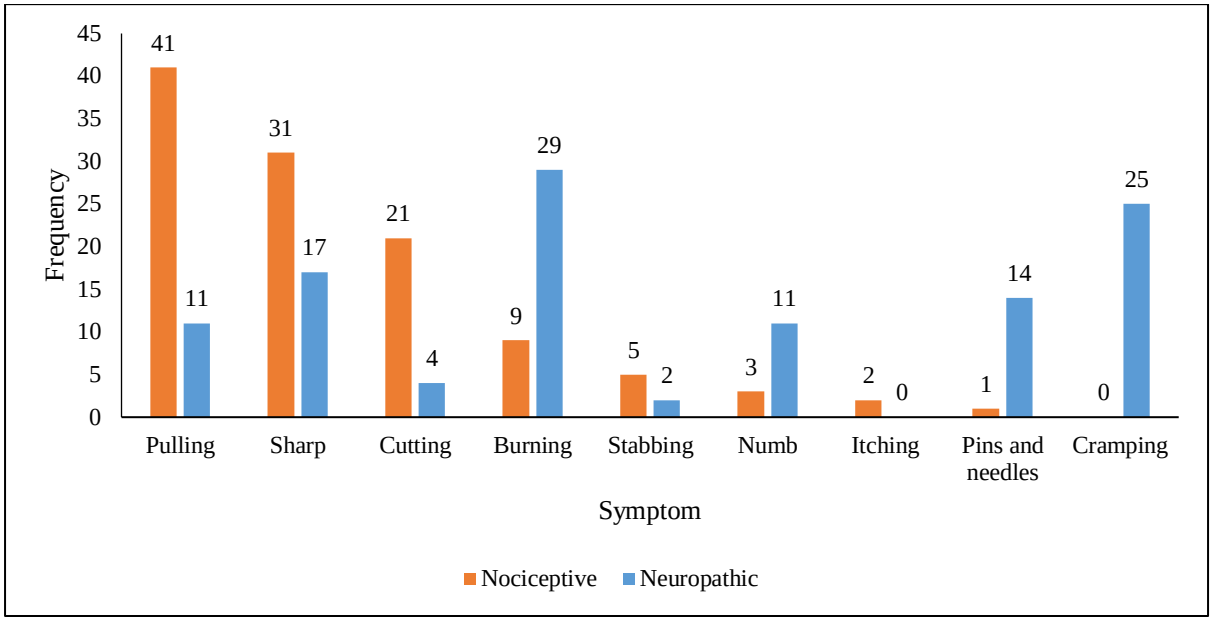

Figure 4.6: **Spontaneous description of isiZulu pain symptom**

4.3.7 English symptoms selected by the neuropathic pain and nociceptive pain participants from prompted isiZulu symptoms list.

Table 4.7 shows the percentages of participants (nociceptive and neuropathic pain patients) respectively, it indicates the symptoms listed on the published DN4 English version. 'Burning/hot' (98.36%)', 'painful cold' (81.99%) and 'pins and needles'; (75.41%) were frequently chosen by neuropathic pain patients. In addition, burning/ hot (75%), painful cold (62.30%) and pins and needles (60.60%) were frequently chosen by nociceptive pain patients. 'Tingling' (47.54%) and (30.0%) were less frequently chosen among neuropathic and nociceptive pain patients respectively.

Table 4.7: Percentages of participants (nociceptive pain participants and neuropathic pain patients) indicating the symptoms listed on the published DN4 English version prompt response.

	Neuropathic pain patients		**Nociceptive pain patients**	
Neuropathic pain Symptoms	Symptom present	Percentage of responses %	Symptom present	Percentage of responses %
Burning/Hot	No	1.64	No	25.00%
	Yes	98.36	Yes	75.0%
Numb	No	39.34	No	20.49
	Yes	60.64	Yes	29.50
Painful	No	4.92	No	11.48
	Yes	95.08	Yes	88.52
Itching	No	34	No	58.00
	Yes	60.66	Yes	41.00
Tinging	No	52.46	No	70.00
	Yes	47.54	Yes	30.00
Electric shock	No	26.23	No	65.57
	Yes	73.77	Yes	34.43
Painful cold	No	18.03	No	37.70
	Yes	81.99	Yes	62.30
Pins and Needles	No	24.59	No	39.54
	Yes	75.41	Yes	60.60

4.3.8 Determination of the symptom that best discriminate between nociceptive and neuropathic pain.

Classifications and regression tree analysis (CART) (figure 4.7) was used to determine the symptoms that provided the best discrimination between individuals with nociceptive and neuropathic pain. The most prominent symptoms for neuropathic pain from the CART analysis model were pulling (kuyadonsa), cramping and cutting. For all patients with ‘pulling ‘ symptoms without other symptoms were categorized as nociceptive pain patients. However, for patients that had pulling, cramping and cutting were classified as neuropathic pain by the model.

The data were divided into a training set and test set using a random 80:20 split of data. The training data (table 4.5) set was used to generate the model, while the test set was used to access the predictive value of the model. The training of the model used 8-folder cross validation, repeated 5 times, with area under the Receiver Operator Curve (ROC) used to select the optimum model. The reason why we divided the data into training and validation sets was to use the validation set to estimate how well is the model trained on the training data and how well it would perform on the unseen data. After testing the cross validation sets starting from K=2, a smaller K value (e.g K=2), didn’t allow enough trained models to evaluate. Furthermore, we used more partitions (larger size of e.g K=10), the outcome was better, however; more splits reduced the size of validation set. Therefore; there were insufficient samples in validation set to confidently evaluate the model. It was at K=8 folds that the model was fit for the sample size.The performance of the final model was assessed using the test data (table 4.6), using accuracy as the outcome measure.

4.4 CART model

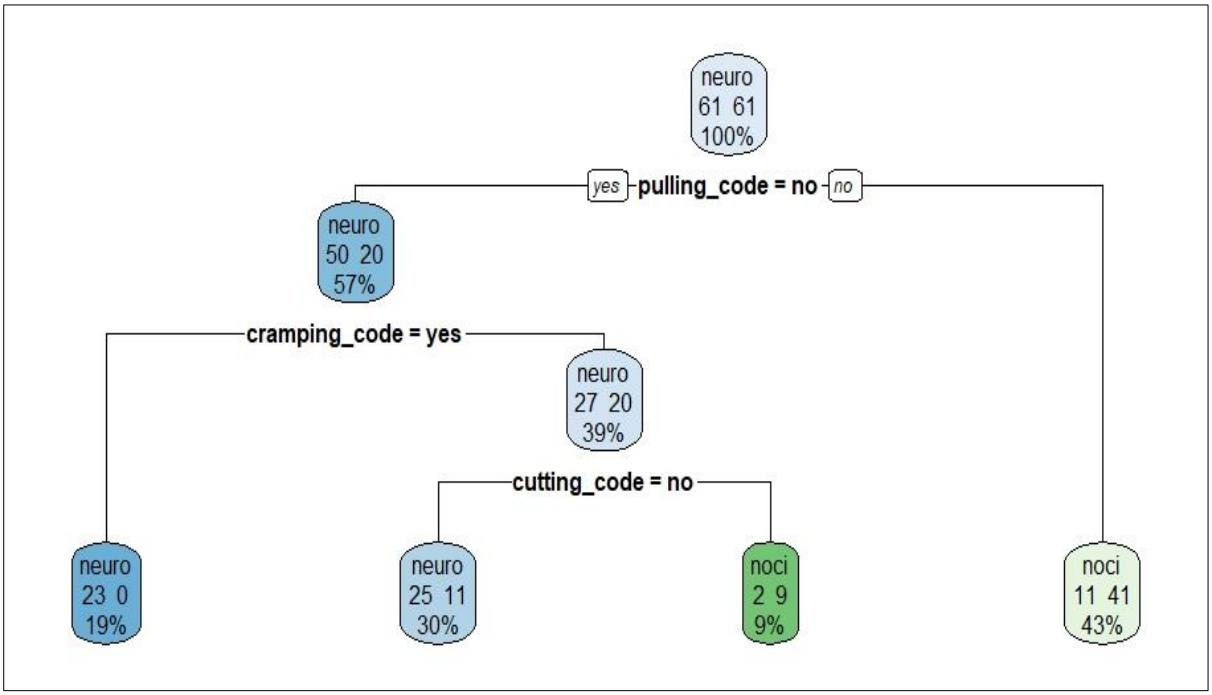

Figure 4.7: **CART analysis flow chart**

Table 4.8: In sample prediction (training data)

		Actual	
		Neuropathic	Nociceptive
Predicted	Neuropathic	32	8
	Nociceptive	13	36

Table 4.9: Out of sample prediction (test data)

		Actual	
		Neuropathic	Nociceptive
Predicted	Neuropathic	16	3
	Nociceptive	0	14

Table 4.10: Test of accuracy, sensitivity, and specificity of test data

Variables	Accuracy	Misclassification error	Sensitivity	Specificity
Out of sample (training data)	90.9%	9.1%	1.00	0.824
In sample	76.4%	23.6%	0.711	0.818

4.4.1 Model with all variables

A logistic regression analysis was performed to determine which of the symptoms had an impact on pain type (nociceptive and neuropathic) of patients. (table 4.11) To achieve this, all the variables identified were used in the logistic regression model. From these variables pulling was the significant symptom associated with both nociceptive and neuropathic pain (p=0.0447).

Table 4.11: Logistic regression analysis of symptoms

	Estimate	SE	Z stats	P value
Constant	-0.6132	0.5862	-1.046	0.2955
Burning(yes)	-1.2080	0.6680	-1.808	0.0706
Stabbing(yes)	1.2950	1.0845	1.194	0.2324
Sharp(yes)	1.0649	0.6776	1.572	0.1160
Numb(yes)	-0.3462	0.9785	-0.354	0.7235
Pulling(yes)	1.2234	0.6095	2.007	0.0447
Itching(yes)	18.8469	10754.0130	0.002	0.9986
Cramping(yes)	-17.6976	2156.7496	-0.008	0.9935
Cutting(yes)	1.4754	0.7911	1.865	0.0622
Pins_needles(yes)	-14.8721	2557.1659	-0.006	0.9954

Table 4.12: Model Summary

Likelihood ratio test	Cox and Snell R square	Nagelkerke R square	Mcfadden
51.381	0.439	0.584	0.416

The Cox and Snell's R-Square statistics indicated approximately 43.9% of the variation in the dependent variable is explained by the logistic model while the Nagelkerke R square value indicated that 58.4% of the variability in the data is explained by the model (table 4.12)

Table 4.13: Hosmer and Lemeshow test

Chi square	df	p- value
8.5136	8	0.385

Table 4.14: Confusion matrix

		Actual	
		Neuropathic	Nociceptive
Predicted	Neuropathic	34	5
	Nociceptive	11	39

Table 4.14 shows the confusion matrix. There were 34 and 39 neuropathic and nociceptive patients correctly classified respectively. However, 11 neuropathic patients were misclassified as nociceptive while 5 nociceptive patients were wrongly classified as neuropathic. The model as a whole is significant and correctly predicts neuropathic or nociceptive patients with an accuracy of 82.0% and shows non-significance on the Hosmer and Lemeshow goodness-of-fit test (0.385) at the 0.05 level, which is evidence of a well-fitting model.

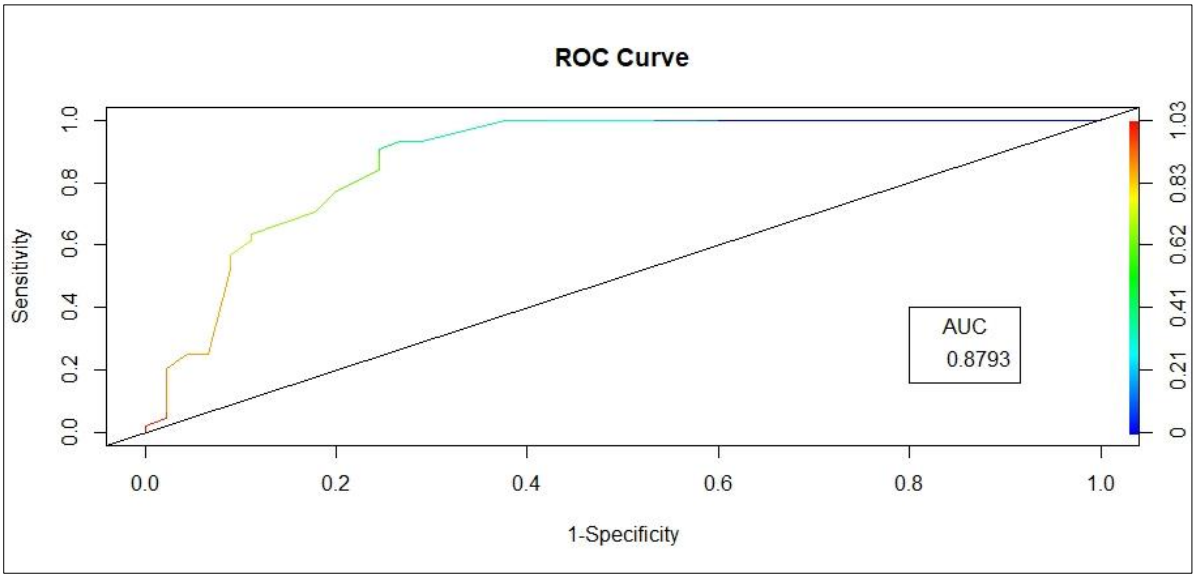

Figure 4.8: **ROC curve for specificity and sensitivity of the logistic regression model in prediction of neuropathic and nociceptive quality of pain**

To evaluate the performance of the model, Receiver operating characteristic (ROC) curve and confusion matrix with cut-off point 0.5 was plotted. Figure 4.8 shows the ROC curve and AUC for the model which used all variables. The AUC score is 0.8793.

