

Characteristics of Pain Assessed with Visual Analog Scale and Questionnaire in Burning Mouth Syndrome Patients: A Pilot Study

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***Aims:** To test the validity of the use of the Douleur Neuropathique en 4 Questions (DN4) questionnaire for burning mouth syndrome (BMS) patients, and to differentiate patients by measuring the time course of the pain in BMS patients over a period of 7 days with a visual analog scale (VAS). **Methods:** Patients completed the DN4 questionnaire and a VAS every hour for 7 days. The data were expressed as mean \pm SEM. Correlations were searched using the Spearman correlation test with a significance level at $P < .05$. **Results:** Data were fully analyzed for the 22 patients (21 females, 1 male, mean [\pm SEM] age 62.7 \pm 2.3 years) for the DN4 and 17 patients for the VAS. DN4 scores ranged from 2 to 7 (mean score: 3.9 \pm 0.3), and 59% of the patients had a DN4 score \geq 4. Burning was found in all the patients, followed by pricking pain (pins and needles) and allodynia (pain on brushing) (both 68%), tingling (45%), numbness (32%), itching (27%), and electrical discharges (23%). Monitoring the hourly time-course of the pain led to the identification of two groups with intermittent or constant pain. In the latter, averaging the VAS for 7 days enabled plotting a curve, the slope of which could be calculated. The range of the slopes was 0.00 to 0.59, and a regular increase of pain during the day was seen for the majority of the patients. **Conclusion:** The findings support the use of DN4 as a tool for screening BMS and reinforce the view that BMS is a clinical manifestation of a neuropathic disease. The methodology of this study can be used for a better description of the patients and the identification of subgroups. J OROFAC PAIN 2013;27:235–242. doi: 10.11607/jop.1038*

Key words: burning mouth syndrome, DN4, pain, visual analog scale

Primary burning mouth syndrome (BMS), also called stomatodynia, is a poorly understood condition with persistent pain of the oral cavity reported as the main complaint. It forms a distinct subgroup among other chronic idiopathic orofacial pains.¹ The prevalence of the disease in the general adult population is low (3.7%), but it increases with age in both women and men, up to 12% in women aged 60 to 69 years.² The most affected group is postmenopausal women.^{3–5}

The physiopathology of BMS is unclear,⁶ but the previously hypothesized “psychogenic” origin has been seriously challenged by numerous studies indicating neuropathic changes occur in BMS patients. Sensory alterations have been described; these include hypoesthesia,⁷ modifications in heat tolerance at the tip of the tongue,⁸ and abnormalities in both the blink reflex⁹ and somatosensory evoked potentials.¹⁰ In addition, histologic examinations of tongue biopsy specimens have revealed alterations in trigeminal somatosensory nerve fibers that reflect axonal degeneration in the epithelial and subpapillary nerve fibers. BMS patients had a lower density of

intraepithelial nerve fibers than a control group,¹¹ and another BMS study reported a higher expression of nerve growth factor (NGF) and TRPV1 (transient receptor potential for vanilloids, type 1) that correlated with pain scores.¹² For these reasons, BMS has been included in the group of small-fiber neuropathies.¹³ However, the effects of anesthesia of lingual peripheral nerve fibers^{14,15} and the differential therapeutic effect of topical clonazepam¹⁶ suggest central as well as peripheral mechanisms are involved. A central impairment is also suggested by imaging studies, which showed alterations of dopaminergic descending controls^{17,18} and cerebral hypo-function.¹⁹

Beyond these insights, the concept of BMS as an entity is challenged by several observations focusing on a mechanism-based comprehension of the disease and by the existence of subgroups of patients with different etiopathogenic mechanisms. In line with this, Jääskeläinen²⁰ recently proposed the existence of three subgroups of BMS patients, with possible consequences for the treatment of the affliction, which is, at the moment, still evolving.^{21,22} Interestingly, BMS patients do not report identical clinical behavior, especially regarding the time course of the pain and the description of their sensations,²³ suggesting that both the time course and perceptual differences between patients could be the clinical expressions of different mechanisms.

Recently, the DN4 (Douleur Neuropathique en 4 questions), a neuropathic pain questionnaire of great clinical interest, has been introduced for neuropathic pain, thus enabling a rapid evaluation of patients with putative neuropathic pain.²⁴ It is composed of 10 items related to the quality of both spontaneous and evoked sensations and has been validated for several types of neuropathic pain with good sensitivity (82.9%) and specificity (89.9%). Considering the likely neuropathic nature of BMS, it may be useful for the specific population of BMS patients. Therefore, the aims of this study were to: (1) test the validity of the use of the DN4 questionnaire for BMS patients and (2) differentiate patients by measuring the time course of the pain in BMS patients over a period of 7 days with a visual analog scale (VAS).

