Original Article

The Maltese version of the DN4 Questionnaire. Initial Validation to Assess Neuropathic Pain in Patients with Chronic Spinal or Spinal-Radicular Pain.

Emanuel Schembri, Victoria Massalha, Liberato Camilleri, Marylin Casha

Abstract

Background: Neuropathic pain is frequently encountered in patients with spinal and spinal-related pain which needs specific treatment. Therefore, the objective of this study was to do an initial linguistic translation and validation of the Maltese DN4 questionnaire to diagnose neuropathic pain in this population.

Methods: The study was designed as a single-blinded, observational, prospective collected data and retrospective analysis. The English and French DN4 questionnaires underwent forward and backward translation, literal assessment and adaptation of the semantic equivalence into the Maltese language, followed by assessment of the Maltese DN4 during the initial patient assessment in patients who met the inclusion criteria.

Results: The total Maltese DN4 score obtained a Cronbach's alpha of 0.735 therefore having satisfactory internal consistency. Test-retest reliability yielded an intraclass correlation coefficient (95% CI) ranging from 0.975 to 0.991 (p<.001), while inter-rater reliability yielded an intraclass correlation coefficient (95% CI) ranging from 0.986 to 0.995 (p<0.001). Both the English and the Maltese DN4 questionnaires obtained the same sensitivity and specificity values of 0.422 and 0.941 respectively, and a positive likehood ratio of 7.153 and a negative likehood ratio of 0.614, at a cutoff score of 4.

Conclusion: The results of this study support the transcultural internal consistency, inter-rater, test-retest reliability, validity of the Maltese DN4 questionnaire to differentiate between neuropathic and nociceptive pain in patients with chronic spinal and spinal-radicular pain. Therefore, this simple tool can be used both in daily clinical practice but also in the clinical research setting to quickly screen for neuropathic pain.

Emanuel Schembri B.Sc.(Hons), PgDip (Pain)*
Physiotherapy Outpatients,
Karin Grech Hospital,
Pieta, Malta.
Master of Science (M.Sc) Candidate, M.Sc Clinical Management of Pain (Headache),
Department of Anaesthesia, Critical Care and Pain Medicine, Deanery of Clinical Sciences,
University of Edinburgh, Edinburgh, UK.
emanuel.a.schembri@gov.mt

Victoria Massalha M.Sc.(H.S.M.),Dip.Physio
Professional Lead,
Physiotherapy services,
Ministry for Health.
Physiotherapy Department,
Faculty of Health Sciences,
University of Malta
Msida, Malta.

Liberato Camilleri B.A. (Educ.), M.Sc., Ph.D.(Lanc.)
Department of Statistics and Operations Research, Faculty of Science,
University of Malta,
Msida, Malta.

Marylin Casha MD MSc MMCFD DESA
Department of Anesthesia,
Pain Management Services,
Mater Dei Hospital,
Msida, Malta.
Faculty of Medicine and Surgery,
University of Malta
Msida, Malta.

**Corresponding author*

Keywords

Neuropathic pain, radiculopathy, validation studies, translations, back pain.

Introduction

The International Association for the Study of Pain (IASP) defined neuropathic pain (NP) as "pain caused by a lesion or disease affecting the somatosensory system."[1] According to the Douleur Neuropathique 4 questions (DN4)[2] and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS),[3] chronic NP was prevalent in 7–10% in the general population (van Hecke et al., 2014).[4] However, 40% of all patients attending German pain clinics had NP characteristics.[5] The bodily regions most affected by chronic NP were the neck and upper limbs, lower back, and lower limbs.[6]

NP tends to be refractory to pharmacological treatment including strong opioids[7] and it leads to a more reduced quality of life compared to nociceptive pain.[8] NP mechanisms are implicated in the etiology of leg pain caused by degenerative spinal changes since the compressed nerve roots show edema, fibrosis, demyelination and axonal degenerative changes in the affected neurons.[9] Therefore, diagnosing NP is crucial for the treatment of degenerative spinal disease. Classical questionnaires like the McGill Pain Questionnaire (MPQ)[10] and the Brief Pain inventory[11] are not sufficiently specific to diagnose NP, although the NP descriptors included in the MPQ may have a diagnostic value. This led to the formulation of NP-specific diagnostic tools, e.g., Neuropathic Pain Scale, LANSS, the Neuropathic Pain Questionnaire, the Pain Detect, ID-pain, and the DN4.

The DN4 questionnaire was developed by the French Group of Neuropathic Pain to diagnose NP. In their initial validation study subjects with spinal and spinal radicular pain were not included.[2] The DN4 was derived from a list of signs and symptoms associated with NP, and it includes a series of four groups of questions consisting of seven sensory descriptors and three signs related to sensory examination. Each of the ten questions has a nominal scale with two possible responses (yes or no) and the total score was generated by summing the binary scores of all the ten items. A cutoff score of 4 yielded a specificity of 89.9% and a sensitivity of 82.9, correctly identifying 86% of the patients with NP. However, the principal limitation of this study was that the gold standard diagnosis of NP was made by the investigators themselves.[2] Afterwards, the DN4 was validated in low back pain (LBP) patients due to herniated discs, spinal stenosis, degenerative disc disease, degenerative lumbar spine, and lumbar scoliosis. 23% of the subjects had a previous spinal surgery which included discectomy, chemonucleolysis, laminectomy, and lumbar arthrodesis. The DN4 obtained a sensitivity of 80% and a specificity of 92%, however the gold standard diagnosis of NP was made by the physicians.[12]

Another study compared the DN4, PainDETECT, LANSS, and the Neuropathic Pain Questionnaire and found that the DN4 was the most sensitive of the four questionnaires [13]. Similarly, a systematic review found that the DN4 and Neuropathic Pain Questionnaire were the most suitable for clinical use.[14] This systematic review stated that the DN4 is a simple and objective instrument with an easy scoring method which consists of a relatively small number of items but highly capable of discriminating between NP and nociceptive pain.

Therefore, the objective of this study was to do an initial linguistic translation and validation of the Maltese DN4 questionnaire to diagnose NP in chronic spinal and spinal-radicular pain. The Maltese DN4 is expected to have a similar diagnostic efficacy when compared to the English DN4 version.