Table 4.15: Out of sample prediction

		Actual	
		Neuropathic	Nociceptive
Predicted	Neuropathic	15	4
	Nociceptive	1	13

Table 4.15 shows the confusion matrix for the out of sample prediction. There were 15 neuro patients who were correctly classified, 13 nociceptive patients were correctly classified. However, 1 neuropathic patient was misclassified as nociceptive while 4 nociceptive patients were wrongly classified as neuropathic.

4.4.2 Model with variables selected through variable selection method (stepwise regression)

The variables used in the logistic regression model below were selected using a stepwise regression approach from the available predictors (table 4.16). The following variables were entered into a stepwise binary regression model to identify independent variables that predict whether the pain experienced by a patient is either neuropathic or nociceptive: burning, stabbing, numbness, pulling, itching, cramping, cutting and pins needles.

Table 4.16: Stepwise regression analysis

	Estimate	*SE*	*Z stats*	*P value*
Intercept	-0.4961	0.5176	-0.959	0.3378
Cramping(yes)	-18.5196	1398.9052	-0.013	0.9894
Cutting(yes)	1.6084	0.7473	2.152	0.0314
Sharp(yes)	1.0784	0.6051	1.782	0.0747
Pulling(yes)	1.0815	0.5814	1.860	0.0629
Burning (yes)	-1.1540	0.6321	-1.826	0.0679

Table 4.17: Model summary

Likelihood ratio test	**Cox and Snell R square**	**Nagelkerke R square**	**Mcfadden**
48.642	0.421	0.561	0.394

Table 4.17 shows the Cox and Snell R square and Nagelkerke R square that provides an indication of the amount of variability in the response variable (scaling operations or not). The Cox and Snell's R-Square statistics indicate approximately 42.1% of the variation in the dependent variable is explained by the logistic model while the Nagelkerke R square value indicates that 56.1% of the variability in the data is explained by the model.

Table 4.18: Hosmer and Lemeshow test

Chi square	df	p- value
3.4615	8	0.9022

In table 4.18, the Hosmer and Lemeshow test did not show statistical significance.

Table 4.19: In sample prediction

		Actual	
		Neuropathic	Nociceptive
Predicted	Neuropathic	34	6
	Nociceptive	11	38

Table 4.19 shows the in sample prediction. There were 34 neuro patients who were correctly classified, 38 nociceptive patients were correctly classified. However, 11 neuropathic patients were misclassified as nociceptive while 6 nociceptive patients were wrongly classified as neuropathic. The model is significant and correctly predicts neuropathic or nociceptive patients with an accuracy of 80.9% and shows non-significance on the Hosmer and Lemeshow goodness-of-fit test (0.902) at the 0.05 level, which is evidence of a well-fitting model.

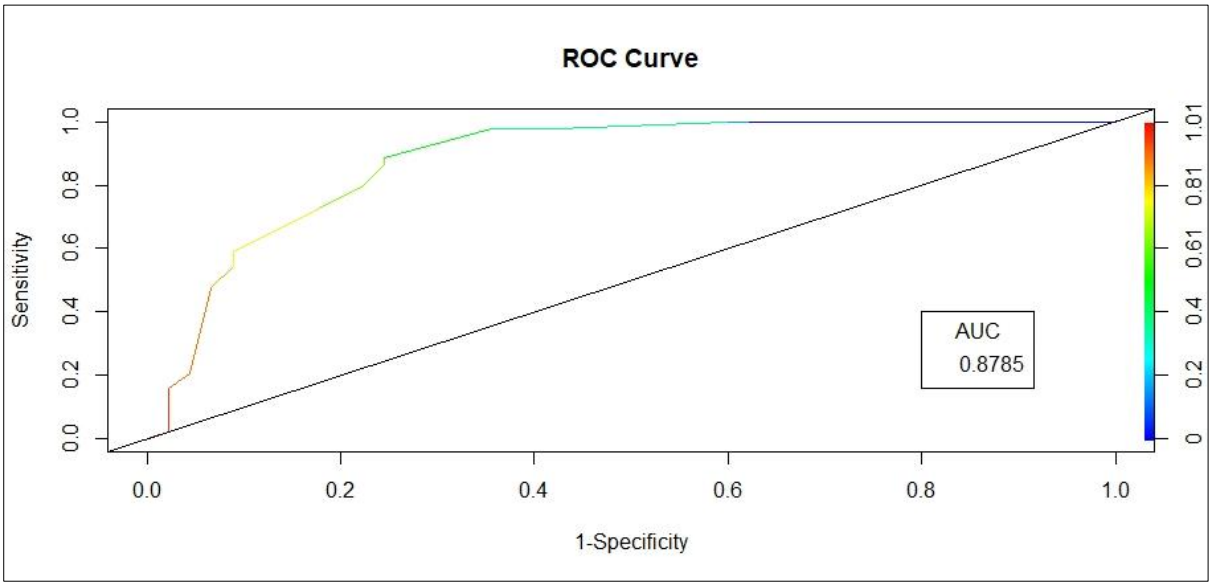

Figure 4.9: **ROC Curve for specificity and sensitivity of stepwise regression model in prediction of neuropathic and nociceptive quality of pain**

To evaluate the performance of the model, Receiver operating characteristic (ROC) curve and confusion matrix with cut-off point 0.5 was plotted. Figure 4.9 shows the ROC curve and AUC for the model which used stepwise regression to select variables. The AUC score is 0.8798.

Table 4.20: Out of sample prediction

		Actual	
		Neuro	Noci
Predicted	Neuro	15	4
	Noci	1	13

Table 4.20 shows the out of sample prediction. There were 15 neuro patients who were correctly classified, 13 nociceptive patients were correctly classified. However, 1 neuropathic patients were misclassified as nociceptive while 4 nociceptive patients were wrongly classified as neuropathic.

Table 4.21: Accuracy, sensitivity, and specificity rates for in sample prediction

Variables	Accuracy	Misclassification error	Sensitivity	Specificity	AUC
Model with all variables	82.0%	18%	0.76	0.89	0.879
Model with variable selection	80.9%	19.1%	0.76	0.86	0.879

Table 4.21 provided the accuracy, sensitivity, specificity and AUC derived from the logistic regression model. The reported sensitivity, accuracy, specificity and AUC are high. The overall accuracy for the model, which used stepwise regression, is 80.9%, sensitivity is 76.0% with specificity of 86.0%. For the model that used all variables, the sensitivity, accuracy and specificity rates derived by the logistic regression model are high yet lower than those derived from same algorithm from feature selection using stepwise regression. Logistic regression using all variables was able to produce classifiers with approximately 76.0% sensitivity, 80.9% accuracy and 87.9% AUC.

4.5 Discussion

The findings of the pain intensity rating showed that the participants had nociceptive and neuropathic pain conditions rated between moderate to severe before the interview (a week before). However, the pain rating only decreased slightly during the interview. This may be due to the effect of the pain medication as the participants reported that they take their pain medication in the morning.

The Wisconsin Brief Pain Questionnaire result outcome established that all our participants had pains at different locations, and the pains were rated between moderate and severe indicating the patients were in pain before and during the interview for them to be able to describe their pain symptoms adequately. In addition, neuropathic pain patients mostly reported their worse pain at the feet and leg and that they felt pain all the time while nociceptive pain patients reported that their pain were worse in the abdomen also all the time (this was because of the set of population of pain patients recruited) nociceptive pain can be at any part of the body insulted by noxious stimulus (Dubin and Patapoutian, 2010). This is consistent with Wadley *et al.*, (2011) that neuropathic pain patients reported pain originating from the legs and feet's region.

Content /conceptual analysis was used to extract the pains symptom by the patients spontaneously in correlation with their prompted symptom. Conceptual analysis was used to evaluate the occurrence of selected terms. Among the pain patients, the symptoms 'burning/hot' ('*kuyashisa*'),'sharp'('*kuyasik*a') and 'cramping' (*'jaqamba'*) symptoms appeared the most frequently used by the neuropathic pain patients followed by 'numb' ('b*ekundikindiki*') and 'pins & needles' ('kuyahlaba ') Spontaneous and prompt response showed 'burning' ,'numb' 'itching', 'pins and needles' and 'painful-cold' were most frequently recalled as how their pain was perceived. However, 'burning' and 'cramping'; were most frequent used by the participants to describe their neuropathic pain. Tingling was less frequently used in spontaneous description of their pain due to inadequate understanding of the term in English language. 'This is consistent with the findings used in developed, translated, and validated neuropathic pain screening tools in European populations and Asia population of DN4, LANSS., PDQ, NPS (LANSS (Bennett, 2001), Neuropathic Pain Questionnaire (Krause and

Backonja, 2003), Bouhassira *et al*., 2005), Portenoy and Committee, 2006) and Freynhagen *et al*., 2006). Nociceptive pain patients frequently used, pulling' ('*ukudonsa*') symptom and 'sharp', 'cutting' ('kuyasika') sensation, as their pain description. The symptom 'cramping' was not frequently found on recently developed neuropathic pain questionnaires (Galer and Jensen, 1997; Bennett, 2001; Krause and Backonja, 2003; Bouhassira *et al*., 2005; Portenoy, 2006). In contrary, the study of Asma *et al*., 2013, 'cramping' ('jaqamba') was used when participants spontaneously described their neuropathic pain symptoms. However, the conceptual analysis engaged in this study suggested that the common symptom between nociceptive pain patients was 'burnnig' 'kuyashisa'

The common and discriminatory symptomatology of nociceptive and neuropathic pain in African language was one of the objectives of this study conducted to extract the semantic symptoms that could differentiate these two types of pains. A content analysis extracted the symptom 'burning/hot' ('*Kuyashisa*') and 'cramping' (*'jaqamba'*) were most frequently used by the neuropathic pain patients followed by 'numb' (' b*ekundikindiki*') and 'pins & needles' ('kuyahlaba') selected from the spontaneous and prompt response. Tingling was less frequently used in spontaneous description of their pain due to less understanding of the term in English language from the prompted symptoms however the term was used only after it was translated to isiZulu prompted response. This is consistent with developed, translated, and validated neuropathic pain screening tools in European populations and Asia population of DN4, LANSS., PDQ, NPS.

These symptoms can also be shared by nociceptive pain patients, for instance nociceptive pain patients frequently use, 'pulling'('*ukudonsa*') symptom and 'sharp' ('*kuyasik* '), 'cutting'('ukusisewa') sensation most frequently.

The symptom 'cramping' was not frequently found on recently developed neuropathic pain questionnaires (Galer and Jensen, 1997; Bennett, 2001; Krause and Backonja, 2003; Bouhassira *et al*., 2005; Portenoy, 2006). However, the present study supported and the study of Asma *et al*., 2013, that reported cramping as one of the reported symptoms 'used when participants spontaneously described their neuropathic pain symptoms I isiZulu population

In this study, classification tree analysis was conducted to extract the symptoms that best described the neuropathic pain symptoms from nociceptive pain patients. The

outcome shows that patients that describe their pain as ‘pulling’ *(’ukudonsa’)* are classified as nociceptive pain patient. Patients whose symptoms was *‘pulling’ ’cramping’ and ‘cutting’* could be classified as neuropathic pain patients. Patients with ‘pulling’ symptom and ‘cramping’ ’symptom without; ‘cutting’ sensation were suggested to be neuropathic pain. The model also indicated that a single symptom could not be a differential diagnosis of neuropathic pain symptom. This outcome was put into testing with logistic regression analysis. A logistic regression analysis was performed to determine which of the symptoms had an impact on pain type (nociceptive and neuropathic) of patients. To achieve this, all the variables (symptoms) identified were used in the logistic regression model. These variables (symptoms) included ‘burning’, ‘stabbing’, ‘numb’, ‘pulling’, ‘itching’, ‘cramping’, ‘cutting’ and ‘pins & needles’. The outcome showed that ‘pulling’, ‘cramping’, and ‘cutting’ were good in determination of neuropathic pain of patients with high sensitivity and specificity. Therefore the newly developed tool (chapter 5) was based on the outcome of this analysis, with these three symptoms and signs of non-neuropathic pain i.e hypoesthesia to touch and hypoesthesia to brushing.

