Pins and Needles, Facts and Feelings.

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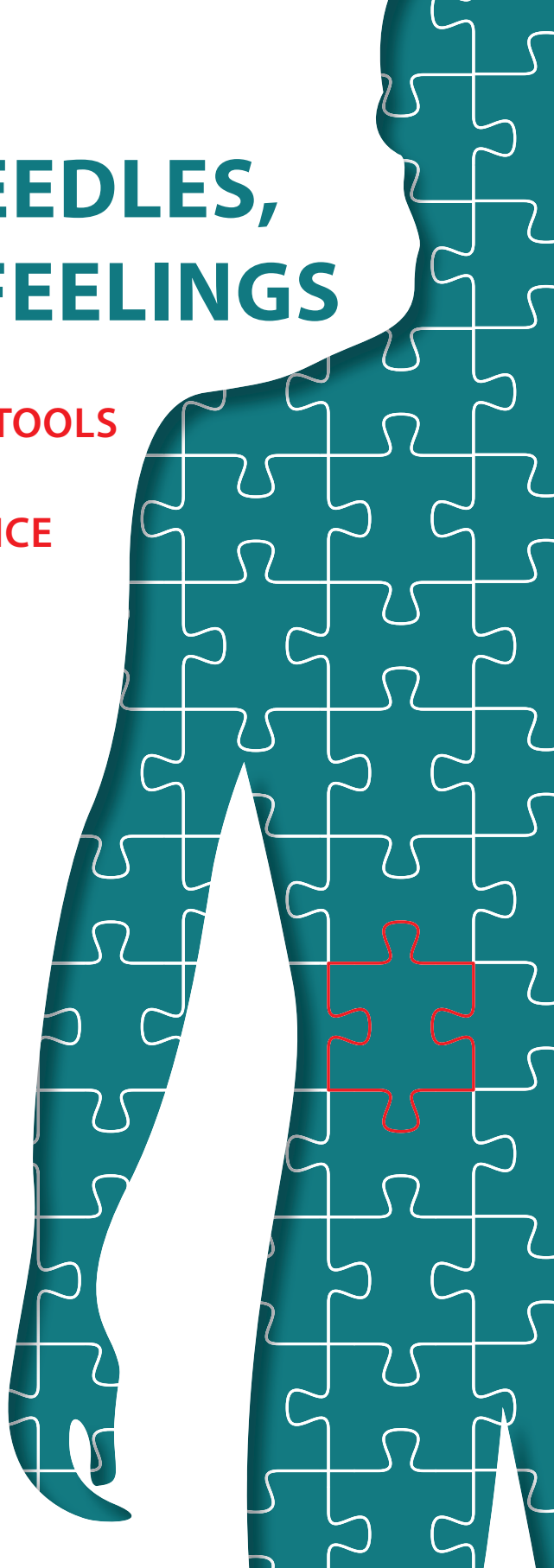
EFFICACY OF SCREENING TOOLS FOR NEUROPATHIC PAIN IN DAILY CLINICAL PRACTICE



HANS TIMMERMAN

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Efficacy of Screening Tools
for Neuropathic Pain in Daily Clinical Practice

Hans Timmerman

Colophon

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Efficacy of Screening Tools
for Neuropathic Pain in Daily Clinical Practice

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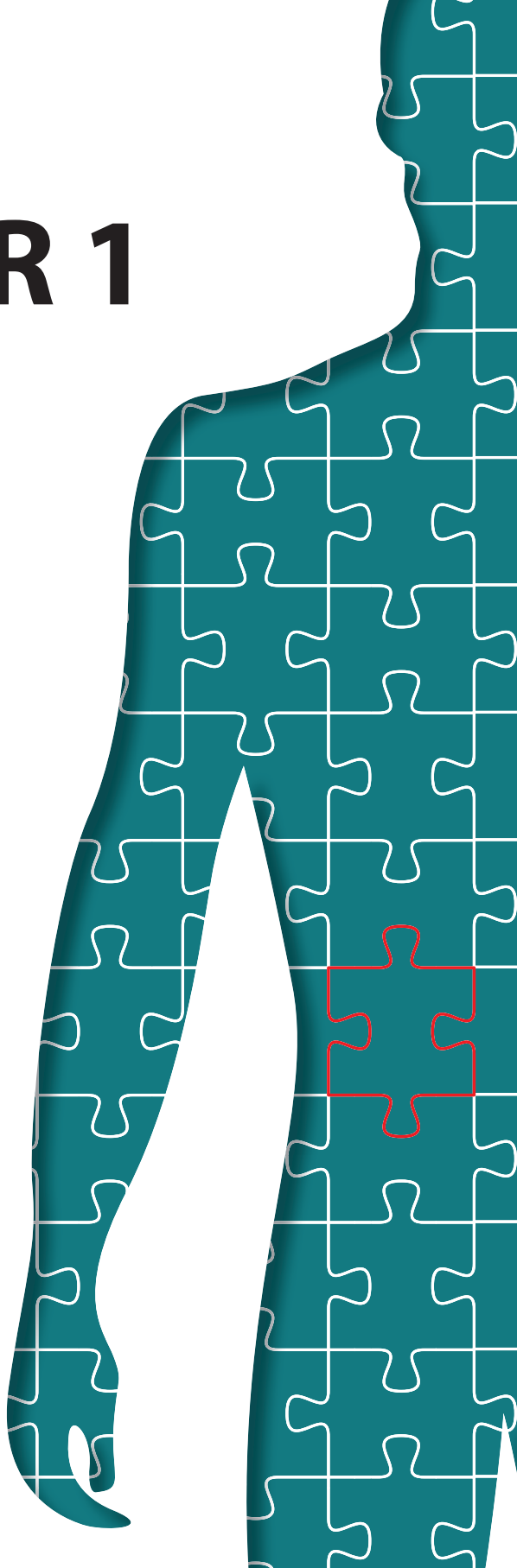
CHAPTER 1

Introduction



GENERAL INTRODUCTION

"Pain is a major healthcare problem worldwide. Although acute pain may reasonably be considered a symptom of disease or injury, chronic and recurrent pain is a specific healthcare problem, a disease in its own right" (IASP 2001).

Pain is a biopsychosocial phenomenon defined as *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"* [1]. Pain is regarded as a subjective experience and thus implies consciousness, as described in 1968 by McCaffery: *"Pain is whatever the experiencing person says it is, existing whenever he says it does"* [2]. Moreover, the patient has to be considered as the expert of his/her own pain, which makes it difficult to document pain objectively, but it also makes pain a highly individual disease which requires a personalized approach and treatment.

Nociception is defined by the IASP as *"the neural process of encoding noxious stimuli"* [3], whereby information about a harmful stimulus is passed on via the activation of nociceptors to the brain. However, nociception alone is not enough to rate a stimulus as pain. To experience a nociceptive stimulus as 'pain', a person is influenced by personal memory, emotions, pathology and cognitive factors [4].

Section1 of the introduction discusses the classification of patients' pain based on the type and duration of the pain. Section 2 describes the neuroanatomy and physiology of pain, neuropathic pain in particular, and provides additional information about pain processing. The epidemiology, burden, costs and consequences of (neuropathic) pain are described in Section 3. Section 4 introduces the assessment of neuropathic pain in daily clinical practice. In Section 5, the requirements for a screening tool for the assessment of (neuropathic) pain are specified. The research questions to be answered in this thesis are then introduced in the final section of the Introduction.

CLASSIFICATION OF PAIN

Pain has multiple causes, and people's response to pain is various and individually fixed, depending on, for example, the circumstances. This section discusses how patients' pain can be classified based on the type and/or duration of pain.

Classification based on type of pain

Nociceptive pain: the IASP define nociceptive pain as *"pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors"* [5]. This type of pain mostly results from a clear, identifiable mechanical, thermal or chemical damage to various parts of the body (somatic: such as skin, bones, muscles; or visceral: abdominal or thoracic internal organs). The pain is felt at the site of the injury or by stimulation of local nociceptors without injury, and is relatively easy to treat [1]. In recent years, pain has also been described as inflammatory pain and visceral pain, both with a more causal than mechanistic orientation. Inflammatory pain is defined as *'a result of activation and sensitization of the nociceptive pain pathway by a variety of mediators released at a site of tissue inflammation'* [6]. Inflammatory pain can be found in patients with, amongst others, rheumatoid arthritis, pancreatitis, or a herpes zoster infection. Visceral pain arises from the internal organs; it often has a diffuse localization due to major perceptive fields, overlap of innervations and 'cross-talking' of innervating nerves. The pain refers to other areas of the body and is associated with motor- and autonomic reflexes [7]. An example of visceral pain is deep pain from the bladder which is referred to the perianal region [8].

Neuropathic pain: in 1994, neuropathic pain was defined as *"Pain initiated or caused by a primary lesion or dysfunction in the nervous system" [1]*. However in 2008, neuropathic pain was redefined as *"Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [9, 10]*. According to the IASP taxonomy, neuropathic pain is not a diagnosis but a *'clinical description which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria'* [9]. It is divided into central and peripheral neuropathic pain. Central neuropathic pain is caused by a lesion or disease of the central somatosensory nervous system, for example in patients with a spinal cord injury or multiple sclerosis. In peripheral neuropathic pain, the lesion or disease is localized in the peripheral somatosensory nervous system, for example in patients with diabetic neuropathy, or as a side effect after treatment for cancer with chemotherapy [9].

Nociplastic pain: in November 2017 (after our study was completed), the International Association for the Study of Pain (IASP) acknowledged nociplastic pain as the third mechanistic descriptor for chronic pain states in addition to nociceptive and neuropathic pain, because in 2008, the term 'dysfunction' was removed from the definition of neuropathic pain [11-14]. It is now defined as *"Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory*

system causing pain" [11]. Patients in this group are in pain but neither from an obvious activation of their nociceptors nor from neuropathy. Nociplastic pain is suggested to be an altered nociceptive function based on clinical, physical and psychological observations and it can occur in combination with nociceptive pain and/ or neuropathic pain. The advantage of this third descriptor is that it gives more recognition to pain as experienced by the patient, and it is intended to improve the diagnosis and treatment of patients with (chronic) pain by creating an extra subdivision. As debate is a fundamental part of an academic environment, there is an ongoing discussion about the use of the term nociplastic pain and its meaning[11-19]. The question then arises, 'What does 'altered nociception' mean?" Does this refer to a change in the nociceptors or is there a change in the signal processing of the nociceptive input, or perhaps both? Nociceptor activity or activity in the pathways/cortical networks is not necessarily pain [12]. Describing a persistent pain condition without a clear medical explanation and without objective criteria for assessment and diagnosis will lead to a continuation of the debate about this new mechanistic descriptor until research provides more insights into this phenomenon [12]. Pain conditions fitting this description are, amongst others, fibromyalgia, CRPS and irritable bowel syndrome [11]. One of the extensively described phenomena which fits the term nociplastic pain is 'central sensitization' [20]. Central sensitization is defined as *"an amplification of neural signaling within the central nervous system that elicits hypersensitivity"* [21, 22]. Moreover, the IASP defines central sensitization as *"an increased response and reduced threshold of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"* [23]. Correctly determining and recognizing central sensitization is important when diagnosing the patient, classifying the patient's pain, and in treatment [20, 24-27]. However, as Kosek et al [16] suggested, the underlying mechanism of nociplastic pain may also be the central sensitization of nociception or nociceptive pathways. Research in the field of nociplastic pain should target identifying the suggested altered nociceptive function in patients with (chronic) pain and, consequently, developing treatment opportunities.

Mixed pain: pain can be classified as an independent condition, but also as part of a 'mixed pain condition' [28, 29] in which, for example, nociceptive pain and neuropathic pain are present in one patient. Because of the coexistence of pain classifications in daily clinical practice, it is better to speak of an absent or present neuropathic pain component in patients' pain (NePC) with respect to mixed pain conditions.

Pain of unknown origin: pain can also be classified as 'pain from an unidentified source'; this used to be termed 'idiopathic pain'. It is now defined as *"pain of unknown cause and origin"* [11].

Classification based on duration of pain

Besides the differentiation in type of pain, patients can be classified based on the duration of their pain. Acute pain is defined as *"pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease"* [30]. Acute pain may induce chronic

pain states [31, 32]; for example after undergoing surgery, it is known that acute pain is followed by chronic pain in 10-50% of patients[33] . The definition of chronic pain is *"pain that extends beyond the expected period of healing"* [1]. Chronic pain is recognized as pain that persists or recurs after normal healing time, and that lacks the acute warning function of physiological nociception [34, 35]. Chronic pain can be present without an identifiable temporal or causal relationship with the injury or disease according to currently available diagnostic methods. In daily clinical practice, pain is regarded as 'chronic' if it lasts for more than (or recurs within) 3-6 months [1].

NEUROANATOMY AND PHYSIOLOGY OF PAIN AND NEUROPATHIC PAIN IN PARTICULAR

In this section, I provide an overview of the physiological mechanisms of pain and the important pain pathways between receptors and the brain.

In normal conditions, pain is a protective natural response to a disease or injury after a body is threatened. The protective function of the nociceptive sensory system is divided into a somatosensory and a homeostatic part. The somatosensory part localizes the disease or injury and causes painful stimuli, followed by corresponding fast motor reflexes. The homeostatic function results in hyperalgesia and autonomic adaptation during the healing phase in pathological conditions [36, 37]. Pain is the result of a complex interaction between signaling systems, modulation that may originate from higher centers, and the unique perception of the individual [8] (figure 1). In addition to the experience of pain, an increase in heart rate and blood pressure, sweating and changes in respiratory behavior can occur after activation of the nociceptors due to sympathetic activation.

The pain signaling pathway

Primary afferents: Nociceptors are receptors (free nerve endings) found in a range of tissues activated by specific painful stimuli such as the free nerve endings of cutaneous nociceptors localized in the epidermal layer of the skin. Other nociceptors, such as the high-threshold mechanoreceptors, respond to mechanical deformation (pressure, stretch, etc.). Another example, polymodal receptors, respond to a variety of tissue damaging inputs (mechanical, temperature and chemical stimuli). Inflammatory mediators such as hydrogen ions (protons), 5-hydoxytryptamine (5-HT), cytokines, bradykinin, histamine, prostaglandins, and leucotrienes, activate and sensitize the free nerve endings of different types of nerve fibers [8]. Aβ fibers generate touch, pressure, proprioception and vibration signals; Aδ may produce acute, well localized sharp pain, and C fibers result in warmth, delayed, and more diffuse pain, and a long-lasting burning sensation. Type III & IV fibers are sensitive to deep (muscular) pressure (table 1) [38, 39]. These primary afferent nerve fibers have cell bodies in the dorsal root ganglia or in the trigeminal ganglion, and terminate in the dorsal horn of the spinal cord [8].

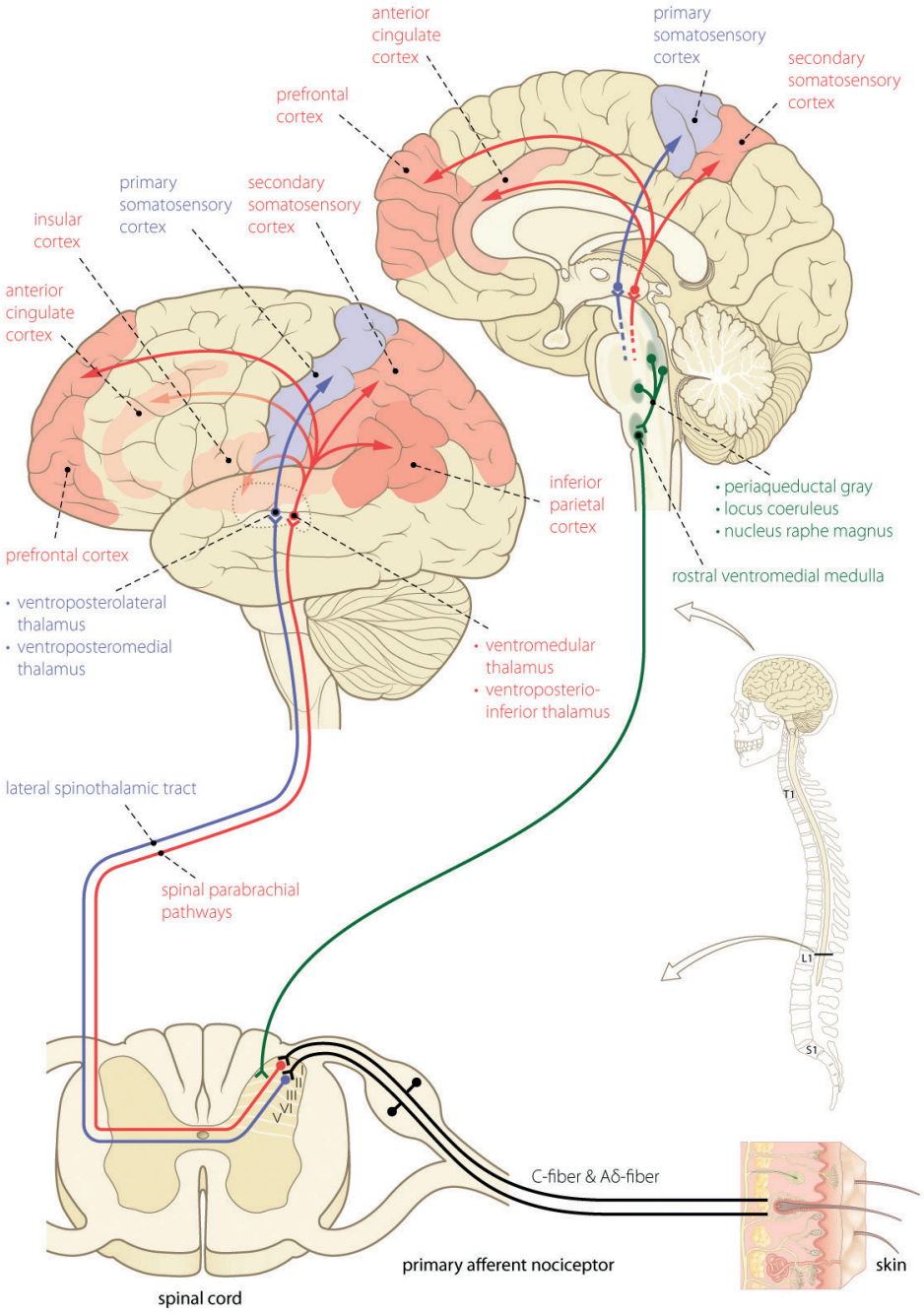


Figure 1: The pain signaling pathway. Illustration: Rogier Trompert Medical Art

Table 1: Sensory modalities, receptors and suggested testing modalities. Adapted from Walk et al [38].

Sensory Modality	Principal receptors	Axon type	Postulated mechanism of allodynia/ hyperalgesia	Testing instruments
Dynamic mechanical	Meissner's Pacinian Hair follicle	**Aβ, some C** **Aβ** **Aβ**	Central sensitization	Brush Cotton wisp Cotton swab
Cutaneous punctuate (blunt)	Merkel Ruffini	**Aβ** **Aβ** **Some C**	Central sensitization	Von Frey hair
Cutaneous punctuate (sharp)	Free nerve endings	**Aδ**	Central sensitization Peripheral sensitization	Pin (wooden cocktail stick)
Deep pressure	Intramuscular afferents	**Type III, IV**	Unknown	Pressure algometer
Vibration	Pacinian	**Aβ**	Unknown	Tuning fork (128Hz)
Innocuous warm	Free nerve endings	**C**	Peripheral sensitization	Heated surface
Innocuous cool	Free nerve endings	**Aδ**	Unknown	Metallic surface at room temperature
Noxious heat	Free nerve endings	**C** **Aδ**	Peripheral sensitization	Heated surface
Noxious cold	Free nerve endings	**C** **Some Aδ**	Reduced inhibition Central sensitization Peripheral sensitization	Cooled surface Metallic surface in ice water

Second order neurons: primary nociceptive afferents synaps onto second order neurons in the spinal dorsal horn in the various Rexed laminae. Moreover, inhibitory interneurons add to the complex structure of the dorsal horn. Information from the nociceptors is integrated and modulated and passed on to the supraspinal centers. Furthermore, descending tracts from higher centers exert their inhibitory effect on the neurons in the dorsal horn [8].

Ascending tracts: the second order neurons cross over to the contralateral side of the myelum and ascend to higher structures via the spinothalamic tract and the spinoreticular tract. The spinothalamic tract (also known as the anterolateral system) is divided in a lateral ('neospinothalamic') tract and an anterior ('paleospinothalamic') tract. The lateral tract transmits pain and temperature, whereas the anterior spinothalamic tract transmits crude touch and firm pressure. Sensations of tactile processing and proprioception are conveyed via the dorsal column-medial lemniscus pathway. The lateral tract is involved in the sensory-discriminative aspect of pain; the anterior tract is involved in the autonomic and affective part of pain. The spinoreticular tract is phylogenetically more ancient than the spinothalamic tract and is involved in the perception of diffuse, emotionally disturbing pain

[8, 40]. It also plays an important role in autonomous functions like breathing, heart and circulation, and the regulation of posture and muscle tone.

The brain: a very important area for pain processing is the thalamus; from there the sensory information is distributed to the cerebral cortex [41]. Via the spinothalamic tracts, the axons terminate in the thalamic nuclei and connect further to the primary and secondary somatosensory cortex, the insula, the anterior cingulated cortex, and the prefrontal cortex [42]. These areas are known for the perception of pain and their interaction with, for example, areas associated with motor function [8]. The cortico-limbic structures integrate the sensation of pain and the pain effect.

Descending tracts: the descending tracts play an important role in pain modulation. Descending pain inhibition is, among others, controlled via neurotransmitters (Noradrenaline and 5-HT). Via the peri-aquaductal grey and the nucleus raphe magnus, the brainstem is involved in reducing pain transmission in the dorsal horn of the spinal cord where incoming stimuli are toned or blocked [8].

Neuropathic pain

Neuropathic pain is a direct result of damage to the nervous system [9]. It can develop after an injury to or a disease affecting the peripheral nerve (peripheral neuropathic pain), or parts of the central nervous system (central neuropathic pain). It is often accompanied by maladaptive changes in the nervous system (changes in the injured neurons and along the ascending and descending modulatory pathways) [43, 44]. Peripheral neuropathic pain can be a result of surgery, as well as, amongst others, from herpes zoster, radiculopathy, diabetes mellitus, chemotherapy, or a peripheral nerve injury [45]. Central neuropathic pain can be a result of stroke ('central post-stroke pain') or, for example, be caused by a neurodegenerative disease like morbus Parkinson [46]. However, not all patients with a lesion or disease in the peripheral or central somatosensory system develop neuropathic pain [39].

The sensory abnormalities which the patient experiences are crucial to the clinical diagnosis of neuropathic pain, and to distinguish this type of pain from nociceptive and nociplastic pain [47]. Nerve damage can result in structural changes in the nerve itself but also to functional changes in the nervous system. These changes may cause a variety of continuous or intermittent symptoms [48]. Patients with neuropathic pain may experience symptoms like burning, painful cold, electric shocks, shooting, stabbing, tingling, pins and needles, numbness and/or itch [47]. Moreover, the pain can be evoked by a stimulus or it can be spontaneous, i.e. pain not evoked by a stimulus [8, 39], and may present as allodynia, hyperalgesia, hyperpathia, hyperesthesia and/or dysesthesia. It can also result in an decreased response to a stimulus, which can be described as analgesia, hypoalgesia and hypoesthesia (Table 2). Provocation of pain can occur via dynamic (e.g. stroking with a brush), and or static (e.g. touching with a finger) stimuli. The symptoms and signs may be similar for both central and peripheral neuropathic pain therefore it is not always easy to judge where the injury or disease affects the nervous system[8].

Table 2: **Clinical manifestation of neuropathic pain. Adapted from Merskey and Bogduk, Classification of Chronic Pain [1, 120].**

Term	Description
Allodynia	Pain due to a stimulus that does not normally provoke pain
Hyperalgesia	An increased response to a stimulus that is normally painful
Hyperesthesia	Increased sensitivity to stimulation
Hyperpathia	A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold
Paresthesia	An abnormal sensation, whether spontaneous or evoked
Dysesthesia	An unpleasant abnormal sensation whether spontaneous or evoked
Analgesia	Absence of pain in response to stimulation that would normally be painful
Hypoalgesia	Diminished pain in response to a normally painful stimulus
Hypoesthesia	Decreased sensitivity to stimulation

Table 3: Changes in the nervous system due to or caused by neuropathic pain and consequences for the patient. Adapted from Colloca et al [39].

Changes in	Description	Consequences
Pain signaling	In patients with neuropathic pain, the changes in the (electrical) properties of the sensory nerves might result in an imbalance between the central excitatory and inhibitory signaling. This leads to an impairment of the inhibitory interneurons and the descending control systems. In the spinal cord, at the level of the dorsal horn neurons, there is a change in the transmission of sensory signals and disinhibition or facilitation mechanisms. An increase in excitation and facilitation and a decrease in inhibition is existing in the peripheral nervous system, the spinal cord and the brain.	Change to a state of hyperexcitability Ongoing changes in the sensory pathway might contribute to the fact that neuropathic pain becomes chronic neuropathic pain
Ion channels	Neuropathy causes changes in the ion channels in the affected nerves which influences the sensory signaling at the spinal level and in the brain.	Experiences by the patient of ongoing pain; numbness and/or evoked pains
Second order nociceptive neurons	An increased excitability of spinal neurons leads to an enhanced response to several sensory modalities. It allows low-threshold mechanosensitive (Aβ & Aδ) afferent nerve fibers to activate the second order nociceptive neurons. These are transmitting sensory information to the brain, and increases the receptive fields of the neurons in a way that a given stimulus is excitating more secondary order nociceptive neurons [20, 121]. Hyperexcitability can be caused by a loss of γ-aminobutyric acid (GABA)- releasing inhibitory interneurons. These inhibitory neurons can switch to utilize excitatory actions in the spinal cord [122]. Moreover, functional changes in non-neuronal cells in the spinal cord (by example microglia and astrocytes) might play a role in the development of hypersensitivity [123].	Generates central sensitization The changes in second order neurons might explain the existence of allodynia Development of hypersensitivity

Table 3 continued

Inhibitory modulation	Inhibitory interneurons and the descending modulatory control systems are less functional in patients with neuropathic pain. Moreover, the brain (the limbic regions) receives transformed and abnormal sensory input via altered projections to the thalamus, cortex and parallel pathways. The cingulate cortex and amygdala are involved in persistent pain and are associated with neuropathic pain comorbidities [124]. Noradrenergic inhibition (via α_2-adrenergic receptors) in the spinal cord is reduced in patients with neuropathic pain. Consequently, enhanced serotonin signaling (via 5-HT2 and 5-HT3 serotonin receptors) becomes more leading.	High pain ratings, anxiety, depression and / or sleeping problems are transmitted as painful messages which dominates the limbic functioning The brainstem excitatory pathways are more important in the maintenance of pain than in pain induction. CPM is impaired or lost in patients with neuropathic pain.
Pain modulation mechanisms	A patient with neuropathic pain might experience mild or even debilitating pain. The difference might be influenced by the modulation of the pain signal in the central nervous system. The perception of pain by the patient can be disinhibited due to a decreased descending endogenous inhibition (known as a less-efficient conditioned pain modulation (CPM) and / or facilitated through sensitization of the ascending pain pathways (known as an enhanced temporal summation). Temporal summation may be increased in patients with as well as without neuropathic pain but in patients with neuropathic pain it is present with a more obvious increase [125].	CPM is less efficient in patients with pain than in healthy controls [126]. Influencing patients' pain modulation mechanisms might be promising for a personalized approach to treat patients with pain [127-129].

Based on animal and human research, it is clear that a lesion of the afferent pathways is necessary to develop neuropathic pain, but various mechanisms may lead to its development. Importantly, these mechanisms are not disease specific [47]. This indicates the complexity of neuropathic pain and draws attention to the importance of identifying the underlying pain mechanism in an individual patient to tailor the treatment regimen [47]. Colloca et al. [39] summarized several changes and alterations resulting from a lesion or disease in the somatosensory system related to neuropathic pain (table 3). These changes can occur in pain signaling with respect to electrical properties, ion channels, second order nociceptive neurons, the inhibitory modulations, and other pain modulation mechanisms, and have consequences for the pain experienced by the patient. Whether these changes in the pain modulation mechanisms are therapeutic targets should be the subject of future research [56-58].

EPIDEMIOLOGY, BURDEN, COSTS AND CONSEQUENCES OF CHRONIC PAIN, AND OF NEUROPATHIC PAIN IN PARTICULAR

Pain is a major clinical, social and economic problem. It has challenged generations of, amongst others, (para-)medical professionals, psychologists and researchers. However, for many patients, pain remains a threat to the quality of their daily lives.

Chronic pain

Epidemiology of chronic pain: based on surveys, chronic pain prevalence estimates range between 10%-30% [49]. In Europe, the prevalence of chronic pain is estimated, on average, to be 19%; in the Netherlands it is 18% [50]: patients in this survey suffered from pain for more than 6 months and had a pain intensity of ≥5 on a Numeric Rating Scale (NRS) ranging from 1 (no pain) to 10 (worst pain imaginable) at their last pain episode. Besides pain, 21% of the patients were diagnosed with depression because of the pain, and 61% had a reduced capacity for regular work. In the previous six months, they had visited a physician between 2-9 times. The majority of these patients were seen in primary care, only 2% of all patients were treated by a pain specialist. One-third of the patients received no treatment, overall 40% reported inadequate management of their pain. Management of patients' pain consisted of prescription medications, non-prescription medications, and/or non-pharmacological treatments such as physical therapy and cognitive behavioral therapy (CBT). The article also described the socio-demographic factors associated with chronic pain: female gender; older age; higher weight, lower socio-economic status; geographical and cultural background; history of alcoholism, employment status/ occupational factors, higher level of catastrophizing, and a history of abuse or interpersonal violence [51-54].

Burden of chronic pain: The most recent estimations of the global burden of disease are likely to underestimate the contribution of chronic pain [55-57]. The physical and emotional burden is high, which results in a lower quality and quantity of life, lower functional status (chronic pain impedes activities in daily life, less capability to work and less working efficiency) and lower mental health [49, 58]. There is a clear correlation between chronic pain and quality of life (QoL). Using the Short Form-36 General health Questionnaire (SF-36), the physical health composite score is about ten points lower in patients with chronic pain than in people with no pain [49]. An effective therapy for patients with chronic pain (a reduction of pain intensity of at least 50%) leads to improvements in fatigue, sleep, depression, QoL and work [49, 59].

Costs of chronic pain: the direct and indirect costs resulting from chronic pain are high. Direct costs are those which can be directly assigned to a disease, such as nursing days, outpatient consultations, operations, and medication, as well as travel expenses and treatment costs incurred by the patient. Indirect costs are those that cannot be attributed directly to a disease. These are, for example, costs incurred during extra years of life, or so-called production losses due to sickness absence. Moreover,

the costs and effects of informal care are also increasingly reflected in these indirect costs. In the USA, [60] chronic pain impacts 100 million adults and the annual costs are estimated at $560 to $635 billion; this is much higher than the economic costs of the six most expensive major diagnoses in the USA: cardiovascular diseases ($309 billion); neoplasms ($243 billion); injury and poisoning ($205 billion); endocrine, nutritional and metabolic diseases ($127 billion), digestive system diseases ($112 billion), and respiratory system diseases ($112 billion). The total costs due to chronic pain in the Netherlands are estimated at over €20 billion, annually [61].

Neuropathic pain

Epidemiology of neuropathic pain: the incidence of neuropathic pain in the Dutch general population [62] is 8.2 cases per 1000 person-years. Neuropathic pain is 63% more common in women than in men and has the highest prevalence in those aged between 70 and 79 [62]. In a systematic review by Van Hecke et al., [63] the population prevalence of pain with neuropathic characteristics was estimated to be between 6.9% and 10%. Moore et al stated that 7% of the patients with chronic pain suffered from pain due to an NePC [49]. Recently, the prevalence of probable neuropathic pain in the USA was estimated to be 10% [64]. In patients with cancer, the prevalence of pain with a neuropathic mechanism was estimated to be 18.7% -21.4% [65]. Due to aging, higher prevalence of diabetes mellitus, surgery, and the increasing incidence of cancer (with and without treatment with surgery and/or chemotherapy), peripheral neuropathic pain will probably be more common in the future because these diseases and their treatments can affect the sensory nervous system [39].

Burden of neuropathic pain: neuropathic pain is associated with a poor general health status; this is comparable to other severe chronic disease. All three dimensions, the physical, psychological, and social dimension are affected [66]. Patients with neuropathic pain have a lower health-related quality of life compared to the general population [67]. A survey using the SF-36 reported that Health-related QoL was as severely affected in patients with neuropathic pain as in patients affected with a coronary artery disease, clinical depression, recent myocardial infarct or inadequately controlled diabetes mellitus [68]. The physical component score of the SF-12 can be qualified as severe impairment: 94% of the included patients with neuropathic pain combined with breakthrough pain scored below the population mean score [69]. As suggested by Attal et al. [70] the specific signs and symptoms of neuropathic pain and the painful and/or unpleasant nature of these symptoms also have an impact on Health-related QoL.

Costs of neuropathic pain: neuropathic pain results in a substantial use of health resources, in particular by patients who have been referred to specialized pain clinics for pain control via primary care or other specialists [71]. The additional health care costs incurred in patients whose pain is mainly treated in pain clinics are compensated by lower costs of other pain management components, resulting in comparable average monthly total costs [71]. In a recent European study, Liedgens et al. concluded that there is an economic and socioeconomic burden due to neuropathic

pain as a result of healthcare and societal costs to the wider economy. The estimated total annual costs per patient with neuropathic pain range from € 9,305 (Italy) to €14,446 (Germany) [72].

THE ASSESSMENT OF NEUROPATHIC PAIN IN DAILY CLINICAL PRACTICE

Neuropathic pain is considered to be 'a difficult clinical entity' because of the lack of a diagnostic gold standard and the inadequate treatment response [73]. Examination, in particular physical examination of the patient, is important to link a patient's pain to a lesion or disease of the somatosensory nervous system. The goal of the assessment is to distinguish the neuropathic pain component from musculoskeletal pain and other types of pain, and to distinguish a neuropathic pain component from pain due to changes in the nociceptive system following, for example, inflammatory pain.

History taking and physical assessment: A key diagnostic item in history taking is the area of abnormal sensation described by the patient. Patients' pain is maximum within this area of sensory deficit. In addition to this 'region of pain', the patient describes pain with a burning, stabbing, lancinating, shooting sensation, together with, for example, tingling, crawling or electrical sensations. Moreover, in history taking, attention should be paid to the time course and the pain intensity [74]. Clinical examination by a (pain-)physician is most important when diagnosing a patient and in follow-up when looking for sensory abnormalities [75]. Patient sensory testing is the most important part (see bed-side examination). We advise that any clinical judgment is based on a comprehensive clinical assessment before classifying patients' pain.

Bedside examination: Bedside examination is an important method as it helps an individual patient clarify the disease and find the affected area corresponding to the injured nervous structure. Positive and negative signs and symptoms, location, quality and intensity of the pain should be tested together to assess a patient's pain. This should also include the testing of touch, vibration, pinprick, cold and warmth. In patients suspected of an NePC, quantification and mapping of motor, sensory and autonomic phenomena is valuable when describing the signs of a neurological dysfunction (for the methods for the assessment of nerve function see table 1). Bedside examinations in patients suspected for NePC provides insights into the pain of individual patients based on neurological examination, where the sensory examination is of major importance. However, the validity of bedside examination for assessing patients with neuropathic pain has yet to demonstrated [76].

Screening tools: Currently, a number of tools are available to screen for or to assess the existence of a neuropathic pain component: NPS [77], LANSS [78], NPQ [79], NPQ-SF [80], NPSI [81], DN4 [82], DN4 (interview, self-report) [82, 83], S-LANSS [84], Pain*DETECT* [28], ID Pain [85], PQAS [86], StEP [87], SF-MPQ-2 [88], FPQ [89] SCIPI [90], and the IT [91]. These instruments are translated or cross-culturally

adapted to different languages and are validated in different patient populations (partly) following the flow diagram in figure 2. For an overview of the objective and description of each instrument, see table 4. In a recently published systematic review regarding the measurement properties of these questionnaires, it was concluded that the Neuropathique Pain Questionnaire (NPQ) [79] and the DN4 [82] were the most suitable for use in daily clinical practice [92]. Screening tools are considered to be useful in identifying patients with a possible neuropathic pain component, especially when used by a non-specialist, and to provide added-value for further diagnostic assessment of the patient [74, 75]. This is their most important advantage; however, these screening instruments should never replace a thorough clinical assessment by a (pain-) physician.

NeuPSIG Grading system: In 2008, Treede et al. [10] presented a grading system for neuropathic pain suitable for both clinical and research purposes. This stepwise approach provides a working hypothesis for the origin of patient pain based on four evaluation criteria: 1) pain with a distinct neuroanatomically plausible distribution; 2) a history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system; 3) demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test; 4) demonstration of the relevant lesion or disease by at least one confirmatory test. A working hypothesis of 'possible neuropathic pain is provided when both criteria 1 & 2 are answered with 'yes': when one of criteria 3 & 4 is fulfilled, then the outcome is 'probable neuropathic pain'. When both criteria 3 & 4 are fulfilled, the outcome is 'definite neuropathic pain' (see figure 3).

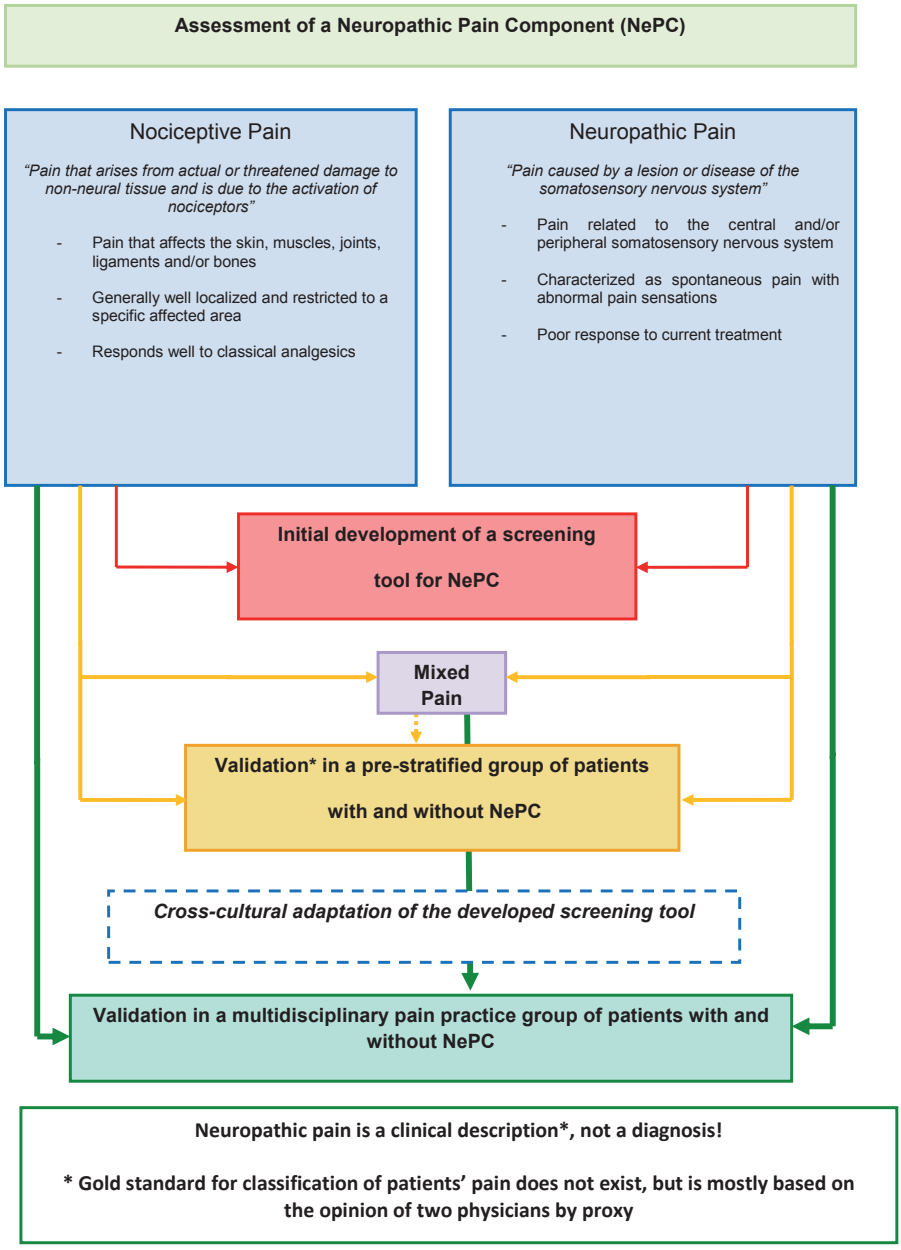


Figure 2: **The validation process of screening instruments for neuropathic pain until 2017**

Table 4: **Characteristics of screening tools and assessment tools for neuropathic pain**

Screening tools for the existence of neuropathic pain					
Tool	**Reference**	**Full name**	**Year**	**Objective**	**Description**
LANSS	[78]	Leeds assessment of neuropathic symptoms and signs	2001	To develop a novel tool for identifying patients in whom neuropathic mechanisms dominate their pain experience	Symptoms, via questions: strange or unpleasant sensations, skin looking different from normal, sensitivity to touch, pain suddenly and in bursts, skin temperature Sensory testing by physician: allodynia, altered pin prick threshold
NPSI	[81]	Neuropathic Pain Symptom Inventory	2004	To develop a new self-questionnaire specifically designed to evaluate the different symptoms of neuropathic pain	10 descriptors of the different symptoms: burning, squeezing, pressure, electric shocks, stabbing, evoked by brush, evoked by pressure, evoked by cold stimuli, pins and needles and tingling 2 items for assessing the duration of spontaneous ongoing and paroxysmal pain
DN4	[82]	Douleur Neuropathique en 4 questions	2005	To develop a clinician-administered questionnaire consisting of both sensory descriptors and signs related to bedside sensory examination	Symptoms, via interview: burning, painful cold, electric shocks, tingling, pins and needles, numbness, itching Signs, via physical examination: hypoesthesia to touch, hypoesthesia to prick, pain caused by brushing
DN4-interview	[82, 83]	Douleur Neuropathique en 4 questions-interview	2005	To develop a clinician-administered questionnaire consisting of sensory descriptors	Symptoms, via interview: burning, painful cold, electric shocks, tingling, pins and needles, numbness, itching
S-LANSS	[84]	Short form-Leeds assessment of neuropathic symptoms and signs	2005	To identify pain of predominantly neuropathic origin, as distinct from nociceptive pain, without the need for clinical examination	Body diagram Level of pain Symptoms, via questions: pins and needles, tingling or prickling, changes of color in the painful area due to pain, allodynia, pain comes suddenly and in bursts (electric shocks, jumping, bursting etc.), skin feeling unusually hot Signs, via self-examination by the patient: rubbing the painful area with finger (discomfort like pins and needles, tingling or burning), pressing in the painful area (numbness or tenderness)

Pain*DETECT*	[28]	Pain*DETECT*-questionnaire	2006	To establish a simple validated screening tool to detect neuropathic pain components in chronic low back pain patients.	Level of pain Body diagram Pain course pattern Radiation of pain Symptoms, via questions: burning sensation, tingling or prickling sensation, allodynia, sudden pain attacks, like electric shocks, cold or heath is painful, numbness, slight pressure triggering pain
ID Pain	[85]	ID Pain	2006	To develop a patient-completed screening tool to help differentiate nociceptive and neuropathic pain.	Body diagram Symptoms, via questions: pins and needles, hot/ burning, numb, electrical shocks, allodynia, pain limited to joints
Sf-MPQ-2	[88]	Expanded and revised version of the Short Form McGill Pain Questionnaire	2009	To develop a single measure of the major symptoms of both neuropathic and non-neuropathic pain	Questions about throbbing pain, shooting pain, stabbing pain, sharp pain, cramping pain, gnawing pain, hot-burning pain, aching pain, heavy pain, tender, splitting pain, tiring-exhausting, sickening, fearful, punishing-cruel, electric-shock pain, cold-freezing pain, piercing, pain caused by light touch, tingling or pins and needles, numbness
SCIPI	[90]	Spinal Cord Injury Pain Instrument	2017	To develop a spinal cord injury specific neuropathic pain screening tool	Questions about pain: electrical or electric shock like, pins and needles or tingling, hot or burning or cold or freezing, skin abnormally sensitive to touch, pain unchanging due to movement, experiencing pain all the time when awake, pain in an area where there is no feeling in the skin overlying that area.

Table 3 continued

Assessment tools for the existence of neuropathic pain

Tool	Ref.	Full name	Year	Objective	Description
NPS	[77]	Neuropathic Pain Scale	1997	To develop a scale which is designed to assess distinct pain qualities associated with neuropathic pain	Symptoms via questions: intensity, sharpness, heat, dullness, cold, sensitivity and itchy. Unpleasantness via question Intensity of deep and surface pain via question
NPQ	[79]	Neuropathic Pain Questionnaire	2003	To develop an assessment instrument intended to measure neuropathic pain based on qualities of pain as they are inferred from pain descriptors	Symptoms, via questions: burning, sensitivity to touch, shooting pain, numbness, electric pain, tingling pain, squeezing pain, freezing pain, unpleasant, overwhelming Circumstances, via questions: increased pain due to touch, increased pain due to weather changes
NPQ-SF	[80]	Neuropathic Pain Questionnaire – Short Form	2003	To develop an assessment instrument intended to measure neuropathic pain based on qualities of pain as they are inferred from pain descriptors with a minimum number of items sufficient to predict diagnostic group membership	Symptoms, via questions: tingling pain, numbness Circumstances, via question: increased pain due to touch
PQAS	[86]	Pain Quality Assessment Scale	2006	To add additional items to the original NPS to become more useful for assessing neuropathic pain and to assess pain qualities associated with non-neuropathic pain	Questions about intensity, sharpness, hot, dull, cold, sensitivity, tenderness, itchy, shooting, numbness, electrical, tingling, cramping, radiating, throbbing, aching, heavy, unpleasantness, intensity of deep and surface pain.
StEP	[87]	Standardized Evaluation of Pain	2009	To develop a tool for a standardized assessment of pain-related symptoms and signs that differentiates pain phenotypes independent of etiology	Structured interview: location, temporal characteristics, quality, pain evoked by body positions, non-painful sensations, current pain Standardized physical examination: skin, touch, blunt pressure, brush movement, vibration, pinprick, warm temperature, cold temperature, temporal summation, straight-leg-raising test

FPQ	[89]	Fabry Pain Questionnaire	2014	A questionnaire specifically designed to assess Fabry disease-associated pain	Questions about how the pain feels, pain duration in pain attacks and pain crisis, pain triggered by touch, cold, warmth or pressure, sensory impairment like tingling or numbness in the painful body area
IT	[91]	Identification Tool	2018	To operationalize the IASP criteria into a clinically convenient procedure	Four screening questions. First two refer to patient history of pain and the neuroanatomically plausibility of the distribution of pain. The third question is about performing simple sensory tests to reveal sensory aberrations. The fourth question is about measuring the size of the area of maximum pain.

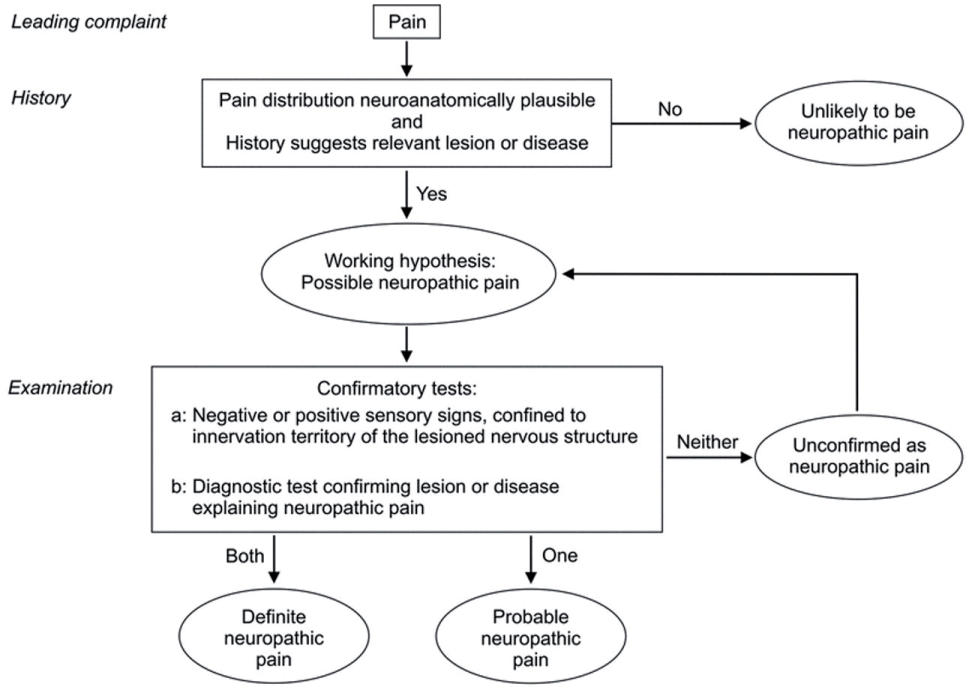


Figure 3: The grading system. Adapted from Treede et al., Neurology, 2008 [10]

Quantitative Sensory testing (QST): QST is defined as *"the analysis of perception in response to external stimuli of controlled intensity"* [76]. The QST-method is based on the German research network of neuropathic Pain (DFNS) protocol and has been precisely described, and reference data are available [93-97]. The detection thresholds, pain thresholds, and pain tolerance thresholds are determined using stimuli applied directly to the skin. The major added-value in comparison with bedside examination is the use of well standardized instruments, such as von Frey filaments, weighted needles, and thermal testing instruments. QST is used in the early diagnosis of diabetic neuropathy as well as in small fiber neuropathies [98]. Moreover, QST may prove of value when describing painful neuropathic diseases and in explaining some of the underlying mechanisms.

The Nijmegen-Aalborg Screening Quantitative Sensory Testing (NASQ) [99] protocol can be used to explore the underlying mechanisms of pain. NASQ screens for changes in pain processing based on a systematic mechanism-oriented approach [99, 100]. To gather information about the neural transmission of 'noxious stimulation', widespread hyperalgesia, and the multiple endogenous modulatory processes in the body, NASQ is used to make either anti-nociceptive or pro-nociceptive pain visible [101]. The NASQ protocol can be used to measure static pain thresholds (making a stimulus response curve for sensory thresholds, pain thresholds and pain tolerance thresholds for

pressure algometry as well as electrical stimuli). Dynamic pain tests such as the Conditioned Pain Modulation (CPM) paradigm [102-104], also known as the "pain inhibits pain" phenomenon, measure an inhibitory mechanism like diffuse noxious inhibitory controls. This indicates that peripheral and central mechanisms play a role in the way the body handles nociception.

Currently, there is cumulative evidence that pain and sensitization play an essential role in the development of chronic pain [105]. An understanding of the pathophysiology of acute pain and of the development of chronic pain are essential to improving patient outcomes and in making a mechanism-based treatment. Both QST and NASQ are difficult to implement in daily clinical practice as they are time consuming and require expensive instrumentation. However, test-retest reliability and the interrater reliability are both classified as good if tests are performed by trained examiners [96].

Neurophysiological techniques: Following the definition of neuropathic pain and to fulfill the NeuPSIG grading criteria, confirmation of a lesion or disease affecting the central or peripheral nervous system is a prerequisite for the outcome 'definite neuropathic pain'. Several techniques are described in the literature, such as nerve conduction studies via electromyography (EMG) testing large-fiber affection in, for example, patients with HIV. Skin wrinkle tests and quantitative sudomotor axon reflex testing (QSART) are used for testing small fibers, and somatosensory evoked potential testing (SSEP) is used to detect sensory abnormalities in, for example, the trunk or proximal limb regions. Nerve ultrasound has proved to provide reliable information for by example nerve entrapments during the diagnostic work-up of neuropathic pain. Positron emission topography (PET) is used to target specific ligands and to access detailed information about the neurotransmitters. Functional magnetic resonance imaging (fMRI) makes it possible to gather information about blood deoxygeneration and changes in metabolites via spectroscopy. Electrophysiological methods, such as the nociceptive withdrawal reflex, and electroencephalography (EEG) including (laser)-evoked potentials and resting-state EEG provide complementary information and reflect real-time activity in the neural system [29, 75, 106-109].

REQUIREMENTS FOR A SCREENING TOOL TO ASSESS (NEUROPATHIC) PAIN

Screening tools for the assessment of NePC such as the Pain*DETECT* and the DN4 are biopsychological measurements. These instruments screen for the presence of NePC via a set of items related to various pain descriptors. The individual items and the outcomes of the questionnaires reflect the patient's perception of the pain. Instruments like the Pain*DETECT* and the DN4 are in current use in daily clinical practice, research and education. Their popularity in daily clinical practice and in research is partly due to their simplicity and ease-of-use when identifying potential patients with

NePC and their immediate provision of information, in particular by non-specialists [47, 110]. BSE and NASQ are other biopsychological measures that examine the negative (loss of function) and positive (augmented excitation, for example hyperalgesia and allodynia) signs, and to gain insights into the underlying lesion or disease [29]. These observations rely, at least partly, on the patients' evaluation of pain and on the physician's experience with performing the tests [111].

It is hard to understand the manifestation, the time course and the impact of patients' pain and therefore difficult to find the right solution or management for patients' pain when symptoms of pain are not systematically documented. An effective diagnosis, prognosis and treatment of patient's pain must be based on the underlying (pain) mechanisms. To achieve this, a number of valid, and reliable tools have been developed to assess chronic pain. The measurement of pain and the underlying pain systems is important to understand its origin, intensity, quality and the progress suffered by the patient during the treatment process, but it has to be accepted that the symptoms as provided by the patient and arising from the clinical examination by the physician only gives a few insights into the underlying pain mechanisms and the pain diseases resulting from a changing somatosensory system [112].

Assessing patients suffering from pain in daily clinical practice serves several goals: screening, diagnosis, therapy and monitoring. The goal of screening is the initial triage of patients, for example by referring them for more diagnostic research or by placing them in a specific clinical treatment trajectory. Individual patients can be classified in specific sub-groups with common underlying pain mechanisms to undergo, for example, a similar pain treatment. Differential diagnosis, prognosis, the prediction of the process and/or outcome of the disease; all these form an important part of the assessment of patients' pain [112]. The choice of therapy is based on a patient's diagnosis and the impact and course of the disease. Moreover, a patient's diagnosis is also related to the disease mechanisms [29, 74, 75]. To increase the chance of a positive treatment outcome, it is necessary to be able to identify responders versus non-responders. However, this is not always possible for patients with pain: the mechanism(s) that underlie the presentation of pain are not always known, which therefore reduces the probability of a correct diagnostic profile and consequently an adequate management of treatment. Finally, the goal of monitoring is to follow the evolution, the treatment response and duration of the disease in patients [112].

Measuring pain

A regular, structured and standardized documentation of the pain suffered by a patient is a prerequisite for an effective and timely treatment and follow-up. An important difference between the avaliable pain measurement instruments is whether the measurements are made in terms of quantity or quality and dimensionality. At a quantitative level, it is necessary to measure how much pain the patient is suffering from (pain intensity), how long the patient has been suffering from the pain (time), and where the pain is located. At a qualitative level the patient will be asked how much

the pain functionally limits the patient (disability), how much it affects the patient's daily life (quality of life), and how the patient deals with the pain (coping). Patients' pain quality can be characterized at a more qualitative level by describing feelings like the feeling of pins and needles, burning, stabbing or itching. Dimensionality reflects either uni-dimensionality, for example the amount of pain, and/or multi-dimensionality, where data comes from multiple perspectives, such as level of pain, experience of pain and behavior [112].

Requirements to measuring instruments

The value of a measurement instrument for pain is determined by its (clinimetrical) quality. This includes the quality of the measurement instruments as well as the performance of the actual measurement. Important indicators are the performance of the translation process, the reliability, validity, responsiveness, and sensitivity for change, as well as quality assurance [112].

Translation and cross-cultural adaptation: translation is the process of translating an instrument from one language into another. The term 'cross-cultural adaptation' is used when both language *and* culture are considered in the process of the preparation of an instrument that is to be used in another language and/or another country to provide equivalency, based on content, between source and target language [113-115]. After translation or cross-cultural adaptation, the instrument's face validity can be assessed, the extent to which a test is subjectively viewed as covering the concept it purports to measure.

Reliability: the reliability of an instrument expresses the measure in which the instrument shows the same result if used again on the same person (test-retest reliability or inter-assessor reliability). The reliability can also be expressed as intra-assessor reliability: will two different assessors reach the same conclusion? The inter- and intra-assessor reliability are both only valid if no changes in the disease, conditions or the circumstances have occurred between the assessments [116].

Validity: the validity of an instrument is the way in which an instrument measures what it intends to measure. This is determined on the basis of a 'gold standard'; an instrument or method for which it has been proven that it documents the presence or absence or the stage of the same condition, and for which people know beforehand that it is 'true', or that it is, at least, the best available test [117]. An instrument can be reliable without being valid, but a valid instrument must be reliable [116]. Important features for screening tools that assess NePC are the construct validity, content validity, criterion validity, and external validity. The theoretical embedding of the neuropathic pain concept is captured in the construct validity: how well does the test measure what it intends to measure. Construct validity consists of convergent and discriminant validity. Convergent validity is achieved when different tools that measure the same concept yield the same results (converge). On the other hand, an instrument must distinguish the concept which it intends to measure from other concepts (discriminate). Content validity refers to the question whether the content of the

instrument (asked questions, used measurement scales) represents all elements of the construct. The term criterion validity refers to the extent to which the outcome of the instrument is related to one or more criterion variables. Criterion validity is accessed via sensitivity, specificity and predictive value. External validity is important to assess and to see to which extent the outcomes obtained with the instrument are generalizable to other situations, other groups of patients, or to other concepts. Diagnostic procedures are used for clinical decisions, and therefore imply a certain risk for a patient as an incorrect diagnosis might harm the patient. From this perspective, it is important to assess the validity of a measuring instrument for each condition and per (sub-)population, as the fact that an instrument is valid for a specific group of patients with a certain diagnosis does not automatically mean that it is also valid for patients who suffer from another condition [112].