Materials and Methods

Diagnostic, Inclusion, and Exclusion Criteria

Subjects included in this study were patients seeking treatment for persistent pain of the oral mucosa in the dental and maxillofacial service of the Groupe Hospitalier Pitié Salpêtrière (GHPS) in Paris, France.

They were included in this study between 2008 and 2010 after anamnesis, clinical examination, and laboratory examination. They all complained of a painful or unpleasant sensation in the mouth in the absence of alterations in the appearance of the oral mucosa or any local or systemic diseases. Inclusion and exclusion criteria followed previously published suggestions in order to include only primary (idiopathic) BMS.^{23,25}

Inclusion criteria were: symptoms of pain in the tongue and/or oral mucosa associated or not associated with subjective oral dryness or loss or alteration of taste sensation; pain present almost every day; pain present for at least 3 months; normal aspect of the oral mucosa; and absence of systemic disorders or laboratory alterations known to be associated with orofacial pain. Exclusion criteria were: subjects under 18 and above 80 years of age; local and regional etiologic explanation for the burning, such as alteration of the oral mucosa, traumatic prosthesis, hyposalivation, and local pathology possibly associated with oral pain (herpes, lichen planus, allergic stomatitis, mucitis); history of systemic disease possibly associated with burning pain (eg, diabetes, anemia, cerebrovascular diseases, multiple sclerosis, malignancies, Sjögren syndrome, lupus, Lyme disease, etc); nutritional deficiencies (vitamins B, iron); allergies to certain food or dental materials; gastroesophageal reflux disorder; use of medications known to be associated with oral burning and/or alteration of taste or sensation, such as angiotensin-converting-enzyme inhibitors and diuretics, anti-vascular endothelial growth factor, neuroleptics, etc; other trigeminal pain, eg, temporomandibular joint pain, all forms of identified trigeminal neuralgias; cognitive, linguistic, and/or communication impairment; inability to understand how to complete the DN4 questionnaire and/or VAS; subjects involved at the same time in another biomedical research; subjects without social insurance.

All patients included in the study had laboratory tests completed to rule out secondary BMS, ie, blood levels of vitamins B6, B9, B12; ferritin; thyroid stimulating hormone, glucose and microbial search (*Candidiasis* and *Helicobacter Pylori*).

Allergy investigations were performed only when clinically suspected and consisted of the standard cutaneous patch tests according to the European Environmental and Contact Dermatitis Research Group (EECDRG),²⁶ with additional tests including metals (mercury, gold, palladium, platinum), acrylic resin components and several oral hygiene products.

When diagnosed with primary BMS, patients were invited to enter the study. The study was approved by the board of the dental service of the GHPS. All

patients agreed to participate and gave written consent in accordance with the Declaration of Helsinki. Patients included in this study filled out the DN4 questionnaire and a VAS for pain (mean score overall for the past week). Then they were asked to complete a 1-week record of their pain with a VAS.

VAS. Patients were given a charting log with a printed 0 to 10 VAS and asked to fill in the VAS for each hour of a day, for 7 days, starting upon awakening and finishing when they went to sleep; 0 was defined as the absence of pain and 10 the maximal pain imaginable. The VAS was collected at the recall visit within 2 weeks after completion of the VAS chart. The examiner then measured the scores and transferred them to a spreadsheet for data analysis. The VAS has already been used in numerous studies on BMS.^{5,25,28-30} If the time of recording interfered with meal time, the patients were asked to report the pain score just before or immediately after the food intake. They were also specifically asked if eating suppressed the pain perception.

DN4. The DN4 is composed of 10 items (Fig 1). The first seven items, called the DN4 interview, are sensory descriptors that may be applicable to the patient's pain. The other three items are related to physical examination-induced signs (touch hypoesthesia, pricking hypoesthesia, and brushing). For each positive item on the DN4, one point is assigned; a score of 4 indicates a probable neuropathic pain. The DN4 was administered by the same examiner, a professor at the dental school with prior experience using this questionnaire in orofacial pain patients. For the tactile static clinical evaluation (item 8), the patient was asked to open his/her mouth and a cotton swab was gently applied first onto the oral mucosa of the cheek, 1.0 cm behind the angle of the lips and 0.5 cm below the intermaxillary keratinized line; this area was symptom-free in all patients, and all patients could feel the contact of the cotton swab. The swab was then applied to the tip of the tongue with approximately the same pressure and the patient asked if he/she felt the contact of the cotton swab. The procedure was repeated three times. The pain prick assessment (item 9) was performed with the sharp end of a dental #6 probe and followed the same protocol, paying attention not to injure the tissue with the probe. For dynamic allodynia (item 10), the cotton swab was rubbed three times at the tip of the tongue.