Materials and Methods

Setting

The study was approved by the research and ethics board at the Rehabilitation Hospital Karen Grech, Malta. The authors of the DN4 Questionnaire authorized its validation to the Maltese language. The study was designed as a single-blinded, observational, prospective collected data and retrospective analysis. The principal interviewer (ES) knew the patient's diagnosis, but the patients were not aware that the objective of the questionnaire was to distinguish between NP and nociceptive pain, therefore obtaining a single blind. Data collection was performed within the Musculoskeletal Physiotherapy Outpatients Department at the Rehabilitation Hospital Karin Grech during the period September to December 2018. The DN4 questionnaire results were collected during the initial physiotherapy assessment for patients referred from Mater Dei Hospital due to chronic spinal or spinal-radicular pain. Signed informed consent was obtained from the patients.

Sample

The inclusion criteria were patients of both

sexes 1) above 18 years of age; 2) visiting the Musculoskeletal Physiotherapy Outpatient's facilities for chronic spinal and/or spinal-radicular pain; 3) with a pain duration of ≥3 months; 4) with moderate or severe pain intensity [scoring 4 or higher on the current pain Numeric Rating Scale (NRS) for spinal or spinal-radicular pain].

Patients were excluded if they had other severe musculoskeletal pain, major comorbidity (e.g., malignant disorders or sepsis), pain of unknown origin, fibromyalgia, complex regional pain syndrome, headache, visceral pain, severe alcoholism or substance abuse, cognitive impairment or intellectual disability, severe depression or psychosis and if unable to understand the questions.

Stages of validation

The validation process of the DN4 questionnaire to the Maltese language was instituted from the original French and English versions, and it consisted of 4 distinct stages: 1) Translation; 2) Retranslation; 3) Literal assessment and adaptation of the semantic equivalence; and 4) Assessment of the target population with the final instrument, according to the previously established methodology.[15]

First Stage- Translation

The first stage consisted of translating the original French DN4 questionnaire by a University Professor in French translations to the Maltese language. Separately, the English DN4 (Appendix 1) was translated by a University Professor in English translations to the Maltese language. The two versions obtained after the translations were simultaneously evaluated by the authors and resulted in one merged version that was submitted to the retranslation process.

Second Stage- Retranslation

The initial Maltese DN4 version was retranslated into the French and into the English language by the respective Professors who carried out the initial translation. Alterations in the initial Maltese DN4 version were conducted at this stage.

Third Stage- Literal assessment and semantic equivalence

The literal assessment and adaptation of semantic equivalence was performed by the authors, all of whom had complete mastery of the Maltese language and understanding of the terms related to this area. The Maltese DN4 version obtained by the retranslation process was compared with the original French and English versions, considering whether the questions were rewritten with the same words (literal assessment) or whether the original meaning had been retained (semantic equivalence). This initial Maltese DN4 questionnaire was pilot tested in a sample of 10 patients with chronic spinal and/or spinal-radicular pain from different social classes and from various educational backgrounds. They answered the first seven questions of the Maltese DN4, inquiring about their understanding of each item. The last three questions of the Maltese DN4 tool, regarding the sensory examination, were not tested at this point. The same was carried out with a group of 5 health professionals at university level, who deal with pain patients. In addition to answering the questions about the degree of understanding, these professionals suggested the use of better terms that could have been applied.

Fourth Stage- Maltese DN4 testing and the 2016 International Association for the Study of Pain NP grading system in the target population

The linguistic validation of the Maltese DN4 questionnaire (Appendix 2) was performed on a sample of 62 patients who met the inclusion and exclusion criteria in order to assess the capacity of the instrument to distinguish nociceptive from NP in chronic spinal and spinal-radicular pain. At this stage a verbal NRS, ranging from zero (no pain) to 10 (maximum pain) and a body chart to document pain location were used.

In the initial physiotherapy assessment, the investigator (ES) asked each patient to describe his/her pain according to the seven NP descriptors using the Maltese DN4 questionnaire. Afterward, the same investigator carried out the sensory examination using a SENSELab Brush-05 (Somedic SenseLab AB, Sösdala, Sweden) to assess for hypoesthesia to brushing and brush allodynia while a 5.1g Semmes-Weinstein monofilament (Baseline Tactile Monofilaments, New York, USA) was used to assess hypoesthesia to fine tactile stimuli, as carried out in the original DN4 validation study.[2] Two repetitions of each of the three sensory tests were performed in the most painful area and compared to the corresponding contralateral aspect. In case of an inconsistent result

between the two test repetitions, the result for the specific testing modality was scored as a normal response.

At the end of the assessment, the investigator (ES) asked the patient to describe his/her pain using the first seven NP descriptors of the English DN4. This approach has been chosen because although a 1-2-day gap would have been ideal to reduce memory bias, however calling the patient back in 1-2 days for the purpose of this study was not feasible within the departmental setting. On the other hand, if the English DN4 examination was carried out 1-2 weeks after the Maltese DN4 exam, there was the possibility that the pain could have changed as a consequence of the physiotherapy treatment or analgesics, thus introducing a bias. For inter-rater reliability, the Maltese DN4 questionnaire was re-administered after the English DN4 exam in all of the subjects (n=62) by a research assistant, blinded to the diagnosis proposed by the principal investigator (ES). To assess test retest reliability, the Maltese DN4 questionnaire was re-administered in all of the subjects (n=62), 2 weeks after the first assessment by the principal investigator. Between the two visits, patients were allowed to take analgesic medications as prescribed by their medical consultant. A score for each positive (1) or negative item (0) was set for all the Maltese and the English DN4 items and the diagnosis of NP was made for a total score equal or larger than 4.

The gold standard diagnosis of NP was based on the medical history, physical exam, electromyography and/or imaging exams as advocated by the IASP NP grading system and each patient was graded as "unlikely NP", "possible NP", "probable NP" and "definite NP".[16] The methodology adopted by Hasvik et al.,[17] specific to using the IASP NP grading system in spinal and spinal-radicular pain was adopted for the purpose of this study.

