RESEARCH PROTOCOL

The role of sensory parameters in predicting clinical outcome after lumbar discectomy

Dr Brigitte Tampin[1,2,3], Prof Christopher Lind[2], A/Prof Helen Slater[3]

[1]Department of Physiotherapy, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

[2]Department of Neurosurgery, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

[3]School of Physiotherapy and Exercise Science, Curtin University, Perth, Western Australia, Australia

Abstract

Lumbar discectomy is considered a safe, efficacious and cost-effective treatment for selected cases of patients with leg pain associated with the presence of a disc protrusion, but despite technically successful surgery, 30% of patients complain of persistent pain on long-term follow up. Identification of possible predictors for a negative outcome is important, in the search for appropriate pre- and/or post-operative care and prevention of persistent disability. There is some evidence in the literature that quantitative sensory testing (QST) measures may play a role in prediction of patients' pain persistency, however, this has never been investigated in patients undergoing lumbar discectomy.

The aim of this study is to determine the predictive value of QST parameters, in combination with previously documented predictor variables such as medical/psychological/cognitive behavioural factors, in patients with lumbar radiculopathy and/or radicular pain, for predicting patients' clinical outcome after lumbar discectomy.

Participants with radiculopathy and/or radicular pain and confirmed imaging diagnosis of nerve root compression will be recruited from the elective surgery waitlist at one hospital. All participants will undergo lumbar discectomy performed by one neurosurgeon. A standardized QST protocol comprising all of the somatosensory sub-modalities that are mediated by different primary afferents (C-, Aδ-, Aβ-) will be performed prior to surgery. QST will be conducted in the patients' main pain area and contralateral side, in the affected dermatome and at a remote control site. The presence of other predictor variables will be captured by questionnaires. Follow-up at 3 months will include QST and measurements of pain intensity, pain descriptors, functional status, health related quality of life, return to work and health care utilisation. A further 1-year follow-up will include the same measurements except QST.

Identification of new predictor variables may assist in the development of pre-surgical screening methods and in targeted pre- and/or post-operative patient care, with the potential to improve patients' functional status, quality of life, work capacity whilst also reducing health care costs associated with persistent disability.

Trial Registration: The Australian New Zealand Clinical Trials Registry (366797); Ethical approval Sir Charles Gairdner Group Human Research Ethics Committee (HREC 2014-064)

INTRODUCTION

Low back pain is one of the most common health problems and affects 80 – 85% of people over their life time [36]. Low back-related leg pain or sciatica, characterised by radiating pain that follows a dermatomal pattern [53],is a common variation of LBP. The prevalence of sciatic symptoms in the general population ranges from 1.2% to 43% in the literature [29]. Although the prognosis is good in most patients, up to 30% of patients continue to have pain for 1 year or longer [54; 56].

Sciatia is most frequently caused by a nerve root compression due to disc herniation [54] and can be accompanied by signs of a nerve root lesion, such as neurological sensory or motor deficits. Patients with sciatica are likely to present with nociceptive as well as neuropathic pain (defined as 'pain caused by a lesion or disease of the somatosensory nervous system' [26]). Neuropathic pain has been shown to be associated with greater pain severity, increased suffering, increased disability, more impaired quality of life and greater health care costs than purely nociceptive low-back related leg pain [16; 43; 44; 45].

Lumbar discectomy is considered a cost-effective treatment for selected cases of patients with leg pain associated with the presence of a disc protrusion [19], but despite technically successful surgery, 30% of patients complain of persistent pain on long-term follow up [10] which is associated with substantial health care costs [38] and reduced work capacity [9].

Numerous risk factors and predictors for a negative outcome of disc surgery have been identified [32], including pain history [34], diagnosis specific clinical features such as size of disc herniation, Lasègue sign [28], pre-surgical intake of medication and poor functional status [37], psychological and cognitive-behavioural factors such as fear avoidance behaviour and negative outcome expectancy [8; 9; 27], pain catastrophizing

[30], depression and anxiety [7; 13; 28]. However, it is not possible to identify an unequivocal predictor due to interactions between several risk factors, large variances in study designs, patient clinical profiles and used outcome measures [32].