The sensitivity of a measuring instrument indicates which percentage of those suffering from certain diseases are (accurately) classified as ill by the measuring instrument [118]. The specificity of the measuring instrument indicates which percentage of a group of people not affected by the disease are (accurately) classified as not being ill [118]. The predictive value (also known as the diagnostic value) gives an indication for the chance that the person with the relevant test result will have the disease or condition now or in the near future [119]. A positive and/or negative predictive value refers to the chance that a disease or condition is present or absent in people with a certain test result. If an instrument has a high sensitivity, only a few patients suffering from the disease or condition are missed, it leads to a higher positive predictive value. If an instrument has a high specificity, only a few patients suffering from the disease or condition are incorrectly classified as suffering from this disease or condition, it results in a higher negative predictive value [119]. The number of people suffering from the disease or condition in the population on whom the measuring instrument is used at any given moment is called the prevalence. The prevalence influences the sensitivity, specificity and the predictive value. When the condition frequently occurs within a population, this will lead to a higher positive predictive value. At a lower prevalence, the number of false-positive test results will increase on the basis of coincidence [119]. For this, the (positive) likelihood ratio can be used which gives an indication of the value of an instrument for increasing certainty about a positive diagnosis [119]. However, as indicated by Altman and Bland [119], a high positive likelihood ratio might show that an instrument is useful, but that it cannot ensure that a positive test is a certainty for the presence of a disease [119].

Responsiveness: in (pain) measurement instruments that are used frequently over a longer period (for example for follow-up research), it is important to know whether the instrument shows any changes that have taken place in that time [116].
Quality of performance: The measuring instrument must be suitable for the situation for which it is to be used (practical applicability), for the purpose of the research (e.g. screening for an epidemiological study or serve as a diagnostic assessment by the physician), the population under

investigation (number and composition of the group) and for the person performing the assessment (e.g. experience, time and costs) [116].

Quality control and assurance: the reproducibility of pain measurements is crucial and depends on the instruction of the patient and a correct measurement by the patient, the physician, the nurse or the researcher. Staff performing the measurements and /or interpreting the results must be trained in how to use the instrument(s) to ensure that these are used in a standardized and reproducible way following the applicable protocols. All staff involved should follow theoretical and/or practical refresher courses to guarantee continuation of equal measuring quality. Participation in regular quality circles also contributes to a consistent and reliable pain measurement and interpretation quality [112].

RESEARCH QUESTIONS IN THIS THESIS

A better characterization of patient pain based on a thorough assessment in daily clinical practice increases the chance of discovering the underlying (pain) mechanisms. This can lead to a better-founded pain diagnosis and is a prerequisite for choosing an effective treatment for the individual patient, if available, as well as for the subpopulation of patients with pain. Screening tools help physicians to assess pain, but they are also valuable for monitoring the progress of patient treatment in research projects, as well as for assessing the incidence/prevalence of a disorder like neuropathic pain. At this moment, the DN4 has been translated into Dutch, whereas the Pain*DETECT* is only validated in its (original) German version with an English translation. The interobserver reliability of the assessment of neuropathic pain in patients between two physicians in the Netherlands in specific patient populations is still unknown.
This is of importance because a 'true' gold standard for the NePC assessment does not yet exist. A valid screening tool would therefore be of value for both family practice and for specialized (academic) pain centers to help and guide the classification of patient pain. Therefore, the aim of two of the studies in this thesis is to assess the psychometric properties of the two screening instruments (Pain*DETECT* and DN4) to assess the neuropathic pain component in a consecutive, daily practice population of patients with low back and leg pain, neck-shoulder pain, or with pain due to a suspected peripheral nerve damage. Validation in a more general population and in a clinical setting is important as the outcome may differ from validation studies set in more controlled, experimental settings with selected patients. A second aim is to assess the possible benefits of BSE and NASQ to distinguish between clinically diagnosed patients with and without NePC.

Question 1: Is a cross-cultural adaptation a prerequisite for achieving a valid Dutch translation of a screening tool for neuropathic pain?

Question 2: What is the reliability of clinical judgment as a surrogate for the lack of an objective gold standard in diagnosing a neuropathic pain component in patients with chronic pain?

Question 3: What are the psychometric properties of the Pain*DETECT* and the DN4 questionnaire when used as screening tools in a daily practice consecutive patient population (patients with low back pain, neck shoulder or arm pain, or pain from a suspected neuropathic origin), not pre-stratified on target outcome, for NePC detection?

Question 4: What is the potential association between clinically diagnosed, via two independent and trained professionals, absent or present NePC, and bedside examination / screening quantitative sensory testing (NASQ) in patients with chronic pain?

OUTLINE OF THIS THESIS

In **chapter 2** we discuss the process of the cross-cultural adaptation of the Pain*DETECT*-questionnaire into Dutch for use in the Netherlands and Belgium. **Chapter 3** describes the interobserver reliability in daily clinical practice for the assessment of neuropathic pain in patients with cancer. **Chapter 4** presents a detailed study protocol for the validation of screening instruments to assess a neuropathic pain component; this is then used for the studies in chapter 5, 6 and 7. In **chapters 5 and 6** we describe the validation of the Pain*DETECT* questionnaire and the DN4 in a consecutive population of patients with chronic pain. In **Chapter 7** we describe the added value of bedside examination and screening-QST to improve neuropathic pain identification in patients with chronic pain. In **chapter 8** I discuss the results of our studies in this thesis in a broad, scientific context and provide suggestions for future directions in (validation) research and for the use of screening tools in daily clinical practice.

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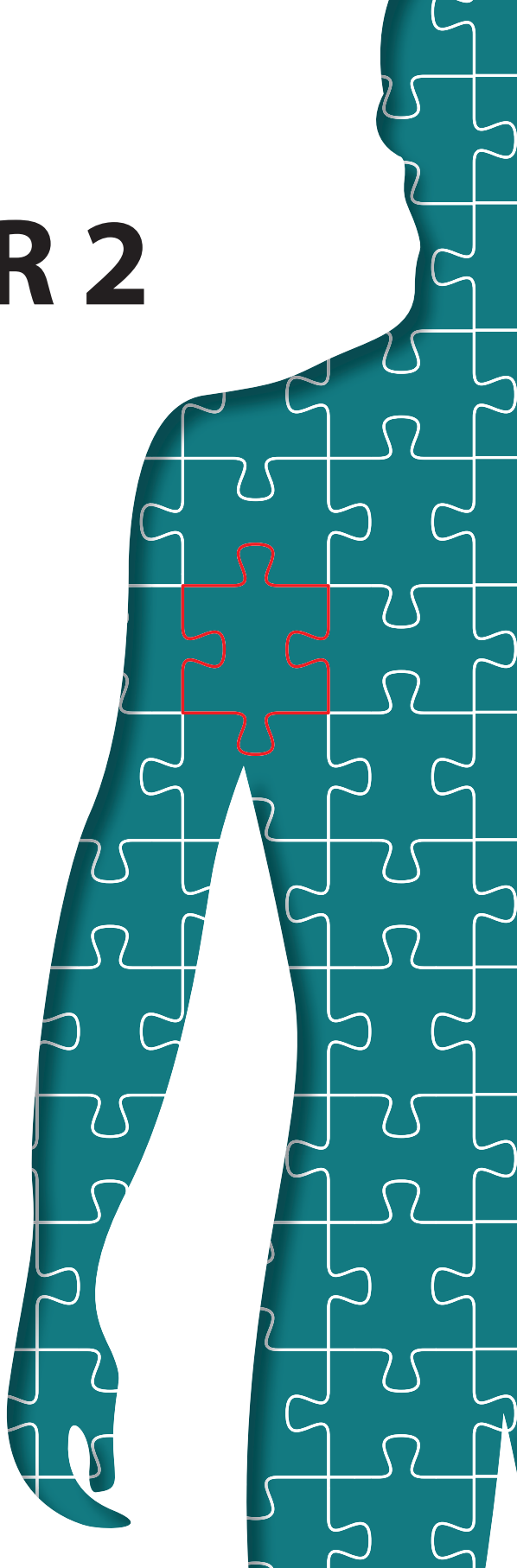
CHAPTER 2

Cross-Cultural Adaptation to the Dutch Language of the Pain*DETECT*-Questionnaire



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ABSTRACT

Background

The Pain*DETECT*-Questionnaire (PDQ) helps to identify neuropathic components in patients suffering from pain. It can be used by clinicians in daily practice and in clinical trials.

Aim

The aim of this study is to perform a translation and cross-cultural adaptation of the PDQ for use in the Netherlands and Belgium.

Methods

The first phase was to translate and cross-culturally adapt the PDQ to Dutch. The second phase was to assess the face validity in the Netherlands and Belgium using qualitative and quantitative data collection.

Results

The length, the readability, and the clarity of the questionnaire were good for all patients. The questionnaire was judged to have a good layout and to be clearly organized.

Conclusion

The PDQ Dutch language Version is a well translated and cross-culturally adapted questionnaire, which might be useful for screening for neuropathic components of pain in the Netherlands and Belgium.

Key Words

Neuropathic pain, translation, cross-cultural adaptation, validation, Pain*DETECT*-Questionnaire, PDQ

INTRODUCTION

Neuropathic Pain (NeP) is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [1]. NeP is characterized by spontaneous pain and abnormal pain sensations [2]. Clinically, NeP is typically described as a constant burning pain with spontaneous sharp exacerbations and somatosensory abnormalities [3]. As a rule, NeP has a considerable impact on the quality of daily life [4]. The incidence of NeP in the Dutch general population is 0.81% or 130.000 new patients in the Netherlands per year. NeP is 63% more common in women than in men and peaks between 70 and 79 years of age [4].

Medical history and (highly valid) screening tools may help to identify or differentiate between NeP, nociceptive pain (NoP), and mixed pain syndromes [5-7]. Since 1996, various questionnaires have been developed in different countries for the screening of neuropathic pain components based on verbal pain description, with or without physical examination or attention to quality of life [8-17]. Such questionnaires have been translated or cross-culturally adapted into different language settings [18-25]. The term "cross-cultural adaptation" is used to define an important process that considers both language and culture in the process of preparing a questionnaire in another language and/or another country to provide equivalency between source and target language based on content [26]. For example, the Netherlands are Dutch speaking, and parts of Belgium are Flemish speaking (almost the same as Dutch, but interpretation and use of some words may vary). Because of slight differences in language and sociocultural characteristics between the Netherlands and Belgium, it is necessary to perform an adaptation in both countries. Moreover, it is useful to have this instruments in a well-adapted Dutch language version not only for national studies but also to permit participation in multinational studies [26-28].

The Pain*DETECT* © Questionnaire (PDQ) (Pfizer GmbH, Berlin, Germany; 2005) was developed in Germany [13] and tested as a reliable screening tool with high sensitivity (85%), specificity (80%), and positive predictive accuracy (83%) for NeP. In the Spanish version of the PDQ sensitivity is 75%, specificity 84%, and the positive predictive value is 92% [25]. The PDQ is a questionnaire that can be filled in by the patients themselves and was devised to screen for neuropathic signs and symptoms without physical examination.

The aim of this study is to achieve a cross-cultural adaptation of the PDQ for use in the Netherlands and Belgium. The Pain*DETECT* © Questionnaire Dutch language version: PDQ_{-DIv} (Pfizer, GmbH, Berlin, Germany; 2008). Subsequently, this PDQ_{-DIv} will be used to assess face validity, as a first step in a validation trajectory for this questionnaire in the Netherlands and Belgium.

METHODS

The medical and ethical review board (CCMO Arnhem/Nijmegen, Nijmegen, the Netherlands) gave approval to conduct this study. All patients signed an informed consent form prior to participation in the study.

Translation of the PDQ

The process of cross-cultural adaptation of the PDQ to Dutch was based on the 10 steps as described in the ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Task Force guidelines [28] (Figure 1). The source questionnaire and the translations by translator 1 (T1), translator 2 (T2), back translator 1 (BT1), and back translator 2 (BT2) together with the preliminary Dutch version (Translation T1 to 2) were discussed item by item in a multidisciplinary expert committee review during the harmonization phase: (AW) a physician experienced in the treatment of (chronic) pain, (AE) a medical psychologist experienced in the translation, development and use of measurement instruments (German native speaker and fluent in Dutch), (RF) the developer of the Pain*DETECT*-questionnaire, physician and experienced in the treatment of (chronic) pain (German native speaker participating by telephone), and (HT) the project manager, in close contact with both the forward- and backward translators, to prepare the pre-PDQ-$_{Dlv}$. Special attention was given to three kinds of equivalence: (1) Semantic equivalence / Idiomatic equivalence: The similarity of meaning of each word or colloquialism in each culture after translation, (2) Experiential equivalence: Assessing the experiences of daily life, and (3) Conceptual equivalence: In different cultures, words can have different conceptual meaning. The committee searched both the source and the (back-) translations for all such equivalences and adapted them to the most fitting meaning in Dutch [26-27]. In the cognitive debriefing phase, the authors used qualitative semi-structured interviews to ask the patients about the questionnaire and their understanding of the questions. It was performed by one researcher from the review committee (HT) in a group of randomly selected patients in an outpatient pain clinic (n = 10, seven women; mean age 58 years [± 16.2 years]) and in a group of researchers (n = 4, two women; mean age 32 [± 4 years]).

Testing the PDQ

After finalizing the translation, the quality of all the different versions in the cross-cultural adaptation process were assessed using a 3-point scale [29]. The items were categorized (Cat.) as (Cat. 1) "different meaning in each version", (Cat. 2) "almost the same meaning in both versions", or (Cat. 3) "exactly the same meaning in both versions". Comparison of items was performed between translation T1 and translation T2 by both forward translators, between back translation BT1 and back translation BT2 by both backward translators. Comparison between the backward translation BT1-2 and the source PDQ was performed by one of the developers of the questionnaire (RF). The final comparison was between the source PDQ and the PDQ-Dlv during the harmonization phase and the review of the cognitive debriefing results. After completion of the whole process, a quality control process was implemented.

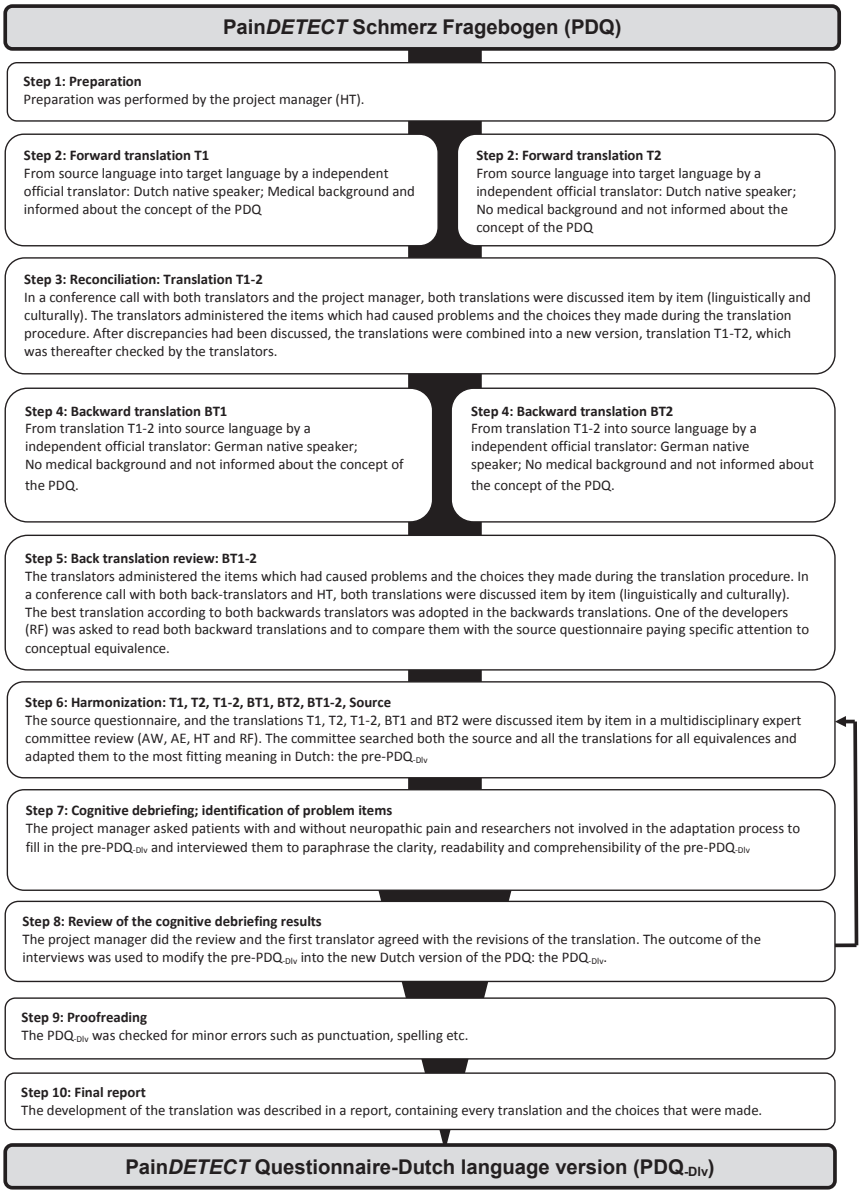

Figure 1: Flow diagram of the cross-cultural adaptation process.

T1: forward translation 1; T2: forward translation 2; BT1: back translation 1; BT2: back translation 2; BT1-2: back translation based on BT1 & BT2; Source: original German Pain*DETECT*-Questionnaire; pre-PDQ-DIv: preliminary Pain*DETECT*-Questionnaire Dutch language version; PDQ-DIv: Pain*DETECT*-Questionnaire Dutch language version.

by two researchers (TS: German native speaker, fluent in Dutch; and JO: Dutch native speaker, fluent in German) who had not been involved in the translation pprocessprocess until that point The face validity was assessed in the Netherlands (N = 30, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands/general practice in the Netherlands) and in Belgium (N = 30; Ziekenhuis Oost-Limburg, Genk, Belgium) based on semi-structured interviews by patients with pain of different origins as diagnosed by a physician. Gender, age, and time necessary to fill in the questionnaire were recorded. The semi-structured interview was based on eight questions (as listed in Table 2 below). All the questions were answered on a Visual Analogue Scale (VAS) of 100 mm. After the patient filled in the VAS on an item, it was followed by an open question in which he or she was encouraged to explain his or her understanding of the item [30].

Statistical Analysis

All data were entered and analyzed in the Statistical Package for the Social Sciences (SPSS version 17.0; SPSS Inc., Chicago, IL, USA) and checked for completeness and normality using the Kolmogorov-Smirnov test. A significance level of $P \leqq 0.05$ was chosen (two-sided). Descriptive statistics were computed, and comparisons between the Netherlands and Belgium at baseline were performed using the Mann-Whitney U-test.

RESULTS

The PDQ consists of 62 items. During the harmonization and cognitive debriefing-phase textual amendments were made (Table 1). The items of the PDQ were linguistically and culturally assessed by the translators and the harmonization group by use of the 3-points scale (Figure 2). When comparing T1 and T2, three items were scored as "different meaning in each version" and 23 items as "almost the same meanings in both versions". Comparison between the backward translation BT1 to 2 and the source showed two items scored as "different meaning in each version" and two items as "almost the same meaning in both versions". A multidisciplinary expert committee (AW, AE, HT, and RF), in close contact with both the forward- and backward translators, was used to prepare the pre-$PDQ_{\text{-DIV}}$. During this harmonization phase, four items were changed based on commentary by one of the developers of the questionnaire and the choice for a more conceptual than literal translation, which would give a better understanding by the patient. In the last comparison, between the source and the $PDQ_{\text{-DIV}}$, there were only two items with almost the same meaning in both versions (these were the items which were changed according to the cognitive debriefing). The quality control of the translation was performed afterward by two researchers (JO & TS) who had not been involved in the translation process until that moment. No item was scored as having different meaning in each version between $PDQ_{\text{-DIV}}$ and the source. Rater A scored 60 times "exactly the same meaning in both versions" (96.8%), rater B 53 times (87.1%) (Figure 3).

Table 1: Changes Made in the Harmonization Phase After the Cognitive Debriefing

Prelimenary PDQ_{-DIv}	*PDQ German version*	PDQ English version	PDQ_{-DIv}	Remarks
Kruis de afbeelding aan die het verloop van uw pijn het beste weergeeft:	Kreuzen Sie das Bild an, welches Ihren Schmerzverlauf am besten beschreibt:	Mark the picture that best describes the course of your pain:	Kruis één afbeelding aan die het verloop van uw pijn het beste weergeeft:	Based on the cognitive debriefing we changed the question: 'Mark the picture that best describes the course of your pain ' in 'Mark one picture that best describes the course of your pain'. 3 of 10 patients have been marking more than one picture.
Straalt de pijn uit naar andere delen van het lichaam?	Strahlt Ihr Schmerz in weitere Körperregionen aus?	Does the pain radiate to other regions of your body?	Straalt de pijn uit naar andere gebieden van het lichaam?	In the preliminary version of the PDQ we asked the patient if the pain was radiating to other body parts. Intended in the original questionnaire was other regions. We changed it on base of the commentary by the developer.
Zo ja, geef dan de richting aan waarin de pijn uitstraalt.	Wenn ja, dann zeichnen Sie bitte die Richtung ein, wohin der Schmerz ausstrahlt.	If yes, please draw the direction in which the pain radiates	Zo ja, teken dan de richting en de plaats waarheen de pijn uitstraalt	Based on the cognitive debriefing we changed the remark:'If yes, please draw the direction in which the pain radiates' into 'If yes, please draw the direction and the place in which the pain radiates' because of the fact that two patients draw a very otal arrow to indicate the direction instead to mark towards the spot till where the pain radiates
Hebt u in het gebied van uw pijn een kriebelend gevoel (zoals mieren, zwakke stroom)?	Haben Sie im bereich Ihrer Schmerzen ein Kribbel- oder Prickelgefühl (wie Ameisenlaufen, Stromkribbeln)?	Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?	Hebt u in het gebied van uw pijn een kriebelend gevoel (zoals mieren, zwakke stroom)?	The word 'prickling' (in German 'Prickelgefühl') could be translated to Dutch as 'prikkend' and 'prikkelend'. 'Prikkend' is also the same as the English word 'stinging' so the Dutch word 'prikkelend' is used in the translation.

Table 1 continued

Hebt u in het gebied van uw pijn schietende pijnaanvallen. Als elektrische schokken?	Haben Sie im Bereich Ihrer Schermz blitzartige, elektrisierende Schmerzattacken?	Do you have sudden pain attacks in the area of your pain, like electric shocks?	Hebt u in het gebied van uw pijn schietende pijnaanvallen, als electrische scheuten?	'electric shocks' Is translated to Dutch as 'elektrisch scheuten'. We choose not the use of the word 'shock' because the meaning of the word is in Dutch like very heavy electrical shocks. The meaning here is about the feeling of the pain and not only about the heaviness of the shock
Deze vragenlijst kan niet de diagnose van een arts vervangen! Deze vragenlijst is bedoeld om te screenen op aanwezigheid van een neuropathische pijncomponent.	Dieser Bogen ersetzt keine ärtzliche Diagnostik! Er dient dem Screening auf Vorliegen einer neuropathischen Schmerzkomponente.	This sheet does not replace medical diagnostics. It is used for screening the presence of a neuropathic component	Deze vragenlijst kan geen medische diagnostiek vervangen! Deze vragenlijst is bedoeld om te screenen op aanwezigheid van een neuropathische pijncomponent.	In the preliminary version we mixed up diagnosis and diagnostics. In the first version we said: 'This questionnaire cannot replace medical diagnosis' instead of 'This questionnaire cannot replace medical diagnostics'. We changed it on base of the commentary by the developer.

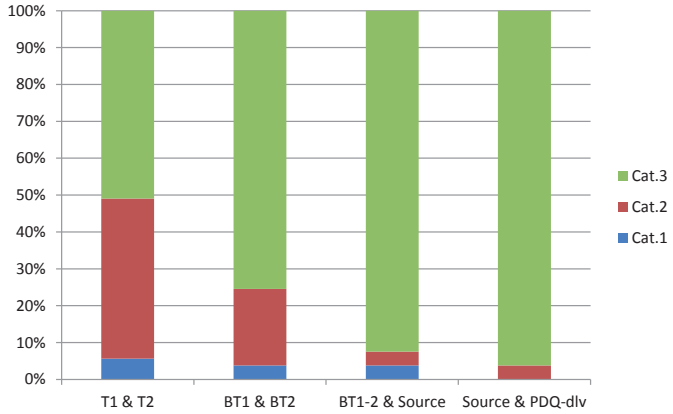

Figure 2: Translation process: degree of agreement.

T1: forward translation 1; T2: forward translation 2; BT1: back translation 1; BT2: back translation 2; BT1-2: back translation based on BT1 and BT2; Source: original German Pain*DETECT*-Questionnaire; PDQ-Dlv: Pain*DETECT*-Questionnaire Dutch language version; Cat.1: different meaning in each version; Cat. 2: almost the same meaning in both versions; Cat. 3: exactly the same meaning in both versions.

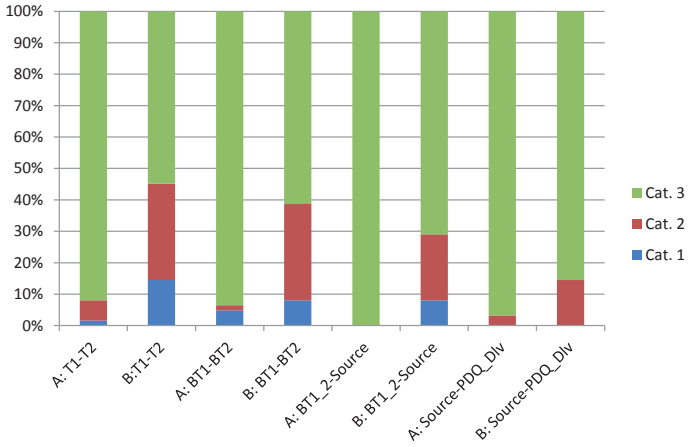

Figure 3: Quality control after the translation process.

A: rater A; B: rater B; T1: translation 1; T2: translation 2; BT1: back translation 1; BT2: back translation 2; BT1-2: back translation based on BT1 & BT2; Source: original German Pain*DETECT*-Questionnaire; PDQ-Dlv: Pain*DETECT*-Questionnaire Dutch language version; Cat.1: different meaning in each version; Cat.2: almost the same meaning in both versions; Cat.3: Exactly the same meaning in both versions.

Table 2: Results of Testing the PDQ-Dlv in Patients in the Netherlands and Belgium

	Total participants (N=60)	The Netherlands (N=30)	Belgium (N=30)	Mann-Whitney U-test
Gender (Man/Women)	36/24	19/11	17/13	
Age (years ± SD)	54 (± 15)	54 (± 15)	52 (± 18)	,338
Duration of the complaints (months (± SD)	79 (± 106)	87 (± 122)	70 (± 90)	,511
Pain score at this moment (NRS 0-10 ± SD)	5.6 (± 2.5)	5.9 (± 2.5)	5.4 (± 2.6)	,531
Strongest pain during the past 4 weeks (NRS 0-10 ± SD)	7.5 (± 2.0)	7.2 (± 2.3)	7.8 (± 1.6)	,401
Painscore during the past 4 weeks on average (NRS 0-10 ± SD)	5.8 (± 2.0)	5.7 (± 2.5)	5.9 (± 1.4)	,926
NoP / unclear / NeP (based on the PDQ-$_{Dlv}$)	21 / 27 / 11	11 / 13 / 6	10 / 14 / 6	
Time to fill in the PDQ-$_{Dlv}$ (seconds (min-max) (± SD)	193 (79-362) (± 77)	207 (83-360) (± 88)	181 (79-362) (± 65)	,417
Is the questionnaire, to your opinion, useful to assess 'pain'? (VAS 0-100 ± SD)	74 (± 20)	75 (± 17)	72 (± 23)	,767
Do you have the feeling that the questionnaire asks about your complaints? (VAS 0-100 ± SD)	77 (± 22)	77 (± 19)	76 (± 24)	,695
What is your opinion about the length of the questionnaire? (VAS 0-100 ± SD)	85 (± 15)	82 (± 15)	88 (± 12)	,166
Are the questions stated in a clear way? (VAS 0-100 ± SD)	85 (± 13)	81(± 14)	89 (± 10)	,030*
Is the questionnaire well organized? (VAS 0-100 ± SD)	82 (± 14)	79 (± 1014)	85 (± 13)	,073
What is your meaning about the readability of the questionnaire? (VAS 0-100 ± SD)	86 (± 11)	83 (± 13)	89 (± 9)	,125
What is your opinion about the difficulty of filling in the questionnaire? (VAS 0-100 ± SD)	78 (± 16)	77 (± 16)	80 (± 16)	,539
What is your opinion about the lay-out of the questionnaire (VAS 0-100 ± SD)	81(± 16)	81 (± 16)	82 (± 16)	,952

NRS, numeric rating scale; SD, standard deviation; VAS, visual analogue scale; NoP, nociceptive pain; NeP, neuropathic pain; PDQ-Dlv, Pain*DETECT* - questionnaire, Dutch language version. *P ≤ 0.05.

In total, 60 patients were asked to fill in the PDQ-$_{DIV}$ to assess the face validity. Twenty-one of 60 patients (35%) forgot to mark the main area of pain ("drawing"). Five patients (12%) forgot to tick the box whether the pain was radiating to other regions of the body or not. One patient did not fill in all the questions because there was no appropriate answer according to the patient. Patients gave their opinion about the usability of the questionnaire on a VAS-scale (0 to 100), in which "0" means totally not useable and "100" means very useable (Table2). Most Belgian and Dutch patients found the PDQ-$_{DIV}$ a clear, readable, well organized, and useful instrument to assess their pain. The question "Are the questions stated in a clear way?" showed a significant difference in favor of the patients from Belgium (P = 0.03, Mann-Whitney U-test). The most common question in the group of sixty patients (n = 14; 23.3%) during the fillingin period was "Should I circle the number or tick the box?" in the questions about the pain at this moment, the strongest pain during the last 4 weeks and on average in the last 4 weeks. After answering the questions in the interview, the patients were challenged to give their thoughts and comments about the PDQ-$_{DIV}$ in words. Most of the patients had no comment. The most frequent comment was that the kind of pain of the patient "did not fit in the questionnaire" (n = 4, 7%). Suggestions made by patients for a next version were the use of less color (n = 1) and increasing font size (n = 1).

DISCUSSION

This study presents the results of the cross-cultural adaptation and face validation of the PDQ into the Dutch language for use in the Netherlands and Belgium. The PDQ was until this moment only published in a German, English, and Spanish language version [13,25]. The quality of a questionnaire used in research is expected to be dependent on the quality of the chosen method for translation [31]. There are many strategies to perform a cross-cultural adaptation [26-28,32,33]. The use of these guidelines improves the linguistic, structure, and cultural equivalence [34]. However, there is a lack of consensus and consistency in quality, methodology and application of these guidelines in healthcare literature [28,35]. The ISPOR guidelines [28] represent a consensus regarding the principles of good practice in translation and cultural adaptation. Their goal is to provide a more conceptual equivalent approach instead of a more literal translation. Because it provides clear recommendations and a detailed multistep approach, the ISPOR guidelines were chosen as method for the translation and cultural adaptation of the PDQ. This study consequently followed these guidelines in the choice of translators, the members of the multidisciplinary expert committee as well as the process of the adaptation. Decisions were discussed with the persons involved in the process either by conference call or by live meetings.

Because differences in instrument formatting and administration may produce variations in response even if meticulous care is taken [36], we opted for the same layout as the original version. In the cognitive debriefing phase and during data collection before the face validity testing, some

patients indicated that in some questions they did not know where in the questionnaire they had to put their answer to that question. They found the questionnaire too colorful and that the colors were distracting. Another difficulty when using the original format was that Dutch translated questions were limited to the space the original developers used in the original version.

Patient interviews were very useful to find out what the patient is thinking and how he interprets the questions in the questionnaire [37]. On the basis of these interviews, we changed two items to make them clearer to the patient and to reduce missing data: "Mark the picture that best describes the course of your pain" was changed into "Mark one picture that best describes the course of your pain". We also changed "If yes, please draw the direction in which the pain radiates" to "If yes, please draw the direction and the place into which the pain radiates". Thirty-five percent of the patients forgot to fill in this drawing but this is not of influence on the outcome score of the questionnaire. The question "Does the pain radiate to other regions of the body?" was not filled in by 7% of the patients. This has an influence on the outcome score. However, owing to the choice to use the same format as the original questionnaire, we were not able to change this item in a manner that there was more attention to the drawing and corresponding questions.

A quality check based on a 3-step scale [29] during and after completion of all the steps recommended by ISPOR was added because during the translation process the comparison was performed only by the translators. Thus, after the translation was completed, two independent researchers were asked to check each step in the translation trajectory. Rater A scored almost the same meaning in both versions two times when comparing the source and the PDQ-$_{DIv}$, and Rater B, who took a more literal rather than a conceptual approach, scored nine items as almost the same meaning in both versions. On the basis of the outcome of all scores, it is clear that a good translation process consists of more than a forward translation and that the steps the authors took in this study are necessary to come to a good cross-cultural adaptation.

The face validity of the PDQ-$_{DIv}$ was assessed in Dutch and Flemish because of the slight differences in the interpretation and use of some words. Therefore, the understanding of questions in the questionnaire may not be equal. In the end, only one significant difference in favor of the patients from Belgium occurred ("are the questions stated in a clear way?"). No further differences were found.

A valid adaptation ("Are the questions easily understood by patients as well as by clinicians/researchers and do they measure the same concept in different languages and countries?") of a questionnaire is necessary for its use in every day clinical practice and also in (inter-)national research to make the outcome comparable in different cultures. Furthermore, cross-cultural adaptation is cheaper, less labor-intensive and less time-consuming than to develop a whole new questionnaire. [27,38]

Publishing a cross-cultural adaptation has a value itself. First, it will help to prevent the existence of multiple versions of an instrument in a given language. Second, it ensures that the large amount of work involved will not be repeated unnecessarily [26]. Third, it gives a clear insight in which choices have been made during the translation process and thus provides important information about the strength of the translation [27]. On the basis of the method used, the reported patient outcome in the cognitive debriefing phase as well as in the face validity assessment and in the quality check, the PDQ-$_{DIV}$ is a well translated and cross-culturally adapted questionnaire for screening on neuropathic pain components in patients in the Netherlands and Belgium. A validation study of the PDQ is now in progress to assess the psychometric properties (ie, sensitivity, specificity, predictive value, and reliability) for different groups of patients in the Netherlands.

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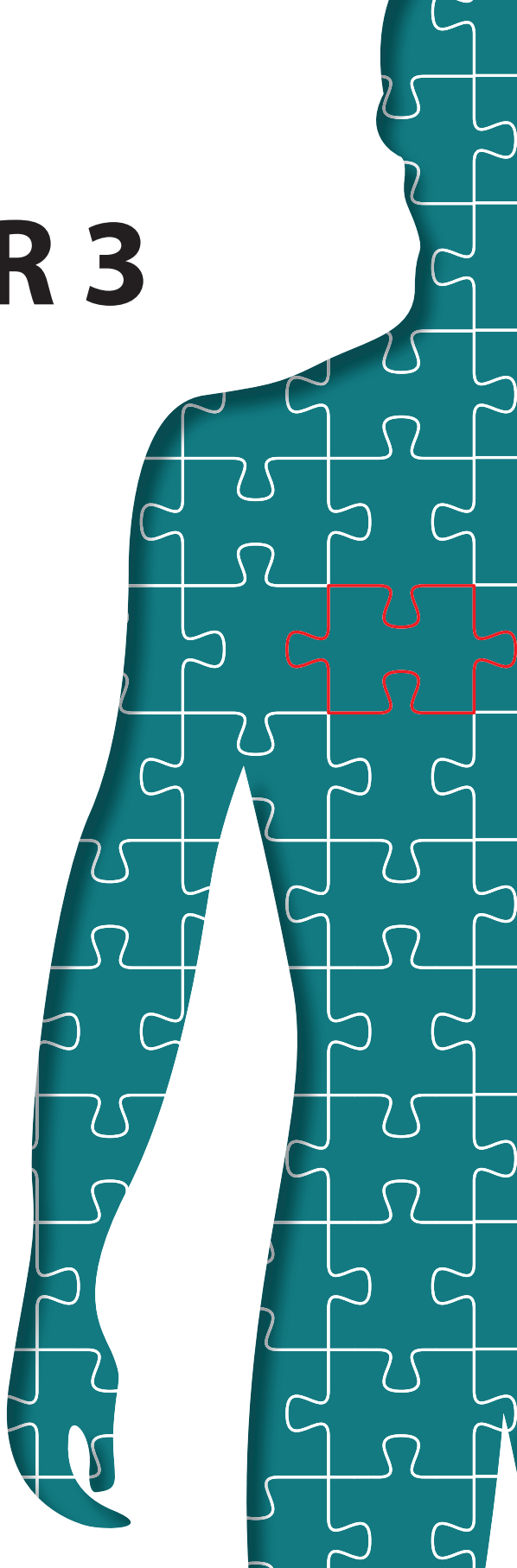
CHAPTER 3

Assessment of Neuropathic Pain in Patients with Cancer: The Interobserver Reliability. An Observational Study in Daily Practice



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ABSTRACT

Background

Neuropathic pain (NeP) is a burdensome problem in all stages of cancer. Although clinical judgment is accepted as a surrogate for an objective gold standard in diagnosing NeP, no publications were found about its reliability.

Objectives

Therefore, levels of agreement on the clinical examination of NeP were estimated by calculating kappa-value (K) and percentage of pair wise agreement (PA) to determine the interobserver reliability of diagnosing NeP.

Setting

The outpatient clinic of medical oncology of the Radboud University Nijmegen Medical Centre.

Method

Patients with cancer with potential NeP complaints were recruited from the outpatient clinic of medical oncology. Physicians were recruited from the department of pain and palliative medicine. Physicians and patients were recruited for participation in an observational study in daily practice. Each patient (N = 34) was examined by 2 specialists via independent clinical assessment. All consultations were video recorded. After each assessment, physicians were asked to indicate the most adequate characterization of the pain: pure NeP, pure nociceptive pain (NoP), mixed pain (MiP), or no pain (NP).

Results

Kappa (K) for the diagnosis of the most adequate pain characterization was 0.50, PA 64.7%. For diagnosing pure NeP K was 0.78 (PA 91.2%), for the NeP component (NeP + MiP) and NoP component (NoP + MiP), it was respectively 0.52 (PA 76.5%) and 0.61 (PA 82.4%). For the diagnosis on the basis of the grading system between physicians, K was 0.34 (PA 52.9%). The intrarater reliability for the diagnosis of an NeP component on the basis of clinical assessment and the NeP component on the basis of the grading system, for pain specialists K was 0.69 (PA 85.3%) and for palliative care specialists K was 0.61 (PA 79.4%).

Limitations

The values of K and the PA for the existence of an NeP component are not satisfying and the clinical agreement between physicians around findings from physical examination should encourage a better standardization of the clinical assessment and classification of pain in patients with cancer in respect with the identification of NeP.

Conclusions

A substantial level of agreement was found for the diagnosis of pure NeP and a moderate level of agreement for the diagnosis of the NeP component was found, both with a PA ≥ 70%. There was only a fair agreement between the physicians regarding the grading system. However, there was a substantial level of (interrater) agreement for the diagnosis of an NeP component and the outcome of the grading system. The findings in this study also suggest that a better standardization of the clinical assessment and classification of pain in patients with cancer with respect to the identification of neuropathic pain is necessary.

Key words

Neuropathic pain, diagnosis, interobserver reliability, agreement, cancer observational study, pain, clinical assessment, diagnostic test

INTRODUCTION

Pain is a burdensome symptom in all stages of cancer. Van den Beuken et al [1] found a prevalence of 55% in patients with cancer in the Netherlands. Of those, 44% suffered from moderate to severe pain [1]. As described in a review, 64% of the patients with metastatic, advanced, or terminal stages of cancer had pain, 59% of patients who were on anticancer treatment and 33% of patients who had been cured from cancer still suffered from pain [1,2]. In patients with cancer who were on opioid treatment by a pain specialist for their pain, almost 40% had neuropathic pain (NeP) alone or in combination with nociceptive or visceral pain [3]. In several other studies, the prevalence of NeP in patients with cancer varied between 17% and 36% [4-7]. This large variability in prevalence between studies can be explained by differences in populations, differences in diagnostic methodologies, and differences in definitions [8].

The International Association for the Study of Pain (IASP) defines NeP as *"pain caused by a lesion or disease of the somatosensory nervous system"* [9].The question arises when (part of) the pain in patients with cancer can be diagnosed as NeP. Despite the attempts to specify the entity of NeP, still no gold standard for the diagnosis of NeP exists [10]. NeP is experienced by the patient and despite the characteristic signs and symptom complex that may be recognized by experienced doctors, it is still difficult to measure objectively. Several screening tools, like the DN4, LANSS, NPQ, and Pain*DETECT* have been developed to indicate the possible existence of NeP [11-15]. Yet, screening tools are no substitute for history taking and physical examination, and they are not intended to be a diagnostic method [12]. Therefore, clinical judgment is the only recommended method to diagnose NeP [10,16]. When standardized diagnostic criteria are lacking, the reliability of diagnostic procedures is usually demonstrated by acceptable levels of agreement among physicians [17-19]. Interobserver reliability is an important measure to assess the agreement of categorical variables such as diagnosis or the interpretation of findings in physical examination [20]. Cohen's kappa is a for chance corrected statistical outcome for interobserver reliability [21]. We used Cohen's kappa and percentage of pair wise agreement to investigate the interobserver reliability and agreement of the diagnosis of NeP in patients with cancer.

METHODS

Patients

Patients were recruited from the outpatient clinic of the department of medical oncology of the Radboud University Nijmegen Medical Centre (RUNMC). Between September and November 2010, all patients who visited the outpatient clinic were screened for pain for another larger study. As part of a larger set of questionnaires, they were also asked to complete the 7-item DN4 questionnaire [13] about the quality of their pain. Inclusion criteria for enrollment in the kappa-study were (1) age

≥ 18 years; (2) diagnosed with cancer (regardless of the type and stage of cancer) or being cured from cancer; (3) at least 2 positive answers on the 7-item DN4 questionnaire in order to enrich the chance of including patients suffering from NeP in the research population.

Exclusion criteria were (1) no consent to be contacted for further research; (2) no permission for video recording of the consultations. Eligible patients were phoned by the researcher (IH). Subsequently, the patients received information by mail. After verbal and written informed consent patient-volunteers were included in the study. They did not receive any benefit from the study; only costs for transportation were reimbursed. This study was approved by the local ethics committee: the Committee on Research Involving Human Subjects region Arnhem-Nijmegen, Nijmegen, the Netherlands.

Patients were examined by experienced pain specialists (N = 4) and palliative care specialists (N = 2), recruited from the department of anesthesiology, pain, and palliative medicine of RUNMC. All 4 participating pain specialists, 2 men and 2 women, median age of 40 (range 32 – 47), had a background as an anesthesiologist. The 2 palliative care specialists, both male, were 58 and 63. One was a medical oncologist and the other an elderly care physician. Years of experience in their actual specialization (pain or palliative care) was 10 years for the pain specialists (range 1 – 18 years) and 13 years for the palliative care specialists (7 and 18 years). All physicians worked full time, but, as a mean, they worked 19 hours per week (10 – 26 hours) in this specific field.

Test Methods

All physicians completed a questionnaire recording their age, gender, professional background, specialty, and number of weekly hours working as a pain specialist or as a palliative care specialist. They were also asked to provide a working definition of NeP, including symptoms and findings at physical examination they considered decisive for NeP. As a part of the preparation of the study, an inquiry was made among the physicians regarding the tools they wanted to use for the physical examination. There was no prearranged set of tools available in the examination rooms, only those recommended by one or more of the participating physicians: pieces of cotton wool, cotton buds, a tuning fork, and a reflex hammer. All physicians had access to the same set of tools. They were allowed to use the Electronic Patient Record (EPR), and instructed to diagnose NeP in the way they were used to in their daily practice.

Before the consultation, each patient completed a set of questionnaires, consisting of repetition of the 7-item DN4 questionnaire [13], the Brief Pain Inventory-Short Form (BPI-SF) [22], and a question about duration and course of their pain over time. Subsequently the patients were randomly assigned to be seen first by the pain specialist or the palliative care specialist and underwent a second assessment by the other specialist after 30 minutes. The physicians were not informed about the selection procedure of the participating patient-volunteers, or about the outcome of the DN4

and BPI-SF. Each physician had 20 minutes for clinical assessment of the patient (history taking and physical examination). However, the physician was allowed to take more time when necessary. After the consultation, the physician had 10 minutes to complete a research form with a tick box for the diagnosis: "NeP," "nociceptive pain (NoP)," or "mixed pain (MiP)" which was categorized as NeP together with NoP or no pain (NP). If there was more than one pain location, physicians were instructed to focus on the location of the worst pain. During the assessments, physicians were blinded to the results of their colleague and patients were instructed not to mention the findings of the other physician. In each session, 4 patients were seen in a row by each physician.

Each assessment was videotaped and evaluated by 2 researchers (IH and AS). Regarding history taking, items of evaluation were words mentioned to characterize the pain, including items of the 7-item DN4 questionnaire, and whether a Numeric Rating Scale (NRS) was mentioned (yes/ no) for scoring intensity of pain. Regarding the physical examination, items of evaluation where performing a physical examination (yes/ no), comparison of affected and healthy body parts (yes/ no), and which tools were used.

Statistical Methods

Because there are no previous data regarding this research topic, it was not possible to perform a reliable power calculation. However, NeP prevalence in patients with cancer is 31%-36% [4-7]. To artificially create a higher probability of patients suffering from NeP, we included only patients who scored 2 or more items on the 7-item DN4 questionnaire during the previous screening study. We assumed NeP prevalence in this specific study group to be 0.5 during the actual study. With an assumed kappa of 0.7, a study power of 80%, and an alpha of 0.05, we estimated that 30 patients were needed. To be able to focus on agreement whether or not an NeP component exists in a patient, kappa's aimed at this specific part were determined. Patients with NeP or with MiP were rated together as having an NeP component. Patients with NoP or with MiP were also rated together as NoP component present. The physicians were, afterwards, asked to rate Treede's Grading System [23] for each patient they had seen. The outcomes "probable" and "definite" were regarded as an NeP component was present. Unlikely and possible were rated as no NeP component was present.

To assess interobserver reliability and agreement of the diagnosis of NeP in patients with cancer, we calculated pair-wise Cohen kappa-values (K), the prevalence index (P*i*), and pair-wise percentages of agreement (PA). K gives the proportion of agreement after chance agreement is removed [21]. The K-value can vary between -1.0 and 1.0 though it usually falls between 0 and 1 [20]. Landis and Koch [24] categorized values of kappa as: none beyond chance (K = 0.00), slight (K = 0.01 – 0.20), fair (K = 0.21 – 0.40), moderate (K = 0.41 – 0.60), substantial (K = 0.61 – 0.80), almost perfect agreement (K = 0.81 – 1.00). P*i* is calculated to quantify the effect of prevalence to K. It is the absolute value of the difference between the number of agreements on positive and negative findings divided by the total number of observations [20,25]. PA represents the number of exact agreements divided

by the number of possible agreements [26]. A K ≥ 0.40 and a PA ≥ 70% is considered indicative of interobserver reliability acceptable for use in clinical practice [24]. Statistics were applied regarding diagnosis, outcome of the grading system [23], and the outcome of the DN4. All data were entered and analyzed in Statistical Package for the Social Sciences (SPSS version 18.0, SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patients

Between September and November 2010, 340 patients visiting the outpatient clinic of the department of medical oncology of the RUNMC completed the pain questionnaire. Of them, 94 scored 2 or more on the 7-item DN4 and gave their consent to be approached for a subsequent pain study (Figure 1). After 56 patients were approached we stopped the inclusion in this study. Eighteen patients refused to join the study due to personal reasons (mainly because of active ongoing chemotherapy schedules). Finally, 38 patients gave their written informed consent. Due to an acute intercurrent illness at the day of the assessments, 3 patients dropped out of the study. Therefore, 35 patients participated in the kappa study. One patient was excluded afterwards, because the 2 physicians had examined different pain locations.

These 34 patients had a median age of 56 (range 36 – 76). There were 8 men (24%), of whom 2 had testis carcinoma, 4 had tumors arising from the digestive system, one had a GIST tumor, and one had a carcinoid. Of the 26 women (76%), 92% had breast cancer (N = 24), one a GIST tumor, and one an angiosarcoma. The duration of the pain in months was at mean 64 months (± SD 100; range 1 – 568 months). Worst pain during the 24 hours before the consultations was experienced as severe in 5 cases (15%), moderate in 21 cases (63%), and mild in 7 cases (7%): mean 5.24 ± SD 2.28; range 0 – 9 (NRS 0 – 10). The average pain in the last 24 hours was at mean 4.19 ± SD 2.15; range 0 – 9 (NRS 0 – 10). The outcome of the BPI-SF for the pain severity score at mean was 4.08 ± SD 2.23; range 0 – 8 (NRS 0 – 10) and for the pain interference score 3.67 ± SD 2.37; range 0 – 9 (NRS 0 – 10). On the repeated 7-item DN4 questionnaire on the day of examination, one patient didn't fill in the questionnaire, one patient scored 0 points, 8 patients scored 2 points, 11 scored 3 points, 10 scored 4 points, 2 patients scored 6 points, and one 7 points. See Table 1 for more detailed patient characteristics.

Table 1: **Summary of the patient characteristics and outcomes of the assessments.**

Gender	Age	Primary type of cancer	Disease stage	Anti-cancer treatment	Worst pain score patient	7-item DN4 score	Physical examination		Clinical cause of pain		Pain diagnosis		Grading system	
							SPC	PS	SPC	PS	SPC	PS	SPC	PS
F	65	Breast	1	S, RT	6	1	1,2,4,8	1,7	Postoperative neuropathy	Triggerpoint pain	NeP	NoP	Definite	Unlikely
M	56	Rectum	2	RT	m	m	1,2,4,8	1	Postradiation pain peri-anal	Triggerpoint pain	NeP	NoP	Definite	Unlikely
F	57	Breast	2	S,RT	6	4	1,2,4,6,8	0	Arthrosis cervical spine	Cervical facet joint pain	NoP	MiP	Unlikely	Probable
F	59	Breast	1	S, RT, C	5	4	1,2,4,6,7,8	2,4,6,7,8	Post surgical nerve injury	Surgery and Chemotherapy	MiP	MiP	Probable	Possible
F	52	Breast	3	S, C	3	3	1,2,4,8	1,2,3,7,8	Metastatic collapse thoracal and lumbar spine	Vertebral metastases	NoP	NoP	Definite	Unlikely
F	56	Breast	2	S, RT, C	5	4	7,8	1,4,6,7,8	Arthrosis	Rheumatoid arthrosis	NoP	NoP	Definite	Unlikely
M	68	Rectum	3	S, C	8	4	2,6,7,8	1,2,4,6,8	Oxaliplatin	Chemotherapy	NeP	NeP	Probable	Probable
F	50	Breast	1	S, RT, C	6	6	1,2,7,8	1,2,8	(1)Postoperative neuropathy after mama amputation (2) allodynia	Periost pain costa	NeP	NeP	Definite	Probable
F	53	Breast	2	S, C	4	3	0	1,4,8	Muscle – and joint-pain	(1) Rheumatoid arthritis or arthrosis (2) Tamoxifen side-effects	NoP	MiP	Definite	Definite
M	36	Testis	1	S,C	9	2	1,2,4,6,8	2,3,6,7,8	Unclear	Unknown	NeP	NeP	Definite	Possible
M	76	Carcinoid	3	S,C	7	4	1,8	2,3,8	Postoperative neuropathy	Intercostal nerve damage with neuralgia	NeP	NeP	Probable	Definite

Table 1 ***continued***

F	59	Breast	3	S, RT, C	9	4	4,7,8	2,3,7,8	(1) Degenerative disorders (2) multiple sclerosis	Vertebral metastasis	MiP	MiP	Probable	Unlikely
F	52	Breast	2	S, RT, C	5	3	1,2,4,8	2,6,8	(1) Arthrosis (2)use of Tamoxifen	Degenerative disorder back	NoP	MiP	Unlikely	Unlikely
F	58	Breast	1	S,C	0	2	1,2,4,6,7	2,3,6,8	No pain	Prothesis	NP	NoP	Unlikely	Unlikely
F	50	Breast	3	S, RT, C	7	2	1,2,8	7	Bone metastasis costae	Visceral bone pain	NoP	NoP	Unlikely	Unlikely
F	65	Breast	3	S, C	4	6	1,2,4,,6	2,3,6,8	Myogene disorders + Fear	Chemotherapy, surgery, backpain and medication	NoP	MiP	Probable	Definite
F	60	Breast	3	S, C	9	4	1, 8	1,2,6,7,	Vertebral metastasis T10/T11	Metastatic disorders with intercostal neuralgia T11-T12	MiP	MiP	Definite	Definite
F	62	Breast	3	S, RT, C	5	3	1,2,4,6,8	2,3,6,7,8	(1)Arm pain: post surgery (2)Hand+Feet pain post taxol	Scar tissue	NP	NoP	Probable	Unlikely
F	49	Breast	2	S, C	4	4	1,2,4,,6,8	2,3,6,8	Chemotherapy	Allodynia, sensibility disorder	NeP	NeP	Probable	Probable
F	46	Breast	2	S, RT, C	7	3	1,2,4,8	1,4,6,8	Post operative, post chemotherapy, nociceptive pain by lymphedema	(1)Axillair lymphe dissection, (2) Radiotherapy, (3) Chemotherapy, (4) Migraine	MiP	MiP	Definite	Definite
F	54	Breast	2	S, C	5	3	1,2,4,6,7,8	2,7,8	Breast surgery	Post surgical scar pain	NeP	NeP	Probable	Probable
F	52	Breast	2	S, RT, C	6	2	8	2,7,8	Anti-oestrogen treatment	Reactive arthritis complaints following hormonal treatment	NoP	MiP	Unlikely	Unlikely
F	61	GIST	3	S, C	8	3	0	2,3,7,8	Missing	Myotendinogen lumbar pain/ sacro iliac joint pain	NoP	NoP	Unlikely	Unlikely

F	57	Breast	1	S, RT, C	3	2	8	1,5,8	(1)epicondylitis lateralis (2)Ablatio, preoperative neuropathy	Multiple surgery	MiP	MiP	Definite	Definite
F	45	Angio-sarcoma	3	C	7	3	1,2,4,6,7,8	0	Bone metastasis spine	Lumbar facet pain with pseudoradicular signs	MiP	MiP	Probable	Unlikely
F	70	Breast	3	S, RT, C	5	3	7,8	0	(1)Plexus brachialis leasion (2) post radiation	(1)plexopathy (2) m.raynaud	NeP	MiP	Definite	Definite
M	69	Rectum	2	S, RT, C	3	0	1,4,7,	1,2,4,8	Degenerative disorders lumbosacral spine	Discopathy lumbar spine with radicular signs	MiP	MiP	Definite	Unlikely
M	56	GIST	4	S	6	2	1,2,4,7,8	7	Tumor localisation	Oncologic process, GIST tumor calve	NoP	NoP	Unlikely	Unlikely
F	55	Breast	1	S, RT, C	7	4	1,2,4,8	7	(1)Surgery (2)Edema	Edema	MiP	NoP	Probable	Unlikely
M	65	Rectum	2	S, RT, C	4	3	0	0	No pain	Postoperative scar tissue pain	NP	NoP	Possible	Unlikely
F	52	Breast	3	S, RT, C	5	2	1,2,6,7,	7,8	Bone metastasis mama carcinoom	Bone metastasis T5	NoP	NoP	Unlikely	Unlikely
F	70	Breast	3	S, C	1	7	1,2,4,6,8	0	Chemotherapy	Chemotherapy induced neuropathy	NeP	NeP	Probable	Probable
M	45	Testis	1	S, C	3	4	1,2,4,6,7,8	2,8	Cisplatinum	Chemotherapy induced neuropathy	NeP	NeP	Probable	Probable
F	44	Breast	1	S, C	1	3	0	0	Surgery	Incision by surgeon	NoP	NoP	Unlikely	Unlikely

Gender: M = male, F = female; Disease stage: 1 = patients who received anti-cancer treatment with curative intent ≥ 6 months ago, 2 = patients receiving anti-cancer treatment with curative intent or last treatment less than 6 months ago, 3 = patients receiving palliative anti-cancer treatment, 4 = no treatment or treatment no longer feasible; Anti-cancer treatment: Previous anticancer therapies S = surgery, RT = radiotherapy, C = chemotherapy, O = other; NRS worst pain patient: Worst pain during 24 hours before consultation: Numeric Rating Scale (NRS) 0 – 10, m = missing; 7-item DN4 score: 7-item DN4 score at day of assessment on all pain locations, m = missing; Pain diagnose: NoP = nociceptive pain, NeP = neuropathic pain, MiP = mixed pain (nociceptive and neuropathic pain), NP = no pain; PS: Pain Specialist; SPC: Specialist Palliative Care; Physical examination: tools or techniques used during physical examination: 0 = none, 1 = soft touch, 2 = pin prick, 3 = piece of cotton wool, 4 = tendon reflexes (reflex hammer), 6 = tuning fork, 7 = stroking over skin with hands, 8 = comparing affected and healthy body parts. P = probable. U = unlikely. D= definite. Po = Possible

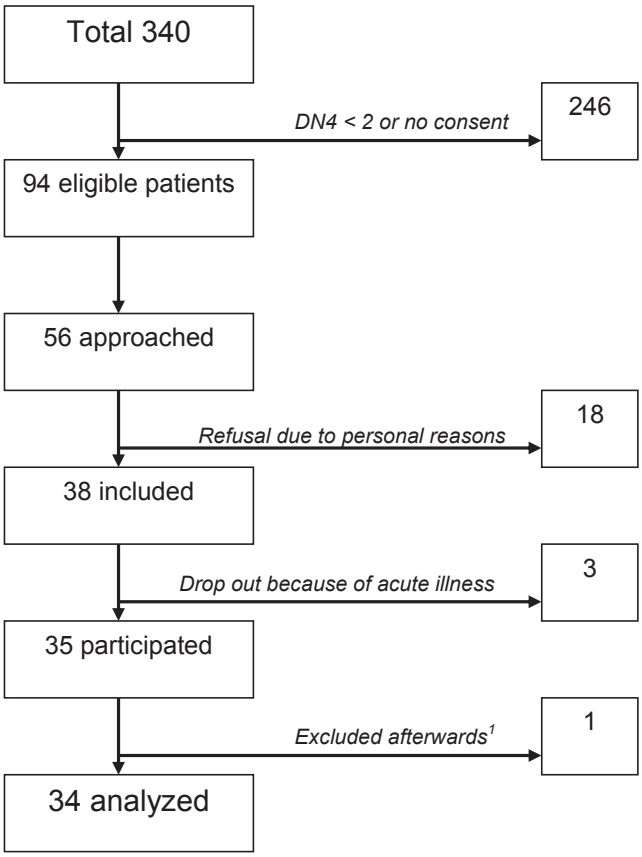

Figure 1: **Flowchart for inclusion of patients**

Physicians

We asked the physicians, in an open question, to give their working definition of NeP: 2 of the pain specialists mentioned the definition suggested by Treede (23), one pain specialist mentioned the DN4-criteria, and the other physicians mentioned definitions containing the words "pain" and "the nervous system/ nerve damage." To the question "what do you think is a decisive symptom for NeP," 3 pain specialists answered that allodynia in general was the decisive symptom and one had the opinion that there was none. The palliative care specialists considered respectively

a changed sensibility and an annoying pain during night the decisive symptom. When asked for the decisive finding for NeP at physical examination, again allodynia was mostly mentioned by the pain specialists, while the palliative care specialists mentioned changed sensibility and hyperpathy (Table 2).