Statistical analysis

The Cronbach's alpha was used to assess internal consistency thereby examining the contribution of each individual item measured by the Maltese DN4. Cronbach's alpha was first assessed for the complete questionnaire; then, each item was removed to assess the independent contribution of each item to the measurement error of the instrument. Moreover, to verify the validity of the DN4 items, factor analysis was used where principal component analysis was used for the extraction method and Varimax with Kaiser Normalization was used for the rotation method. The Kaiser-Meyer-Olkin (KMO) Measure and Bartlett's Test of Sphericity were conducted to determine whether the data had factorial validity. To verify the agreement between each individual item of the Maltese DN4 and the English DN4 questionnaires, the Cohen Kappa was used because these items had a nominal scale (yes or no). Since the scores had a metric scale, the Intraclass correlation coefficient (ICC) was used to assess inter-rater reliability and measure the agreement of the results obtained by two different raters for each item and for the total score of the DN4 questionnaire in all of the subjects (n=62). The test-retest reliability was assessed by comparing the initial and the second Maltese DN4 examination by the same investigator (ES) at two weeks in all of the subjects (n=62), by using the ICC. Receiver-operator characteristics (ROCs) analysis was carried out to assess the sensitivity and specificity of both the English and Maltese DN4 total scores in distinguishing patients who had NP defined by the IASP gold standard diagnosis. All statistical analyses were performed by using the SPSS version 25 statistics package (SPSS Inc., Chicago, IL, USA). In all statistical analysis, a 0.05 level of significance was adopted, where p-values less than 0.05 criterion indicated statistical significance. Item 10 of both the Maltese and the English DN4 was removed from the statistical analysis since no subject reported positive to this item.

Results

Sample description

Figure 1. provides a flow diagram of the participants. The baseline demographic and descriptive data of the 62 participants who took part in the study is presented in table 1. Overall, the subjects were composed of 51.61% males and 48.39% females. The completion rate was 53.9%. Patients with NP showed a significant higher mean current NRS (p<0.001) and highest NRS score (p<0.016) compared to the subjects with nociceptive pain. The most common causes for NP were spinal stenosis and spinal surgery, whilst a degenerative spine was the most common cause for nociceptive pain.