An additional approach to explore predictive factors for pain persistency may lie in the investigation of sensory parameters, measured by quantitative sensory testing (QST). QST has been widely used to obtain reliable quantitative measures of large and small sensory nerve fibre dysfunction, manifesting as presence of sensory loss and/or enhanced pain sensitivity (hyperalgesia, allodynia) [22; 42; 47], a feature of central sensitisation and key mechanisms in the development and maintenance of persistent pain, in particular neuropathic pain [25]. Hence QST is a valuable tool to investigate clinical sensory phenotypes and to help interpret the pain mechanisms underlying associated clinical pain presentations.

Several studies used QST for characterisation of post-operative pain [1; 2; 11; 20; 30; 57; 58]. Heat pain thresholds predicted postoperative pain intensity three months after surgery in pain free patients undergoing surgical correction of thorax malformation, and cold and pressure pain thresholds predicted pain-related disability after 6 months in this cohort [30]. Furthermore, cold hyperalgesia measured in patients in the acute stage after sustaining a whiplash injury was a significant predictor of poor outcome at long-term follow up [49].

QST data on patients with lumbar radiculopathy/sciatica are scarce. QST has been employed in this population in the affected dermatomal area to assess the function of sensory nerve fibers [17; 35; 59] and the recovery of nerve fiber function after lumbar decompression [33]. Preoperative loss of C-fibre function (measured by warm detection thresholds) was documented as negative predictive factor for lumbar microdiscectomy in 39 patients undergoing surgical decompression[33]. However, no study to date has established the QST sensory profile of this patient cohort in relation to their main pain area, as is required for the assessment of neuropathic pain [21] and as proposed for the current study.

There is some evidence that some sensory fibre populations may be more effected by nerve root compression than others [17; 46] and that the difference in the extent of sensory fibre loss may account for variability of resulting symptoms such as sensory loss and/or enhanced pain sensitivity [24]. This may explain the identification of sub-groups of patients with differing sensory profiles, as observed in patients with cervical radiculopathy [52] and as documented in a large epidemiological study on 2094 patients with painful lumbar radiculopathy [31]. The identification of sub-groups in the latter study was based on pain descriptors of a neuropathic pain screening tool (painDETECT) [15].

It is postulated that differences in sensory profiles and underlying pain mechanisms may account for differences in responsiveness to pharmaceutical intervention targeting neuropathic pain associated with radiculopathy [3; 6; 43], and may account for differences in clinical outcome after discectomy. The proposed study will provide further insight into the underlying pain mechanisms in a patient population undergoing surgical treatment.

OBJECTIVES

The overall aim of this project is to determine the predictive value of somatosensory characteristics in participants with lumbar radiculopathy/radicular pain, for predicting participants' clinical outcome after lumbar discectomy. Somatosensory characteristics will be explored using QST. Specific aims are:

i. To establish the QST somatosensory profile of participants with lumbar radiculopathy/radicular pain before and after surgery
ii. To investigate if there is an association between pre-surgical QST parameters and clinical outcome (functional status, pain intensity,health-related quality of life (HRQoL), return to work, confidence in recovery, health care utilisation, global perceived impression of change, bothersomeness) after lumbar microdiscectomy

Hypotheses:

1. There will be sub-groups of participants with differing somatosensory profiles before surgery.
2. There will be a difference in QST profiles between participants with and without persistent pain after surgery.

3. Sensory profiles showing enhanced pain sensitivity will be associated with pain persistency and functional status at 3 months and at 1 year follow-up after surgery.

RESEARCH PLAN

Research question: Is there an association between pre-surgical quantitative sensory testing parameters and clinical outcome after lumbar microdiscectomy?