4.6 Conclusion

Several translated neuropathic pain screening tools had been developed and validated in different languages’ the systematic review reported (Chapter 3) showed a high sensitivity and high specificity of these tools. Content analysis has been able to extract the common symptom used by the nociceptive pain patients (‘pulling, sharp and cutting’) and neuropathic pain patients (‘burning, ‘painful-cold’) in isiZulu. Symptom description spontaneously and prompted responses in nociceptive and neuropathic pain patients showed that ‘burning’ and ‘cramping ’ symptom appeared to be the symptoms most frequently described in nociceptive pain patients. Furthermore, nociceptive pain patients most frequently used symptoms ‘pulling’, ‘sharp’ cutting’ to describe their pain. ‘Burning’ symptom was common to the neuropathic pain patient and nociceptive pain patients’ other symptoms like painful-cold, cramping terms were only used during the prompt assessment by both nociceptive pain and neuropathic pain patients

In conclusion, there is a need for improved epidemiology data and development of an effective diagnose tool for neuropathic pain screening tools in South Africa. The growing need of this nature is due to increase in the population of patients with neuropathic pain as mentioned in chapter one of this thesis. This prevalence might

continue to increase as there is increase in population of patients with HIV infection and diabetes. Due to this fact, it is important to develop a screening tool for its immediate and effective diagnosis.

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CHAPTER 5 -ASSESSMENT OF A NEW ISIZULU NEUROPATHIC PAIN SCREENING TOOL COMPARED TO ISIZULU VERSION OF DN4

5.1 Introduction

Despite advances in the treatment of pain, its diagnosis and effective management still poses a challenge. The assessment of pain requires thorough scrutiny on the symptoms based on the way they are perceived by the patient. Due to the subjective experience of pain and the differences in culture, language, ethnic and interpersonal factors among different individuals, the adaptability of these assessments may be compounded by these factors. Consequently, this poses a challenge in effectively managing pain in the clinical setting.

Importantly, language and culture are among the pivotal factors necessary for the effective assessment of pain. This has been validated by Dubuisson and Melzack, 1976. They reported that pain can be assessed by verbal description using different words and phrases based on the pain intensity. Accordingly, culture forms the basis that which directs human behaviour in any given situation. Therefore, in the context of expressing pain, its influence on the communication of pain is of great importance. In addition, pain may erroneously be anticipated, resulting in misconception in characteriterising it by clinicians. This is evident in that the inability to understand the cultural meaning of pain, the non-verbal and verbal language of pain, and the patient's ability to cope with pain may not be well understood by the health care practitioners.

South Africa is rich in cultural diversity, possessing high language diversity. It has 11 officially spoken languages. These languages include isiZulu, isiXhosa, Afrikaans, Sesotho sa Leboa, English, Setswana, Sesotho, Xitsonga, SiSwati, Tshivenda and isiNdebele. Accordingly, IsiZulu is the most spoken local language followed by isiXhosa. Although isiZulu is mostly spoken in KwaZulu-Natal province, due to migration of the Zulu nation to other provinces such as Gauteng (Egoli the city of Gold), this language has become the most adaptable language in communities, including taxi rank, malls and hospitals.

A feasibility study was conducted to assess the functionality of the outcome of this newly developed neuropathic pain screening tool in isiZulu. This is a very important step in translation research to test the strength of the tool in the population that was designed for (Chronic pain patients). This instrument is expected to have a good specificity, sensitivity, positive predictive value and accuracy above 60% before it is

ranked suitable for the test larger population with chronic pain (nociceptive and neuropathic pain test population).

5.2 Methodology

Participants: forty-three (n = 43) participants (male and females) with chronic condition (nociceptive or neuropathic pain). Neuropathic (n = 20) and Nociceptive pain (n = 23) origin were recruited from the Chronic Pain Clinic at Helen Joseph Hospital and Orthopedic and Arthritics clinic of Charlote Maxake Academic hospital, Johannesburg.

5.2.1 Inclusion criteria

Participants must be 18 years or older, they were diagnosed by a physician at the respective pain clinic as having chronic pain (pain duration > three months) of at least moderate intensity (score > 4 on an 11-point numerical pain rating scale), and isiZulu was the primary language of communication. Participants with pain of unknown origin, mixed pain (neuropathic and non-neuropathic) and widespread pain were excluded. Participants gave consent for participation of the study.

5.2.2 Protocol

1. **Clinical diagnosis:** Two pain specialists at the each clinic independently gave the clinical diagnosis based on their clinical examinations, medical history of the participants and their experience.
2. **Interview**: The investigator, who was unaware of the clinical diagnosis of the participant, administered i) a direct translation from English DN4 to isiZulu of the DN4 questionnaire, ii) the English version of the DN4 questionnaire, and iii) the newly developed tool (figure 5.2). The semantic component of the new tool was derived from the development phase of the project, while the assessment of clinical signs were used as the same tests (hypoesthesia to brush and pin-prick sensitivity) (Lees and Hurwitz., 2019), used in the DN4. A second investigator administered the same set of questionnaires to the participants within 30 minutes of the first interview. The order in which each interviewer administered the three questionnaires and the order in which the participants were seen by the two interviewers was randomized according to a pre-determined randomization schedule.

   The last set of data was collected telephonically, due to Covid-19 restrictions at the hospitals. This process was repeated telephonically with the same patients.

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5.2.3 Statistical analysis

Receiver Operating Characteristic curve (ROC analysis) was performed to assess the sensitivity and specificity of the three questionnaires (English DN4, isiZulu DN4, and the new tool), and to determine scoring cut-off scores for the diagnosis of neuropathic or non-neuropathic pain using the full tool (semantic and physical assessments, semantic components only, physical assessment only). Cohen's kappa was used to assess inter-rater agreement between the two interviewers for the overall classification (neuropathic vs non-neuropathic) and individual scale items of the translated DN4 and the new tool. Wilcoxon signed ranked test was used to assess differences in magnitudes between scale scores.

5.3 Results

A total of (n = 43) participants were recruited for this study, nociceptive pain patients (n =20) 58.2%, neuropathic pain Np patients (n = 23) 41.8%. The mean age of all the participants included was 33.4±12.1 years SD). Among females (83.6%) and males: (16.4%) all the participants spoke isiZulu-language as home language. Participants with mix pain were excluded participants whose home language were not isiZulu and were below 18 years.

In addition, table 5.1 shows that 78.3% of neuropathic participants were females with 21.7% and males. Moreover, 87.5% of the nociceptive participants were females and 12.5% were males. A Fisher's exact test odd association indicated that there was no association between gender and pain type (p= 0.4672).

Table 5.1 Demographic and clinical characteristics according to pain type.

	Nociceptive	Neuropathic
Number	20	23
Age (years) SD	51.2±13.6	56.6±9.11
Females (%)	87.5	78.3

Males (%)	12.5	21.7

Figure 5.1 shows the original DN4 questionnaire in English to assess the neuropathic pain characteristic of a patient. In addition, figure 5.2 shows the translated isiZulu DN4 questionnaire.

DN4 – QUESTIONNAIRE

To estimate the probability of neuropathic pain, please answer yes or no for each item of the following four questions.

INTERVIEW OF THE PATIENT

QUESTION 1:

Does the pain have one or more of the following characteristics?

	YES	NO
Burning	❑	❑
Painful cold	❑	❑
Electric shocks	❑	❑

QUESTION 2:

Is the pain associated with one or more of the following symptoms in the same area?

	YES	NO
Tingling	❑	❑
Pins and needles	❑	❑
Numbness	❑	❑
Itching	❑	❑

EXAMINATION OF THE PATIENT

EXAMINATION OF THE PATIENT

QUESTION 4:

Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

	YES	NO
Hypoesthesia to touch	❑	❑
Hypoesthesia to pinprick	❑	❑

QUESTION 5:

In the painful area, can the pain be caused or increased by:

Brushing? .....

YES = 1 point **NO = 0 point**

Patient's score: /0

Figure 5.1:**DN4 -English version screening tool**

DN4 – QUESTIONNAIRE

Ukulinganisela ubungako obungaba khona bobuhlungu bemizwa, uyacelwa ukuba uphendule ngo-yebo noma cha kuleyo naleyo nto ebalulwe emibuzweni emine elandelayo.

INGXOXOMBUZO YESIGULI

UMBUZO 1:

Kungabe ubuhlungu bunesisodwa noma ngaphezulu lwezimpawu (characteristics) ezilandelayo?

	YEBO	CHA
Ukushisa	❑	❑
Umkhuhlane obuhlungu	❑	❑
Ukushokheka	❑	❑

UMBUZO 2:

Kungabe ubuhlungu buhlobene nolulodwa noma ngaphezulu kulezi zimpawu ezilandelayo endaweni eyodwa?

	YEBO	CHA
Ukunsonsotha	❑	❑
Inkwantshu	❑	❑
Ubundikindiki	❑	❑
Ukuluma	❑	❑

UKUHLOLWA KWESIGULI

UKUHLOLWA KWESIGULI

UMBUZO 3:

Kungabe ubuhlungu busendaweni lapho ukuhlolwa emzimbeni kungaveza uphawu olulodwa noma ngaphezulu kwezilandelayo?

	YEBO	CHA
Ukuba ndikindiki uma uthintwa	❑	❑
Ukuba ndikindiki uma uncinzwa ngophini	❑	❑

UMBUZO 4:

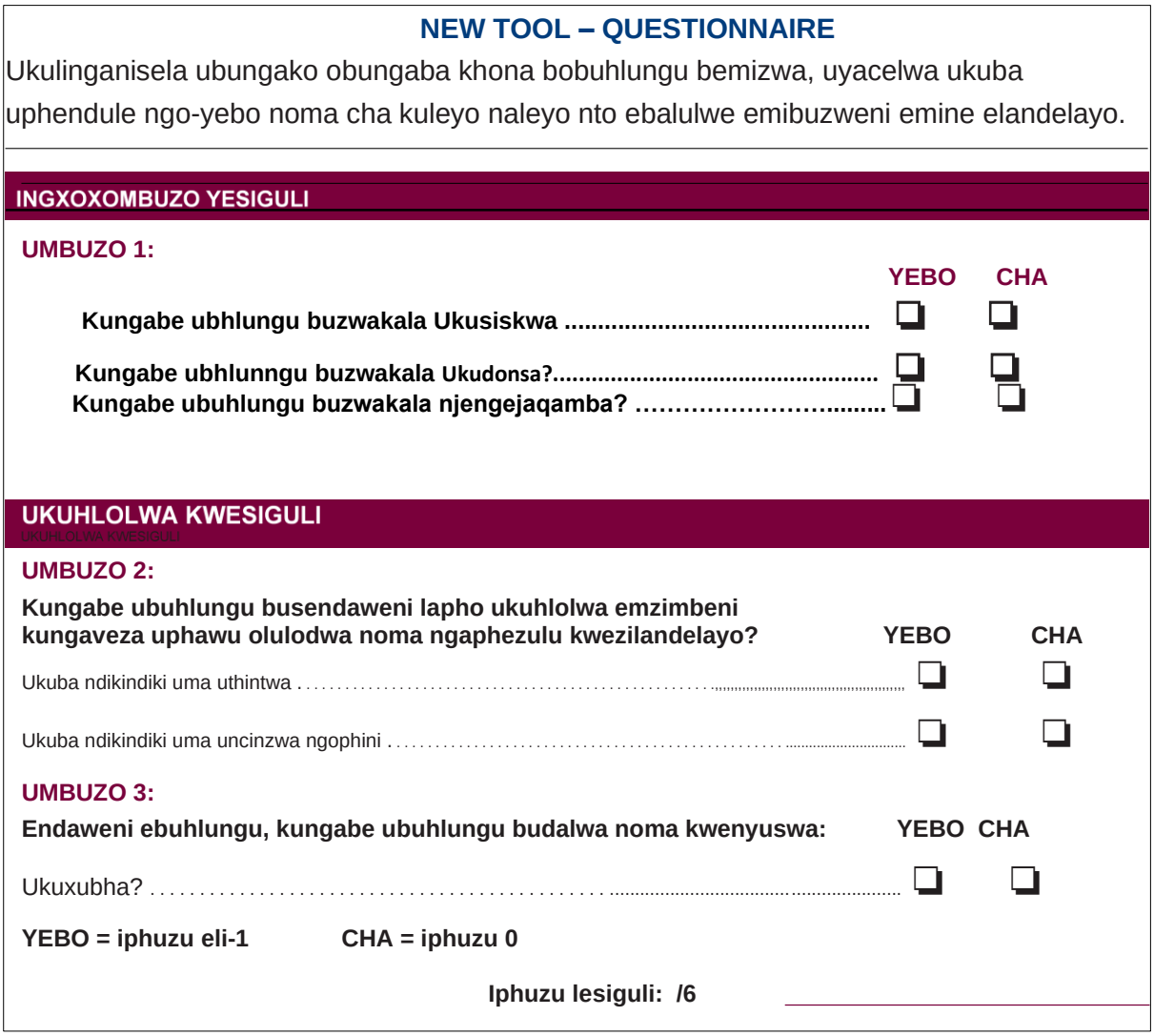
Endaweni ebuhlungu, kungabe ubuhlungu budalwa noma kwenyuswa:	YEBO	CHA
Ukuxubha?	❑	❑

YEBO = iphuzu eli-1 **CHA = iphuzu 0**

Iphuzu lesiguli: /10 _____

Figure 5.2: **Translated DN4 in isiZulu**

Figure 5.3 shows the newly developed neuropathic pain screening tool in isiZulu. Patients that scored 5 and above on a scale of 6 questions were classified neuropathic pain patients using this tool. However, patients that scored less than 5 were classified as nociceptive pain patients.



