ASSESING CRITERION VALIDITY OF THE MODIFIED S-LANSS FOR THE DETECTION OF NEUROPATHIC OROFACIAL PAIN CONDITIONS

A THESIS SUBMITTED TO THE FACULTY OF

UNIVERSITY OF MINNESOTA

BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MASTER OF SCIENCE

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March 2016

Acknowledgment

I would like to express my gratitude and profound admiration for Donald R. Nixdorf, who always knew how to guide me, teach me, and encourage me. He is an excellent professor, an outstanding advisor, and a better person.

I also want to thank the members of my committee Justin Durham, Alan Law and Ruby Nguyen for their advice, corrections and inestimable help, but especially I want to thank Estephan J. Moana-Filho for his patience and dedication.

To Sara Shueb and Barbara Fonseca Alonso, the persons who made possible my project by collecting the data.

To all the members of the TMD and Orofacial pain department, who made me feel like at home even at -30°C.

And to Flavia Kapos, my example, my friend, my sister.

Dedication

To my parents, who curiously will never understand these lines. They support me, love me, and make me a better person every day of my life. They give me strength from thousand miles away, and trust me even when I doubt about myself. There are no words to express what they mean to me. I hope that they can feel proud of this thesis, because they made it possible.

ABSTRACT

Objective: To evaluate the accuracy of a questionnaire designed for the identification of intraoral pain with neuropathic characteristics in a clinical orofacial pain sample population.

Methods: 136 participants with 4 orofacial pain diagnoses (temporomandibular disorders [TMD, n=41], acute dental pain [ADP, n=41], trigeminal neuralgia (TN, n=19), persistent dentoalveolar pain disorder [PDAP, n=14]) and a group of pain-free controls (n=21) completed the modified S-LANSS, an adaptation of the original questionnaire devised to detected patients suffering from intraoral pain with neuropathic characteristics. Psychometric properties (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]) were calculated in two analyses with two different thresholds: 1) Detection of pain with neuropathic characteristics: PDAP + TN were considered positive, and TMD + ADP + controls were considered negative per gold standard (expert opinion). 2) Detection of PDAP: PDAP was considered positive and TMD + ADP were considered negative per gold standard. For both analyses, target values for adequate accuracy were defined as ≥80% for sensitivity and specificity.

Results: For detection of orofacial pain with neuropathic characteristics (PDAP + TN), the modified S-LANSS presented with the most optimistic threshold sensitivity of 52% (95% CI: 34-69%), specificity of 70% (95% CI: 60-79%), PPV of 35% (95% CI: 22-51%), and NPV of 82% (95% CI: 72-89%). For detection of PDAP only, with the most optimistic threshold sensitivity was 64% (95% CI: 35-87%), specificity 63% (95% CI: 52-74%), PPV 23% (95% CI: 11-39%) and NPV 91% (95% CI: 81-97%).

Conclusion: Based on *a priori* defined criteria, the modified S-LANSS did not show adequate accuracy to detect intraoral pain with neuropathic characteristics in a clinical orofacial pain population.

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INTRODUCTION

Neuropathic pain, defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (1), is estimated to have a worldwide prevalence ranging from 6.9 to 10.0% (2). There are several potential underlying mechanisms for this type of pain, and identification of which mechanism(s) are involved in a given patient supports therapeutic decisions (3). The diagnostic process is often time consuming and expensive, involving several care providers and increasing patient´s frustration (4-6). Failure in obtaining an accurate early diagnosis for neuropathic pain is thought to be a key reason that makes it difficult to treat, increases associated care costs, and adversely impacts the quality of life and functionality of patients suffering from it (7, 8).

Neuropathic pain in the orofacial region is thought to be relatively uncommon, however our knowledge on its occurrence is limited (9). Trigeminal neuralgia (TN), an intense paroxysmal pain felt in the distribution of one or more branches of the trigeminal nerve, is one of the most well-described neuropathic conditions affecting the face and oral cavity (10). According to a recent review of neuropathic pain in the orofacial region, TN annual incidence has been estimated as 4 cases per 100,000 in the United States and a lifetime prevalence of 0.7 per 100,000 people per year in the United Kingdom(9).

Another chronic pain affecting the orofacial region that has been suggested to be neuropathic in nature is atypical odontalgia (11), also referred to as persistent dentoalveolar pain disorder (PDAP) (12). Classic studies reported that its prevalence ranges between 3-6% (13, 14), and Polycarpou et al. in 2005 reported that in a sample of patients the prevalence of persistent pain after successful root canal

treatment was 12% (21 out of 175 patients) (15). However, a review of the literature that adjusted the calculations considering all subjects enrolled in previous studies that were clinically determined to have PDAP after root canal treatment (RTC), estimated that 1.6% of patients who underwent the procedure fit the criteria for that condition (16). Results from a prospective cohort study based on community practices, as opposed to studies that recruit subjects from referrals to tertiary practices, suggested that such frequency may be 0.5% (2/390) in a conservative calculation or 1.13% (4/354) in a more aggressive one (17). The diagnoses derived in these studies were based on expert clinical opinion in a process of exclusion, and due to the rule-out process they usually are inefficient, being time consuming and burdensome for both providers and patients.

A different approach to help the diagnostic process is to use a questionnaire (18, 19) to identify patients exhibiting features consistent with underlying neuropathic pain mechanisms. Different questionnaires have been created, validated and employed for this purpose in neuropathic pain patients including: Neuropathic Pain Questionnaire (NPQ), Douleur Neuropathique en 4 questions (DN4), painDETECT, ID-Pain, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), and its self-reported version S-LANSS (20, 21, and 22). In the orofacial region, PainDETECT was used with painful post-traumatic trigeminal nerve injuries (23) and a modified version of the S-LANSS was used to assess the prevalence of neuropathic pain post-RCT (24). The latter study reported that 7% of these post-RCT patients presented with neuropathic pain features, which is significantly higher than recent literature reports (0.5% to 1.6%) (16, 17). The order of magnitude difference in the reported prevalence between these two approaches, and the lack of evidence regarding the accuracy of questionnaires for detecting neuropathic pain manifesting within the orofacial region, suggest a significant discrepancy of results between using the

modified S-LANSS and the current gold-standard of clinical evaluation to achieve that goal. Thus the objective of the present study was to assess criterion validity of the modified S-LANSS questionnaire to identify patients with neuropathic orofacial pain, i.e., TN and PDAP, when comparing:

1. Participants with neuropathic pain (PDAP and TN) against participants with non-neuropathic orofacial pain conditions (temporomandibular disorders and acute dental pain) and pain-free controls.
2. PDAP participants against participants with non-neuropathic orofacial pain conditions (temporomandibular disorders and acute dental pain).