***Figure 1**: Flow diagram of the participants in the study*

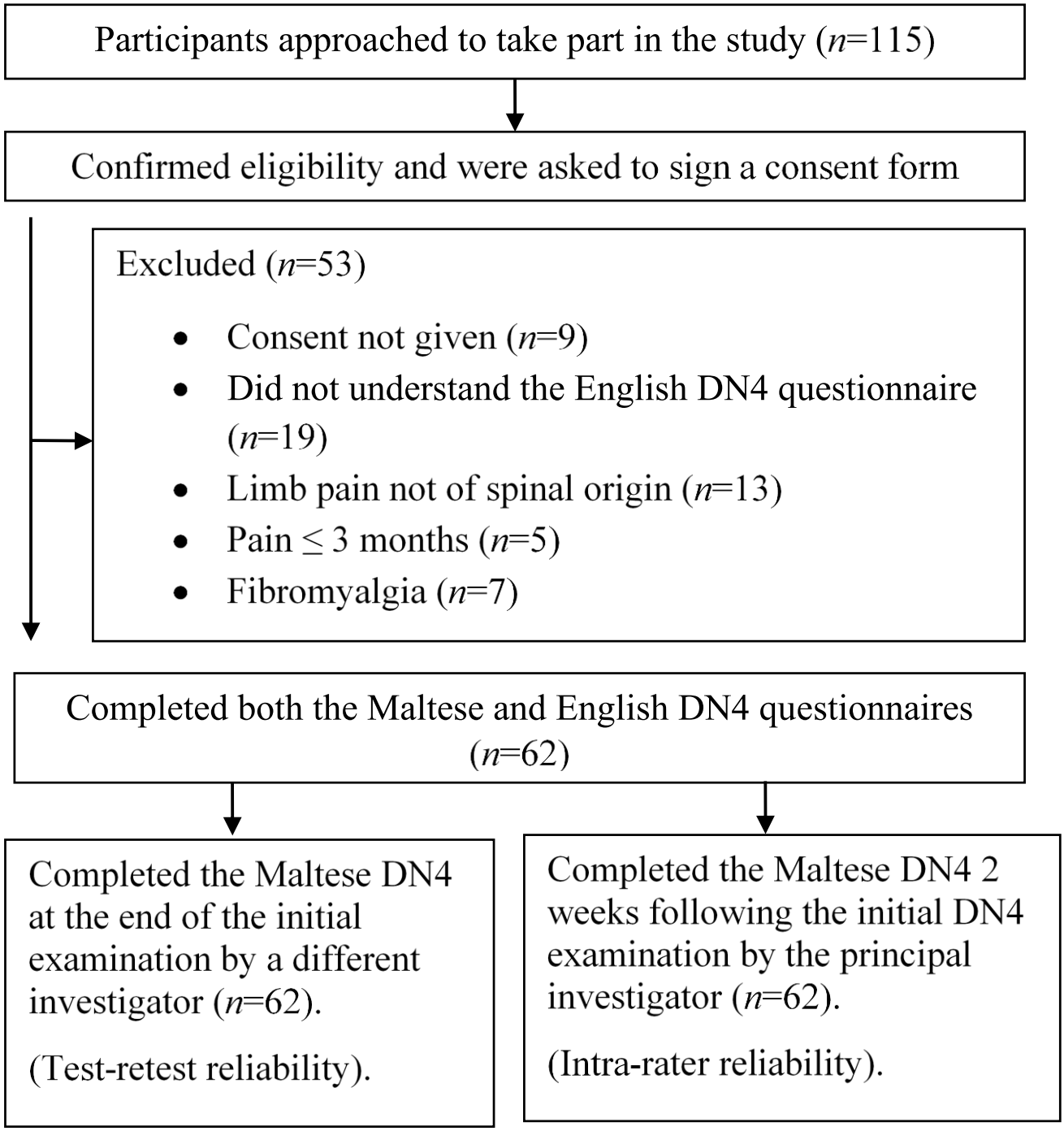


***Table 1**: Descriptive statistics of the subjects in the study*

	Neuropathic pain according to the DN4 (score > 4) (*n*=20)	**Nociceptive pain according to the DN4 (score < 4) (*n*=42)**	***P*-value (p <0.05)**
Number of subjects with lumbar related pain	18	36	
Number of subjects with cervical related pain	2	6	
Number of subjects who had undergone previous spinal surgery	6	4	
Mean age (years) (range)	56.5 (18-81)	60.0 (35-83)	0.338
% female	60%	54%	
Current number of analgesic drug classes consumed (range)	0.90 (0-3)	0.93 (0-3)	0.914
Mean lowest NRS (range)	3.20 (0-8)	2.02 (0-9)	0.073
Mean current NRS (range)	7.40 (4-10)	5.43 (4-10)	<0.001
Mean highest NRS (range)	9.20 (8-10)	8.19 (5-10)	0.016
Mean years with spinal pain	5.88 (3months-17years)	5.81 (3 months-50 years)	0.978
Mean Maltese DN4 interview score (score out of 7)	3.80 (3-7)	0.93 (0-3)	<0.001
Mean total Maltese DN4 score (score out of 10)	5.10 (4-8)	1.27 (0-3)	<0.001
Spinal pathologies on MRI	Stenosis *n*=6 Spinal surgery *n*=6 Disc herniation *n*=5 Degenerative spine *n*=3	Degenerative spine *n*=10 Disc herniation *n*=9 Stenosis *n*=9 Spondylolisthesis *n*=6 Spinal surgery *n*=4 Myofascial origin *n*=3 Modic changes *n*=1	
Two-tailed tests were carried out assuming a 0.05 level of significance.			

In addition, both the mean Maltese DN4 interview score and the total Maltese DN4 score were significantly higher (p<0.001) in the NP population. The predominant presenting symptom in the nociceptive pain group as graded by the Maltese DN4 was axial LBP, while in the NP group it was leg pain. The two most commonly mentioned Maltese DN4 NP descriptors for spinal and spinal-radicular pain were items 1. Ħruq (75%) and 5. Tingiż (75%) (table 2). No adverse events occurred due to the administration of both the English and the Maltese DN4 questionnaires.

Validity of the items in the instrument

Factor analysis

The data has factorial validity if the Kaiser Meyer Olkin (KMO) value exceeds the 0.5 threshold value, and the Bartlett's p- value is less than the 0.05 level of significance. In this data set, both criteria are satisfied indicating that factor analysis is essential. The scree plot (figure 2) can be used to identify the number of dimensions (factors) in a data set. In this particular data set, the scree elbow occurs at the third component indicating that the first two dimensions (factors) should be retained, where their eigenvalues (2.937 and 1.485) both exceed the threshold value 1. Moreover, these dimensions explain 49.134% of the total variation in the data (table 3). The vast majority of the Correlation Coefficients are positive indicating that participants scoring high in one item tend to score high on the others (table 4).

Factor loadings

The factor loadings (table 5) show that the first seven items are loading heavily on dimension 2, while items 8 and 9 are loading heavily on dimension 1.

Internal consistency, inter-rater reliability and test-retest reliability

The Cronbach's alpha measures the internal consistency between the related items, and it ranges from 0 to 1. A Cronbach's alpha above 0.7 indicates satisfactory internal consistency between the items. The Maltese DN4 questionnaire obtained a Cronbach's alpha of 0.735 exceeding the 0.7 threshold value indicating satisfactory internal consistency between the items and the vast majority of the inter item correlations are positive. Moreover, the Cronbach's alpha decreases when an item is removed, particularly item 4. Tnemnin, item 5. Tingiż and item 6. Stat imtarrax (table 6). This indicates that these three items contribute most to the internal consistency of the items and have the largest impact when measuring NP in spinal and spinal-radicular pain. On the other hand, the Cronbach's alpha increases slightly when removing item 2. Kesħa li tweġġa', indicating that this item contributes least to the internal consistency of the items and has lowest impact when measuring NP of spinal origin.

Table 2: *Maltese DN4 responses: Pain descriptors and the sensory examination*

Maltese DN4 item	Number of times mentioned (% of those who were diagnosed with NP by the Maltese DN4) (n=20)
1. Ħruq	15 (75%)
2. Kesħa li tweġġa'	2 (10%)
3. Xokkijiet	11 (55%)
4. Tnemnim	14 (70%)
5. Tingiż	15 (75%)
6. Stat imtarrax	14 (70%)
7. Ħakk	5 (25%)
8. Hypoesthesia malli tmissha	12 (60%)
9. Hypoesthesia mat-tingiz	14 (70%)
10. Ibbraxxjar	0 (0%)