NEW TOOL – QUESTIONNAIRE

Ukulinganisela ubungako obungaba khona bobuhlungu bemizwa, uyacelwa ukuba uphendule ngo-yebo noma cha kuleyo naleyo nto ebalulwe emibuzweni emine elandelayo.

INGXOXOMBUZO YESIGULI

UMBUZO 1:

	YEBO	CHA
Kungabe ubhlungu buzwakala Ukusiskwa	❑	❑
Kungabe ubhlunngu buzwakala Ukudonsa?.....	❑	❑
Kungabe ubuhlungu buzwakala njengejaqamba? ……..	❑	❑

UKUHLOLWA KWESIGULI

UKUHLOLWA KWESIGULI

UMBUZO 2:

Kungabe ubuhlungu busendaweni lapho ukuhlolwa emzimbeni kungaveza uphawu olulodwa noma ngaphezulu kwezilandelayo?	YEBO	CHA
Ukuba ndikindiki uma uthintwa	❑	❑
Ukuba ndikindiki uma uncinzwa ngophini	❑	❑

UMBUZO 3:

Endaweni ebuhlungu, kungabe ubuhlungu budalwa noma kwenyuswa:	YEBO	CHA
Ukuxubha?	❑	❑

YEBO = iphuzu eli-1 **CHA = iphuzu 0**

Iphuzu lesiguli: /6

Figure 5.3: **New Neuropathic pain screening tool**

5.3.1 Assessment of reliability and validity of isiZulu-DN4:

Confusion matrix was used to analyze the strength of different thresholds in determination of sensitivity. specificity, positive predictive value, and negative predictive value. At cut off 8, the specificity was 0.81, sensitivity was 0.70, PPV 0.73 ad the PV was 0.79 which is the optimum cut off for the use of the isiZulu translated version of DN4.

Table 5.2: Test of validly of isiZulu direct translation of DN4

Cut-off	Prediction	Reference/Actual Neuro***	Noci****	Accuracy	Sensitivity	Specificity	PPV*	NPV**
4	**Neuro*** **	23	31	o.44	1.0	0.03	0.43	1.00
	Noci** **	0	1					
5	**Neuro*** **	21	31	0.40	0.91	0.03	0.40	0.33
	Noci** **	2	1					
6	**Neuro*** **	21	21	0.58	0.91	0.34	0.50	0.35
	Noci** **	2	11					
7	**Neuro*** **	20	14	0.69	0.87	0.56	0.59	0.86
	Noci** **	3	18					
8	**Neuro*** **	16	6	0.76	0.70	0.81	0.73	0.79
	Noci** **	7	26					
9	**Neuro*** **	12	2	0.76	0.52	0.94	0.86	0.73

PPV* Positive predictive value, NPV** Negative Predictive Value Neuro Neuropathic pain patient,***

Noci* Nociceptive pain patient***

Table 5.3: Test of validity of neuropathic pain in isiZulu developed screening tool

		Reference/Actual						
Cut-off	**Prediction**	**Neuro**	**Noci**	**Accuracy**	**Sensitivity**	**Specificity**	**PPV***	**NPV****
2	Neuro***	20	31	0.44	1.00	0.03	0.43	1.00
	Noci****	0	1					
3	Neuro***	23	32	0.45	1.00	0.06	0.43	1.00
	Noci	0	2					
4	Neuro***	22	25	0.53	0.96	0.22	0.47	0.88
	Noci	1	7					
5	Neuro***	19	2	0.89	0.83	0.94	0.90	0.88
	Noci	4	30					

PPV Positive predictive value,NPV** Negative Predictive Value, Neuro*** Neuropathic pain patient,*

*Noci**** Nociceptive pain patient*

On the newly developed tool, (Table 5.3) At cut off 5, the specificity was 0.83, sensitivity was 0.94, PPV 0.90 and the PV was 0.88 which is the optimum cut off for the use of the newly developed isiZulu screening tool.

5.4 Discussion

Forward and backward translation of the neuropathic pain symptoms was carried out twice between the spontaneous and prompt response by our participants. This is very important in translation research for adequate understanding of the symptoms. For example, ‘ burning /hot’ was frequently used, in both nociceptive and neuropathic pain patients and therefore; translated by professional isiZulu translator as ’Kuyashisa ‘.

The symptoms that were predicted as a determinant of neuropathic pain were assessed in chronic neuropathic and nociceptive pain patients. The three tools were administered by two investigators independently. (isiZulu translated DN4, The English version of DN4 and the New tool of DN4.). The reliability and validity of these instruments were measured by evaluating the accuracy of the instrument by determining the sensitivity, specificity, positive predictive value and Negative Predictive value. At threshold 5, the new tool performance was higher than other tools (isiZulu- DN4 and English-DN4). Accuracy to determine the neuropathic pain quality was 89%, sensitivity 83%, specificity 94%. This agreed with the translated DN4 of the Arabic DN4 (Chartila *et al*,2017) and the Brazilian-Portuguese version of DN4 (Santos *et al*.,2010). Cohens Kappa value was 0.849, indicating an almost perfect agreement between the two specialists that rated the participants independently. The Cohens kappa value was statistically significant (p-value<0.001).

5.5 Conclusion

The findings of this study indicate that this tool is reliable in differentiating patients with neuropathic quality from non-neuropathic pain patient in a population that speak isiZulu. In addition, these findings suggest that the newly developed tool may be useful in epidemiological data of neuropathic pain patients who understand and speak isiZulu.

CHAPTER 6 -GENERAL DISCUSSION AND CONCLUTION

6.1 Introduction

In the chapters 3 to 5 of the present thesis, I provide comprehensive discussion of the findings of my research. In this chapter, I will however give a contextual narrative for the earlier chapters 3 to 5 and then discuss the possible clinical significance of my research as well as its limitations.

6.2 Systematic review on the psychometric, reliability and validity of neuropathic pain screening tools (DN4, LANSS and PDQ) between 01 January 2001 and 19th July 2019.

A systematic review was conducted on the reliability and validly of translated version of DN4, LASS as PD-Q between 2001 and 2019. The result showed that sensitivity and specificity of the DN4 studies ranged from 75% to 100% and 37.3% to 99% respectively. The internal reliability (Cronbach α) of the translated version of the DN4 ranged from 0.55-0.862. This indicate that this instrument is a reliable in measuring the neuropathic quality of a pain patient across the regional, ethnicity and cultural population, DN4-iterview also showed a good sensitivity range (84%-99%), specificity (58.3%-90%), Positive predictive value (71%-89,2%) and negative predictive value (69.4%-91.4%).

The sensitivity and specificity of the LANSS studies ranged from 72.6% to 100% and 58.3% to 90% respectively. The internal reliability (α) of the translated version of the LANSS ranged from 0.67-0.96. Positive Predictive Value was between 85%-99% and the negative predictive value was 84.3%-98.2%. S- LASS also perform well with sensitivity 84%-99% to 84.3-98.2%, Positive predictive Value was between 67.4%-96.2%, Negative predictive Value (69.4%-91.4%).

The sensitivity and specificity of the PDQ studies ranged from 71% to 98% and 66% to 93% respectively. The internal reliability (α) of the translated version of the PDQ ranged from 0.81-0. 86. All these instruments from the translated version from showed that they are reliable I their languages and valid to diagnose patients with neuropathic quality from none-neuropathy pain

6.3 Development of neuropathic pain screening tools in isizulu

The second study focused on development of neuropathic pain screening tool in isiZulu. We explored the characterization of neuropathic and nociceptive pain from recruited pain patients in isiZulu language from different hospital associated with University of Witwatersrand, Johannesburg.

Neuropathic and nociceptive pain often share some characteristic but are different from each other both in etiology and clinical manifestations. Neuropathic pain is a type of disease with different clinical manifestation at different stages of its progression. However, the management can be challenging but the earlier detection using the current clinical examination (Nerve's conduction velocity and somatosensory evoked potential) which do not give a specific diagnosis could still be of help. Unfortunately, a more specific clinical diagnosis procedure is required but is expensive as mentioned in chapter 1 of this thesis.

Pain expert/ and clinicians require an easy-to-use procedure fast and less expensive qualitative testing tool with high sensitivity and high specificity to diagnosis patient with neuropathic pain in their clinical set up. The development several neuropathic pain diagnostic screen tool has been of huge help. These are tool developed and validated (LANSS, NPQ, ID pain, DN4) in different languages, with high specificity, high sensitivity, and High positive predictive value) as mentioned as mentioned in the earlier chapter.

None of this instrument has been developed and tested in Africa Language for Africa population suffering for neuropathic pain condition as mentioned in chapter one. The study of Dubuisson and Melzacz, 1976 showed that some terms or phrase adequately identify neuropathic pain like burning, numbness, itching, electric shock symptom. This provided the background for the development of neuropathic pain screening tool in the local languages *descriptor). Some were developed with only descriptive symptoms while some were developed with both symptoms and signs (clinical examination. like hypoesthesia or both pin-prick and touch).

The outcome of our study showed that symptoms ' burning/hot ' and 'cramping ' emerged as the most frequently used by neuropathic pain patients to describe their

pain. While pulling and sharp description were used more frequently by the nociceptive pain patients to describe their pain symptoms. Most common symptoms frequently used by nociceptive and neuropathic pain description are pulling, sharp, burning, camping, and cutting. However, the result of the classification ad regression tree analysis showed that pulling, cramping and cuttings are common symptoms described both patient (nociceptive pain and neuropathic pain patient. Burning symptom is often used in most of the developed neuropathic pain questionnaire as a single term common to spontaneous and prompt symptom description of neuropathic pain. This is also consistent with translated version of the developed questionnaire in European, American,Arabic and Asia countries.

Our results showed that tingling was least frequently used symptoms spontaneously. The percentage of participants responding to 'tingling' in prompt responds was higher than spontaneous that is, participants understood the term in isiZulu better than the English Our participant level of education might be responsible for the low understanding of the English word 'tingling '. A model was developed on the outcome of the neuropathic and nociceptive pain to find out the discriminating term between neuropathic and nociceptive pain.

The outcome 'Pulling' alone indicates nociceptive, pulling with crampingand cutting implies neuropathic symptoms.'Pulling' with 'Cramping' without cutting implies nociceptive pain. These symptoms were used in conjunction with neuropathic signs (Hypoesthesia to brush and touch) to construct a new neuropathic pain screening tools and tested in a population of patients with either neuropathic pain or nociceptive pain. A confusion matrix was used to evaluate the performance of the tool.

6.4 Pilot study of the screening tool

The result showed that at threshold 5, the specificity of the instrument had an accuracy of 80% sensitivity 83%, specificity 94%, positive predictive value 90%, negative predictive value 88% and the Cohen Kappa value of 0.849 indicating that the interrater assessment by the two raters is almost perfect.

6.5 Limitations

The study highlights a few limitations. Firstly, the sample size is small in epidemiological terms although it is the largest population size for this type of study in

the target population. The study is cross-sectional and it precludes conclusions about causal relationships. The higher percentage of the participants were female compared to male population. This is expected due to cultural believe in isiZulu speaking community, women are more open to disclose their medical condition while men are very strict in expressing their personal issues. (Cohen, 2019). In addition, pparticipants could have felt intimidated when the terms that were read to them were not fully understood and instead of responding with “I do not understand the term,” participants responded with “no,” despite being told that it was acceptable if they did not understand the term. It was difficult to judge if participants truly understood the term or not, and we based the results on the manner in which participants responded, for example, how hesitant or puzzled a participant was when responding to the question. The environment in which the interview was carried out and recorded was not the most suitable as it was prone to noise and there may have been interruptions when individuals, not part of the study design, would occasionally walk into the room where the interview was taking place. The above may have distracted participants and the recordings were occasionally unclear to the transcribing and translating company due to the noise. We suggest conducting interview research in rooms that are completely silent and prone to as little disturbance as possible. Furthermore, due to the COVID-19 pandemic, most of the hospitals were not accessible for research purposes. Therefore, follow-up was done telephonically with patients and posed a challenge because the interviewer and translator spoke to the patients independently. These limitations should be considered for future language studies based on interview nature, as improving the overall study design will result in improved and more accurate data for qualitative research. Finally, development of the new tool in the present thesis was tested only in isiZulu speaking patients, hence, generalization and applicability of our findings to other populations of the Nguni tribe (isiXhosa and isiNdebele) might be limited. Therefore, future studies on translating screening tools to other local languages should be conducted and validated in the specific populations.