Data Analyses

The data were collected and analyzed using SPSS version 14.0. The different quantitative variables are expressed in terms of their mean and standard error

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 have one or more of the following characteristics?

	yes	no
1- Burning	<input type="checkbox"/>	<input type="checkbox"/>
2- Painful cold	<input type="checkbox"/>	<input type="checkbox"/>
3- Electric shocks	<input type="checkbox"/>	<input type="checkbox"/>

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

	yes	no
4- Tingling	<input type="checkbox"/>	<input type="checkbox"/>
5- Pins and needles	<input type="checkbox"/>	<input type="checkbox"/>
6- Numbness	<input type="checkbox"/>	<input type="checkbox"/>
7- Itching	<input type="checkbox"/>	<input type="checkbox"/>

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	<input type="checkbox"/>	<input type="checkbox"/>
9- Hypoesthesia to prick	<input type="checkbox"/>	<input type="checkbox"/>

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

	yes	no
10- Brushing	<input type="checkbox"/>	<input type="checkbox"/>

Fig 1 DN4 questionnaire (from Bouhassira et al²⁴).

of the mean (SEM), whereas the qualitative variables are given as their absolute value and percentage. The correlations between data were tested by using the Spearman correlation test for nonparametric data. The level of significance was fixed at $P < .05$.

Results

Description of the Sample

Twenty-two patients were diagnosed with primary BMS, and they completed the DN4 and VAS. At the recall visit 2 weeks later, 3 patients had not properly completed the VAS score and 2 did not attend the second visit, which resulted in 22 questionnaires to be analyzed for DN4 and 17 for VAS. One patient took a nap, in the morning, which temporarily interrupted the VAS recording. Among the primary BMS patients, 21 were females and 1 was male. The mean age \pm SEM of the sample was 62.7 ± 2.3 . In the female group, 18 were menopausal women, 1 reported irregular menstrual cycles, 1 had history

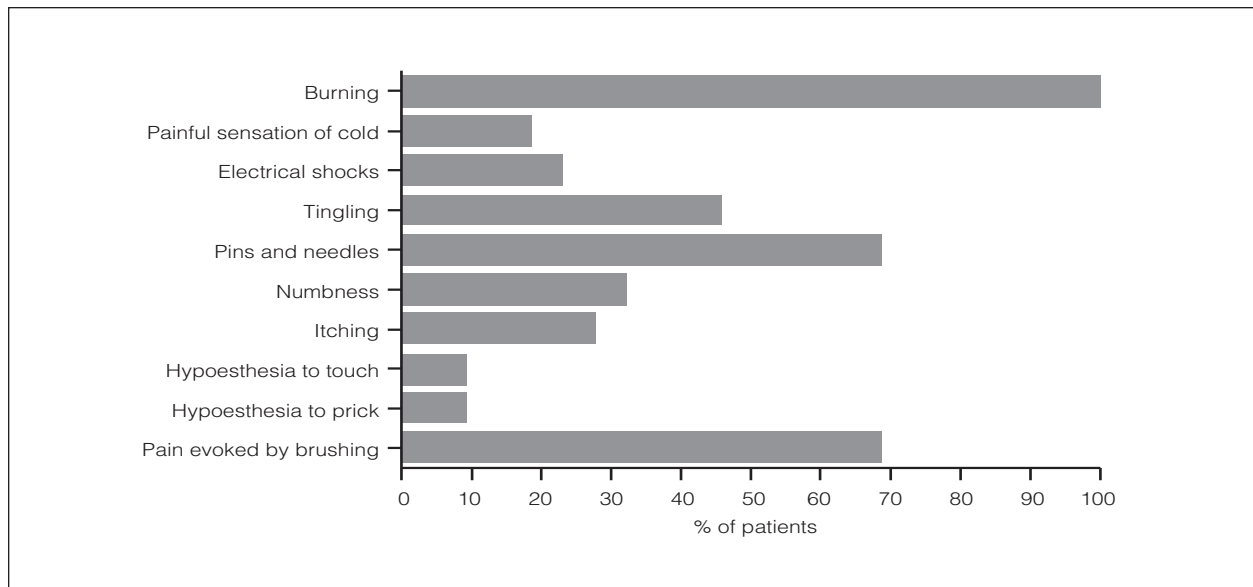


Fig 2 Distribution of the items of the DN4 questionnaire, expressed as percentage of the sample (n = 22).