METHODS

Study design

This cross-sectional study used a convenience sample for each of the five different groups. Four groups consisted of participants presenting with one of the following orofacial pain conditions: persistent dentoalveolar pain disorder (PDAP), trigeminal neuralgia (TN), temporomandibular disorder (TMD), and acute dental pain (ADP). A fifth group of pain-free participants was also included as a negative control. This study was part of a parent study designed to identify question items to be used for the initial development of a screening questionnaire for PDAP. That parent study was conducted following ethical oversight by the University of Minnesota (UMN) Institutional Review Board (IRB: 1104S98353) and all the participants provided informed consent prior to their participation. The Standards for Reporting Diagnostic accuracy studies (STARD) criteria were used for reporting results (25).

Setting

Participants with TN, PDAP, and TMD were recruited by orofacial pain experts at the UMN School of Dentistry clinics and a private pain clinic in Plymouth, MN. Participants with ADP diagnoses were recruited from an endodontic specialist private practice. All dentists recruiting participants were board certified in their respective disciplines. Controls were recruited from the UMN School of Dentistry clinics by approaching pain-free patients, relatives and friends accompanying the participants, and people from the UMN community. Participants were compensated $25 for their time.

Eligibility criteria

Participants with specific pain diagnoses, or lack thereof for controls, were the reference standard for this study. They were recruited via convenience sampling. The diagnoses of TMD were derived using the DC/TMD (26) and included myalgia, and arthralgia categories. TN criteria were derived from the ICHD-II Diagnostic Criteria for Classical Trigeminal Neuralgia (27). PDAP criteria followed a published expert consensus criteria (12). ADP diagnoses included were irreversible pulpitis and/or symptomatic apical periodontitis and were operationalized following the diagnostic descriptions of the American Association of Endodontists (28). For more details of the diagnostic criteria used, see table (Table 1).

Additional inclusion Criteria for all participants:

- Age, 18 years old and older.
- Participants were able to cooperate and respond to the questions in English.

Note; participants with comorbid migraine headaches or tension-type headaches were eligible as long as they were not experiencing their headache pain at the time of questionnaire completion.

Exclusion Criteria for all participants:

- History of traumatic injuries to the orofacial region, TMJ surgery or inter-articular steroid injection.
- Major systemic illness related to altered pain sensitivity, such as rheumatoid arthritis or fibromyalgia.
- Inability to give informed consent.

- Subject within prior qualitative research performed to generate questionnaire items (29, 30)

Data management and statistical analyses

Data entry was performed by two of the participating clinicians and was cross-checked for accuracy by a third investigator. Data were managed within a spreadsheet (Microsoft Excel 2012 for Windows: Microsoft Corporation).

The Statistical software STATA release 13 (Stata Corp LP, College Station, TX) was used to calculate sensitivity, specificity, positive and negative predictive values, and 95% confidence intervals. Differences between groups were calculated performing Kruskal-Wallis analysis.

Questionnaire administration

The modified S-LANSS (Figure 1) for intraoral pain was completed by participants enrolled in the parent study, along with five other questionnaires. The order of presentation of the questionnaires was randomized in a permuted block fashion to control for potential order effects. Participants either completed the questionnaire after their clinical appointment or a mailing option was also offered.

Questionnaire response options and scoring

In the original S-LANSS (20) each question has a dichotomous response (Yes/No). Unpublished analyses performed by our group assessing instrument accuracy by comparing PDAP patients and pain free controls responses revealed a sensitivity of 53% and a specificity of 100% for the S-LANSS using this dichotomous scoring.

Based on these results, a bipolar five point ordinal system of responses (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree) was utilized with the goal of increasing the discriminative range of possible responses, and also increase the potential to adjust the threshold value for a positive score. In order to maintain the same scoring procedure as the original S-LANSS, scores were collapsed so that the new range of responses could correspond with a dichotomous score in each question. As for the original S-LANSS, minimum and maximum scores were 0 and 24 respectively, with a cut-off score of ≥12 being considered "likely neuropathic".

Determination of adequate sensitivity and specificity

What is considered acceptable in diagnostic tools and screening questionnaires is context specific, depending on factors such as disease prevalence, associated health costs, and morbidity/mortality related with false-negatives (type II error). Target values for adequate accuracy were defined as ≥80% for sensitivity based on the need of early detection to avoid unnecessary treatments or worsening of the condition, and that neuropathic pain conditions have low prevalence and no mortality associated with it. Target value for specificity was also established as ≥80% considering that the treatment of neuropathic pain involves medications with are commonly associated with significant adverse effects and/or invasive surgical procedures. In addition, sensitivity and specificity of the original validation study for the LANSS (83% and 87% respectively) (31) and S-LANSS (74%-76%) (20), and the intention to use of this questionnaire as a screening and not as a diagnostic tool were also taken into account to determine threshold for accuracy.

Analyses plan

Two separate analyses were performed where the gold standard for diagnosis was clinical evaluation done by experts in the field:

1. Neuropathic pain sensitivity and specificity: to test the ability to distinguish neuropathic pain diagnoses from non-neuropathic pain diagnoses, TN and PDAP participants without comorbid TMD were considered as disease positive while ADP, TMD and pain-free control participants were considered as disease negative; and
2. PDAP sensitivity and specificity: to test the ability to distinguish PDAP from non-neuropathic conditions PDAP participants were considered as disease positive while acute dental pain and TMD were considered as disease negative.