Figure 2: *Scree plot*

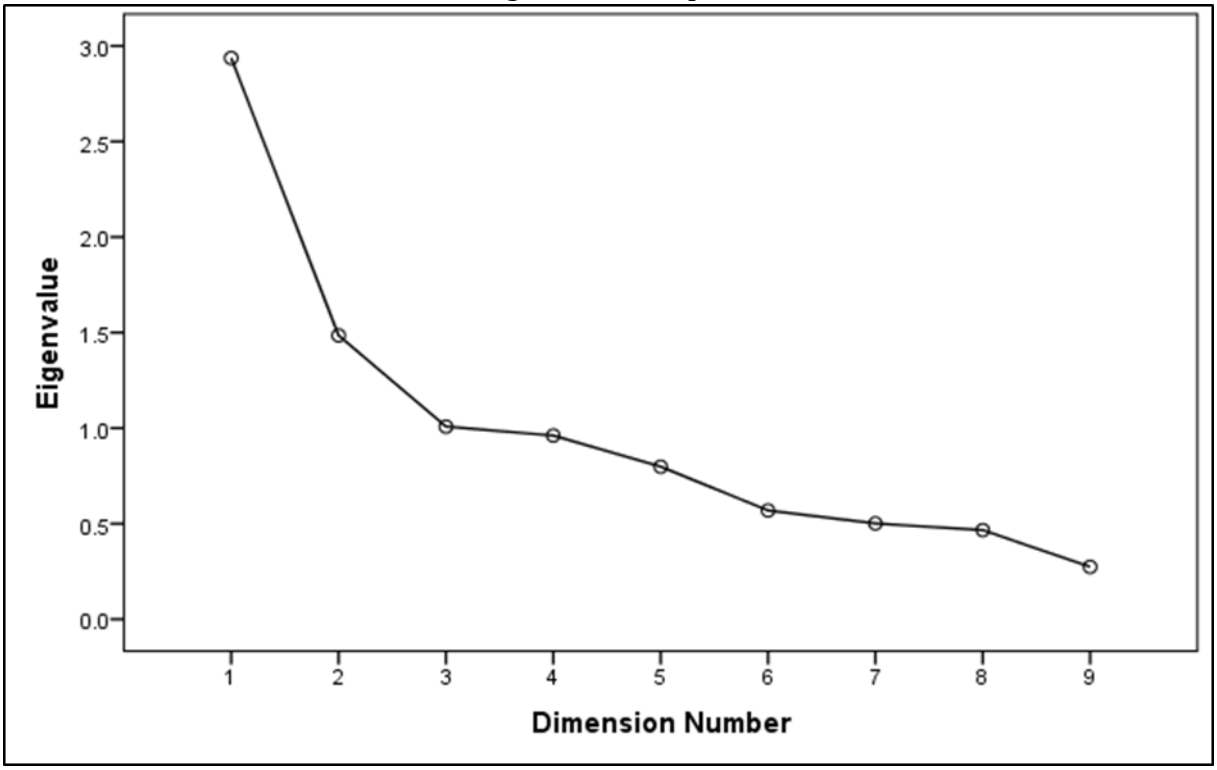


Table 3: *Total Variance Explained*

Dimension	Initial Eigenvalues			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	2.937	32.633	32.633	2.272	25.246	25.246
2	1.485	16.501	49.134	2.150	23.888	49.134

Table 4: *Inter-Item Correlation Matrix*

	Ħruq	Kesħa li tweġġa’	Xokkijiet	Tnemnin	Tingiż	Stat imtarrax	Ħakk	Hypoesthesia malli tmissha	Hypoesthesia mat-tingiż
Ħruq	1.000	0.043	0.245	0.197	0.393	0.168	0.176	0.357	0.121
Kesħa li tweġġa’	0.043	1.000	0.015	0.061	0.266	0.186	0.198	-0.032	-0.058
Xokkijiet	0.245	0.015	1.000	0.363	0.249	0.421	0.172	0.227	0.083
Tnemnin	0.197	0.061	0.363	1.000	0.367	0.427	0.330	0.190	0.380
Tingiż	0.393	0.266	0.249	0.367	1.000	0.343	0.411	0.191	0.268
Stat imtarrax	0.168	0.186	0.421	0.427	0.343	1.000	0.319	0.238	0.352
Ħakk	0.176	0.198	0.172	0.330	0.411	0.319	1.000	-0.032	-0.058
Hypoesthesia malli tmissha	0.357	-0.032	0.227	0.190	0.191	0.238	-0.032	1.000	0.531
Hypoesthesia mat-tingiż	0.121	-0.058	0.083	0.380	0.268	0.352	-0.058	0.531	1.000

Table 5: *Factor Loadings*

	Dimension	
	1	2
Ħruq		0.303
Kesħa li tweġġa’		0.547
Xokkijiet		0.407
Tnemnin		0.493
Tingiż		0.667
Stat imtarrax		0.538
Ħakk		0.774
Hypoesthesia malli tmissha	0.806	
Hypoesthesia mat-tingiż	0.807	

Table 6: *Cronbach`s Alpha to the items of the instrument*

	Item-Total Statistics
	Cronbach's Alpha if the Item is Deleted
1. Ħruq	0.719
2. Kesħa li tweġġa’	0.745
3. Xokkijiet	0.712
4. Tnemnin	0.689
5. Tingiż	0.687
6. Stat imtarrax	0.685
7. Ħakk	0.727
8. Hypoesthesia malli tmissha	0.711
9. Hypoesthesia mat- tingiż	0.713

Table 7*: Cohen Kappa values for each item of the Maltese DN4*

Item	**Kappa Value**	***P*-Value**
1. Ħruq	1.00	<0.001
2. Kesħa li tweġġa’	1.00	<0.001
3. Xokkijiet	1.00	<0.001
4. Tnemnin	0.756	<0.001
5. Tingiż	0.633	<0.001
6. Stat imtarrax	0.796	<0.001
7. Ħakk	0.880	<0.001
8. Hypoesthesia malli tmissha	1.00	<0.001
9. Hypoesthesia mat- tingiż	1.00	<0.001
10. Ibbraxxjar	1.00	<0.001

Table 8*: Inter-rater agreement of the Maltese DN4*

		Rater 2		
		Positive	Negative	Total
Rater 1	Positive	20	0	20
	Negative	0	42	42
Total		20	42	62

Table 9: *Test-retest of the Maltese DN4*

		Rater 1 (retest)		
		Positive	Negative	Total
Rater 1 (test)	Positive	20	0	20
	Negative	1	41	42
Total		21	41	62