6.6 Conclusion

In conclusion the development and validation of neuropathic pain screening tool in isiZulu showed that it is an effective diagnostic tool, simple to understand and less time consuming. Furthermore, the mere forward and backward-translation of existing questionnaires were not applicable in isiZulu language as they could not reach

semantic, conceptual, experiential and idiomatic equivalence to guarantee that they are culturally acceptable for South African isiZulu pain patients. However, adopting this questionnaire in clinical settings should be in conjunction with clinical examination. Moreover, to our knowledge there has not been a study that developed a neurophathic pain screening tool in any of the South African local languages. This is a novel study that highlighted the necessity of translating screening tools in to the local language for the effective diagnosis and management of neuropathic pain. South Africa has 11 official languages, future studies should be directed towards development of neuropathic pain screening tools in other remaining languages.

6.7 Implications of the study

Several neuropathic pain screening tools have been developed to assist in making the diagnosis of neuropathic pain explicit; however, they all were developed in European, Arabic and Asian languages, and we have found that the familiarity of isiZulu speakers with the terminology used in these screening tools to describe pain symptoms, even if translated, is poor. This poor understanding means that the sensitivity and specificity of these screening tools would be compromised, which has implications for the effective management of a patient's pain. The development of this isiZulu screen tool will assist the clinician in proper diagnosis of this type of pain compared with nociceptive pain diagnosis.

6.8 Scientific contribution of the study

Chapter 3 of this study was on systematic review on psychometrics, reliability and validity properties of commonly used neuropathic pain screening tools (DN4, LANSS and PDQ) aimed to identify, evaluate, and summarize the findings of all relevant individual studies over fourteen years, thereby making the available evidence more accessible to decision makers. Our outcome indicted that all screening tools were reliable and valid to distinguish neuropathic pain from non-neuropathic pain in their test population but none can be used alone without clinical testing procedures. This study was accepted for publication in International journal of Medicine and medical research.

Chapter 4 part of the study was on development of neuropathic pain screening tools in isiZulu: Neuropathic pain affects 6-8% of the general adult population. It is reported by 27% of chronic pain patients and 40% of cancer patients, yet no standardized diagnostic test for neuropathic pain have been developed. A number of screening tools

have been developed based on verbal pain descriptors, with or without limited clinical examination, to identify individuals with neuropathic pain. Over the past decade these neuropathic pain screening tools have been validated in a wide range of pain populations, as well as translated into many languages, to discriminate between neuropathic and non-neuropathic pain none of these have been developed in African languages. This study developed a new neuropathic pain screening tool in isiZulu language, an African language for clinical diagnosis of neuropathic pain patient in isiZulu speaking community of South Africans. To our Knowledge, this is the first study to develop a neuropathic pain screening tool in a South African language. This will enhance epidemiological data available for future scientific research in pain.

6.9 Publications

- The systematic review section of this study has been accepted for publication and it will be published in the next issue of international journal of Medical sciences and clinical research.
- The second manuscript is ready for review titled: Development of neuropathic pain screening tool in isiZulu. It will be submitted to the international journal of pain and pain management.
- The third manuscriptis titled: Pilot study on the validation of neuropathic pain screening tool in isiZulu.

6.10 My role in this research

This was a collaboratve effort, due to the nature of the study. It involved clinicians, translators and interpreters. None the less, my role in the study was to critically execute the study protocol and ethics application; familiarise and execute as described in chapter 2 (methods) the design and planning of the study including collecting data ; to analyse and interpret the data and finally to write the thesis.

APPENDIX 1

ETHICAL CLEARANCE

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10004, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: Phillip Tobias Building, 2nd Floor Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za. Fax +27 (0)11-717-1265

19 March 2015

To Whom It May Concern

SUBJECT: CONFIRMATION OF STUDY APPROVAL

Protocol Ref No: M150245

Protocol Title: Characterisation of the Quality of Nociceptive and Neuropathic Pain Conditions in Isizulu

Principal Investigator: Prof P Kamerman

Department: Physiology

This letter serves to confirm that the Human Research Ethics Committee (Medical) has approved the above mentioned study. In order for a clearance certificate to be issued, the researcher is required to submit written approval to conduct the study in your district/institution.

Should you have any queries, you may contact me at tel 011 717 1252/1234/2700 or by email Zanele.ndlovu@wits.ac.za.

Yours Faithfully,

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
19 MAR 2015
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

Ms Zanele Ndlovu
Administrative Officer
Human Research Ethics Committee (Medical)

APPENDIX 2

Participant Questionnaire

MEDICAL INFORMATION

1. Mass (kg): _____ 4. Date of Birth _____
2. Height (m): _____ 5 Home language _____
3. Do you have a history of: ___ 6.Highest level of schooling _____

		Comments/additional information
Diabetes mellitus	☐ Yes ☐ No ☐ Unknown	If yes, How long have you been diabetic: ☐ weeks ☐ Months ☐ Years Type of Diabetes: ☐ Type 1 ☐ Type 2 **Latest HBA1c (if available):**
HIV	☐ Yes ☐ No ☐ Unknown	If yes, On ART: ☐ Yes ☐ No **If yes,** Current regimen: Any previous exposure to d4T or ddI: ☐ Yes (which:) ☐ No Latest CD4 T-cell count (if available):

Herpes Zoster	☐ Yes ☐ No ☐ Unknown	If yes, Anatomical region: Date: Do you still have pain?:
Surgery	☐ Yes ☐ No	If yes, Reason: Anatomical region: Date:
Arthrides	☐ Yes ☐ No ☐ Unknown	If yes, Type (if known):
Multiple sclerosis	☐ Yes ☐ No ☐ Unknown	
Stroke	☐ Yes ☐ No ☐ Unknown	If yes, Time since stroke:

Spinal cord injury	☐ Yes ☐ No ☐ Unknown	If yes, Time since injury: Level of injury: Anatomical regions affected:
Alcohol consumption	☐ Yes ☐ No ☐ Unknown	If yes, How often is alcohol consumed: ☐ Daily ☐ Weekly ☐ Monthly Type of alcohol consumed: ☐ Beer ☐ Wine ☐ Spirits Quantity of alcohol consumed per day/week/month: ☐ One can/glass ☐ two-three cans/glasses ☐ More than three cans/glasses

Cause:

5. Current analgesic/anti-inflammatory medications

Drug name	**Reason for treatment**

WISCONSIN BRIEF PAIN QUESTIONNAIRE (WBPQ) (adapted)
We would like you to tell us about any pain you might be experiencing and also indicate where you are experiencing this pain.

a. Do you currently have any pain?

☐ No ☐ Yes

b. Have you had any pain in the last month?

☐ No ☐ Yes

c. We would like to find out where in your body you have experienced pain *(Indicate on the table below where the participant has experience pain in the last month - tick the appropriate box/boxes)*

Have you had pain in any of the following areas:			If Yes to any site, answer these questions			
			Is the pain		State the cause if the pain was caused by a recent **injury** (e.g., falling, in a car crash, bumping your head, burning yourself on the stove)	Mark the **one site** with the worst pain
			On the **surface** (skin)	**Deep** (inside)		
	No	Yes				
Head						
Shoulders						
Arms						
Hands						
Chest						
Abdomen						
Low back						
Private parts						
Legs						
Feet						
Joints						
Muscles						

No pain	0	1	2	3	4	5	6	7	8	9	10	Pain bad as you can imagine
	None	Mild			Moderate				Severe			

Using the scale in front of you ,what time of day is your pain at its **worst**?

In the morning	During the day	At night	All the time

Using the scale in front of you, which best describes your pain at its **least** in the last week (A rating of 10 would indicate pain so severe as to prohibit all activity; the worst pain you can imagine).

No pain	0	1	2	3	4	5	6	7	8	9	10	pain bad as you can imagine
	None	Mild			Moderate				Severe			

Using the scale in front of you, which best describes how much pain you have **right now**:

No pain	0	1	2	3	4	5	6	7	8	9	10	pain bad as you can imagine
	None	Mild			Moderate				Severe			

If you currently have odd/strange/painful feelings or discomfort in your feet, how well does each of the following words describe this feeling or discomfort? Please rate the severity of these symptoms using the scale (mild, moderate of severe pain):

Symptom	**Symptom presence** (tick one)			**Are you familiar with any of these terms** (yes/no, if yes: which?)	**Do you know an English word that means the same?** (yes/no, if yes: what?)	**Do you know a better isiZulu word for the sensation?** (yes/no, what?)
	NO	**UNSURE**	**YES**			
a) Hot / burning *isiZulu: kuyashisa / kuyavutha*						
b) Numbness *isiZulu: Ndikindiki (numb) Ziyalala (they are sleeping) Ziyasinda (they become heavy)*						
c) Painful / sore / aching *isiZulu: kubuhlungu*						
d) Itching *isiZulu: kuyaluma*						

e)	Tingling *isiZulu:* ***Ziyakitaza***						
f)	Electric shocks *isiZulu:* ***kudonseka imisipha (feels like an electric shock),ugesi (electric shock),Engathi kuyoshoka (electric shock)***						
g)	Painful cold *isiZulu:* ***Ukubanda/ ziyabanda Ziyagodola, Ziyabanda kakhulu (very cold)***						
h)	Pins-and-needles *isiZulu:*						

APPENDIX 3

NEUROPATHY PAIN SCALE

Appendix

NEUROPATHY PAIN SCALE

Instructions: There are several different aspects of pain which we are interested in measuring: pain **sharpnes heat/cold, dullness, intensity,** overall **unpleasantness,** and **surface vs. deep** pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree o how *sweet* a piece of pie might be (the *intensity* of the sweetness), but some might enjoy it more if it were sweeter whil others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quie and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. I short, the *intensity* of a sensation is not the same as how it makes you feel. A sound might be unpleasant and still be quie (think of someone grating their fingernails along a chalkboard). A sound can be quiet and "dull" or loud and "dull."

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, *hoı much* it hurts and *how unpleasant* or annoying it is. Although often the intensity of pain has a strong influence on hov unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very ba about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at al dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate ver high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactl what you experience.

1. Please use the scale below to tell us how **intense** your pain is. Place an "X" through the number that best describes the intensity of your pain.

No pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense** pain sensation imaginable

2. Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include

6. Please use the scale below to tell us how **sensitive** your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

Not sensitive	0	1	2	3	4	5	6	7	8	9	10	The most **sensitive** sensation imaginable ("raw skin")

7. Please use the scale below to tell us how **itchy** your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."

Not itchy	0	1	2	3	4	5	6	7	8	9	10	The most **itchy** sensation imaginable ("like poison oak")

8. Which of the following best describes the **time** quality of your pain? Please check only one answer.

( ) I feel a background pain all of the time **and** occasional flare-ups (break-through pain) some of the time.

Describe the background pain:_____

Describe the flare-up (break-through) pain:_____

( ) I feel a single type of pain all the time. Describe this pain:_____

( ) I feel a single type of pain only sometimes. Other times, I am pain free.

Describe this occasional pain:_____

9. Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how **unpleasant** your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable." Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how **unpleasant** your pain feels.

Not unpleasant	0	1	2	3	4	5	6	7	8	9	10	The most **unpleasant** sensation imaginable ("intolerable")

10. Lastly, we want you to give us an estimate of the severity of your deep versus surface pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.

HOW INTENSE IS YOUR *DEEP* PAIN?

No **deep** pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense deep** pain sensation imaginable

HOW INTENSE IS YOUR *SURFACE* PAIN?

No **surface** pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense surface** pain sensation imaginable

Appendix

NEUROPATHY PAIN SCALE

Instructions: There are several different aspects of pain which we are interested in measuring: pain **sharpness heat/cold, dullness, intensity,** overall **unpleasantness,** and **surface vs. deep** pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree o how *sweet* a piece of pie might be (the *intensity* of the sweetness), but some might enjoy it more if it were sweeter whil others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quie and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. I short, the *intensity* of a sensation is not the same as how it makes you feel. A sound might be unpleasant and still be quie (think of someone grating their fingernails along a chalkboard). A sound can be quiet and "dull" or loud and "dull."

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, *hov much* it hurts and *how unpleasant* or annoying it is. Although often the intensity of pain has a strong influence on hov unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very ba about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at al dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate ver high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactl what you experience.

