Clinical Study

Predictors for Persistent Neuropathic Pain – A Delphi Survey

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Background: Chronic neuropathic pain has a major effect on quality of life. In order to prevent neuropathic pain from becoming chronic and improve neuropathic pain care, it is important to identify predictors associated with the persistence of neuropathic pain.

Objective: To identify potential predictors associated with the persistence of neuropathic pain.

Study Design: A 2-round Delphi study.

Setting: University Medical Center and Pain Management Research Center

Methods: A 2-round Delphi study was conducted among 17 experts in the field of neuropathic pain. Selection of the panel was based on the citation index ranking for neuropathic pain-related research and/or membership in the neuropathic pain special interest group of the International Association for the Study of Pain (IASP), complemented with experts with demonstrated field knowledge.

Potential predictors were categorized according to the International Classification of Functioning, Disability and Health model. Participants were asked to identify important predictors, suggest new predictors, and grade the importance on a 0-10 scale. For the second round, predictors were considered important if the median score was ≥ 7 and the interquartile range (IQR) ≤ 3.

Results: In the first round, 20 predictors were selected and 58 were added by the experts (patient characteristics [15], environmental factors [25], functions & structure [4], participation & health related quality of life [14]). In the second round, 12 predictors were considered important (patient characteristics [4; e.g., depression, pain catastrophizing], environmental factors [surgery as treatment for neuropathic pain], functions & structure [6; e.g., allodynia, duration of the complaints], participation & trait anxiety/depression as a part of health related quality of life). Presence of depression and pain catastrophizing were considered the most important predictors for chronic neuropathic pain (median ≥ 8;IQR ≤ 2).

Limitations: The study design did not include plenary discussion among the experts. The meaning of the individual topics used in this study could have been subject to interpretation bias.

Conclusions: Overall, psychological factors and factors related to sensory disturbances were considered important predictors for persistence of neuropathic pain. Activity related factors and previously received paramedical and alternative treatment were considered to be less important. The list of possible predictors obtained by this study may serve as a basis for development of a clinical prediction rule for chronic neuropathic pain.

Key words: Neuropathic pain, chronic pain, persistence, Delphi study, opinion, predictors, ICF model.

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Neuropathic pain (NP) arises as a consequence of activity generated within the nociceptive system without adequate stimulation of its peripheral sensory endings (1). It appears to be more common than initially expected, is associated with more intense pain than other forms of pain, and considerably impairs patients' quality of life (2-7). Currently, approximately 6-8% of the general population reports chronic pain with a neuropathic component (8). Furthermore, due to the aging population, it is assumed that the prevalence of chronic neuropathic pain (CNP) will increase in the future. Therefore, the health care system should provide more efficient care to cope with an increased quantity of patients (5). A variety of factors has been suggested to be associated with the development of CNP.

Knowledge about predictors for CNP may lead to timely identification of patients with a possible adverse disease course, and prompt preventive measures or result in more intensive treatment for patients at risk. Therefore, in order to improve NP care, it is important to identify possible predictors for CNP. From the literature it is known that age (9-17), sex (11,13,18), pain catastrophizing (19), numbness (20), different measures of pain intensity (14,21) — such as the predictive value of the Visual Analog Scale (VAS) > 5 at baseline for postherpetic neuralgia (PHN) at 3 and 6 months (10), and a Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) score ≥ 12 in the postoperative period as a predictor for CNP after 3 months (22) — and prodromal symptoms and intensity of the rash (9,12) have been identified as predictors for NP or CNP. Women (12) and impaired Health-Related Quality of Life (HRQoL) (3) have been described as negative effect-modifying factors. Contrarily, severe depressive symptomatology (23) was reported as a positive effect-modifying factor. Nonetheless, the amount of research performed into identifying predictive factors for NP or the persistence of NP remains limited. However, unpublished scientific knowledge and knowledge gathered in a practical setting may be available, and clinicians and other experts involved in the treatment of neuropathic pain may have an idea about prognostic factors from their clinical experience. This information can be acquired using a Delphi survey technique. This is a method for the systematic collation of judgments, through which agreement can be achieved in a given area of uncertainty when empirical evidence is lacking (24,25). Participants in a Delphi survey do not have to meet face-to-face (24), so it is relatively simple to assemble a group of experts from all over the world (29).