To these ends, we performed the following response item collapsing procedures:

1a) Scores were collapsed so that “strongly agree” and “agree” were considered as a positive response, while “neither agree nor disagree”, “disagree”, and “strongly disagree” were considered as negative.

1b) Scores were collapsed so that “strongly agree”, “agree” and “neither agree nor disagree” were considered as a positive response, while “disagree”, and “strongly disagree” were considered as negative.

Point estimates and 95% confidence intervals were calculated for sensitivity, specificity, positive and negative predictive values.

Calculation

The determination of “reference” status (disease positive or negative per gold standard) was derived from the clinical evaluation performed within the parent study, while the “index” status (test results as positive or negative) was determined by the

modified S-LANSS scores computed as described above. Sensitivity, specificity, and positive and negative predictive values were calculated for total scores (Figure 2), and also for each specific item.

RESULTS

Study participants

A total of 136 participants with 4 orofacial pain diagnoses (temporomandibular disorders [TMD, n=41], acute dental pain [ADP, n=41], trigeminal neuralgia (TN, n=19), persistent dentoalveolar pain disorder [PDAP, n=14]) and a group pain-free controls (n=21) completed the modified S-LANSS. The original sample from the parent study consisted in 146 participants. Data for 10 participants were excluded from the analyses because they had a neuropathic and a non-neuropathic pain diagnoses, which would make it unclear which category the participant should be included in. Of these 10 participants, 8 had comorbid diagnosis of PDAP and TMD while 2 were diagnosed with both TN and TMD. As expected due to the convenience sampling employed, statistically significant differences in demographic, socioeconomic and pain characteristics were observed between groups (Table 2).

Results of neuropathic pain sensitivity and specificity

1a) “Strongly agree”, “agree” as positive: sensitivity of 27% (95% CI: 13-46%) and a specificity of 80% (95% CI: 71-87%) were obtained (Table 3).

1b) “Strongly agree”, “agree” “neither agree nor disagree”, as positive: a sensitivity of 52% (95% CI: 34-69%) and a specificity of 70% (95% CI: 60-79%) were obtained (Table 3) (Figure 3).

Results of PDAP sensitivity and specificity

2a) “Strongly agree”, “agree” as positive: a sensitivity of 29% (95% CI: 8-58%) and a specificity of 74% (95% CI: 64- 83%) were obtained (Table 3).

2b) “Strongly agree”, “agree” “neither agree nor disagree”, as positive: a sensitivity of 64% (95% CI: 35-87%) and a specificity of 63% (95% CI: 52-74%) were obtained (Table 3) (Figure 3).

Results of item analysis for neuropathic pain

1a) “Strongly agree”, “agree” as positive: questions # 1, 2 and 5 had specificity >80% but sensitivity <33%. On the other hand questions # 3 and 7 presented greater sensitivity than specificity with results in between 50% to 58% (Table 4).

1b) “Strongly agree”, “agree” “neither agree nor disagree” as positive: sensitivity and specificity were more similar due to the overall increase of sensitivity (Figure 4). Question 4a had sensitivity and specificity that approximated the pre-determined target value for accuracy, with a sensitivity of 67% (95% CI: 48-82%) and specificity of 73% (95% CI: 63-81%) (Table 4)

Results of item analysis for PDAP

2a) Agree and strongly agree as positive: Questions 1, 2, 4a and 5 had specificity >74% but sensitivity <43%. Question # 7 showed a sensitivity of 71% and specificity

of 37%, and in questions # 6 and 3 sensitivity and specificity were more equal with results in between 40% and 59% (Table 5).

2b) Neither agree nor disagree, agree and strongly agree as positive: overall sensitivity increased and sensitivity and specificity were similar (Figure 5). The question with more balanced and higher score was question # 5, with a sensitivity of 71% (95% CI: 42-2%) and a specificity of 72% (95% CI: 61-81%) (Table 5).

DISCUSSION

Overall, the modified S-LANSS questionnaire was found to have low sensitivity for neuropathic pain diagnoses when compared to non-neuropathic pain diagnoses (TMD, ADP) and pain-free controls, and also when PDAP participants only were compared to non-neuropathic pain diagnoses (TMD, ADP). Individual item analyses revealed similar findings where sensitivity and specificity for both comparisons were low. None of the individual questions had sensitivity and specificity >80%, which was our target for accuracy to be considered acceptable. After adjusting threshold values for a positive score to increase sensitivity (“strongly agree”, “agree” “neither agree nor disagree” considered as positive), overall and question specific sensitivity did increase (Figure 3-5). However, sensitivity and specificity continued to be well below our target values, which suggest that this modified questionnaire is not appropriate in its current format to detect neither neuropathic pain in the orofacial region nor PDAP alone.

The use of questionnaires to aid in the diagnosis of neuropathic pain has been employed in other areas of medicine (18, 19). Based on the difference of the local anatomy and function of the trigeminal somatosensory system (32, 33), it is

reasonable to think that a questionnaire developed to assess spinally-mediated neuropathic pain may not be acceptable for pain presenting within the trigeminal innervation territory (face, oral cavity). Therefore, objective measurements of psychometric properties need to be determined to validate or not such rationale.

Elias et al. in 2014 assessed the painDETECT to classify 56 patients with post-traumatic inferior alveolar nerve injury, and their results suggested that the painDETECT questionnaire is not a sensitive instrument for detecting neuropathic orofacial pain (23). A modified version of the S-LANSS was used by Klasser et al in 2011 with the main objective of determining the prevalence of neuropathic pain after non-surgical root canal treatment (34). In this study, 2,338 questionnaires were mailed and 250 (10.7%) patients returned completed questionnaires; from those, 18 (7%) respondents met scoring criteria for neuropathic pain. A possible explanation of these results could be the inaccuracy of the selected questionnaire to detect pain with neuropathic characteristic in the oral cavity, as our study has shown. Other possible reasons for such a large occurrence estimate included potential response bias (35), low response rate (10.7%), or the lack of clinical examination to exclude other conditions that can present with similar symptoms as post-RCT pain such as TMD or existence of remnant dental pathology (17).