Table 2: Individual opinions from participating physicians about diagnosing neuropathic pain in general.

	Specialists Palliative Care	Pain Specialists
Working definition for neuropathic pain	Pain or troublesome experience of the patient that can be traced back to a possible or demonstrated change in the function of the nerve or central nervous system.	Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (Treede, 2008). (2x)
	Pain related to the peripheral or central nervous system.	Pain as a consequence of nerve damage or neurological dysfunction including sensitization.
		DN4-criteria.
Decisive symptom for neuropathic pain	Changed sensibility (experienced as pain/ troublesome).	Pain at normal touch.
		None.
		Allodynia.
	Especially pain during nighttime, mostly annoying.	Allodynia (dynamic and static) and abnormal sensations.
Decisive sign at physical examination for neuropathic pain	Changed sensibility in an area of pain experience.	Allodynia. (2x)
		Allodynia static and dynamic.
	Hyperpathy.	Sensorial abnormality.

Test Results

The K and PA between paired physicians for the characterization of pain (NeP, MiP, NoP, or NP) was 0.50 (64.7%) ($P < 0.000$). For diagnosing NeP K was 0.78, P*i* 0.44, and PA 91.2%; for MiP it was respectively 0.53, 0.38, and 79.4%; and for NoP it was 0.31, 0.26, and 67.6%. The K for the NeP component (by summing the diagnoses of pure NeP and MiP) was 0.52 ($P = 0.002$), P*i* was 0.18, and PA was 76.5%. For the NoP component (by summing the diagnoses of pure NoP and MiP) K was 0.61, P*i* was 0.35, and PA was 82.4%.

The interobserver reliability and the pair-wise agreement between the pain specialist and the palliative care specialists regarding the grading system (unlikely, possible, probable, and definite neuropathic pain) showed a K of 0.34 and a PA of 52.9%. The comparison between the NeP component, following from the diagnosis of the physician and the outcome of the grading system (the outcomes probable and definite were regarded as an NeP component was present) gave for the pain specialists a K of 0.69, P*i* 0.26, and PA of 85.3%. For the palliative care specialists it was respectively 0.61, 0.03, and 79.4%. The comparison between the NeP component, following from the diagnosis of the physician and the outcome of the DN4 (7-items, a "yes" on ≥ 3 items is considered as having NeP) gave for the pain specialists a K of 0.24, P*i* 0.36, and PA of 66.7%. For the palliative care specialists it was respectively 0.16, 0.27, and 57.6%. The comparison between the outcome of the grading system (the outcomes probable and definite were regarded as an NeP component was present) and the outcome of the DN4 (7-items, a "yes" on ≥ 3 items is considered as having NeP) gave for the pain specialists a K of 0.34, P*i* 0.42, and PA of 72.7%. For the palliative care specialists it was respectively 0.32, 0.15, and 63.6%.

Secondly, items from history taking and physical examination were assessed by video recording and analyzed afterwards. In 27 out of 34 cases the palliative care specialists asked for a pain score and the pain specialists asked in 21 cases. Most frequently asked items of the DN4 during history taking were tingling (23 times by the palliative care specialists and 15 times by the pain specialists), numbness (18 times by both), and burning (12 versus 19 times). During physical examination, the cotton bud was most often used. The palliative care specialists used the sharp side of a cotton tip 22 times and the pain specialists 18 times. The soft side of it was used 25 times by the palliative care specialists and 10 times by the pain specialists. Of the available tools, the cotton wool was used the least: 9 times by the pain specialists while the palliative care specialists did not use it at all.

Table 3: The kappa coefficient (*K*) and the percentage of pair-wise (PA) agreement between physicians calculated for the patients' diagnosis.

	k-value	Approx. Sig.	Categorized value of kappa	P*i*	PA-value (%)
Diagnosis (NeP, MiP, NoP, NP)	0.50	0.000*	Moderate	---	64.7
NeP (NeP versus MiP + NoP + NP)	0.78	0.000 *	Substantial	0.44	91.2
MiP (MiP versus NeP + NoP + NP)	0.53	0.001 *	Moderate	0.38	79.4
NoP (NoP versus NeP + MiP + NP)	0.31	0.08	Fair	0.26	67.6
NePcomponent (NeP + MiP versus NoP + NP)	0.52	0.002*	Moderate	0.18	76.5
NoPcomponent (NoP + MiP versus NeP + NP)	0.61	0.000*	Substantial	0.35	82.4

k-value: Kappa value; 95% CI: 95% confidence interval; Approx. Sig.: Approximate significance; *: significant, P ≤ 0,05; Pi: Prevalence index; Pavalue: Pair-wise Agreement-value; NeP: neuropathic pain; MiP: mixed pain; NoP: nociceptive pain; NP: no pain; Fair: κ = 0.21 – 0.40; Moderate: κ = 0.41 – 0.60; Substantial: κ = 0.61 – 0.80.

Table 4: **The kappa coefficient (*K*) and the percentage of pair-wise agreement (PA), calculated for the NeP component, grading system, and DN4.**

	k-value	Approx. Sig.	Categorized value of kappa	P*i*	PA-value (%)
Grading PS & Grading SPC (unlikely-possible-probable-definite)	0.34	0.001*	Fair	---	52.9
PS: NePcomponent & Grading NePcomponent (NeP + MiP versus Grading probable + definite)	0.69	0.000*	Substantial	0.26	85.3
SPC: NePcomponent & Grading NePcomponent (NeP + MiP versus Grading probable + definite)	0.61	0.000*	Substantial	0.03	79.4
PS: NePcomponent & DN4 (NeP + MiP versus DN4)	0.24	0.160	Fair	0.36	66.7
SPC: NePcomponent & DN4 (NeP + MiP versus DN4)	0.16	0.475	Slight	0.27	57.6
PS: Grading NePcomponent & DN4 (Grading probable + definite versus DN4)	0.34	0.053	Fair	0.42	72.7
SPC: Grading NePcomponent & DN4 (Grading probable + definite versus DN4)	0.32	0.026*	Fair	0.15	63.6

k-value: Kappa value; 95% CI: 95% confidence interval; Approx. Sig.: Approximate significance; *: significant, P ≤ 0,05; Pi: Prevalence index; Pavalue: Pair-wise Agreement-value; PS: Pain Specialist; SPC: Specialist Palliative Care; DN4: Douleur Neuropatique en 4 Questions (Questionnaire); NeP component: Neuropathic pain component (diagnosis NeP or MiP); Grading NeP component: only "probable" and "definite" are counted as NeP component; MiP: mixed pain; NoP: nociceptive pain; Grading: Grading system by Treede et al [23]; Slight: κ = 0.10 – 0.20; Fair: κ = 0.21 – 0.40; Moderate: κ = 0.41 – 0.60; Substantial: κ = 0.61 – 0.80.

DISCUSSION

In this real-life type of study, we found a substantial level of interobserver reliability for diagnosing pure NeP and a moderate level of interobserver reliability for the diagnosis of an NeP component, between pain specialists and specialists in palliative care, both with a K ≥ 0.40 and a PA ≥ 70%. A K of ≥ .40 and a PA of ≥ 70% is indicative of interobserver reliability and acceptable for clinical use [25]. The reliability of the diagnosis of NeP by a physician is an important consideration in clinical practice because it has direct treatment implications for the individual patient. We performed this kappa study to see if the diagnosis of NeP is a reliable diagnosis because an objective gold standard for this diagnosis is lacking. As an example, in validation studies of questionnaires screening for NeP 2 physicians were both examining the same patient to serve as a substitute gold standard for diagnosis [13,14]. But until now no proof of this concept was given. According to the literature [20,25,27,28] we chose to use the kappa-value as well as the PA and P*i*. The level of agreement for NeP component either as a part of MiP or as pure NeP appeared moderate. Regarding MiP we found a moderate but significant level of agreement which suggests that the clinical picture is less straight

forward. Probably, a combined pain syndrome is a less clear outcome, explaining the lower kappa. For pure NoP the physician pairs only had a fair, non significant level of agreement. The PA-value for NoP was below 70% and thus considered as not acceptable for clinical use. This might be due to the focus of the physicians: the instruction of the physician was to diagnose NeP in the way they were used to in their daily practice. Probably there was less attention to NoP. For NoP component the level of agreement was substantial.

Although the participating physicians used different descriptions for NeP, a high consensus existed for the decisive symptom and sign for NeP, namely allodynia or a description of allodynia. However, allodynia is not a decisive symptom for NeP, because it might also be present in patients with nociceptive pain, especially in inflammatory conditions.

The presented results indicate that the specialists used very different diagnostic criteria for neuropathic pain. This was confirmed most notably by the working definition used by the investigators, which corresponded to the IASP definition of neuropathic pain in only one third of the investigators (Table 2). In conclusion, the majority of the participating physicians didn't know the current definition of neuropathic pain and use "personalized" inappropriate diagnostic criteria in their daily practice.

In this study, we also have used the grading system by Treede et al [23], filled in by both physicians after the clinical examination of the patient. Comparing the diagnosis of the existence of an NeP component with the outcome of the grading system per physician, we found a substantial intraobserver reliability with a PA ≥ 70%, indicating a good reliability and useful in clinical practice. However, the comparison on the outcome of the grading system (unlikely, possible, probable, or definite) between both physicians gave a fair reliability and a low PA (< 70%), indicating a poor reliability between both physicians and therefore it might be less useful in clinical practice. Moreover, the grading system will not necessarily provide the right diagnosis. In a patient suffering from MiP, the NoP part may be paramount. The physicians' diagnosis (NeP, MiP, NoP, or NP) had a moderate reliability, but also a low PA < 70%. All this indicates that it is difficult to categorize the kind of pain the patient is suffering from, as well with the physicians' diagnosis as with the grading system. It can be questioned whether the clinical judgment should be regarded as a gold standard for the diagnosis of NeP because both clinicians might be wrong in their diagnosis even with values of K > 0.5 and a PA of 70%.

Our study measured the interobserver reliability of 2 physicians diagnosing NeP in patients with pain from cancer and taking the grading system and the DN4 into account. The focus of the study was to diagnose the kind of pain and not on which specific diagnostic tests were used in the diagnostic process. Mostly, kappa studies are used to report the reliability of specific diagnostic tests in patients or from clinical data [18,29-31]. Comparing the outcome of the physicians diagnosis

on the existence of an NeP component with the outcome of the 7-item DN4 we found only a fair (K < 0.40) reliability for the pain specialists and a slight interobserver reliability for the palliative care specialists (both with a PA ≤ 70%). In the paper of Garcia de Paredes et al [7] it was described that only half of the patients with cancer suffering from NeP had a positive score on the DN4 compared with the clinicians diagnosis. They suggested investigating if a specific cut-off score for the DN4 for patients with NeP from cancer would fit better. The same was suggested in the study by Mercadente et al [32] for the LANSS, NPQ, and NPQ-SF. This study also indicates that the DN4, at this moment, is less valid and thus less useful in clinical practice for screening for NeP in patients with cancer pain.

During the pain history taking, the pain specialists asked for a pain intensity score only 21 out of 34 times and the palliative care specialists 27 times. A marginal comment should be made on this statement, as the physicians were only instructed to diagnose the type of pain. However, one expects a pain intensity score to be a standard item during a pain history taking. During the observation of the clinical examination of the patients, in 10 of 68 cases (Table 1), no clinical examination was performed, and in many cases only one sensory modality was tested. It has been recommended [16] that (a) clinical bedside (sensory) examination of a patient with suspected NeP includes testing of touch/vibration, cold, warmth, and pain sensibility (pinprick) and (b) the outcomes should be compared with the findings in the contra lateral region or in a region without pain (not performed in 21 of 68 cases).

To our knowledge, this is the first study to determine the interobserver reliability of the diagnosis of NeP in patients with cancer. Participation of patients, examination rooms that were equipped as real consultation rooms, and instructing the physicians to perform the diagnosing procedure as they usually do, all contributed to collect reliable information about the current state of daily practice in this hospital. Besides, by using a video camera that was almost invisible to the physician and patient, the consultation was not disturbed by the researchers.

While the patient number (N = 34) is sufficient for a reliable kappa study, the number of participating physicians was low and unequal: 4 participating pain specialists and 2 palliative care specialists. Another weak aspect was the fact that one of the palliative care specialists was a medical oncologist and the other an elderly care physician. Yet, both of them had palliative care as their main task for at least 7 years. However, both the pain specialists and the palliative care specialists will be more experienced than usual physicians in pain and NeP and our findings cannot be interpreted for a broader group of physicians. Furthermore, in the questionnaire, patients were asked about all sites of pain; whereas in the clinical examination, physicians were instructed to focus on the site of worst pain. The majority of patients had breast cancer. This high number is an adequate representation as breast cancer is the most frequent type of cancer among women in the Netherlands (www.cijfersoverkanker.nl) and many of them suffer from chronic pain [33,34]. The incidence of NeP in this study is artificially high in comparison with the normal population in the oncology outpatient

clinic. Because we used a score of at least 2-points on the 7-item DN4 as an inclusion criterion for this study, the presence of NeP was more likely and thus enlarged the possibility of diagnosing NeP. For now it is not sure that in a situation of a lower incidence of NeP the kappa values will be the same. The physicians were also more triggered and focused on NeP than on NoP because we asked their working definition of NeP, the symptoms and findings at physical examination they considered decisive for NeP, and their self-efficacy in diagnosing NeP. This is probably the cause of a lower kappa-value in patients with NoP. Finally, the worst pain did not necessarily originate from the cancer or anti-cancer treatment. Patients sometimes had comorbidity causing the (worst) pain, for example rheumatoid arthritis.

CONCLUSIONS

We found a substantial level of agreement for the diagnosis of NeP and a moderate level of agreement for diagnosing an NeP component, both with a PA ≥ 70%. This study shows preliminary evidence that the clinical judgment of NeP in patients with cancer is reliable. Implementation of the proposed criteria for categorizing NeP as definite, probable, possible, or unlikely might be a step forward [23] to come to more diagnostic clarity for NeP. As stated by Bennett et al [8] a standardized approach is essential for clinical assessment, for appropriate treatment, and for clinical research. Despite the lack of a gold standard for diagnosing NeP, our study shows that physicians have a good agreement in the diagnosis of pure NeP. For MiP however, the level of agreement is moderate but with a high PA. Based on these findings, in MiP we suggest the opinion of a second physician to enlarge the chance of a correct diagnosis and thereby of adequate pain treatment. Especially in more complex pain syndromes, the recognition of NeP component needs attention. Since the treatment of NeP and MiP or NoP is quite different according to the international guidelines, a strict delineation and certitude about the correct diagnosis is of upmost importance and will influence the result of consequent pharmacological treatment schemes [35]. Taking into account the different pain mechanisms of NeP and NoP and working mechanisms of the medications, it is important to have an adequate pain diagnosis for optimal pain treatment with the least side effects. The general value of the findings for validating physician assessment of neuropathic cancer pain in this study is limited to our centre and participating physicians in order to confirm their relevance and general interest. However, the findings in this study suggest that a better standardization of the clinical assessment and classification of pain in patients with cancer in respect to the identification of neuropathic pain is necessary. Moreover, we recommend a further study on how to improve the level of agreement in, and the validity of, the clinical diagnosis of NeP by systematically analyzing the history taking and the different (diagnostic) tools used in pain assessment and how standardizing the diagnostic process can improve the level of agreement and validity in clinical circumstances [16,23].

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CHAPTER 4

Detecting the neuropathic pain component in the clinical setting: a study protocol for validation of screening instruments for the presence of a neuropathic pain component

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ABSTRACT

Background

The presence of nerve damage plays a key role in the development and prognosis of chronic pain states. Assessment of the presence and severity of a neuropathic pain component (NePC) is key in diagnosing chronic pain patients. Low back pain (LBP) and neck and shoulder pain (NSP) are highly prevalent and clinically important medical and societal problems in which a NePC is frequently present. The more severe the NePC, the worse the course of the pain, its prognosis and the results of treatment. Reliable and standardised diagnosis of the NePC remains difficult to achieve. Standardized and validated screening tools may help to reliably identify the NePC in individual chronic pain patients. The aim of this study is to validate the Dutch language versions of the Pain*DETECT* Questionnaire (PDQ-$_{Dlv}$) and the 'Douleur Neuropathique 4 Questions' (DN4-$_{Dlv}$) for use in primary and specialist medical care settings to screen for a NePC in patients with chronic pain due to (1) LBP, (2) NSP or (3) known peripheral nerve damage (PND).

Methods / design

The study design is cross-sectional to assess the validity of the PDQ-$_{Dlv}$ and the DN4-$_{Dlv}$ with 2 weeks follow-up for test-retest reliability and 3 months follow-up for monitoring and prognosis. 438 patients with chronic pain due to (1) LBP, (2) NSP or (3) PND will be included in this study. Based on the IASP definition of neuropathic pain, two physicians will independently assess whether the patient has a NEPC or not. This result will be compared with the outcome of the PDQ-$_{Dlv}$ & DN4-$_{Dlv}$, the grading system for neuropathic pain, bed side examination and quantitative sensory testing. This study will further collect data regarding prevalence of NePC, general health status, mental health status, functioning, pain attribution and quality of life.

Discussion

The rationale for this study is to provide detailed information on the clinimetric quality of the PDQ-$_{Dlv}$ and DN4-$_{Dlv}$ in Dutch speaking countries. Our innovative multi-factorial approach should help achieve more reliable diagnosis and quantification of a NePC in patients with chronic pain.

Trial registration

The Netherlands National Trial Register (NTR3030).

Keywords

Pain*DETECT* questionnaire, PDQ, DN4, Validation, Low back pain, Neck-shoulder pain, Peripheral nerve damage

BACKGROUND

The International Association for the Study of Pain (IASP, 2011) defines Neuropathic Pain (NeP) as 'pain caused by a lesion or disease of the somatosensory nervous system' (http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698 #Neuropathicpain). This definition will be used in this study because of its diagnostic specificity, anatomic precision and the usefulness in clinical as well as research conditions [1]. NeP plays an important role in the development and prognosis of chronic pain states. A relevant example is patients with low back pain (LBP) and neck-shoulder pain (NSP), which are both highly prevalent and clinically important medical and societal problems: In this context, the more severe the NeP, the worse the pain course, the prognosis and the results of treatment [2-5].

The incidence of NeP in the Dutch general population is 0.81% or 130.000 new patients in the Netherlands per year. NeP is 63% more common in women than in men and peaks between 70 and 79 years of age [6]. LBP as well as NSP are among the top 10 health problems encountered in general practice. For men and women, respectively, the prevalence of LBP and/or NSP in the general practice is in the range of 55 – 86 and 24 – 113 per 1000 patients a year. In general practice, radiating pain from the low back or neck occurs in men and women in respectively 4 – 8 and 10 patients per 1000 patients [7] (http://www.nationaalkompas.nl/gezondheid-en-ziekte/ ziekten-en-aandoeningen/bewegingsstelsel-en-bindweefsel/ nek-en-rugklachten/ omvang/). The prevalence of chronic pain syndromes due to peripheral nerve damage (PND) is 3,3 per 1000 per year [8].

Strictly speaking, the diagnosis of neuropathic pain is a patho-anatomical diagnosis presuming knowledge regarding nerve injury which is difficult to obtain in the clinical situation. Thus in the clinical context it is better to speak of a neuropathic pain component (NePC), which is a clinical syndrome based on a typical set of clinical symptoms and signs. Clinically, a NePC is characterized by spontaneous pain and abnormal pain sensations [9]. NeP is typically described as a spontaneous ongoing burning or shooting pain with spontaneous sharp exacerbations and somatosensory abnormalities after a (non-) noxious stimulus [10].

As a rule, a NePC has a considerable impact on the quality of daily life [6]. Hence it is important for physicians in daily practice (specialist care as well as primay care) to diagnose the presence and severity of a NePC in individual patients. In clinical practice it is, however, often difficult to reliably diagnose a NePC in (sub)acute and chronic pain of the low back and neck shoulder region. The diagnosis of a NePC is at present primarily based on clinical examination by a physician including sensory examination. Quantitative sensory testing (QST) may provide extra information for selected clinical cases and in the research context [11,12].

Because a reliable diagnosis of the neuropathic pain component is often difficult to accomplish in routine practice [2], it would be helpful to have a screening tool to detect such a component for clinical triage and epidemiological purposes [12,13]. Apart from optimal sensitivity and specificity, such a screening tool should be easy to use in clinical practice, not only for the first visit but also during follow up. The availability of such a simple, validated, Dutch language screening tool should improve diagnosis and quantification of a NePC and hence lead to better therapy. At present, no specific (validated) instrument to determine the neuropathic component in LBP, NSP and PND is available in the Dutch language. The Pain*DETECT*-Questionnaire (PDQ) [2] and the Douleur Neuropatique 4 Questions (DN4) [14] were originally developed and validated in Germany and France, respectively. Both are considered to be reliable screening tools with a high sensitivity, specificity and positive predictive value. Recently, the DN4 and the PDQ have been translated into a Dutch language version (Dlv) by Van Seventer et al [15] and Timmerman et al [16], respectively.

Validation of the Dutch versions of DN4-$_{Dlv}$ and PDQ-$_{Dlv}$ will improve the identification of a NePC in Dutch primary and specialist medical care, also facilitating remote follow up evaluation by telephone, internet or post for clinical and scientific purposes. We chose an innovative approach which should lead to a more reliable identification and quantification of a NePC in patients with chronic pain. This study will help define patient groups at risk for a NePC and will help to understand and assess the variability and burden of a NePC in individual patients.

The aim of this study is to establish the clinimetric quality, including 2-weeks test-retest reliability, of the PDQ-$_{Dlv}$ and the DN4-$_{Dlv}$ for use in primary care and specialist medical care settings in Dutch speaking countries for patients with chronic pain due to LBP, NSP or known peripheral nerve damage (PND). Follow-up for monitoring and prognosis properties of DN4-$_{Dlv}$ and PDQ-$_{Dlv}$ for a NePC will be done over a period of 3 months. Additional data will be collected regarding NEPC prevalence, general health status, mental health status, functioning, pain attribution and health related quality of life in patients with chronic pain.

METHODS

The medical and ethical review board Committee on Research Involving Human Subjects region Arnhem-Nijmegen, Nijmegen, the Netherlands, has given approval to conduct this study, Dossier number: 2008/348; NL 25343.091.08; The Netherlands National Trial Register NTR3030.

Design

In this study a cross-sectional, observational, research design with 3-months follow up will be used to study the clinimetric quality of the DN4-$_{Dlv}$ and PDQ-$_{Dlv}$ (Figure 1).

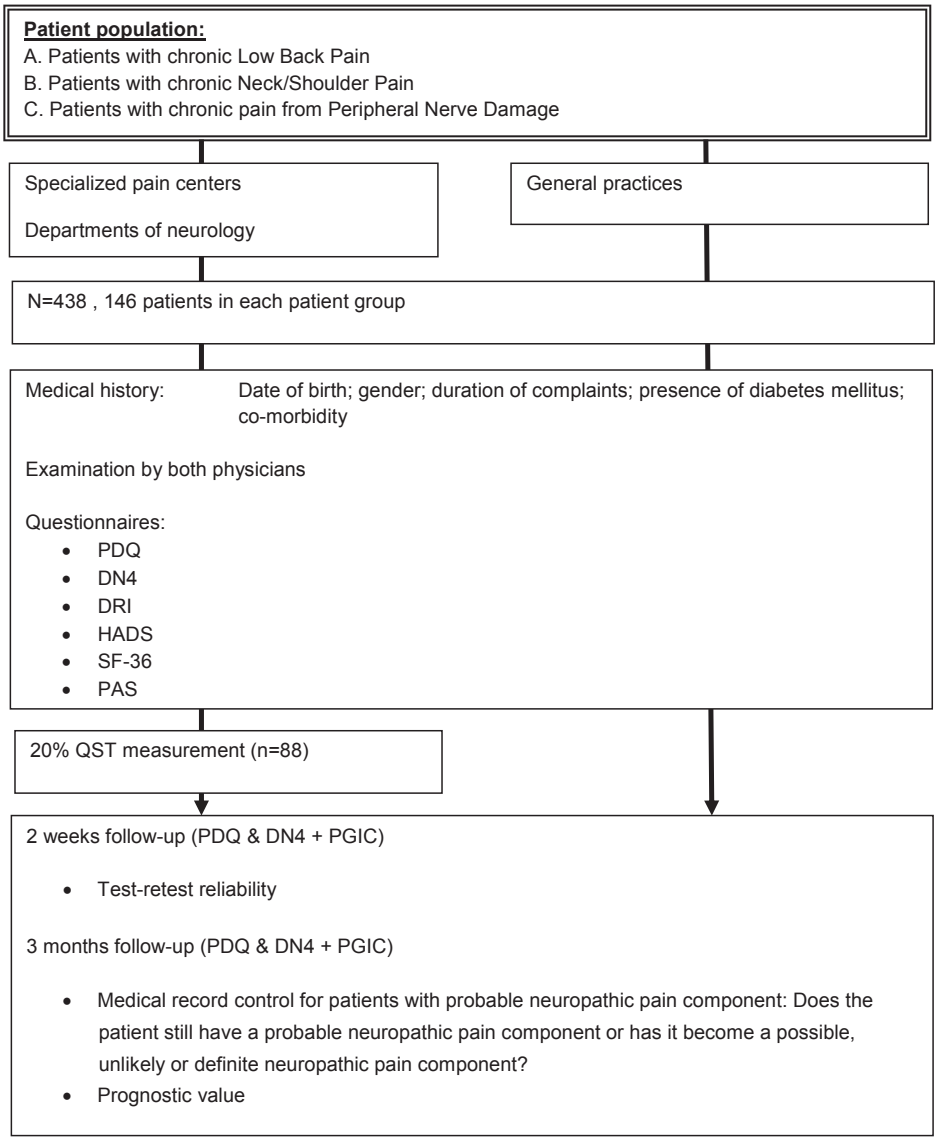

Figure 1: Flow-diagram of the study.
PDQ: Pain*DETECT* questionnaire; DN4: Douleur neuropatique 4 questions; DRI : Disability rating index; HADS: Hospital anxiety depression scale; RAND-36: RAND 36-item health survey; PAS: Pain attribution scale; QST: Quantitative sensory testing; PGIC: Patients global impression of change.

Setting

Multicenter recruitment will be take place in academic pain centres, non-academic pain centres and non-academic departments of neurology. Patients will be seen by the two physicians during normal office hours, or when that is not possible during a special office hour for this study. Furthermore, patients willing to participate in this study from general practices will also be included in this study via a special office hour in the clinical trainings centre of Radboud university medical center (Radboudumc).

Each patient will be seen by two physicians, independently of each other, working in the same institute. The medical background of the participating physicians is diverse (experienced pain specialists, pain specialist trainees, experienced neurologists and experienced general practitioners).

Participants

The patients will be recruited non-selectively and consecutively in the period from September 2009 till July 2013. Inclusion criteria: Male and female adult patients (>18 years of age) with chronic (>3 months) LBP or NSP radiating into respectively leg(s) or arm(s) or patients with chronic pain due to PND. Exclusion criteria: Patients diagnosed with malignancy, compression fractures, patients with painful syndromes of unknown origin or associated with diffuse pains (such as ankylosing spondylitis or fibromyalgia), severe mental illness, chronic alcoholism or substance abuse, inability to fill in the questionnaire adequately, or incapable of understanding Dutch. Subjects can leave the study at any time for any reason without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. When an individual subject leaves the study all the information from the patient will be kept in the database, and possibly be used for data analysis or withdrawal analysis. Such patients will be replaced.

Measurements

At the first visit, each patient will be seen by two physicians who will question and examine the patients. They will then independently classify the patients' pain as pain with or without a NePC, based in the IASP NeP criteria and supported by a standardized assessment form. Next, the patient will complete seven questionnaires (including the PDQ and the DN4). Twenty percent of the patients will additionally undergo QST measurement following the first visit. Two weeks and three months after the initial visit three follow-up questionnaires will be sent to the patient by mail.

Demographics

Date of birth, gender, weight (Kg), length (m), nationality, nationality of origin, pain medication, smoking (cigarettes a day), alcohol consumption (units per day) and education level will be assessed by use of a self completed questionnaire. Pain at this moment will be assessed by use of a numeric rating scale (0-10, NRS). Medical co-morbidity, duration of complaints (years/months), presence of diabetes mellitus (yes/no), presence of HIV (yes/no), presence of herpes (yes/no) and undergoing of

chemotherapy (yes/no) are based on interview by the physician and noted by the physician on the standardized assessment form.

Pain classification

At each centre participating patients will be examined by two (rater A and B) independent and trained pain physicians, two experienced neurologists or two experienced general practitioners, working independently of each other and blinded to the diagnosis of the other physician. To achieve standardization of the history and clinical examination all participating physicians will be trained at the sites. Both physicians will classify the pain regarding the presence or absence of a NePC based on history and clinical examination. Level of certainty of the physicians regarding the pain component classification will be assessed by use of a Visual Analogue Scale (VAS, range 0-100). The findings are noted on the standardized assessment form by the physician. To monitor the quality of the clinical examination random quality checks, by expected/ unexpected visits, will be used.

Grading system

The grading system for neuropathic pain as proposed by Treede et al. [1] will be used as a secondary comparison with the outcome of both the PDQ-$_{DIV}$ and DN4-$_{DIV}$ and with the outcome of the original pain classification by the two physicians. This system provides a working hypothesis for the origin of patients' pain. The criteria are graded on basis of history and testing in medical examination [1]: (1) Pain with a distinct neuroanatomically plausible distribution; (2) A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system; (3) Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test; (4) Demonstration of the relevant lesion or disease by at least one confirmatory test lesion or disease explaining NeP. When the criteria 1-4 are all fulfilled the pain will be graded as possessing a 'definite NePC'. Criteria 1 and 2 and either 3 or 4 will be graded as 'probable NePC'. Criteria 1 & 2 without criteria 3 or 4 will be graded as 'possible NePC'. The pain is 'unlikely to have a NePC' when no criteria, or only criteria 1 or 2, are graded as present (Table 1). The answers (yes or no) to the four criteria are noted by the physician on the standardized assessment form. Three months after the first consultation by the two physicians the medical record of patients with 'probable NePC' according to the grading system will be controlled: i.e. does the patient still have probable NePC, or does he now have definite NePC?.

Table 1: **Outcome of the grading system [1]**

Criteria 1:	*Criteria 2:*	*Criteria 3:*	*Criteria 4:*	*Outcome of the grading system*
Pain with a distinct neuro-anatomically plausible distribution	**History suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system**	**Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test**	**Demonstration of the relevant lesion or disease by at least one confirmatory test lesion or disease explaining NeP**	
-	-	-	-	*Unlikely to be NeP*
V	-	-	-	*Unlikely to be NeP*
-	*V*	-	-	*Unlikely to be NeP*
V	*V*	-	-	*Possible NeP*
V	*V*	*V*	-	*Probable NeP*
V	*V*	-	*V*	*Probable NeP*
V	*V*	*V*	*V*	*Definite NeP*

NeP: Neuropathic Pain; V: present; -: absent.

Bedside examination

Bed-side examination of the patient is performed by both physicians. The aim of this examination is to find possible abnormalities suggestive for a relevant lesion or disease which affects the peripheral or central somatosensory system [17]. The value of bed-side examination within the clinical examination is that it will give insight in the pathology and the localization of the lesion or disease which is causing the pain. Touch, pin prick, pressure, cold, heath, vibration and temporal summation were included in the examination to provide proof of a NePC [10,12,18]. This evaluation will be assessed in a standardized way. The location indicated by the patient as the one with maximum pain will be compared with the mirrored location on the contra lateral side. If the pain has a double sided character a location without pain as close as possible to the original mirror site will be tested for comparison. The outcome is noted by the physician on the standardized assessment form: a) Is there a sensation b) is the sensation unpleasant or c) is the sensation painful (all scored as Yes, No or Unclear). The response of the patient will be noted on the assessment form. The following tests will be performed in all patients: Mechanical static allodynia by blunt pressure with a finger at a force which normally doesn't evoke pain; Dynamic mechanical allodynia by stroking the skin with a Soft Brush (SENSElab™, Brush-05, Somedic AB, Hörby, Sweden), one movement of 1-2 centimeter and three movements of 1-2 centimeters (wind-up response); Mechanical pinprick allodynia by touch of the skin with a plastic safety pin and a Von Frey hair (TOUCH TEST®, 5.07, 10.0 g, North Coast Medical Inc., Gilroy, USA). Heat allodynia by using TipTherm® (TipTherm, Brüggen, Germany) in a baby-bottle warmer (ISI mini Baby Bottle Warmer, Assen, the Netherlands) set at 45 degrees Celsius; Cold allodynia with an ice cube placed on the skin for 2 seconds and Vibration with a Tuning fork (128 Hz; Medipharchem, Wormerveer, the Netherlands) applied to joint, bone or soft tissue in the region of the pain.

Quantitative sensory testing

Over the last two decades, QST has been developed to complement traditional neurological bedside examination in the analysis of somatosensory aberrations [19,20]. In theory, greater precision in assessing the functionality of the somatosensory systems is the main advantage of QST over standard bedside examination. QST improves diagnostic procedures and can be helpful for treatment monitoring [11,21]. The protocol we chose is the Nijmegen Aalborg Screening QST Paradigm (NASQ Paradigm) [22]. This maps pain sensitivity at multiple sites by measuring the responses (i.e. painful sensations) evoked by mechanical and electrical non invasive stimuli and measures the patient's capacity to modulate pain using the Conditioned Pain Modulation [23], previously termed Diffuse Noxious Inhibitory controls (DNIC) or Heterotopic Noxious Conditioning Stimulation (HNCS) [24]. In this study the QST is used to quantify alterations in sensory processing due to the NePC (sensory profiling) in a sub-sample of patients with LBP, NSP and PND (20% of the total population under study, n = 88, equally but randomly divided over all three pain syndromes). Instructions are standardized and will be read to the patient from an instruction sheet. Pressure Pain Thresholds (PPT) will be tested by use of an pressure algometer (Somedic sales AB, Hörby,

Sweden). PPT will be measured on the left and right bodyside once at each location: Thenar (middle part), musculus trapezius pars median (middle part), musculus rectus femoral (15 cm above patella) and m. abductor hallucis (middle part). Electrical pain thresholds (EPT) will be tested by use of the QST-3 device (JNI Biomedical ApS, Klarup, Denmark) on the left and right body side. Measurement locations are the musculus trapezius pars median (middle part) and the musculus rectus femoris (20 cm above patella). Electrical pain thresholds (EPT) are assessed and expressed in milli-Ampère. Single pulse evoked pain measurement is performed by one pulse at 150% of the EPT and assessed on a VAS. Summation (i.e. Electric Wind-Up response (E-WUR)) is measured by a train of five pulses at 150% of the EPT and assessed on as VAS. Conditioned Pain Modulation (CPM) [23,25] will be assessed. Electrical Pain Tolerance Thresholds (EPTT) (test stimulation) are assessed and expressed in milli-Ampère on the m. Rectus femoris contralateral to the dominant hand. The noxious stimulus (conditioning stimulation) is to immerse the dominant hand until the wrist in a bucket filled with water and icecubes ('Ice water bucket test') [24] for 'as long as possible, until the moment that the sensation becomes unbearable and you want to stop directly". The pain will be recorded every 10 seconds on a NRS. The duration of the immersion (with a maximum of three minutes) will be recorded and the pain at the end of the immersion will be asked. Afterwards, again the EPTT and the PPT on the contra lateral m. rectus femoris are assessed.

Douleur neuropathique 4 questions (DN4)

The DN4 [14,15] (© Pfizer bv. Capelle a/d Ijssel, the Netherlands) consists of 10 items in total, divided in two questions and two physical examination tests, and is developed to screen components of NeP resulting in a yes/no answer for the presence of NeP. Questions 1 & 2 are sensory descriptors and have to be filled in by the patient or assessed by the physician by interview; questions 3 & 4 are based on a sensory examination by the physician. Question 3 includes two items related to sensory deficits: 'Is the pain located in an area where the physical examination may reveal one or more of the following characteristics? Touch hypoesthesia and/or pricking hypoesthesia. Question 4 includes 1 item related to evoked pain: 'In the painful area, can the pain be caused or increased by brushing? Examination of sensitivity to touch (one movement) will be performed with the use of a soft brush (SENSElab™, Brush-05, Somedic AB, Hörby, Sweden). The soft brush will also be used to evaluate tactile (i.e. dynamic mechanical) allodynia (wind-up, with three movements). Examination of sensitivity to touch and pricking will be performed with the use of a Von Frey hair (TOUCH TEST®, 5.07, 10.0 g, North Coast Medical Inc., Gilroy, USA). Pressure allodynia (i.e. static mechanical allodynia) is tested by blunt pressure with a finger at a pressure that does not provoke pain in a normally sensitive area [14]. The findings in the physical tests are noted by the physician on the standardized assessment form. The cut-off score for the diagnosis of NeP for the 10-item' DN4 was determined on 4 times 'yes' out of 10 (score range 0-10). This score gave the highest percentage of correctly identified patients (86%), sensitivity (82,9%) and specificity (89,9%). The 7-item' DN4-interview (score range 0-7) has a cut-off score of 3 times 'yes' out of 7 which resulted in a percentage of correctly identified patients of 79, 5%, 78% sensitivity and 81,2% specificity [14].

Pain*DETECT*-Questionnaire (PDQ)

The PDQ (© Pfizer Pharma GmbH 2005, Pfizer bv 2009. Cappelle a/d IJssel, the Netherlands) was developed in Germany [2,16]. The questionnaire can be filled in by the patients themselves and was devised to screen for the presence of a NePC without physical examination. Scoring is performed using a scoring manual and results in a final screening score for the presence of a NePC: 'negative,' a NePC is unlikely (<15%, score range 0-12); 'unclear', result is ambiguous, however a NePC can be present (score range 13-18); or 'positive', a NePC is likely (>90%, score range 19-38). The PDQ was tested as a reliable screening tool with a percentage of correctly identified patients of 83% for NeP, sensitivity of 85% and a specificity of 80% [2].

Additional questionnaires

Functioning: Disability Rating Index (DRI) [26]. The self- administered DRI inquires, in a clinical setting, in 12 items about specified activities (Dressing, Out-door walks, Climbing stairs, Sitting longer time, Standing bent over a sink, Carrying a bag, Making a bed, Running, Light work, Heavy work, Lifting heavy objects, Participating in exercise/sports). Score range is from 0 to 100 for each item on a Visual Analogue Scale (VAS). A higher score indicates more disability. The DRI has a good responsiveness (p = 0,0001) and a good test-retest correlation of 0,95. The inter- and Intra-rater reproducibility were respectively 0.99 and 0.98 [26]. Mental health status: The Hospital Anxiety Depression Scale (HADS) [27] will be used to assess the presence of anxiety and depressive states of patients. This self-administered questionnaire is divided into an anxiety subscale (HADS-A) and a depression subscale (HADS-D), both containing 7-items with a score range of 0-21. The HADS-$_{Dlv}$ [28] has a good test-retest reliability for HADS-A, HADS-D and the total HADS (respectively 0.89; 0.86 and 0.91 p =0.001). The correlation between the anxiety and the depression subscale was high (0.43 to 0.73) [28]. Based on the review by Bjelland [29] a cut-off score for both the HADS-A and the HADS-D of 8+ gives the best balance in sensitivity and specificity (approximately 0.80 for sensitivity and specificity). Pain Attribution: Pain Attribution Scale (PAS) Additional questions to study the attribution of the pain in patients. On a 5-point Likert-scale the patient is asked to rate the influence of several items on the pain complaints. Rating is from 'totally not of influence on the pain complaints' to 'very much of influence on the pain complaints'. Quality of life: The RAND 36-item Health Survey (RAND-36) [30] is developed to investigate the health related quality of life. The short, self-administered questionnaire consists of 8 different scales: Physical functioning, social functioning, role limitations (physical problem), role limitations (emotional problem), mental health, pain, general health perception and health change. The psychometric quality of the RAND-36-$_{Dlv}$ was studied by van der Zee [31,32]. Change (Follow-up, 2 weeks and 3 months): The Patients Global Impression of Change (PGIC) is a patient rated instrument which measures changes over time on a seven-points scale. Score range is from 1 (very much worse) to 7 (very much improved) [33-35].

Power calculation

In an unselected cohort of chronic LBP patients, 37% had a high probability of a NePC [2]. Sensitivity and specificity of the PDQ is respectively 85% and 80% [2] and the sensitivity and specificity of the DN4 are respectively 83% and 90% [14]. The expected sensitivity and specificity of the Dutch versions of both questionnaires is set at 80% with an prevalence of 37% and the required lower 95% confidence limit > 0.55. According to Flahault et al the N_{cases} is 40. From the equation in the first formula by Flahault, the $N_{controls} = 68$ [36]. Without prior knowledge of the individual case-control status, the sample size must be determined such that, with high probability (e.g. 95%), the sample contains sufficient numbers of cases and controls. According to the second formula by Flahault et al: $N_{total} = 132$, in each group. Thus in each group 146 patients will be included (10% drop out). It is expected that this recruitment will be achievable in the 10 general practices, 4 pain treatment centres and 2 departments of neurology chosen.

Data

All data will be collected from the patients and the physicians on paper and stored by Radboudumc. Data management and monitoring will be performed within MACRO (MACRO, version 4.1.1.3720, Infermed, London, United Kingdom).

Statistical analysis

To establish the clinimetric quality of the PDQ_{-DIV} and the $DN4_{-DIV}$ a comparison will be made between the outcome of both the screening questionnaires and the original pain classification, the Grading system by Treede at al. [1], the bedside examination and the QST measurements. The prevalence of a NePC in patients with LBP and NSP in the Netherlands will be assessed by extrapolating the outcome of this study to the Dutch population. The monitoring and prognosis of the patient over a period of three months by use of the PDQ_{-DIV} and the $DN4_{-DIV}$ will be recorded. Data analysis and statistics will be performed by use of Statistical Package for the Social Sciences (SPSS version 18.0, SPSS Inc., Chicago, Illinois, USA). All statistical tests will be two-tailed, for all statistical analysis the type 1 error will be set on 5%.

Descriptive statistics: The quantitative variables will be described using mean, standard deviation (SD) and range; Qualitative variables will be described using frequency and percentages. To assess central position, dispersion and distribution of variables, the Kolmogorov-Smirnov test will be used. *Univariate analysis:* Both the physicians assessments (by rater A and B) will serve as the 'gold standard' to assess the presence of a NePC. The internal consistency of both the physicians assessments and the physical examination tests of the DN4 will be separately established for rater A and B by calculating Cronbach's α that assesses the contribution of each item to the precision of the measurement by both the physicians assessments and the examination items of the DN4 questionnaire.

Inter-rater reliability: will be assessed by the agreement of the results obtained by raters A and B for both the physicians assessments and the examination items of the DN4. Agreement was determined by calculating the Cohen's kappa coefficient.

Test-retest reliability: will be assessed for the PDQ and DN4, after two weeks of completion of the questionnaires during the first visit. Stability of the questionnaire will be analyzed by measuring the intra-class correlation coefficient and by use of Cohen's kappa coefficient of agreement.

Prognosis and monitoring: will be assessed for the PDQ and DN4, after three months of completion of the questionnaires during the first visit. Stability of the questionnaire will be analyzed by measuring the intra- class correlation coefficient and by use of Cohen's kappa coefficient of agreement.

Correlations: will be calculated between scores and continuous variables using Pearson correlation coefficient (i.e. correlation between DN4, PDQ and both the physicians assessments). A students-t test for independent groups or a Mann-Whitney's U test (non-normal distribution) will be used to compare respectively continuous or ordinal variables between patients with and without a neuropatic pain component

Multivariate analysis: Sensitivity and specificity percentage of well classified observations and Youden index (i.e. sensitivity + specificity-1) will be calculated for different values of the score of the questionnaire by logistical regression analysis. Positive and negative predictive value for both instruments will also be calculated. The corresponding ROC (receiver operating characteristics) curves will be plotted and AUC calculated using the trapezoid method. Discriminant analysis will be used to analyze complementarily of PDQ and DN4 to each other.

DISCUSSION

The rationale for this study is to provide detailed information on the clinimetric quality, including test-retest reliability, of the PDQ-$_{DIV}$ and DN4-$_{DIV}$ in patients with LBP, NSP or PND regarding of diagnosing a NePC. A validation of these questionnaires is necessary for its use in everyday clinical practice and also in (inter-)national research to make the outcome comparable in different countries. The key question of this study is whether a NePC as assessed by the physician is reflected in the outcome of the PDQ-$_{DIV}$ and DN4-$_{DIV}$. In already published articles both questionnaires have proven to be useful in daily clinical practice and for research purposes with good clinimetric qualities [2,14].

This study chose an innovative and wide ranging approach to diagnose a NePC in patients in based on a more reliable identification and qualification of a NePC. In the absence of an internationally

accepted 'gold standard' [12] the challenge was to find a method to examine the patients in a standardized manner to assess a NePC. The opinion of two physicians about a NePC, the most frequently used standard, will be used in this study and is also used in the original validation studies by Freynhagen et al [2] and Bouhassira et al. [14]. Together with the grading system [1], sensory bed-side examination and QST we will aim to confirm the diagnosis of a NePC, also following the NeuPSIG guidelines for the assessment of neuropathic pain [12]. Screening for nerve damage on basis of sensory bed side examination will be performed by both the physicians. The aim of this examination is to find possible abnormalities suggestive for a relevant lesion or disease which affects the peripheral or central somatosensory system [17]. The value of bed-side examination within the clinical examination is that it will give insight into the pathology and the localization of the lesion or disease which is causing the pain. Touch, pin prick, pressure, cold, heath, vibration and temporal summation were included in the examination to assess the NePC of pain [10,12,18]. For heat allodynia we use a Tip-Therm^{R} in a baby-bottle warmer at 45 degrees Celsius. To our knowledge we are the first to use this method. Because a bottle warmer has a reasonably good thermostat, the temperature of the water inside, and thus the TipTherm^{R}, will be kept at the set temperature. In this study we did not use the DFNS sensory testing protocol [19,20] but our own NASQ-protocol. This because we were interested in using QST to assess the altered pain processing, including changes in function of endogenous pain modulation, that may underlie chronic pain conditions, instead of testing small and large nerve-fibre function and the nerve damage related sensory changes [21].

This study will aim to try to define patient groups at risk and to understand and assess the variability and burden of a NePC in individual patients. The PDQ [2] outcome is an ordinal scale, ranging from zero to thirty-eight (a neuropathic pain component is unlikely-neuropathic pain component is likely) and thus the question logically arises whether the PDQ is suitable for the assessment of the amount of nerve damage.

By the choice for a non-selective consecutive patient recruitment in specialized pain clinics, neurology clinics as well as general practices this study aims to validate the PDQ$_{-DIv}$ and DN4$_{-DIv}$ in a general, unselected chronic pain population. To date, almost all screening questionnaires are validated in a defined, restricted, population, recruited in specialized pain clinics and pre-selected by precise medical diagnosis (lumbar radicular pain, diabetic polyneuropathy, postherpetic neuralgia etc.). Our choice of a non-selcted population might lead to a lower sensitivity and specificity of the PDQ$_{-DIv}$ and DN4$_{-DIv}$ in this study than published in the original validation studies [2,14]. However, the choice for a non-consecutive population has the advantage of providing more information relevant to ordinary clinical practice, in that it is relevant to the unselected 'general population'.

In conclusion, this study seeks to identify the association between patient' symptoms, the signs as found in the bedside examination and outcome of the QST measurements, the general and mental

health status, functioning, pain attribution and quality of life with regard to the outcome of the PDQ-$_{Dlv}$ and DN4-$_{Dlv}$ in patients with chronic pain due to LBP, NSP or PND.

TRIAL STATUS

This study is ongoing. The expected end date of patient recruitment in this study is July 1, 2013.

ABBREVIATIONS

CPM: Conditioned pain modulation; DN4: Douleur neuropathique 4 questions; DN4-$_{Dlv}$: Douleur neuropathique 4 questions dutch language version; DNIC: Diffuse noxious inhibitory control; DRI: Disability rating index; HADS: Hospital anxiety depression scale; LBP: Low back pain; NASQ paradigm: Nijmegen otali screening QST paradigm; NeP: Neuropathic pain; NePC: Neuropathic pain component; NRS: Numeric rating scale; NSP: Neck shoulder pain; PAS: Pain attribution scale; PDQ: Pain*DETECT* questionnaire; PDQ-$_{Dlv}$: Pain*DETECT* questionnaire dutch language version; PGIC: Patients global impression of change; RAND-36: RAND 36-item health survey; Radboudumc: Radboud University medical center; QST: Quantitative sensory testing; VAS: Visual analogue scale.

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CHAPTER 5

Avoiding Catch-22: validating the Pain*DETECT* in a population of patients with chronic pain

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ABSTRACT

Background

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system and is a major therapeutic challenge. Several screening tools have been developed to help physicians detect patients with neuropathic pain. These have typically been validated in populations pre-stratified for neuropathic pain, leading to a so called *"Catch-22 situation:" "a problematic situation for which the only solution is denied by a circumstance inherent in the problem or by a rule"*. The validity of screening tools needs to be proven in patients with pain who were not pre-stratified on basis of the target outcome: neuropathic pain or non- neuropathic pain. This study aims to assess the validity of the Dutch Pain*DETECT* (Pain*DETECT*-DIV) in a large population of patients with chronic pain.

Methods

A cross-sectional multicentre design was used to assess Pain*DETECT*-DIV validity. Included where patients with low back pain radiating into the leg(s), patients with neck-shoulder-arm pain and patients with pain due to a suspected peripheral nerve damage. Patients' pain was classified as having a neuropathic pain component (yes/no) by two experienced physicians ("gold standard"). Physician opinion based on the Grading System was a secondary comparison.

Results

In total, 291 patients were included. Primary analysis was done on patients where both physicians agreed upon the pain classification (n = 228). Compared to the physician's classification, Pain*DETECT*-DIV had a sensitivity of 80% and specificity of 55%, versus the Grading System it achieved 74 and 46%.

Conclusion

Despite its internal consistency and test-retest reliability the Pain*DETECT*-DIV is not an effective screening tool for a neuropathic pain component in a population of patients with chronic pain because of its moderate sensitivity and low specificity. Moreover, the indiscriminate use of the Pain*DETECT*-DIV as a surrogate for clinical assessment should be avoided in daily clinical practice as well as in (clinical-) research. Catch-22 situations in the validation of screening tools can be prevented by not pre-stratifying the patients on basis of the target outcome before inclusion in a validation study for screening instruments.

Trial registration

The protocol was registered prospectively in the Dutch National Trial Register: NTR 3030.

Keywords

Pain*DETECT* questionnaire, Reliability, Validity, Sensitivity, Specificity, Screening tool, Neuropathic pain, Pain, Clinical assessment, Low back pain, Neck shoulder arm pain, Peripheral nerve damage

BACKGROUND

The International Association for the Study of Pain defines neuropathic pain as *"pain caused by a lesion or disease of the somatosensory nervous system"* and states that *"neuropathic pain is not a medical diagnosis but a clinical description which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria"* [1]. In the clinical context it is better to speak of a present or an absent neuropathic pain component (present- or absent NePC) with respect to so called mixed-pain conditions [2, 3] in which neuropathic pain and nociceptive pain both exist. Clinically, NePC is considered to manifest specific symptoms and signs [4, 5]. The classification of NePC is usually based on history and physical examination including (bedside-) sensory testing [6, 7]. The correct classification of NePC is important for patients because NePC has a considerable impact on the quality of daily life [8] and for physicians since the treatment differs strongly from that of patients without NePC [6, 9, 10].

An easy to use and validated screening tool for clinical triage and epidemiological purposes could aid uniform classification and quantification of NePC and hence lead to better therapy, particularly when used by non-specialists [6-8, 11-15].

The Pain*DETECT* is such a patient friendly screening tool for the screening for neuropathic pain. It was originally developed and validated in Germany [2] based on two groups of patients (patients with pain of predominantly neuropathic origin or of predominantly nociceptive origin) with at least a 40% score on a visual analogue scale for pain (VAS; 0-100). The gold standard used in this study was the assessment of the pain type based on the examination by two experienced pain specialists. This resulted in a percentage of correctly identified patients of 83% for neuropathic pain, a sensitivity of 85 and 80% specificity [2]. Subsequently, validation studies were performed in Spain [16], Turkey [17], Japan [18], India (Hindi) [19] and Korea [20]. Since the introduction of the Pain*DETECT* this instrument has been used in many clinical and epidemiological studies [21]. In a Danish study, based on Pain*DETECT* outcome, NePC was present [22] in about 40% of the patients with musculoskeletal pain.

In the above-mentioned validation studies [2, 16-20], the validity of the Pain*DETECT* as a screening tool was performed in pre-stratified groups of patients based on the target outcome (pain of predominantly neuropathic origin or of predominantly nociceptive origin and limitation to pain scores). The inclusion of only patients with a known pain classification on forehand might lead to a prerequisite for the determination of validity of the Pain*DETECT*. For this situation, the term *"Catch-22"* is used in the English language for *"a problematic situation for which the only solution is denied by a circumstance inherent in the problem or by a rule"* [23]. It was firstly described in Joseph Heller's novel Catch-22 which describes a general situation in which an individual has to accomplish two actions that are mutually dependent on the other action that must be completed first.

The objective of this study is to further validate the Pain*DETECT* as a screening tool for use in daily outpatient practices for detecting a NePC. The current validation study is being conducted in a general patient population having common chronic pain syndromes, not pre-stratified on the target outcome: low back with leg pain (LBLP), neck-shoulder-arm pain (NSA pain) or a suspected peripheral nerve damage pain (suspected PND pain).

METHODS

The study was conducted in a cross-sectional, observational, research design with two weeks and three months follow up to study the clinimetric quality (i.e. reliability and validity) of the Pain*DETECT*. This study, to detect a NePC in patients suffering from chronic pain, was approved by the medical and ethical review board Committee on Research Involving Human Subjects region Arnhem-Nijmegen, Nijmegen, the Netherlands, Dossier number: 2008/348; NL 25343.091.08 and conducted in accordance with the declaration of Helsinki and the declaration of the World Medical Association. As required, written informed consent was obtained from patients prior to study participation. The protocol is registered in the Dutch National Trial Register: NTR 3030. The Pain*DETECT* was translated and cross-culturally adapted into the Dutch language (Pain*DETECT* $_{-DIV}$) (© Pfizer Pharma GmbH 2005, Pfizer bv 2008. Cappelle a/d Ijssel, the Netherlands) in a separate study [24] before the commencement of the present validation study. In this study, the same methodology was used as in the previously published protocol [25] and as employed in a simultaneous study regarding the validity of the DN4 [26] .

Patients

The patients were recruited from October 2009 until July 2013. Multicenter recruitment took place in the Netherlands in three academic centers specialized in pain medicine, three non-academic centers specialized in pain medicine and one non-academic department of neurology. The question to participate in the study was asked by the patients' own physician. At that moment they only had a provisional diagnosis: LBLP, NSA pain or pain due to a suspected PND (Conditions associated with a lesion of the peripheral somatosensory system). These three groups of patients include a majority of the patients referred towards an academic or peripheral pain clinic from the general practitioner. Patients had to be diagnosed for the initial cause of the pain as classified according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)-2015-WHO Version 2015 [27]. Importantly, patients were not pre-stratified on the target outcome: the existence of NePC yes or no [28]. Patients, when willing to participate, were included when they met the following inclusion criteria: Male or female adult patients (> 18 years of age) with chronic (≥3 months) LBLP or NSA pain radiating into leg (s) or arm (s) respectively or patients with chronic pain due to a suspected PND. Exclusion criteria were: Patients diagnosed with an active malignant disorder, compression fractures, patients with diffuse pains (pains with an origin

in muscles, bones or joints: such as fibromyalgia or ankylosing spondylitis), severe mental illness, chronic alcoholism or substance abuse, inability to fill in the questionnaire adequately or incapable of understanding the Dutch language.