METHODS

Study Design: Prospective longitudinal observational study

Study population*:* Participants will be recruited from the elective neurosurgery waiting list for lumbar microsurgical discectomy at Sir Charles Gairdner Hospital. In order to optimize standardization of data collection, only participants whose surgery will be performed at Osborne Park Hospital will be selected for recruitment. In this way it is guaranteed that surgery will always be performed by the same neurosurgeon (Prof. Lind), minimising variability in surgical care. The time allocation for surgeries and follow-up appointments is fixed, therefore controlling for any bias due to time differences of assessments between patients. Participants will be assessed in the week prior to surgery and in the morning prior to the follow-up appointment with the surgeon at 3 months.

Sample Size: Between 2010 and 2011 approximately 54 lumbar discectomies were performed at Osborne Park Hospital. The number of discectomies increased in 2012 to 41 and in 2013 to 70. A sample of 70 participants is feasible for this study, considering the exclusion criteria, loss to follow up and the given time frame of the PI's fellowship.

The Oswestry Disability Index (ODI) will be used as primary outcome measure after surgery. The scoring of ODI is between 0-100 (100 maximum disability).
10 points or 30% score improvement is the cut-off point for minimal important change [48]. A sample size of 40 participants is required to detect 10 units pre-post surgery with a power of 80% and 5% level of significance.

The inclusion criteria for the symptomatic participants will be as follows: age 18 to 65 years; symptom duration of > 3 months; clinical diagnosis of lumbar radiculopathy (defined as conduction block along a spinal nerve or nerve root, manifesting clinically with dermatomal sensory loss or myotomal weakness or reflex changes [5]) and leg pain in L5 or S1 dermatomal distribution; demonstrable clinically relevant abnormality on imaging studies indicating nerve root compression at the relevant spinal level; person listed on the elective neurosurgery surgery waitlist for the procedure of lumbar discectomy.

Exclusion criteria include diabetes and vascular disease (i.e. any disease affecting the vascular system and potentially affecting the sensation testing in any of the body regions to be assessed, e.g. Raynaud's disease, peripheral arterial disease; other neurological or psychiatric disease; previous lumbar surgery; a history of any disorders that potentially might affect the sensation in the hand (negative control site) to be tested and an insufficient level of English to understand and fill out the questionnaires. Each participant must be able to understand the instructions/requirements for the quantitative sensory testing procedures and be able to give a reliable response that does not depend on translation and is not vulnerable to misinterpretation.

Reference data from healthy control subjects (HC) will be obtained in order to compare if symptomatic participants differ from a healthy cohort. HCs will be matched for age and gender to the symptomatic participant groups and will be recruited from the local community. Subjects with a history of current pain or a chronic pain condition or any of the exclusion criteria described for the symptomatic participant group will be excluded, including taking medications that influence pain perception (e.g. analgesics, non-steroidals, antidepressants). The number of HC subjects to be tested has to be determined during the course of the study, as reference data have to be obtained from at least 8 male and 8 female HC subjects [4] for each maximal pain area nominated by the symptomatic participants. The minimum number of 8 is based on recommendations of the DNFS and their published methodology [4]. Participants with either L5 or S1 radicular pain will be included in the study, hence it is anticipated that 4 body regions may be nominated as maximal pain area (thigh L5 and S1 distribution, lower leg L5 and S1 distribution).

Testing protocol

The initial patient assessment will take approximately 2.5 hours. The participant's pain history, including pain distribution and pain behaviour will be recorded and a clinical examination for determination of neurological deficits will be conducted (reflex, strength and sensation testing).

The following measurements will be taken either in interview format or via questionnaires. Finally QST will be performed.