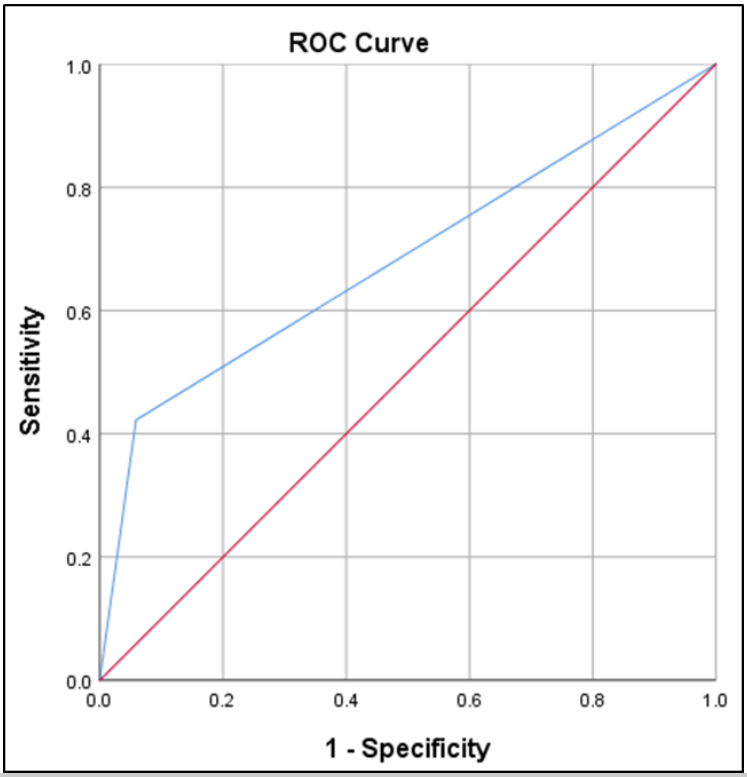
Table 10: *Agreement in the diagnosis of NP between the Maltese DN4 and the English DN4 total score*

		DN4 (English version)		
		Positive	Negative	Total
DN4 (Maltese version)	Positive	20	0	20
	Negative	0	42	42
Total		20	42	62

Table 11*: Agreement between the Maltese DN4 and the clinical classification based on the International Association for the Study of Pain (IASP) grading system*

		IASP NP Grading System		
		Positive	Negative	Total
DN4 (For both the Maltese and English versions)	Positive	19	1	20
	Negative	26	16	42
Total		45	17	62

Figure 3*: Receiver operating characteristic (ROC) curve and area under curve (AUC) for the total score of the English/Maltese DN4 questionnaire. Either tools obtained a sensitivity of 0.422 and a specificity of 0.941 at a cut off score of ≥4. Both the Maltese and the English DN4 obtained a positive likehood ratio of 7.153 and a negative likehood ratio of 0.614.*



The Cohen Kappa was used to measure the reliability between each item of the Maltese and the English DN4 questionnaires. There was satisfactory agreement between each individual item of the Maltese and the English DN4 tools, ranging from 0.633 to 1.00 (p<0.001), with six out of the ten Maltese DN4 items obtaining a Kappa score of 1.00 (p<0.001) (table 7).

Inter-rater agreement for the total Maltese DN4 score (table 8) was very good, having an ICC (95% CI) ranging from 0.986 to 0.995 (p<0.001) (n=62). At an interval of 2 weeks, the test-retest ICC (95% CI) for the total Maltese DN4 score ranged from 0.975 to 0.991 (p<0.001) (n=62) (table 9).

Psychometric validation

According to the IASP grading system of the 62 cases assessed, 22 (35.5%) were classified as having "definite" NP, 23 (37.1%) were classified as having "probable" NP, 9 (14.5%) were classified as having "possible" NP, and 8 (12.9%) who did not have NP according to the IASP NP grading system. The current study adopted the methodology of Abdallah et al.,[18] were a DN4 score of ≥4 was comparable to a IASP NP grading of "probable" and "definite" NP, while a DN4 score of ≤3 was comparable to a IASP grading of "possible" or the "absence" of NP. Therefore the 4 categories of the IASP grading system were grouped into 2 sections.

There was perfect agreement between the English and the Maltese DN4 questionnaires in classifying subjects with either NP or nociceptive pain (table 10). Therefore, when compared to the gold standard IASP NP grading system, both the English and the Maltese DN4 questionnaires obtained the same sensitivity and specificity values of 0.422 and 0.941 respectively, at a cutoff point of 4 (table 11) (figure 3). The area under the ROC curve (0.682) was significantly larger than the 0.5 threshold value since the p-value (0.028) is less than the 0.05 level of significance. Moreover, the 95% CI of the area under the ROC curve ranges between 0.546 and 0.818, which excludes the 0.5 threshold value (figure 3). Both the Maltese and the English DN4 obtained a positive likehood ratio of 7.153 and a negative likehood ratio of 0.614.

Discussion

This study provided the initial validation of the Maltese DN4 questionnaire for assessing NP of chronic spinal and spinal-radicular pain and it also found that the English and the Maltese DN4 possess a similar diagnostic power. In fact, there was perfect agreement between the final score between of the English and Maltese DN4 questionnaires in diagnosing patients with NP.

Until the present day there was no specific pain questionnaire in the Maltese language that was capable of distinguishing between NP and nociceptive pain. On the other hand, Dr. Gatt should be accredited with performing the translation of the MPQ, a first for the Maltese language.[19] The NP descriptors in the original MPQ can have a diagnostic value for NP, however more specific questionnaires like the DN4 thanks to its sensory examination can diagnose NP better. There are several similarities and differences in comparing the Maltese DN4 to the Maltese MPQ by Dr. Gatt. Items 1. Ħruq, 3. Xokkijiet and 4. Tnemnin of the Maltese DN4 are also present in the Maltese MPQ. Interestingly, item 6. Numbness of the English DN4 was translated to 6. Stat imtarrax in the Maltese DN4 and to "Torqodlok" in the Maltese MPQ. This portrays the similarity in meaning of certain Maltese words. Item 5. Tingiż of the Maltese DN4 was not mentioned in the Maltese MPQ, while item 2. Kesħa li tweġġa' was referred to as "kiesah silg" in the Maltese MPQ. Even though these have a similar meaning in Maltese, the former adds a painful dimension, while the wording in the MPQ does not imply pain, but rather an intense cold.