Table 1 Main Characteristics of the Sample

Patient	Age (y)	Sex	Duration of pain (mo)	Type of pain	VAS	DN4
MOH	36	F	36	I	2.0	4
DAL	59	F	12	I	0.2	2
FOR	55	F	24	I	1.1	4
KOZ	64	F	48	I	1.1	4
KIL	83	F	8	I	0.3	2
GUE	55	M	18	I	1.3	5
FAB	73	F	84	C	5.4	6
LAT	62	F	72	C	5.0	4
PET	70	F	36	C	5.8	3
PEN	44	F	84	C	2.5	2
MIS	68	F	3	C	2.4	5
CUV	69	F	24	C	4.9	3
LEV	64	F	72	C	6.2	3
LEM	63	F	13	C	2.4	5
NOU	78	F	96	C	3.6	4
AUD	66	F	48	C	6.2	3
CRI	70	F	24	C	5.3	4
KAP	56	F	6	C	0.2	3
GON	72	F	180	C	9.4	4
LEI	57	F	48	C	8.9	7
FEB	60	F	72	C	3.3	7
BAS	55	F	24	C	6.7	2
Mean	62.7		46.9		3.8	3.9
SEM	2.3		8.7		0.6	0.3

I = intermittent pain; C = continuous pain. The VAS score is the average pain felt during the week preceding the examination.

of a progesterone implant, 1 had undergone gonadectomy 8 years ago, and 1 was problem-free. The general features of the sample are given in Table 1. The pain was mainly felt at the tip of the tongue and to a smaller extent in other mucosal regions (principally retroincisal palate and lower lip, data not shown).

DN4 and VAS. The mean duration of the symptoms was 46.9 ± 8.7 months (range, 3 to 180 months). The mean pain score during the previous week for the overall sample was 3.8 ± 0.6 . DN4 scores ranged from 2 to 7 with a mean score of 3.9 ± 0.3 . All the patients had at least two items indicative of neuropathic pain, and most of them had three (82%). Of the 22 patients, 13 (59%) had a DN4 score ≥ 4 . Burning was found in all the patients (Fig 2), followed by pricking pain (pins and needles) and allodynia (pain on brushing) (both 68%), tingling (45%), numbness (32%), itching (27%), and electrical discharges (23%). Less-often encountered symptoms were cold pain (18%) and tactile and pricking hypoesthesia (both 9%). For patients with a DN4 ≥ 4 , the most frequent association was burning (100%), pins and needles, dynamic allodynia, and tingling (all 77%), followed by numbness (54%), itching (38%), cold pain (31%), electrical discharges (15%), and tactile and pricking hypoesthesia (8%). Eight patients out of 22 reported that the pain was suppressed during eating.

The DN4 can also be used in its short form (called DN4i interview or DN4i), considering only the first and second set of questions asked of the patient.²⁴ In the present study, 14 patients out of 22 (64%) had a score of DN4i ≥ 3 .

Examination of individual logs indicated that 6 patients experienced intermittent pain and 11 constant pain. For this latter group, averaging the VAS for the 7 days allowed plotting a curve for each patient, the slope of which could be calculated. In one patient, the pain tended to decrease the last 2 hours of her day, which resulted in a negative slope (-0.07) that was not representative of the pain behavior. For this patient, the slope was calculated only with the ascending side (slope 0.05). The overall range of the slopes in the patients with constant pain was 0.00 to 0.59 . All of these patients, except for one who had a steady pain, which was already present at the time of awakening, had an overall increase of the pain during the day. For 3 patients with constant pain, a slight remission was observed with the advancing day, especially at late evening. For patients with constant pain, there was an overall increase of the pain during the day (equation of the mean curve, $y = 0.21x + 1.85$). No patient was symptom-free for an entire day. Individual examples of pain behaviors are shown in Fig 3.

Significant correlations were found between mean VAS and duration of pain ($r = 0.58$, $P = .004$) and slope/duration of the pain ($r = 0.51$, $P = .03$). No significant correlations were found between DN4/duration, DN4/VAS mean, and DN4/slope.