Our research group also used the modified S-LANSS to assess PDAP patients and pain-free controls (unpublished data). We found sensitivity of 53% and specificity of 100% for PDAP were obtained, questioning the use of the modified S-LANSS for screening such condition in a clinical setting. These results lead to the hypothesis that the unidimensionality of the modified S-LANSS could be the underlying reason for such findings. In order to improve it by increasing its sensitivity, an ordinal system

of responses and exclusion of participants with neuropathic pain and comorbid TMD were implemented in the present study. However, the results herein reported were still deemed unacceptable based on our target value for accuracy (sensitivity and specificity >80%).

Results of individual item analysis (Table 4, 5) suggested two types of questions, ones with sensitivity significantly below our threshold that capture information related to autonomic-like features, and ones with specificity considerably below 80% related with pain experienced to a non-painful stimulus (*a.k.a*., allodynia). In the orofacial region, self-examination is greatly restricted due to reduce visual access to the person's own oral cavity. This lack of unimpeded observation of the involved tissues, and the different relationship between neuropathic pain conditions and autonomic system when compared with other areas of the body may explain why questions # 1, 2 and 5 and had low sensitivity in all analyses. Allodynia, or pain when the tissue is "gently rubbed" or "gently pressed" is an excellent indicator of neuronal dysfunction but it is also a normal physiological response when the involved tissue is inflamed, something that occurs with odontogenic disease and such a positive response is part of the diagnostic process of dental disease (i.e., digital palpation of the buccal tissue apical to the involved tooth (36)). This can explain why questions # 3, 6 and 7 had low specificity. Question number # 4 showed higher results when neuropathic pain groups were compared against the rest but low sensitivity when PDAP group was compared independently, suggesting that it could be an appropriate item to detect neuralgia-like pain but not a more continuous type of neuropathic pain.

The present study used important methodology to minimize bias. To facilitate clinical applicability STARD criteria checklist was followed (25).The use of a modified

response scoring (ordinal scale) allowed for different cut-point to be assessed in an attempt to maximize sensitivity. The inclusion of patients with painful clinical conditions known to be misdiagnosed as neuropathic orofacial pain allowed for a more clinically meaningful comparison rather than using only pain-free controls that pose no diagnostic dilemma. The gold-standard clinical evaluation of patients to determine diagnostic status and to rule out presence of comorbid orofacial pain disorders within the study samples was also fundamental.

As any other studies, there were limitations to be considered. A convenience sample was used, and the number of the neuropathic pain participants was small, especially the PDAP group. Due to participants' time constraints, a few and were allowed to complete it without supervision. This increased the possibility of error due to misunderstanding of what was being asked. While patients with comorbid pain conditions, such as fibromyalgia and rheumatoid arthritis were excluded for participating in this study to reduce sources of bias, comorbid mood disorders (37, 38) and analgesic medication use were not.

In summary, one way to work on improving treatment outcomes for patient with neuropathic orofacial pain is to identify them early on within the pathophysiology process of their chronic pain disorder so that interventions can occur at an earlier stage, before the nociceptive processes become less adaptable (39-41). One method of obtaining this is via the use of screening questionnaires. Another benefit of using such questionnaires is to help guide the diagnostic process, avoiding unnecessary diagnostic testing and irreversible treatments, such as root canal treatments and teeth extractions, which are known to be costly and contribute to the chronification of the patients' pain (30). The use of a screening questionnaire with acceptable

sensitivity and specificity in routine clinical practice would go a long way in potentially achieving the above goals. The results in this study suggest that the modified S-LANSS does not have the pre-requisite characteristics that would enable it to function satisfactorily in a regular dental clinical environment. Therefore there is still a need to develop a questionnaire as a screening tool for neuropathic pain conditions manifesting in the face and mouth, considering the anatomical and functional differences for this region.

Table 1. Diagnostic criteria for the orofacial pain conditions studied

Condition	History	Objective findings	Radiological findings
Persistent dentoalveolar pain (PDAP)	Persistent (least 8 hours/day ≥15 days per month for ≥3 months) pain (IASP definition), localized (dentoalveoalr region), close temporal relationship to a causal event or not.	Dental exam normal ,neurological exam normal	X-Rays normal, CT scan normal, MRI normal
Trigeminal neuralgia (TN)	Paroxysmal attacks of intense, sharp, superficial or stabbing pain or/and precipitated from trigger areas or by trigger factors, lasting from <1 second to 2 minutes, affecting 1 or more branches of the trigeminal nerve, stereotyped in the individual patient and not attributed to another disorder	There is no clinically evident neurological deficit	
Temporomandibular disorders (TMD): Local myalgia	Pain in last 30 days of muscle origin that is affected by jaw movement, function, or parafunction, and replication of this pain occurs with provocation testing of the masticatory muscles	Confirmation of pain location(s) in the temporalis/masseter muscle(s); and report of familiar pain in the temporalis/masseter muscle(s) with palpation or maximum unassisted or assisted opening movement(s).	
TMD: Myofascial pain	Pain in last 30 days of muscle origin as described for myalgia with pain spreading beyond the site of palpation but within the boundary of the muscle	Confirmation of pain location(s) in the temporalis/masseter muscle(s); and report of familiar pain with palpation of the temporalis/masseter muscle(s); and report of pain spreading beyond the site of palpation but within the boundary of the muscle.	
TMD: Myofascial pain with referral	Pain in last 30 days of muscle origin as described for myalgia with referral of pain beyond the boundary of the muscle. Spreading pain may also be present.	Confirmation of pain location(s) in the temporalis/masseter muscle(s); and report of familiar pain with palpation of the temporalis/masseter muscle(s); and report of pain at a site beyond the boundary of the muscle being palpated.	
TMD: Arthralgia	Pain in last 30 days of joint origin that is affected by jaw movement, function, or parafunction.	Confirmation of pain location in the area of the TMJ(s); and report of familiar pain in the TMJ with Palpation of the lateral pole/around the lateral pole; OR Maximum unassisted or assisted opening, lateral, or protrusive movement(s).	
Acute dental pain (ADP): symptomatic irreversible pulpitis	Sharp pain upon thermal stimulus, lingering pain, spontaneity (unprovoked pain) and referred pain	Deep caries, extensive restorations, or fractures exposing the pulpal tissues. Pulp testing positive for increased pain	It may be crown radiolucency
Acute dental pain (ADP): symptomatic apical periodontitis	Painful response to biting and/or percussion or palpation	Pain to percussion and/or palpation	It may be periapical radiolucency

Table 2. Demographics, socioeconomics, and pain characteristics for all five groups.