1. Please use the scale below to tell us how **intense** your pain is. Place an "X" through the number that best describes the intensity of your pain.

No pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense** pain sensation imaginable

2. Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include

APPENDIX 4

THE LANSS PAIN SCALE

THE LANSS PAIN SCALE

Leeds Assessment of Neuropathic Symptoms and Signs

NAME_____ **DATE**_____

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

- Think about how your pain has felt over the last week.
- Please say whether any of the descriptions match your pain exactly.

1) Does your pain feel like strange, unpleasant sensations in your skin? Words like pricking, tingling, pins and needles might describe these sensations.

a) NO - My pain doesn't really feel like this..... (0)

b) YES - I get these sensations quite a lot..... (5)

2) Does your pain make the skin in the painful area look different from normal? Words like mottled or looking more red or pink might describe the appearance.

a) NO - My pain doesn't affect the colour of my skin..... (0)

b) YES - I've noticed that the pain does make my skin look different from normal .... (5)

3) Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.

a) NO - My pain doesn't make my skin abnormally sensitive in that area..... (0)

b) YES - My skin seems abnormally sensitive to touch in that area..... (3)

4) Does your pain come on suddenly and in bursts for no apparent reason when you're still. Words like electric shocks, jumping and bursting describe these sensations.

a) NO - My pain doesn't really feel like this ..... (0)

b) YES - I get these sensations quite a lot ..... (2)

5) Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations

a) NO - I don't really get these sensations..... (0)

b) YES - I get these sensations quite a lot ..... (1)

B. SENSORY TESTING

Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pin-prick threshold (PPT).

1) ALLODYNIA

Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

a) NO, normal sensation in both areas ..... (0)

b) YES, allodynia in painful area only ..... (5)

2) ALTERED PIN-PRICK THRESHOLD

Determine the pin-prick threshold by comparing the response to a 23 gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently on to the skin in a non-painful and then painful areas.

If a sharp pin prick is felt in the non-painful area, but a different sensation is experienced in the painful area e.g. none / blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

a) NO, equal sensation in both areas ..... (0)

b) YES, altered PPT in painful area ..... (3)

SCORING:

Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE (maximum 24) .....

APPENDIX 5

NEUROPATHIC PAIN SCORING

Please name the site of pain which is *most severe or disturbing* for you (eg, arm, foot, etc):

For all of the following questions, please rate your pain at the site you just listed.
Please use the space below to describe your pain in your own words:

Please use the items below to rate your pain as it *usually* feels. Indicate a number which represents your pain on each scale. For example, if you have no burning pain, you would rate the first item "0". If you have the worst burning pain imaginable, you would rate it "100". If neither of those fits your pain because it is in between, choose a number which *fits* your pain.

1. Burning Pain

0 ←——————→ 100		
No Burning Pain	Worst Burning Pain Imaginable	Please rate your *usual* pain: _____

2. Overly Sensitive to Touch

0 ←——————→ 100		
No Oversensitivity	Worst Oversensitivity Imaginable	Please rate your *usual* pain: _____

3. Shooting Pain

0 ←——————→ 100		
No Shooting Pain	Worst Shooting Pain Imaginable	Please rate your *usual* pain: _____

4. Numbness

0 ←——————→ 100		
No Numbness	Worst Numbness Imaginable	Please rate your *usual* pain: _____

5. Electric Pain

0 ←——————→ 100		
No Electric Pain	Worst Electric Pain Imaginable	Please rate your *usual* pain: _____

6. Tingling Pain

0 ←——————→ 100		
No Tingling Pain	Worst Tingling Pain Imaginable	Please rate your *usual* pain: _____

7. Squeezing Pain

0 ←——————→ 100		
No Squeezing Pain	Worst Squeezing Pain Imaginable	Please rate your *usual* pain: _____

8. Freezing Pain

0 ⟵⟶ 100		
No Freezing Pain	Worst Freezing Pain Imaginable	Please rate your *usual* pain: _____

9. How unpleasant is your usual pain?

0 ⟵⟶ 100		
Most Unpleasant Pain Imaginable	Worst Unpleasant Pain Imaginable	Please rate your *usual* pain: _____

10. How Overwhelming is your usual pain?

0 ⟵⟶ 100		
Most Over-whelming Pain Imaginable	Worst Over-whelming Pain Imaginable	Please rate your *usual* pain: _____

We are also interested in learning what circumstances cause changes in your pain. Please write the number that indicates the amount you experience each of the following:

11. Increased pain due to touch

0 ⟵⟶ 100		
No Increase At All	Greatest Increase Imaginable	Please rate your *usual* pain: _____

12. Increased pain due to weather changes

0 ⟵⟶ 100		
No Increase At All	Greatest Increase Imaginable	Please rate your *usual* pain: _____

	Score		Coefficient		Product
1. Burning Pain	_____	×	0.006	=	_____
2. Overly Sensitive to Touch	_____	×	0.005	=	_____
3. Shooting Pain	_____	×	0.005	=	_____
4. Numbness	_____	×	0.020	=	_____
5. Electric Pain	_____	×	–0.008	=	_____
6. Tingling Pain	_____	×	0.010	=	_____
7. Squeezing Pain	_____	×	–0.004	=	_____
8. Freezing Pain	_____	×	0.004	=	_____
9. How unpleasant is usual pain?	_____	×	0.006	=	_____
10. How overwhelming is usual pain?	_____	×	–0.003	=	_____
11. Increased pain due to touch	_____	×	0.006	=	_____
12. Increased pain due to weather changes	_____	×	–0.005	=	_____
Constant					–1.408
TOTAL DISCRIMINANT FUNCTION SCORE:				=	_____

APPENDIX 6

DN4 NEUROPATHIC PAIN QUESTIONNAIRE

DN4 Questionnaire

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

INTERVIEW OF THE PATIENT

Question 1: Does the pain have one or more of the following characteristics?

	yes	no
1 - **Burning**		
2 - **Painful cold**		
3 - **Electric Shocks**		

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

	yes	no
4 - **Tingling**		
5 - **Pins and Needles**		
6 - **Numbness**		
7 - **Itching**		

EXAMINATION OF THE PATIENT

Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

	yes	no
8 - **Hypoesthesia to touch**		
9 - **Hypoesthesia to prick**		

Question 4: In the painful area, can the pain be caused or increased by:

	yes	no
10 - **Brushing**		

APPENDIX 8

PAINDETECT QUESTIONNAIRE

Item	Score
*Gradation of pain**	
• Do you suffer from a burning sensation (e.g. stinging nettles) in the marked areas?	0–5
• Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?	0–5
• Is light touching (clothing, a blanket) in this area painful?	0–5
• Do you have sudden pain attacks in the area of your pain, like electric shocks?	0–5
• Is cold or heat (bath water) in this area occasionally painful?	0–5
• Do you suffer from a sensation of numbness in the areas that you marked?	0–5
• Does slight pressure in this area, e.g. with a finger, trigger pain?	0–5
Pain course pattern	
Please select the picture that best describes the course of your pain:	
 Persistent pain with slight fluctuations	0
 Persistent pain with pain attacks	–1
 Pain attacks without pain between them	+1
 Pain attacks with pain between them	+1
Radiating pain	
Does your pain radiate to other regions of your body? Yes/No	+2/0

*For each question: never, 0; hardly noticed, 1; slightly, 2; moderately, 3; strongly, 4; very strongly, 5
Questions used to document pain, but which were not used in the scoring, are not shown

Appendix 9

CERTIFICATE OF TRANSLATION

Translation Certificate

This is to certify that the translation of the document entitled:

DN4 Questionnaire Probability of Neuropathic Pain

From English into Zulu has been completed to the best of the ability of our translator and is true to the meaning and wording of the original English text. The translation were carried out by the following translator:

English to Zulu by Boni Zungu

Simon Kemisho Managing Director

04 March 2020

Date

S. Kemisho (MD) - T. Kemisho (Administrator) - website: www.translationworld.co.za - email: skemisho@global.co.za
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APPENDIX 10

TURN-IT-IN PLAGIARISM REPORT

T R Fagbohun final thesis

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REFERENCES

Agnew, D. C. and Merskey, H. (1976) 'Words of chronic pain', Pain, 2(1), pp. 73–81.

Alexander, N. (2004) 'The politics of language planning in post-apartheid South Africa', in Language Problems & Language Planning, pp. 113–130.

Algudairi, G., Aleisa, E. and Al-Badr, A. (2019) 'Prevalence of neuropathic pain and pelvic floor disorders among females seeking physical therapy for chronic low back pain', Urology Annals, 11(1), pp. 20–26.

Alkan, H. *et al*. (2013) 'Turkish version of the paindetect questionnaire in the assessment of neuropathic pain: A validity and reliability study', Pain Medicine (United States), 14(12), pp. 1933–1943.

Arendt-Nielsen, L. *et al*. (2018) 'Assessment and manifestation of central sensitisation across different chronic pain conditions', European Journal of Pain (United Kingdom). 22(2); pp 215-241

Atkinson, J. H., Kremer, E. F. and Ignelzi, R. J. (1982) 'Diffusion of pain language with affective disturbance confounds differential diagnosis', Pain, 12(4), pp. 375–384.

Baral, P., Udit, S., & Chiu, I. M. 2019. Pain and immunity: implications for host defence. *Nature reviews. Immunology*, *19*(7), 433–447.

Barbosa, M. *et al*. (2014) 'Cross-cultural psychometric assessment of the leeds assessment of neuropathic symptoms and signs (LANSS) pain scale in the Portuguese population', Pain Practice, 14(7), pp. 620–624.

Baron, E.C., Davies, T. and Lund, C., 2017. Validation of the 10-item centre for epidemiological studies depression scale (CES-D-10) in Zulu, Xhosa and Afrikaans populations in South Africa. *BMC psychiatry*, *17*(1), pp.1-14.

Baron, R. and Tölle, T. R. (2008) 'Assessment and diagnosis of neuropathic pain.', Current opinion in supportive and palliative care, 2(1), pp. 1–8.

Batistaki, C., Lyrakos, G., Drachtidi, K., Stamatiou, G., Kitsou, M. C., *et al*. (2016) 'Translation, Cultural Adaptation, and Validation of Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and Self-Complete Leeds Assessment of Neuropathic

Symptoms and Signs (S-LANSS) Questionnaires into the Greek Language', Pain Practice. Blackwell Publishing Inc., 16(5), pp. 552–564.

Bayot, A., Viadel, J. V. H. and de Julián, L. F. (2005) 'Análisis factorial exploratorio y propiedades psicométricas de la escala de competencia parental percibida. Versión para padres/madres (ecpp-p)', relieve - Revista Electronica de Investigacion y Evaluacion Educativa, 11(2), pp. 113–126.

Bennett, M. (2001) 'The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs', Pain, 92(1), pp. 147–157.

Bennett, M. I. *et al*. (2012) 'Prevalence and aetiology of neuropathic pain in cancer patients: A systematic review', Pain, 153(2), pp. 359–365.

Bennett, R. (1999) 'Emerging concepts in the neurobiology of chronic pain: Evidence of abnormal sensory processing in fibromyalgia', Mayo Clinic Proceedings. Mayo Foundation for Medical Education and Research, 74(4), pp. 385–398.

Blackmore, D. and Siddiqi, Z.A., 2016. Pinprick testing in small fiber neuropathy: accuracy and pitfalls. Journal of clinical neuromuscular disease, 17(4), pp.181-186.

Bouhassira, D. *et al*. (2005) 'Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)', Pain, 114(1), pp. 29–36.

Bouhassira, D. *et al*. (2008) 'Prevalence of chronic pain with neuropathic characteristics in the general population', Pain, 136(3), pp. 380–387.

Boureau, F., Doubrère, J. F. and Luu, M. (1990) 'Study of verbal description in neuropathic pain', Pain, 42(2), pp. 145–152.

Brinck, E.C., Tiippana, E., Heesen, M., Bell, R.F., Straube, S., Moore, R.A. and Kontinen, V. (2018) 'Perioperative intravenous ketamine for acute postoperative pain in adults'. *Cochrane Database of Systematic Reviews*, (12).

Brod, M. *et al*. (2015) 'Burden of Illness of Diabetic Peripheral Neuropathic Pain: A Qualitative Study', Patient. Springer International Publishing, 8(4), pp. 339–348.

Campbell, J. N., & Meyer, R. A. 2006. Mechanisms of neuropathic pain. *Neuron*, *52*(1), 77–92.
Carr, D. B. and Goudas, L. C. (1999) 'Acute pain', Lancet, 353(9169), pp. 2051–2058

Chandler, J. (2018) Chronic Pain: Physiological Foundations , Chronic Pain : Western Oregon University. Honors Senior Theses/Projects. 159. pp 1-36

Chatila, N. *et al*. (2017) 'Validation of a New Arabic Version of the Neuropathic Pain Diagnostic Questionnaire (DN4)', Pain Practice, 17(1), pp. 78–87.