Therefore, by means of a Delphi survey, we sought to identify potential predictors associated with persistent NP.

Methods

A 2-round Delphi survey was conducted among experts in the field of neuropathic pain. The expert panel composition was based on ranking in the citation index for neuropathic pain-related research and/or membership of the working group NEUropathic Pain Special Interest Group (NEUPSIG) of the International Association for the Study of Pain (IASP). The selected experts were required to work in a discipline involved in treating neuropathic pain patients and/or have a wide extent of research or clinical expertise in the field. Furthermore, experts with demonstrable specific field knowledge and coordinators of Dutch pain clinics were invited to participate in the panel of experts. Since the outcome of this study was intended to be used for the development of a prediction rule for a clinical setting, we aimed to include a majority of experts with clinical expertise.

Using e-mail and regular mail, experts were invited to participate in the study. Selected experts received information about the study's goal, the study's importance, the study's procedure and expected time cost; these were accompanied by a request for participation. Three weeks after sending the original invitation, experts who did not respond received a reminder letter and e-mail. Experts who agreed to participate received their first questionnaire within 4 weeks.

The first questionnaire contained a list of possible predictors which were categorized according to the World Health Organization International Classification of Functioning, Disability and Health (ICF) model, i.e., personal factors; environmental factors; functions & structure; activities; and participation and HRQoL (27). Predictors were included on the basis of a literature search and subsequent discussion by our project team.

In the first round's questionnaire, experts were asked to point out factors which they believed to be possible predictors for persistent neuropathic pain. The given answering options were yes, no, or no opinion. The questionnaire consisted of 50 items: 13 items for each of the domains personal factors and environmental factors; 21 items for the domain functions & structure, including symptoms (13 items) and factors of dysregulation (8 items); one item for the domain activi-

Table 1. *Items included in the first questionnaire.*

Personal Patient Factors	Environmental Patient Factors	Functions and Structure
General patient characteristics Age Gender Education Work status Absence or presence of: Depression Trait anxiety Pain coping Pain catastrophizing Fear of movement Physical comorbidity Patient Global Impression of Chance Patient Global Impression of Efficacy Patient Global Expectancy of Prognosis	Social support Complaint related variables: Underlying cause Treatment for neuropathic pain: Drug use Invasive pain treatment Surgery Paramedical treatment Alternative treatment Treatment other than for neuropathic pain: Drug use Invasive pain treatment Surgery Paramedical treatment Alternative treatment	Duration of the complaints Absence or presence of: (Spontaneous) pain Allodynia – general Allodynia – tactile Allodynia – deep pressure Allodynia – movement Hyperesthesia Hypoesthesia Hyperalgesia Hypoalgesia Dysesthesia Paresthesia Hyperpathia Summation / wind-up Dysregulation of: The autonomic nervous system Heart rate variability (HRV) The sensory nervous system Decreased diffuse noxious inhibitory control (DNIC) The endocrine system Abnormal sleep/wake rhythm and/or sleeping problems The immune system Th1/Th2 ratio
Activities	**Participation & HRQoL**	
Activities	Participation Health Related Quality of Life	

ties; and 2 items for participation and HRQoL (Table 1). Experts were invited to add variables and make comments on the provided list of variables. A reminder was sent to experts not responding within one month. As an arbitrary criterion for expert agreement, variables were selected which at least 75% of the experts indicated to be a potential predictor for CNP. These variables were included in the second round.

In the second round questionnaire, participants were asked to grade the importance of the remaining potential predictors of the first questionnaire, along with the items added by the experts, on a Numeric Rating Scale (NRS) (0 = absolutely no possible predictor; 10 = very important possible predictor). Once again, experts were provided with the opportunity to make comments on the list of variables. Also in this round, a reminder was sent to experts who did not respond within the given time range.

In both questionnaires, experts had the opportunity to refrain from answering if they had insufficient knowledge about a specific item. Only data in which an actual judgment was given were included in the analysis. Therefore, percentages were determined with exclusion of the option "no opinion."