	PDAP n= 14	TN n= 19	TMD n= 41	ADP n= 41	CONTROL n= 21	P-VALUE*
Mean age (SD)	53 (11.96)	62 (17.64)	45 (17.45)	48 (11.85)	45 (13.59)	0.0015
Gender (female)	86%	63%	85%	56%	62%	0.14
Race (white)	100%	96%	90%	78%	90%	**
Income (>$50,000/year)	50%	42%	39%	59%	52%	0.12
Education (at least some college)	79%	84%	83%	85%	100%	0.0002
Toothache (yes)	79%	47%	29%	100%	0%	0.0001
Mean duration of the pain in the last 6 months in days (SD)	174 (16.46)	119 (68.07)	118 (66.04)	50 (60.84)	0.48 (1.50)	0.0001
Mean pain intensity now (0-10/10) (SD)	4.79 (2.91)	3.42 (3.25)	3.80 (2.16)	4.76 (2.52)	0.62 (0.50)	0.0001
Mean worst pain intensity (0-10/10) (SD)	6.64 (2.62)	8.89 (1.37)	7.31 (2.09)	6.68 (2.79)	0.67 (0.48)	0.0001

* Kruskal-Wallis test

** P-value for race was not possible because of group sizes

Table 3. Results for sensitivity, specificity, positive and negative predictive values

	Neuropathic group vs Non-neuropathic and Controls		PDAP vs Non-neuropathic	
	Yes (SA, A)	Yes (SA, A, NAD)	Yes (SA, A)	Yes (SA, A, NAD)
Sensitivity (95% CI)	27 (13-46)	52 (34-69)	29 (8- 58)	64 (35- 87)
Specificity (95% CI)	80 (71-87)	70 (60-79)	74 (64-83)	63 (52-74)
PPV (95% CI)	30 (15-49)	35 (22-51)	16 (5-36)	23 (11-39)
NPV (95% CI)	77 (68-85)	82 (72-89)	86 (76-93)	91 (81-97)

SA=Strongly Agree. A=Agree. NAD=neither agree nor disagree. PPV=positive predictive value. NPV= negative predictive value

Table 4. Results of item analysis for neuropathic pain group

Neuropathic group vs Non-neuropathic and Controls

	Yes (SA, A)				Yes (SA, A, NAD)			
	(%) (95% CI)				(%) (95% CI)			
Item	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
1	33 (18-52)	80 (71-87)	34 (19-53)	79 (70-86)	48 (31-66)	75 (65-83)	38 (24-54)	82 (73-89)
2	6 (1-20)	96 (90-99)	33 (4-78)	76 (68-83)	18 (7-35)	78 (68-85)	21 (8-40)	75 (65-83)
3	58 (39-75)	52 (42-62)	28 (18-40)	79 (68-88)	70 (51-84)	48 (38-58)	30 (20-41)	83 (71-92)
4a	58 (39-75)	84 (75-99)	53 (35-70)	86 (78-92)	67 (48-82)	73 (63-81)	44 (30-59)	87 (78-93)
5	33 (18-52)	85 (77-91)	42 (23-63)	80 (71-87)	55 (36-72)	77 (67-84)	43 (28-59)	84 (75-91)
6	45 (28-64)	67 (57-76)	31 (18-45)	79 (69-87)	55 (36-72)	59 (49-69)	30 (19-43)	80 (70-89)
7	52 (34-69)	50 (40-60)	25 (15-36)	76 (64-86)	55 (36-72)	58 (48-68)	30 (19-43)	80 (70-88)

SA=Strongly Agree. A=Agree. NAD=neither agree nor disagree. PPV=positive predictive value. NPV= negative predictive value

Table 5. Results of item analysis for PDAP only

PDAP vs Non-neuropathic								
Yes (SA, A)					Yes (SA, A, NAD)			
(%) (95% CI)					(%) (95% CI)			
Item	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
1	36 (13-65)	74 (64-83)	19 (7-39)	87 (77-94)	50 (23-77)	70 (58-79)	22 (9-40)	89 (79-95)
2	14 (2-43)	95 (88-99)	33 (4-78)	87 (78-93)	36 (13-65)	73 (62-82)	19 (6-38)	87 (77-94)
3	50 (23-77)	40 (30-52)	13 (5-24)	83 (67-93)	57 (29-82)	35 (25-47)	13 (6-24)	83 (66-93)
4a	36 (13-65)	79 (69-87)	23 (8-45)	88 (78-94)	50 (23-77)	67 (56-77)	21 (9-38)	89 (78-95)
5	43 (18-71)	82 (72-89)	29 (11-52)	89 (80-95)	71 (42-92)	72 (61-81)	30 (16-49)	94 (85-98)
6	57 (29-82)	59 (47-69)	19 (9-34)	89 (77-96)	71 (42-92)	50 (39-61)	20 (10-33)	91 (79-98)
7	71 (42-92)	37 (26-48)	16 (8-28)	88 (73-97)	71 (42-92)	28 (19-39)	15 (7-25)	85 (66-96)

SA=Strongly Agree. A=Agree. NAD=neither agree nor disagree. PPV=positive predictive value. NPV= negative predictive value

Figure 1. Modified S-LANSS for intraoral pain

1. I have 'pins and needles', tingling or prickly sensations in the area where I have pain. **(5)**

   STRONGLY DISAGREE DISAGREE NEITHER AGREE NOR DISAGREE AGREE STRONGLY AGREE

2. The painful area in my mouth changes color (*perhaps looks more mottled or more red*) when the pain is particularly bad. **(5)**