In the analysis of internal consistency, each of the seven Maltese NP descriptors obtained very good Cohen Kappa values (range 1.00-0.633, p<0.001) compared to the English DN4 indicating similarity in meaning between the individual terms whilst underlying the importance of each item of the questionnaire. The bilingual aspect of the Maltese population probably contributed for the Maltese DN4 questionnaire to obtain the excellent Cohen Kappa values in this translation. In addition, both the Maltese and the English DN4 versions categorized the subjects in an identical way. The test-retest and the intra-rater reliabilities of the Maltese DN4 were satisfactory. Therefore, the DN4 is considered stable over time and between different examiners. In the analysis of the reproducibility of the instrument, it was observed that the group of health professionals had a greater understanding of the Maltese DN4 questionnaire, which is justified by their knowledge and familiarity with the terms used in the DN4. A number of the patients

presented with difficulties in understanding some of the items, which is reasonable considering the lower educational background of this population compared to the health professionals.

The sensitivity of both the English and Maltese versions was low compared to the original DN4 validation study, while the specificity was higher. The low sensitivity for both English and Maltese DN4 versions could be due to linguistic specificities, cultural differences, the methodology of the study and the pathology under investigation. However, most importantly, contrary to previous DN4 translations which used the physician's or the examiner's NP diagnosis, this study adopted the objective IASP NP grading system as the gold standard to diagnose NP, therefore altering the sensitivity and the specificity of the DN4 compared to its initial validation study. Also, in the original developmental study of the DN4 patients with spinal and spinal-radicular pain were excluded. Nonetheless the high specificity and a positive likehood ratio of 7.153 of both tools, makes the DN4 as a valid and quick screening tool for diagnosing NP.

Furthermore, there is a growing body of evidence showing that the sensitivity of the DN4 varies with the underlying condition. In subjects with failed back surgery syndrome the sensitivity of the DN4 was 62%[20], in cervical or lumbar radiculopathy it was 76%[21] and 80% in subjects with LBP radiating to the lower limbs.[12]

Recently, VanDenKerkhof et al.,[22] found that the sensitivity of the DN4 was 72.1% in lumbosacral radiculopathy. However, in this study the gold standard diagnosis of NP was not explicitly provided but the terms used in the IASP grading system including "no", "possible", "probable" and "definite" were used. However, a limitation of this study is that all the study subjects had a previous diagnosis of NP thus increasing the sensitivity compared to what would be obtained in a sample of patients with heterogeneous pain, like in our study. According to VanDenKerkhof et al.,[22] the most commonly mentioned NP descriptors for lumbosacral radiculopathy were item 6. Numbness (88%), item 1. Burning (70%) and item 4. Tingling (70%). In the general, the three most common NP descriptors were ongoing burning pain (65.4%), paroxysmal electric shock-like pain (57.0%) and brush-evoked pain (54.9%)[23], with most patients reporting a coexistence of heterogeneous sensory signs and symptoms.[24] In the current Maltese sample, item 1. Ħruq (75%) and item 5. Tingiż (75%) of the Maltese DN4 were the most prevalent NP descriptors used in cases of subjects with NP.

Weakness and strength of the study

The current study included only patients with chronic spinal or spinal-radicular pain for the validation of the Maltese DN4 questionnaire This unique feature, however, poses certain limitations on the generalizability to other NP conditions which can be assessed using the DN4. Thus, this is one of the main limitations of this study.

One of the strengths of this study compared to previous DN4 translations into other languages is the adoption of the IASP NP grading system as the gold standard. Previous translations have adopted either the physicians´ or an expert or the investigators´ NP diagnosis as the gold standard, therefore introducing a subjective bias and potentially overestimating the diagnostic power of the DN4. Contrarily, the criteria proposed by the IASP system are objective and reproducible therefore limiting bias. Another strength of the current study is the adoption of the same inclusion and exclusion criteria as those used in the development study of the original DN4 questionnaire.

Conclusion

The results of this study support the transcultural internal consistency, inter-rater, test-retest reliability and validity of the Maltese DN4 questionnaire to differentiate between NP and nociceptive pain in patients with chronic spinal and spinal-radicular pain due to degenerative spinal disease. Therefore, this simple tool can be used both in daily clinical practice but also in the clinical research setting.

Summary box

What is already known about this subject:

- A significant proportion of spinal and spinal-radicular pain has a neuropathic pain component.
- The IASP grading system is considered the gold standard for diagnosing NP.
- Considering that the grading system can be a lengthy procedure, diagnostic questionnaires like the DN4 can quickly screen for

neuropathic pain in the busy clinical setting.

What are the new findings:

- The Maltese version of the DN4 has the same diagnostic powers as the English DN4 in chronic spinal and spinal-radicular pain.
- Both the English and the Maltese DN4 are quick to administer and easy to score.
- Contrarily to previous studies, which used the physicians´ diagnosis of NP as the gold standard, both the English and the Maltese DN4 exhibited a lower sensitivity but an excellent specificity in diagnosing NP when compared to the IASP NP grading system.

Acknowledgments

Special thanks for their help in translating the English DN4 and French DN4 to the Maltese language:

Prof. Charles Briffa of the Department of Translation, Terminology, and Interpreting Studies, (Faculty of Arts, University of Malta) who lectures on the theory and practice of translation for special purposes (including the specialised translation of medical language from English to Maltese) to post-graduate students.

Chev. Laurent Seychell, Pr. des Universités.

Funding

Emanuel Schembri received funding from the Endeavour Scholarship Scheme (Malta). Scholarships are part-financed by the European Union - European Social Fund (ESF) - Operational Programme II – Cohesion Policy 2014-2020 "Investing in human capital to create more opportunities and promote the well-being of society."

The other authors did not receive any funding in relation to this study.