- Duration of pain (part of Örebro Musculoskeletal Screening Questionnaire (Short form) [18]
- Pain intensity of back and leg pain (11- point numerical rating scale (NRS)
- Health care utilisation
- Bothersomeness of back and leg pain
- Confidence in recovery ('great deal', 'moderate', 'no confidence', 'do not know') [37]
- Intake of medication
- Sleep quality (Visual Analogue Scale) [52]
- Duration of inability to work
- Functional status (Oswestry Disability Index) [14]
- Anxiety and Depression (Hospital Anxiety and Depression Scale) (HADS) [23]
- Pain descriptors (painDETECT) [15]
- Fear avoidance behaviour (Tampa Scale for Kinesiophobia) [51]
- Pain catastrophizing (Pain catastrophizing Scale) [50]
- Health-related quality of life (Short form-36 health questionnaire) (SF-36v2®) [55]
- Risk assessment for persistent pain (Örebro Musculoskeletal Screening Questionnaire) (Short form) [18]

The degree of nerve root compression [39] will be determined by a neurosurgery registrar who is blind to the participant's enrolment into the study.
HC participants will complete the HADs and SF 36 questionnaire and their sleep quality will be determined.

Quantitative sensory testing

Standardized QST will be performed according to the QST protocol of DFNS [41; 42]. The protocol includes the following assessments: cold and warm detection thresholds, ;he number of paradoxical heat sensations during the procedure of alternating warm and cold stimuli; cold and heat pain thresholds; mechanical detection threshold; mechanical pain threshold; stimulus-response functions: mechanical pain sensitivity and dynamic mechanical allodynia; wind-up ratio*;* vibration detection threshold and pressure pain threshold.

QST measurements will be taken from the main pain area nominated by the symptomatic participant, as required for the assessment of neuropathic pain [21] and the contralateral side [21] and from the ipsilateral hand dorsum as a remote control site, plus thermal and mechanical detection thresholds will be assessed in the relevant dermatome (L5, S1) on the symptomatic side. Testing sites in HC subjects will be matched to the sites tested in symptomatic participant. Testing of the full QST protocol will take approximately 30 minutes per test area. Testing of dermatomal detection thresholds will take less than 10 minutes.

Outcome assessment 3 months postoperatively

- Functional status Oswestry [14]
- Pain intensity
- Pain descriptors [15]
- Health-related quality of life [55]
- Return to work (yes/no)
- Health care utilisation
- Medication intake
- Patient Global Impression of Change Scale [12]
- Bothersomenes of back and leg pain
- QST in previously tested maximal pain area and dermatome (appr. 40 minutes)

The assessment will take approximately one hour.

Outcome assessment 1 year postoperatively:

The same questionnaires as at 3 months will be mailed to the participants.

Statistical analysis

QST data will be log-transformed prior to statistical analysis except those data which are normally distributed as raw data [42]. To compare and illustrate participants' QST data profiles with the group mean of age/gender matched healthy controls particpants' data will be z-transformed for each single parameter by using the following expression: Z-score = $(\text{Mean}_{\text{single proband}} - \text{Mean}_{\text{healthy controls}})/\text{SD}_{\text{healthy controls}}$ [42]. Z-values will be calculated based on the HC group data.

Differences of z-score QST data between the symptomatic participant group and HC and tested body regions will be compared using a two-way analysis of covariance (ANCOVA) with tested body areas (maximal pain area, hand) as the within-subjects factor. Group (participants/controls) will be entered as between-subjects factors. Anxiety, depression and fear avoidance scores will be entered as covariates to account for potential influence of these factors on pain responses [40]. Depending on data distribution, differences of some predictor variables (Oswestry Disability Index [14], HADS [23],Tampa Scale for Kinesiophobia [51], SF-36v2® [55]) between patients and HC will be compared using parametric (t-Test) or non-parametric tests (Mann-Whitney-U test).

Differences in outcome measures pre- and post-surgery will be compared using repeated measures ANOVA in case of normal distribution of variables, and the Friedman's Test for non-normal distributed data. Multivariate regression analyses will be performed to assess associations between the predictor variables, QST measures and the outcome variables.

Acknowledgement

This study is funded by the Western AustralianDepartment of Health and the Raine Medical Research Foundation as well as the School of Physiotherapy and Exercise Science, Curtin University, Perth, Western Australia.

References

[1] Aasvang EK, Brandsborg B, Christensen B, Jensen TS, Kehlet H. Neurophysiological characterization of postherniotomy pain. Pain 2008;137:173-181.