   STRONGLY DISAGREE DISAGREE NEITHER AGREE NOR DISAGREE AGREE STRONGLY AGREE

3. My pain makes the affected tooth, gum or mouth region abnormally sensitive to touch. *Getting unpleasant sensations when lightly stroking the tooth, gum or mouth region, or getting pain when food touches that area inside your mouth might describe this abnormal sensitivity*. **(3)**

   STRONGLY DISAGREE DISAGREE NEITHER AGREE NOR DISAGREE AGREE STRONGLY AGREE

4a. My pain comes on suddenly and in bursts for no apparent reason when I'm still. *Words like electric shock, jumping and bursting describe these sensations.* **(2)**

   STRONGLY DISAGREE DISAGREE NEITHER AGREE NOR DISAGREE AGREE STRONGLY AGREE

4b. On about how many days have you had tooth, gum or mouth pain in the past 6 months? (Every day = 180 days)

   ___ ___ ___**DAYS**

5. In the region where I have pain, it feels as though the temperature has changed abnormally. *Words like hot and burning describe these sensations.* **(1)**

STRONGLY DISAGREE DISAGREE NEITHER AGREE NOR DISAGREE AGREE STRONGLY AGREE

6. *Gently **rub** the painful area with your index finger and then rub a non-painful area (for example, an area of gum tissue on the opposite side of your mouth).* **(5)**

   After rubbing the painful area I feel discomfort, like pins and needles, tingling or burning in the painful area that is different from the non-painful area.

STRONGLY DISAGREE DISAGREE NEITHER AGREE NOR DISAGREE AGREE STRONGLY AGREE

*7. Gently **press** on the painful area with your finger tip then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question).* **(3)**

   After pressing on the painful area I feel numbness or tenderness in the painful area that is different from the non-painful area.

STRONGLY DISAGREE DISAGREE NEITHER AGREE NOR DISAGREE AGREE STRONGLY AGREE

Figure 2. 2x2 tables and formulas

	Gold standard disease +	Gold standard disease -
Test results disease +	A	B
Test results disease -	C	D