References:

1. Treede R, Jensen T, Campbell J, Cruccu G, Dostrovsky J, Griffin J, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. Neurology. 2007 Apr; 70(18): 1630-1635.
2. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lantéri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005 Mar; 114(1-2): 29-36.
3. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain. 2001 May; 92(1-2): 147-157.
4. van Hecke O, Austin S, Khan R, Smith B, Torrance N. Neuropathic pain in the general population: A systematic review of epidemiological studies. Pain. 2014 Apr; 155(4): 654-662.
5. Freynhagen R, Baron R, Gockel U, Tölle T. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Current Medical Research and Opinion. 2006 Oct; 22(10): 1911-1920.
6. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain. 2008 Jun; 136(3): 380-387.
7. Schembri E. Are Opioids Effective in Relieving Neuropathic Pain? SN Comprehensive Clinical Medicine. 2018 Jan; 1: 30-46.
8. Smith B, Torrance N, Bennett M, Lee A. Health and Quality of Life Associated With Chronic Pain of Predominantly Neuropathic Origin in the Community. The Clinical Journal of Pain. 2007 Feb; 23(2): 143-149.
9. Sekiguchi M, Kikuchi S, Myers R. Experimental Spinal Stenosis. Spine. 2004 May; 29(10): 1105-1111.
10. Melzack R. The McGill Pain Questionnaire: Major properties and scoring methods. Pain. 1975 Sep; 1(3): 277-299.
11. Daut R, Cleeland C, Flanery R. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain. 1983 Oct; 17(2): 197-210.
12. Attal N, Perrot S, Fermanian J, Bouhassira D. The Neuropathic Components of Chronic Low Back Pain: A Prospective Multicenter Study Using the DN4 Questionnaire. The Journal of Pain. 2011 Oct; 12(10): 1080-1087.
13. Bisaga W, Dorazil M, Dobrogowski2 J, Wordliczek J. A comparison of the usefulness of selected neuropathic pain scales in patients with chronic pain syndromes: a short communication. Adv Pall Med. 2010; 9: 117-122.
14. Mathieson S, Maher C, Terwee C, Folly de Campos T, Lin C. Neuropathic pain screening questionnaires have limited measurement properties. A systematic review. Journal of Clinical Epidemiology. 2015 Aug; 68(8): 957-966.
15. Guillemin F. Cross-cultural Adaptation and Validation of Heatth Status Measures. Scandinavian Journal of Rheumatology. 1995; 24(2): 61-63.
16. Finnerup N, Haroutounian S, Kamerman P, Baron R, Bennett D, Bouhassira D, Cruccu G, Freeman R, Hansson P, Nurmikko T, Raja S, Rice A, Serra J, Smith B, Treede R, Jensen T. Neuropathic pain. Pain. 2016 Aug; 157(8): 1599-1606.
17. Hasvik E, Haugen A, Gjerstad J, Grøvle L. Assessing neuropathic pain in patients with low back-related leg pain: Comparing the painDETECT Questionnaire with the 2016 NeuPSIG grading system. European Journal of Pain. 2018 Jul; 22(6): 1160-1169.

18. Abdallah F, Morgan P, Cil T, Escallon J, Semple J, Chan V. Comparing the DN4 tool with the IASP grading system for chronic neuropathic pain screening after breast tumor resection with and without paravertebral blocks. Pain. 2015 Apr; 156(4): 740-749.
19. Gatt D. Development of a Maltese Pain Questionnaire. MSc thesis. 2002: University of Wales College of Medicine, UK.
20. Markman J, Kress B, Frazer M, Hanson R, Kogan V, Huang J. Screening for Neuropathic Characteristics in Failed Back Surgery Syndromes: Challenges for Guiding Treatment. Pain Medicine. 2015 Mar; 16(3): 520-530.
21. Scholten-Peeters W, Epping R, Rooker S, Verhagen A. The validity of the Dutch painDETECT and the DN4 questionnaire for neuropathic pain in patients with suspected cervical or lumbar radiculopathy: A diagnostic accuracy study. Manual Therapy. 2016 Sep; 25: e98.
22. VanDenKerkhof E, Stitt L, Clark A, Gordon A, Lynch M, Morley-Forster P, Nathan H, Smyth C, Toth C, Ware M, Moulin D. Sensitivity of the DN4 in Screening for Neuropathic Pain Syndromes. The Clinical Journal of Pain. 2017 Jan; 34(1): 30-36.
23. Truini A, Garcia-Larrea L, Cruccu G. Reappraising neuropathic pain in humans—how symptoms help disclose mechanisms. Nature Reviews Neurology. 2013; 9: 572-582.
24. Attal N, Fermanian C, Fermanian J, Lanteri-Minet M, Alchaar H, Bouhassira D. Neuropathic pain: Are there distinct subtypes depending on the aetiology or anatomical lesion? Pain. 2008 Aug; 138(2): 343-353.

Appendix 1. 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 of 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	___	___

The total score is calculated as the sum of the 10 items and the cut-off value for the diagnosis of neuropathic pain is a total score of 4/10.

Bouhassira D, Attal N, Alchaar H, et al. "Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)." Pain 114.1-2 (2005): 29-36.

Appendix 2. Il-Kwestjonarju DN4

Jekk jogħġbok kompli dan il-kwestjonarju billi tittikkja tweġiba waħda għal kull parti f'dawn l-4 mistoqsijiet li ġejjin:

L-Intervista lill-Pazjent/a

L-ewwel mistoqsija: L-uġigħ għandu xi waħda, jew aktar, minn dawn il-karatteristiċi?

	IVA	LE
1. Ħruq	___	___
2. Kesħa li tweġġa'	___	___
3. Xokkijiet	___	___

It-tieni mistoqsija: L-uġigħ marbut ma' wieħed, jew aktar, minn dawn is-sintomi fl-istess naħa?

	IVA	LE
4. Tnemnim	___	___
5. Tingiż	___	___
6. Stat imtarrax	___	___
7. Ħakk	___	___

L-Eżami tal-Pazjent/a

It-tielet mistoqsija: L-uġigħ jinsab f'naħa fejn l-eżami fiżiku jista' jikxef waħda, jew aktar, minn dawn il-karatteristiċi?

	IVA	LE
8. Hypoesthesia malli tmissha	___	___
9. Hypoesthesia mat-tingiż	___	___

Ir-raba' mistoqsija: Fin-naħa li tuġgħek, jista' l-uġigħ ikun ġej jew jiżdied minn

	IVA	LE
10. Ibbraxxjar?	___	___

L-iskor totali huwa kkalkulat mill-għadd ta' dawn l-10 *items* il-valur li jimmarka l-limitu għad-dijanjosi tal-uġigħ newropatiku huwa skor totali ta' 4/10.

TOTAL

_____

Bouhassira D., et al, "Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)". *Pain* 114.1-2 (2005): 29-36.