[2] Aasvang EK, Brandsborg B, Jensen TS, Kehlet H. Heterogeneous sensory processing in persistent postherniotomy pain. Pain 2010;150:237-242.

[3] Baron R, Freynhagen R, Tölle TR, Cloutier C, Leon T, Murphy TK, Phillips K, on behalf of the A0081007 Investigators. The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy. Pain 2010;150:420-427.

[4] Blankenburg M, Meyer D, Hirschfeld G, Kraemer N, Hechler T, Aksu F, Krumova EK, Magerl W, Maier C, Zernikow B. Developmental and sex differences in somatosensory perception - a systematic comparison of 7- versus 14-year-olds using quantitative sensory testing. Pain 2011;152:2625-2631.

[5] Bogduk N. On the definitions and physiology of back pain, referred pain, and radicular pain. Pain 2009;147:17-19.

[6] Brötz D, Maschke E, Burkard S, Engel C, Mänz C, Ernemann U, Wick W, Weller M. Is there a role for benzodiazepines in the management of lumbar disc prolapse with acute sciatica? Pain 2010;149:470-475.

[7] Chaichana KL, Mukherjee D, Adogwa O, Chen JS, McGirt MJ. Correlation of preoperative depression and somatic perception scales with postoperative disability and quality of life after lumbar discectomy. J Neurosurg Spine 2011;14:261-267.

[8] den Boer JJ, Oostendorp RAB, Beems T, Munneke M, Evers AWM. Continued disability and pain after lumbar disc surgery: The role of cognitive-behavioral factors. Pain 2006;123:45-52.

[9] den Boer JJ, Oostendorp RAB, Beems T, Munneke M, Evers AWM. Reduced work capacity after lumbar disc surgery: The role of cognitive-behavioral and work-related risk factors. Pain 2006;126:72-78.

[10] den Boer JJ, Oostendorp RAB, Beems T, Munneke M, Oerlemans M, Evers AW. A systematic review of bio-psychosocial risk factors for an unfavourable outcome after lumbar disc surgery. Eur Spine J 2006;15:527-536.

[11] Duale C, Guastella V, Morand D, Cardot J-M, Aublet-Cuvelier B, Mulliez A, Schoeffler P, Escande G, Dubray C. Characteristics of the neuropathy induced by thoracotomy: A 4-month follow-up study with psychophysical examination. . Clin J Pain 2011;27:471-480.

[12] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9-19.

[13] Edwards RR, Klick B, Buenaver L, Max MB, Haythornthwaite JA, Keller RB, Atlas SJ. Symptoms of distress as prospective predictors of pain-related sciatica treatment outcomes. Pain 2007;130:47-55.