The data were processed using MS Excel 2003 (Microsoft Corporation, Redmond, WA). Statistical analyses were performed using the SPSS 15.0 statistical software package (SPSS Inc., Armonk, NY). For selecting the most important predictors for persistent NP, we defined an interquartile range (IQR) classification of ≤ 3 as an indicator for expert agreement. Together with the IQR, we arbitrarily defined the optimal cutoff value at a median of 7, based on procedures followed in a comparable Delphi survey (28).

Results

Out of 43 experts invited, 21 (50%) agreed to participate in the project and returned the first questionnaire. These experts came from the Netherlands (7), the United States of America (7), Germany (3), France (2), Italy (1) and Australia (1). Nine experts declined: 5 because of workload, 3 because of insufficient clinical experience, and one because of retirement. Thirteen experts did not respond to our request. Participating experts were professors or PhDs working in the fields of neurology, anesthesiology, pain research, medical psychology and behavioral science, and a nurse practitioner working in the field of pain.

Table 2. *Possible predictors after the 1st round.*

Main Category	Variable	≥75%
Personal patient factors		
	Age	85.7
	Absence or presence of depression	100
	Absence or presence of trait anxiety	100
	Absence or presence of pain coping	77.8
	Absence or presence of pain catastrophizing	90.5
	Absence or presence of fear of movement	79
	Patient Global Expectancy of Prognosis	90
Environmental factors		
	Underlying cause of the complaints	81
	Surgery as treatment for Neuropathic Pain	75
Functions and structure		
	Duration of the complaints	90
	Symptoms	
	Allodynia – general	82.4
	Allodynia – tactile	82.4
	Hyperpathia	80
	Factors of dysregulation	
	The sensory nervous system	88.9
	Decreased Diffuse Noxious Inhibitory Control (DNIC)	93.8
	The endocrine system	78.6
	Abnormal sleep/wake rhythm and/or sleeping problems	88.2
Activities		
	Activities	88.9
Participation and HRQoL		
	Participation	89.5
	Health Related Quality of Life	100

In the first round, 20 predictors, representing all categories of the model, were considered to be possible predictors for persistent neuropathic pain (Table 2).

For patient characteristics, factors selected by at least 75% of the experts were primarily of a psychological nature, such as the absence or presence of depression (100%), trait anxiety (100%), pain coping (78%), pain catastrophizing (91%) and fear of movement (79%). Also, age (86%) and Patient Global Expectancy of Prognosis (90%) were frequently chosen by the experts. General patient characteristics were selected less often, such as gender (55%), education (38%) and work status (60%). Within the environmental factors category, 2 factors were classified as potential predictors for persistence of NP: underlying cause of the complaints (81%) and surgery as treatment for neuropathic pain (75%). For both subcategories containing specific treatment for NP and treatment in general, the lowest prognostic influence was expected for paramedical treatment (respectively 21% and 7%) and for complementary medicine (respectively 17% and 8%). Regarding the category symptoms of NP within the functions and structure domain, allodynia (82%), tactile allodynia (82%), and hyperpathia (80%) were considered to be

possible predictors. For other symptoms, such as hyperesthesia (60%), hypoalgesia (37%), and paresthesia (40%), experts expected low predictive influence. There was expert agreement for sensory nervous system dysregulation (89%), including the suggested test for decreased diffuse noxious inhibitory control (DNIC) (94%), and for endocrine system dysregulation (79%), including assessment of abnormal sleep/wake rhythm and/or sleeping problems (88%). For immune system dysregulation (64%) and dysregulation of the autonomic system (56%), expert agreement was insufficient for inclusion in the second Delphi round. The item duration of the complaints was also frequently selected by the experts (90%). The factor activities were considered to be a possible predictive factor with a score of 89%. Finally, experts agreed about variables for participation (90%) and HRQoL (100%).

Fifty-eight predictors, distributed over 4 categories—patient characteristics (15), environmental factors (25), functions & structure (4) and participation and HRQoL (14) —were added by the experts (Table 3). Within the latter topic, the addition of variables was a consequence of subdividing HRQoL into 13 constituting components, as suggested by one of the experts.