Sensitivity: A/A+C

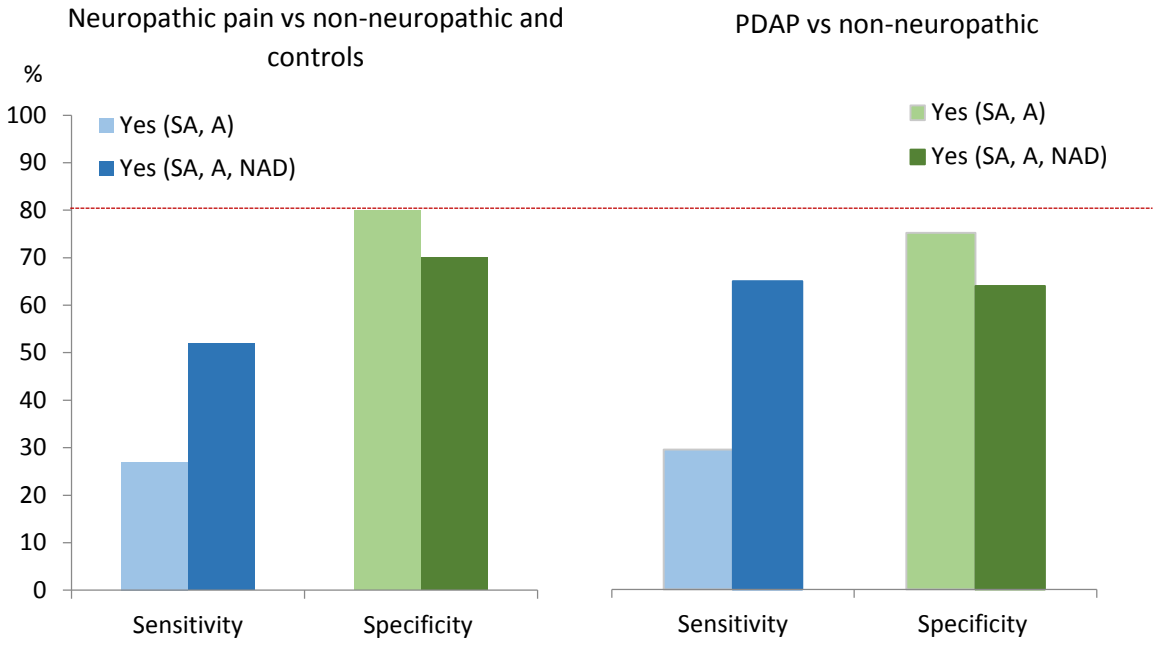
Specificity: B/B+D

Positive predictive values: A/A+B *

Negative predictive values: C/C+D *

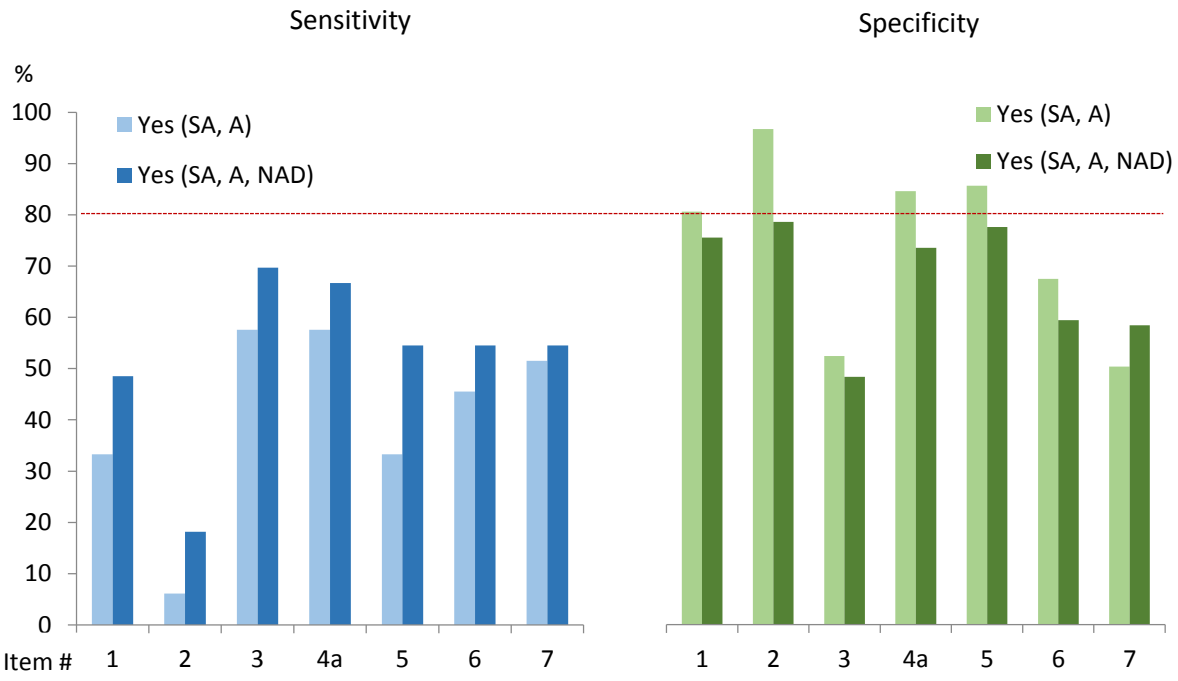
* Positive and negative predictive values should be interpreted with caution because these calculations are dependent on the prevalence of the disorder(s) and the population of interest, and this study sample was not generated to represent a specific population.

Figure 3. Sensitivity and specificity with different positive thresholds for neuropathic pain group vs non-neuropathic pain group and controls comparison, and PDAP vs non-neuropathic pain group comparison.



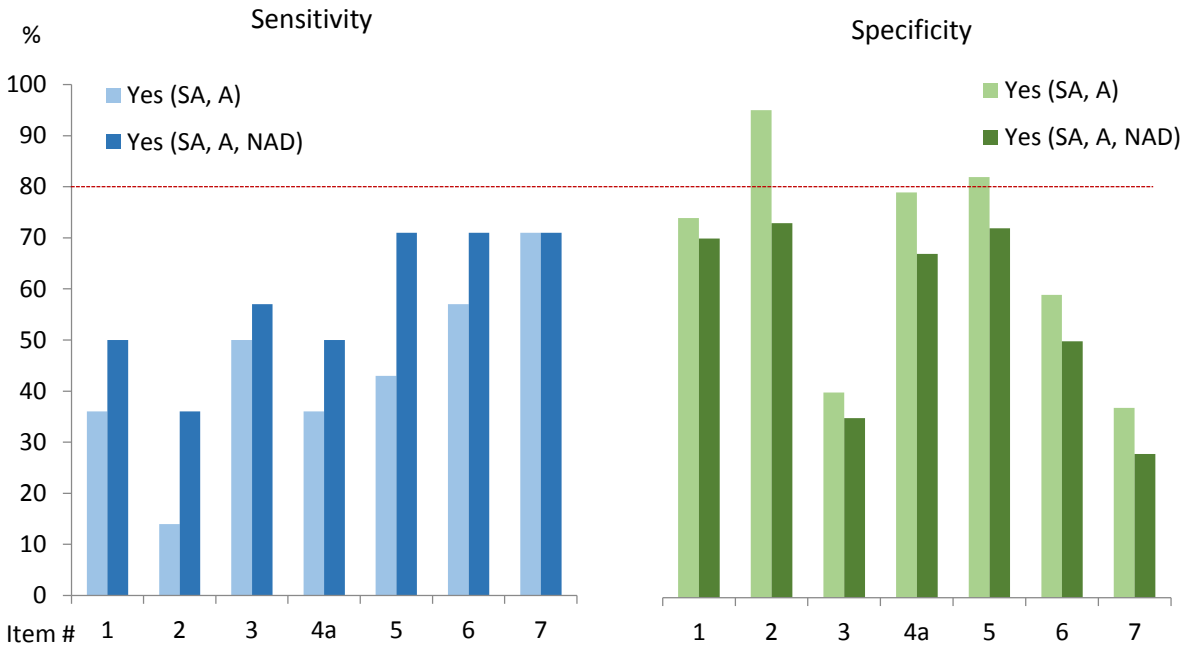
SA=Strongly Agree. A=Agree. NAD=neither agree nor disagree.

Figure 4. Sensitivity and specificity per question with different positive thresholds for neuropathic pain group vs non-neuropathic and controls comparison.



SA=Strongly Agree. A=Agree. NAD=neither agree nor disagree.

Figure 5. Sensitivity and specificity per question with different positive thresholds for PDAP group vs non-neuropathic group comparison.



SA=Strongly Agree. A=Agree. NAD=neither agree nor disagree.

(1) Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008 Apr 29;70(18):1630-1635.

(2) van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain 2014 Apr;155(4):654-662.

(3) Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003 Nov;60(11):1524-1534.

(4) Closs SJ, Staples V, Reid I, Bennett MI, Briggs M. The impact of neuropathic pain on relationships. J Adv Nurs 2009 Feb;65(2):402-411.

(5) Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015 Feb;14(2):162-173.

(6) Freynhagen R, Bennett MI. Diagnosis and management of neuropathic pain. BMJ 2009 Aug 12;339:b3002.

(7) Andrew R, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. Pain Pract 2014 Jan;14(1):79-94.

(8) Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. Neurology 2007 Apr 10;68(15):1178-1182.

(9) Zakrzewska JM, Linskey ME. Trigeminal neuralgia. BMJ Clin Evid 2014 Oct 6;2014:1207.

(10) van Kleef M, van Genderen WE, Narouze S, Nurmikko TJ, van Zundert J, Geurts JW, et al. 1. Trigeminal neuralgia. Pain Pract 2009 Jul-Aug;9(4):252-259.

(11) Baad-Hansen L. Atypical odontalgia - pathophysiology and clinical management. J Oral Rehabil 2008 Jan;35(1):1-11.