[14] Fairbank JCT, Pynsent PB. The Oswestry Disability Index. Spine 2000;25:2940-2953.
[15] Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: A new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911-1920.
[16] Freynhagen R, Baron R, Tölle T, Stemmler E, Gockel U, Stevens M, Maier C. Screening of neuropathic pain components in patients with chronic back pain associated with nerve root compression: a prospective observational pilot study (MIPORT). Curr Med Res Opin 2006;22:529-537.
[17] Freynhagen R, Rolke R, Baron R, Tölle TR, Rutjes A-K, Schu S, Treede R-D. Pseudoradicular and radicular low-back pain - A disease continuum rather than different entities. Answers from quantitative sensory testing. Pain 2008;135:65-74.
[18] Gabel CP, Burkett B, Melloh M. The shortened Örebro Musculoskeletal Screening Questionnaire: Evaluation in a work-injured population. Man Ther 2013;18:378-385.
[19] Gibson JNA, Waddell G. Surgical interventions for lumbar disc prolapse. Cochrane Database Syst Rev 2007:Art. No.: CD001350. DOI: 001310.001002/14651858.CD14001350.pub14651854.
[20] Gottrup H, Andersen J, Arendt-Nielsen L, Jensen TS. Psychophysical examination in patients with post-mastectomy pain. Pain 2000;87:275-284.
[21] Haanpää M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, Cruccu G, Hansson P, Haythornthwaite JA, Iannetti GD, Jensen TS, Kauppila T, Nurmikko TJ, Rice ASC, Rowbotham M, Serra J, Sommer C, Smith BH, Treede R-D. NeuPSIG guidelines on neuropathic pain assessment. Pain 2011;152:14-27.
[22] Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: Clinical and research application in neuropathic pain states. Pain 2007;129:256-259.
[23] Härter M, Reuter K, Gross-Hardt K, Bengel J. Screening for anxiety, depressive and somatoform disorders in rehabilitation - validity of HADS and GHQ-12 in patients with musculoskeletal disease. Disabil Rehabil 2001;23:737-744.
[24] Huang C, Zou W, Lee K, Wang E, Zhu X, Guo Q. Different symptoms of neuropathic pain can be induced by different degrees of compressive force on the C7 dorsal root of rats. Spine J 2012;12:1154-1160.
[25] Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 2003;102:1-8.
[26] Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice ASC, Treede R-D. A new definition of neuropathic pain. Pain 2011;152:2204-2205
[27] Johansson A-C, Linton SJ, Rosenblad A, Bergkvist L, Nilsson O. A prospective study of cognitive behavioural factors as predictors of pain, disabiltiy and quality of life one year after lumbar disc surgery. Disabil Rehabil 2010;32:521-529.
[28] Kohlboeck GP, Greimel KVP, Piotrowski WPMD, Leibetseder MP, Krombholz-Reindl MMD, Neuhofer RMD, Schmid AMD, Klinger RP. Prognosis of multifactorial outcome in lumbar discectomy: A prospective longitudinal study investigating patients with disc prolapse. Clin J Pain 2004;20:455-461.
[29] Konstantinou KP, Dunn KMP. Sciatica: Review of epidemiological studies and prevalence estimates. Spine 2008;33:2464-2472.
[30] Lautenbacher S, Huber C, Schöfer D, Kunz M, Parthum A, Weber PG, Roman C, Griessinger N, Sittl R. Attentional and emotional mechanisms related to pain as

predictors of chronic postoperative pain: A comparison with other psychological and physiological predictors. Pain 2010;151:722-731.
[31] Mahn F, Hüllemann P, Gockel U, Brosz M, Freynhagen R, Tölle TR, Baron R. Sensory symptom profiles and co-morbidities in painful radiculopathy. PLoS One 2011;6:e18018.
[32] Mannion A, Elfering A. Predictors of surgical outcome and their assessment. Eur Spine J 2006;15:S93.
[33] Nygaard ØP, Kloster K, Mellgren SI. Recovery of sensory nerve fibres after surgical decompression in lumbar radiculopathy: Use of quantitative sensory testing in the exploration of different populations of nerve fibres. J Neurol Neurosurg Psychiatry 1998;64:120-123.
[34] Nygaard OP, KLoster R, Solberg T. Duration of leg pain as a predictor of outcome after surgery for lumbar disc herniation: a prospective cohort study with 10year follow up. J Neurosurg 2000;92:131-134.
[35] Nygaard ØP, Mellgren SI. The function of sensory nerve fibers in lumbar radiculopathy: Use of quantitative sensory testing in the exploration of different populations of nerve fibers and dermatomes. Spine 1998;23:348-352.
[36] Organisation WH. The burden of musculoskeletal conditions at the start of the new millennium. i-x. World Health Organ Tech Rep Ser 2003;919:1-218.back cover.
[37] Ostelo RWJG, Vlaeyen JWS, van den Brandt PA, de Vet HCW. Residual complaints following lumbar disc surgery: prognostic indicators of outcome. Pain 2005;114:177-185.
[38] Parker SL, Xu R, McGirt MJ, Witham TF, Long DM, Bydon A. Long-term back pain after a single-level discectomy for radiculopathy: incidence and health care cost analysis. J Neurosurg Spine 2010;12:178-182.
[39] Pfirrmann CWA, Dora C, Schmid MR, Zanetti M, Hodler J, Boos N. MR Image–based grading of lumbar nerve root compromise due to disk herniation: Reliability study with surgical correlation. Radiology 2004;230:583–588.
[40] Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. Pain 2000;84:65-75.
[41] Rolke R, Baron R, Maier C, Tölle TR, Treede R-D, Beyer A, Binder A, Birbaumer N, Birklein F, Bötefür IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihöfner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. Pain 2006;123:231-243.
[42] Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede RD. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10:77-88.
[43] Saldaña MT, Navarro A, Pérez C, Masramón X, Rejas J. A cost-consequences analysis of the effect of pregabalin in the treatment of painful radiculopathy under medical practice conditions in primary care settings. Pain Pract 2010;10:31-41.
[44] Saldaña MT, Navarro A, Pérez C, Masramón X, Rejas J. Patient-reported-outcomes in subjects with painful lumbar or cervical radiculopathy treated with pregabalin: Evidence from medical practice in primary care settings. Rheumatol Int 2010;30:1005-1015.
[45] Schmidt CO, Schweikert B, Wenig CM, Schmidt U, Gockel U, Freynhagen R, Tölle TR, Baron R, Kohlmann T. Modelling the prevalence and cost of back pain with