All variables with an expert agreement of at least 75% (20) were included in the second round, completed with the items added by the experts (58). This second questionnaire was returned by 17 experts, which means 4 experts (19%) dropped out between the first and the second round. Based on the previous defined median cut-off value of 7, together with an IQR $\leq$ 3, 12 items were identified as important predictors for persistent neuropathic pain (Table 4). Nine of these items were previously identified as possible predictors in the first round (absence or presence of depression, trait anxiety, pain coping and catastrophizing, duration of the complaints, surgery as treatment for NP, allodynia, tactile allodynia, and hyperpathia). Three added factors—continued high pain and duration of continuing pain, trait anxiety/depression as part of HRQoL—were also graded as important predictive factors.

Compared to the first round, the personal factors age (median 6, IQR 4), fear of movement (median 6, IQR 3) and Patient Global Expectancy of Prognosis (median 6, IQR 2.5) were not considered important predictors, as was the underlying cause of the complaints (median 7, IQR 3.5) in the domain environmental factors. With regard to factors of dysregulation, neither the sensory nervous system (median 6, IQR 2.5) or the endocrine system (median 5.5, IQR 1.5), nor their suggested assessment techniques (DNIC [median 6, IQR 3]) and abnormal sleep/wake rhythm and/or sleeping problems (median 6, IQR 1), were considered to be important predictors in the second round. Finally, activities (median 6, IQR 2) and participation (median 6, IQR 2) were considered less important.

Based on these expert findings, the strongest predictors for persistence of neuropathic pain were the presence of depression and pain catastrophizing (median $\geq$ 8, IQR $\leq$ 2).

Discussion

In our Delphi study, psychological factors and factors related to sensory disturbances were recognized by the experts as important predictors of persistent neuropathic pain. The most important predictors were the absence or presence of depression and pain catastrophizing. To our knowledge, a Delphi study has not been performed for this purpose before.

The predictors that emerged from this study were distributed over most of the domains covered by the International Classification of Functioning, Disability and Health model (27). In the literature, several of the predictors identified in our study have been named as predictors for the development of neuropathic pain. Specifically, pain coping was reported to be predictive for developing phantom limb pain (29,30), forms of allodynia, and postherpetic neuralgia (PHN) (31,32). In addition, other predictors found in our study were reported previously in the literature as specific predictors for persistent NP. In this context, pain catastrophizing was reported as a predictor for chronic PHN (19), and depression and trait anxiety were both found to be predictors for chronic herpes zoster pain (33). Also, depressive symptomatology was considered to be a negative effect-modifier in people with chronic NP after spinal cord injury (23). Continued high pain intensity was found to be a predictor for chronic herpes zoster pain (33). The latter also proved to be the case for PHN patients (10,34,35). A similar correlation between previously experienced pain and CNP for neuropathic pain disorders in general has been described (13).

Several predictors were identified in this study that were not described previously in the context of development of chronic neuropathic pain. For chronic pain in general, however, most of these predictors have been reported to be predictive for its development. This was the case for trait anxiety/depression as a part of HRQoL (36), previous duration of continuing pain (37), and surgery for neuropathic pain (37-39). Only hyperpathia, a