Physicians' assessment

Patients were examined for the presence of NePC by two physicians which was considered to be the "gold standard" in this study. The physicians (pain specialists, pain specialist in training or neurologists always operated in differently composed pairs) worked independently from each other and were blinded to the classification made by the other physician. The physicians were not selected on basis of age, years of experience as a physician or other criteria. A full medical history was taken followed by a thorough clinical examination. A bedside examination (touch, pin prick, pressure, cold, heat and temporal summation) to assess patients' pain [25] was based on the European Federation of Neurological Societies (EFNS) guidelines [29, 30], the IASP Neuropathic Pain Special Interest Group (NeuPSIG) guidelines on neuropathic pain assessment [6] and the guidelines for assessment of neuropathic pain in primary care [7]. Patients' pain was classified by the physician as pain with present- or absent-NePC. The NeuPSIG Grading System for neuropathic pain as proposed by Treede et al. [31] was used as a secondary comparison with the outcome of the Pain*DETECT*-$_{\text{DIV}}$. The assessment of the Grading System was implemented in the standardized assessment protocol and thus included in the diagnostic work-up of the patients [25]. The outcomes "probable" and "definite" were regarded as "present-NePC". "Unlikely" and "possible" were rated as "absent-NePC" [32-34]. All participating physicians underwent standard medical training, belonging to the classic medical curriculum, and examination of the (central) nervous system in particular. To achieve standardization of history and assessment of NePC presence in patients included in this study all participating physicians underwent a training in the performance of the clinical examination of the patients (including sensory (bedside) examination and use of the NeupSIG Grading System) [25]. Training of the physicians took place at the participating center. During the execution of the study, the study coordinator (HT) visited the participating centers on a regularly basis to answer questions, to see if the necessary equipment was always available and to keep an eye on the inclusion of patients. Based on the order of assessment, the physician who performed the first assessment was called physician A and the physician who performed the assessment as a second physician was named physician B. However, the order of the physicians was based on availability during the study.

Pain*DETECT*-$_{\text{DIV}}$ and other questionnaires

The Pain*DETECT*-$_{\text{DIV}}$ (© Pfizer Pharma GmbH 2005, Pfizer bv 2008. Cappelle a/d Ijssel, the Netherlands) [2, 24] was designed as a simple, patient self-administered screening tool to screen for the presence of neuropathic pain without physical examination. This instrument consists of one item about the pain course pattern, one about radiating pain and seven items about the gradation of pain. An overall score is generated and ranges between -1 and 38. Additionally, there are three items about pain severity (current, worst and average pain) included in the Pain*DETECT*. For the

original German version [2] the outcome was as follows: '-1 – 12: negative', neuropathic pain is unlikely; 13-18: 'unclear'; result is ambiguous, however neuropathic pain can be present; 19-38 'positive,' neuropathic pain is likely.

The patient completed five questionnaires (including the Pain*DETECT*-DIV directly after the clinical assessment by the participating physicians but without any interference by the physicians. The researcher (HT) was available for help via telephone or in person when it was not clear how to fill in the questionnaires. Besides screening for NePC via the Pain*DETECT*-DIV [24], the disability of the patient was assessed via the Disability Rating Index (DRI) [35]. The existence of an anxiety disorder and/or depression were assessed via the Hospital Anxiety Depression Scale (HADS) [36-38] and the Pain Attribution Scale (PAS) was used to assess patients attribution of his or hers pain. Quality of life was determined via the RAND 36-item Health Survey (RAND-36) [39-41]. Two weeks and three months after the initial visit the follow-up questionnaires (the Patients Global Impression of Change (PGIC) [42-44] and the Pain*DETECT*-DIV) were sent to the patient by mail.

Data

All data gathered from patients and physicians was collected on paper and stored at the Radboudumc, Nijmegen, The Netherlands. Data management and monitoring were performed within MACRO (MACRO, version 4.1.1.3720, Infermed, London, United Kingdom).

Statistical methods

Power calculation for this study was based on an expected NePC prevalence of 37% in an unselected cohort of patients with chronic low back pain [2]. Sensitivity and specificity of the Pain*DETECT* were assessed in the original validation study as respectively 85 and 80% [2]. The sensitivity and specificity of the Pain*DETECT*-DIV was, on forehand, expected to be 80% with a prevalence of 37%. The lower 95% confidence limit was required to be >0.55. According to the calculations following the formulas by Flahault et al. [45] 132 patients with LBLP, NSA pain or suspected PND pain were needed so that the sample size contained a sufficient numbers of cases and controls [25].

Qualitative variables were presented as frequencies and percentages. The quantitative variables were presented as mean and standard deviation (SD) or as median and inter quartile range (IQR). Based on the classifications of the two physicians, all patients were categorized as absent-NePC, NePC or 'undetermined' (i.e. the classification by both physicians jointly was not equal).

One-way ANOVA (with additional Tukey's studentized range post-hoc test) or Kruskal-Wallis test were used to study differences between the three groups (NePC, absent-NePC, Undetermined).

Intraclass correlation (ICC) was used to assess reproducibility ('test-retest reliability') of the Pain*DETECT*-DIV between the fixed time points (baseline versus two weeks & baseline versus three

months). The ICC and responsiveness of the Pain*DETECT*-$_{DIV}$ were assessed between each point of measurement.

A receiver operating characteristic (ROC) curve was calculated and the area under the curve (AUC) with 95% confidence interval is presented to indicate the discriminatory power of the Pain*DETECT*-$_{DIV}$ to discriminate patients classified as with or without a NePC. The classification was based on the physicians' assessment outcome or based on the Grading System outcome, respectively. The theoretical maximum of the AUC is 100%, indicating a perfect discrimination and 50% is equal to tossing a coin. The optimal cut-off point of the Pain*DETECT*-$_{DIV}$ – sum score was calculated under the condition of equal-costs of misclassification, using the Youden-index. Sensitivity, specificity, positive and negative predictive values and the likelihood ratio in the population in this study was calculated at this cut-off point. Also, the 'number needed to diagnose (NND)' was assessed [46] by use of the formula: NND = 1/ [Sensitivity – (1-specificity)]. A clinical screening tool for the demonstration of a neuropathic pain component is considered valid if it has a high sensitivity, specificity and a high positive predictive value. For the measurement of the usefulness of the screening tool the likelihood ratio will be used [47].

The agreement between the pain classification by the physicians, the NeuPSIG Grading Systems and the Pain*DETECT*-$_{DIV}$ (yes: ≥11, no:< 11) outcome was evaluated by using Cohen's kappa (K), prevalence index (Pi) and percentage of pair wise agreement (PA) [25]. A K ≥ 0.40 and a PA ≥ 70% is considered indicative of interobserver reliability which is acceptable for use in clinical practice [48].

Data analysis and statistics were performed by use of Statistical Package for the Social Sciences (SPSS version 20.0, SPSS Inc., Chicago, Illinois, USA). Two-tailed p-value below 0.05 was considered statistically significant.

RESULTS

Patient population

In this study 330 patients, not pre-stratified on the target outcome, with chronic LBLP, NSA pain or suspected PND pain were assessed for eligibility. Two patients did not give their informed consent. Exclusion (n = 37) was due to not fulfilling the in- and exclusion criteria (n = 13); not returning the baseline questionnaires by the patient (n = 16); missing pain classification by one physician (n = 5) or both physicians (n = 3). In eight patients the assessment of the grading system (secondary comparison) was missing by one or both physicians. Finally, 291 patients participated in the study between October 2009 and July 2013. According to the international classification of diseases (ICD-10, version 2015) [27] these patients were classified as follows: 8 patients suffered from pain related to endocrine, nutritional and metabolic diseases (chapter IV); 75 patients from diseases of

the nervous system (chapter VI); 1 patient from diseases of the circulatory system (chapter IX); 189 patients from diseases of the musculoskeletal system and connective tissue (chapter XIII); 1 patient from diseases of the genito-urinary system (chapter XIV); 3 patients from symptoms, signs and ill-defined conditions, and 14 patient from injury, poisoning or other consequences of external causes.

Numbers of recruitment in the different participating hospitals (all in the Netherlands) were as follows: Reinier de Graaf Gasthuis, Delft n = 86; ErasmusMC, Rotterdam n = 62; Radboudumc, Nijmegen n = 59; Bernhoven Ziekenhuis, Oss n = 56; Rijnstate Ziekenhuis, Arnhem n = 15; St. Anna ziekenhuis, Geldrop n = 12 and UMC Utrecht, Utrecht n = 1. 132 patients had LBLP with radiation in one or two legs (45.4%), 51 NSA pain with radiation into one or both arms (17.5%) and 108 (37.1%) had suspected PND pain. The group of patients with suspected PND consisted of 86 patients with pain who were treated because of breast cancer (surgery and/or radiation and/or chemotherapy and/or hormonal therapy). The remaining 22 patients had pain because of various reasons: peripheral nerve damage (n = 12), polyneuropathy (n = 3), central post stroke pain (n = 2), Complex Regional Pain Syndrom (n = 2) and spinal radicular pain (n = 3).

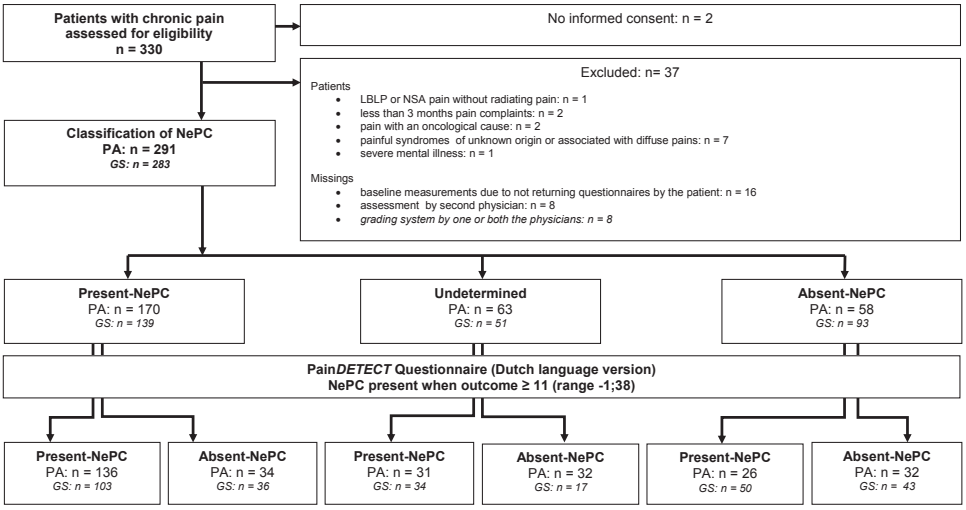

Figure 1: Flow diagram for the validation of the Pain*DETECT*-DIv.

PA: Physicians' assessment; GS: Neuropathic pain special interest group Grading System; Present-NePC: Neuropathic pain component present; Undetermined: both physicians disagree with each other about the presence of a neuropathic pain component; Absent-NePC: No neuropathic pain component present; n = number of patients in analysis

After assessment by physicians A and physicians B, 170 patients were classified as having present-NePC, 58 as absent-NePC. In 63 patients the two physicians made a non-concordant pain classification, so the outcome based on the physicians assessment was classified as 'undetermined'. Based on the NeuPSIG Grading System in 139 patients NePC was classified as present, in 93 patients NePC was absent and in 51 patients the two physicians made a non-concordant pain classification in which the outcome was classified as 'undetermined' (see Figure 1: Flow Diagram).

Social-demographic and clinical details of the 291 patients were analyzed and divided from each other based on the pain classification (see Table 1). No statistically significant differences were found between absent-NePC, present-NePC and undetermined for gender, age, height, weight, body mass index (BMI), education, medication, duration of pain, quality of life, disability, pain attribution, anxiety disorder and depression. Moreover, no statistically significant differences were observed between absent-NePC and present-NePC for pain (current, worst and average pain).

Physicians

During this study 62 various physicians (pain specialist, pain specialist-fellow or neurologist), from seven different hospitals, assessed all included patients. All patients were assessed two times by two different physicians. Of all participating physicians, 21 physicians assessed ≤2 patients during the execution of the study, 23 physicians saw ≤9 patients, 10 physicians saw ≥10 patients and 8 physicians saw ≥20 patients.

Evaluation of the Pain*DETECT*-DIV

The mean score of the Pain*DETECT*-DIV (Range – 1;38) for patients classified as absent-NePC was 10.7 (SD± 5.7); for patients classified as present-NePC it was 15.7 (SD ± 6.3) and for patients with an undetermined outcome it was 11.8 (SD ± 5). As calculated based on a one-way ANOVA with Tukey's studentized range post-hoc test, there was a statistical significant difference between absent-NePC and present-NePC ($P < 0.001$) and between present-NePC and undetermined ($P < 0.001$). No significant difference was seen between absent-NePC and undetermined ($P = 0.57$). Patients pain course pattern and if the pain was radiating to other regions of the body were not significantly different between the three groups. Pain descriptors (burning, tingling or prickling, painful light touching, sudden pain attacks, temperature evoked pain, numbness sensation and pressure evoked pain) were all statistically significant discriminators for the presence of NePC ($P \leq 0.005$) except for pressure evoked pain ($P = 0.07$). See Table 2 for the Pain*DETECT*-DIV outcomes divided according to the pain classification by the physicians (presentNePC, absent-NePC or undetermined) (See Table 2).

Table 1: Socio-demographic and clinical characteristics of the patients related to physicians agreement for the existence of a NePC

NePC		Absent		Present		Undetermined	
		N	n (%) Mean (±SD) Median [IQR]	N	n (%) Mean (±SD) Median [IQR]	N	n (%) Mean (±SD) Median [IQR]
Gender		58		170		63	
	Male		25 (43%)		56 (33%)		17 (27%)
	Female		33 (57%)		114 (67%)		46 (73%)
Age (Years)		58	55 ± 12	170	56 ± 11	63	58 ± 13
Height (cm)		55	172 ± 9	164	172 ± 8	62	170 ± 9
Weight (kg)		55	84 ± 25	167	80 ± 17	62	80 ± 16
BMI (kg/m²)		54	28 ± 8	164	27 ± 5	62	27 ± 5
Education		56		164		63	
	Functional illiterate		(0%)		(0%)		2 (3.3%)
	Primary education		2 (3.6%)		14 (8.5%)		6 (9.8%)
	Secondary education		32 (57.1%)		98 (59.8%)		38 (62.3%)
	Postgraduate		22 (39.3%)		52 (31.7%)		15 (24.6%)
Medication (% yes)		55	31 (56.9%)	168	111 (66.1%)	61	35 (57.4%)
Pain (NRS; 0-10)							
	Current pain	57	5 [3 – 7]	167	6 [3 – 7]	61	4 [1 – 7]
	Worst pain (past four weeks)	57	8 [5 – 9]	167	8 [7 – 9]	61	7 [5 – 8]
	Average pain (past four weeks)	57	6 [3.5 – 7]	167	6 [5 – 8]	61	6 [3 – 7]
Duration of pain (months)		57	72 ± 90	169	60 ± 76	62	49 ± 46
Quality of life							
	Physical functioning	58	57 ± 27	170	51 ± 25	62	55 ± 29
	Role functioning physical	58	43 ± 42	170	35 ± 41	61	41 ± 45
	Role functioning emotional	58	80 ± 35	169	70 ± 43	61	73 ± 42
	Social functioning	58	43 ± 14	170	44 ± 11	62	46 ± 10
	Bodily pain	58	55 ± 24	170	56 ± 25	62	46 ± 25
	Mental health	58	60 ± 6	170	61 ± 10	61	62 ± 7
	Vitality	58	51 ± 10	170	49 ± 12	61	50 ± 11
	General health	57	58 ± 14	165	57 ± 14	60	55 ± 12
	Health change	58	38 ± 24	170	40 ± 26	63	42 ± 27
Disability	Total	53	46 ± 27	158	48 ± 24	57	40 ± 26
Pain attribution							
	Somatic	53	5.2 ± 4.3	156	6.0 ±4.0	58	5.2 ± 3.9
	Psychological	58	2.0 ± 2.9	164	2.2 ± 3.2	60	2.9 ± 3.0
	Social	57	1.6 ± 2.2	163	2.0 ± 2.6	61	2.4 ± 2.6
Anxiety disorder		57	14 (24.6%)	167	46 (27.5%)	60	18 (30.0%)
Depression		57	14 (24.6%)	166	46 (27.7%)	61	11 (18.0%)

Classification for the existence of NePC is based on physicians assessment of the patients. NePC: neuropathic pain component; Absent: NePC is absent; Present: NePC is present; Undetermined: both physicians disagree with each other about the existence of a neuropathic pain component; N: total number of patients in analysis; n: number of patients; %: percentage; SD: Standard deviation; IQR: Inter quartile range.

Table 2: The median (IQR) of the items of the Pain*DETECT* by physicians agreement for the existence of a NePC

NePC	Absent		Present		Undetermined	
Pain*DETECT* item	**N**	**n (%) Median [IQR] Mean (±SD)**	**N**	**n (%) Median [IQR] Mean (±SD)**	**N**	**n (%) Median [IQR] Mean (±SD)**
Pain course pattern	58		162		59	
Persistent pain with slight fluctuations		19 (33%)		53 (33%)		17 (29%)
Persistent pain with pain attacks		14 (24%)		58 (36%)		17 (29%)
Pain attacks without pain between them		16 (28%)		32 (20%)		20 (34%)
Pain attacks with pain between them		9 (16%)		18 (11%)		5 (9%)
Radiating pain (% yes)	51	41 (78%)	154	112 (73%)	57	38 (67%)
Gradation of pain						
Burning	55	0 [0 – 2]	170	1 [0 – 3]	62	0 [0 – 2.25]
Tingling or prickling	55	1 [0 – 3]	170	2 [0 – 3]	63	1 [0 – 3]
Painful light touching	55	0 [0 – 1]	169	1 [0 – 2]	63	0 [0 – 1]
Sudden pain attacks	55	2 [0 – 3]	167	3 [1 – 4]	62	2 [0 – 3]
Temperature evoked pain	54	0 [0 – 1]	170	1 [0 – 2]	63	1 [0 – 1]
Numbness sensation	56	2 [0 – 3]	170	3 [2 – 4]	63	3 [1 – 4]
Pressure evoked pain	55	2 [1 – 3]	170	3 [1 – 4]	63	2 [1 – 3]
Total sum score Pain*DETECT*	58	10 [6.75 – 15.25] 10.7 (± 5.75)	170	16 [11 – 20] 15.7 (± 6.3)	63	10 [8 – 15] 11.8 (± 5)

Classification of NePC is based on physicians assessment of the patients. NePC: neuropathic pain component; Absent: NePC is absent; Present: NePC is present; Undetermined: both physicians disagree with each other about the existence of a neuropathic pain component; N= total number of patients in analysis; n= number of patients; IQR: inter quartile range; SD: standard deviation; Range: 0 = never; 1 = hardly noticed; 2 = slightly; 3 = moderately; 4 = strongly; 5 = very strongly; Total sum score Pain*DETECT*: Sum score calculation of the Pain*DETECT*.

Table 3: **The AUC and the sensitivity / specificity at the optimal cut-off point of the Pain*DETECT* under the condition of equal costs of misclassification to classify NePC by the classification and the Grading System of the physicians**

Pain*DETECT* versus classification by:	NePC		AUC %	(95%CI)	Cut -off	Sens %	(95% CI)	Spec %	(95% CI)
	Absent (n)	Present (n)							
Assessment A	83	208	69.8	(0.63-0.77)	9	86.0	(0.81-0.90)	45.8	(0.36-0.57)
Assessment B	96	195	67.2	(0.61-0.74)	11	75.4	(0.69-0.81)	52.1	(0.42-0.62)
Assessment A=Assessment B	**58**	**170**	**72.1**	**(0.65-0.80)**	**11**	**80.0**	**(0.73-0.85)**	**55.2**	**(0.43-0.67)**
LBLP	28	75	75.4	(0.65-0.86)	11	84.0	(0.74-0.91)	64.3	(0.46-0.79)
NSA pain	18	23	62.9	(0.46-0.80)	9	82.6	(0.63-0.93)	44.4	(0.25-0.66)
Suspected PND pain	12	72	75.5	(0.63-0.88)	15	55.6	(0.44-0.67)	91.7	(0.65-0.99)
Grading A	114	172	58.9	(0.52-0.66)	11	73.3	(0.66-0.79)	43.9	(0.35-0.53)
Grading B	130	158	58.6	(0.52-0.65)	14	57.6	(0.50-0.65)	59.2	(0.51-0.67)
Grading A = Grading B	**93**	**139**	**61.3**	**(0.54-0.69)**	**11**	**74.1**	**(0.66-0.81)**	**46.2**	**(0.37-0.56)**
LBLP	60	48	63.1	(0.52-0.74)	12	70.8	(0.57-0.82)	55.0	(0.43-0.67)
NSA pain	24	13	48.9	(0.28-0.69)	18	30.8	(0.13-0.58)	87.5	(0.69-0.96)
Suspected PND pain	9	78	66.0	(0.45-0.87)	13	64.1	(0.53-0.74)	77.8	(0.45-0.94)
Assessment A = Grading A	63	155	69.1	(0.61-0.77)	11	76.1	(0.69-0.82)	55.6	(0.43-0.67)
Assessment B = Grading B	77	139	67.1	(0.60-0.74)	11	76.3	(0.69-0.83)	52.0	(0.41-0.63)
Assessment A = Grading A = Assessment B = Grading B	43	118	67.9	(0.59-0.77)	11	78.0	(0.70-0.85)	53.0	(0.39-0.68)

Classification of NePC is based on (both) physicians' assessment of the patients and / or on (both) the NeuPSIG Grading Systems. NEPC: Neuropathic pain component existing; Absent NePC: Neuropathic pain component not existing; AUC: Area under curve; 95%CI: 95% confidence interval; Cut-off: Cut-off value; Sens.: Sensitivity; Spec.: Specificity; LBLP: Patients with low back and leg pain; NSA pain: Patients with neck-shoulder-arm pain; suspected PND pain: Patients with pain due to a suspected peripheral nerve damage

Validity

The gold standard for presence of the NePC in this study was the concordant opinion of both physicians. On basis of this gold standard, patients with an identical pain classification were included in the initial analysis (n = 228): 58 patients were classified as absent-NePC (25.4%) and 170 were classified as present-NePC (74.6%)(see Table 3 and Additional file 1: Table S1). A ROC-curve was constructed for Pain*DETECT*-DIv (see Figure 2). Based on the gold standard, Pain*DETECT*-DIv sensitivity was (at maximal Youden-index) 80%, specificity 55.2%, positive predictive value 84% and the positive likelihood ratio was 1.78. Based on the neuropathic pain Grading System, the sensitivity was 74.1%, specificity 46.2%, positive predictive value 67.3%, and positive likelihood ratio of 1.38.

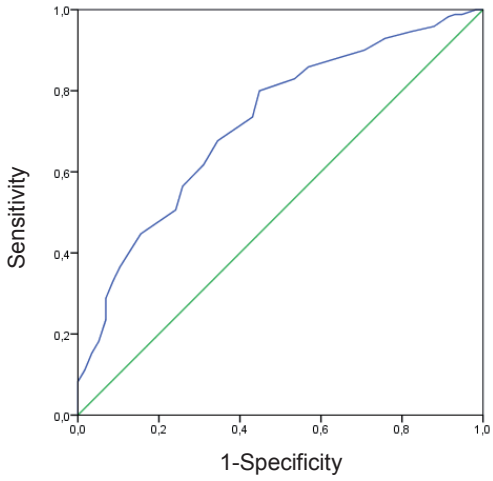

Figure 2: Receiver operating characteristics and area under the curve (AUC) for the total score of the Pain*DETECT*-DIv versus the presence of a neuropathic pain component as classified by two physicians (n = 228; undetermined patients are not included).

X-axis: 1-Specifity; Y-axis: Sensitivity

We also constructed ROC-curves for the classification by solely physicians A or B and according to the neuropathic pain Grading System by physicians A or B and all the combinations. Except for classification of patients' pain based on the description of physicians A and the outcome of the Grading System by physicians B all cut-off scores were calculated at 11-points out of 38: The sensitivity ranges from 57.6-86.1% and specificity from 43.9-59.2%. The classification of patients' pain based on the classification of physicians A resulted in a cut-off score of 9-points: Sensitivity 86.1% and specificity 45.8%. The classification of patients' pain based on the Grading System according to physicians B resulted in a cut-off score of 14-points: Sensitivity of 57.6% and specificity of 59.2%. In Table 3 and Additional file 1: Table S1 we present the number of patients with LBLP, NSA pain or suspected PND pain, in total and per group based on physicians' assessment and/or the Grading

System. Values of the AUC, cut-off value, sensitivity and specificity are provided (see also Additional file 1: Table S1 for a more detailed analysis of the diagnostic accuracy of the Pain*DETECT*-DIv: AUC, cut-off value, sensitivity, specificity positive and negative predictive values, positive likelihood ratios and the number needed to diagnose (NND).

Patients were screened on a NePC (positive outcome) by two physicians, two times the Grading System, and the patient completed the Pain*DETECT*-DIv. All the possible outcome combinations were computed based on the outcome: Is a NePC present, or not? In 283 patients all the five outcome variables were available and are displayed in a Venn-diagram [49] (see Figure 3). In 92 patients (32.5%), five times a positive outcome variable was found, indicating presence of NePC. In 23 patients all outcome variables were negative (8.1%), thus indicating absence of NePC. One positive outcome was detected in 39 patients (13.8%), two positive outcomes in 28 patients (9.9%), three in 49 patients (17.3%), and four in 52 patients (18.4%).

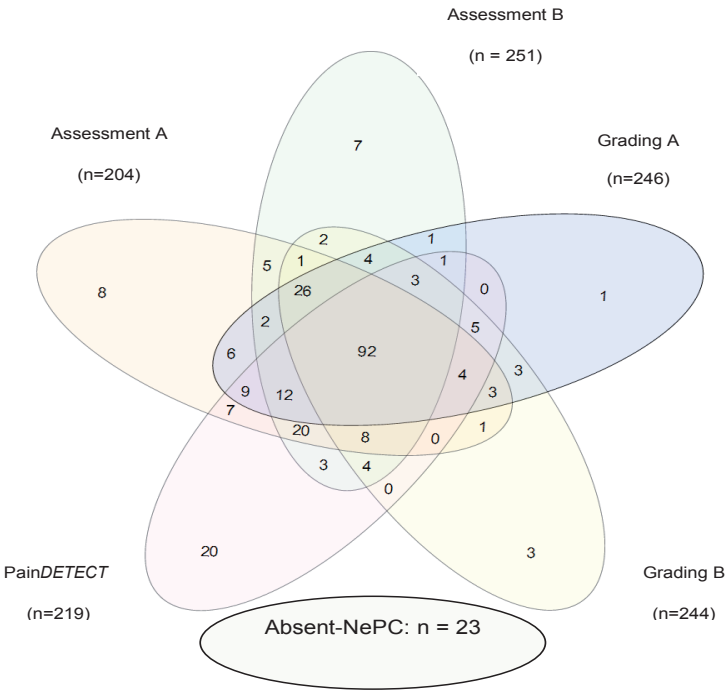

Figure 3: VENN-Diagram of all the five outcomes per patient.

Physicians A: classification of a neuropathic pain component (NePC) exists; Physicians B: NePC exists; Grading A: NePC exists according to the Grading System by physicians A; Grading B: NePC exists according to the Grading System by physicians B; Pain*DETECT*-DIv: Outcome of the Pain*DETECT*-DIv indicates the existence of a NePC. Absent-NePC: No NePC exists according to physicians, Grading Systems and the Pain*DETECT*-DIv

Reliability

To determine the interobserver reliability between the physicians, the Grading System and the outcome of the Pain*DETECT*-$_{DIV}$ for the classification of a (absent-) NePC, Cohen's kappa (K) and percentage of pair wise agreement (PA) were assessed (see Table 4). K for the classification of patients' pain (absent-NePC or NePC) by the physicians was 0.49, with a PA of 78.4% (Pi=0.38; n=291). The K for the classification of patients' pain based on the Grading System was 0.63 and PA was 82% (Pi = 0.16; n = 283). The outcome of K and PA regarding the Pain*DETECT*-$_{DIV}$ compared to the classification of physicians A was respectively 0.34 and 74.6% (Pi = 0.48; n = 291). Compared to physicians B it was 0.27 and 67.7% (Pi = 0.33; n = 291). Comparing the outcome of the Pain*DETECT*-$_{DIV}$ to the outcome of the Grading System, was 0.18 and 61.5% (Pi = 0.27; n = 286) for physicians A, and 0.17 and 58.3% (Pi = 0.05; n = 288) for physicians B.

Table 4: The kappa coefficient between the classification on basis of the assessment by the physicians, the Grading Systems and the Pain*DETECT*

		Pain*DETECT* (yes / no)	Grading A	Grading B	Assessment B
Assessment A	n	291	286	288	291
	K	0.34	0.48	0.32	0.49
	PA	74.6	76.2	67.4	78.4
	P*i*	0.48	0.32	0.26	0.38
Assessment B	n	291	286	288	
	K	0.27	0.38	0.48	
	PA	67.7	71.0	75.0	
	P*i*	0.33	0.28	0.22	
Grading A	n	286		283	286
	K	0.18		0.63	0.38
	PA	61.5		82.0	71.0
	P*i*	0.27		0.16	0.28
Grading B	n	288			
	K	0.17			
	PA	58.3			
	P*i*	0.05			

Classification of NePC is based on physicians' assessment of the patients and on the Grading Systems. N = number of patients in the analysis; K = Cohen's kappa coefficient; PA (%) = percentage of agreement between two outcome variables; Pi = Prevalence index

Stability and responsiveness of the Pain*DETECT*-$_{DIV}$ over time was assessed over a period of two weeks. The mean sum score of the Pain*DETECT*-$_{DIV}$ at baseline for the total group was 13.8 ± 6.3. The mean sum score after two weeks was 14.1 ± 6.1. Test-retest reliability via ICC was 0.83 (95%CI 0.79-0.87; n = 268). Taking into consideration the fact that patients' pain should not have changed (outcome based on the PGIC), because otherwise the ICC would not reflect the consistency of the Pain*DETECT*-$_{DIV}$, and a time gap of 7-21 days was allowed (to rule out the early or delayed return of questionnaires) between the first and second Pain*DETECT*-$_{DIV}$, the ICC was 0.87 (95% CI 0.81-0.91; n = 123). After three months, with no change in the degree of patients' pain and a time gap of 60-120 days between the first and third PainDETECT-$_{DIV}$, ICC was 0.86 (95% CI 0.79-0.91; n = 102).

DISCUSSION

This study demonstrates the clinimetric quality of the Pain*DETECT*-$_{DIV}$, a screening instrument for the presence of a NePC, on a large population of patients, with chronic pain due to low back with leg pain, neck-shoulder-arm pain or pain due to a suspected peripheral nerve damage as normally present in a physician's daily practice. Because the patients were included without pre-stratification on the target outcome, previous Catch-22 situations in the assessment of the validity of screening instruments were avoided. Under these conditions, the Pain*DETECT*-$_{DIV}$ failed to be predictive for the existence of a NePC due to a moderate sensitivity and low specificity, irrespective of comparison with the expert opinion via the classification by two physicians (gold standard) as well as with the outcome of the NeuPSIG Grading System. Moreover, the predictive values were also not indicating that the Pain*DETECT*-$_{DIV}$ is a valid screening tool for the assessment of a NePC. The likelihood ratios were also not suggestive for the usefulness of this instrument.

Validation studies with patients pre-stratified for NePC

We found an optimal cut-off score for the Pain*DETECT*-$_{DIV}$ of ≥11 points corresponding to a sensitivity of 80% and a specificity of 55%. In the original development and validation study of the Pain*DETECT* by Freynhagen et al. [2] a sensitivity and specificity of 84% was found. The gold standard in their study was the examination by two experienced pain specialists. The study was performed at ten different specialized pain centers. Only patients with 'typical' neuropathic or nociceptive entities (i.e. no 'unclear' outcome) and only patients with a VAS of >40 mm (0 – 100 mm) were included. In the Spanish validation study by De Andrés et al. [16] only patients with a VAS ≥40 mm and a known classification (by one experienced specialist) of neuropathic pain, mixed pain or nociceptive pain were included. It revealed a sensitivity and specificity of 81% when patients with the classification of neuropathic pain or nociceptive pain were included. The inclusion of patients with mixed pain in the neuropathic pain group resulted in a sensitivity of 84% and specificity of 78%. The Korean version of the Pain*DETECT* [20] was validated based on the study by De Andrés [16] in patients with chronic pain and with a NRS ≥ 3 (NRS 0-10). The gold standard was the independent diagnosis of

the patient by two experienced pain physicians. It revealed a sensitivity of 82% and a specificity of 92% based on a cut-off score of ≥19 (range – 1; 38). In the validation of the Turkish version of the Pain*DETECT* [17] patients were included with the classification of pain type (i.e. NePC) being assessed beforehand (based on the opinion of two expert pain physicians) and patients suffering from pain of three centimeters or more (VAS 0-10 cm). Sensitivity and specificity were respectively 78 and 83%. The Hindi version of the Pain*DETECT* [19] was validated in patients with neuropathic and in patients with non-neuropathic pain based on a conventional single assessment by one physician. At a optimal cut off point of ≥18 sensitivity was 83% and the specificity was 84%.

In a cohort of patients with a spinal cord injury for more than one year, pain lasting more than six months and a pain intensity of more than three on a NRS (0-10) a sensitivity was found of 68% and specificity of 83% [50].

The present study included patients with chronic pain without limits to the minimal pain intensity or other limitations. At the moment of inclusion in the study our patients had only a provisional diagnosis (LBLP, NSA pain, suspected PND pain) established in primary or secondary care without further refinement or confirmation. Then, after referral to a (non-) academic pain clinic, they were assessed as to their complaints for the first time at study inclusion. Thus this was a 'real-life' clinical out-patient population. Avoiding patient selection due to pre-stratification to the outcome target makes our study unique and clinically more relevant as compared to other studies on the same topic and is crucial for the validation of a screening instrument.

Validation studies with patients not pre-stratified for NePC

In a study by Gauffin et al. [51] in patients diagnosed with fibromyalgia (n = 158) a cut-off score of 17 was found with a sensitivity of 79% and specificity of 53% (Gold standard: the classification by one experienced physician). This study, like ours, did not pre-stratify patients according to the pain classification either, and patients were not excluded because of a low pain level. The outcome of Gauffin's sensitivity analyses in this fibromyalgia study was comparable to our study. Tampin et al. [34] found, based on the examination by a physical therapist, a sensitivity and specificity of the Pain*DETECT* of respectively 64 and 62% (cut-off score 18.5) in a population of patients with neck/upper limb pain (n = 122). In our study, the outcome for patients with neck-shoulder-arm pain was 83 and 44% respectively (cut-off score of ≥9).

Grading system

In this study the physicians assessed patients for the presence of a NePC according to the Grading System [31]. Probable neuropathic pain and definite neuropathic pain were combined as present-NePC, and non neuropathic pain and possible neuropathic pain were combined in absent-NePC. Sensitivity and specificity of the Pain*DETECT*-$_{DIV}$ resulted to be 74 and 46% respectively (Cut-off score 11 out of 38, n = 232). Using the classification of patients' pain based solely on the Grading System

by one physician results in a lower validity than based on the physicians assessment. This might suggest that the classification of patients' pain based on the Grading System is less accurate than the classification based on the physicians' assessment in respect to the outcome of the Pain*DETECT*-DIv. However, the grading system was assessed by the same physician who also performed the physician's assessment so it is also possible that the physician had difficulties to classify patients pain based on the Grading System or vice versa. When using the physicians' assessments as well as the Grading Systems of both physicians (n = 161), sensitivity was 78%, specificity was 53% and the cut-off score was 11: The same poor result as for the gold standard. In the papers by Vaegter et al. [33] and Tampin et al. [34] the Pain*DETECT* was also compared with the NeuPSIG Grading System. In both papers, like in ours, the outcome of the Grading System was not comparable to the outcome of the Pain*DETECT*. As stated by Finnerup et al. [52] the Pain*DETECT* (and other screening tools for the assessment of neuropathic pain) is only to alert the physician to further assess the patient who may have a NePC.

NePC classification

The initial classification of patients' pain in our study was based on an interview and (clinical/physical) examination by trained (pain-) physicians. There is a lack of consensus with respect to the classification of a NePC in patients with pain of different origins [53]. Moreover, a lack of standardization of assessment methods increases the number of undetected or poorly classified patients which leads to a variation in the classification accuracy (i.e. sensitivity and specificity) of screening tools caused by differences in strategy and patient population [15, 54]. Bouhassira and Attal recently stated that neuropathic pain is "a consistent clinical entity, but it is multidimensional in terms of its clinical expression, with different sensory profiles, potentially reflecting specific pathophysiological mechanisms" [55]. As stated by Scholz et al. [53] physical tests are more useful to identify patients with neuropathic back pain than interview questions. To reach a more unified classification system to differentiate between present-NePC and absent-NePC a standardized assessment of symptoms and signs is necessary [53]. However, these tests are not able to confirm the relation between the potential lesion or disease of the nerve and the pain directly: The classification of neuropathic pain should be based on clinical examination and the interpretation should be placed in the clinical context of patients' pain [55].

In this study we used a mandatory standardized assessment [25] in addition to the medical history and physical examination which were performed according to the physicians' standards. The clinical assessment and the use of the Grading System showed that in 18-22% of the patients a non-consistent assessments was present resulting in an 'undetermined' status. In Freynhagens paper [2] it was 5%. This difference might be due to the inclusion of patients with a less clear absent or present NePC in our study which might reflect what happens in the assessment of a NePC in usual clinical care. Moreover, this also might occur in the treatment of patients with chronic pain. Based on both the physician's assessments, almost 75% of the patients in this study had a neuropathic pain

component. This might be due to several facts. (1) Patients with LBLP or NSA pain were only included when the pain was radiating into the leg(-s) respectively the arm(-s) and were not removed from this study when they had mixed pain. Moreover, patients with radiating pain are more suspected to have a NePC. (2) There is a possibility that neuroplastic changes are interpreted as neuropathy in patients with chronic LBLP. (3) Patients were recruited in secondary and tertiary pain clinics. This might have led to a inclusion of patients who were more difficult to treat in primary care and (4) we included 108 patients with suspected peripheral nerve damage. Almost 60% of the patients after treatment for breast cancer has pain [56]. Based on the recent review by Ilhan et al. [57], in patients who reported pain following breast cancer treatment the pooled prevalence of neuropathic pain from screening questionnaires ranged from 32.6 to 58.2%. Following the NeuPSIG Grading System the prevalence ranged from 29.5 to 57.1%. Based on these numbers, patients after breast cancer can be regarded as patients suspected of neuropathic pain due to peripheral nerve damage. However, the Pain*DETECT*-DIv (compared to the gold standard and the NeuPSIG Grading System) as used in our study seems not valid for the assessment of patients with neuropathic pain based on a suspected PND in which the majority of patients was suffering of pain after treatment for breast cancer.

Strengths and weaknesses

There are several strengths in this study. Firstly, we included a large population of patients with diagnoses who are regularly seen in daily clinical practice. Secondly, there was no pre-stratification on the target outcome, clear inclusion criteria and almost no exclusion criteria. Thirdly, we used the NeuPSIG Grading System [31, 52] as a secondary comparison. The main purpose of the Grading System is to help in the classification of the pain as neuropathic [52]. In our study, the Grading System was added to the standardized assessment form which had to be filled in by the physician. There are also some weaknesses in this study. The use of the Grading System within the clinical assessment (including bed-side examination) is a strong aspect of our study, but the outcome of the clinical examination as well as the outcome of the Grading System might be influenced by each other. However, combining the physicians' assessment with the Grading System might have made the 'gold standard' even stronger but also might have led to a cross-contamination. Secondly, diagnosing NePC by assessing patients' pain by two separate physicians in our and in other studies is considered as the 'Gold Standard'. However, classifying patients' pain may be done more objectively by establishing a damaged nerve and by diagnosticating in a more detailed clinical way. Moreover, the breakdown of clinical grounds for in- and exclusion could also have been assessed and captured in more detail. Thirdly, 62 physicians participated. This might have led to the inclusion of younger, less clinical experienced physicians. However, it reflects 'real life' practice and limits the risk of systematic bias in the classification of patients' pain and bias based on assumptions about the existence of a NePC. Moreover, all physicians followed the standardized training as described. Fourthly, almost only patients with peripheral causes of pain were selected. This can be considered as a methodological drawback. Moreover, because we did not include patients with, by example, low back pain without irradiation to the leg who would probably be diagnosed as absent-NePC the

specificity might decrease. Fifthly, there is an apparent lack of objective tests to determine whether the somatosensory fibers were affected, in particular the small fibers. This can be seen as crucial since objective data are mandatory to reach a definite neuropathic pain classification in the grading system. Lastly, in a following study we would collect data from the patients who were not able to participate in the study to prevent inclusion bias. In this study this was not possible because of ethical regulations.

CONCLUSIONS

The Pain*DETECT*-$_{DIV}$ has a good internal consistency and test-retest reliability but is not an effective screening tool for the assessment of a neuropathic pain component in a population of patients with chronic pain, irrespective of the chosen comparison because of its moderate sensitivity and low specificity. However, the agreement by both the physicians and the agreement with the grading systems (performed by the physicians) were also not impressive. Moreover, the differences in the cut-off scores for the different comparisons reflects the fact that agreement in a not pre-stratified to the target outcome patient population is not easy to accomplish. Using the Pain*DETECT*-$_{DIV}$ (for screening purposes or as a surrogate for clinical assessment) may result in unreliably separating NePC presence from non-presence in patients with chronic pain in clinical outpatient practices and in research settings. Catch-22 situations in the validation of screening tools can be prevented by not pre-stratifying the patients on basis of the target outcome before inclusion in a validation study for screening instruments. For now, classifying patients pain still needs the clinical assessment based on history and physical examination including bed-side sensory testing by the physician and cannot be replaced by the use of the Pain*DETECT*.

ABBREVIATIONS

AUC: Area Under the Curve; BMI: Body Mass Index; CI: Confidence Interval; DRI: Disability Rating Index; EFNS: European Federation of Neurological Societies; HADS: Hospital Anxiety and Depression Scale; IASP: International Association for the Study of Pain; ICC: Intraclass Correlation; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th revision; IQR: Inter Quartile Range; K: Cohen's kappa; LBLP: Low Back with Leg Pain; NePC: Neuropathic Pain Component; NeuPSIG: Neuropathic Pain Special Interest Group; NND: Number Needed to Diagnose; NRS: Numeric Rating Scale; NSA pain: Neck-Shoulder-Arm pain; NTR: National Trial register; PA: Percentage of Agreement; Pain*DETECT*-$_{DIV}$: Pain*DETECT* Dutch language version; PAS: Pain Attribution Scale; PGIC: Patient Global Impression of Change; Pi: Prevalence index; PND: Peripheral nerve damage pain; RAND-36: RAND 36-item health Survey; ROC: Receiver Operating Characteristic;

SD: Standard Deviation; SPSS: Statistical package for the Social Sciences; VAS: Visual Analogue Scale; WHO: World Health Organization

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AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the medical and ethical review board Committee on Research Involving Human Subjects region Arnhem- Nijmegen, Nijmegen, the Netherlands, Dossier number: 2008/348; NL 25343.091.08 and conducted in accordance with the declaration of Helsinki and the declaration of the World Medical Association. As required, written informed consent was obtained from patients prior to study participation. The protocol is registered in the Dutch National Trial Register: NTR 3030.

SUPPLEMENTARY MATERIALS

Additional file 1:

Table S1: The AUC and the sensitivity / specificity at the optimal cut-off point of the Pain*DETECT* under the condition of equal costs of misclassification to classify a NePC by the diagnosis and the grading system of the physicians for the total group and according the pain locations.

	NePC	Absent NePC	AUC	(95%CI)	Youden index	Cut-off	T+	F+	F-	T-	Sens %	95% CI	Spec %	95% CI	NND	PPV %	NPV %	PLR	95% CI	NLR	95% CI	DOR	95% CI	P [Z+]	P [Z-]	FPR %	FNR %
Diagnosis																											
A	**208**	**83**	**69.8**	**(0.631-0.766)**	**0.318**	**9**	**179**	**45**	**29**	**38**	**86.06**	**(0.807 -0.901)**	**45.78**	**(0.355-0.565)**	**3.14**	**79.91**	**56.72**	**1.59**	**(1.293-1.949)**	**0.30**	**(0.202-0.459)**	**5.21**	**(2.908-9.341)**	**71.48**	**28.52**	**54.22**	**13.94**
LBLP (n)	95	37	71.7	(0.621-0.813)	0.381	12	67	12	28	25	70.53	(0.607-0.788)	67.57	(0.515-0.804)	2.63	84.81	47.17	2.17	(1.342-3.524)	0.44	(0.297-0.64)	4.99	(2.201-11.29)	71.97	28.03	32.43	29.47
NSA PAIN (n)	28	23	62.3	(0.463-0.783)	0.335	9	24	12	4	11	85.71	(0.685-0.943)	47.83	(0.292-0.670)	2.98	66.67	73.33	1.64	(1.08-2.499)	0.30	(0.11-0.814)	5.5	(1.443-20.959)	54.90	45.10	52.17	14.29
sPND (n)	85	23	72.3	(0.610-0.836)	0.344	15	83	19	2	4	97.65	(0.918-0.994)	17.39	(0.07-0.371)	6.65	81.37	66.67	1.18	(0.977-1.43)	0.14	(0.026-0.693)	8.74	(1.49-51.244)	78.70	21.30	82.61	2.35
KPND (n)	21	1	90.5	(0.779-1.000)	0.905	7	19	0	2	1	90.48	(0.711-0.974)	100	(0.207-1)	1.11	100	33.33	-	-	0.10	(0.025-0.356)	-	-	95.45	4.55	0.00	9.52
Breast (n)	64	22	72.4	(0.601-0.848)	0.334	15	33	4	31	18	51.56	(0.396-0.634)	81.82	(0.615-0.927)	3.00	89.19	36.73	2.84	(1.133-7.1)	0.59	(0.43-0.816)	4.79	(1.459-15.733)	74.42	25.58	18.18	48.44
B	**195**	**96**	**67.2**	**(0.609-0.735)**	**0.275**	**11**	**147**	**46**	**48**	**50**	**75.38**	(0.689-0.809)	**52.08**	**(0.422-0.618)**	**3.64**	**76.17**	**51.02**	**1.57**	**(1.258-1.967)**	**0.47**	**(0.346-0.645)**	**3.33**	**(1.987-5.578)**	**67.01**	**32.99**	**47.92**	**24.62**
LBLP (n)	84	48	70.9	(0.619-0.799)	0.423	11	67	18	17	30	79.76	(0.7-0.87)	62.5	(0.484-0.748)	2.37	78.82	63.83	2.13	(1.453-3.113)	0.32	(0.201-0.522)	6.57	(2.98-14.479)	63.64	36.36	37.50	20.24
NSA PAIN (n)	28	23	58.7	(0.430-0.744)	0.219	17	11	4	17	19	39.29	(0.236-0.5)76	82.61	(0.629-0.930)	4.57	73.33	52.78	2.26	(0.829-6.157)	0.73	(0.517-1.045)	3.07	(0.823-11.485)	54.90	45.10	17.39	60.71
sPND (n)	83	25	66.3	(0.558-0.768)	0.326	16	37	3	46	22	44.58	(0.344-0.553)	88.00	(0. 7-0.958)	3.07	92.50	32.35	3.71	(1.251-11.03)	0.63	(0.495-0.802)	5.9	(1.637-21.248)	76.85	23.15	12.00	55.42
KPND (n)	21	1	69.0	(0.491-0.890)	0.667	11	14	0	7	1	66.67	(0.454-0.828)	100	(0. 207-1)	1.50	100	12.50	-	-	0.33	(0.182-0.61)	-	-	95.45	4.55	0.00	33.33
Breast (n)	62	24	66.8	(0.552-0.784)	0.310	16	27	3	35	21	43.55	(0.319-0.559)	87.50	(0.69-0.957)	3.22	90.00	37.50	3.48	(1.165-10.422)	0.65	(0.495-0.842)	5.4	(1.457-20.008)	72.09	27.91	12.50	56.45
A=B	**170**	**58**	**72.1**	**(0.646-0.796)**	**0.352**	**11**	**136**	**26**	**34**	**32**	**80.00**	(0.734-0.853)	**55.17**	**(0.425-0.673)**	**2.84**	**83.95**	**48.48**	**1.78**	(1.328-2.398)	**0.36**	(0.248-0.53)	**4.92**	**(2.597-9.332)**	**74.56**	**25.44**	**44.83**	**20.00**
LBLP (n)	75	28	75.4	(0.650-0.858)	0.483	11	63	10	12	18	84.00	(0.741-0.906)	64.29	(0.458-0.793)	2.07	86.30	60.00	2.35	(1.417-3.904)	0.25	(0.138-0.448)	9.45	(3.514-25.414)	72.82	27.18	35.71	16.00
NSA PAIN (n)	23	18	62.9	(0.455-0.804)	0.271	9	19	10	4	8	82.61	(0.629-0.930)	44.44	(0.246-0.663)	3.70	65.52	66.67	1.49	(0.945-2.341)	0.39	(0.14-1.096)	3.8	(0.915-15.779)	56.10	43.90	55.56	17.39
sPND (n)	72	12	75.5	(0.632-0.878)	0.472	15	40	1	32	11	55.56	(0.441-0.665)	91.67	(0.646-0.985)	2.12	97.56	25.58	6.67	(1.009-44.035)	0.48	(0.356-0.661)	13.75	(1.685-112.198)	85.71	14.29	8.33	44.44
KPND (n)	20	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Breast (n)	52	12	77.1	(0.640-0.902)	0.472	15	29	1	23	11	55.77	(0.423-0.684)	91.67	(0.646-0.985)	2.11	96.67	32.35	6.69	(1.009-44.391)	0.48	(0.483-0.0684)	13.87	(1.666-115.434)	81.25	18.75	8.33	44.23
Grading																											
A	**172**	**114**	**58.9**	**(0.520-0.658)**	**0.171**	**11**	**126**	**64**	**46**	**50**	**73.26**	**(0.662-0.793)**	**43.86**	**(0.351-0.53)**	**5.84**	**66.32**	**52.08**	**1.30**	**(1.084-1.571)**	**0.61**	**(0.441-0.842)**	**2.14**	**(1.297-3.531)**	**60.14**	**39.86**	**56.14**	**26.74**
LBLP (n)	62	69	60.6	(0.509-0.704)	0.248	12	45	33	17	36	72.58	(0.604-0.821)	52.17	(0.406-0.635)	4.04	57.69	67.92	1.52	(1.135-2.028)	0.53	(0.331-0.836)	2.89	(1.39-5.999)	47.33	52.67	47.83	27.42
NSA PAIN (n)	17	**30**	50.3	(0.329-0.677)	0.127	18	5	5	12	25	29.41	(0.133-0.531)	83.33	(0.664-0.927)	7.85	50.00	67.57	1.76	(0.595-5.235)	0.85	(0.599-1.197)	2.08	(0.505-8.601)	36.17	63.83	16.67	70.59
SPND (n)	93	**15**	63.0	(0.467-0.793)	0.335	13	56	4	37	11	60.22	(0.501-0.696)	73.33	(0.481-0.891)	2.98	93.33	22.92	2.26	(0.96-5.311)	0.54	(0.366-0.805)	4.16	(1.232-14.061)	86.11	13.89	26.67	39.78
KPND (n)	16	**6**	51.6	(0.237-0.795)	0.292	13	10	2	6	4	62.50	(0.386-0.815)	66.67	(0.3-0.903)	3.43	83.33	40.00	1.88	(0.568-6.185)	0.56	(0.241-1.314)	3.33	(1.462-24.052)	72.73	27.27	33.33	37.50
Breast (n)	77	**9**	69.7	(0.508-0.886)	0.375	13	46	2	31	7	59.74	(0.486-0.7)	77.78	(0.453-0.937)	2.67	95.83	18.42	2.69	(0.781-9.252)	0.52	(0.332-0.806)	5.19	(1.011-26.67)	89.53	10.47	22.22	40.26
B	**158**	**130**	**58.6**	**(0.520-0.652)**	**0.168**	**14**	**91**	**53**	**67**	**77**	**57.59**	**(0.498-0.650)**	**59.23**	**(0.506-0.673)**	**5.94**	**63.19**	**53.47**	**1.41**	**(1.104-1.808)**	**0.72**	**(0.568-0.902)**	**1.97**	**(1.232-3.161)**	**54.86**	**45.14**	**40.77**	**42.41**
LBLP (n)	56	75	62.3	(0.524-0.722)	0.216	14	36	32	20	43	64.29	(0.512-0.755)	57.33	(0.461-0.679)	4.63	52.94	68.25	1.51	(1.086-2.09)	0.62	(0.417-0.931)	2.42	(1.186-4.934)	42.75	57.25	42.67	35.71
NSA PAIN (n)	19	32	48.7	(0.311-0.663)	0.191	19	6	4	13	28	31.58	(0.154-0.54)	87.50	(0.719-0.95)	5.24	60.00	68.29	2.53	(0.816-7.826)	0.78	(0.561-1.09)	3.23	(0.776-13.446)	37.25	62.75	12.50	68.42
sPND (n)	83	23	59.1	(0.458-0.724)	0.279	13	9	16	10	16	47.37	(0.273-0.683)	50.00	(0.336-0.664)	-38	36.00	61.54	0.95	(0.527-1.704)	1.05	(0.608-1.824)	0.9	(0.289-2.804)	37.25	62.75	50.00	52.63
KPND (n)	15	6	49.4	(0.213-0.776)	0.267	14	9	2	6	4	60.00	(0.358-0.802)	66.67	(0.3-0.903)	3.75	81.82	40.00	1.80	(0.54-6.004)	0.60	(0.259-1.389)	3	(0.411-21.881)	71.43	28.57	33.33	40.00
Breast (n)	68	17	62.6	(0.476-0.776)	0.338	13	43	5	25	12	63.24	(0.514-0.737)	70.59	(0.469-0.867)	2.96	89.58	32.43	2.15	(1.007-4.59)	0.52	(0.336-0.807)	4.13	(1.302-13.088)	80.00	20.00	29.41	36.76
A=B	**139**	**93**	**61.3**	**(0.539-0.687)**	**0.203**	**11**	**103**	**50**	**36**	**43**	**74.10**	**(0.662-0.807)**	**46.24**	**(0.365-0.563)**	**4.92**	**67.32**	**54.43**	**1.38**	**(1.114-1.705)**	**0.56**	**(0.392-0.8)**	**2.46**	**(1.41-4.294)**	**59.91**	**40.09**	**53.76**	**25.90**
LBLP (n)	48	60	63.1	(0.524-0.739)	0.258	12	34	27	14	33	70.83	(0.568-0.818)	55.00	(0.425-0.669)	3.87	55.74	70.21	1.57	(1.128-2.197)	0.53	(0.323-0.87)1	2.97	(1.329-6.631)	44.44	55.56	45.00	29.17
NSA PAIN (n)	13	24	48.9	(0.284-0.694)	0.183	18	4	3	9	21	30.77	(0.127-0.576)	87.50	(0.69-0.957)	5.47	57.14	70.00	2.46	(0.647-9.365)	0.79	(0.534-1.172)	3.11	(0.575-16.833)	35.14	64.86	12.50	69.23
sPND (n)	78	9	66.0	(0.453-0.867)	0.419	13	50	2	28	7	64.10	(0.53-0.739)	77.78	(0.453-0.937)	2.39	96.15	20.00	2.88	(0.84-9.903)	0.46	(0.292-0.73)	6.25	(1.215-32.16)	89.66	10.34	22.22	35.90
KPND (n)	14	4	50.9	(0.159-0.859)	0.321	14	8	1	6	3	57.14	(0.326-0.786)	75.00	(0.301-0.954)	3.11	88.89	33.33	2.29	(0.394-13.245)	0.57	(0.25-1.308)	4	(0.329-48.656)	77.78	22.22	25.00	42.86
Breast (n)	64	5	71.3	(0.486-0.939)	0.456	13	41	1	22	4	65.08	(0.528-0.757)	80.00	(0.376-0.964)	2.22	97.62	15.38	3.25	(0.559-18.958)	0.44	(0.251-0.759)	7.46	(0.784-70.847)	92.56	7.35	20.00	34.92
Diagnosis A = Grading A	**155**	**63**	**69.1**	**(0.610-0.771)**	**0.317**	**11**	**118**	**28**	**37**	**35**	**76.13**	**(0.688-0.822)**	55.56	**(0.433-0.672)**	**3.16**	**80.82**	**48.61**	**1.71**	**(1.282-2.289)**	**0.43**	**(0.301-0.614)**	**3.99**	**(2.146-7.404)**	**71.10**	**28.90**	**44.44**	**23.87**
LBLP (n)	60	35	71.4	(0.607-0.821)	0.407	12	45	12	15	23	75.00	(0.628-0.842)	65.71	(0.492-0.792)	2.46	78.95	60.53	2.19	(1.352-3.54)	0.38	(0.231-0.627)	5.75	(2.314-14.289)	63.16	36.84	34.29	25.00
NSA PAIN (n)	15	18	56.1	(0.360-0.763)	0.244	9	12	10	3	8	80.00	(0.548-0.93)	44.44	(0.246-0.663)	4.09	54.55	72.73	1.44	(0.887-2.338)	0.45	(0.144-1.402)	3.2	(0.666-15.381)	45.45	54.55	55.56	20.00
sPND (n)	80	10	74.2	(0.578-0.907)	0.438	13	51	2	29	8	63.75	(0.528-0.734)	80.00	(0.49-0.943)	2.29	96.23	21.62	3.19	(0.913-11.132)	0.45	(0.296-0.693)	7.03	(1.399-35.374)	88.89	11.11	20.00	36.25
KPND (n)	16	1	87.5	(0.713-1.000)	0.875	7	14	0	2	1	87.50	(0.64-0.965)	100	(0.207-1)	1.14	100	33.33	-	-	0.13	(0.034-0.457)	-	-	94.12	5.88	0.00	12.50
Breast (n)	64	9	72.8	(0.543-0.913)	0.418	13	41	2	23	7	64.06	(0.518-0.747)	77.78	(0.453-0.937)	2.39	95.35	23.33	2.88	(0.838-9.922)	0.46	(0.286-0.746)	6.24	(1.195-32.563)	87.67	12.33	22.22	35.94
Diagnosis B = Grading B	**139**	**77**	**67.1**	**(0.598-0.743)**	**0.282**	**11**	**106**	**37**	**33**	**40**	**76.26**	**(0.685-0.826)**	**51.95**	**(0.41-0.628)**	**3.55**	**74.13**	**54.79**	**1.59**	**(1.236-2.038)**	**0.46**	**(0.317-0.66)**	**3.47**	**(1.918-6.288)**	**64.35**	**35.65**	**48.05**	**23.74**
LBLP (n)	50	42	72.3	(0.619-0.827)	0.411	11	42	18	8	24	84.00	(0.715-0.917)	57.14	(0.422-0.709)	2.43	70.00	75.00	1.96	(1.354-2.836)	0.28	(0.141-0.557)	7	(2.648-18.506)	54.35	45.65	42.86	16.00
NSA PAIN (n)	16	20	55.2	(0.354-0.749)	0.275	19	6	2	10	18	37.50	(0.185-0.614)	90.00	(0.699-0.972)	3.64	75.00	64.29	3.75	(0.872-16.132)	0.69	(0.462-1.043)	5.4	(0.913-31.933)	44.44	55.56	10.00	62.50
sPND (n)	73	15	69.2	(0.572-0.812)	0.430	13	46	3	27	12	63.01	(0.516-0.732)	80.00	(0.548-0.93)	2.32	93.88	30.77	3.15	(1.128-8.8)	0.46	(0.312-0.689)	6.82	(1.764-26.326)	82.95	17.05	20.00	36.99
KPND (n)	15	1	63.3	(0.387-0.880)	0.600	12	9	0	6	1	60.00	(0.358-0.802)	100	(0.207-1)	1.67	100	14.29	-	-	0.40	(0.215-0.743)	-	-	93.75	6.25	0.00	40.00
Breast (n)	58	14	70.1	(0.568-0.835)	0.424	13	37	3	21	11	63.79	(0.509-0.75)	78.57	(0.524-0.924)	2.36	92.50	34.38	2.98	(1.072-8.269)	0.46	(0.297-0.714)	6.46	(1.618-25.791)	80.56	19.44	21.43	36.21
Diagnosis A = Grading A = Diagnosis B = Grading B	**118**	**43**	**67.9**	**(0.586-0.772)**	**0.315**	**11**	**92**	**20**	**26**	**23**	**77.97**	**(0.697-0.845)**	**53.49**	**(0.389-0.675)**	**3.18**	**82.14**	**46.94**	**1.68**	**(1.2-2.342)**	**0.41**	**(0.266-0.639)**	**4.07**	**(1.94-8.535)**	**73.29**	**26.71**	**46.51**	**22.03**
LBLP (n)	43	26	73.2	(0.610-0.853)	0.453	11	36	10	7	16	83.72	(0.700-0.919)	61.54	(0.425-0.776)	2.21	78.26	69.57	2.18	(1.315-3.602)	0.26	(0.126-0.556)	8.23	(2.655-25.505)	62.32	37.68	38.46	16.28
NSA PAIN (n)	12	12	48.3	(0.244-0.721)	0.167	18	4	2	8	10	33.33	(0.138-0.609)	83.33	(0.552-0.953)	6.00	66.67	55.56	2.00	(0.448-8.936)	0.80	(0.498-1.284)	2.5	(0.361-17.315)	50.00	50.00	16.67	66.67
sPND (n)	63	5	72.5	(0.521-0.929)	0.467	13	42	1	21	4	66.67	(0.544-0.771)	80.00	(0.376-0.964)	2.14	97.67	16.00	3.33	(0.572-19.408)	0.42	(0.238-0.73)	8	(0.841-76.133)	92.65	7.35	20.00	33.33
KPND (n)	14	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Breast (n)	49	5	74.7	(0.535-0.959)	0.494	13	34	1	15	4	69.39	(0.558-0.805)	80.00	(0.376-0.964)	2.02	97.14	21.05	3.47	(0.595-20.224)	0.38	(0.208-0.703)	9.07	(0.933-88.108)	90.74	9.26	20.00	30.61

PD-Q: PainDETECT questionnaire; NEPC: Neuropathic pain component existing; Absent-NePC: Neuropathic pain component not existing; AUC: Area under curve; 95%CI: 95% confidence interval; T+: True positive; F+: False positive; F-: False negative; T-: True negative; Sens.: Sensitivity; Spec.: Specificity; NND: Number needed to diagnose; +PPV: Positive predictive value; -NPV: Negative predictive value; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; DOR: Diagnostic odds ratio; P [Z+]:a-priori chance for the existence of a NePC; P [Z-]:a-priori chance for no existence of a NePC; FPR: False positive ratio; FNR: False negative ratio; A: Physician A; B: Physician B; LBLP: Patients suffering from low back pain with leg pain; NSA PAIN: Patients suffering from neck shoulder pain with arm pain; sPND: Patients suffering from a suspected peripheral nerve damage; KPND: Patients suffering from a known peripheral nerve damage; Breast: patients suffering of pain after breast cancer treatment.