Discussion

DN4

The DN4 is an interesting tool for neuropathic pain detection, with a sensitivity of 82.9% and specificity of 89.9%,²⁴ which has been validated in a sample of neuropathic pain conditions including nerve trauma (49.5%), postherpetic neuralgia (13.5%), polyneuropathies (13.5%), benign tumor (1.1%), spinal cord injury (5.6%), post-stroke pain (12.4%), and multiple sclerosis (4.5%). It has been used for evaluating a secondary BMS in case there is a lingual nerve lesion,³¹ but not yet for evaluating the neuropathic character of idiopathic BMS. The questionnaire is easy to complete and can be part of the routine clinical evaluation at chairside, complementary to quantitative sensory testing (QST).³² All items were easily understood by the patients. A possible bias may occur in the mechanical sensitivity, which is usually assessed in DN4 by comparing the affected area to an adjacent non-affected area or to the same contralateral area. This is not possible in BMS, where dysesthesias are mostly bilateral at the tip of the tongue but also often affect the back of the tongue. It was then decided to compare the

mechanical sensations at the tip of the tongue with those at the cheek mucosa. A cotton swab was used as a nonpainful tactile stimulus and a sharp dental probe as a painful stimulus instead of von Frey hairs, which are not part of the usual equipment in the dental office. Another option would have been to compare absolute mechanical thresholds obtained with von Frey hairs to a reliable database of normal subjects, but such a database is lacking.^{33,34}

In the present study, all the patients had at least two items of neuropathic pain and most of them had three (82%); 59% of them had a score above cut-off, indicating that BMS can be regarded as a neuropathic pain for a majority of patients. This finding is another indication of the neuropathic nature of BMS, at least for some of the patients. The use of the DN4 allowed the researchers to quantify the observation of different sensory components, and this finding may be useful for further interstudy comparisons. Burning pain was confirmed as the main complaint, followed by pricking pain and mechanical allodynia, the latter reinforcing the results of Ito et al,³⁵ who observed that mechanical stimulation of the tongue elicited stronger and longer pain than thermal stimulation. This observation can be useful for building animal models of BMS.

Time Course of the Pain

It can be argued that filling out a questionnaire every hour for 7 days may result in excessive attention on the part of the patient towards his/her pain and subsequently modify the pain perception,³⁶ but VAS is, nevertheless, considered a reliable measure when monitoring pain on a long-term basis.^{37,38} Taking charts of VAS scores over a period of 7 days and calculating subsequent VAS mean slopes allowed the researchers to differentiate two groups of patients: a group with intermittent pain and a group experiencing continuous pain that increased during the day. This method permitted a better description of the pain behavior than previous reports that gave only its general features. For example, Grushka⁴ described the pain of BMS patients as rising slowly throughout the day for all patients of the sample: "The burning may progressively increase throughout the day, reaching its greatest intensity by late afternoon and into early evening" with variations in the individual time course. "The daily pain pattern was consistent among subjects: burning usually began by midmorning (for 59% of the BMS subjects) or early afternoon (9%), and maximum pain intensity was reached by early evening (75%)." In the present study, some of the patients had constant pain, not increasing during the day and/or sometimes