Table 3. *List of predictors added by the experts after the 1st round.*

Personal Patient Factors	
General patient characteristics:	Religion Satisfaction with work Motivation for continuing work Family factors (congenital) Unresolved grief Anger at circumstances that caused the pain Anger at circumstances instigated by the pain
Physical comorbidity:	Presence of another pain inflicting condition Other physical comorbidity
Mental comorbidity:	Post-traumatic stress disorder Obsessive compulsive disorder Other mental comorbidity
Cognitions	Cognitions of the disease Cognitions of treatment Other cognitive variables
Environmental Patient Factors	
Family situation Family history (i.e., parent with chronic pain) History of childhood abuse Compensation claims / disability payments	
Complaint-related variables:	First causality of the pain Time duration between pain onset and therapy start Number of successful treatments Number of unsuccessful treatments Traumatic cause of the pain
Treatment for neuropathic pain:	Effect of treatment Medication: Dosage and duration of drug use Medication: Effect of medication Invasive pain treatment In case of surgery: Applied technique In case of surgery: Quality of post-operative analgesia In case of surgery: Maximal pain score on VAS-scale In case of surgery: Opioid-induced hyperalgesia
Treatment other than for neuropathic pain:	Effect of treatment Medication: Dosage and duration of drug use Medication: Effect of medication Invasive pain treatment In case of surgery: Applied technique In case of surgery: Quality of post-operative analgesia In case of surgery: Maximal pain score on VAS-scale In case of surgery: Opioid-induced hyperalgesia
Functions and Structure	
History of the pain Duration of continuing pain Continued high pain Extent of the injury	
Activities	None
Participation and HRQoL	
Health-Related Quality of Life	Bodily pain Daily activities Self care Physical functioning Social functioning Mobility Vitality Experienced health Disabilities caused by physical health problems Disabilities caused by emotional problems Trait anxiety/depression Cognition (memory, concentration) Mental health

Table 4. *Important predictors after the 2nd round.*

Predictive Factors	Median	IQR (25-75)
Personal patient factors		
Absence or presence of:		
Depression	8	8-6
Trait anxiety	7	8-6
Pain coping	7	8-5.5
Pain catastrophizing	8	8.5-6.5
Environmental factors		
Surgery as treatment for neuropathic pain	7	8-5
Structure and functions		
Duration of the complaints	7	8-5.5
Duration of continuing pain	7	8-5.5
Continued high pain	7	8-7
Allodynia – general	7	8-5
Allodynia – tactile	7	8-5.5
Hyperpathia	7	8-5.5
Participation and HRQoL		
Trait anxiety/depression as part of HRQoL	7	8-6

painful syndrome characterized by a painful reaction to a repetitive stimulus (40), has not been described in the context of developing either NP or chronic pain.

In addition, the literature provides support for variables which were not among the most important predictors of CNP identified in our study: hypoesthesia (31,35), hyperalgesia (36), age (9,10,13-15,34,39), prodromal symptoms (9), numbness (20), different measures of pain intensity such as LANSS (22) or NRS (21), severity of coetaneous manifestation (35) and DNIC (42).

These discrepancies between our results and the literature findings may be related to the focus of previous reported research on single diseases or specific patient groups. Furthermore, some articles were not specifically aimed at identifying predictors.

We used the ICF model as a conceptual framework to find possible predictors for CNP. We started with factors which represented all domains of the model, in order to depart from a comprehensive perspective of disease development.

However, some domains of the ICF model were considered less important, such as activities, participation, HRQoL, and factors of dysregulation. This agrees with current literature, where the amount of information regarding these domains of the ICF model is generally limited.

The literature provides only a few studies underlining the predictive value of daily activities for a negative disease outcome in neuropathic pain syndromes (34,43). Likewise, only recently a study showed that participation expressed as relations with other people and working ability (indirectly modulated by experienced pain) was predictive for the development of PHN (34). One possible explanation for the fact that activities and participation are only anecdotally described in the context of health status prediction might be that both are normally seen as outcomes of a disease rather than as predictors for disease progression.

One exception was found in the importance the experts ascribed to trait anxiety/depression as a part of HRQoL. The fact that this HRQoL domain stands out may possibly be related to the fact that both trait anxiety and depression were considered important predictors as personal factors in a general sense in this study. Whether developing chronic neuropathic pain and general trait characteristics of anxiety and depression are predictive, or are only predictive in the context of HRQoL, remains to be determined.

All aspects considered, research appears to be required to establish the role of activities, participation, and quality of life as predictors for the disease course of CNP or chronic pain in general.

The findings of our study indirectly relate to pathophysiological perspectives underlying the development of chronic pain. Applying a systems approach, dysregulation of interlinked subsystems, in particular the central nervous system, the endocrine system and immune system, have been postulated as a reason for pain to become chronic (44). Consequently, prolonged dysregulation in one of the subsystems might lead to chronic pain, whereby different pathophysiological mechanisms were suggested as markers for these dysregulations (45) (i.e., decreased heart rate variability and HPA axis disturbances for autonomic dysregulation, decreased DNIC for sensory nervous system dysregulation, sleep disturbances as a marker of endocrine system dysregulation, and skewed Th1/Th2 ratio for immune system dysregulation). Although the system dysregulations proposed as predictors in our study were not directly considered to be important predictors, individual factors associated with these dysregulations (i.e., depression, pain catastrophizing and anxiety for the HPA axis dysbalance, allodynia and hyperpathia for sensory nervous system dysregulation) were identified as important predictors.