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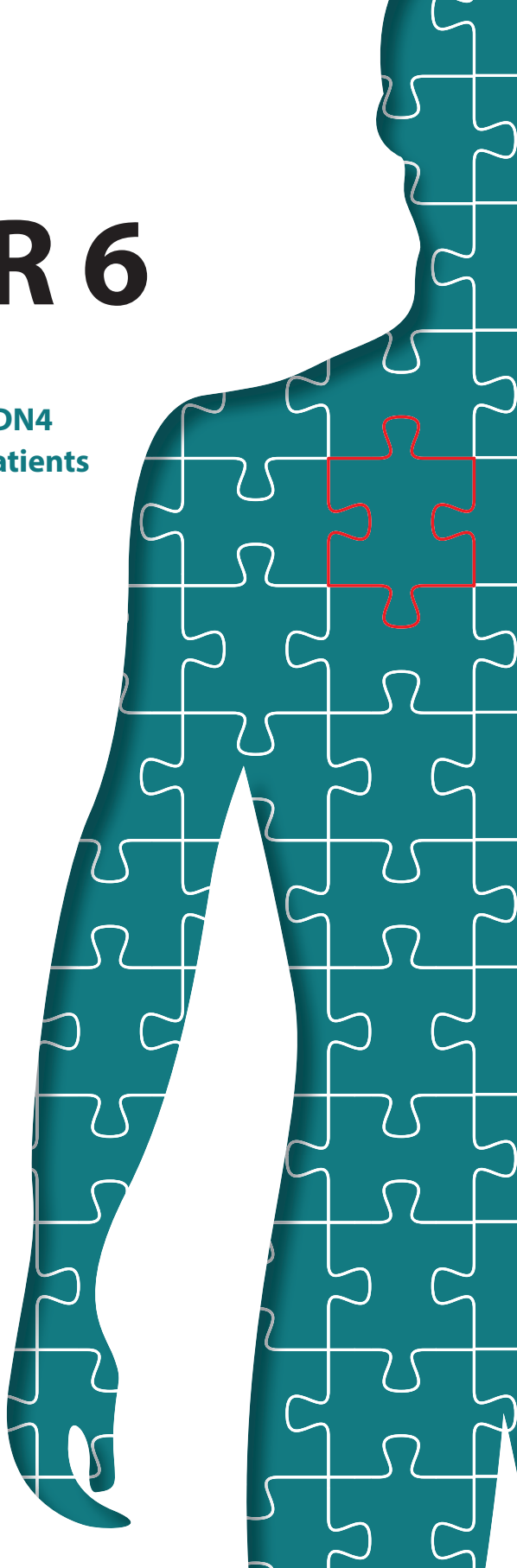
CHAPTER 6

Investigating the validity of the DN4 in a consecutive population of patients with chronic pain



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ABSTRACT

Neuropathic pain is clinically described as pain caused by a lesion or disease of the somatosensory nervous system. The aim of this study was to assess the validity of the Dutch version of the DN4, in a cross-sectional multicentre design, as a screening tool for detecting a neuropathic pain component in a large consecutive, not pre-stratified on basis of the target outcome, population of patients with chronic pain. Patients' pain was classified by two independent (pain-)physicians as the gold standard. The analysis was initially performed on the outcomes of those patients (n = 228 out of 291) in whom both physicians agreed in their pain classification. Compared to the gold standard the DN4 had a sensitivity of 75% and specificity of 76%. The DN4-symptoms (seven interview items) solely resulted in a sensitivity of 70% and a specificity of 67%. For the DN4-signs (three examination items) it was respectively 75% and 75%. In conclusion, because it seems that the DN4 helps to identify a neuropathic pain component in a consecutive population of patients with chronic pain in a moderate way, a comprehensive (physical-) examination by the physician is still obligate.

Data Availability Statement

All relevant data are within the paper and its Supporting Information files.

Funding

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Competing interests

This project is supported by an unrestricted grant from Pfizer. This unrestricted grant does not alter our adherence to PLOS ONE policies on sharing data and materials. The authors declare that they have no other competing interests.

INTRODUCTION

Neuropathic pain is described as pain caused by a lesion or disease of the somatosensory nervous system and requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria [1]. Moreover, neuropathic pain is a clinical description and not a diagnosis [1]. In daily clinical practice it is to our opinion more appropriate to speak of a present neuropathic pain component (present NePC) or absent neuropathic pain component (absent NePC) [2, 3]. This because the pain experienced by the patient in the clinical context may be caused by both neuropathic- as well as nociceptive mechanisms (also known as 'mixed pain') [2, 4-6]. The main features of neuropathic pain components are, in clinical practice, the painful signs and symptoms in a region of altered sensations (numbness or increased sensitivity) [6]. The assessment of neuropathic pain is nowadays primarily based on history and physical examination including (bedside-)sensory testing [7-9] to assess patients' pain.

Since current pharmacological treatment of patients with and without a NePC differs strongly, a correct pain classification is imperative [7, 10]. The availability of a simple and validated screening tool to determine the presence of NePC for clinical triage and epidemiological purposes can assist in detection of NePC [7, 8, 11-16]. This is especially true when this tool can be used by non pain specialists.

The original French validation study of the 'Douleur Neuropathique en 4 Questions' (DN4) [17] was performed in patients with neuropathic pain resulting from, for example, nerve trauma or post herpetic neuralgia. Patients with non-neuropathic pain were, amongst other diagnoses, suffering from osteoarthritis. All included patients had pain of at least a moderate severity (≥ 40 on a 100mm visual analogue scale). Pain classification in this study was based on medical history, physical examination, electromyography and/or imaging by two independently working physicians. DN4 application resulted in a sensitivity of 83% and a specificity of 90% [17]. As indicated in a systematic review by Mathieson et al [16] the classification of a NePC may differ between clinicians and may be more difficult when there are patients included with mixed pain and with all levels of pain. This reflects the patient population in a daily clinical practice, but might have an influence on the validity. Moreover, the accuracy of screening tools is dependent on the standardization of the assessment strategy [18]. Translation/ cross-cultural adaptation and/or validation of the DN4 was performed in more than 75 languages [19-31].

The neuropathic pain special interest group (NeuPSIG) grading system [32] is developed by Treede et al in 2008 and updated in 2016 [33]. It is a system to help the clinician to determine the certainty of the pain classification for the existence of a NePC in an individual patient: non-neuropathic pain; possible, probable or definite neuropathic pain. The grading system is suggested to be helpful in the assessment of the pain classification in clinical practice [34-38].

The aim of this study was to assess the validity and reliability of the DN4 as a screening tool for use in daily outpatient practices to detect a NePC in a, not pre-stratified on the target outcome, consecutive patient population having chronic pain syndromes due to low back and leg pain (LBLP), neck-shoulder-arm-pain (NSAP) or pain of suspected neuropathic origin (PSNO).

METHODS

This validity and reliability study had a cross-sectional, longitudinal, research design with a 2-weeks and 3-months follow-up period. Comparisons were made between the DN4 (as a whole and for the symptom questions and signs tests separately) and the classification of patients' pain by two, independently working, physicians (the gold standard) as well as with the grading system.

The study was approved by the Committee on Research Involving Human Subjects region Arnhem-Nijmegen, Nijmegen, the Netherlands, (dossier number: 2008/348; NL 25343.091.08) which counts for participation of the Dutch academic pain centers (Radboud University Medical Center, Nijmegen; Utrecht University Medical Center, Utrecht; Erasmus Medical Center, Rotterdam), Dutch non-academic pain centers (Bernhoven Ziekenhuis, Oss; St.Anna Ziekenhuis, Geldrop) and a Dutch non-academic department of neurology (Rijnstate Ziekenhuis, Arnhem). Participation of Dutch non-academic pain center in Delft, the Netherlands (Reinier de Graaf gasthuis) was approved by Medisch Ethische Toestings Commissie Zuidwest Holland (dossier number: 10-145). The study protocol was registered in the Dutch National Trial Register (NTR3030).

We used the same methodology as in the published protocol [39] and as employed in a simultaneous study regarding the validity of the Pain*DETECT* (Timmerman et.al / Under review by BMC Neurology).

Participants

Consecutive patients (first time visitors of the participating centers) without pre-stratification based on the target outcome [40] were included in the study between October 2009 until July 2013. Patients were asked to participate by their doctor. Each patient signed informed consent before participation in the study.

At that time, there was only a rough diagnosis: LBLP, NSAP or PSNO. Inclusion criteria: Male and female adult patients (≥18 years of age) with chronic (≥3 months) LBLP or NSAP radiating into respectively leg(s) or arm(s) or patients with chronic pain due to a PSNO (pain associated with a lesion or disease of the peripheral somatosensory system). Exclusion criteria: Patients diagnosed with malignancy; compression fractures; patients with diffuse pains (such as fibromyalgia or ankylosing spondylitis); severe mental illness; chronic alcoholism or substance abuse; inability to fill in the questionnaire adequately or incapable of understanding the Dutch language.

Physicians

The physicians (pain specialists, pain specialist fellows or neurologists always operating in differently composed pairs) participating in this study were not selected on basis of age, experience as a physician or any other criteria. Classification of patients' pain was based on the NeuPSIG guidelines on neuropathic pain assessment [7] and recorded as absent NePC or present NePC. Pain classification was performed consecutively on the same patient by two physicians and categorized afterwards in three groups: absent NePC, present NePC or 'undetermined' (i.e. the pain classification of the two physicians was not the same). A full medical history and clinical examination including sensory bedside examination (touch, pinprick, pressure, cold, heath and temporal summation) was taken [7, 8, 39, 41, 42] and was considered to be the gold standard when assessed by two physicians. The NeuPSIG grading system [32, 33] was used as a secondary comparison with the outcome of the DN4 and was assessed by both the physicians separately. The outcomes "probable" and "definite" were regarded as present NePC. "unlikely" and "possible" as absent NePC [38, 43, 44]. The physicians worked independently of each other and were blinded to the pain classification of the other physician. Each physician was allowed to perform the clinical examination in the way he or she is used to do but were supported by a standardized assessment form [39]. In this form, the pain score, a body map to indicate the localization of patients pain, the sensory examination and the four questions of the grading system had to be filled in by the physician. The participating physicians were trained in a standardized way (presentation about the study and the outcome parameters and a practical training on how to use the (measurement) instruments), by the investigator (HT) or by a designated person on location before participation in the study. Practical training was focused on the classification of NePC, the assessment of the grading system, the performance of bed-side examination tests and the performance and assessment of the examination items of the DN4.

In this study, 62 physicians (pain specialist, pain specialist-fellow or neurologist) participated. The physicians who were classifying patients' pain at the first session were called 'Physicians A'. The physicians who performed the classification at the second session, were called 'Physicians B'.

Measurements

Douleur Neuropathique en 4 questions (DN4). The DN4 [17, 20, 25] (Pfizer bv. Capelle a/d Ijssel, the Netherlands) consists of 10 items in total and is developed to screen for symptoms and signs of neuropathic pain resulting in a yes/no answer for the presence of neuropathic pain. This instrument is divided into two questions (seven answers, DN4-symptoms: score range 0-7) and two physical examination tests (three answers, DN4-signs: score range 0-3). The examination items of the DN4 regarding the signs (hypoesthesia to touch, hypoesthesia to prick and brushing) were incorporated in the sensory examination part of the standardized assessment form and were carried out according the original publication by Bouhassira et al [17]. This assessment form was filled in by both physicians separately. The seven symptom items are consisting of characteristics (Burning, painful cold, electric shocks) and symptoms (Tingling, pins and needles, numbness, and itching).

The patient completed the DN4-symptoms directly after the clinical assessments by the physicians but without interference. The researcher (HT) or a nurse was available for help in person or via telephone when it was not clear fort the patient how to fill in the questionnaires.

The items of the DN4 are scored based on a yes (1 point) /no (0 points) answer. This leads to a score range of 0-10 when the symptoms (range 0-7 points) as well as the signs (range 0-3 points) items are included. Values in the DN4 who were not filled in were considered as 'no' (0 points). However, in the reliability analysis these data were not incorporated.

Patient global impression of change (PGIC). The Patients Global Impression of Change (PGIC) [11, 45-47] was used to assess the change of pain complaints, based on the patients' own impression of change over time, during the follow-up period (7-points scale: Very much improved-very much worse). Follow-up took place two weeks and three months after the initial visit. To compare the outcome of the DN4 in the follow-up period the pain complaints as addressed by the patient had to be unchanged.

Time-line

All baseline measurements (the assessment by the physicians, the grading system by both physicians as well as filling in the questionnaires by the patient) took place on preferably the same day. The PGIC [45-47] and the DN4-symptoms (sensory testing for the DN4-signs was not performed) were sent to the patient after two weeks and three months with instructions how to fill them in by mail. Also for the follow-up measurements help was available in person or via telephone when it was not clear how to fill in the questionnaires.

Data

All data was collected on paper and stored by Radboudumc, Nijmegen, The Netherlands. Data management and monitoring were performed within MACRO (MACRO, version 4.1.1.3720, Infermed, London, United Kingdom). Data analysis and statistics was performed by use of Statistical Package for the Social Sciences (IBM SPSS statistics 22, SPSS Inc., Chicago, Illinois, USA).

Statistical analysis

According to the power-calculation in the protocol 132 patients with LBLP, NSAP or PSNO were needed such that the sample size contains adequate numbers of cases and controls [39]. Qualitative variables are presented as frequencies and percentages. The quantitative variables are presented as mean and standard deviation (SD) or as median and inter quartile range (IQR).

The agreement between any of the two combinations of the two observers (pain classification by the physician and the outcome of the grading system) to establish a present NePC or absent NePC, and of the DN4 (DN4 / DN4-symptoms / DN4-signs outcome) was evaluated

by use of Cohen's kappa (K), prevalence index (Pi) and percentage of pair wise agreement (PA). The categorization of the kappa values are, according to the categorization of observer agreement by Landis and Koch [48], none beyond chance (K ≤ 0.00); slight (K = 0.01-0.20); fair (K = 0.21-0.40); moderate (K = 0.41-0.60); substantial (K = 0.61-0.80) and (almost) perfect agreement (K = 0.81-1.00). A K ≥ 0.40 and a PA ≥ 70% is considered indicative of interobserver reliability acceptable for use in clinical practice [48]. Moreover, also the interobserver reliability of the examination items in the DN4-signs were tested.

Based on the classifications of the two phyicians, all patients were categorized as absent NePC, present NePC or 'undetermined' (i.e. the pain classification of the two physicians was not the same).

Statistical significant differences between absent NePC and present NePC were determined by use of students t-test (Interval scales), Mann-Whitney U-test groups (ordinal scales) or via Chi^2-test (nominal scale). The statistical significant differences between present NePC, absent NePC and the Undetermined group was assessed by use of One-way ANOVA (with additional Tukey's studentized range post-hoc test) or Kruskal-Wallis test. Chi^2 test was also used to analyze the nominal outcome scale of the DN4 regarding the three groups.

A factor analysis was used to study the structure of the DN4 in such a way that variables that were thought to reflect a smaller number of underlying variables were observed. This method was performed for all three versions of the DN4 (DN4; DN4-symptoms and DN4-signs). Principal axis factoring was used as the extraction method. The varimax rotation with Kaiser normalization was used. Extraction of the factors was based on Eigenvalues being greater than 1.0. Cronbach's alpha was used to calculate the internal consistency of the factors constructed. The results are only shown for the Physicians A (the assessment of the patient by the first physician). The outcomes by the Physicians B (the assessment of the patient by the second physician) are shown in S1 Table. However, the conclusions, which are drawn, are identical for physicians A and for physicians B.

A receiver operating characteristic (ROC) curve was calculated for the DN4 and the DN4 signs by both the physicians A and B and for the DN4-symptoms as filled in by the patient. The area under the curve (AUC) with 95% confidence interval was presented to indicate the discriminatory power of the DN4 to discriminate patients by present NePC or absent NePC. This dichotomy was based on the physicians' assessment outcome or based on the grading system outcome, respectively. The theoretical maximum of the AUC is 100%, indicating a perfect discrimination and 50% is equal to tossing a coin. An AUC between 0.9 and 1 is considered to be excellent, an AUC between 0.8 and 0.9 is good and between 0.7 and 0.8 is fair. An AUC between 0.6 and 0.7 is considered to be poor. Between 0.5 and 0.6 the AUC is considered to be failed [49-52]. The optimal cut-off point of the DN4 was calculated under the condition of equal-costs of misclassification using the Youden-index. Sensitivity, specificity, positive and negative predictive values and the likelihood ratio in the

population in this study was calculated at this cut-off point. The outcome results were averaged between both physicians and the 95% confidence intervals were noted with respect to the lowest and highest level.

Clinimetrics of the DN4 based on both the physicians assessment and/or both the grading system outcome were assessed for the DN4, the DN4-symptoms and for the DN4-signs items. A screening tool for the presence of a NePC is considered valid if it has a high sensitivity, specificity, high positive predictive value and a high positive likelihood ratio [53]. Intraclass correlation (ICC) was used to assess reproducibility ('test-retest reliability') of the DN4-symptoms between the predetermined time points (baseline versus two weeks & baseline versus three months). Based on the guidelines by Cicchetti et al. [54, 55] an ICC <0.40 indicates poor level of clinical significance. The level is fair when the ICC is between 0.40 and 0.59, good between 060 and 0.74 and excellent when the ICC is between 0.75 and 1.00. To assess the test-retest reliability patients' pain should not have changed (outcome based on the PGIC) because otherwise the ICC would not reflect the consistency of the DN4. Test-retest reliability was assessed for those questionnaires returned within 7-21 days for the two weeks test-retest reliability and 60-120 days for the three months test—retest reliability. The ICC and responsiveness of the DN4-symptoms was assessed at each point of measurement.

Two-tailed p-value below 0.05 was considered statistically significant.

RESULTS

Patients

In this study 330 consecutive patients were assessed for eligibility (Figure 1). Of these, 291 participated in the study between October 2009 and July 2013. Two patients did not give their informed consent. Exclusion (n = 37) was because of not fulfilling the in- and exclusion criteria (n = 13): patients with LBLP or NSAP without radiating pain: n = 1; patients with less than 3 months pain complaints: n = 2; patients with pain with an oncological cause: n = 2; patients with painful syndromes of unknown origin or associated with diffuse pains: n = 7; patients with severe mental illness: n = 1; missing baseline measurements due to not returning questionnaires by the patient: n = 16; missing pain classification based on the grading system by one physician (n = 5) or both the physicians (n = 3). 132 patients had LBLP with radiation in one or two legs (45.4%), 51 NSAP with radiation in one or both arms (17.5%) and 108 patients (37.1%) had PSNO: 86 patients with pain after treatment for breast cancer (surgery and chemotherapy and/or radiation therapy and/or hormonal therapy). Twenty-two patients had pain for various reasons: peripheral nerve damage (n = 12), radicular pain (n = 3), polyneuropathy (n = 3), CRPS (n = 2) and post stroke pain (n = 2). The gold standard for presence of the NePC in this study was the concordant clinical opinion of both physicians. After pain classification by two physicians, 170 patients were classified as present

NePC, 58 as absent NePC and in 63 patients the two physicians made a different pain classification: 'undetermined'. Using the grading system, 139 patients were assigned as having a present NePC, 93 patients as absent NePC and 51 patients were assigned as undetermined. The DN4 was full filled by the patients at a median of one day (IQR 0-5 days) following the assessments by the physicians.

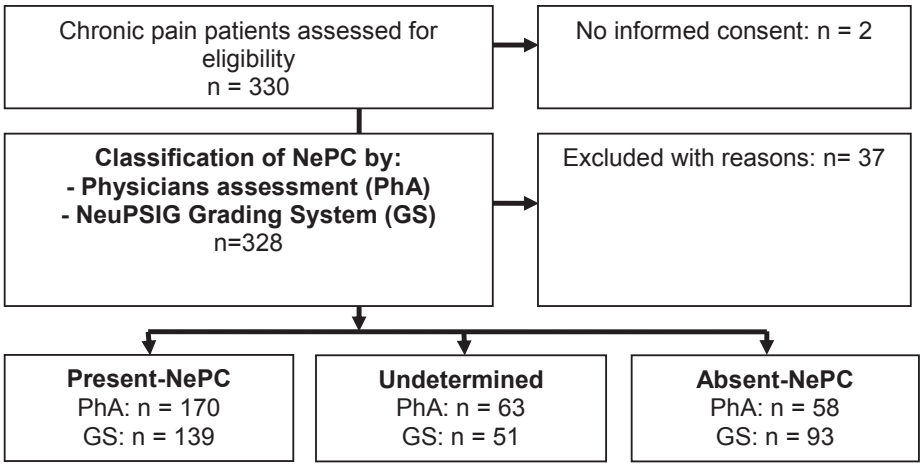

Figure 1: Flow diagram for the outcome of the physicians assessment and the NeuPSIG grading system.

Present NePC: present neuropathic pain component; Undetermined: Both physicians disagree with each other about the existence of a neuropathic pain component; Absent NePC: absent neuropathic pain component; n = total number of patients in analysis PhA: Physicians assessment; GS: Neuropathic pain special interest group grading system (missing pain classification based on the grading system: n = 8).

Clinical and social-demographic details of the 291 patients were analyzed based on their pain classification. No statistically significant differences were found between present NePC and absent NePC for gender, age, height, weight, BMI, medication and duration of pain. Also no statistically significant difference was observed between absent NePC and present NePC regarding current-,worst – and average pain (Table 1).

The proportion of agreement after chance agreement is removed (Cohen's Kappa, K) for the classification of patients' pain (absent NePC or present NePC) by the physicians was 0.49 (moderate), with a PA of 78.4% (Pi = 0.38; n = 291). For the classification of patients' pain on basis of the grading system K was 0.63 (good) and PA was 82% (Pi = 0.16; n = 283). The outcome of K and PA regarding the DN4 compared to the outcome of the assessment by physicians A was respectively 0.34 (fair) and 69.8% (Pi = 0.33; n = 275). Compared to the outcome of

Table 1: Clinical and socio-demographic characteristics of the patients related to physicians agreement for the existence of a neuropathic pain component.

NePC		Absent		Present			Undetermined		
		N		N		*P*	N		P
Total number of patients		58		170			63		
Gender						*0.163[c]*			*0.164[c]*
	Male		25 (43%)		56 (33%)			17 (27%)	
	Female		33 (57%)		114 (67%)			46 (73%)	
Age (Years) [#]		58	55 ± 12	170	56 ± 11	*0.594[a]*	63	58 ± 13	*0.522[d]*
Height (cm) [#]		55	172 ± 9	164	172 ± 8	*0.845[a]*	62	170 ± 9	*0.250[d]*
Weight (kg) [#]		55	84 ± 2	167	80 ±17	*0.382[a]*	62	80 ± 16	*0.461[d]*
BMI (kg/m²) [#]		54	28 ± 8	164	27 ±5	*0.436[a]*	62	27 ± 5	*0.593[d]*
Medication use^		55	56.9%	168	66.1%	*0.414[c]*	61	57.4%	*0.423[c]*
Duration of pain (months)#		57	72 ± 90	169	60 ± 76	*0.327[a]*	62	49 ± 46	*0.247[d]*
Pain*	Current pain	57	5 (3-7)	167	6 (3-7)	*0.577[b]*	61	4 (1-7)	*0.084[e]*
(NRS; 0-10)	Worst pain during the past four weeks	57	8 (5-9)	167	8 (7-9)	*0.371[b]*	61	7 (5-8)	*0.053[e]*
	Average pain during the past four weeks	57	6 (3.5-7)	167	6 (5-8)	*0.233[b]*	61	6 (3-7)	***0.018[e]***

Classification for the existence of NePC is based on physicians assessment of the patients.

NePC: neuropathic pain component; Absent: NePC is absent; Present: NePC is present; Undetermined: both physicians disagree with each other about the existence of a neuropathic pain component; N: total number of patients in analysis; n: number of patients; ^ percentage; # Standard deviation; * Inter quartile range. A: physicians A; B: Physicians B; P value for significant difference between groups ($P \leq 0.05$) by use of different analyse methods: a: Students t-test; b: Mann-Whitney U test; c: Chi-square; d: One-Way ANOVA; e: Kruskal-Wallis test.

the assessment by physicians B it was 0.33 (fair) and 69.2% (Pi = 0.30; n = 263). Comparing the outcome of the DN4 to the outcome of the grading system, it was 0.35 (fair) and 69.1% (Pi = 0.22; n = 272) for physicians A, and 0.32 (fair) and 67.3%(Pi = 0.19; n = 260) for physicians B (Table 2). The interobserver reliability for 'hypoesthesia to touch' as well as for 'brushing' was respectively K = 0.59 (moderate) (PA = 79.7%) and K = 0.53 (moderate)(PA = 76.6%). The interobserver reliability for 'hypoesthesia to prick' was K = 0.21 (fair); PA = 87% (Table 3).

Table 2: **The kappa coefficient between the classification on basis of the assessment by the physicians, the grading systems, the DN4 and the kappa coefficient between both physicians regarding the DN4-signs.**

		Classification physician B	Grading A	Grading B	DN4 A	DN4 B	DN4-Symptoms	DN4-Signs A	DN4-Signs B
Classification physician A	n	**291**	**286**	288	275	263	288	279	266
	K	**0.49**	**0.48**	0.32	0.34	0.34	0.32	0.37	0.26
	PA	**78.4**	**76.2**	67.4	69.8	70.0	67.4	70.3	64.4
	P*i*	**0.38**	**0.32**	0.26	0.33	0.31	0.26	0.30	0.30
Classification physician B	n		286	**288**	275	263	288	279	266
	K		0.38	**0.48**	0.33	0.33	0.21	0.39	0.37
	PA		71.0	**75.0**	69.1	69.2	62.8	71.0	70.7
	P*i*		0.28	**0.22**	0.29	0.30	0.25	0.26	0.28
Grading A	n			**283**	272	259	283	**276**	262
	K			**0.63**	0.35	0.31	0.14	**0.54**	0.31
	PA			**82.0**	69.1	67.2	58.6	**77.5**	67.2
	P*i*			**0.16**	0.22	0.23	0.19	**0.19**	0.21
Grading B	n				272	260	285	**276**	**263**
	K				0.29	0.32	0.13	**0.53**	**0.45**
	PA				65.4	67.3	57.2	**76.8**	**73.4**
	P*i*				0.18	0.19	0.14	**0.14**	**0.16**
DN4 A	n					**257**	**275**	**275**	257
	K					**0.76**	**0.62**	**0.52**	0.29
	PA					**88.7**	**81.8**	**76.7**	65.8
	P*i*					**0.21**	**0.19**	**0.17**	0.19
DN4 B	n						**263**	**257**	**263**
	K						**0.65**	**0.40**	**0.45**
	PA						**82.9**	**71.2**	**73.4**
	P*i*						**0.18**	**0.21**	**0.17**
DN4-symptoms	n							276	263
	K							0.15	0.10
	PA							58.7	56.3
	P*i*							0.17	0.16
DN4-Signs A	n								**260**
	K								**0.55**
	PA								**78.4**
	P*i*								**0.18**

n = total number of patients in the analysis; K = Cohen's kappa value; PA (%) = percentage of agreement between two outcome variables; Pi = Prevalence index

Table 3: The kappa coefficient between both physicians regarding the DN4-signs.

		Hypoesthesia to touch DN4-signs B	**Hypoesthesia to prick** DN4-signs B	**Brushing** DN4-signs B
Hypoesthesia to touch DN4-signs A	n	**222**		
	K	**0.59**		
	PA	**79.7**		
	P*i*	**0.10**		
Hypoesthesia to prick DN4-signs A	n		244	
	K		0.21	
	PA		87.3	
	P*i*		-0.82	
Brushing DN4-signs A	n			**222**
	K			**0.53**
	PA			**76.6**
	P*i*			**0.11**

n = total number of patients in the analysis; K = Cohen's kappa value; PA (%) = percentage of agreement between two outcome variables; Pi = Prevalence index

In 253 patients all the six outcome variables (two times the physicians' assessment, two times the grading system and The DN4 by physician A and DN4 by physician B was available. In 83 patients (32.8%), the pain was classified as present NePC in all outcomes and in 22 patients (8.7%) it was six times negative, indicating absent NePC, so the agreement on all the six measures was 41.5% (the percentage of agreement based on both the gold standards and both the grading systems only was 56.9%).

Factor analysis

Table 4 shows the loading factor of the items of the DN4 according to the rotated component matrix factor analysis with Kaiser normalization. The analysis was performed by use of the 10 questions in the DN4 and revealed a 4-factor solution explaining 59.3% of the variance for the first physicians' assessment (physicians A): Factor 1 included two items (hypoesthesia to touch, brushing) indicating that there was an inter-relation between those items (Cronbach's α: 0.87). Factor 2 included three items (painful cold, tingling, hypoesthesia to prick) (Cronbach's α: 0.37). Factor 3, consisted of four items (burning, electric shocks, pins and needles, numbness); Cronbach's α: 0.51). Factor 4 consisted of one item (itching) (Table 4). In the S1 Table we provided the factor analysis for both the physicians assessments (A & B), the DN4 symptoms solely and the DN4signs for both physicians' assessments (A & B). Internal consistency of all the components of the DN4 for the physicians A at baseline was assessed via Cronbach's α: 0.57; for the physicians B it was 0.55. Cronbach's α for DN4-symptoms was 0.52. Cronbach's α for the DN4-signs for A and B were respectively 0.68 and 0.66.

Table 4: Loading factors of the items of the DN4 according to the rotated component matrix factor analysis.

DN4	Component (Physicians A)			
	1	2	3	4
Burning	0.25	0.28	**0.29**	0.15
Painful cold		**0.62**		
Electric shocks			**0.72**	
Tingling		**0.68**		
Pins and needles		0.35	**0.45**	0.27
Numbness			**0.71**	
Itching				**0.86**
Hypoesthesia to touch	**0.87**			
Hypoesthesia to prick	0.38	**0.63**		
Brushing	**0.90**			
Cronbach's alpha	*0.81*	*0.37*	*0.51*	

Loading factors < 0.25 are omitted to improve readability

Items of the DN4

The DN4-symptoms (pain descriptors) burning, electric shocks, tingling, pins and needles, and numbness were statistically significant associated (Chi^2) with the classification by the physicians (absent NePC, present NePC or undetermined), $p<0.05$. The descriptors 'painful cold' ($p = 0.210$) and 'itching' ($p = 0.409$) were not associated with the outcome of the classification. The DN4-signs (examination items) hypoesthesia to touch, pricking and brushing were statistically significant associated (Chi^2) with the classification by the physicians (absent NePC, present NePC or undetermined), $p<0.05$.

The median of the total sum score of the DN4 for patients classified as absent NePC was 2, the median for the DN4-symptoms items was 2 and for the DN4-signs items the median was 0; for patients classified as present NePC it was at median 5, 3 and 2, respectively. As calculated based on the Kruskal-Wallis test there was for the sum scores of the DN4, the DN4-symptoms items and the DN4-signs items a statistical significant difference between absent NePC and present NePC ($P<0.001$), between present NePC and undetermined ($P<0.001$) and between absent NePC and undetermined ($P<0.001$). In Table 5 the outcomes for all individual items and the three DN4 scales (for physicians A as well as for physicians B) are presented according to the pain classification by the physicians (Table 5).

Table 5: The median (IQR) and percentages of the items of the DN4 by physicians agreement of a NePC.

NePC		Absent		Present			Undetermined		
		N		N		*P*	N		*P*
Total number of patient		58		170			63		
DN4-Symptoms^	Burning	56	12 (21%)	161	77 (48%)	***0.001***[a]	57	22 (39%)	***0.002***[a]
	Painful Cold	54	6 (11%)	154	34 (22%)	*0.078*[a]	53	11 (21%)	*0.210*[a]
	Electric Shocks	55	18 (33%)	162	87 (54%)	***0.007***[a]	55	19 (35%)	***0.005***[a]
	Tingling	55	29 (53%)	160	110 (69%)	***0.032***[a]	57	28 (49%)	***0.011***[a]
	Pins and Needles	52	19 (37%)	157	101 (60%)	***0.000***[a]	58	27 (47%)	***0.001***[a]
	Numbness	54	29 (54%)	165	131 (79%)	***0.000***[a]	59	42 (71%)	***0.001***[a]
	Itching	51	10 (20%)	149	25 (17%)	*0.646*[a]	56	14 (25%)	*0.409*[a]
DN4-signs^	Hypoesthesia to touch A	42	9 (21%)	153	102 (67%)	***0.000***[a]	60	16 (27%)	***0.000***[a]
	B	41	11 (27%)	151	101 (67%)	***0.000***[a]	49	18 (37%)	***0.000***[a]
	Hypoesthesia to prick A	47	0 (0%)	162	20 (12%)	***0.011***[a]	58	3 (5%)	***0.017***[a]
	B	48	0 (0%)	159	21 (12%)	***0.008***[a]	53	1 (2%)	***0.002***[a]
	Brushing A	43	9 (21%)	157	110 (70%)	***0.000***[a]	55	14 (25%)	***0.000***[a]
	B	43	13 (30%)	151	99 (66%)	***0.000***[a]	52	19 (37%)	***0.000***[a]
Total sum score DN4 A* (0-10)		47	2 (1-3)	166	5 (3-6)	***0.000***[b]	62	3 (2-4)	***0.000***[c]
Total sum score DN4 B* (0-10)		48	2 (2-3,75)	159	5 (3-6)	***0.000***[b]	56	3 (2-4.75)	***0.000***[c]
Total sum score DN4 symptoms* (0-7)		57	2 (1-3)	168	3 (2-5)	***0.000***[b]	63	2 (2-4)	***0.000***[c]
Total sum score DN4 signs A* (0-3)		49	0 (0-0)	168	2 (1-2)	***0.000***[b]	62	0 (0-1)	***0.000***[c]
Total sum score DN4 signs B* (0-3)		49	0 (0-1)	161	2 (0-2)	***0.000***[b]	56	0 (0-2)	***0.000***[c]

Classification for the existence of NePC is based on physicians assessment of the patients.

NePC: neuropathic pain component; Absent: NePC is absent; Present: NePC is present; Undetermined: both physicians disagree with each other about the existence of a neuropathic pain component; N: total number of patients in analysis; n: number of patients; ^ percentage; * Inter quartile range. A: physicians A; B: Physicians B; P value for significant difference between groups (P _ 0.05) by use of different analyse methods: a: Chi-Squared; b: Mann-Whitney U test; c: Kruskal-Wallis test.

Validity

We constructed ROC-curves for the DN4, the DN4-symptoms and the DN4-signs with respect to the classification by physician A or B and according to the neuropathic pain grading system by physician A or B and all the combinations (Concordant assessment by physicians A and B together, concordant grading system by Physicians A and B together and concordant grading system for Physicians A and B together with the concordant grading system by physicians A and B). This because of the chosen gold standard and the grading system in which patients were classified by two different physicians. This might have lead to differences in the outcomes relative to the individual outcome

by the physician. In Figure 2 the ROC-curve is displayed for the DN4 (physicians A and physicians B), DN4-symptoms and the DN4-signs (physicians A and physicians B) (Figure 2).

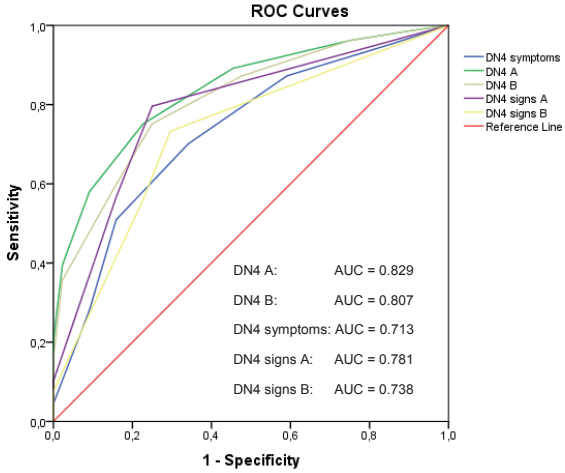

Figure 2: The ROC curve of the DN4, DN4 symptoms and the DN4 signs to the probability of the presence of NePC as classified based on the assessment by the physicians (A and B).

DN4: Doleur Neuropathique en 4 questions; DN4-symptoms: the items filled in by the patient; DN4 A: DN4-symptoms filled in by the patient and DN4-signs as assessed by physicians A; DN4 B: DN4-symptoms filled in by the patient and DN4-signs as assessed by physicians B; DN4 signs A: DN4-signs as assessed by physicians A; DN4 signs B: DN4-signs as assessed by physicians B.

Based on the gold standard the sensitivity of the DN4 was on average (at maximal Youden- index, cut off point: 4/10) 75% (95% CI 0.68-0.81), specificity 76% (95% CI 0.61-0.86), positive predictive value 92% and the positive likelihood ratio was 3.09 (95% CI 1.82-5.39) (Table 5; S2 Table). For patients with LBLP the sensitivity was on average 75% and specificity was on average 81%. For patients with NSAP the averaged sensitivity was 73% and the specificity was on average 72%. For patients with pain due to a PSNO it was respectively, on average, 70% and 78%. The sensitivity of the DN4-symptoms was, in respect to the gold standard, 70% (95% CI 0.63-0.77) and the specificity was 67% (95% CI 0.54-0.78) (at maximal Youden-index, cut off point 3/7). Analysis of the DN4-signs solely resulted in an average sensitivity of 75% (95% CI 0.66-0.82) and an average specificity of 75% (95% CI 0.58-0.87) (at maximal Youden-index, cut off point 1/3). With the outcome based on the grading system the sensitivity was on average 76% (95% CI 0.68-0.82) and the specificity was 64% (95% CI 0.51-0.74) (at maximal Youden-index, cut off point 4/10). (Table 6; S2 Table).

Table 6: **The area under the curve and the sensitivity / specificity at the optimal cut-off point of the DN4 under the condition of equal costs of misclassification to classify a neuropathic pain component by the classification and the grading system of the physicians.**

	Present NePC	Absent NePC	AUC	(95%CI)	Youden index	Cut-off	Sens %	95% CI	Spec %	95% CI	PPV %	NPV %	PLR	95% CI
Classification A=B														
DN4 A	**166**	**47**	**0.829**	**0.767-0.890**	**0.513**	**4**	**75**	**0.676-0.807**	**77**	**0.628-0.864**	**92**	**46**	**3.19**	**1.889-5.394**
LBLP	72	26	0.823	0.738-0.90	0.544	4	74	0.624-0.824	81	0.621-0.915	91	53	3.83	1.72-8.517
NSAP	23	10	0.763	0.576-0.950	0.439	3	74	0.535-0.875	70	0.397-0.892	85	54	2.46	0.927-6.547
PSNO	71	11	0.836	0.713-0.959	0.543	5	63	0.518-0.736	91	0.623-0.984	98	28	6.97	1.067-45.558
DN4 B	**159**	**48**	**0.807**	**0.742-0.872**	**0.498**	**4**	**75**	**0.678-0.81**	**75**	**0.612-0.851**	**91**	**47**	**2.99**	**1.819-4.927**
LBLP	67	26	0.821	0.736-0.906	0.554	4	75	0.631-0.835	81	0.621-0.915	91	55	3.88	1.744-8.637
NSP	21	11	0.725	0.529-0.921	0.442	4	71	0.5-0.862	73	0.434-0.903	83	57	2.62	0.961-7.135
PSNO	71	11	0.777	0.644-0.910	0.397	4	76	0.65-0.845	64	0.354-0.848	93	29	2.09	0.947-4.62
DN4-symptoms	**168**	**57**	**0.713**	**0.634-0.791**	**0.369**	**3**	**70**	**0.629-0.766**	**67**	**0.537-0.775**	**86**	**43**	**2.11**	**1.441-3.082**
LBLP	74	28	0.716	0.606-0.826	0.348	3	72	0.605-0.806	61	0.424-0.764	83	45	1.82	1.126-2.953
					0.348	4	53	0.415-0.637	82	0.644-0.921	89	40	2.95	1.296-6.723
NSAP	23	18	0.661	0.484-0.837	0.374	3	65	0.449-0.812	72	0.491-0.875	75	62	2.35	1.052-5.238
PSNO	71	11	0.764	0.611-0.918	0.431	3	70	0.59-0.798	73	0.434-0.903	94	28	2.58	0.972-6.858
DN4-signs A	**168**	**49**	**0.781**	**0.709-0.852**	**0.537**	**1**	**76**	**0.692-0.82**	**78**	**0.641-0.87**	**92**	**49**	**3.39**	**2.003-5.75**
LBLP	73	26	0.744	0.637-0.850	0.479	1	67	0.557-0.768	81	0.621-0.942	91	47	3.49	1.562-7.799
NSAP	23	11	0.783	0.632-0.933	0.565	1	57	0.368-0.744	100	0.741-1.000	100	52	---	---
PSNO	72	12	0.763	0.608-0.917	0.417	1	92	0.83-0.961	50	0.254-0.746	92	50	1.83	1.037-3.242
DN4-signs B	**161**	**49**	**0.738**	**0.660-0.816**	**0.447**	**1**	**73**	**0.66-0.795**	**71**	**0.576-0.822**	**89**	**45**	**2.57**	**1.632-4.033**
LBLP	68	26	0.742	0.636-0.847	0.455	1	65	0.528-0.75	81	0.621-0.915	90	47	3.36	1.501-7.541
NSAP	21	11	0.777	0.606-0.948	0.576	1	67	0.454-0.828	91	0.623-0.984	93	59	7.33	1.104-48.691
PSNO	72	12	0.628	0.463-0.794	0.167	1	83	0.731-0.902	33	0.138-0.609	88	25	1.25	0.827-1.89
					0.167	2	67	0.552-0.765	50	0.254-0.746	89	20	1.33	0.74-2.403

Grading A=B														
DN4 A	138	81	0.771	0.709-0.833	0.396	4	75	0.676-0.818	64	0.533-0.738	78	60	2.10	1.549-2.861
DN4 B	135	75	0.744	0.673-0.814	0.382	4	76	0.677-0.82	63	0.514-0.727	7	59	2.02	1.487-2.755
DN4-symptoms	139	91	0.610	0.537-0.684	0.179	4	45	0.373-0.536	73	0.626-0.806	72	46	1.65	1.128-2.414
DN4-signs A	138	84	0.855	0.803-0.908	0.653	1	86	0.787-0.904	80	0.7-0.87	87	77	4.23	2.748-6.495
DN4-signs B	135	77	0.759	0.691-0.827	0.466	1	78	0.701-0.84	69	0.578-0.781	81	64	2.50	1.769-3.52

DN4: Douleur neuropathique en 4 questions; present NePC: Neuropathic pain component existing; Absent NePC: Neuropathic pain component not existing; AUC: Area under curve; 95%CI: 95% confidence interval; Sens: Sensitivity; Spec.: Specificity; PPV: Positive predictive value; A: Physicians A; B: Physicians B; LBLP: Patients suffering from low back and leg pain; NSAP: Patients suffering from neck shoulder arm pain; PSNO: Patients suffering from pain due to a suspected neuropathic origin.

In Table 6 and S2 Table we present the number of patients per group, values of the AUC, Youden index, cut-off score, true positives, false positives, false negatives, true negatives, sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, the diagnostic odds ratio, the a-priori chance for the existence (or not) of a NePC and false positive and negative ratios for all validity outcomes (DN4 A & B, DN4-symptoms, DN4-signs A & B) divided according to the pain classification and divided into LBLP, NSAP and PSNO (Table 6 and S2 Table).

Test-retest reliability

Stability and responsiveness of the DN4-symptoms over time was assessed over a period of two weeks. The median sum score (IQR) of the DN4 at baseline for the total group was 3 (2-4), after two weeks it was 3 (2-4). Taking into consideration the fact that patients' pain should not have changed (outcome based on the PGIC) because otherwise the ICC would not reflect the consistency of the DN4, test-retest reliability via ICC was 0.84 (excellent) (95%CI 0.80-0.87; n = 265). For the time gap of 7-21 days (to rule out the early or delayed return of questionnaires) between the first and second DN4-symptoms the ICC was 0.85 (excellent) (95% CI 0.79-0.90; n = 122). After three months, with no change in patients pain and a time gap of 60-120 days between the first and third DN4-symptoms, ICC was 0.79 (excellent) (95% CI 0.70-0.86; n = 102).

DISCUSSION

The DN4 seems, in this study, to help to identify a neuropathic pain component in a consecutive population of patients with chronic pain in a moderate way.

Reliability

We used the concordant opinion about the classification of patients' pain by two physicians as the gold standard. It is disputable if the term gold standard is practicable. However, as written by Versi [56, 57] *"the gold standard is not the perfect test but merely the best available test. … Against which newer tests can be compared"*. There are studies regarding the validity of the DN4 using only one physician's opinion [21, 30]. To our opinion it is preferable to use two physicians as the gold standard, which is also performed in the original validation study of the DN4 [17]. This might lead to less false positive or false negative outcomes which, of course, will lead to a more accurate validity outcome. The physicians in this study agreed on pain classification in 78% of the patients. In other studies without pre-stratification of patients on the target outcome the results for the physicians agreement were 53% [25] and 89% [27]. The kappa coefficient between the DN4 as filled in by physician A compared to the DN4 by physician B was 'good' with a high percentage of agreement. Test-retest reliability of the DN4-symptoms in this study was excellent. Based on these results DN4 seems to be reliable. However, it is possible that an instrument is reliable without being valid [58].

Validity

To quantify the screening ability of the DN4, for the existence of a NePC, sensitivity and specificity can be used [59]. However, in clinical practice we want to know how many patients with a positive score on the DN4 really does have a NePC. To report this, the positive and negative predictive values are important because they give the proportion of patients with positive or negative test results which are correctly diagnosed [60]. The predictive value depends on the prevalence of NePC in the group of patients under study [60]. In our study the prevalence of NePC was high, 75%. The higher the prevalence of NePC in the group under study the more sure it is that a positive outcome of the DN4 indicates the presence of a NePC, but the less sure it is that a negative DN4 outcome indicates absent NePC [60]. The likelihood ratio gives an indication of the value of the DN4 for increasing certainty about a positive diagnosis [60]. A higher likelihood ratio might indicate that the DN4 is useful, but is still not sure that a positive outcome of the DN4 is a good indicator for the presence of a NePC [60]. In the literature there are, as far as we know, no 'cut-off' scores for the validity indices. In our study we found a sensitivity of 75% (DN4-symptoms 70%), a specificity of 76% (DN4-symptoms 67%), positive predictive value of 92%, negative predictive value of 46% and the positive and negative likelihood ratios were respectively 3.09 and 0.34. In the original study by Bouhassira et al. [17] patients with only 'typical' neuropathic or nociceptive entities and a VAS of ≥40 mm (0-100mm) were included. They found a sensitivity of 83% and a specificity of 90%. For the DN4-symptoms the sensitivity was 78% and the specificity 81%. The Dutch version of the DN4 [20] was validated before in a consecutive group of patients suffering from chronic pain for more than three months with a pain score of 5 or higher on a 0-10 numeric rating scale (NRS) [25]. For the DN4 a sensitivity of 75% and a specificity of 79% was found. For the DN4-symptoms version sensitivity was 74% and the specificity 79%. Van Seventer et al. concluded that the DN4 was a diagnostic tool with a good ability to discriminate between neuropathic pain and nociceptive pain [25]. However, the paper by Bouhassira et al. [17] and the paper by Van seventer et al. [25] both didn't report the predictive values and likelihood ratios. Inappropriate screening might result in higher health care costs due to more diagnostic testing or even lead to a harmful treatment for the patient [61]. It seems that the validity indices in our study are resulting in a lower score for the DN4 as in the original publication [17] and than in other studies [4, 21, 23-28, 30, 31, 62-67]. This might have several reasons. At first, we did not pre-stratify on the target outcome. In studies, besides the original validation study [17] with pre-stratification on the target outcome [23, 24, 26, 28, 31] (neuropathic or non-neuropathic pain), the sensitivity of the DN4 was ranging from 90% [26] till 100% [24], the specificity from 93% [24]-97% [23, 28]. In studies where there was no pre-stratification on the target outcome (neuropathic or non-neuropathic pain), the sensitivity of the DN4 was ranging from 80% [21] till 100% [30], the specificity ranges from 78% [21, 27] till 87% [30]. These results are showing that the validity of the DN4 is lower in studies without pre-stratification than in studies were patients were stratified based on their pain classification before entering the study. In studies with specified diseases as spinal cord injury [64]; diabetes [63, 64]; leprosy [65, 66]; FBSS [67], chronic low back pain [4] and in patients with cancer before starting with chemotherapy [68], the sensitivity (62%-100%) and specificity (44%-

93%) ranges were much wider. Our results, also when separated into results for LBLP, NSAP and PSNO, falls within these ranges. This indicates that the neuropathic pain component is not always clear and/or easy to classify by use of the DN4 in the different medical conditions. Secondly, in our study we did not have a minimum level of pain as an inclusion criteria. In seven studies a minimal level of pain (on a rating scale of 0-10) was not an inclusion criteria [21, 23, 31, 62, 63, 65, 66]. In other studies a level ≥ three [64, 67], ≥ four [4, 17, 24, 26, 28, 30] or ≥ five [25, 27] is set as an inclusion criterium. As shown by Perez et al [21], pain severity has a major influence on the sensitivity and specificity of the DN4. A severity of < 40 mm on a 0-100mm VAS resulted in a sensitivity of 56% and a specificity of 67%. For moderate pain (between 40mm en 70mm on a 0-100mm VAS) it was 85% and 84% respectively, and >70 mm sensitivity was 80% and specificity was 74% [21]. In a study by Marksman [67] in patients after FBSS it was showed that the presence of neuropathic characteristics, as determined by the DN4, was associated with a higher pain intensity. These facts are crucial for the validation of a screening instrument because such a tool must be valid for use in daily clinical out-patient practice and/or for epidemiological purposes.

As a second comparison, we validated the DN4 in comparison with the grading system [21, 32]. In this study, we combined 'unlikely' and possible neuropathic pain as absent NePC and probable and definite as present NePC, which resulted in an average sensitivity for the DN4 of 76% and an average specificity of 64%. In patients with a failed back surgery syndrome [67], the validation of the DN4 resulted in a sensitivity of 62% and a specificity of 44%. In a study by Sadler et al [69] where patients with neuropathic pain were compared to musculoskeletal pain the sensitivity was 76% and the specificity was 70%. However, in patients with a more mixed pain the sensitivity and specificity descended to 59% and 70% respectively. Abdallah et al [36] compared the DN4 with the grading system in patients after breast tumor resection with and without paravertebral blocks. This resulted in a sensitivity of 90% and a specificity of 60% to identify patients with chronic neuropathic pain based on the outcome of the grading system. However, this outcome was not validated by (expert) physicians. The distinction between possible neuropathic pain and probable or definite neuropathic pain is of high importance because the outcome forms the basis for selecting a different treatment strategy [34]. The combination of outcomes in our study might have resulted in a lower sensitivity and a bit higher specificity in comparison with the classification in the study of Abdallah et al [36].

Bouhassira [17] presented the DN4 as a clinician-administered questionnaire. In different studies not a physician but a research coordinator [30], a nurse [25] or the patient self [25, 70] filled in the DN4. In our study we gave the patient the questionnaire with the 7-items (DN4-symptoms) to fill them in after the physical examinations. The three examination-items (DN4-signs) were incorporated in the standardized assessment form which should be filled in by the physician. We presented the DN4 total sum score as well as the DN4-signs score separately for physicians A and B. This is due to the fact that it is only possible to have one outcome when the sign-items were performed by one physician.

Strength and weaknesses

There are several strengths in this study. At first, this study reflects daily clinical practice. In this study, we included a large cohort of patients irrespective of the predominant origin of the pain and level of pain which corresponds to a typical daily clinical patient population. These patients were associated with the most common specified medical conditions for pain (i.e. LBLP or NSAP or PSNO) and classified by two, independently working, physicians. Moreover, patients were referred from primary care to secondary and tertiary pain clinics and were assessed for their complaints for the first time at the time of inclusion in this study. This limits the risk of systematic bias and also reflects daily clinical practice. Secondly, we used a standardized assessment form in which the bedside examination and the grading system [32, 33] and the DN4-signs were incorporated. This might, however, have led to an influence on each other which made the physician more sure about the final classification of patients pain and thus made the gold standard stronger. There are also some weaknesses in this study. As said before, we have not used the DN4-symptoms as a interview by a physician but as a questionnaire which has to be filled in by the patient. This might have had an influence on the reliability and validity. In the revised EFNS guidelines on neuropathic pain assessment [42] it is suggested that "The seven sensory descriptors can be used as a self-report questionnaire with similar results". Moreover, above the official Dutch version [20, 25] of the DN4 is written in Dutch: "To be completed by the patient". In the paper by van Seventer et al the agreement between the patient administered and a nurse administered was good till very good for the first seven items [25]. It would be of interest to see if there are differences in the outcome when the DN4 is filled in by the patient himself or as an interview by the pain physician. Questions by the patient to the nurse of via telephone to the researcher regarding the DN4 were very rare. However, we didn't keep track of the questions. Another limitation is the fact that we only tested the test-retest reliability regarding the DN4-symptoms and not the DN4-signs to prevent the patient to come back to the hospital only for these test-items. Another weakness is the gold standard which is, for now, the best measure for the existence of a neuropathic pain component but the result is still open for discussion.