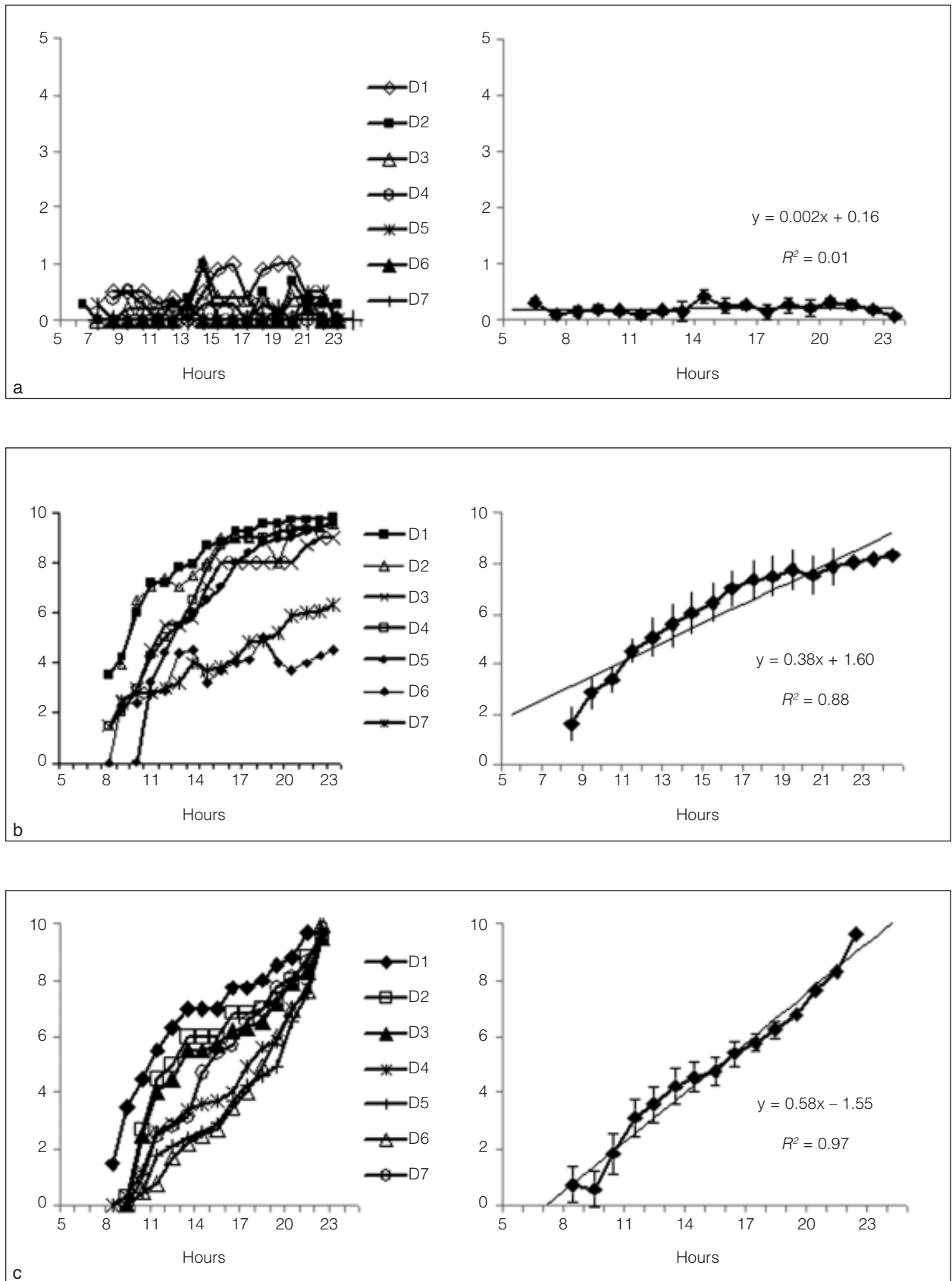


Fig 3 Individual examples of daily VAS time course (left) for each day (D1–D7) and mean VAS over 7 days (right). (a) Intermittent pain. (b and c) Continuous pain with different time courses and slopes.

weakening with the advancing day, especially at late evening, as also recently noted by Forssell et al.³⁹ The method used here leads also to a more precise description of the pain than that of Lamey and Lewis,⁴⁰ who proposed a classification based on the time course of the pain distinguishing three groups: type 1, characterized by a constant pain, of gradual appearance, with a tendency to worsen during the day, reaching maximum intensity at evening, as reported also by Grushka⁴; type 2, characterized by a constant pain, with equal intensity throughout the day; and type 3, in which pain would be intermittent. The results of the present study do not fit with this description. For example, type 1 patients in Lamey and Lewis' study had no pain upon awakening. In the present study, the majority of patients had a small amount of pain at awakening. There is also a discrepancy regarding type 3, described as patients who were symptom-free for days. No patient in the present study was symptom-free for an entire day. It can also be noted that the present method consisted of collecting data without trying to assign a patient to a predefined group, as for example in the Clifford et al study,⁴¹ which asked the patient, with the help of pain profile diagrams based on Lamey and Lewis' classification, to state to which group they belonged.

Conclusions

This study has validated the use of the DN4 for screening patients with BMS and indicates its neuropathic character. Despite the low number of patients included, the findings indicate the methodology is useful for obtaining a better description of the patients' perceptions. The use of standardized charts for the precise location and behavior of the pain will allow interstudy comparisons, or for example, to monitor the transformation of BMS complaints over time. The DN4 can also be used in its short form (DN4 interview or DN4i), suitable, for example, for telephonic epidemiologic surveys. In this study, 14 patients out of 22 (64%) had a score of DN4i ≥ 3 , which is the cut-off with a sensitivity (78%) and specificity (81%).²⁴ The use of the VAS might also be valuable for a more accurate description of the daily behavior of the disease, for example, in trying to correlate circadian biological parameters with the perception of the pain.

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