neuropathic components in the general population. Eur J Pain 2009;13:1030-1035.
[46] Scholz J, Mannion RJ, Hord DE, Griffin RS, Rawal B, Zheng H, Scoffings D, Philips A, Guo J, Laing RJC, Abdi S, Decosterd I, Woolf CJ. A novel tool for the assessment of pain: Validation in low back pain. PLoS Med 2009;6:1-16.
[47] Shy ME, Frohman EM, So YT, Arezzo JC, Cornblath DR, Giuliani MJ, Kincaid JC, Ochoa JL, Parry GJ, Weimer LH. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2003;60.
[48] Smeets R, Koeke A, Lin C-W, Ferreira M, Demoulin C. Measures of function in low back pain/disorders. Arthritis Care Res 2011;63:S158-S173.
[49] Sterling M, Jull G, Kenardy J. Physical and psychological factors maintain long-term predictive capacity post-whiplash injury. Pain 2006;122:102-108.
[50] Sullivan MJL, Bishop SC, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychol Assess 1995;7:524-532.
[51] Swinkels-Meerwisse EJCM, Swinkels RAHM, Verbeek ALM, Vlaeyen JWS, Oostendorp RAB. Psychometric properties of the Tampa Scale for kinesiophobia and the fear-avoidance beliefs questionnaire in acute low back pain. Man Ther 2003;8:29-36.
[52] Tampin B, Slater H, Hall T, Lee G, Briffa NK. Quantitative sensory testing somatosensory profiles in patients with cervical radiculopathy are distinct from those in patients with nonspecific neck-arm pain. Pain 2012;153:2403-2414.
[53] Valat J-P, Genevay Sp, Marty M, Rozenberg S, Koes B. Sciatica. Best Practice & Research Clinical Rheumatology 2010;24:241-252.
[54] Vroomen PCAJ, de Krom MCTFM, Slofstra PD, Knottnerus JA. Conservative treatment of sciatica: A systematic review. J Spinal Disord 2000;13:463-469.
[55] Ware JE. SF-36 Health Survey update. Spine 2000;25:3130-3139.
[56] Weber H, Holme I, Amlie E. The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam. Spine 1993;18:1433-1438.
[57] Werner MU, Kehlet H. Characterization of persistent postoperative pain by quantitative sensory testing. European Journal of Pain Supplements 2010;4:203-207.
[58] Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best L-A, Granot M. Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. Pain 2008;138:22-28.
[59] Zwart JA, Sand T, Unsgaard G. Warm and cold sensory thresholds in patients with unilateral sciatica: C fibers are more severely affected than A-δ fibers. Acta Neurol Scand 1998;97:41-45.