Suggestions for the validation of neuropathic pain screening tools

Validation of screening tools should be performed in a standardized manner and described in detail, but performed in a setting which is comparable to a daily clinical practice. A research setting might be different from a clinical setting and thus might have influence on the patient and on the study results. The group of patients as well as the physicians under study should be comparable to the patients/physicians for who the tool is intended. Pre-stratification on the target outcome must be avoided (especially the exclusion of the so called mixed pain), because this will lead to a non-clinical situation and thus decreases the validity and generalizability of the instrument [16, 71].

CONCLUSION

The validity of DN4-signs is equal to the DN4 outcome and, importantly, both are more valid than the DN4-symptoms alone. It seems that the patients' symptoms and signs doesn't reliably reflect the underlying mechanisms, indicating there is a need for a more objective way to assess patients' pain to facilitate improvement in the treatment of patients with pain. The physicians' assessment cannot be replaced by a screening tool as the DN4, but gives the physician a little hint towards the (non-) existence of neuropathic pain component.

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SUPPLEMENTARY MATERIAL

Supplement Table S1: Loading factors of the three versions of the DN4 according to the rotated component matrix factor analysis

DN4	Component (Physicians A)				Component (Physicians B)		
	1	2	3	4	1	2	3
Burning	0.251	0.279	**0.292**	0.149		**0.542**	
Painful cold		**0.616**				**0.497**	
Electric shocks			**0.719**			0.287	**0.649**
Tingling		**0.676**				**0.425**	0.418
Pins and needles		0.353	**0.445**	0.271		**0.636**	
Numbness			**0.709**	---	0.262	**0.602**	
Itching				**0.857**		**0.484**	
Hypoesthesia to touch	**0.872**				**0.905**		
Hypoesthesia to prick	0.375	**0.630**			0.297		**0.579**
Brushing	**0.896**				**0.907**		
Cronbach's alpha	*0.809*	*0.370*	*0.509*		*0.836*	*0.482*	*0.236*

Loading factors < 0.25 are omitted to improve readability

DN4-symptoms	Component	
	1	2
Burning	**0.439**	
Painful cold	**0.515**	
Electric shocks		**0.715**
Tingling		**0.654**
Pins and needles	**0.529**	0.347
Numbness	**0.625**	
Itching	**0.684**	
Cronbach's alpha	*0.476*	*0.368*

Loading factors < 0.25 are omitted to improve readability

DN4-signs	Component (Physicians A)	Component (Physicians B)
	1	1
Hypoesthesia to touch	**0.881**	**0.912**
Hyopoesthesia to prick	**0.515**	**0.405**
Brushing	**0.880**	**0.895**
Cronbach's alpha	*0.675*	*0.663*

DN4-examination via component matrix; One component extracted, the solution couldn't be rotated.

Supplement Table S2: **The area under the curve and the sensitivity / specificity at the optimal cut-off point of the DN4 under the condition of equal costs of misclassification to classify a neuropathic pain component by the classification and the grading system of the physicians.**

	Present NePC	Absent NePC	AUC	Std. Error	Asymp. Sig.	95%CI	YI	Cut-off	T+	F+	F-	T-	Sens %	Spec %	+PV %	-PV %	+LR	-LR	P[Z+]	P[Z-]	FPR %	FNR %
Classification																						
A vs DN4-7	**206**	**82**	**0.693**	**0.035**	**0.000**	**0.625-0.761**	**0.338**	3	**140**	**28**	**66**	**54**	**68**	**66**	**83**	**45**	**1.99**	**0.49**	**72**	**28**	**34**	**32**
LBLP (n)	94	37	0.689	0.050	0.001	0.591-0.788	0.298	3	61	13	33	24	65	65	82	42	1.85	0.54	72	28	35	35
NSAP (n)	28	23	0.658	0.081	0.054	0.499-0.818	0.366	3	20	8	8	15	71	65	71	65	2.05	0.44	55	45	35	29
PSNO (n)	84	22	0.726	0.060	0.001	0.608-0.843	0.384	3	59	7	25	15	70	68	89	38	2.21	0.44	79	21	32	30
Classification																						
B vs DN4-7	**193**	**95**	**0.645**	**0.034**	**0.000**	**0.578-0.711**	**0.245**	**4**	**90**	**21**	**103**	**74**	**47**	**78**	**81**	**42**	**2.11**	**0.69**	**67**	**33**	**22**	**53**
LBLP (n)	83	48	0.684	0.047	0.000	0.592-0.777	0.348	4	41	7	42	41	49	85	85	49	3.39	0.59	63	37	15	51
NSAP (n)	28	23	0.586	0.081	0.293	0.427-0.746	0.208	3	18	10	10	13	64	57	64	57	1.48	0.63	55	45	43	36
PSNO (n)	82	24	0.611	0.065	0.098	0.484-0.739	0.159	3	54	12	28	12	66	50	82	30	1.32	0.68	77	23	50	34
Classification																						
A=B vs DN4-7	**168**	**57**	**0.713**	**0.040**	**0.000**	**0.634-0.791**	**0.369**	**3**	**118**	**19**	**50**	**38**	**70**	**67**	**86**	**43**	**2.11**	**0.45**	**75**	**25**	**33**	**30**
LBLP (n)	74	28	0.716	0.056	0.001	0.606-0.826	0.348	3	53	11	21	17	72	61	83	45	1.82	0.47	73	27	39	28
								4	39	5	35	23	53	82	89	40	2.95	0.58	73	27	18	47
NSAP (n)	23	18	0.661	0.090	0.081	0.484-0.837	0.374	3	15	5	8	13	65	72	75	62	2.35	0.48	56	44	28	35
PSNO (n)	71	11	0.764	0.078	0.005	0.611-0.918	0.431	3	50	3	21	8	70	73	94	28	2.58	0.41	87	13	27	30
Classification																						
A vs DN4-10A	**203**	**72**	**0.766**	**0.030**	**0.000**	**0.717-0.836**	**0.394**	**4**	**142**	**22**	**61**	**50**	**70**	**69**	**87**	**45**	**2.29**	**0.43**	**74**	**26**	**31**	**30**
LBLP (n)	91	35	0.775	0.042	0.000	0.692-0.859	0.448	4	59	7	32	28	65	80	89	47	3.24	0.44	72	28	20	35
NSAP (n)	28	15	0.726	0.088	0.015	0.554-0.898	0.395	2	26	8	2	7	93	47	76	78	1.74	0.15	65	35	53	7
PSNO (n)	84	22	0.777	0.052	0.000	0.675-0.879	0.459	5	50	3	34	19	60	86	94	36	4.37	0.47	79	21	14	40
Classification																						
B vs DN4-10B	**184**	**79**	**0.736**	**0.032**	**0.000**	**0.673-0.798**	**0.365**	**4**	**130**	**27**	**54**	**52**	**71**	**66**	**83**	**49**	**2.07**	**0.45**	**70**	**30**	**34**	**29**
LBLP (n)	76	42	0.759	0.043	0.000	0.674-0.844	0.470	4	52	9	24	33	68	79	85	58	3.19	0.40	64	36	21	32
NSAP (n)	26	13	0.664	0.094	0.098	0.481-0.848	0.269	3	19	6	7	7	73	54	76	50	1.58	0.50	67	33	46	27
								4	17	5	9	8	65	62	77	47	1.70	0.56	67	33	38	35
PSNO (n)	82	24	0.683	0.061	0.007	0.563-0.802	0.258	6	28	2	54	22	34	92	93	29	4.10	0.72	77	23	8	66
Classification																						
A=B vs DN4-10A	**166**	**47**	**0.829**	**0.031**	**0.000**	**0.767-0.890**	**0.513**	**4**	**124**	**11**	**42**	**36**	**75**	**77**	**92**	**46**	**3.19**	**0.33**	**78**	**22**	**23**	**25**
LBLP (n)	72	26	0.823	0.043	0.000	0.738-0.908	0.544	4	53	5	19	21	74	81	91	53	3.83	0.33	73	27	19	26
NSAP (n)	23	10	0.763	0.095	0.018	0.576-0.950	0.439	3	17	3	6	7	74	70	85	54	2.46	0.37	70	30	30	26
PSNO (n)	71	11	0.836	0.063	0.000	0.713-0.959	0.543	5	45	1	26	10	63	91	98	28	6.97	0.40	87	13	9	37
Classification																						
A=B vs DN4-10B	**159**	**48**	**0.807**	**0.033**	**0.000**	**0.742-0.872**	**0.498**	**4**	**119**	**12**	**40**	**36**	**75**	**75**	**91**	**47**	**2.99**	**0.34**	**77**	**23**	**25**	**25**
LBLP (n)	67	26	0.821	0.043	0.000	0.736-0.906	0.554	4	50	5	17	21	75	81	91	55	3.88	0.31	72	28	19	25
NSAP (n)	21	11	0.725	0.100	0.039	0.529-0.921	0.442	4	15	3	6	8	71	73	83	57	2.62	0.39	66	34	27	29
PSNO (n)	71	11	0.777	0.068	0.003	0.644-0.910	0.397	4	54	4	17	7	76	64	93	29	2.09	0.38	87	13	36	24

DN4: Douleur neuropathique en 4 questions; Present NEPC: Neuropathic pain component existing; Absent NePC: Neuropathic pain component not existing; AUC: Area under curve; Std.Error: Standard error; Asymp. Sig.: Asymptotic Significance; 95%CI: 95% confidence interval; Sens.: Sensitivity; Spec.: Specificity; +DV: Positive diagnostic value; -DV: Negative diagnostic value; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; P[Z+]: a-priori chance for the existence of a NePC; P[Z-]: a-priori chance for no existence of NePC; FPR: False positive ratio; FNR: False negative ratio; A: Physician A; B: Physician B; LBLP: Low back and leg pain; NSAP: Neck shoulder arm pain; PSNO: Pain of suspected neuropathic origin

	Present NePC	Absent NePC	AUC	Std. Error	Asymp. Sig.	95%CI	YI	Cut-off	T+	F+	F-	T-	Sens %	Spec %	+PV %	-PV %	+LR	-LR	P[Z+]	P[Z-]	FPR %	FNR %
Grading																						
A vs DN4-7	**171**	**112**	**0.608**	**0.034**	**0.002**	**0.541-0.675**	**0.179**	**4**	**78**	**31**	**93**	**81**	**46**	**72**	**72**	**47**	**1.65**	**0.75**	**60**	**40**	**28**	**54**
LBLP (n)	61	69	0.620	0.049	0.019	0.523-0.717	0.215	4	29	18	32	51	48	74	62	61	1.82	0.71	47	53	26	52
NSAP (n)	17	30	0.558	0.087	0.514	0.388-0.728	0.149	2	15	22	2	8	88	27	41	80	1.20	0.44	36	64	73	12
PSNO (n)	93	13	0.690	0.073	0.027	0.547-0.833	0.375	4	42	1	51	12	45	92	98	19	5.87	0.59	88	12	8	55
Grading																						
B vs DN4-7	**158**	**127**	**0.572**	**0.034**	**0.038**	**0.505-0.638**	**0.127**	**3**	**101**	**65**	**57**	**62**	**64**	**49**	**61**	**52**	**1.25**	**0.74**	**55**	**45**	**51**	**36**
LBLP (n)	56	74	0.612	0.050	0.029	0.513-0.711	0.198	4	27	21	29	53	48	72	56	65	1.70	0.72	43	57	28	52
NSAP (n)	19	32	0.484	0.089	0.846	0.309-0.658	0.054	5	4	5	15	27	21	84	44	64	1.35	0.94	37	63	16	79
PSNO (n)	83	21	0.562	0.070	0.380	0.425-0.699	0.115	3	53	11	30	10	64	48	83	25	1.22	0.76	80	20	52	36
Grading	**139**	**91**	**0.610**	**0.038**	**0.005**	**0.537-0.684**	**0.179**	**4**	**63**	**25**	**76**	**66**	**45**	**73**	**72**	**46**	**1.65**	**0.75**	**60**	**40**	**27**	**55**
A=B vs DN4-7	48	60	0.638	0.054	0.014	0.531-0.744	0.250	4	24	15	24	45	50	75	62	65	2.00	0.67	44	56	25	50
LBLP (n)	13	24	0.513	0.102	0.899	0.314-0.712	0.074	3	8	13	5	11	62	46	38	69	1.14	0.84	35	65	54	38
NSAP (n)	78	7	0.730	0.077	0.045	0.580-0.880	0.436	4	34	0	44	7	44	100	100	14		0.56	92	8	0	56
PSNO (n)																						
Grading	**170**	**102**	**0.741**	**0.030**	**0.000**	**0.681-0.800**	**0.357**	**4**	**124**	**38**	**46**	**64**	**73**	**63**	**72**	**58**	**1.96**	**0.43**	**63**	**38**	**37**	**27**
A vs DN4-10A	60	65	0.728	0.045	0.000	0.639-0.817	0.346	4	42	23	18	42	70	65	65	70	1.98	0.46	48	52	35	30
LBLP (n)	17	24	0.643	0.086	0.122	0.475-0.812	0.248	4	12	11	5	13	71	54	52	72	1.54	0.54	41	59	46	29
NSAP (n)	93	13	0.772	0.072	0.002	0.631-0.914	0.445	4	70	4	23	9	75	69	95	28	2.45	0.36	88	12	31	25
PSNO (n)																						
Grading B vs DN4-10 B	**153**	**107**	**0.708**	**0.033**	**0.000**	**0.644-0.772**	**0.321**	**4**	**112**	**44**	**41**	**63**	**73**	**59**	**72**	**61**	**1.78**	**0.46**	**59**	**41**	**41**	**27**
LBLP (n)	52	65	0.723	0.049	0.000	0.628-0.819	0.377	4	38	23	14	42	73	65	62	75	2.07	0.42	44	56	35	27
NSAP (n)	18	21	0.545	0.095	0.632	0.358-0.732	0.190	4	12	10	6	11	67	52	55	65	1.40	0.64	46	54	48	33
PSNO (n)	83	21	0.701	0.071	0.005	0.562-0.840	0.356	3	77	12	6	9	93	43	87	60	1.62	0.17	80	20	57	7
Grading A=B vs DN4-10A																						
LBLP (n)	**138**	**81**	**0.771**	**0.032**	**0.000**	**0.709-0.833**	**0.396**	**4**	**104**	**29**	**34**	**52**	**75**	**64**	**78**	**60**	**2.10**	**0.38**	**63**	**37**	**36**	**25**
NSAP (n)	47	56	0.754	0.049	0.000	0.658-0.850	0.393	6	21	3	26	53	45	95	88	67	8.34	0.58	46	54	5	55
PSNO (n)	13	18	0.641	0.101	0.186	0.444-0.838	0.269	4	10	9	3	9	77	50	53	75	1.54	0.46	42	58	50	23
	78	7	0.877	0.068	0.001	0.745-1.000	0.626	4	60	1	18	6	77	86	98	25	5.38	0.27	92	8	14	23
Grading A=B vs DN4-10B																						
LBLP (n)																						
NSAP (n)	**135**	**75**	**0.744**	**0.036**	**0.000**	**0.673-0.814**	**0.382**	**4**	**102**	**28**	**33**	**47**	**76**	**63**	**78**	**59**	**2.02**	**0.39**	**64**	**36**	**37**	**24**
PSNO (n)	45	53	0.754	0.050	0.000	0.655-0.852	0.413	4	33	17	12	36	73	68	66	75	2.29	0.39	46	54	32	27
	12	15	0.550	0.113	0.661	0.329-0.771	0.217	4	9	8	3	7	75	47	53	70	1.41	0.54	44	56	53	25
	78	7	0.761	0.103	0.023	0.558-0.964	0.507	3	73	3	5	4	94	57	96	44	2.18	0.11	92	8	43	6

DN4: Douleur neuropathique en 4 questions; Present NEPC: Neuropathic pain component existing; Absent NePC: Neuropathic pain component not existing; AUC: Area under curve; Std.Error: Standard error; Asymp. Sig.: Asymptotic Significance; 95%CI: 95% confidence interval; Sens.: Sensitivity; Spec.: Specificity; +DV: Positive diagnostic value; -DV: Negative diagnostic value; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; P[Z+]: a-priori chance for the existence of a NePC; P[Z-]: a-priori chance for no existence of NePC; FPR: False positive ratio; FNR: False negative ratio; A: Physician A; B: Physician B; LBLP: Low back and leg pain; NSAP: Neck shoulder arm pain; PSNO: Pain of suspected neuropathic origin

	Present NePC	Absent NePC	AUC	Std. Error	Asymp. Sig.	95%CI	YI	Cut-off	T+	F+	F-	T-	Sens %	Spec %	+PV %	-PV %	+LR	-LR	P[Z+]	P[Z-]	FPR %	FNR %
Classification A = Grading A																						
Vs DN4-7	**154**	**62**	**0.691**	**0.040**	**0.000**	**0.612-0.770**	**0.311**	**3**	**105**	**23**	**49**	**39**	**68**	**63**	**82**	**44**	**1.84**	**0.51**	**71**	**29**	**37**	**32**
LBLP (n)	59	35	0.698	0.055	0.001	0.590-0.805	0.292	4	29	7	30	28	49	80	81	48	2.46	0.64	63	37	20	51
NSAP (n)	15	18	0.613	0.101	0.270	0.415-0.811	0.278	3	10	7	5	11	67	61	59	69	1.71	0.55	45	55	39	33
PSNO (n)	80	9	0.801	0.063	0.003	0.677-0.924	0.418	2	69	4	11	5	86	56	95	31	1.94	0.25	90	10	44	14
Classification A = Grading A																						
Vs DN4-10A	**153**	**54**	**0.831**	**0.030**	**0.000**	**0.772-0.890**	**0.499**	**4**	**116**	**14**	**37**	**40**	**76**	**74**	**89**	**52**	**2.92**	**0.33**	**74**	**26**	**26**	**24**
LBLP (n)	58	33	0.813	0.044	0.000	0.726-0.900	0.512	4	42	7	16	26	72	79	86	62	3.41	0.35	64	36	21	28
NSAP (n)	15	12	0.725	0.105	0.048	0.519-0.931	0.433	2	14	6	1	6	93	50	70	86	1.87	0.13	56	44	50	7
PSNO (n)	80	9	0.876	0.048	0.000	0.782-0.969	0.600	5	48	0	32	9	60	100	100	22		0.40	90	10	0	40
Classification B = Grading B																						
Vs DN4-7	**139**	**76**	**0.636**	**0.039**	**0.001**	**0.560-0.713**	**0.232**	**4**	**67**	**19**	**72**	**57**	**48**	**75**	**78**	**44**	**1.93**	**0.69**	**65**	**35**	**25**	**52**
LBLP (n)	50	42	0.704	0.054	0.001	0.597-0.811	0.373	4	27	7	23	35	54	83	79	60	3.24	0.55	54	46	17	46
NSAP (n)	16	20	0.559	0.100	0.545	0.364-0.755	0.188	3	11	10	5	10	69	50	52	67	1.38	0.63	44	56	50	31
PSNO (n)	73	14	0.600	0.084	0.239	0.436-0.764	0.158	3	48	7	25	7	66	50	87	22	1.32	0.68	0.84	16	50	34
Classification B = Grading B																						
Vs DN4-10B	**135**	**61**	**0.787**	**0.034**	**0.000**	**0.720-0.854**	**0.441**	**4**	**106**	**21**	**29**	**40**	**79**	**66**	**83**	**58**	**2.28**	**0.33**	**69**	**31**	**34**	**21**
LBLP (n)	47	37	0.838	0.044	0.000	0.751-0.924	0.565	4	38	9	9	28	81	76	81	76	3.32	0.25	56	44	24	19
NSAP (n)	15	10	0.637	0.114	0.255	0.413-0.861	0.300	4	12	5	3	5	80	50	71	63	1.60	0.40	60	40	50	20
PSNO (n)	73	14	0.728	0.084	0.007	0.564-0.893	0.418	3	67	7	6	7	92	50	91	54	1.84	0.16	84	16	50	8
Classification A = Grading A = Classification B = Grading B vs DN4-7	**118**	**42**	**0.670**	**0.048**	**0.001**	**0.576-0.765**	0.286	4	**59**	**9**	**59**	**3**	**50**	**79**	**87**	**36**	**2.33**	**0.64**	**0.74**	**0.26**	**0.21**	**0.50**
LBLP (n)	43	26	0.721	0.063	0.002	0.598-0.844	0.366	4	24	5	19	21	56	81	83	53	2.90	0.55	0.62	0.38	0.19	0.44
NSAP (n)	12	12	0.549	0.123	0.686	0.307-0.791	0.250	3	8	5	4	7	67	58	62	64	1.60	0.57	0.50	0.50	0.42	0.33
PSNO (n)	63	4	0.750	0.095	0.095	0.563-0.937	0.476	4	30	0	33	4	48	100	100	11		0.52	0.94	0.06	0.00	0.52
Classification A = Grading A = Classification B = Grading B vs DN4-10 A	**117**	**34**	**0.859**	**0.033**	**0.000**	**0.795-0.923**	0.551	4	**92**	**8**	**25**	**26**	**79**	**76**	**92**	**51**	**3.34**	**0.28**	**0.77**	**0.23**	**0.24**	**0.21**
LBLP (n)	42	24	0.857	0.045	0.000	0.769-0.946	0.577	4	33	5	9	19	79	79	87	68	3.77	0.27	0.64	0.36	0.21	0.21
NSAP (n)	12	6	0.667	0.143	0.261	0.386-0.947	0.333	3	10	3	2	3	83	50	77	60	1.67	0.33	0.67	0.33	0.50	0.17
PSNO (n)	63	4	0.937	0.043	0.004	0.853-1.000	0.778	4	49	0	14	4	78	100	100	22		0.22	0.94	0.06	0.00	0.22
Classification A = Grading A = Classification B = Grading B vs DN4-10 B	**114**	**34**	**0.822**	**0.040**	**.000**	**0.745-0.900**	0.504	4	**91**	**10**	**23**	**24**	**80**	**71**	**90**	**51**	**2.71**	**0.29**	**0.77**	**0.23**	**0.29**	**0.20**
LBLP (n)	40	24	0.878	0.042	0.000	0.795-0.961	0.617	4	33	5	7	19	83	79	87	73	3.96	0.22	0.63	0.38	0.21	0.18
NSAP (n)	11	6	0.561	0.159	0.688	0.250-0.872	0.318	4	9	3	2	3	82	50	75	60	1.64	0.36	0.65	0.35	0.50	0.18
PSNO (n)	63	4	0.758	0.128	0.085	0.506-1.000	0.500	2	63	2	0	2	100	50	97	100	2.00	0.00	0.94	0.06	0.50	0.00

DN4: Doeleur neuropathique en 4 questions; Present NEPC: Neuropathic pain component existing; Absent NePC: Neuropathic pain component not existing; AUC: Area under curve; Std.Error: Standard error; Asymp. Sig.: Asymptotic Significance; 95%CI: 95% confidence interval; Sens.: Sensitivity; Spec.: Specificity; +DV: Positive diagnostic value; -DV: Negative diagnostic value; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; P[Z+]: a-priori chance for the existence of a NePC; P[Z-]: a-priori chance for no existence of NePC; FPR: False positive ratio; FNR: False negative ratio; A: Physician A; B: Physician B; LBLP: Low back and leg pain; NSAP: Neck shoulder arm pain; PSNO: Pain of suspected neuropathic origin.

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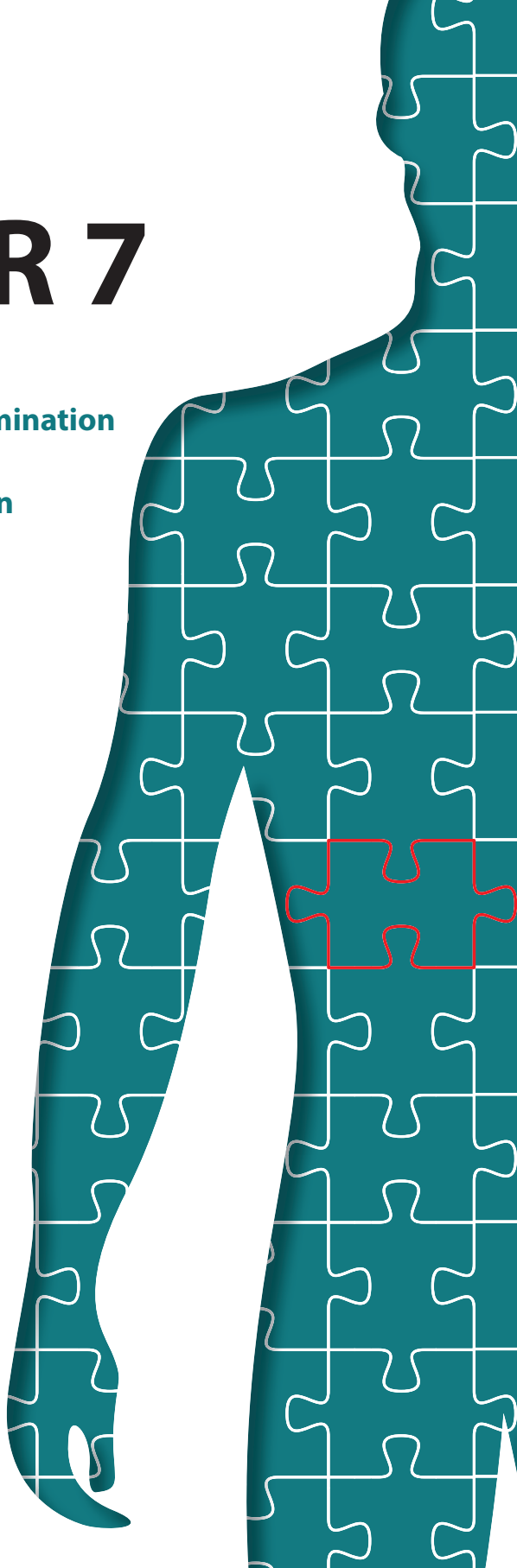
CHAPTER 7

The added value of bedside examination and screening QST to improve neuropathic pain identification in patients with chronic pain



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ABSTRACT

Background

The assessment of a neuropathic pain component (NePC) to establish the neurological criteria required to comply with the clinical description is based on history taking, clinical examination, and quantitative sensory testing (QST) and includes bedside examination (BSE). The objective of this study was to assess the potential association between the clinically diagnosed presence or absence of an NePC, BSE, and the Nijmegen-Aalborg screening QST (NASQ) paradigm in patients with chronic (≥3 months) low back and leg pain or with neck shoulder arm pain or in patients with chronic pain due to suspected peripheral nerve damage.

Methods

A total of 291 patients participated in the study. Pain (absence or presence of neuropathic pain) was assessed independently by two physicians and compared with BSE (measurements of touch [finger, brush], heat, cold, pricking [safety pin, von Frey hair], and vibration). The NASQ paradigm (pressure algometry, electrical pain thresholds, and conditioned pain modulation) was assessed in 58 patients to generate new insights.

Results

BSE revealed a low association of differences between patients with either absent or present NePC: heat, cold, and pricking sensations with a von Frey hair were statistically significantly less common in patients with present NePC. NASQ did not reveal any differences between patients with and without an NePC.

Conclusion

Currently, a standardized BSE appears to be more useful than the NASQ paradigm when distinguishing between patients with and without an NePC.

Keywords

quantitative sensory testing, NASQ, Nijmegen-Aalborg screening QST, clinical assessment, diagnostic accuracy

INTRODUCTION

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as *"pain caused by a lesion or disease of the somatosensory nervous system"*. It is a clinical description rather than a clinical diagnosis which would require *"a demonstrable lesion or disease that satisfies the established neurological diagnostic criteria"* [1]. In the general population, 6%-8% suffer from neuropathic pain [2-4]. Nociceptive pain is defined as *"pain that arises from actual or threatened damage to non-neural tissue and is due to activation of nociceptors"*. This allows us to distinguish between patients with neuropathic pain (classification based on an abnormally functioning somatosensory nervous system) and nociceptive pain (classification based on a normally functioning somatosensory nervous system). Because co-existence of both conditions (mixed pain condition) is frequently observed in daily clinical practice, La Cesa et al. suggest using the presence or absence of a neuropathic pain component (absent or present NePC) [5]. NePC assessment is based on history taking, clinical examination, and (quantitative) sensory testing and includes bedside examination (BSE) [6-8]. Clinical examination alone can never offer proof that a specific pain is of neuropathic origin, but it provides supporting evidence for alterations in the functioning of the nervous system [6]. According to the IASP neuropathic pain special interest group (NeuPSIG), abnormal sensory findings should be neuroanatomically plausible when an NePC is present, and the sensory signs should be associated with the neuroanatomically plausible distribution compatible with an underlying relevant lesion or disease of the somatosensory nervous system [9,10]. As part of a bedside clinical neurological examination, sensory testing can identify negative sensory symptoms such as hypoalgesia or hypoesthesia and/or positive sensory symptoms such as allodynia and hyperalgesia [5]. According to Haanpää et al. [6] BSE can possibly identify where the pathology causing the pain can be found in the central nervous system.

In the last decades, quantitative sensory testing (QST) has complemented traditional neurological BSE tests. QST uses psychophysical tests defined as stimuli with predetermined physical properties based on specific measurement protocols for the analysis of somatosensory aberrations [11-13]. QST measures responses to sensory stimuli and can be used to assess somatosensory system function [11-12], the measurement of the altered peripheral and/or central pain sensitivity [14-16], and descending pain modulation [17,18]. QST is thought to offer greater precision and reliability when assessing somatosensory system functionality than a standard BSE [19,20] because of the use of controlled automated devices. There is evidence that QST improves the diagnostic process of patients with pain, and that it may be valuable when monitoring for a specific anti-neuropathic treatment [21,22]. Moreover, an altered pain modulation can be assessed on the basis of signs and symptoms of peripheral and central sensitization [17,23-25] and by the use of conditioned pain modulation (CPM) [19,26]. CPM is a physiological phenomenon that can be used to assess the quality of the endogenous pain inhibitory pathway, also known as the "pain inhibits pain" phenomena [27]. The Nijmegen-Aalborg screening QST (NASQ) [15,16,24,28] measures pain and central pain

processing under standardized conditions using defined stimuli and experienced intensity ratings. There is no "gold standard" for the diagnosis of NePC, and the association between NePC and BSE/NASQ has not yet been fully evaluated. There is a need for studies to more objectively identify the presence of an NePC and to assess the diagnostic accuracy of BSE and NASQ for NePC [5].
The objective of this study was to assess the potential association between clinically diagnosed absent or present NePC and BSE and NASQ in patients with chronic (≥3 months) low back and leg pain (LBLP) or with neck shoulder arm pain (NSAP) radiating into the leg(s) or arm(s), or in patients with chronic pain due to suspected peripheral nerve damage (sPND).

METHODS

This study is based on a cross-sectional, observational research design to generate new insights into the clinical assessment of NePC. It is a sub-analysis of a study approved by the medical and ethical review board Committee on Research Involving Human Subjects, region Arnhem-Nijmegen, Nijmegen, the Netherlands, dossier number: 2008/348; NL 25343.091.08.

In the original study conducted between October 2009 and June 2013, we validated the Dutch Pain*DETECT* [29] and the DN4 [30,31]. The Pain*DETECT* [32] and the DN4 [33] were both developed to screen for the presence of neuropathic pain. The patient self-administered Pain*DETECT* is a simple screening tool with no need for physical examination. The instrument consists of one item about the pain course pattern, one about radiating pain, and seven questions about the gradation of pain. The clinician-administered DN4 consists of a total of 10 items with yes/no answers. It is divided into two questions (symptoms) and two physical examination tests (signs). The two sign items were incorporated in the sensory examination part of the standardized assessment form [28]. The protocol was registered in the Dutch National Trial Register: NTR 3030 and published by Timmerman et al. [28] Patients provided written informed consent after screening, but before participation in the study.

Participants

We recruited patients as part of the Dutch validation studies concerning the Pain*DETECT* and the DN4. Inclusion criteria were male and female adult patients aged over 18 years with chronic(≥3months) LBLP or NSAP, or patients with chronic pain due to sPND. We excluded patients suspected for or diagnosed with malignancy; compression fractures; patients with diffuse pains such as fibromyalgia or ankylosing spondylitis; severe mental illness; chronic alcoholism or substance abuse; inability to fill in the questionnaire adequately; or incapable of understanding the Dutch language.

Pain classification

Classification of patients' pain was based on the NeuPSIG guidelines on neuropathic pain assessment [6]. Pain classification was performed consecutively but blinded for the outcome on the same patient independently by two physicians working in different compositions, and then categorized into three groups: "absent NePC", "present NePC" where both physicians were in agreement, or "undetermined NePC" in cases where they did not agree. A full medical history and clinical examination including sensory BSE was taken [6,7,21,28,34] and considered as the gold standard for NePC diagnosis.

Bedside examination

Multicenter recruitment took place in the Netherlands in three academic pain centers and in four non-academic pain centers. A standardized BSE [28] was independently performed by two physicians during the validation study for the two neuropathic pain screening tools. Prior to the study, the physicians were trained in the standardized evaluation of patients with chronic pain using specific modalities such as touch, pin prick, pressure, cold, heat, vibration, and temporal summation. The location indicated by the patient as having maximum pain was compared with the mirrored location on the contralateral side. When the pain had a double-sided character, a location without pain but as close as possible to the original mirror site was tested for comparison. Patients were asked the following: 1) is a sensation present? 2) is the sensation unpleasant? Or 3) is the sensation painful? (all scored as yes, no, or unclear) The outcome was noted by the physician on the standardized assessment form [28]. The following tests were performed consecutively on each patient independently by two physicians: 1) mechanical static allodynia via blunt pressure with a finger at a force that normally does not evoke pain; 2) dynamic mechanical allodynia via stroking the skin with a Soft Brush (SENSElabTM, Brush-05, Somedic AB, Hörby, Sweden), 2a) one movement of 1-2 centimeter and 2b) three movements of 1-2 centimeters (wind-up response); 3) mechanical pinprick allodynia via touch of the skin with 3a) a plastic safety pin and 3b) a Von Frey hair (TOUCH TEST®, 5.07, 10.0 g, North Coast Medical Inc., Gilroy, CA, USA); 4) heat allodynia by use of TipTherm® (TipTherm, Brüggen, Germany) in a baby-bottle warmer (ISI mini Baby Bottle Warmer, Assen, the Netherlands) set at 45 degrees Celsius; 5) cold allodynia with an ice cube placed on the skin for 2 seconds; and 6) vibration with a tuning fork (128 Hz; Medipharchem, Wormerveer, the Netherlands) applied to joint, bone, or soft tissue in the region of the pain.

Nijmegen-Aalborg screening QST

Patients for the additional NASQ part of the study were recruited in one academic pain center and two non-academic pain centers. After screening in the clinical department, patients were asked to participate. The NASQ was performed in a random sub-sample of 20% of the patient population (LBLP, NSAP, and sPND) by a trained and experienced researcher (HT) [28]. The NASQ paradigm [15,16,24,28] was used as screening protocol. The NASQ screens for changes in pain processing based on a systematic mechanism-oriented approach [16]. It maps pain sensitivity at multiple sites by measuring the responses (ie, painful sensations) evoked by mechanical and electrical non-

invasive stimuli, and measures the patient's capacity to modulate pain using the CPM. Instructions were standardized and read to each patient from an instruction sheet.

Pressure pain threshold (PPT) test

A pressure algometer (Somedic AB) was used to measure PPTs bilaterally at each location, expressed in kilo Pascal: thenar (middle part), musculus trapezius pars median (middle part), musculus rectus femoris (15 cm above patella), and musculus abductor hallucis (middle part). In addition to the analysis with an average value over these eight measurement points, we performed additional analyses in the four central measurement points: musculus trapezius pars median (both sides) and musculus rectus femoral (both sides), and the four peripheral measurement points: thenar (both sides) and m. abductor hallucis (both sides).

Electrical pain thresholds

The QST-3 device (JNI Biomedical ApS, Klarup, Denmark) was used to measure electrical pain thresholds (EPTs) on the left and right body side. Measurement locations were the musculus trapezius pars median (middle part) and the musculus rectus femoris (20 cm above patella). Thresholds were assessed and expressed in milli-Ampère. EPTs were measured as electrical pain detection threshold (EPDT) when the current started to feel pain, and as electrical pain tolerance threshold (EPTT) when the current was as high as the patient could tolerate.

CPM response

We assessed CPM [17,27] via the PPT (CPMp) and the EPT (CPMe) on the m. rectus femoris contralateral to the dominant hand. The noxious stimulus (conditioning stimulation) was to immerse the dominant hand to the wrist in a bucket filled with water and ice cubes (ice water bucket [IWB] test) [25]. The patient was instructed to "keep the hand in the water for as long as possible, until the moment that the sensation becomes unbearable and you want to stop directly". Pain was recorded every 10 seconds on the numeric rating scale. The duration of the immersion (with a maximum of 180 seconds) was recorded and the pain intensity at the end of the immersion was also registered. The PPT and the EPT were then assessed again on the contralateral m. rectus femoris. The response was calculated by subtracting the outcome of the pre-measurement from the outcome of the post-measurement. The CPM values were calculated using the following formulas:

$$CPMp=([PPT_{post} - PPT_{pre}]/PPT_{pre}) * 100$$
$$CPMe=([EPT_{post} - EPT_{pre}]/EPT_{pre}) * 100$$

CPM was regarded as "positive" when the outcome of the calculation was equal or higher than zero and negative when it was below zero.

Data

All data were collected on paper from the patients and the physicians and stored at Radboudumc, Nijmegen, the Netherlands. Data management and monitoring were performed using MACRO (MACRO, version 4.1.1.3720, InferMed, London, UK). Data analysis and statistics were performed using Statistical Package for the Social Sciences (SPSS version 20.0, SPSS Inc., Chicago, IL, USA).

Statistical methods

Qualitative variables are presented as frequencies and percentages. Quantitative variables are presented as mean and SD or as median and interquartile range. The chi-square test was used to test for significant differences between nominal outcome data. Cramér's *V* was used as a measure of association between two nominal variables, giving a value between 0 and 1. Mann-Whitney *U*-test was used to test the differences between present and absent NePC. Kruskal-Wallis test was used to study differences between the three (absent NePC, present NePC, and undetermined) groups. We used Cohen's Kappa and the percentage of pair wise agreement to determine the agreement between the BSE between the patient's first and second assessment. A two-tailed *p*-value below 0.05 was considered statistically significant.

RESULTS

In total, 330 patients with chronic LBLP, NSAP, or sPND were assessed for eligibility. Two patients did not provide informed consent prior to inclusion in the study. Thirty-seven patients were excluded because of not meeting the inclusion and exclusion criteria (n=13); not returning the baseline questionnaires (n=16), and missing pain classification by one physician (n=5) or both physicians (n=3).

BSE was performed in this study in 291 patients by 62 different physicians from seven hospitals. The present NePC group (n=170) consisted of 75 patients with LBLP, 23 patients with NSAP, and 72 patients with sPND. The absent NePC group (n=58) consisted of 28 patients with LBLP,18 patients with NSAP, and 12 patients with sPND. For the undetermined group (n=63), the numbers were 29, 10, and 24, respectively (see Figure 1 and Table 1).

The NASQ was performed in a total of 69 patients. Patients were excluded after the NASQ measurements were made: not fulfilling the inclusion and exclusion criteria (n=9) or a missing assessment by a second physician (n=2). Finally, a total of 58 patients (56 Dutch natives, 1 German native, and 1 of Chinese/Indonesian origin) were included in the analysis: 25 with LBLP, 25 with NSAP, and 8 with sPND. After NePC assessment by the physicians, 16 patients were classified as absent NePC, 29 with present NePC, and 13 patients with an undetermined outcome. The absent NePC group, present NePC group, and undetermined group had 4, 14, and 7 patients with LBLP; 12, 7, and 5 patients with NSAP; and 0, 7, and 1 patient(s) with sPND, respectively (see Figure 1 and Table 1).

Table 1: **Socio-demographic characteristics for the patients included in the BSE and the NASQ examination related to the physicians' agreement for theexistence of a NePC**

		Total Group	Absent NePC	Present NePC	P-value	Undetermined NePC	P-value
Bed-side examination		**n (%) Median (IQR) (N=291)**	**n (%) Median (IQR) (N=58)**	**n (%) Median (IQR) (N=170)**	**(N=228)**	**n (%) Median (IQR) (N=63)**	**(N=291)**
Sex	*Male*	98 (34%)	25 (43%)	56 (33%)	*0.163*[a]	17 (27%)	*0.164*[a]
	Female	193(66%)	33 (57%)	114 (67%)		46 (73%)	
Age (years)		57 (49;64)	57 (50;62)	57 (49;64)	*0.935*[b]	57 (49;67)	0.831[c]
BMI (kg/m^2)		26 (24;30)	26 (23;30)	26 (24;30)	*0.943*[b]	27 (24;30)	0.688[c]
Pain	*Current pain*	5 (3;7)	5 (3;7)	6 (3;7)	*0.577*[b]	4 (1;7)	*0.084*[c]
(NRS; 0-10)	*Worst pain*	8 (6;9)	8 (5;9)	8 (7;9)	*0.371*[b]	7 (5;8)	*0.053*[c]
	Average pain	6 (4;7)	6 (3.5;7)	6 (5;8)	*0.233*[b]	6 (3;7)	***0.018***[c]
Duration of Pain (months)		36 (18;60)	48 (18;60)	31 (18;60)	*0.445*[b]	36 (14;60)	0.733[b]
Quantitative sensory testing		**n (%) Median (IQR) (N=58)**	**n (%) Median (IQR) (N=16)**	**n (%) Median (IQR) (N=29)**	**(N=45)**	**n (%) Median (IQR) (N=13)**	**(N=58)**
Sex	*Male*	(53%)	9 (56%)	15 (52%)	*0.771*[a]	7 (54%)	*0.958*[a]
	Female	27 (47%)	7 (44%)	14 (48%)		6 (46%)	
Age (years)		58 (52;64)	59 (52;63)	58 (52;64)	*0.669*[b]	56 (52;65)	*0.906*[c]
BMI (kg/m^2)		27 (25;31)	26 (23;30)	27 (25;31)	*0.674*[b]	28 (25;32)	*0.908*[c]
Pain	*Current pain*	6 (5;7)	6 (5;7)	6 (5;7)	*0.887*[b]	5 (2;8)	*0.613*[c]
(NRS; 0-10)	*Worst pain*	8 (7;9)	8 (8;9)	8 (7;9)	*0.740*[b]	8 (8;9)	*0.706*[c]
	Average pain	7 (6;7)	7 (6;7)	7 (6;8)	*0.424*[b]	7 (5;8)	*0.567*[c]
Duration of Pain (months)		36 (18;78)	52 (30;227)	26 (18;81)	*0.069*[b]	24 (12;57)	*0.104*[c]

Notes: Classification for the existence of NePC is based on physicians' assessment of the patients. Absent NePC, no NePC is present; Present NePC, NePC is present; p-value, value for significant difference between groups (p≤0.05); N, total number of patients in analysis; a, Chi-square test; b, Mann-Whitney U-test; c, Kruskal-Wallis test. Bold values are statistically significant (p≤0.05).

Abbreviations: BSE, bedside examination; NASQ, Nijmegen–Aalborg screening quantitative sensory testing; NePC, neuropathic pain component; BMI, body mass index; NRS, numeric rating scale; median (IQR), median with interquartile range (25%–75%).

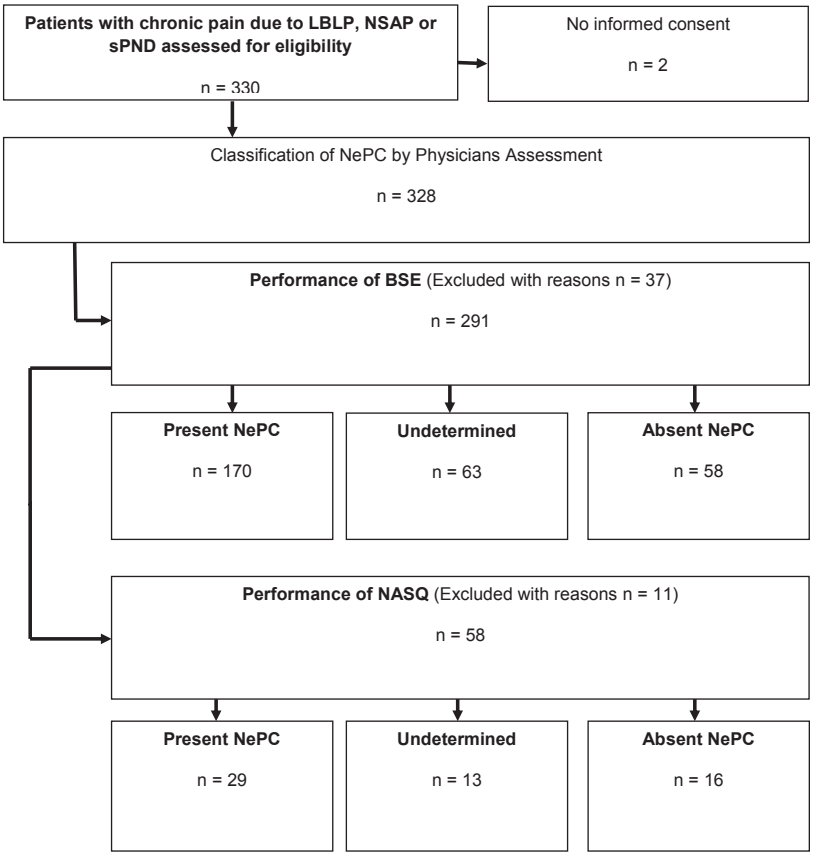

Figure 1: Flow diagram for the performance of the BSE and NASQ in patients with chronic pain with respect to the physicians' assessment.

Notes: n, number of patients in analysis; Present NePC, NePC is present; Undetermined, both physicians disagree with each other about the presence of a NePC; absent NePC, no NePC is present. **Abbreviations:** LBLP, low back and leg pain; NSAP, neck shoulder arm pain; sPND, suspected peripheral nerve damage; BSE, bedside examination; NePC, neuropathic pain component; NASQ, Nijmegen- Aalborg screening quantitative sensory testing.

In Tables 2 and S1, we have shown the outcome of the BSE based on the inter-physician agreement on the existence of an NePC. In the first assessment by the physician, the answers on the question "is there a sensation (yes, no, unclear) during testing for heat, cold, touch (brush 3 times), and pricking (both safety pin and von Frey hair)" were significantly lower ($p \leq 0.05$) for yes in the group with present NePC compared to the absent NePC group. In the second assessment, the scores for the question "is there a sensation (yes, no, unclear) of heat, cold, touch, (only brush 1 time), and

Table 2: **Bedside examination outcome based on inter-physician (A-B) agreement on the presence of a NePC**

	First assessment							Second assessment							Agreement between physicians	
		Absent NePC		*Present NePC*					*Absent NePC*		*Present NePC*					
	N total	**n**	**%**	**n**	**%**	***P-value***	***V***	**N total**	**n**	**%**	**n**	**%**	***P-value***	***V***	**K**	**PA (%)**
Touch (finger)																
sensation	290	58	95	169	95	*0.964*	*0.003*	289	58	97	168	96	*0.965*	*0.003*	*0.177*	*93.3*
unpleasant	288	57	35	168	45	*0.181*	*0.089*	289	58	33	168	48	*0.049*	*0.131*	*0.378*	*69.5*
painful	286	57	28	167	37	*0.215*	*0.083*	288	57	25	168	41	***0.026***	*0.149*	*0.315*	*68.8*
Heat																
sensation	283	57	91	166	68	***0.001***	*0.230*	287	57	91	167	66	***0.000***	*0.247*	*0.435*	*77.6*
unpleasant	283	57	16	166	16	*0.707*	*0.056*	287	57	16	167	21	*0.396*	*0.057*	*0.319*	*79.9*
painful	283	57	7	166	9	*0.626*	*0.065*	287	57	12	167	14	*0.775*	*0.019*	*0.258*	*90.0*
Cold																
sensation	275	55	93	165	75	***0.016***	*0.194*	284	58	93	168	75	***0.003***	*0.196*	*0.320*	*77.6*
unpleasant	274	55	2	164	12	*0.052*	*0.164*	284	58	7	168	11	*0.338*	*0.064*	*0.333*	*87.6*
painful	273	54	0	164	5	*0.178*	*0.126*	284	58	2	168	6	*0.197*	*0.086*	*0.477*	*95.4*
Touch (brush1 time)																
sensation	288	58	93	167	81	*0.104*	*0.142*	286	57	93	167	79	***0.017***	*0.160*	*0.264*	*79.6*
unpleasant	288	58	2	167	7	*0.156*	*0.095*	287	57	2	168	7	*0.132*	*0.100*	*0.384*	*93.7*
painful	288	58	0	167	2	*0.234*	*0.079*	287	57	0	168	4	*0.148*	*0.096*	*0.387*	*97.3*
Touch (brush 3 times)																
sensation	290	58	97	169	85	***0.021***	*0.153*	289	58	91	169	80	*0.055*	*0.127*	*0.303*	*82.7*
unpleasant	291	58	2	170	7	*0.130*	*0.100*	290	58	0	169	12	***0.006***	*0.182*	*0.197*	*89.4*
painful	291	58	0	170	2	*0.308*	*0.067*	290	58	0	169	5	*0.092*	*0.112*	*0.351*	*96.9*
wind-up	284	56	0	167	8	*0.056*	*0.161*	276	50	0	164	12	***0.029***	*0.182*	*0.188*	*87.1*
Pricking (safety pin)																
sensation	289	58	95	168	79	***0.006***	*0.183*	290	58	91	169	82	*0.080*	*0.116*	*0.240*	*79.6*
unpleasant	290	58	19	169	31	*0.180*	*0.123*	290	58	24	169	31	*0.298*	*0.069*	*0.357*	*73.4*
painful	290	58	10	169	20	*0.227*	*0.114*	290	58	16	169	21	*0.388*	*0.057*	*0.286*	*78.3*

Pricking (von Frey hair)															
sensation	289	58	91	168	68	***0.003***	*0.230*	288	57	91	169	68	***0.001***	*0.229*	*0.455*	*79.0*
unpleasant	289	58	7	168	14	*0.228*	*0.114*	288	58	16	167	20	*0.475*	*0.048*	*0.329*	*81.6*
painful	289	58	3	168	7	*0.473*	*0.081*	288	58	12	167	10	*0.590*	*0.036*	*0.402*	*90.6*
Vibration															
sensation	291	58	79	170	69	*0.060*	*0.157*	288	58	81	167	66	*0.089*	*0.147*	*0.358*	*73.3*
unpleasant	290	57	5	170	10	*0.528*	*0.075*	290	58	5	169	11	*0.275*	*0.107*	*0.225*	*85.4*
painful	291	58	3	170	8	*0.517*	*0.076*	290	58	0	169	7	*0.114*	*0.138*	*0.435*	*93.0*

Notes: Classification of the presence of NePC is based on physicians' assessment of the patient. N, the number of patients; %, the percentage of positive answers (yes) on the questions: Sensation: Is there a sensation?; Unpleasant: Is the sensation unpleasant?; Painful: Is the sensation painful?; p-value=p-value for statistical significant difference between groups (outcome of chi-square test, $p \leq 0.05$). Bold values are statistically significant ($p \leq 0.05$).

Abbreviation: NePC, neuropathic pain component; V, value of Cramér's V; K, Kappa value; PA, percentage of agreement

Table 3: **Patient NASQ values related to physicians' agreement for the presence of a NePC**

		Total Group		Congruent outcome by the physicians		Absent NePC		Present NePC		P-value
		N		N		N		N		
Pressure (kPa)	Summed total	39	872(516;1117)	30	858 (506;1125)	5	846 (729;1086)	25	929 (465;1132)	*0.718*[b]
	Central	56	866 (542;1068)	43	872 (545;1058)	15	892 (600;989)	28	793(435;1068)	*0.558*[b]
	Peripheral	39	794 (526;1084)	30	793 (516;1095)	5	800 (701;1066)	25	787 (488;1106)	*0.676*[b]
CPM	Positive	23	58%	19	61%	3	60%	16	62%	*0.948*[a]
	Negative	17	43%	12	39%	2	40%	10	39%	
	No change Response	40	131 (-13;225)	31	109 (3;221)	5	13 (-31;176)	26	155 (24;222)	*0.259*[b]
	CPM-value	40	7.2 (-14;25)	31	7 (-18;23)	5	3 (-19;16)	26	7.7 (-16;34)	*0.591*[b]
EPDT (mA)	Total mean	53	11 (7;17)	42	12 (8;17)	16	11 (6;20)	26	12 (8;17)	*0.969*[b]
CPM	Positive	13	81%	10	40%	8	80%	2	100%	*0.488*[a]
	Negative	3	19%	2	8%	2	20%	0		
	No change			13	52%				3 (0.4;---)[c]	
	Response	16	0.8 (0.03;4)	12	2 (0,2;5)	10	2 (-0.05;4.0)	2	26 (18;--)[c]	*0.747*[b]
	CPM-value	16	7.7 (0.3;30)	12	20 (3;34)	10	15 (-0.2;37)	2		*0.667*[b]
EPTT (mA)	Total mean	25	10 (8;22)	19	13 (8;23)	3	13 (10;--)[c]	16	12 (8;22)	*0.314*[b]
CPM	Positive	17	68%	13	68%	3	100%	10	63%	*0.200*[a]
	Negative	8	32%	6	32%	0	---[c]	6	38%	
	No change Response	25	0.5 (-0.2;2)	19	0.5(-0,2;2)	3	2 (1;---)[c]	16	0.4 (-0.3;2)	*0.117*[b]
	CPM-value	25	7 (-2;16)	19	7 (-2;17)	3	12 (9;--)[c]	16	4.8 (-3;16)	*0.219*[b]
IWB-test	Latency (s)	41	20 (10;170)	32	40 (10-180)	5	40 (10;170)	27	40 (10;180)	*0.960*[b]

Notes: Classification of presence of NePC is based on physicians' assessment of the patients. Absent, NePC is absent; Present, NePC is present; Undetermined, both physicians disagree with each other about the existence of an NePC; N, number of patients in the analysis; CPM > ± 10%: patients included in the analysis with a CPM of more than 10% difference from zero. a, Chi-square test; b, Mann-Whitney U- test. P≤0.05 is considered statistically significant; c, due to the low number of patients in the analysis, IQR is not given in the 75% range.

Abbreviations: NASQ, Nijmegen–Aalborg screening quantitative sensory testing; NePC, neuropathic pain component; CPM, conditioned pain modulation; EPDT, electrical pain detection threshold; EPTT, electrical pain tolerance threshold; IWB, ice water bucket; IQR, interquartile range.

pricking (von Frey hair only)" were significantly lower (p=0.05) for yes in the group with present NePC with a lower percentage of "yes" compared to the absent NePC. The scores for the questions "is the touch with a finger unpleasant?" and "is touch with a brush unpleasant?" were higher for the second assessment for the group with present NePC (p=0.049 and p=0.006, respectively). "Painful for touch with a finger" was more common in patients with present NePC (p=0.026) in the second assessment. "Wind-up" was more common in patients with present NePC compared to the patients with absent NePC (first assessment p=0.056; second assessment p=0.029). In Table S1, we have shown the outcome of the BSE based on the inter-physician agreement for the occurrence of NePC for patients with LBLP, NSAP, and sPND.

The outcomes of the NASQ measurements related to physician agreement for the existence of NePC are presented in Table 3. No significant difference was detected for pressure, EPDT, EPTT, and duration of submerging the hand in the IWB between the absent, present, and undetermined NePC groups. We found no congruency between the CPMp and the CPMe. When basing the CPM classification on pressure values, the significance disappeared for the outcome of the CPM test based on electricity values (response p=0.440, CPM-value p=0.374). This was also true when the CPM electricity test outcome was used to analyze the response and CPM value for pressure (p=0.728 and p=0.810, respectively). Moreover, in the IWB test, we found no significant differences regarding the duration (latency) of submerging the hand between the positive and negative CPM test for both the pressure and electricity conditions (p=0.120 and p=0.711, respectively).

DISCUSSION

The aim of this study was to assess the potential association between a clinically diagnosed absent or present NePC, BSE, and NASQ in patients with chronic pain. BSE revealed minor differences, with a low association between patients with present NePC and patients with absent NePC following independent clinical NePC assessment by two independent physicians, while none were found with NASQ.

Bedside examination

We used BSE based on mechanical and thermal testing procedures, performed by two physicians independently and blinded for the results of the other [28]. The added value of BSE is that it gives insights into the pathology and the localization of the nerve lesion or disease causing the pain [6,7,35,36].

The BSE results showed statistical significant differences between patients with absent NePC and patients with present NePC. BSE revealed that the sensation of heat, cold, wind-up response (with a brush, three times), pricking with a safety pin, and pricking with a von Frey hair was less common

in patients with a present NePC than in those with an absent NePC. In addition, wind-up response occurred more often in patients with present NePC than in those with absent NePC.

Screening QST

We used the NASQ to assess the altered pain processing, including changes in function of endogenous pain modulation as a secondary test battery [15,28]. The NASQ test protocol has standardized instructions, an important prerequisite to ensure reliability of the measurements [20,37]. We found no differences between patients with absent and present NePC regarding PPTs, electrical pain (tolerance) thresholds, and CPM outcomes (number of positive and negative CPM outcomes, the response, the CPM value, and the latency times when submerging the hand in ice water). Granovsky [38] reported that patients with chronic neuropathic pain express a less efficient (negative) CPM. In our study, we could not confirm this when comparing patients with LBLP, NSAP, or sPND with and without NePC. As suggested by Graven-Nielsen and Arendt-Nielsen [39], lower PPTs may be indicative for central sensitization. We also could not find any differences in the pain thresholds of patients with and without NePC. Moreover, a difference in CPM may also suggest a central dysfunction. However, based on our results, we cannot state that there are signs of central sensitization or altered central pain processing as might be suspected because of lower pain thresholds for pressure pain or an impaired CPM, because we did not include age, sex, and education matched controls, which would be necessary to draw these higher level conclusions.