One of the advantages of a Delphi survey is the possibility to disclose expert knowledge that is not cap-

tured in the scientific literature. Furthermore, different viewpoints, depending upon the specific background of the expert, can be incorporated in the generation of information. In our study, 58 items were added by the experts, of which 2 were considered as important predictors in the final analysis. Another strength of the procedure followed in the present study is the flexibility that allowed experts to respond at their convenience, without the requirement of travel time (24). The Delphi procedure followed in our study requires high participant motivation, since other people are not present to stimulate individual contributions (24). The limited dropout rate between rounds in our study may be an expression of the value placed by the contributors on the identification of predictors for the disease course of NP. In addition, by inviting experts from different disciplines and continents, the generalizability of the outcome might be increased.

However, some limitations have to be taken into account regarding the method of our investigation. The procedure followed in our study did not allow for plenary discussion of the value of individual predictors. Possibly, another model with a different set of predictors could have emerged as a consequence of the discussion dynamics. On the other hand, our approach allowed the experts to express opinions in relative anonymity. A point of discussion is the number of consultation rounds that have been used in this study. In order to limit the amount of burden for the experts, a 2 round approach, which has been used successfully in previous Delphi procedures, was chosen (28,45). However, other Delphi approaches could have been chosen allowing more than 2 consultation rounds (24), which could have led to different outcomes than found in our study.

Another point of discussion is the possible difference in interpretation of the proposed predictors. Since we provided no additional definition regarding the topics, their meaning could have been subject to interpretation bias. A possible example of this can be found in the difference in acceptance of "paramedical treatment" as a potential predictor for CNP. Dutch experts responded positively on this (where physiotherapy and occupational therapy are referred to as paramedical treatment), whereas none of the other experts chose this option (possibly interpreting this as referring to emergency care). This might also be the case for the rather broad term "activities."

Furthermore, the multidisciplinary background of the experts can also introduce a bias in the direction of the clinical or scientific orientation of the experts in question. For instance, respondents with specific (or exclusive) expertise in the field of postherpetic neuralgia, may choose the predictors related to this specific disease, and these may differ from those in other neuropathic pains. Although the statistical consensus approach used in our study by combining different disciplinary perspectives most probably reduced this directional bias, we cannot rule out a possible influence of this kind. In line with this issue, our approach to identify predictors for persistent neuropathic pain in general did not allow for the identification of disease specific predictors. The clinical value of the predictors identified in this study, and the possible disease specificity of certain predictors, therefore remain to be determined. Whether or not the predictive value of the factors hold true in a clinical setting can only be established in a prospective cohort study following the disease course of acute neuropathic pain patients with a sufficient follow-up period.

How the term "chronic" neuropathic pain is defined needs to be addressed. From a mechanistic perspective, the requirements for persistent complaints of NP may be present from the start, and as such NP by definition should be considered a form of chronic pain. However, in the scope of our study we used the term chronic in a temporal sense, that is, persistent neuropathic pain, in order to distinguish between those cases where neuropathic pain is resolved before the time frame usually considered as a cut off point for chronic pain (i.e., 3-6 months or more) and those that do proceed into the chronic phase. We acknowledge, however, that the definition of chronic pain in general remains an ongoing discussion, and consensus in this regard remains to be established.

Taking all considerations into account, we conclude that the list of possible predictors obtained by this study may serve as a basis for the development of a prediction rule for CNP, which will help identify patients at risk for persistent pain, and enable tailor-made interventions for NP patients, thereby reducing patient and societal burdens associated with NP.

Overall, psychological factors and factors related to sensory disturbances are considered to be important possible predictors for CNP, with the presence of depression and pain catastrophizing indicated as the most important predictors.