(12) Nixdorf DR, Drangsholt MT, Ettlin DA, Gaul C, De Leeuw R, Svensson P, et al. Classifying orofacial pains: a new proposal of taxonomy based on ontology. J Oral Rehabil 2012 Mar;39(3):161-169.

(13) Marbach JJ, Hulbrock J, Hohn C, Segal AG. Incidence of phantom tooth pain: an atypical facial neuralgia. Oral Surg Oral Med Oral Pathol 1982 Feb;53(2):190-193.

(14) Brooke RI. Atypical odontalgia. A report of twenty-two cases. Oral Surg Oral Med Oral Pathol 1980 Mar;49(3):196-199.

(15) Polycarpou N, Ng YL, Canavan D, Moles DR, Gulabivala K. Prevalence of persistent pain after endodontic treatment and factors affecting its occurrence in cases with complete radiographic healing. Int Endod J 2005 Mar;38(3):169-178.

(16) Nixdorf D, Moana-Filho E. Persistent dento-alveolar pain disorder (PDAP): Working towards a better understanding. Rev Pain 2011 Dec;5(4):18-27.

(17) Nixdorf DR, Law AS, John MT, Sobieh RM, Kohli R, Nguyen RH, et al. Differential Diagnoses for Persistent Pain Following Root Canal Treatment: A Study in the National Dental PBRN. Northwest Dent 2015 Jul-Aug;94(4):33-40.

(18) Gonzalez YM, Schiffman E, Gordon SM, Seago B, Truelove EL, Slade G, et al. Development of a brief and effective temporomandibular disorder pain screening questionnaire: reliability and validity. J Am Dent Assoc 2011 Oct;142(10):1183-1191.

(19) Hapak L, Gordon A, Locker D, Shandling M, Mock D, Tenenbaum HC. Differentiation between musculoligamentous, dentoalveolar, and neurologically based craniofacial pain with a diagnostic questionnaire. J Orofac Pain 1994 Fall;8(4):357-368.

(20) Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. J Pain 2005 Mar;6(3):149-158.

(21) Bennett MI, Attal N, Backonja MM, Baron R, Bouhassira D, Freynhagen R, et al. Using screening tools to identify neuropathic pain. Pain 2007 Feb;127(3):199-203.

(22) Mathieson S, Maher CG, Terwee CB, Folly de Campos T, Lin CW. Neuropathic pain screening questionnaires have limited measurement properties. A systematic review. J Clin Epidemiol 2015 Aug;68(8):957-966.

(23) Elias LA, Yilmaz Z, Smith JG, Bouchiba M, van der Valk RA, Page L, et al. PainDETECT: a suitable screening tool for neuropathic pain in patients with painful post-traumatic trigeminal nerve injuries? Int J Oral Maxillofac Surg 2014 Jan;43(1):120-126.

(24) Klasser GD, Kugelmann AM, Villines D, Johnson BR. The prevalence of persistent pain after nonsurgical root canal treatment. Quintessence Int 2011 Mar;42(3):259-269.

(25) Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. The Standards for Reporting of Diagnostic Accuracy Group. Croat Med J 2003 Oct;44(5):635-638.

(26) Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Groupdagger. J Oral Facial Pain Headache 2014 Winter;28(1):6-27.

(27) Olesen J. The international classification of headache disorders. 2nd edition (ICHD-II). Rev Neurol (Paris) 2005 Jul;161(6-7):689-691.

(28) Gutmann JL, Baumgartner JC, Gluskin AH, Hartwell GR, Walton RE. Identify and define all diagnostic terms for periapical/periradicular health and disease states. J Endod 2009 Dec;35(12):1658-1674.

(29) Durham J, Exley C, John MT, Nixdorf DR. Persistent dentoalveolar pain: the patient's experience. J Orofac Pain 2013 Winter;27(1):6-13.

(30) Durham J, Nixdorf DR. Healthcare pathway and biopsychosocial impact of persistent dentoalveolar pain disorder: a qualitative study. Int Endod J 2014 Dec;47(12):1151-1159.

(31) Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain 2001 May;92(1-2):147-157.

(32) Shankland WE,2nd. The trigeminal nerve. Part I: An over-view. Cranio 2000 Oct;18(4):238-248.

(33) Renton T, Egbuniwe O. Pain. Part 2a: Trigeminal Anatomy Related to Pain. Dent Update 2015 Apr;42(3):238-40, 242-4.

(34) Klasser GD, Kugelmann AM, Villines D, Johnson BR. The prevalence of persistent pain after nonsurgical root canal treatment. Quintessence Int 2011 Mar;42(3):259-269.

(35) Park RW. Interpreting Epidemiologic Evidence: Strategy for Study Design and Analysis. Healthc Inform Res 2011 Sep;17(3):196-197.

(36) Newton CW, Hoen MM, Goodis HE, Johnson BR, McClanahan SB. Identify and determine the metrics, hierarchy, and predictive value of all the parameters and/or methods used during endodontic diagnosis. J Endod 2009 Dec;35(12):1635-1644.

(37) Lerman SF, Rudich Z, Brill S, Shalev H, Shahar G. Longitudinal associations between depression, anxiety, pain, and pain-related disability in chronic pain patients. Psychosom Med 2015 Apr;77(3):333-341.

(38) Manfredini D, Borella L, Favero L, Ferronato G, Guarda-Nardini L. Chronic pain severity and depression/somatization levels in TMD patients. Int J Prosthodont 2010 Nov-Dec;23(6):529-534.

(39) Tomoyasu Y, Higuchi H, Mori M, Takaya K, Honda Y, Yamane A, et al. Chronic orofacial pain in dental patients: retrospective investigation over 12 years. Acta Med Okayama 2014;68(5):269-275.

(40) Basser DS. Chronic pain: a neuroscientific understanding. Med Hypotheses 2012 Jan;78(1):79-85.

(41) Gerschman JA. Chronicity of orofacial pain. Ann R Australas Coll Dent Surg 2000 Oct;15:199-202.