Limitations

We would have preferred to use the German Research Network on Neuropathic Pain (DFNS) [11,12] to BSE because of the standardization of the complete test procedure (written test instructions, application of the test stimuli, and data analyses) [12,40]. However, due to time constraints in a patient care setting, it was not possible and preferable to use such a research test battery. Moreover, in simulating daily clinical practice, fulfilling the DFNS protocol is not applicable due to instrument availability and the associated costs in all participating sites. BSE as used in our study is easy to learn (one training session before execution of the study) and to carry out in daily clinical practice. Another strength of the study is that we included a range of locations and a large group of patients with chronic pain arising from different origins, which is comparable to patients in a daily clinical (pain) practice. A limitation of the BSE examination is that we only used the question "Is there a sensation?" This may have led to a lower estimation of the outcomes because the patients and/or physicians may have interpreted the question was only being related to the presence of hypoesthesia, hypoalgesia, or analgesia (answer "no": negative signs) rather than assessing the presence of hyperalgesia or allodynia positively (answer "yes"). In a following study, we will change this to a more open question that can be interpreted both ways. We did not use verbal standardized instructions, although all participating professionals were trained in a standardized way and so this is another possible limitation of our BSE method. This may have led to differences in the questioning by the physicians, thereby influencing the patients' answers and the test outcome. The order of the

BSE tests was not randomized and so there may be an order effect resulting from the previously performed test. Moreover, both physicians tested the same patient directly following each other. Although the second physician was not aware of the first results, this may have also influenced our results. Furthermore, there was no correction for multiple testing while several statistical analyses were performed. Because of this, the results must be interpreted with caution.

Another possible limitation is the fact that we only included a small group of patients with chronic pain measured via NASQ; 8 patients with sPND. This may have affected our outcome because they have a different disease origin compared to patients with LBLP or NSAP. For future NASQ research, we would suggest collecting normative data preferably matched for age, sex, and education level. With these data, the value of NASQ for clinical monitoring disease progression and the response of individual patients on treatment can be evaluated.

CONCLUSION

Using a standardized BSE to assess sensory dysfunction indicating the presence or absence of an NePC appears to be preferable compared to the NASQ paradigm in patients with chronic pain. However, further development of both assessments is desirable. The BSE should be adapted to detect sensory differences between absent and present NePC; the NASQ paradigm should be able to measure altered pain processing and endogenous pain modulation in patients with chronic pain due to present or absent NePC. We postulate that this will lead to a greater contribution to the assessment of neuropathic components of patients' pain.

ACKNOWLEDGEMENTS

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DISCLOSURE

This study was performed within DALI for PAIN, a national program that focuses on neuropathic pain care optimalisation. DALI for PAIN is an initiative of Pfizer. This project was supported by an unrestricted grant from Pfizer. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors report no other conflicts of interest in this work.

SUPPLEMENTARY MATERIAL

Table S1: Bedside examination outcome based on inter physician agreement on the presence of an NePC for the total group and for patients with LBLP, NSAP, or sPND separately

		First assessment							Second assessment							Agreement between physicians	
			Absent NePC		Present NePC					Absent NePC		Present NePC					
		N total	n	%	n	%	*P-value*	*V*	N total	n	%	n	%	*P-value*	*V*	*K*	*PA (%)*
Touch (Finger)																	
Sensation	**Total**	290	58	95	169	95	*0.964*	*0.003*	289	58	97	168	96	*0.965*	*0.003*	*0.177*	*93.3*
	LBLP	131	28	100	74	99	*0.536*	*0.061*	132	28	100	75	96	*0.283*	*0.106*	*-0.015*	*96.0*
	NSAP	51	18	89	23	91	*0.796*	*0.040*	50	18	94	22	95	*0.884*	*0.023*	***0.787***	***97.5***
	sPND	108	12	92	72	92	*1.000*	*0.000*	107	12	92	71	97	*0.344*	*0.104*	*-0.053*	*91.3*
unpleasant	**Total**	288	57	35	168	45	*0.181*	*0.089*	289	58	33	168	48	***0.049***	*0.131*	*0.378*	*69.5*
	LBLP	130	27	22	74	30	*0.456*	*0.074*	132	28	25	75	28	*0.761*	*0.030*	*0.242*	*70.3*
	NSAP	51	18	44	23	44	*0.951*	*0.010*	50	18	33	22	45	*0.436*	*0.123*	*0.388*	*70.0*
	sPND	107	12	50	71	62	*0.433*	*0.086*	107	12	50	71	69	*0.198*	*0.141*	*0.318*	*68.3*
painful	**Total**	286	57	28	167	37	*0.215*	*0.083*	288	57	25	168	41	***0.026***	*0.149*	*0.315*	*68.8*
	LBLP	130	27	19	74	22	*0.734*	*0.034*	132	28	18	75	43	*0.425*	*0.079*	*0.202*	*73.3*
	NSAP	51	18	33	23	44	*0.509*	*0.103*	50	18	28	22	41	*0.386*	*0.137*	*0.297*	*67.5*
	sPND	105	12	42	70	51	*0.532*	*0.069*	106	11	36	71	58	*0.185*	*0.146*	*0.275*	*63.8*
Heat																	
sensation	**Total**	283	57	91	166	68	***0.001***	*0.230*	287	57	91	167	66	***0.000***	*0.247*	***0.435***	***77.6***
	LBLP	127	27	96	71	69	***0.004***	*0.288*	131	27	96	75	68	***0.003***	*0.290*	***0.579***	***84.5***
	NSAP	48	18	89	23	74	*0.230*	*0.188*	50	18	100	22	86	*0.103*	*0.258*	*0.286*	*82.5*
	sPND	108	12	83	72	65	*0.215*	*0.135*	106	12	67	70	57	*0.536*	*0.068*	*0.301*	*67.1*
unpleasant	**Total**	283	57	16	166	16	*0.707*	*0.056*	287	57	16	167	21	*0.396*	*0.057*	*0.319*	*79.9*
	LBLP	127	27	22	71	8	*0.153*	*0.196*	131	27	19	75	13	*0.514*	*0.065*	*0.117*	*79.4*
	NSAP	48	18	6	23	9	*0.702*	*0.060*	50	18	6	22	18	*0.230*	*0.190*	*0.231*	*87.5*
	sPND	108	12	17	72	25	*0.742*	*0.084*	106	12	25	70	30	*0.725*	*0.039*	***0.424***	***76.8***
painful	**Total**	283	57	7	166	9	*0.626*	*0.065*	287	57	12	167	14	*0.775*	*0.019*	*0.258*	*90.0*
	LBLP	127	27	7	71	3	*0.494*	*0.120*	131	27	11	75	8	*0.625*	*0.048*	*-0.057*	*87.6*
	NSAP	48	18	6	23	9	*0.702*	*0.060*	50	18	6	22	14	*0.397*	*0.134*	*0.286*	*90.0*
	sPND	108	12	8	72	15	*0.741*	*0.084*	106	12	25	70	20	*0.693*	*0.044*	*0.355*	*80.5*
Cold																	
sensation	**Total**	275	55	93	165	75	***0.016***	*0.194*	284	58	93	168	75	***0.003***	*0.196*	*0.320*	*77.6*
	LBLP	130	28	96	74	80	***0.038***	*0.205*	131	28	96	75	79	***0.031***	*0.213*	***0.458***	***85.3***
	NSAP	43	15	87	22	86	*0.979*	*0.004*	50	18	100	22	95	*0.360*	*0.145*	*0.302*	*89.2*
	sPND	102	12	92	69	65	*0.186*	*0.204*	103	12	75	71	65	*0.489*	*0.076*	*0.148*	*62.5*
unpleasant	**Total**	274	55	2	164	12	*0.052*	*0.164*	284	58	7	168	11	*0.338*	*0.064*	*0.333*	*87.6*

	LBLP	129	28	4	73	10	*0.489*	*0.119*	131	28	7	75	5	*0.727*	*0.034*	*0.357*	*91.1*
	NSAP	43	15	0	22	9	*0.230*	*0.197*	50	18	0	22	18	*0.057*	*0.302*	***0.641***	***94.6***
	sPND	102	12	0	69	16	*0.294*	*0.174*	103	12	17	71	15	*0.918*	*0.011*	*0.217*	*80.0*
painful	**Total**	273	54	0	164	5	*0.178*	*0.126*	284	58	2	168	6	*0.197*	*0.086*	***0.477***	***95.4***
	LBLP	129	28	0	73	0	*0.534*	*0.062*	131	28	4	75	1	*0.464*	*0.072*	*-0.007*	*97.0*
	NSAP	42	14	0	22	5	*0.418*	*0.135*	50	18	0	22	14	*0.103*	*0.258*	***0.478***	***94.4***
	sPND	102	12	0	69	10	*0.462*	*0.138*	103	12	0	71	8	*0.296*	*0.115*	***0.582***	***93.8***
Touch (brush1 time)																	
sensation	**Total**	288	58	93	167	81	*0.104*	*0.142*	286	57	93	167	79	***0.017***	*0.160*	*0.264*	*79.6*
	LBLP	130	28	100	73	90	*0.089*	*0.169*	132	28	100	75	88	*0.055*	*0.189*	*0.187*	*88.1*
	NSAP	51	18	89	23	96	*0.409*	*0.129*	48	17	100	22	86	*0.113*	*0.254*	*0.278*	*89.7*
	sPND	107	12	83	71	68	*0.533*	*0.123*	106	12	67	70	67	*0.974*	*0.004*	*0.178*	*64.2*
unpleasant	**Total**	288	58	2	167	7	*0.156*	*0.095*	287	57	2	168	7	*0.132*	*0.100*	*0.384*	*93.7*
	LBLP	130	28	4	73	6	*0.826*	*0.022*	132	28	0	75	3	*0.383*	*0.086*	*0.385*	*97.0*
	NSAP	51	18	0	23	9	*0.200*	*0.200*	48	17	0	22	18	*0.063*	*0.297*	*0.374*	*62.3*
	sPND	107	12	0	71	10	*0.256*	*0.125*	106	12	8	71	8	*0.989*	*0.001*	*0.375*	*90.2*
painful	**Total**	288	58	0	167	2	*0.234*	*0.079*	287	57	0	168	4	*0.148*	*0.096*	*0.387*	*97.3*
	LBLP	130	28	0	73	1	*0.534*	*0.062*	132	28	0	75	3	*0.383*	*0.086*	*-0.013*	*97.0*
	NSAP	51	18	0	23	0	---	---	48	17	0	22	5	*0.373*	*0.143*	*0.000*	*97.4*
	sPND	107	12	0	71	4	*0.468*	*0.080*	107	12	0	71	4	*0.468*	*0.080*	***0.654***	***97.6***
Touch (brush 3 times)																	
sensation	**Total**	290	58	97	169	85	***0.021***	*0.153*	289	58	91	169	80	***0.055***	*0.127*	*0.303*	*82.7*
	LBLP	132	28	100	75	96	*0.283*	*0.106*	132	28	100	75	93	*0.161*	*0.138*	*0.222*	*94.2*
	NSAP	51	18	89	23	96	*0.409*	*0.129*	50	18	100	22	86	*0.103*	*0.258*	*0.279*	*90.0*
	sPND	107	12	100	71	70	***0.029***	*0.239*	107	12	58	72	65	*0.642*	*0.051*	*0.190*	*65.1*
unpleasant	**Total**	291	58	2	170	7	*0.130*	*0.100*	290	58	0	169	12	***0.006***	*0.182*	*0.197*	*89.4*
	LBLP	132	28	4	75	5	*0.711*	*0.036*	132	28	0	75	8	*0.123*	*0.152*	*0.136*	*91.3*
	NSAP	51	18	0	23	87	*0.200*	*0.200*	50	18	0	22	23	***0.031***	*0.342*	*0.304*	*90.0*
	sPND	108	12	0	72	8	*0.299*	*0.113*	108	12	0	72	13	*0.195*	*0.141*	*0.198*	*86.9*
painful	**Total**	291	58	0	170	2	*0.308*	*0.067*	290	58	0	169	5	*0.092*	*0.112*	*0.351*	*96.9*
	LBLP	132	28	0	75	3	*0.383*	*0.086*	132	20	0	75	4	*0.283*	*0.106*	*0.386*	*97.1*
	NSAP	51	18	0	23	0	---	---	50	18	0	22	5	*0.360*	*0.145*	*0.000*	*97.5*
	sPND	108	12	0	72	1	*0.681*	*0.045*	108	12	0	72	6	*0.403*	*0.091*	*0.388*	*96.4*
wind-up	**Total**	284	56	0	167	8	*0.056*	*0.161*	276	50	0	164	12	***0.029***	*0.182*	*0.188*	*87.1*
	LBLP	131	28	0	75	7	*0.304*	*0.152*	125	26	0	71	7	*0.310*	*0.155*	*0.296*	*91.8*
	NSAP	48	16	0	22	9	*0.215*	*0.201*	44	12	0	22	5	*0.290*	*0.270*	*0.145*	*87.1*
	sPND	105	12	0	70	10	*0.468*	*0.136*	107	12	0	71	15	*0.143*	*0.161*	*0.116*	*81.5*
Pricking (safety pin)																	
sensation	**Total**	289	58	95	168	79	***0.006***	*0.183*	290	58	91	169	82	*0.080*	*0.116*	*0.240*	*79.6*
	LBLP	132	28	100	75	85	***0.032***	*0.211*	132	28	100	75	92	*0.123*	*0.152*	*0.046*	*85.4*
	NSAP	51	18	94	23	91	*0.702*	*0.060*	50	18	100	22	95	*0.360*	*0.145*	***0.481***	***95.0***
	sPND	106	12	25	71	35	*0.489*	*0.079*	108	12	58	72	67	*0.574*	*0.061*	*0.176*	*64.6*

unpleasant	**Total**	290	58	19	169	31	*0.180*	*0.123*	290	58	24	169	31	***0.298***	*0.069*	*0.357*	*73.4*
	LBLP	132	28	21	75	31	*0.519*	*0.113*	132	28	32	75	32	*0.989*	*0.001*	***0.456***	***76.7***
	NSAP	51	18	11	23	17	*0.572*	*0.088*	50	18	11	22	32	*0.119*	*0.247*	*0.106*	*72.5*
	sPND	107	12	25	71	35	*0.489*	*0.076*	108	12	25	72	31	*0.697*	*0.043*	*0.308*	*69.9*
painful	**Total**	290	58	10	169	20	*0.227*	*0.114*	290	58	16	169	21	***0.388***	*0.057*	*0.286*	*78.3*
	LBLP	132	28	14	75	15	*0.826*	*0.061*	132	28	18	75	17	*0.950*	*0.006*	*0.265*	*79.6*
	NSAP	51	18	0	23	13	*0.111*	*0.249*	50	18	11	22	27	*0.204*	*0.201*	*0.082*	*77.5*
	sPND	107	12	17	71	27	*0.457*	*0.082*	108	12	17	72	22	*0.664*	*0.047*	*0.364*	*77.1*
Pricking (von Frey hair)																	
sensation	**Total**	289	58	91	168	68	***0.003***	*0.230*	288	57	91	169	68	***0.001***	*0.229*	***0.455***	***79.0***
	LBLP	132	28	96	75	82	***0.045***	*0.245*	132	28	96	75	75	***0.013***	*0.245*	*0.291*	*77.7*
	NSAP	51	18	94	23	91	*0.702*	*0.060*	50	18	100	22	91	*0.189*	*0.208*	***0.787***	***97.5***
	sPND	106	12	75	70	54	*0.180*	*0.148*	106	11	64	72	54	*0.556*	*0.065*	***0.423***	***71.6***
unpleasant	**Total**	289	58	7	168	14	*0.228*	*0.114*	288	58	16	167	20	*0.475*	*0.048*	*0.329*	*81.6*
	LBLP	132	28	4	75	16	*0.353*	*0.142*	131	28	18	74	14	*0.580*	*0.055*	*0.171*	*81.4*
	NSAP	51	18	0	23	13	*0.111*	*0.249*	50	18	11	22	32	*0.119*	*0.247*	***0.437***	***85.0***
	sPND	106	12	25	70	17	*0.752*	*0.083*	107	12	17	71	23	*0.648*	*0.050*	***0.410***	***80.2***
painful	**Total**	289	58	3	168	7	*0.473*	*0.081*	288	58	12	167	10	*0.590*	*0.036*	***0.402***	***90.6***
	LBLP	132	28	4	75	4	*0.823*	*0.062*	131	28	14	74	8	*0.349*	*0.093*	*0.292*	*90.2*
	NSAP	51	18	0	23	8	*0.111*	*0.249*	50	18	6	22	14	*0.397*	*0.134*	***0.531***	***92.5***
	sPND	106	12	8	70	7	*0.909*	*0.048*	107	12	17	71	10	*0.483*	*0.077*	***0.450***	***90.1***
Vibration																	
sensation	**Total**	291	58	79	170	69	*0.060*	*0.157*	288	58	81	167	66	*0.089*	*0.147*	*0.358*	*73.3*
	LBLP	132	28	71	75	68	*0.218*	*0.172*	131	28	71	74	58	*0.217*	*0.122*	***0.446***	***74.5***
	NSAP	51	18	89	23	78	*0.369*	*0.140*	50	18	94	22	91	*0.673*	*0.067*	*0.136*	*82.5*
	sPND	108	12	83	72	68	*0.284*	*0.117*	107	12	83	71	66	*0.484*	*0.132*	*0.242*	*67.5*
unpleasant	**Total**	290	57	5	170	10	*0.528*	*0.075*	290	58	5	169	11	*0.275*	*0.107*	*0.225*	*85.4*
	LBLP	132	28	4	75	8	*0.571*	*0.105*	132	28	0	75	7	*0.304*	*0.152*	*0.362*	*91.3*
	NSAP	50	17	6	23	9	*0.738*	*0.053*	50	18	6	22	23	*0.130*	*0.239*	*0.133*	*87.2*
	sPND	108	12	8	72	13	*0.838*	*0.065*	108	12	17	72	13	*0.855*	*0.061*	*0.155*	*79.8*
painful	**Total**	291	58	3	170	8	*0.517*	*0.076*	290	58	0	169	7	*0.114*	*0.138*	***0.435***	***93.0***
	LBLP	132	28	4	75	9	*0.720*	*0.080*	132	28	0	75	3	*0.562*	*0.106*	*0.380*	*94.2*
	NSAP	51	18	0	23	13	*0.111*	*0.249*	50	18	0	22	14	*0.103*	*0.258*	***0.640***	***95.0***
	sPND	108	12	8	72	8	*0.919*	*0.045*	108	12	0	72	8	*0.299*	*0.113*	*0.381*	*90.5*

Notes: Classification for the existence of NePC is based on the physicians' assessment of the patient. N, the number of patients; %, the percentage of positive answers (yes) on the questions; Sensation, Is there a sensation?; Unpleasant, Is the sensation unpleasant?; Painful, Is the sensation painful?; p-value, p value for statistical significant difference between groups (outcome of chi-square test, $p \leq 0.05$). Bold values are statistically significant ($p \leq 0.05$).

Abbreviations: NePC, neuropathic pain component; LBLP, low back and leg pain; NSAP, neck shoulder arm pain; sPND, suspected peripheral nerve damage; V, value of Cramér's V; K, Kappa value; PA, percentage of agreement.

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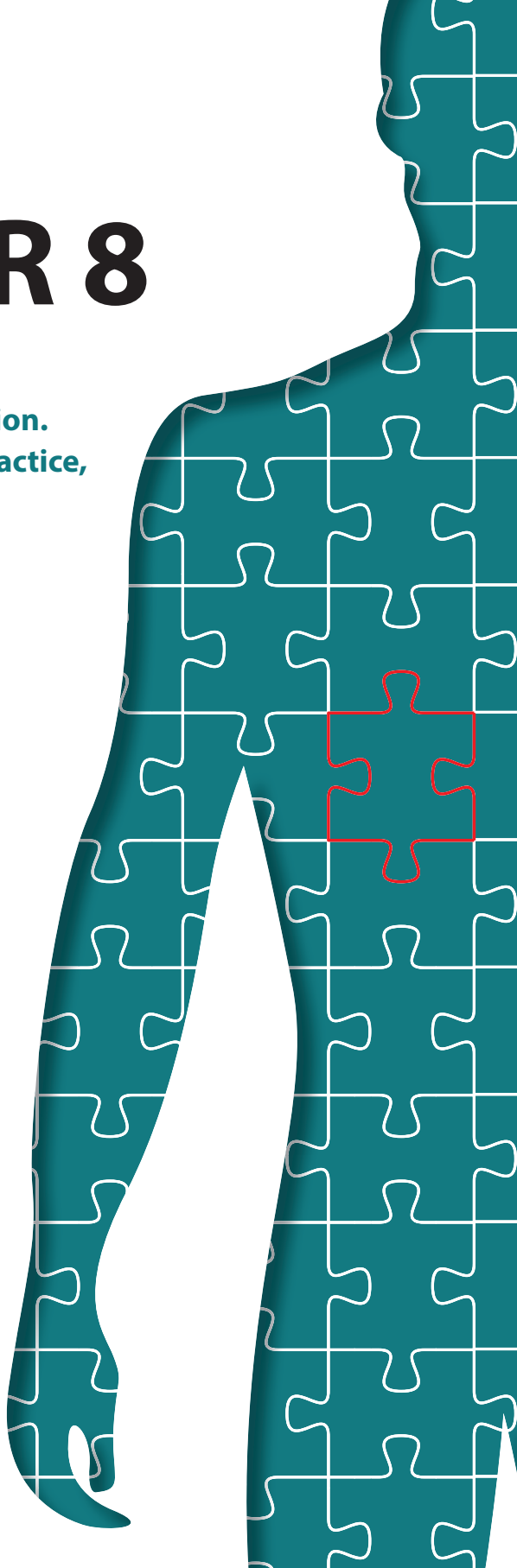
CHAPTER 8

General conclusions and discussion. Recommendations for clinical practice, education, future research, and societal impact



GENERAL CONCLUSIONS AND RECOMMENDATIONS

In this thesis we investigated the psychometric properties and efficacy of screening tools for neuropathic pain for use in a consecutive population of patients with low back and leg pain, neck-shoulder-arm pain, or with pain due to suspected peripheral nerve damage to assist the physician in the assessment of a neuropathic pain component as seen in daily clinical (pain-) practice. We selected this group of patients for our study because they are different from the other groups assessed in previous validation studies. The group consists of a consecutive patient population as seen in daily clinical outpatient practice where there is no pre-stratification on the target outcome, and no minimum level of pain. In our articles, we prefer to use the term 'neuropathic pain component' instead of neuropathic pain because the pain experienced by the patient in daily clinical practice may be caused by neuropathic, nociceptive, and/or nociplastic mechanisms (also known as 'mixed pain'). Neuropathic pain is distinguishable from nociceptive pain in two ways [1]: 1) nociceptive pain requires transduction to transfer a non-electrical signal to an electrochemical signal, whereas neuropathic pain is based on a direct stimulation of the (injured) nerve; 2) most people with nociceptive pain recover in a certain time, whereas patients with neuropathic pain based on an injury of a nerve often retain persistent pain. As Cohen and Mao stated [1], there is a considerable overlap between neuropathic and nociceptive pain regarding patho-physiological mechanisms and response to treatment, so they can possibly be seen as 'different points on the same continuum' [1]. Currently, multiple tests are available to screen for or to assess neuropathic pain, but their verified accuracy is missing and there is no 'gold standard' questionnaire [2] . This can lead to errors in prevalence studies, incorrect and expensive clinical treatment, and, most relevant clinically, increasing disabilities for the patient.

Our studies show that current screening methods and tools for identifying the type of patients' pain are simply not accurate enough for a definite pain classification, and that this presents a number of challenges: (1) the risk of starting inadequate, inappropriate or non-efficacious therapies solely based on these classifications is high; (2) research in the field of treatment for pain is at risk because of the lack of distinction between classification outcomes; (3) exploring nociception or pain as a disease in its own right or as a symptom of a disease, trauma or disorder remains a problem; (4) identifying the type of pain, in particular mixed pain with components of nociceptive pain, neuropathic pain and/or nociplastic pain is difficult. These show that we need valid and reliable assessment tools more directly related to the underlying pain mechanisms. Figure 1 presents a suggested path for developing and validating screening tools in a way more related to daily clinical practice.

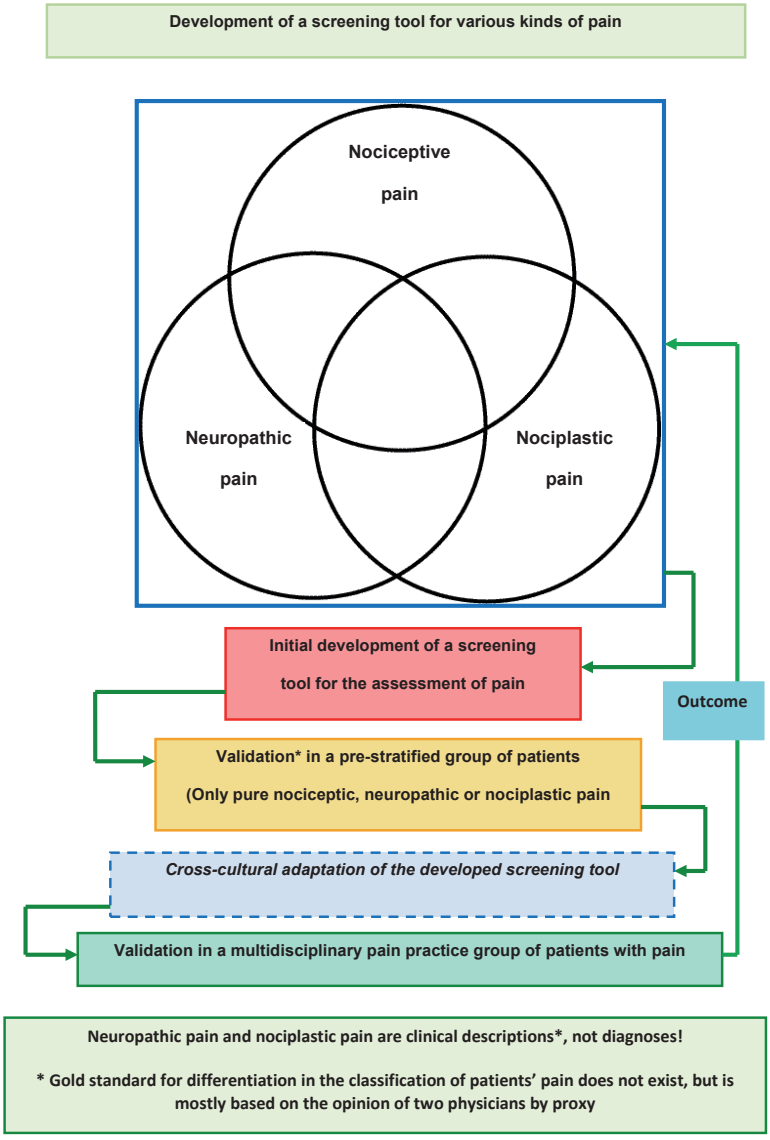


Figure 1: The proposed pathway for the validation process of screening instruments for the classification of patients' pain

Many advances for researching the mechanisms of pain, like molecular and genetic medicine or more advanced physiological research tools (like functional magnetic resonance imaging (fMRI), electro encephalography (EEG) and laser evoked potentials (LEPs)), are currently in their infancy; it will take long time before they become applicable in daily clinical practice. Therefore, as long these diagnostic tools are not generally available to and practical for daily clinical practice, we need more refined screening and/or assessment tools. These should then have greater reliability and validity

than currently available methods, and should be applicable to both primary care and specialist academic pain centers. This will remain challenging as long as there is no true gold standard to diagnose neuropathic pain. Until then, in current medical pain practice, diagnosis is formed on history-taking, and physical assessment. The latter includes bedside examination (as suggested in the NeuPSIG Grading System, [3]) and remains foremost as this is, however slightly, associated with the pain classification 'absent or present NePC'.

The research questions we addressed were:

Question 1: Is a cross-cultural adaptation a prerequisite for achieving a valid Dutch translation of a screening tool for neuropathic pain?

Question 2: What is the reliability of clinical judgment as a surrogate for the lack of an objective gold standard in diagnosing a neuropathic pain component in patients with chronic pain?

Question 3: What are the psychometric properties of the Pain*DETECT* and the DN4 questionnaire when used as screening tools in a daily practice consecutive patient population (patients with low back pain, neck shoulder or arm pain, or pain from a suspected neuropathic origin), not pre-stratified on target outcome, for NePC detection?

Question 4: What is the potential association between clinically diagnosed, via two independent and trained professionals, absent or present NePC, and bedside examination / screening quantitative sensory testing (NASQ) in patients with chronic pain?

Our research program was designed to answer these questions, as discussed in the thesis Introduction, and to provide recommendations for daily clinical practice and future research.

Answer to question 1: A cross-cultural adaptation is a prerequisite for the correct translation and validation of measurement instruments such as screening tools for the assessment of NePC.

Recently, the Pain*DETECT* was used in an American prevalence study [4]. Freynhagen et al [5] translated the original German version into English, however did not provide any information about the translation process. Tampin et al. noted that the English language version of the Pain*DETECT* has not yet been validated[6]. Although the test-retest reliability turned out to be good, the validity of the English language version of the Pain*DETECT* is thus still questionable [6]. The outcome of the American prevalence study was that, in addition to the estimation of the prevalence of neuropathic pain in the USA, the prevalence of probable neuropathic pain among Blacks and Hispanics was consistently higher than among Whites (per age and sex group). This interpretation is, of course, possible, however, the Pain*DETECT* was not cross-culturally adapted and validated for use in the USA and thus the variance may be a result of, for example, a difference in interpretation of the questions in the instrument. It may also be questioned whether the cut-off points of the Pain*DETECT* are valid in patients with various chronic pain conditions and different cultural backgrounds. Moreover, the authors only used the English language version, which may also have influenced the outcome[4].

In our study **(Chapter 2)** which included Dutch-speaking patients from both Belgium and the Netherlands, we found a number of differences based on culture and/or language perception. The Belgian participants rated the clearness of the questions and the organization of the questionnaire almost 10% higher than Dutch participants. This may be attributed to the slight cultural differences in interpretation and use of some words between the Dutch and the Belgians.

Based on these issues, we state that a well-performed, cross-culturally adapted version should be used instead of a 'traditional' forward / forward-backward translation before using an instrument in another culture and/or language. We therefore followed and recommend that other groups follow the published guidelines [7-9] to achieve the highest equivalence with the original tool in language, structure and meaning.

Answer to question 2: The clinical judgment by two physicians is reliable as a replacement for the lack of a gold standard when diagnosing a neuropathic pain component in patients with chronic pain in clinical practice

Although clinical judgment is accepted as a surrogate for an objective gold standard in the assessment of NePC, the reliability of this surrogate outcome is unknown. We therefore conducted a study to find out if the agreement of two observers, based on pain classification by the physicians and by the Grading System as entered by the physician, is acceptable to differentiate between neuropathic and non-neuropathic pain in daily clinical practice. If the kappa-value is ≥ 0.4 and the percentage of agreement is ≥ 70%, the outcome is considered acceptable for use in daily clinical practice [10].

We looked at interobserver reliability of the assessment of neuropathic pain (based on clinical diagnosis via experienced clinical judgment) in patients with pain resulting from cancer of different origins. We found a moderate level of agreement between the physicians for the assessment of the neuropathic pain component (NePC) in patients with cancer **(Chapter 3)**. In patients with low back and leg pain, neck shoulder arm pain, and patients with pain due to suspected peripheral nerve damage, interobserver reliability was also moderate **(Chapters 5 and 6)**. Moreover, we found a moderate agreement between clinical assessment and the Grading System when comparing the evaluation by one clinician to the result of the Grading System on an individual level. A comparison of the outcome of the Grading System by only one of the physicians to the clinical assessment of the other physician resulted in an insufficient level of agreement (table 1).

Table 1: The agreement between the physician assessment and the Grading Systems.

	Assessment physician B	Grading physician A	Grading physician B
Assessment physician A	+	+	-
Assessment physician B		-	+
Grading physician A	-		+
Grading physician B	+	+	

+: Kappa value ≥ 0.4 & Percentage of Agreement ≥ 70%

-: Kappa value < 0.4 & Percentage of Agreement < 70%

In our study on the interobserver reliability of the pain classification in 34 patients with cancer, the agreement of the classification of patients' pain between the physicians was 59% **(Chapter 3)**. In validation studies **(Chapters 5 and 6)** we analyzed 228 of 291 patients (78%) classified with congruent pain by the physicians. In the original Pain*DETECT* [5] and the DN4 [11] validation studies, the agreement of the pain classification by two physicians was 95% and 96% respectively. This difference can be explained by the fact that both original validation studies only included prestratified patients with clear neuropathic or nociceptive pain syndromes, which was not the case in our study. In a systematic review by Mathieson et al. on measurement properties of neuropathic pain screening instruments [12], they reported that many validation studies exclude patients with mixed pain conditions, which may influence their sensitivity and specificity. However, they found no consistent trend resulting in a higher or lower sensitivity and specificity when patients with mixed pain were included when compared to the original validation studies [12]. In addition, they concluded that not including patients with possible mixed pain in validation studies limits the generalizability of the screening instruments when used in daily clinical practice [12].

The gold standard for assessing a neuropathic pain component

As stated in the introduction of this thesis, neuropathic pain is defined as *"Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [13, 14].* In the absence of a 'true diagnostic gold standard' to support a mechanism-based pain classification for nociceptive pain or neuropathic pain, clinical judgement may serve as an appropriate alternative reference standard [15, 16]. Moreover, as stated by Cleeland et al, [17] there is currently no single, adequate diagnostic method to reliably assess neuropathic pain.

The robustness of the gold standard in our study on the interobserver reliability in patients with cancer **(Chapter 3)** was improved by including only those patients with a considered present neuropathic pain component or pure nociceptive pain. In the validation studies **(Chapters 5 and 6)** we ruled out all incongruent outcomes (no agreement of the pain classification after independent assessment). Based on our results regarding agreement between the participating physicians, the question arises whether the chosen gold standard (congruent diagnosis by two, independently working, physicians) is beneficial or not. Because of the different definitions of neuropathic pain and differences in evaluation methods for neuropathic pain, the reliability of the accepted gold standard is open to question. To minimize this problem, we used a standardized assessment form, and all physicians were trained to reach a high level of standardization of assessment execution **(Chapters 5 and 6)**.

The assessment of neuropathic pain component following the Grading System

Further to the clinical diagnosis regarding presence or absence of a neuropathic pain component, we also used the NeuPSIG Grading System as proposed by Treede et al. in 2008 [14] **(Chapters 3, 5 and 6)**. The Grading System is recommended by the Neuropathic Pain Special Interest Group of the IASP [12, 18, 19]. In patients with neck/upper limb pain, the Grading System proved to be applicable, however it requires time and expertise to conduct this Grading System [20]. Based on this Grading System, we found a 68% agreement between the physicians in patients with cancer **(Chapter 3)**. In our validation studies, the congruent outcome based on the Grading System between two physicians was 80% **(Chapters 5 and 6)**. The classification of patients with pain or without NePC based on the Grading System in our studies was comparable to the outcome of the physicians' assessment as shown in table 1. Konopka et al. [21] showed that there was an incongruence between clinical diagnosis of neuropathic pain and the outcome in the Grading System in patients who were previously clinically diagnosed as suffering from neuropathic pain. Only 60% were graded with probable or definite neuropathic pain, the other patients were classified with unlikely or possible neuropathic pain. Furthermore, the sensory signs based on quantitative sensory testing (QST) [22, 23] were the same between patients classified as probable or definite neuropathic pain (these patients had a similar QST profile), but the signs were different between patients classified as probable or definite neuropathic pain compared to those patients graded as unlikely.

The NeuPSIG Grading System was updated in 2016 by Finnerup et al. [3] (see figure 2). Several adjustments were made to better reflect daily clinical practice. The most important adjustment to the updated Grading System is the addition that even 'definite neuropathic pain' does not mean there is a causality [3]. 'Definite neuropathic pain' only refers to the fact that a physician via history taking, physical examination, and supplementary testing is able to clinically confirm that the patient has a neurological lesion that might explain a patient's pain [3]. In line with this, it is always important to consider whether other causes of patients pain may be present. This confirms the observation that currently, there is no true gold standard to diagnose neuropathic pain.

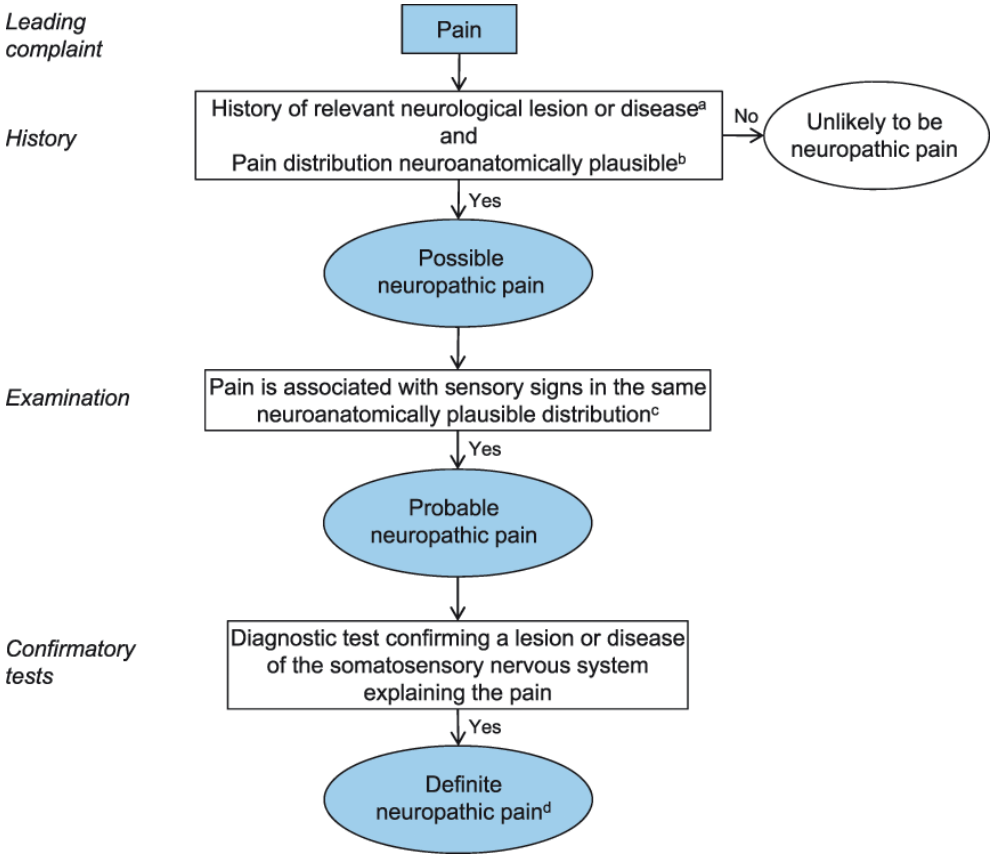


Figure 2. Flowchart of the updated Grading System as proposed in 2016. Adapted from Finnerup et al., Pain, 2016 [3].

a, pain suspected to be related to a lesion or disease of the somatosensory system which is associated with neuropathic pain. **b**, the pain distribution as described by the patient is in line with the assumed lesion or disease. **c**, the area of sensory signs is in the same neuroanatomically plausible distribution. **d**, when the location and nature of the lesion or disease are able to explain patients' pain, probable neuropathic pain confirmed by confirmatory tests is called definite neuropathic pain.

These issues raise questions about the different causes of patients' neuropathic pain component and the manifestation of the signs and symptoms: is the clinical picture of the neuropathic pain component following a nerve injury due to surgery (for example pain due to amputation or (major) nerve lesion) the same as a radicular pain syndrome due to a herniated disc? Are the signs and symptoms of a patient with trigeminal neuralgia the same as in the glove and sock distribution in patients with chemotherapy-induced neuropathy? It seems clear that this is not the case. Moreover, the classification based on the Grading System, screening tools like the DN4 or the Pain*DETECT*, and quantitative sensory testing via bedside examination or the Nijmegen-Aalborg Screening QST, should be viewed individually. For example, in the original articles on Pain*DETECT* (2006) [5] and DN4 (2005) [11], patients with osteoarthritis were viewed as patients with pain of predominantly nociceptive origin, thus they were included in the validation studies as no NePC. Recent studies show that patients with pain resulting from osteoarthritis in which neuropathic pain features (based on neuropathic pain screening tool outcome or pathophysiologic mechanisms) are present, may thus require a different treatment paradigm than patients with osteoarthritis without NePC [24-27]. However, they also confuse the use of screening tools because the validity in patients with a different diagnosis may be challenged. This shows that, in neuropathic pain classification, the patient, the disease as such, and the manifestation of the disease, must all be taken into account when patients are assessed as an individual, unique, patient, and that a tailor-made treatment regimen should be proposed.

Based on current insights, a surrogate gold standard, two independently working, well-trained, experienced and blinded professionals as used in our studies can be improved by narrowing the clinical consensus on signs and symptom. Moreover, meticulously following the guidelines leads to an improved use of the Grading System. Bedside examination and quantitative sensory testing, testing the descending pathways (pain modulation systems) and, for example, neuro-imaging may also be of value when looking for ways to improve the diagnostic gold standard for the assessment of a neuropathic pain component in patients with pain [28, 29].

Answer to question 3: The DN4, but not the Pain*DETECT,* is of value in the screening for a neuropathic pain component

In their original study, Freynhagen et al. revealed a sensitivity of 85% and a specificity of 80% for the Pain*DETECT* [5]. The DN4 developed by Bouhassira et al. [11] showed a sensitivity of 83% and a specificity of 90%. For the DN4-symptoms, interview only, sensitivity was 78% and specificity 81%. In our studies of comparisons with the physicians' assessment as the "gold standard", we conclude that the cross-culturally adapted Pain*DETECT (*sensitivity of 80% and specificity of 55%, figure 3a) is not an effective screening tool because of its moderate sensitivity and low specificity in a consecutive population of patients with low back and leg pain, neck-shoulder pain, or with pain due to a suspected peripheral nerve damage **(Chapter 5)**. We tested the DN4 in the same group of patients as the Pain*DETECT;* this appeared to be moderately helpful in identifying a neuropathic

pain component (NePC) (sensitivity of 75% and specificity of 76%, figure 3b). The DN4-symptoms had a sensitivity of 70% and a specificity of 67% (figure 3c) and is thus less valid in both daily clinical practice and clinical research. (**Chapter 6)**.

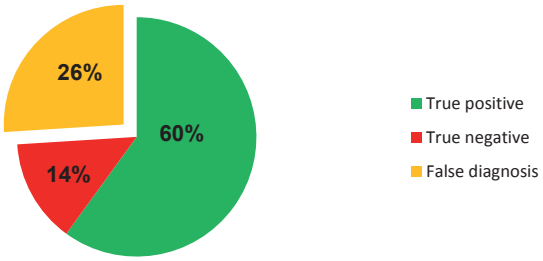


Figure 3a: Pain*DETECT*: 26% of patients have a false diagnosis [108]

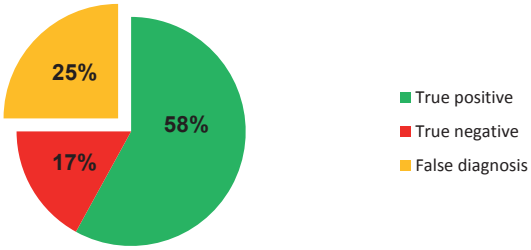


Figure 3b: DN4: 25% of patients have a false diagnosis [61].

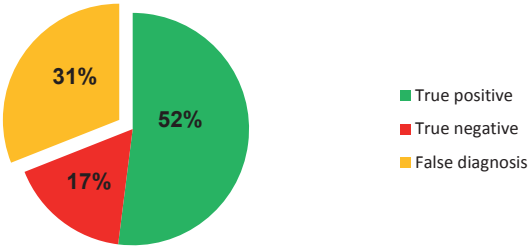


Figure 3c: DN4 symptoms: 31% of patients have a false diagnosis [61].

Figure 3: The outcome of the screening tool (Pain*DETECT* or DN4) classified as true positive, true negative or false outcome in respect to the clinical assessment by both the physicians in our studies [61, 108]

Screening tools for NePC fail in their identification and classification of patients in about 10-20% of all cases [12, 19]. However, in published validation studies, the reported sensitivity and specificity are higher or lower than in the original papers [5, 11]: For the Pain*DETECT* [5, 20, 30-42], sensitivity ranges from 18% [35] – 95% [36] and specificity from 51% [40] – 100% [37] (figure 4). The sensitivity

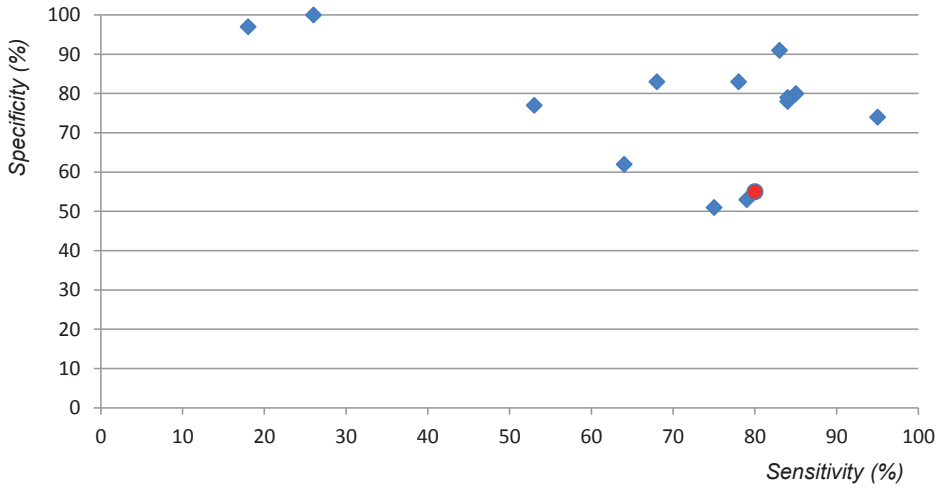


Figure 4: Comparing the sensitivity and specificity of the different validation studies as performed for the Pain*DETECT*

The red dot represents the validation study presented in this thesis [108]; Blue squares represent the individual papers published by different research groups [5, 20, 30-38, 40, 42]

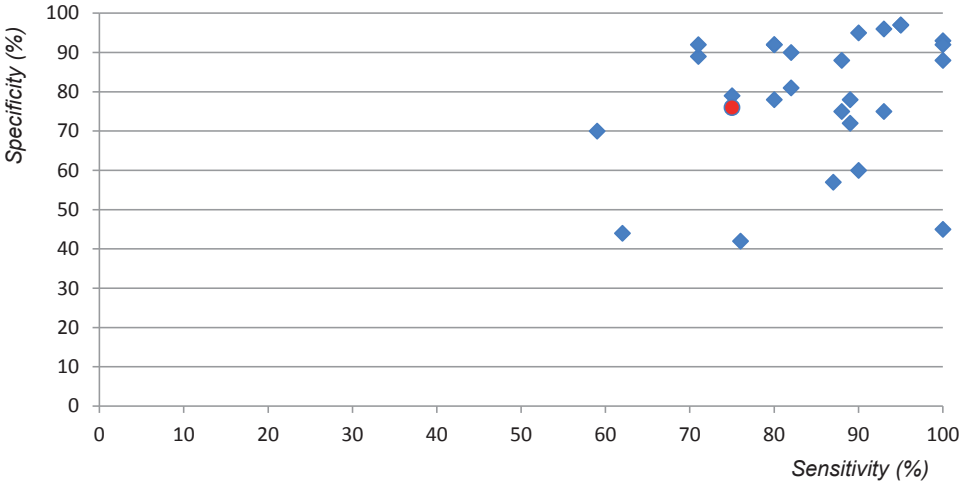


Figure 5: Comparing the sensitivity and specificity of the different validation studies as performed for the DN4

The red dot represents the validation study presented in this thesis [61]. Blue squares represent the individual papers published by different research groups [11, 30, 35, 37, 40, 43-60, 62, 64, 109]

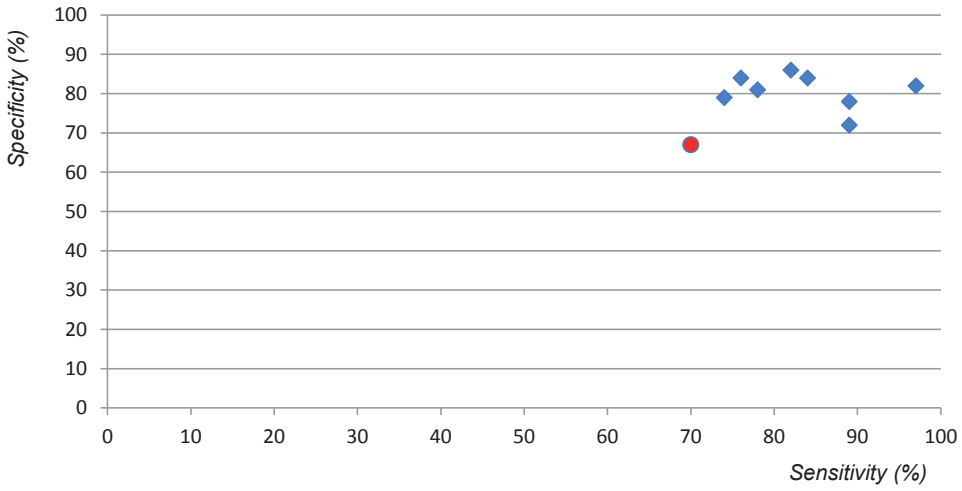


Figure 6: Comparing the sensitivity and specificity of the different validation studies as performed for the DN4-interview

The red dot represents the validation study presented in this thesis [61]. Blue squares represent the individual papers published by different research groups [11, 39, 48, 50, 59, 64-66]

of the DN4 [11, 30, 35, 37, 40, 43-63] ranges from 59% [51] -100% [44, 49, 58] and specificity from 42% [40] – 97% [45, 54] (figure 5). For the DN4-syptoms [11, 39, 48, 50, 59, 61, 63-65], sensitivity was 70% [61] -97% [59] and specificity 67% [61] – 86% [66] (figure 6). These wide ranges of sensitivity and specificity are due to several differences in the diagnosis of the patients, differences in inclusion criteria such as level of perceived pain, and differences in the performance of the 'gold standard'.

In 2017, Epping et al published a paper on the validation of the DN4 and the Pain*DETECT* in the Netherlands [40]. Their group and ours worked simultaneously but independently from each other and found comparable outcomes. Epping's group used the consensus expert diagnosis based on the Grading System as the gold standard. Their DN4 had a sensitivity of 76% and a specificity of 42%, the Pain*DETECT* had 75% and 51% respectively. In our studies **(Chapter 5 and 6),** we reported a DN4 sensitivity of 76% and a specificity of 64%; for the Pain*DETECT* our results were 74% and 46% respectively when compared with the Grading System. We can conclude that the outcomes of these two independent studies are more or less comparable. Both studies demonstrate that the probability of correctly identifying neuropathic pain is quite low. The only difference between both studies was that the specificity of the DN4 in our study was higher. This may be due to the fact that we incorporated the DN4-signs in our standardized assessment form **(Chapter 4 and 6)** and that this may have influenced the pain classification. Epping's group tested the DN4 independently from the initial assessment with a medical specialist and a physiotherapist working independently of

each other. Hasvik et al. [67] compared the Pain*DETECT* to clinical examination based on the 2016 Grading System; they concluded that the Pain*DETECT* performed poorly compared to the Grading System in patients with low back-related leg pain, and considered it unreliable for classifying or grading a neuropathic pain component.

In May 2018, Attal, Bouhassira and Baron published their review [68]. They state that *"screening questionnaires help clinicians to identify neuropathic pain easily, particularly in patients with complex medical conditions".* They illustrated their statement with the medical story of a patient with the complex medical condition of spinal cord injury. However, they reported lower discriminative values for patients with lower back or neck pain; this may have been caused by the absence of a gold standard in these conditions [20, 40, 56, 69]. Based on our results **(Chapter 2, 3, 4, 5 and 6)** the presented numbers of sensitivity and specificity (figure 4, 5 and 6) and issues raised regarding screening tools, we think that a screening tool is, at best, an instrument that is suggestive for the presence of a NePC, but that it should always be followed by an extended interview and comprehensive clinical neurological examination to confirm that a patient's pain is a direct consequence of a lesion or a disease affecting the somatosensory system. However, we note that combining both physicians' assessments, the Grading Systems performed by the physicians, the Pain*DETECT* and the DN4, might not be practicable in daily clinical practice.

Figure 7 shows the combined classifications following clinical assessments by the physicians, the Grading Systems, and the screening instruments of those patients where all six outcomes were available (n=274). The agreement of the classification based on the assessment by the physicians regarding present and absent-NePC was 78% (164 NePC, 49 absent-NePC, figure 7a). Based on the Grading System, the agreement between physicians was 82% (139 NePC, 85 Absent-NePC, figure 7b). Combining both the physicians scores and the Grading Systems (figure 7c) resulted in an agreement of 50% (118 NePC, 20 absent-NePC). Combining all six assessments (both physicians' assessments, both the Grading Systems, the outcome of the Pain*DETECT*, and the DN4) of the 274 patients included in the analysis, only 74 (27%) had a congruent outcome regarding an NePC. In 20 patients (7%), all six outcomes confirmed the absence of NEPC. The agreement between all outcomes was 34%; thus in 66% of patients at least one assessment was aberrant (figure 7d). This indicates that it is not necessarily 'better' to have more assessments about patients' pain complaints because false-positive and false-negative outcomes occur in all classifications **(Chapter 5 and 6)**. Together, these results show that a full clinical assessment of the patient, together with modern technical investigations such as imaging, laboratory testing, and electrophysiological testing, is required [17, 18, 29, 70-76]. To conclude, there is widespread use of screening tools to detect NePC, but they have a low to moderate reliability. Our studies show that the use of the Pain*DETECT* cannot be recommended as a screening or diagnostic instrument to improve diagnosis, management and treatment of NePC in patients with low back and leg pain, neck-shoulder pain, or with pain due to a suspected peripheral nerve damage. We show that the DN4 does help, moderately, to identify NePC

in a consecutive population of patients seen in daily clinical practice, but that a comprehensive (physical) examination by the physician is still necessary.

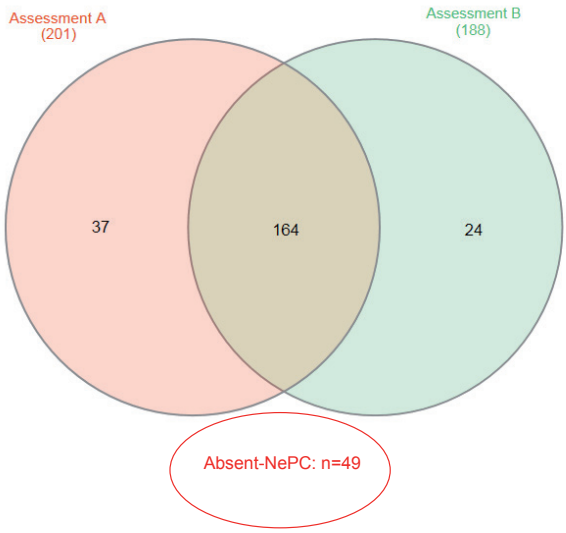


Figure 7a: VENN-Diagram [110] of the outcomes of the assessments by physicians A and B

Assessment A: classification of a neuropathic pain component according to the assessment by physician A (NePC) present; Assessment B: NePC present according to the assessment by physician B.

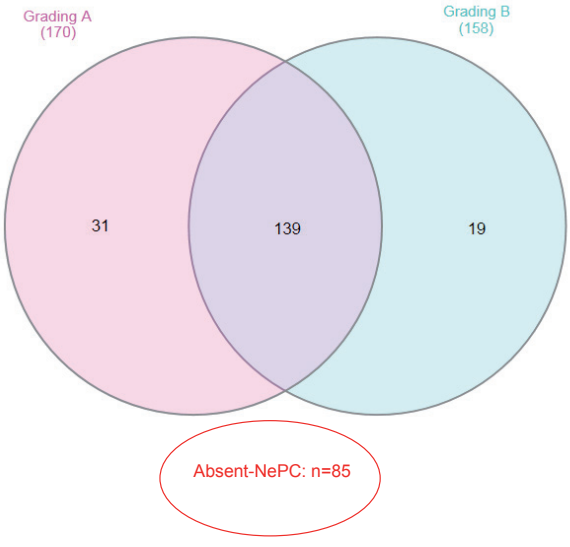


Figure 7b: VENN-Diagram [110] of the outcomes of the Grading Systems by physician A and B

Grading A: NePC present according to the Grading System by physician A; Grading B: NePC present according to the Grading System by physician B;

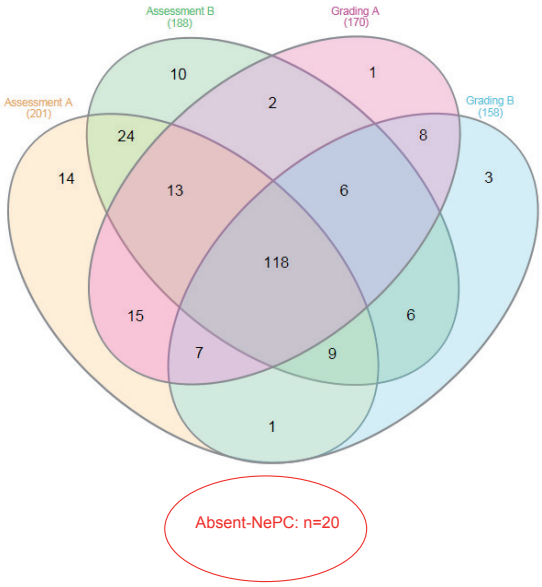


Figure 7c: VENN-Diagram [110] of the assessments and of the Grading System by physicians A and B

Assessment A: classification of a neuropathic pain component according (NePC) to the assessment by physician A present; Assessment B: NePC present according to the assessment by physician B; Grading A: NePC present according to the Grading System by physician A; Grading B: NePC present according to the Grading System by physician B.