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References

1. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. *Neurology* 2008; 70:1630-1635.
2. Doth AH, Hansson PT, Jensen MP, Taylor RS. The burden of neuropathic pain: A systematic review and meta-analysis of health utilities. *Pain* 2010; 149:338-344.
3. Otto M, Bach FW, Jensen TS, Sindrup SH. Health-related quality of life and its predictive role for analgesic effect in patients with painful polyneuropathy. *Eur J Pain* 2007; 11:572-578.
4. Thomson S, Jacques L. Demographic characteristics of patients with severe neuropathic pain secondary to failed back surgery syndrome. *Pain Pract* 2009; 9:206-215.
5. Toth C, Lander J, Wiebe S. The prevalence and impact of chronic pain with neuropathic pain symptoms in the general population. *Pain Med* 2009; 10:918-929.
6. Hegarty D, Goroszeniuk T. Peripheral nerve stimulation of the thoracic paravertebral plexus for chronic neuropathic pain. *Pain Physician* 2011; 14:295-300.
7. Frey ME, Manchikanti L, Benyamin RM, Schultz DM, Smith HS, Cohen SP. Spinal cord stimulation for patients with failed back surgery syndrome: A systematic review. *Pain Physician* 2009; 12:379-397.
8. Freynhagen R, Bennett MI. Diagnosis and management of neuropathic pain. *BMJ* 2009; 339:b3002.
9. Choo PW, Galil K, Donahue JG, Walker AM, Spiegelman D, Platt R. Risk factors for postherpetic neuralgia. *Arch Intern Med* 1997; 157:1217-1224.
10. Coen PG, Scott F, Leedham-Green M, Nia T, Jamil A, Johnson RW, Breuer J. Predicting and preventing post-herpetic neuralgia: Are current risk factors useful in clinical practice? *Eur J Pain* 2006; 10:695-700.
11. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: A maladaptive response of the nervous system to damage. *Annu Rev Neurosci* 2009; 32:1-32.
12. Jung BF, Johnson RW, Griffin DR, Dworkin RH. Risk factors for postherpetic neuralgia in patients with herpes zoster. *Neurology* 2004; 62:1545-1551.
13. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. *Lancet* 2006; 367:1618-1625.
14. Margot-Duclot A, Tournebise H, Ventura M, Fattal C. What are the risk factors of occurence and chronicity of neuropathic pain in spinal cord injury patients? *Ann Phys Rehabil Med* 2009; 52:111-123.
15. Opstelten W, Mauritz JW, de Wit NJ, van Wijck AJ, Stalman WA, van Essen GA. Herpes zoster and postherpetic neuralgia: Incidence and risk indicators using a general practice research database. *Fam Pract* 2002; 19:471-475.
16. Werhagen L, Hultling C, Molander C. The prevalence of neuropathic pain after non-traumatic spinal cord lesion. *Spinal Cord* 2007; 45:609-615.
17. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. Neuropathic pain in diabetes, prediabetes and normal glucose tolerance: The MONICA/KORA Augsburg Surveys S2 and S3. *Pain Med* 2009; 10:393-400.
18. Zuniga JR. Management of third molar-related nerve injuries: Observe or treat? *Alpha Omegan* 2009; 102:79-84.
19. Haythornthwaite JA, Clark MR, Pappagallo M, Raja SN. Pain coping strategies play a role in the persistence of pain in post-herpetic neuralgia. *Pain* 2003; 106:453-460.
20. Nienhuijs SW, Boelens OB, Strobbe LJ. Pain after anterior mesh hernia repair. *J Am Coll Surg* 2005; 200:885-889.
21. Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain* 2003; 103:249-257.
22. Searle RD, Simpson MP, Simpson KH, Milton R, Bennett MI. Can chronic neuropathic pain following thoracic surgery be predicted during the postoperative period? *Interact Cardiovasc Thorac Surg* 2009; 9:999-1002.
23. Rintala DH, Holmes SA, Courtade D, Fiess RN, Tastard LV, Loubser PG. Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Arch Phys Med Rehabil* 2007; 88:1547-1560.
24. Delbecq AL, Van de Ven AH, Gustafson DH. Group techniques for program planning: A guide to nominal group and delphi processes. *Journal of applied behavioral science* 1975; [This reference is incomplete. The journal's Web site archive does not list this article being published in 1975. A book with this title by these authors was published in 1986 by Green Briar Press.]
25. Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CF, Askham J, Marteau T. Consensus development methods, and their use in clinical guideline development. *Health Technol Assess* 1998; 2:i-88.
26. Lindeman CA. Delphi survey of priorities in clinical nursing research. *Nurs Res* 1975; 24:434-441.
27. World Health Organization. International Classification of Functioning, Disability and Health (ICF). WHO, Geneva, 2001.
28. Brunner F, Lienhardt SB, Kissling RO, Bachmann LM, Weber U. Diagnostic criteria and follow-up parameters in complex regional pain syndrome type I--a Delphi survey. *Eur J Pain* 2008; 12:48-52.
29. Hill A. The use of pain coping strategies by patients with phantom limb pain. *Pain* 1993; 55:347-353.
30. Jensen MP, Ehde DM, Hoffman AJ, Patterson DR, Czerniecki JM, Robinson LR. Cognitions, coping and social environment predict adjustment to phantom limb pain. *Pain* 2002; 95:133-142.
31. Haanpaa M, Laippala P, Nurmikko T. Allodynia and pinprick hypesthesia in acute herpes zoster, and the development of postherpetic neuralgia. *JPain*