Cherry, C. L. *et al*. (2005) 'Evaluation of a clinical screening tool for HIV-associated sensory neuropathies', Neurology, 65(11), pp. 1778–1781.

Chichorro, J. G., Porreca, F. and Sessle, B. (2017) 'Mechanisms of craniofacial pain', Cephalalgia, 37(7), pp. 613–626.

Clark, C. W. *et al*. (2002) 'Unidimensional pain rating scales: a multidimensional affect and pain survey (MAPS) analysis of what they really measure', Pain, 98(3), pp. 241–247. .

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: Global use of the Brief Pain Inventory. Annals, Academy of Medicine, Singapore, 23(2), 129–138

Cohen, R. (2019) 'Strangers and Migrants in the Making of African Societies: A Conceptual and Historical Review', Fudan Journal of the Humanities and Social Sciences, 12(1), pp. 45–59.

Colloca, L. *et al*. (2017) 'Neuropathic pain', Nature Reviews Disease Primers, 3, pp. 1–20.

Colloca, L., Ludman, T., Bouhassira, D., Baron, R., Dickenson, A. H., Yarnitsky, D., Freeman, R., Truini, A., Attal, N., Finnerup, N. B., Eccleston, C., Kalso, E., Bennett, D. L., Dworkin, R. H., & Raja, S. N. 2017. Neuropathic pain. *Nature reviews. Disease primers*, *3*, 17002.
Costigan, M., Scholz, J. and Woolf, C. J. (2009) 'Neuropathic Pain: A Maladaptive Response of the Nervous System to Damage', Annual Review of Neuroscience, 32(1), pp. 1–32.

Dansie, E. J. and Turk, D. C. (2013) ‘Assessment of patients with chronic pain’, British Journal of Anaesthesia, 111(1), pp. 19–25.

De Andrés, J. *et al*. (2012) ‘Cultural Adaptation and Validation of the painDETECT Scale Into Spanish’, The Clinical Journal of Pain, 28(3), pp. 243–253.

Dhanju, S. *et al*. (2019) ‘The impact of comorbid pain and depression in the United States: Results from a nationally representative survey’, Scandinavian Journal of Pain, 19(2), pp. 319–325.

Dieleman, J. P. *et al*. (2008) ‘Incidence rates and treatment of neuropathic pain conditions in the general population☆’, Pain, 137(3), pp. 681–688.

Dubin, A. E. and Patapoutian, A. (2010) ‘Nociceptors: The sensors of the pain pathway’, *Journal of Clinical Investigation*, 120(11), pp. 3760–3772.

Dubuisson, D. and Melzack, R. (1976) ‘Classification Multiple of Clinical Group Descriptions Analysis by Discriminant’, Experimental Neurology, 487, pp. 480–487.

Dueñas, M. *et al*. (2016) ‘A review of chronic pain impact on patients, their social environment and the health care system’, Journal of Pain Research, 9, pp. 457–467.

Eriksen, M.B. and Frandsen, T.F. (2018) ‘The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review’. *Journal of the Medical Library Association: JMLA*, *106*(4), p.420.

Eusebi, P., 2013. Diagnostic accuracy measures. *Cerebrovascular Diseases*, *36*(4), pp.267-272.

Finnerup, N. B. and Baastrup, C. (2012) ‘Spinal cord injury pain: Mechanisms and management’, Current Pain and Headache Reports, 16(3), pp. 207–216.

Finnerup, N. B. and Jensen, T. S. (2006) ‘Mechanisms of disease: Mechanism-based classification of neuropathic pain - A critical analysis’, Nature Clinical Practice Neurology. 2(2);pp. 107-115

Finnerup, N. B. *et al*. (2015) ‘Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis’, The Lancet Neurology, 14(2), pp. 162–173..

Finnerup, N.B. (2013) ‘Pain in patients with spinal cord injury’. *PAIN*®, *154*, pp.S71-S76.

Firmin, L. *et al*. (2014) ‘Axon diameters and conduction velocities in the macaque pyramidal tract’, Journal of Neurophysiology, 112(6), pp. 1229–1240.

Franz, S. *et al*. (2017) ‘Spinal Cord Injury Pain Instrument and painDETECT questionnaire: Convergent construct validity in individuals with Spinal Cord Injury’, European Journal of Pain (United Kingdom). 21(10), pp. 1642-1656

Galer, B. S. and Jensen, M. P. (1997) ‘Development and preliminary validation of a pain measure specific to neuropathic pain: The Neuropathic Pain Scale’, Neurology, 48(2), pp. 332–338.

Gilron, I., Baron, R. and Jensen, T. (2015) ‘Neuropathic Pain: Principles of Diagnosis and Treatment’, Mayo Clinic Proceedings. Elsevier, 90(4), pp. 532–545.

Gold, M. S. and Gebhart, G. F. (2010) ‘Nociceptor sensitization in pain pathogenesis’, Nature Medicine, 16(11), pp. 1248–1257.

Gudala, K., Ghai, B. and Bansal, D. (2017) ‘Neuropathic Pain Assessment with the PainDETECT Questionnaire: Cross-Cultural Adaptation and Psychometric Evaluation to Hindi’, Pain Practice, 17(8), pp. 1042–1049.

Gustorff, B. *et al*. (2008) ‘Prevalence of self-reported neuropathic pain and impact on quality of life: A prospective representative survey’, Acta Anaesthesiologica Scandinavica. 52(1), pp. 132-136

Haefeli, M. and Elfering, A. (2006) ‘Pain assessment’, European Spine Journal, 15(S1), pp. S17–S24.

Ham, O.-K. *et al*. (2015) ‘Consistency and Accuracy of Multiple Pain Scales Measured in Cancer Patients From Multiple Ethnic Groups’, Cancer Nursing, 38(4), pp. 305–311.

Hamdan, A *et al*. (2014) ‘Diagnostic accuracy of two questionnaires for the detection of neuropathic pain in the Spanish population’, European Journal of Pain (United Kingdom), 18(1), pp. 101–109.

Harifi, G., Ouilki, I., El Bouchti, I., Ait Ouazar, M., Belkhou, A., Younsi, R., Amine, M., Tazi, I., Abouqal, R., Niamane, R. and El Hassani, S., 2011. Validity and reliability of the Arabic adapted version of the DN4 questionnaire (Douleur Neuropathique 4 Questions) for differential diagnosis of pain syndromes with a neuropathic or somatic component. *Pain Practice*, *11*(2), pp.139-147.

Head, K. A. (2006) 'Peripheral neuropathy: Pathogenic mechanisms and alternative therapies', Alternative Medicine Review, 11(4), pp. 294–329..

Herdman, R. C. and Jensen, J. E. (1997) 'Introduction to the Nervous System and Nervous Tissue', in Technological Forecasting and Social Change, pp. 381–417.

Jacob, T. (2006) 'Low back pain incident episodes: a community-based study', The Spine Journal, 6(3), pp. 306–310.

Jensen, T. S. *et al*. (2006) 'New perspectives on the management of diabetic peripheral neuropathic pain', Diabetes and Vascular Disease Research, 3(2), pp. 108–119.

Kamerman, P. R. *et al*. (2020) 'Almost 1 in 5 South African adults have chronic pain: a prevalence study conducted in a large nationally representative sample', PAIN,(2020).

Kim, H. J. *et al*. (2016a) 'Validation of the Korean version of the DN4 diagnostic questionnaire for neuropathic pain in patients with lumbar or lumbar-radicular pain', Yonsei Medical Journal, 57(2), pp. 449–454.

Koc, R. and Erdemoglu, A. K. (2010) 'Validity and reliability of the Turkish Self-administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire.', Pain medicine (Malden, Mass.), 11(7), pp. 1107–14.

Krause, S. J. and Backonja, M.-M. (2003) 'Development of a Neuropathic Pain Questionnaire', The Clinical Journal of Pain, 19(5), pp. 306–314.

Lantheaume, S. (2018) 'Utilisation de la thérapie EMDR dans le traitement d'un ESPT après cancer du sein', Journal de Therapie Comportementale et Cognitive, 28(1), pp. 17–22.

Latremoliere, A. and Woolf, C. J. (2009) ‘Central sensitization: a generator of pain hypersensitivity by central neural plasticity.’, The journal of pain, 10(9), pp. 895–926.

Lees, A.J. and Hurwitz, B. (2019) ‘Testing the reflexes’. *Bmj*, *366*.

Lewis, R.J., 2000, May. An introduction to classification and regression tree (CART) analysis. In *Annual meeting of the society for academic emergency medicine in San Francisco, California* (Vol. 14).

Liampas, A., Rekatsina, M., Vadalouca, A., Paladini, A., Varrassi, G. and Zis, P. (2021) ‘Pharmacological management of painful peripheral neuropathies: a systematic review’. *Pain and Therapy*, *10*(1), pp.55-68.

Loeser, J. D. and Treede, R. D. (2008) ‘The Kyoto protocol of IASP Basic Pain Terminology’, Pain, 137(3), pp. 473–477.

López-de-Uralde-Villanueva, I. *et al*. (2018) ‘Validación y fiabilidad de la versión española de la escala autoadministrada de Evaluación de Signos y Síntomas Neuropáticos de Leeds (S-LANSS)’, Neurología, 33(8), pp. 505–514.

Luijendijk, H.J., 2021. How to create PICO questions about diagnostic tests. BMJ Evidence-Based Medicine.
Lunn, M. and Manji, H. (2012) ‘Neuropathies’, Medicine (United Kingdom), 40(10), pp. 546–552.

Madani, S. P. *et al*. (2014) ‘Validity and Reliability of the Persian (Farsi) Version of the DN4 (Douleur Neuropathique 4 Questions) Questionnaire for Differential Diagnosis of Neuropathic from Non-Neuropathic Pains’, Pain Practice, 14(5), pp. 427–436.

Magge, R. S. and DeAngelis, L. M. (2015) ‘The double-edged sword: Neurotoxicity of chemotherapy’, Blood Reviews, 29(2), pp. 93–100.

Maritz, J. *et al*. (2010) ‘HIV neuropathy in South Africans: Frequency, characteristics, and risk factors’, Muscle and Nerve, 41(5), pp. 599–606.

Marshall, A. (2018) ‘slow touch and fast nociception : exploratio of the interactio btweenn noxious and innocuous mechanical and touch sensation A thesis submitted

in partial fulfilment of the requirements of Liverpool John', in Phd Pulished Thesis, pp. 1–166..

Mathieson, S., Maher, C.G., Terwee, C.B., De Campos, T.F. and Lin, C.W.C., 2015. Neuropathic pain screening questionnaires have limited measurement properties. A systematic review. *Journal of clinical epidemiology*, *68*(8), pp.957-966.

Matsubayashi, Y. *et al*. (2013) 'Validity and Reliability of the Japanese Version of the painDETECT Questionnaire: A Multicenter Observational Study', PLoS ONE. Edited by K. Ikeda, 8(9), p. e68013. .

Matsuki, Y. *et al*. (2018) 'Reliability and validity of the Japanese translation of the DN4 Diagnostic Questionnaire in patients with neuropathic pain', Journal of Anesthesia, 32(3), pp. 403–408.

McCarberg, B. and Billington, R. (2006) 'Consequences of neuropathic pain: Quality-of-life issues and associated costs', American Journal of Managed Care, 12(SUPPL. 9), pp. 263–268.

Melzack, R. *et al*. (1986) 'Trigeminal neuralgia and atypical facial pain: Use of the McGill pain questionnaire for discrimination and diagnosis', Pain, 27(3), pp. 297–302.

Merskey, N. (1994) 'Classification of Chronic Pain—Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms', in Task force on taxonomy of the International Association for the study of pain. IASP Press, pp. 41–43.

Meyer-Rosberg, K. *et al*. (2001) 'Peripheral neuropathic pain - A multidimensional burden for patients', European Journal of Pain, 5(4), pp. 379–389.

Moher, D. *et al*. (2015) 'Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement', Systematic Reviews, 4(1), p. 1.

Mphahlele, N., Mitchell, D. and Kamerman, P. (2008) 'Validation of the Wisconsin Brief Pain Questionnaire in a Multilingual South African Population', Journal of Pain and Symptom Management, 36(4), pp. 396–412.

Nanna Brix Finnerup, R. K. and and Troels Staehelin Jensen (2021) 'Neuropathic pain assessement 1', in Neuropathic pain, pp. 1–30.

Ngyende, A. (2011) Statistical Release, SA Statistical release (Revised) P0301.4 Census. South Africa.

Nicholas, M. *et al*. (2019) 'The IASP classification of chronic pain for ICD-11: Chronic primary pain', Pain, 160(1), pp. 28–37.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E. and Chou, R., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*, *372*.

Park, C., Lee, Y. W., *et al*. (2015) 'Cross-cultural adaptation and linguistic validation of the korean version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale', Journal of Korean Medical Science, 30(9), pp. 1334–1339.