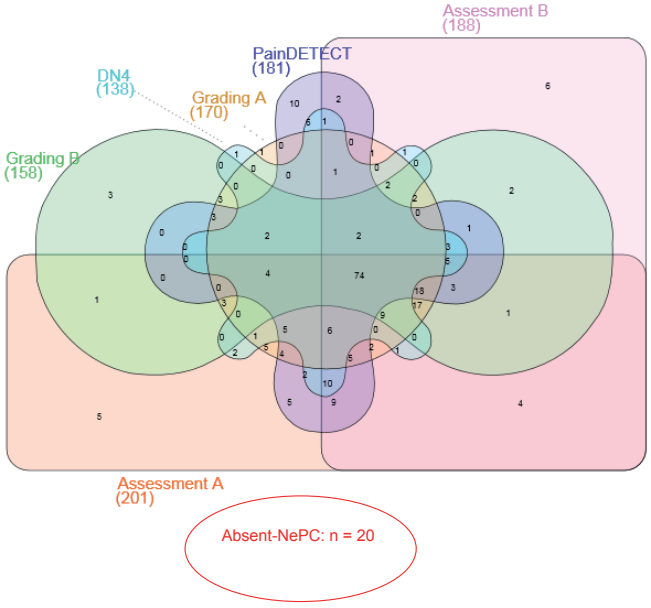


Figure 7d: VENN-Diagram [110] of all six outcomes per patient (Assessment by the physicians, Grading System by the physicians, Pain*DETECT*, and the DN4).

Assessment A: classification of a neuropathic pain component (NePC) according to the assessment by physician A present; Assessment B: NePC present according to assessment by physician B; Grading A: NePC present according to the Grading System by physician A; Grading B: NePC present according to the Grading System by physician B; Pain*DETECT*: outcome of the Pain*DETECT* indicates the presence of NePC. Absent-NePC: No NePC present according to the physicians, the Grading Systems, the Pain*DETECT* and the DN4.

Answer to question 4: Bed-side examination, but not NASQ, has a limited value in the classification of NePC

In Chapter 7, we discuss the value of bedside examination (BSE) and screening quantitative sensory testing following the Nijmegen-Aalborg Screening Quantitative Sensory Testing protocol (NASQ). We show that BSE revealed small differences between patients with either absent or present NePC, whereas NASQ did not reveal any differences (**chapter 7**).

Bedside examination (BSE) is recommended as a method to identify positive and negative sensory signs in several guidelines for assessing neuropathic pain components [16, 18, 29, 70-74, 76-79]. Clinical examination can never prove that pain is of a neuropathic origin, but it can indicate an altered function of patients' nervous system [18]. BSE can also indicate the presence of other pathological processes which may cause pain. As a supplement to neurophysiological testing, BSE can answer the question to where in the somatosensory system the lesion or disease that generates neuropathic pain can be found [80]. Moreover, the classification of clinical symptoms in patients with NePC based on a mechanism-based approach may be useful to quantify sensory signs [81]. As stated by Garcia-Larrea [79], neuropathic pain is especially associated with lesions of temperature and pain pathways (A-delta and C-fibers, spino-thalamo-cortical tracts). We demonstrated (**chapter 7**) that heat sensation, cold sensation, wind-up response, and pricking was less present in patients with NePC.

Unfortunately, BSE data from other studies are scarce. Most published studies used the quantitative sensory testing protocol (QST) following the German Research Network on Neuropathic Pain (DFNS) [22, 23, 82]. Comparison of BSE results with QST following the DFNS protocol is questionable, because the DFNS uses a very strict protocol which is only appropriate for trained persons using a standardized protocol in certified clinical neurological/ neurophysiological laboratories [83]. As far as we are aware, this is not the case when performing BSE tests to find support for the presence of neuropathic pain. However, there is a great emphasis on BSE in the diagnostic work-up of patients with pain in daily clinical practice. Unfortunately, very little has been published on BSE data for groups of patients and for individual patient outcomes alongside the clinical classification of patients' pain.

Spahr et al [84] stated that the methods used in clinical examination and the paradigms used to detect NePC may fail in patients with low back pain (LBP). Based on tactile threshold discrimination and 2-point discrimination (both methods were not used in our study, **Chapter 7**), they found that patients with chronic low back pain had an increased tactile threshold and 2-point discrimination when compared to healthy controls. In the comparison between patients with chronic low back pain with and without NePC, patients with NePC had an increased tactile threshold in comparison with those without. This suggests that there are differences in the clinical profiles of patients with LBP with and without NePC (assessment of symptom profiles instead of evidence for a direct consequence of a lesion or a disease affecting the somatosensory system), and that the symptoms might origin from an underlying maladaptive plasticity of the nervous system [84]. Leffler and Hansson [85] compared the outcome of clinical BSE to the outcome of standardized QST in a research setting in patients with a painful traumatic peripheral nerve injury. They concluded that the individual outcome of BSE compared to standardized QST outcome frequently differed in patients. This may be due to differences in, for example, performance of the applied stimuli. This was most frequently observed in the assessment for sensibility for touch. The differences may be explained by looking at what can be considered as a 'normal' outcome and what a 'pathological' outcome. Moreover, the variety in methodology (standardization, equipment) and conduction (force, position etc.) of the given test stimuli may have contributed to differences between BSE and QST. In conclusion, sensory profiling of patients with NePC based on QST may result in a more stratified and personalized treatment regimen [86, 87], but QST is not directly interchangeable with BSE, as explained above [85].

NASQ is intended to assess the processing of pain in patients [88-90]. Our intention before starting this study was to identify whether the assessment of NASQ benefited the classification of pain by, for example, identifying peripheral or central sensitization. However, the Nijmegen-Aalborg Screening QST (NASQ) protocol showed no association with neuropathic pain. We found no signs of central sensitization (widespread hyperalgesia, descending inhibition [91]) in patients with and without NePC included in our study. This contrasts with findings by Freynhagen et al [92] and Woolf et al [93] who suggest that central sensitization is most manifest in patients with NePC. It is still unclear whether this is due to the fact that our patients had no central sensitization, because the test methodology was not refined enough to detect central sensitization, or otherwise. Granovsky [94] stated that patients with NePC expressed less efficient CPM compared those without. However, we found no differences in the CPM **(Chapter 7)**. The differences between our results and the literature may be due to several facts such as the low number of patients included and no inclusion of matched, healthy controls. However, another reason may have been the forced separation of patients with pain into either nociceptive or neuropathic pain. With today's knowledge, our studies would possibly have had the benefit of the recently proposed threefold separation [95], however the term nociplastic pain did not exist when we started our studies. In patients with nociplastic pain, altered nociceptive functions (hypersensitivity), with a regional or widespread pain distribution do exist [95]. According to the IASP, central sensitization is *"an increased response and reduced threshold*

of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input " [96]. The underlying mechanism of nociplastic pain is probably the central sensitization of the nociceptive pathways [95].

RECOMMENDATIONS FOR CLINICAL PRACTICE, EDUCATION, FUTURE RESEARCH AND SOCIETAL IMPACT

From the results of our research and the discussion on each of the four research questions, we have formulated a number of specific recommendations that we trust will lead to improvements in the diagnosis and treatment of pain for the patients and for the specialists involved in their care,

RECOMMENDATIONS FOR THE CLASSIFICATION OF PAIN IN DAILY CLINICAL PRACTICE

We recommend that the classification of a neuropathic pain component should be based on history taking, physical (neurological) examination, bedside examination, and up-to-date diagnostic testing.

Our studies show that it is extremely important to pay attention to a clearer identification of patients with pain, and to correctly classify them in terms of suffering from nociceptive, neuropathic or nociplastic pain components or a combination of them; we have shown that their treatment response may be dependent on it.

The classification of neuropathic pain in daily clinical practice should be based on accurate (neurological) history taking and performing a neurological examination. History taking reveals the characteristics and distribution of a patient's pain. The clinical examination also reveals possible negative and positive sensory signs and their association with the underlying lesion or disease. This can be performed via a standard neurological examination combined with a bedside examination. Finally, a diagnostic test such as R3 reflex testing, cutaneous response reduction (skin wrinkle test) test, nerve ultrasound, quantitative sudomotor axon reflex testing, quantitative sensory testing, laser-evoked potentials, pin-prick evoked potentials, electrophysiological testing, fMRI and skin biopsy may all help to confirm the lesion or disease in the somatosensory system which explains the pain [3, 71, 79]. However, as discussed, a factual relationship based on diagnostic testing between nerve damage and a patient's pain has not yet been verified but the search for this connection remains of great importance for improving patient treatment [71] **(Chapters 3,4,5,6 and 7)**.

We recommend that pain classification should be standardized in daily clinical practice as this will lead to new insights and improve patient outcomes.

By examining the patient in a standardized but individual way (history taking, physical examination, bedside examination and, when possible, confirmatory test procedure(s)), the clinician will be better able to classify a patient's pain based on the clinical criteria and thus to design a personalized pain treatment program.

The Grading System is intended to be used in individual patients in daily clinical practice as well as in clinical research [3]. One advantage of this system [3, 14] is to help in the standardized classification of neuropathic pain. By using the Grading System methodology when examining a patient, it is possible to grade the certainty of NePC existence on an ordinal scale: no neuropathic pain, possible neuropathic pain, probable neuropathic pain, and definite neuropathic pain [3]. However, currently the Grading System cannot be seen as a 'gold standard' for neuropathic pain; it is a clinical assessment guideline which assists in classifying a patient's pain. An outcome of probable neuropathic pain in a patient should be reason for the physician to consider initiating treatment according to the guidelines about treating patients with neuropathic pain [97]. To use and to rely on the Grading System, it is important for the physicians to be experienced, and that they have the skills and resources to assess their patient in the best possible way [3]. **(Chapters 3, 4, 5 and 6)**.

We recommend that screening questionnaires should be used with caution, when assessing a neuropathic pain component in a daily clinical consecutive population of patients with chronic pain.

Screening tools like the DN4 or Pain*DETECT* only provide a slight indication of the presence of NePC; they may therefore lead to misclassifying a patient's pain.

Our studies show that false identification with respect to the presence or absence of NePC may be the case in a substantial number of patients. It can be concluded that a clinical examination of the patient is a prerequisite; a screening tool is not a diagnostic test and can thus never replace a physician's examination[12]. Moreover, it is always true that "a patient" is much more than the outcome of the questionnaire(s), and that a patient's pain is whatever the patient says it is **(Chapters 5 and 6)**.

We recommend that a bedside examination forms a part of the diagnostic work-up of patients' pain.

After history taking, bedside examination is of second-most importance when examining the (cause or mechanism) of the patient's pain. It takes time to examine the patient and the sensory disturbances should be noted on a body map.

Bedside examination will provide the physician with an overview of a patient's pain and may better support a pain diagnosis and thus be valuable when monitoring a patient's pain and treatment effects. BSE should be performed in a standardized way, guided by clear instructions to the patient. Our results suggest a low association between BSE and classification of a patient's pain, however it may assist the so-called *'fingerspitzengefühl'* with which physicians classify patients' pain in daily clinical (primary) care as pain with or without a neuropathic component **(Chapter 5,6 and 7)**.

We recommend that combining pain classification strategies to become 'more sure' of a patient's pain classification is not standard daily clinical practice.

Our studies show that there is no proof that it is 'better' to have more assessments about a patient's pain complaints, as false-positive and false-negative outcomes occur in all classifications **(Chapters 5 and 6)**.

Running more and different clinical assessments about the type of a patient's pain may not be beneficial for the patient; it may even harm the patient due to, for example, delay of treatment. As Goscinny and Uderzo stated in their inimitable way: *"…appelle plutôt des medicines!…Je fais venir tous les medicines de la garnison!.... Tu ne crains pas l'intervention des medicines…? En groupe ils sont plus meurtriers qu'une legion armée jusqu-aux dents!"* [98].

RECOMMENDATIONS FOR IMPROVING PHYSICIAN EDUCATION AND TRAINING FOR CLASSIFYING PATIENTS' PAIN

We recommend that more attention should be paid to patients with pain, and to pain as a disease in its own right

Based on the epidemiology of pain, the reduced health related quality of life, lower functional status, and lower mental health, in combination with the high direct and indirect costs associated with patients with chronic pain, it is of utmost importance to create awareness about this major personal and socioeconomic problem.

Each patient has his or her own 'pain', and that makes patients experts in their own pain based on personal memory, emotions, cognitive factors, and pathology **(Chapter 1)**. Currently, pain is undervalued in daily clinical practice [99]. It is therefore important to pay greater attention to a patient's pain and to make greater financial resources available to fund scientific research in the field of pain to identify potential mechanisms and to examine treatment effects. The first step in this might be by raising the general public's awareness of the epidemiology, burden, costs and consequences of pain via newspapers, radio, television, and participation in research as a (healthy) volunteer etc. **(Chapter 1).**

We recommend that more education in the use of screening- and diagnostic instruments should be provided at an undergraduate, graduate and postgraduate level for everyone working with people with pain

To assess pain, physicians should use a biopsychological model to address the somatic, cognitive, emotional, behavioral, spiritual and social dimensions. Munrinson et al. [100] studied students in the preclinical phase and concluded that the integration of the cognitive and the affective dimension is related to the basic knowledge about emotional development and is associated with a high degree of student satisfaction. Moreover, physicians should address pain with an integrated view of patho-physiology and clinical care, but this is only possible if this is based on a long term vision for pain education, wherein the patient plays a central role [100]. Another aspect of education is improving learning about and using guidelines. Clinical practice guidelines are not always exactly followed by the physician due to a number of factors like a lack of awareness, a lack of agreement, and a lack of outcome expectancy [101].

Education in the field of pain should be, amongst others, targeted towards identifying symptoms and signs, improving knowledge about screening, and assessing patients with pain (via, amongst others, screening tools as the Pain*DETECT* and the DN4 and the use of the Grading System). A proposed pain medicine model developed by Wolff and Groen (APC, UMCG; 2016) includes different steps in the diagnostic work-up of the patient to come to personalized pain treatment:1) The pain complaint (patient history, body examination, additional examination); 2) supposed (anatomical) substrate; 3) pathophysiology; 4) pain mechanisms / pain diagnosis; 5) bio-psycho-social-spiritual; 6) conclusion; 7) management; and 8) repetition. Based on the statement *"pain is whatever the patient says it is, existing whenever he/she says it does"* [102] I would suggest moving the Bio-Psycho-Social-Spiritual part of the model forward to second position, as this element has important consequences for patients with pain and leads to their daily-living limitations. Improving this knowledge may have consequences for therapy regimes, amongst other factors. Additionally, it is important to implement evaluation methods to measure and optimize treatment efficacy. Moreover, better training in how to educate patients about their disease, master coping skills, and improving knowledge of available self-care options may be beneficial [103]. Under ideal conditions this should be done in a continuous learning environment combined with the possibility to quickly react to new insights and for example, changes in treatment opportunities.

We recommend improving the knowledge and expectations about the psychometric values of evaluation / screening tools of the person interpreting it.

Based on our results **(Chapters 5, 6 and 7)** and the other studies about the validity of screening tools for assessing neuropathic pain, it is important for those interpreting the results to have a better knowledge of the tool's correct use and an understanding of its psychometric values. Each tool, instrument or test results in false positive and/or false negative results. If treating physicians are

aware of these, they can be taken into account when evaluating the outcome of the instrument in question.

RECOMMENDATIONS FOR THE IMPROVEMENT OF FUTURE RESEARCH

We recommend that patients with neuropathic pain should be treated more optimally; we have to be able to better identify crucial pain markers.

Neuropathic pain, as far as we can identify it, is characterized by a poor response to treatment with medication. The conversion rate of medication needed to treat for 50% pain relief differs greatly: 3.6 for tricyclic antidepressants, 6.4 for serotonin-noradrenaline reuptake inhibitor, 7.7 for pregabalin, and 6.3 for gabapentin [97]. We should aim for a therapy that has a higher conversion rate by gaining a better understanding of pain mechanisms and being better able to assess these mechanisms. Unfortunately, a 'one fits all' treatment regime does not fit the needs of an individual patient with pain. To further develop precise and personalized treatment, we need to develop a more detailed assessment strategy and matching treatment regimens. To find a real 'gold standard' for the diagnosis of NePC would be extremely valuable, however this is not expected in the short term. We recommend that more research should be conducted on the recently updated Grading System and the implementation of nociplastic pain as a third mechanistic descriptor, both in the laboratory and, in particular in daily clinical practice.

Collecting data (signs, symptoms, outcome measures) may influence the individual physician's clinical practice based on experience (pattern recognition), as well as research. 'Big data' may enable us to recognize patterns in individual patients or in groups of patients, even where there is a great deal of variability in individual patient outcomes **(Chapters 3, 4, 5, 6 and 7)**.

We do not recommend NASQ when differentiating between nociceptive pain and the existence of a neuropathic pain component; this needs further evaluation to determine the mechanisms of nociplastic pain

The acknowledgement of the third mechanism-based descriptor of pain, nociplastic pain, by the International Association for the Study of Pain (IASP) has led to new opportunities for the use of NASQ. To better differentiate between pain mechanisms, a phenomenon as central sensitization might be accessed via the measurement of pain thresholds and/or changes in the endogenous pain system. NASQ should be further developed and more research should be conducted to see whether NASQ offers benefits for the assessment of patients with pain **(Chapter 7)**.

We recommend that the screening tools used when assessing a neuropathic pain component should have a very high sensitivity, specificity and positive likelihood ratio.

A screening tool to detect neuropathic pain should have a high sensitivity to identify the patients with NePC; they should also have a high specificity to recognize patients without NePC. Moreover, the predictive value must be high to ensure that a positive test indicates the presence of NePC. However, the likelihood ratio should also be given in the result sections of research papers as this indicates how much more likely a positive test will be present in a patient with NePC compared to a patient without NePC. Finally, when reporting on the validity of a screening tool, test-retest reliability should also be stated in the paper [104-106] **(Chapters 5 and 6)**.

RECOMMENDATIONS FOR IMPROVING THE ORGANIZATION OF PAIN CARE AND SOCIETAL IMPACT

We recommend that patients should be better identified and stratified; this will lead to a better organization and the health-economic optimization of and inclusion of patients in specialized treatment programs.

In the future, improved identification and stratification of patients will lead to, in addition to greater satisfaction about treatment, a positive effect on the health economy: reducing the costs of medical care. Of even greater importance is the improvement in health care and a decrease in the burden of chronic pain disease. Moreover, improvements in daily clinical practice will facilitate a faster return to work, less direct costs, less indirect costs, better education in (para-) medical schools, and a better stepped wedge care.

Health and healthy behavior are important issues for the near future; the World Health Organization emphasize the need, *"to promote health and development, and prevent or reduce risk factors for health conditions associated with use of tobacco, alcohol, drugs and other psychoactive substances, unhealthy diets, physical inactivity and unsafe sex"* [107]. Education, self-management, and physical activity are issues that should be further developed by, amongst others, pain physicians and researchers in the field of pain, but always together with patients with pain.

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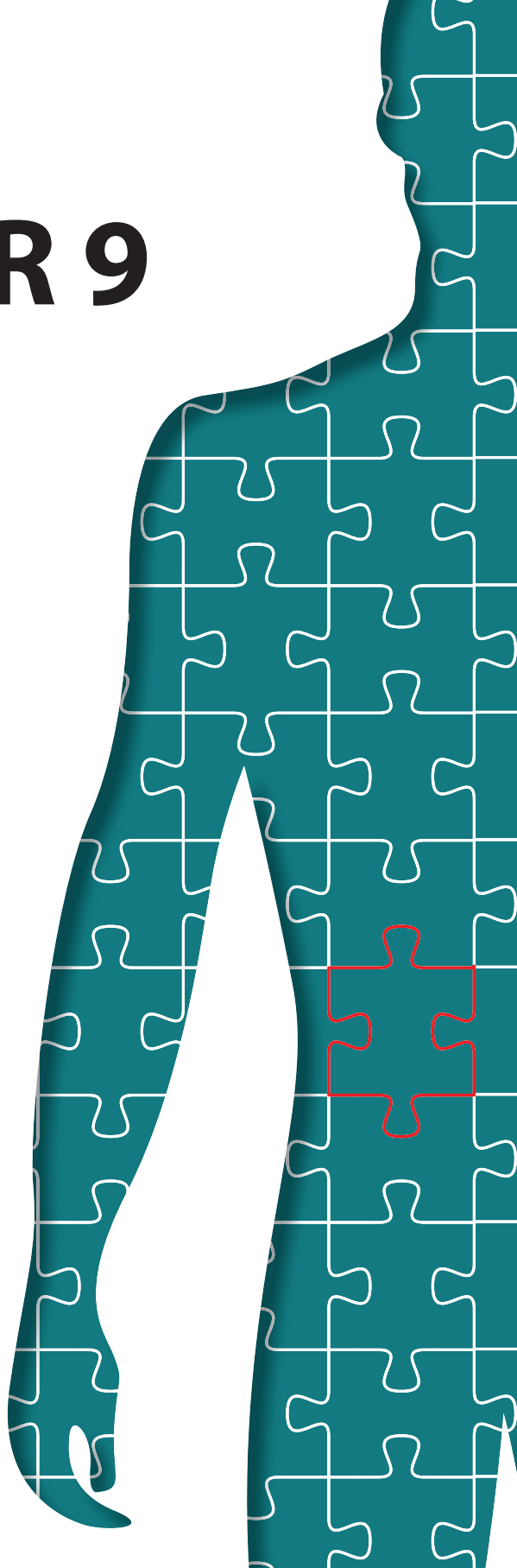
CHAPTER 9



SUMMARY

Pain is described as (1): *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" and as* (2): *"whatever the experiencing person says it is, existing whenever he says it does"*. The first is a definition of pain as a psychosocial phenomenon, the second is a more patient orientated description of pain as a subjective experience. The experience of pain by the patient is thus influenced by personal memory, emotions, pathology and cognitive factors.

The introduction of this thesis, **chapter 1**, is divided into five sections. In the first section we describe the classification of patients pain based on the type of pain and on the duration of pain. The type of pain can be classified as: (1) nociceptive pain: *"pain that arises from actual or threatened damage to non-neural tissue and is due to activation of nociceptors*'; (2) neuropathic pain: *"pain arising as a direct consequence of a lesion or disease affecting the somatosensory system*"; (3) nociplastic pain: *"pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing pain*"; (4) mixed pain or as (5) pain of unknown origin. Based on the duration, pain can be classified as acute or chronic pain (pain within or beyond the expected period of healing). The second section gives an overview of physiological mechanisms of pain and the important pathways for pain between receptors and the brain. In section three we describe the epidemiology, burden, costs and consequences of chronic pain and of neuropathic pain in particular. Section four provides an overview of the assessment of neuropathic pain in daily clinical practice: history taking and physical assessment, bedside examination, screening tools, the NeuPSIG grading system, quantitative sensory testing and neurophysiologic techniques. The requirements for a screening tool to assess (neuropathic) pain are described in section five.

The objectives of this thesis were to assess the psychometric properties of the Pain*DETECT* and the DN4 in a consecutive daily practice population of patients with low back and leg pain, neck-shoulder arm pain or with pain due to a suspected peripheral nerve damage. A second aim was to assess the possible benefits of bed side examination and the Nijmegen Aalborg Screening QST to distinguish between clinically diagnosed patients with and without a neuropathic pain component.

In **chapter 2** we described the process of the cross-cultural adaptation of the Pain*DETECT* into the Dutch language for use in the Netherlands and Belgium. According to the literature the Pain*DETECT* helps to identify a neuropathic pain component in patients suffering from pain in daily practice as well as in clinical trials. A prerequisite for a valid screening instrument in the Dutch language was to go through an extensive translation and cross-cultural adaptation process. The first phase in this study was to translate and cross-culturally adapt the Pain*DETECT* into Dutch via the internationally accepted ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Task Force

guideline. The second phase was to assess the face validity in the Netherlands and Belgium using qualitative and quantitative data collection. Patients from Belgium and the Netherlands participated in this study. The length, the readability and the clarity of the questionnaire were good for all patients. The questionnaire was judged to have a good lay-out (formatting and administration were the same as in the original German version to prevent variations in response) and to be clearly organized. In conclusion, the Pain*DETECT* Dutch language version might be useful, based on only the face validity, for screening for neuropathic pain components in the Netherlands and Belgium based.

Chapter 3 is about the reliability of the clinical judgment as an accepted surrogate for an objective gold standard in diagnosing neuropathic pain. However, until this moment no publications were available about the reliability of this diagnosis. This reliability is of importance because the diagnosis of neuropathic pain has important treatment implications. In this study the levels of agreement on the clinical examination of neuropathic pain were estimated by calculating the kappa-value and percentage of pair wise agreement to determine the interobserver reliability of the assessment of neuropathic pain in patients with cancer. Each patient was examined by two specialists via an independent clinical assessment as performed in daily clinical practice. After each assessment physicians were asked to indicate the most adequate characterization of the pain: pure neuropathic pain, pure nociceptive pain, mixed pain, or no pain. A substantial level of agreement was found for the diagnosis of pure neuropathic pain but the values of agreement for the existence of a neuropathic pain component were not satisfying. There was only a fair agreement between the physicians regarding the NeuPSIG grading system. In patients with cancer in respect to the identification of neuropathic pain the agreement between physicians, as an outcome of reliability in the assessment of neuropathic pain, based on physical examination is in need for a better standardization of the clinical assessment and classification of pain.

In **chapter 4** we described in detail the study protocol for our studies as stated in chapter 5, 6 and 7. The aim of the studies in **chapter 5** and **chapter 6** was to assess the validity of the Dutch versions of the Pain*DETECT* and the DN4 in a large population of patients with chronic pain as seen in daily clinical practice: patients with chronic low back and leg pain, with neck shoulder arm pain and in patients with chronic pain due to suspected peripheral nerve damage. Screening tools have been developed to assist the physician to assess patients with neuropathic pain. These tools have typically been validated in patients who were pre-stratified for the outcome of neuropathic pain. The validity of these screening tools needs to be proven in patients with pain who were not pre-stratified on basis of the target outcome: neuropathic pain or non- neuropathic pain. A cross-sectional multicentre design was used to assess the validity of both instruments. Patients with low back pain radiating into the leg(s), patients with neck-shoulder-arm pain and patients with pain due to a suspected peripheral nerve damage were included. Patients' pain was classified as having a neuropathic pain component (yes/no) by two experienced physicians ("gold standard"). Physicians opinion based on the NeuPSIG Grading System was used a secondary comparison. Based on the results of the

study in **chapter 5** the Dutch version of the Pain*DETECT* was not an effective screening tool for a neuropathic pain component in a population of patients with chronic pain because of its moderate sensitivity and low specificity. Moreover, the indiscriminate use of the Pain*DETECT* as a surrogate for clinical assessment should be avoided in daily clinical practice as well as in (clinical-) research. The study in **chapter 6** showed that the DN4 seems to be helpful in the identification of a neuropathic pain component because of a moderate sensitivity and specificity, but a comprehensive (physical-) examination by the physician is still obligate.

The objective of the study in **chapter 7** was to assess the potential association between the clinically diagnosed presence or absence of a neuropathic pain component, bed side examination, and the Nijmegen-Aalborg screening QST paradigm. Bed side examination consisted of measurements of touch [finger, brush], heat, cold, pricking [safety pin, von Frey hair], and vibration). The Nijmegen Aalborg paradigm (pressure algometry, electrical pain thresholds, and conditioned pain modulation) was assessed to generate new insights. Bed side examination revealed statistical significant differences between patients with either an absent or present neuropathic pain component. The Nijmegen Aalborg Screening QST did not reveal any differences between patients with and without a neuropathic pain component. Based on our study it can be concluded that a standardized bed side examination is more useful than the Nijmegen Aalborg screening QST to distinguish between patients with and without a neuropathic pain component.

In **chapter 8** we discussed our main findings as included in this thesis with respect to the recent literature. Recommendations were addressed for clinical practice, education, future research and societal impact. These recommendations will lead to improvements in the assessment and treatment of pain for the patients as well as for the (pain-) physicians involved in the care for patients.

SAMENVATTING

Pijn wordt beschreven als (1): *"een onplezierige, sensorische en emotionele ervaring die is geassocieerd met actuele of potentiële weefselschade of beschreven wordt in termen van zulke schade"* en als (2): *"dat wat de patiënt die pijn heeft zegt dat het is en deze treedt op als de patiënt zegt dat deze optreedt"*. De eerste is een definitie van pijn als een psychosociaal fenomeen, de tweede is een meer patiëntgerichte beschrijving van pijn als een subjectieve ervaring. De ervaring van pijn door de patiënt wordt dus mede beïnvloed door persoonlijk geheugen, emoties, pathologie en cognitieve factoren.

De introductie van dit proefschrift, **hoofdstuk 1**, is verdeeld in vijf secties. In het eerste deel beschrijven we de classificatie van pijn van de patiënt op basis van het soort pijn en de duur van pijn. De soort pijn kan worden geclassificeerd als: (1) nociceptieve pijn: *"pijn die voortkomt uit actuele of dreigende schade aan niet-neurogeen weefsel en die het gevolg is van activatie van nociceptoren"*; (2) neuropathische pijn: *"de pijn is een direct gevolg van een beschadiging of ziekte van het perifere of het centrale zenuwstelsel"*; (3) nociplastische pijn: *"pijn die voortkomt uit een veranderde nociceptie ondanks dat er geen duidelijk bewijs van daadwerkelijke of bedreigde weefselbeschadiging is die de activering veroorzaakt van perifere nociceptoren en er ook geen bewijs voor ziekte of laesie van het somatosensorische systeem is die pijn veroorzaakt"*; (4) gemengde pijn of als (5) pijn van onbekende oorsprong. Gebaseerd op de duur, kan pijn worden geclassificeerd als acute of chronische pijn (pijn binnen of na de verwachte periode van genezing). Het tweede deel geeft een overzicht van fysiologische mechanismen van pijn en de belangrijke banen voor pijn tussen receptoren en de hersenen. In sectie drie beschrijven we de epidemiologie, de belasting, de kosten en de gevolgen van chronische pijn en van neuropathische pijn in het bijzonder. Deel vier geeft een overzicht van de beoordeling van neuropathische pijn in de dagelijkse klinische praktijk: het uitvoeren van anamnese en lichamelijk onderzoek, oriënterend neurologisch onderzoek, screeningsinstrumenten, het NeuPSIG beoordelingssysteem, kwantitatieve sensorische testen (QST) en neurofysiologische technieken. De eisen die gesteld worden aan een screeningsinstrument om (neuropathische) pijn te beoordelen, worden beschreven in deel vijf.

De doelstellingen van dit proefschrift waren het beoordelen van de psychometrische eigenschappen van de Pain*DETECT* en de DN4 (screeningsinstrumenten voor neuropathische pijn) in een populatie van opeenvolgende patiënten uit de dagelijkse klinische praktijk met lage rug- en beenpijn, nek-schouder-armpijn of pijn ten gevolge van een vermoedelijke perifere zenuwbeschadiging. Een tweede doel was om de mogelijke voordelen van oriënterend neurologisch onderzoek en de Nijmegen Aalborg Screening QST te beoordelen om onderscheid te maken tussen klinisch gediagnosticeerde patiënten met en zonder een neuropathische pijncomponent.

In **hoofdstuk 2** hebben we het proces van de cross-culturele aanpassing van de Pain*DETECT* vanuit het Duits naar de Nederlands taal voor gebruik in Nederland en België beschreven. Volgens de literatuur helpt de Pain*DETECT* bij het identificeren van een neuropathische pijncomponent bij patiënten met pijn in de klinische praktijk en in klinisch onderzoek. Een voorwaarde om een valide screeningsinstrument in de Nederlandse taal te verkrijgen was om eerst een uitgebreide vertaling en een cross-cultureel aanpassingsproces te doorlopen. De eerste stap in deze studie was om de Pain*DETECT* in het Nederlands te vertalen, cross-cultureel aan te passen op basis van de internationaal aanvaarde ISPOR-richtlijn voor het vertalen, en linguïstisch valideren van door de patiënt gerapporteerde uitkomsten. De tweede fase was om de indruksvaliditeit in Nederland en België te beoordelen met behulp van kwalitatieve en kwantitatieve gegevensverzameling. Hiervoor namen patiënten uit België en Nederland deel aan de studie. De lengte, de leesbaarheid en de duidelijkheid van de vragenlijst was goed volgens de patiënten. De vragenlijst had een goede lay-out (opmaak en wijze van invullen was hetzelfde als in de originele Duitse versie om variaties in respons te voorkomen) en er was een duidelijke organisatie binnen de vragenlijst. De conclusie uit deze studie was dat de Nederlandse versie van Pain*DETECT* mogelijk nuttig kan zijn, gebaseerd op alleen de indruksvaliditeit, voor screening op de aanwezigheid van neuropathische pijncomponenten bij patiënten in Nederland en België.

Hoofdstuk 3 gaat over de betrouwbaarheid van het klinische oordeel als geaccepteerd surrogaat voor een objectieve goud standaard bij het diagnosticeren van neuropathische pijn. Tot op dit moment waren er geen publicaties beschikbaar over de betrouwbaarheid van deze diagnose. Deze betrouwbaarheid is belangrijk omdat de diagnose neuropathische pijn implicaties voor de behandeling heeft. In deze studie werden de niveaus van overeenstemming over het klinisch onderzoek van neuropathische pijn vastgesteld door de kappa-waarde en het percentage paarsgewijze overeenstemming te berekenen, om zo de interbeoordelaarsbetrouwbaarheid van de diagnose neuropathische pijn bij patiënten met kanker te bepalen. Elke patiënt werd door twee specialisten onderzocht via een onafhankelijke klinische beoordeling zoals uitgevoerd in de dagelijkse klinische praktijk. Na elke beoordeling werd de artsen gevraagd om de meest adequate karakterisering van de pijn aan te geven: pure neuropathische pijn, pure nociceptieve pijn, gemengde pijn of geen pijn. Er werd een substantieel niveau van overeenstemming gevonden voor de diagnose van pure neuropathische pijn, maar de waarden van overeenkomst voor het bestaan van een neuropathische pijncomponent voldeden niet. Er was wel een redelijke overeenkomst tussen de artsen met betrekking tot het NeuPSIG beoordelingssysteem. Bij patiënten met kanker is er in de overeenstemming tussen artsen voor de identificatie van neuropathische pijn, als een uitkomst van betrouwbaarheid, echter nog duidelijk behoefte aan een betere standaardisatie van de klinische beoordeling en classificatie van pijn.

In **hoofdstuk 4** hebben we het studieprotocol voor onze studies in detail beschreven, zoals gebruikt in hoofdstuk 5, 6 en 7.

Het doel van de studies in **hoofdstuk 5** en **hoofdstuk 6** was om de validiteit te beoordelen van de Nederlandse versies van de Pain*DETECT* en de DN4 in een grote populatie van patiënten met chronische pijn zoals gezien in de dagelijkse klinische praktijk: patiënten met chronische lage rugpijn met ook pijn in de benen, met pijn in de nek en de schouder of arm en bij patiënten met chronische pijn als gevolg van vermoedelijk een perifere zenuwbeschadiging. Screeningsinstrumenten zijn ontwikkeld om de arts te helpen bij het beoordelen van patiënten met neuropathische pijn. Deze hulpmiddelen zijn doorgaans gevalideerd bij patiënten die vooraf gestratificeerd waren voor de uitkomst van neuropathische pijn. De validiteit van deze screeningsinstrumenten moet echter ook worden bewezen bij patiënten met pijn die niet vooraf zijn gestratificeerd op basis van het doelresultaat: neuropathische pijn of niet-neuropathische pijn. Een cross-sectioneel multicenter studie design werd gebruikt om de validiteit van beide instrumenten te beoordelen. Patiënten met lage rugpijn uitstralend in het been (of benen), patiënten met nek-schouder-arm pijn en patiënten met pijn als gevolg van een vermoedelijke perifere zenuwbeschadiging werden geïncludeerd. De pijn van de patiënt werd door twee ervaren artsen geclassificeerd op de aanwezigheid van een neuropathische pijncomponent (ja / nee) ("goud standaard"). De mening van artsen op basis van het NeuPSIG-beoordelingssysteem werd gebruikt als secundaire vergelijking. Op basis van de resultaten van het onderzoek in **hoofdstuk 5** bleek de Nederlandse versie van de Pain*DETECT* geen effectief screeningsinstrument voor de aanwezigheid van een neuropathische pijncomponent in een populatie van patiënten met chronische pijn vanwege de matige sensitiviteit en lage specificiteit. Bovendien moet het kritiekloos gebruik van de Pain*DETECT* als surrogaat voor klinische beoordeling worden vermeden in de dagelijkse klinische praktijk evenals in (klinisch-) onderzoek. De studie in **hoofdstuk 6** toonde aan dat de DN4 nuttig lijkt te zijn bij de identificatie van een neuropathische pijncomponent die is gebaseerd op een matige sensitiviteit en specificiteit. Echter, een uitgebreid (lichamelijk) onderzoek door de arts is nog steeds nodig.

Het doel van de studie in **hoofdstuk 7** was om de mogelijke associatie te bepalen tussen de klinisch gediagnosticeerde aanwezigheid of afwezigheid van een neuropathische pijncomponent, oriënterend neurologisch onderzoek en het Nijmegen-Aalborg Screening QST paradigma. Oriënterend neurologisch onderzoek bestond uit metingen van aanraking (vinger, kwast), hitte, kou, prikken (Pinprick, von Frey haar) en trilling. Het Nijmegen-Aalborg Screening QST paradigma (drukalgometrie, elektrische pijndrempels en geconditioneerde pijnmodulatie) werd onderzocht om mogelijke nieuwe inzichten te genereren. Oriënterend neurologisch onderzoek toonde statistische significante verschillen tussen patiënten met een aan- of afwezige neuropathische pijncomponent. De Nijmegen-Aalborg Screening QST bracht geen verschillen aan het licht tussen patiënten met en zonder een neuropathische pijncomponent. Op basis van ons onderzoek kan worden geconcludeerd dat een gestandaardiseerd oriënterend neurologisch onderzoek zinvoller is dan het Nijmeegse-Aalborg screening QST paradigma om onderscheid te maken tussen patiënten met en zonder een neuropathische pijncomponent.

In **hoofdstuk 8** bespraken we onze belangrijkste bevindingen zoals opgenomen in dit proefschrift met betrekking tot de recente literatuur. Er werden aanbevelingen gedaan voor de klinische praktijk, het onderwijs, toekomstig onderzoek en de maatschappelijke impact. Deze aanbevelingen zullen leiden tot verbeteringen in de beoordeling en behandeling van pijn voor de patiënten evenals voor de (pijn-)artsen die betrokken zijn bij de zorg voor patiënten.

DATA MANAGEMENT

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands has given approval to conduct these studies.

The studies in this thesis (chapter 2, 4,5,6 and 7) were performed within DALI for PAIN, a national program that focuses on neuropathic pain care optimization. DALI for PAIN is an initiative of Pfizer. This project is supported by an unrestricted grant from Pfizer. This project is stored on the Radboudumc, department of anesthesiology, pain and palliative medicine H-Disc as DALI-08 TIM. The study in chapter 3 was co-funded by the Netherlands Organisation for Health Research and Development and stored on the Radboudumc, department of anesthesiology, pain and palliative medicine H-Disc under ANES ARCHIEF as Kappa/Validatie.

In our studies patients received questionnaire booklets containing the written informed consent during the physical examination moment, after two weeks and after three months. The participating physicians filled in the research form on paper. The paper data were stored in the department archive (Radboudumc, room M333.04.424), closet number 7. The data of chapter 3 is stored in the bunker (Radboudumc, room M333.02.210) under archive number 43, closet E.

All paper data were entered into the computer by use of MACRO software (MACRO, version 4.1.1.3720, Infermed, London, United Kingdom). Data management and monitoring were also performed within MACRO. An audit trail was incorporated to provide evidence of the activities that has altered the original data. The privacy of the participants in this study is warranted by use of encrypted and unique individual subject codes. This code correspondents with the code on the patient- and physicians booklets.

Data where converged from MACRO to Excel (Microsoft Office, Redmond, Washington, USA) and then to SPSS (SPSS Inc., Chicago, Illinois, USA). In November 2013 the data is monitored by dr. M. Kox, department of Intensive Care, Radboudumc, Nijmegen, the Netherlands.

The patient data for the analyses of the studies as presented in chapter 2, 4, 5,6, and 7 is stored on the departments' H-drive (H:\ANES\ResearchPipa\DALI-08 TIM\Investigators file\34 Database lock) in SPSS format: (chapter 2) FaceValidity_PDQ_B_NL_Anonymous, (chapter 4,5, 6 and 7) PaDoVa database 2014, (chapter 7) PaDoVa database + Cx_QST 2014. The data for chapter 3 is stored on the departments' H-drive (H:\ANES\ResearchUnit\ARCHIEF\STUDIE ARCHIEF\ANES ARCHIEF).

The data will be saved for 15 years after termination of the study (July 1, 2013). Using these patient data in future research is only possible after a renewed permission by the patient as recorded in the informed consent. The datasets analyzed during these studies are available from the corresponding author on reasonable request.

CURRICULUM VITAE

Hans Timmerman is born on September 25, 1969 in Lunteren (municipal of Ede, the Netherlands), and grew up in Bemmel, a small village between Arnhem and Nijmegen.

After primary and secondary school in Bemmel he went to Nijmegen to study Physical Therapy at the HAN University of Applied Sciences. At the age of twenty Hans got his license as a physical therapist. After his graduation Hans worked in several hospitals, institutions and private practices. In 1995 he started his own private practice in Arnhem. The revalidation of patients with low back pain, neck shoulder pain and sports injuries were his specialisms. During this period he followed several post-graduation courses in the field of physical therapy. Besides his own practice he worked as the staff sports physical therapist for the Royal Dutch Fencing Association during training and national competitions but also during European and World Championships.

In 2003 he had to give up his private practice because of the limitations due to a serious illness he suffered a few years before. At the same moment, he started his study Physical Therapy Sciences at the Utrecht University, Academy of Health Sciences. He graduated in 2007 with a thesis called *"Can preoperative exercise assist the patient with cancer?"*. Until today Hans is still involved in research regarding the prehabilitation of patients before surgery.

Hans started in 2008 as a scientific researcher/PhD student in the Department of Anesthesiology, Pain and Palliative Medicine at the Radboud university medical center in Nijmegen. His research was about the validation of screening instruments for use in a consecutive, daily clinical practice population of patients with low back and leg pain, neck-shoulder pain or with pain due to a suspected peripheral nerve damage to assist the physician in the assessment of a neuropathic pain component. During his PhD trajectory Hans followed several additional courses in methodology and statistics. Nowadays he is frequently asked as a reviewer for several peer-reviewed journals.

Besides this research topic he participated and still participates in several other projects and cooperations in the field of pain-research and education about (the measurement of) pain in and outside the Radboudumc. In 2016 he and his team won the Lowlands Science Grant to investigate the influence of preferred and disliked music on pain experience (Title: *Meer of Minder Pijn met Muse*). In 2017 he was part of the team who obtained the Great National Research Grant to investigate the pain sensitivity of the Dutch public (Title: *Pijngevoeligheid bij het zien van pijn bij mannen en vrouwen*). An important issue in both projects was to raise awareness by the general public about the necessity of research in the field of pain and to let the people participate in pain research.

Hans has one daughter named Anna (born in 2000) and is living together with Nathalie van Schayk in Nijmegen.

PUBLICATION LIST

Publications, PubMed indexed:

1. **Timmerman H**, Wolff AP, Bronckhorst E, Wilder-Smith OHG, Schenkels M, van Dasselaar NT, Huygen FJPM, Steegers MAH, Vissers KCP. *Avoiding Catch-22: validating the PainDETECT in a population of patients with chronic pain.* **BMC Neurology.** 2018, Jun 29;18(1):91.

2. **Timmerman H**, Vissers KCP, Wolff AP, Wilder-Smith OHG. *The added value of bed-side examination and screening-QST to improve neuropathic pain identification in patients with chronic pain*. **Journal of Pain Research.** 2018, Jul 10;11:1307-1318.

3. Van Vliet J, Tieleman AA, Verrips A, **Timmerman H**, van Dongen RTM, van Engelen BGM, Wilder-Smith OHG. *Qualitative and Quantitative Aspects of Pain in Patients with Myotonic Dystrophy Type 2.* **Journal of pain.** 2018, Aug;19(8):920-930.

4. van Helmond N, **Timmerman H**, Olesen SS, Drewes AM, Kleinhans J, Wilder-Smith OH, Vissers KCP, Steegers MAH. *A Quantitative Sensory Testing Paradigm to Obtain Measures of Pain Processing in Patients Undergoing Breast Cancer Surgery.* **Journal Of Visualized Experiments (JOVE).** 2018, Jan 18;(131).

5. **Timmerman H**, Steegers MAH, Goeman J, Wilder-Smith OHG, Schenkels M, van Dasselaar NT, Huygen FJPM, Wolff A, Vissers K. *Investigating the validity of the DN4 in a consecutive population of patients with chronic pain.* **PLoS One.** 2017, Nov 30;12(11):e0187961.

6. Van Helmond N, **Timmerman H**, van Dasselaar N, van der Pol C, Vissers K, Wilder-Smith OH, Steegers M. *High body mass index is a risk factor for moderate to severe chronic postoperative pain after breast cancer treatment.* **Pain Physician.** 2017; 20:E661-E671

7. **Timmerman H**, Wilder-Smith OH, van Weel C, Wolff AP, Vissers KCP. 2014. *Detecting the neuropathic pain component in the clinical setting: A study protocol for validation of screening instruments for the presence of a neuropathic pain component.* **BMC Neurology.** 2014; 14:94 (May 2, 2014)

8. Van Haren IEPM, **Timmerman H**, Potting CM, Blijlevens NMA, Staal JB, Nijhuis-van der Sanden G. *Physical exercise for patients undergoing hematopoietic stem cell transplantation: systematic review and meta-analyses of randomized controlled trials.* **Physical Therapy.** 2013. April; 93(4):514-28.

9. **Timmerman H**, Wolff AP, Schreyer T, Outermans J, Evers AWM, Freynhagen R, Wilder-Smith OH, van Zundert J, Vissers KCP. *Cross-cultural adaptation to the Dutch language of the PainDETECT Questionnaire*. **Pain Practice.** 2013; 3: 206-214.

10. **Timmerman H**, Heemstra I, Schalkwijk A, Verhagen C, Vissers K, Engels Y. *Assessment of neuropathic pain in patients with cancer: The Interobserver reliability. An observational study in daily practice*. **Pain Physician.** 2013;16: 569-580

11. Chua NHL, **Timmerman H**, Vissers KCP, Wilder-Smith OH. *Multi-modal Quantitative sensory testing in patients with unilateral chronic neck pain: an exploratory study*. **MYOPAIN (*f.k.a. Journal of Musculoskeletal Pain)*.** December 2012, Vol. 20, No. 4 , Pages 292-299.

12. **Timmerman H**, de Groot J, Hulzebos E, de Knikker R, Kerkkamp H, van Meeteren N. *Feasibility and preliminary effectiveness of preoperative therapeutic exercise in patients with cancer. A pragmatic study*. **Physiotherapy Theory and Practice.** 2011. *Feb; 27 (2) 117-24.*

Publications, not PubMed indexed:

1. **Timmerman H**, Wilder-Smith O. *Richtlijn voor de Onderzoeker. Een gestandaardiseerde testbatterij voor Kwantitatief Sensorisch Testen volgens de regels van de Deutsche Forschungsverbundes Neuropathischer Schmerz (DFNS)*. Officiële Nederlandse vertaling van het DFNS protocol *(Versie 2.1-Dlv)*. **German Research Network on Neuropathic Pain (DFNS).** München, Germany. 2013

2. **Timmerman H**, Wolff AP, van Rijswijk ECAM, Vissers KCP. *Comment on StEP* (Scholz J, Mannion RJ, Hord DE, Griffin RS, Rawal B, et al.). *A Novel Tool for the Assessment of Pain: Validation in Low Back Pain*. **PLoS Medicine** 2009. *6 (4): e1000047. doi: 10.1371/journal.pmed. 1000047).*

3. De Groot J, de Knikker H, **Timmerman H**, Hulzebos E, Kerkkamp H, van Meeteren N. *Preoperatief fysiotherapeutisch trainingsprogramma voor oncologiepatienten: in Utrecht een MUST*. **Fysiopraxis.** 2007 (2): 28-31.

Publications, submitted:

1. Van Heusden-Scholtalbers LAG, **Timmerman H**, Bonenkamp H, van Goor H, Nijhuis-van der Sanden MWG, Staal BJ. *Preoperative physical exercise training for patients scheduled for major abdominal surgery. A systematic review and meta-analysis.* 2019. **(Cochrane Review, Submitted)**

2. **Timmerman H**, van de Linde L, van Boekel R, Bronkhorst E, Vissers K, van der Wal S, Steegers, M. *The effect of preferred music versus disliked music on pain thresholds in healthy volunteers.* 2019. **(Submitted)**

3. van den Elzen NGA, Daman V, Duijkers M, Wijnhoven E, Otte K, **Timmerman H**, Olde Rikkert MGM. *The Bach-Sinatra effect of enhancing muscle power in older people. A randomized crossover study.* 2019. **(Submitted)**

4. van Boekel R, **Timmerman H**, Bronkhorst E, Vissers KCP, Steegers M. *The validity of the Dutch version of the Pain Sensitivity Questionnaire.* 2019. **(Submitted)**

Books and Bookchapters:

1. **Timmerman H**, van den Broeke EN, Wilder-Smith OH. 2014. *Hoofdstuk 7: Meetinstrumenten voor pijn* in: Handboek Pijnbestrijding (Translated: *Chapter 7: Measurement instruments for Pain* in: Handbook Pain Treatment*)*. Uitgeverij de Tijdstroom, Utrecht, the Netherlands.

Posters and poster presentations:

1. Schuttert I, **Timmerman H**, Groen GW, Wolff AP. *Effects of Tapentadol on chronic pain and parameters of central sensitisation. A prospective, open label, randomized cross-over study with pregabaline as comparator (PRINCE study).* SPBR 2018, Groningen, the Netherlands.

2. Schuttert I, **Timmerman H**, Groen GW, Wolff AP. *Central sensitisation in patients with chronic low back pain radiating to the leg (CLaSSICO STUDY).* SPBR 2018, Groningen, the Netherlands.

3. **Timmerman H**, Wolff AP, Wilder-Smith OH, Vissers KCP. *Screening for a neuropathic pain component: a mission impossible?* e-Poster presentation. 8th World Congress of the World Institute of Pain 2016, New York, USA.

4. **Timmerman H**, van Dasselaar NT, Wolff AP, Wilder-Smith OH, Steegers MAH, Vissers KCP. *The validity of the PDQ in patients after treatment for breast cancer.* 5th international congress of neuropathic pain special interest group: NeuPSIG 2015, Nice, France.

5. Van Vliet J, Verrips A, **Timmerman H**, van Dongen R, Wilder-Smith H, van Engelen E. *Karakterisering van pijn in patiënten met myotone dystrofie type 2.* Wetenschappelijke vergadering van de Neurologie 2015, Nunspeet, the Netherlands.

6. **Timmerman H**, Wolff A, van Dasselaar N, Steegers M, Wilder-Smith O, Vissers K. *The validity of the DN4 in patients after breast cancer.* 7th World Congress of the World Institute of Pain 2014, Maastricht, the Netherlands.

7. Van der Wal S, Steegers M, Radema S, De Graaf W, **Timmerman H**, Vaneker M, Vissers K. *A case report: lowdose intravenous lidocaine for chronic chemotherapy induced peripheral neuropathy. 7th World* Congress of the World Institute of Pain 2014, Maastricht, the Netherlands.

8. **Timmerman H**, Heemstra I, Schalkwijk A, Verhagen C, Engels Y, Vissers K.*The interobserver reliability of the diagnosis of neuropathic pain in patients with cancer: a kappa study.* World Congress International Association for the Study of Pain 2012, Milan, Italy

9. **Timmerman H**, Wolff AP, Schreyer T, Outermans J, Evers AWM, Freynhagen R, Wilder-Smith OH, van Zundert J, van Rijswijk E, Vissers KCP. *Crossculturele adaptatie van de Nederlandstalige PainDETECT vragenlijst*. NHG-Wetenschapsdag 2011, Nijmegen, The Netherlands

10. **Timmerman H**, Wolff AP, Schreyer T, Outermans J, Evers AWM, Freynhagen R, Wilder-Smith OH, van Zundert J, van Rijswijk E, Vissers KCP. *Cross-cultural adaptation of the PainDETECT questionnaire to the Dutch language.* World Congress on Physical Therapy 2011, Amsterdam, The Netherlands

(Congress) Presentations and lectures:

1. **Timmerman, H**. *AUWCH! PAIN is no FUN!!* Lectures for children held in the framework of Radboud Invites (Science Weekend). 2018, Radboud University Nijmegen, the Netherlands

2. **Timmerman H**. *Use of evaluation scales: Measuring the pain experience*. WIP Benelux-WAPMU: International evidence-based medicine symposium, 2017, Nijmegen, the Netherlands.

3. **Timmerman H**. *How do you communicate your science? About Lowlands Science and the Media.* Radboud Post Doc Initiative, 2017, Nijmegen, the Netherlands

4. **Timmerman H**, de Groot J, Hulzebos E, de Knikker R, Kerkkamp H, van Meeteren N. *Feasibility of preoperative therapeutic exercise in patients with cancer. Royal Dutch Congress of Physical Therapy, 2007, Amsterdam, The Netherlands*

5. **Timmerman H**, de Groot J, Hulzebos E, de Knikker R, Kerkkamp H, van Meeteren N. *Feasibility and patient believes of preoperative therapeutic exercise in patients with cancer.* Dutch Congress on Psychology in Patients with Oncology, 2007, Utrecht, The Netherlands.

Grants, Awards and Prices:

1. Steegers M, van Boekel R, **Timmerman H**, van der Wal S, Blaney Davidson E. *Pijngevoeligheid bij het zien van pijn bij mannen en vrouwen.* **Groot Nationaal Onderzoek**. NWO/NTR. 2017, Hilversum, the Netherlands.

2. **Timmerman H**, van der Wal S, Groot M, Steegers M. 2016. *More or Less Pain with Muse. The influence of music on pain.* Winner of the **Grant for Lowlands Science** 2016, Biddinghuizen, the Netherlands.

PhD Portfolio

Institute for Health Sciences
Radboudumc

Name PhD candidate: *H. Timmerman*	***PhD period:*** *16-06-2008 – 03-05-2019*
Department: *Anesthesiology, Pain and Palliative Medicine*	***Promotor(s):*** *prof. dr. K.C.P. Vissers* *prof. dr. A.P. Wolff*
Graduate School: *Radboud Institute for Health Sciences*	***Co-promotor(s):*** *prof. dr. M.A.H. Steegers* *dr. O.H.G. Wilder-Smith*

	Year(s)	ECTS
TRAINING ACTIVITIES		
a) Courses & Workshops		
- Basiscursus Regelgeving en Organisatie van Klinische Trials (NFU, Utrecht, the Netherlands)	2018 2014 2010	2.0
- Training for Coaches (Radboudumc, Nijmegen, the Netherlands)	2016	0.5
- Media Training (PAO Heyendaal, Nijmegen, the Netherlands)	2016	0.2
- Introductie tot de Nijmeegse Curricula (PAO Heyendaal, Nijmegen, the Netherlands)	2015	0.2
- Meta Analyses (LUMC, Boerhaave, leiden, the Netherlands)	2013	1.0
- Systematic reviews of Measurement Instruments (VUMC, Amsterdam, the Netherlands)	2013	0.3
- Presentation Skills (Radboud in'to languages, Nijmegen, the Netherlands)	2012	1.5
- Advanced Conversation (Radboud in'to languages, Nijmegen, the Netherlands)	2011	1.5
- Quantitative Sensory Testing (DFNS, Bochum, Germany)	2010	0.3
- Academic Writing (Radboud in'to languages, Nijmegen, the Netherlands)	2009	3.0
b) Seminars & lectures		
- AUWCH! PAIN is no FUN!! Lectures for children about pain (Radboudumc, Nijmegen, the Netherlands)	2018	0.2
- How do you communicate your science? About Lowlands Science and the Media (Radboudumc, Nijmegen, the Netherlands)	2017	0.1
c) Symposia & congresses		
- IASP (Boston, USA)	2018	1.0
- EFIC (Copenhagen, Denmark)	2017	1.0
- WIP-Benelux (Nijmegen, the Netherlands) oral presentation	2017	0.3
- WIP (New York, USA) poster presentation	2016	1.0
- NeuPSIG (Nice, France) poster presentation	2015	1.0
- WIP (Maastricht, the Netherlands) poster presentation	2014	1.0
- NeuPSIG (Toronto, Canada)	2013	1.0
- IASP Research Symposium (Arnhem, the Netherlands)	2013	0.5
- IASP (Milan, Italy)	2012	1.0
- EFIC (Hamburg, Germany)	2011	1.0
- WCPT (Amsterdam, the Netherlands) poster presentation	2011	0.3
- NeuPSIG (Athens, Greece)	2010	1.0
- NeuPSIG Satellite (London, UK)	2008	1.0

d) Other		
Reviewer Scientific Papers	2012-...	5.0
- PLoS ONE		
- Pain Practice		
- Pain Medicine		
- BMC Neurology		
- Yonsei Medical Journal		
- Journal of Pain Research		
- Current Medical Research & Opinion		
- Journal of Back and Musculoskeletal Rehabilitation		
- Transactions on Neural Systems and Rehabilitation Engineering		
TEACHING ACTIVITIES		
e) Lecturing		
- Measuring Pain (Psychology, Radboud University)	2019	0.2
- Coach for Medical Students (1st, 2nd and 3rd year students)	2016-...	28.0
- Minor Pain and Palliative Medicine	2018-...	1.0
- Capita Selecta Co-Assistants	2012-2017	1.0
- Education Pain and Pain treatment (5KNW7)	2011-2017	5.0
f) Supervision of internships / other		
- Supervisor research internship, Master Medicine, Radboud University Medical Center. Student: Ludo van de Linde	2016-2017	1.0
- Project leader 'More or Less Pain With Muse' (Lowlands Science, Biddinghuizen, the Netherlands)	2016	10
TOTAL		**72.3**

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