Symptom Manage 2000; 20:50-58.

32. Haanpaa ML, Laippala PA, Nurmikko TJ. Thermal and tactile perception thresholds in acute herpes zoster. *Eur J Pain* 1999; 3:375-386.
33. Dworkin RH, Hartstein G, Rosner HL, Walther RR, Sweeney EW, Brand L. A high-risk method for studying psychosocial antecedents of chronic pain: the prospective investigation of herpes zoster. *J Abnorm Psychol* 1992; 101:200-205.
34. Drolet M, Brisson M, Schmader K, Levin M, Johnson R, Oxman M, Patrick D, Camden S, Mansi JA. Predictors of postherpetic neuralgia among patients with herpes zoster: A prospective study. *J Pain* 2010; 11:1211-1221.
35. Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. *Pain* 1996; 67:241-251.
36. Smith BH, Torrance N, Bennett MI, Lee AJ. Health and quality of life associated with chronic pain of predominantly neuropathic origin in the community. *Clin J Pain* 2007; 23:143-149.
37. Mackinnon SE, Dellon AL. Results of treatment of recurrent dorsoradial wrist neuromas. *Ann Plast Surg* 1987; 19:54-61.
38. Poobalan AS, Bruce J, King PM, Chambers WA, Krukowski ZH, Smith WC. Chronic pain and quality of life following open inguinal hernia repair. *Br J Surg* 2001; 88:1122-1126.
39. Stokvis A, Henk Coert J, van Neck JW. Insufficient pain relief after surgical neuroma treatment: Prognostic factors and central sensitisation. *J Plast Reconstr Aesthet Surg* 2010; 63:1538-1543.
40. Vissers KC. The clinical challenge of chronic neuropathic pain. *Disabil Rehabil* 2006; 28:343-349.
41. Wilder-Smith OH, rendt-Nielsen L. Postoperative hyperalgesia: Its clinical importance and relevance. *Anesthesiology* 2006; 104:601-607.
42. Yarnitsky D, Crispel Y, Eisenberg, E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M. Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain* 2008; 138:22-28.
43. Ekman P, Moller H, Hedlund R. Predictive factors for the outcome of fusion in adult isthmic spondylolisthesis. *Spine (Phila Pa 1976)* 2009; 34:1204-1210.
44. Chapman CR, Tuckett RP, Song CW. Pain and stress in a systems perspective: Reciprocal neural, endocrine, and immune interactions. *J Pain* 2008; 9:122-145.
45. Dincler S, Bachmann LM, Buchmann P, Steurer J. Predictors of intra- and postoperative complications in laparoscopic colorectal surgery: Results of an expert survey. *Dig Surg* 2006; 23:110-114.