Perez, C. *et al*. (2007) 'Validity and reliability of the Spanish version of the DN4 (Douleur Neuropathique 4 questions) questionnaire for differential diagnosis of pain syndromes associated to a neuropathic or somatic component', Health and Quality of Life Outcomes, 5.

Pillay, P. *et al*. (2015) 'Pharmacological treatment of painful HIV-associated sensory neuropathy', South African Medical Journal, 105(9), pp. 769–772.

Portenoy, R. (2006) 'Development and testing of a neuropathic pain screening questionnaire: ID Pain', Current Medical Research and Opinion, 22(8), pp. 1555–1565.

Quattrini, C. and Tesfaye, S. (2003) 'Understanding the impact of painful diabetic neuropathy', Diabetes/Metabolism Research and Reviews, 19(SUPPL. 1), pp. 2–8.

Raja, S. N. *et al*. (2010) 'Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment', The Lancet Neurology, 9(8), pp. 807–819.

Reinhardt, K.R., Oh, L.S., Schottel, P., Roberts, M.M. and Levine, D., 2012. Treatment of Lisfranc fracture-dislocations with primary partial arthrodesis. *Foot & ankle international*, *33*(1), pp.50-56.

Rienstra, M., Lubitz, S.A., Mahida, S., Magnani, J.W., Fontes, J.D., Sinner, M.F., Van Gelder, I.C., Ellinor, P.T. and Benjamin, E.J., 2012. Symptoms and functional

status of patients with atrial fibrillation: state of the art and future research opportunities. *Circulation*, *125*(23), pp.2933-2943.
Rolke, R. *et al*. (2006) 'Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values', Pain, 123(3), pp. 231–243.

Roy, T. and Ghosh, S. (2013) 'Screening and measurement tools for neuropathic pain: Their role in clinical research and practice', International Journal of Pharmaceutical Sciences Review and Research, 21(2), pp. 97–107

Sadosky, A. *et al*. (2014) 'Pain severity and the economic burden of neuropathic pain in the United States: BEAT Neuropathic Pain Observational Study', ClinicoEconomics and Outcomes Research, 6, pp. 483–496.

Sahadew, N. and Singaram, V. S. (2019) 'A diabetes profile of the eight districts in the public health sector, Eastern Cape Province, South Africa', South African Medical Journal, 109(12), pp. 957–962.

Schaible, H. G., Ebersberger, A. and Natura, G. (2011) 'Update on peripheral mechanisms of pain: Beyond prostaglandins and cytokines', Arthritis Research and Therapy, 13(2), pp. 1–8.

Schestatsky, P. *et al*. (2011) 'Brazilian Portuguese Validation of the Leeds Assessment of Neuropathic Symptoms and Signs for Patients with Chronic Pain', Pain Medicine, 12(10), pp. 1544–1550.

Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, Benoliel R, Cohen M, Cruccu G, Davis KD, Evers S, First M, Giamberardino MA, Hansson P, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Nurmikko T, Perrot S, Raja SN, Rice ASC, Rowbotham MC, Schug S, Simpson DM, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ, Barke A, Rief W, Treede RD; Classification Committee of the Neuropathic Pain Special Interest Group (NeuPSIG). The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain*,160(1):53-59.
Serrie, A. and Servière, J. (2014) 'Pain: definitions, concepts and mechanisms in humans and farm animals', Advances in Animal Biosciences, 5(3), pp. 297–309. .

Shaikh, A., Bentley, A. and Kamerman, P. R. (2013) ‘Symptomatology of Peripheral Neuropathy in an African Language’, PLoS ONE. Edited by G. Forloni, 8(5), p. e63986.

Shaw, J. E., Sicree, R. A. and Zimmet, P. Z. (2010) ‘Global estimates of the prevalence of diabetes for 2010 and 2030’, Diabetes Research and Clinical Practice, pp. 4–14. .

Shreffler, J. and Huecker, M.R., 2020. Diagnostic testing accuracy: Sensitivity, specificity, predictive values and likelihood ratios.

Skaper, S. D., Facci, L. and Giusti, P. (2013) ‘Glia and mast cells as targets for palmitoylethanolamide, an anti-inflammatory and neuroprotective lipid mediator’, Molecular Neurobiology, 48(2), pp. 340–352.

Smith, B. H. and Torrance, N. (2012) ‘Epidemiology of neuropathic pain and its impact on quality of life’, Current Pain and Headache Reports, 16(3), pp. 191–198.

Spahr, N. *et al*. (2017) ‘Distinguishing between nociceptive and neuropathic components in chronic low back pain using behavioural evaluation and sensory examination’, Musculoskeletal Science and Practice. Elsevier Ltd, 27, pp. 40–48.

Spallone, V. *et al*. (2012) ‘Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy’, Diabetic Medicine. Blackwell Publishing Ltd, 29(5), pp. 578–585..

Spanos, K. *et al*. (2015) ‘Validation of the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire and its correlation with visual analog pain scales in Greek population’, Journal of Diabetes and its Complications. Elsevier Inc., 29(8), pp. 1142–1145.

Starr, D. A. (2011) ‘HHS Public Access’, Physiology & behavior, 176(1), pp. 139–148.

Staud, R. and Rodriguez, M. E. (2006) ‘Mechanisms of Disease: pain in fibromyalgia syndrome’, Nature Clinical Practice Rheumatology, 2(2), pp. 90–98.

Staud, R. and Smitherman, M. L. (2002) ‘Peripheral and central sensitization in fibromyalgia: pathogenetic role.’, Current pain and headache reports, 6(4), pp. 259–266.

Sykioti, P. *et al*. (2015) ‘Validation of the Greek Version of the DN4 Diagnostic Questionnaire for Neuropathic Pain’, Pain Practice, 15(7), pp. 627–632. .

Szczudlik, A., Dobrogowski, J., Wordliczek, J., Stępień, A., Krajnik, M., Leppert, W., Woroń, J., Przeklasa-Muszyńska, A., Kocot-Kępska, M., Zajączkowska, R. and Janecki, M., 2014. Diagnosis and management of neuropathic pain: review of literature and recommendations of the Polish Association for the Study of Pain and the Polish Neurological Society–part two. Neurologia i Neurochirurgia Polska, 48(6), pp.423-435.

Terkawi, A. S., Abolkhair, A., *et al*. (2017) ‘Development and validation of Arabic version of the douleur neuropathique 4 questionnaire’, Saudi Journal of Anaesthesia, 11(5), pp. S31–S39. .

Tesfaye, S. *et al*. (2010) ‘Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments’, Diabetes Care, 33(10), pp. 2285–2293. .

Timmerman, H. *et al*. (2013) ‘Cross-Cultural Adaptation to the Dutch Language of the PainDETECT-Questionnaire’, 13(3), pp. 206–214..

Torrance, N. *et al*. (2006) ‘The Epidemiology of Chronic Pain of Predominantly Neuropathic Origin. Results From a General Population Survey’, The Journal of Pain, 7(4), pp. 281–289.

Torrance, N. *et al*. (2014) ‘Estimating the burden of disease in chronic pain with and without neuropathic characteristics: Does the choice between the EQ-5D and SF-6D matter?’, Pain, 155(10), pp. 1996–2004.

Torsney, C. and MacDermott, A. B. (2006) ‘Disinhibition opens the gate to pathological pain signaling in superficial neurokinin 1 receptor-expressing neurons in rat spinal cord’, Journal of Neuroscience, 26(6), pp. 1833–1843.

Torta, R., Ieraci, V. and Zizzi, F. (2017) ‘A Review of the Emotional Aspects of Neuropathic Pain: From Comorbidity to Co-Pathogenesis’, Pain and Therapy. Springer Healthcare, 6(S1), pp. 11–17.

Toth, C., Lander, J. and Wiebe, S. (2009) ‘The Prevalence and Impact of Chronic Pain with Neuropathic Pain Symptoms in the General Population’, Pain Medicine, 10(5), pp. 918–929..

Trevethan, R., 2017. Sensitivity, specificity, and predictive values: foundations, pliabilities, and pitfalls in research and practice. *Frontiers in public health*, *5*, p.307.

Tsang, S., Royse, C.F. and Terkawi, A.S., 2017. Guidelines for developing, translating, and validating a questionnaire in perioperative and pain medicine. *Saudi journal of anaesthesia*, *11*(Suppl 1), p.S80.

Türkel, Y. *et al*. (2014) ‘Validation of self-report version of the Leeds Assessment of neuropathic symptoms and signs score for identification of neuropathic pain in patients from northern Turkey’, Advances in Clinical and Experimental Medicine, 23(4), pp. 599–603.

Umeda, M. and Kim, Y. (2019) ‘Gender differences in the prevalence of chronic pain and leisure time physical activity among US adults: A NHANES study’, International Journal of Environmental Research and Public Health, 16(6).

Unal-Cevik, I., Sarioglu-Ay, S. and Evcik, D., 2010. A comparison of the DN4 and LANSS questionnaires in the assessment of neuropathic pain: validity and reliability of the Turkish version of DN4. *The Journal of Pain*, *11*(11), pp.1129-1135.

United Nations Joint Programme on HIV/AIDS (UNAIDS) (2019) ‘UNAIDS Data 2019’, p. 476.

Urch, C. E. and Dickenson, A. H. (2008) ‘Neuropathic pain in cancer’, European Journal of Cancer, 44(8), pp. 1091–1096.

Van Hecke, O. *et al*. (2014) ‘Neuropathic pain in the general population: A systematic review of epidemiological studies’, Pain. International Association for the Study of Pain, 155(4), pp. 654–662

Vermelis, J.M., Wassen, M.M., Fiddelers, A.A., Nijhuis, J.G. and Marcus, M.A. (2010). ‘Prevalence and predictors of chronic pain after labor and delivery’. *Current Opinion in Anesthesiology’*, *23*(3), pp.295-299.

Voepel-Lewis, T. *et al*. (2011) ‘Do 0–10 Numeric Rating Scores Translate into Clinically Meaningful Pain Measures for Children?’, Anesthesia & Analgesia, 112(2), pp. 415–421. .

Wadley, A. L. *et al*. (2011) ‘HIV neuropathy risk factors and symptom characterization in stavudine-exposed South Africans’, Journal of Pain and Symptom Management. Elsevier Inc, 41(4), pp. 700–706.

Walters, E. T. (2019) ‘Adaptive mechanisms driving maladaptive pain: How chronic ongoing activity in primary nociceptors can enhance evolutionary fitness after severe injury’, Philosophical Transactions of the Royal Society B: Biological Sciences, 374(1785).

Woolf, C. J. (2004) ‘Pain: Moving from Symptom Control toward Mechanism-Specific Pharmacologic Management’, Annals of Internal Medicine, 140(6), pp. 441–451. .

Woolf, C. J. (2011) ‘Central sensitization: implications for the diagnosis and treatment of pain.’, Pain, 152(3 Suppl), pp. S2-15.

Woolf, C. J. and Ma, Q. (2007) ‘Nociceptors-Noxious Stimulus Detectors’, Neuron, 55(3), pp. 353–364.

Woolf, C. J. and Mannion, R. J. (2009) ‘Neuropathic pain: aetiology, symptoms ,mechanisms ,and management’, The Thoracic and Cardiovascular Surgeon, 353(6), pp. 1959–1965. .

Woolf, C. J. *et al*. (1998) ‘Towards a mechanism-based classification of pain?’, Pain, 77(3), pp. 227–229.

Xu, Q., & Yaksh, T. L. 2011. A brief comparison of the pathophysiology of inflammatory versus neuropathic pain. *Current opinion in anaesthesiology*, *24*(4), 400–407.

Yam, M. F. *et al*. (2018) ‘General pathways of pain sensation and the major neurotransmitters involved in pain regulation’, International Journal of Molecular Sciences, 19(8).

Yang, Q. *et al*. (2014) ‘Persistent Pain after Spinal Cord Injury Is Maintained by Primary Afferent Activity’, Journal of Neuroscience, 34(32), pp. 10765–10769.

Yang, S. and Chang, M. C. (2019) ‘Chronic pain: Structural and functional changes in brain structures and associated negative affective states’, International Journal of Molecular Sciences, 20(13).

Yawn, B. P. *et al*. (2009) ‘The Prevalence of Neuropathic Pain: Clinical Evaluation Compared with Screening Tools in a Community Population’, Pain Medicine, 10(3), pp. 586–593.

Younger, J., McCue, R. and Mackey, S. (2009) ‘Pain outcomes: A brief review of instruments and techniques’, Current Pain and Headache Reports, 13(1), pp. 39–43'.

Yucel, A. *et al*. (2004) ‘Results of the leeds assessment of neuropathic symptoms and signs pain scale in Turkey: A validation study’, Journal of Pain, 5(8), pp. 427–432.

Zimmermann, M. (2001) ‘Pathobiology of neuropathic pain’, European Journal of Pharmacology, pp. 23–37.