

Review and recommendations

## NeuPSIG guidelines on neuropathic pain assessment

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### ABSTRACT

This is a revision of guidelines, originally published in 2004, for the assessment of patients with neuropathic pain. Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system either at peripheral or central level.

Screening questionnaires are suitable for identifying potential patients with neuropathic pain, but further validation of them is needed for epidemiological purposes. Clinical examination, including accurate sensory examination, is the basis of neuropathic pain diagnosis. For more accurate sensory profiling, quantitative sensory testing is recommended for selected cases in clinic, including the diagnosis of small fiber neuropathies and for research purposes.

Measurement of trigeminal reflexes mediated by A-beta fibers can be used to differentiate symptomatic trigeminal neuralgia from classical trigeminal neuralgia. Measurement of laser-evoked potentials is useful for assessing function of the A-delta fiber pathways in patients with neuropathic pain. Functional brain imaging is not currently useful for individual patients in clinical practice, but is an interesting research tool. Skin biopsy to measure the intraepidermal nerve fiber density should be performed in patients with clinical signs of small fiber dysfunction.

The intensity of pain and treatment effect (both in clinic and trials) should be assessed with numerical rating scale or visual analog scale. For future neuropathic pain trials, pain relief scales, patient and clinician global impression of change, the proportion of responders (50% and 30% pain relief), validated

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neuropathic pain quality measures and assessment of sleep, mood, functional capacity and quality of life are recommended.

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## 1. Introduction

Neuropathic pain causes suffering and disability for many patients, and is an important public health problem. Treatment recommendations have been published recently [110]. The Assessment Committee of the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) has produced recommendations on the assessment of neuropathic pain in primary care [176]. This current recommendation is directed at pain specialists, neurologists and clinical researchers. The European Federation of Neurological Societies (EFNS) guidelines on assessment of patients with neuropathic pain assessment were published in 2004 [84]. In this paper, we have updated and extended these guidelines by including assessment of epidemiology, psychological aspects, and autonomic nervous function. The EFNS classification of papers and grading of the recommendations was applied where possible, but due to lack of sufficient guidance in some areas the classification was not possible use in all parts of the review.

Neuropathic pain has been recently redefined by NeuPSIG as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” [452]. This implies that neuropathic pain can arise from a lesion affecting either the peripheral or the central nervous system. The current IASP definition is “pain initiated or caused by a primary lesion or dysfunction of the nervous system” [295]. The new definition proposed by NeuPSIG replaces “dysfunction” with “disease” to distinguish neuropathic pain from pain such as that caused by neuroplastic plastic changes in response to strong nociceptive stimulation. The term “nervous system” is replaced by the “somatosensory system” to distinguish neuropathic pain from pain caused by lesions in other parts of the nervous system, e.g., pain associated with muscular spasticity associated with lesions of central motor pathways [153]. The process of diagnosing neuropathic pain, proposed for both clinical and research purposes, is presented in Fig. 1 [452].

As diseases and lesions affecting the somatosensory system can be either painful or painless, our standpoint is to address patients with pain, i.e., neuropathic pain, rather than neuropathy. The challenge is to differentiate neuropathic pain from other types of pain and to diagnose the lesion or disease causing the pain. Recommendations on traditional neurological diagnostic tests to the essential diagnostic step of confirming a lesion or disease of the somatosensory system were not within the scope of the current work. Standard neurophysiological responses to electrical stimuli, such as nerve conduction studies and somatosensory evoked potentials, are useful to demonstrate, locate and quantify damage along the peripheral and central pathways, but they do not assess the function of nociceptive pathways [84]. Regarding the diagnosis of neuropathy we refer to recent guidelines [119–122]; diagnostic algorithms of peripheral neuropathies and central nervous system diseases causing neuropathic pain are beyond the scope of this review.

The objectives of this article are to: (1) assess the incidence and prevalence of neuropathic-type pain in the population, (2) evaluate the sensitivity of the various methods for assessing patients with neuropathic pain, (3) evaluate the methods in assessing standard treatments, and (4) propose, where required, new studies that may help to clarify unsolved issues.

## 2. Methods

### 2.1. Search strategy

An informatician searched systematically the Medline and Cochrane databases. Topics not covered by the EFNS guideline were searched from 1950 to 2008 and the topics that were covered by the EFNS guideline were searched from 2002 to 2008. Relevant MeSH terms and freetext words were used to delineate neuropathic pain conditions and the topics (i.e., different assessment tools or aspects). Searches were limited to original articles published in English. The SIGN filters [514] were used to define different types of studies. More detailed information on the searches is provided in e-Appendix 1. Additional searches included bibliographies of the retrieved papers and relevant handbooks. The most recent publications (available online but not in databases) were searched by the Assessment committee members.

### 2.2. Selection criteria

The Assessment committee members reviewed abstracts and titles for relevance. Then, at least two committee members reviewed papers meeting the inclusion criteria. An additional committee member arbitrated any disagreements. Only full original communications were included. Only studies with “definite” and “probable” neuropathic pain conditions [452] were included. Studies on mixed pain conditions were included only if the neuropathic pain component was reported separately. For topics with a high number of high-quality publications (e.g., assessment of treatment efficacy, see e-Table 4, or assessment of disability, see e-Table 6), we used more stringent inclusion criteria, whereas for topics with few published papers (e.g., microneurography) even case reports were included.

### 2.3. Data analysis and quality assessment

Classification of evidence and recommendation grading adhered to the EFNS standards [55] (Table 1), and the information was retrieved to the evidence tables (e-Tables 1–15). For those parts with insufficient guidance for classification, the classification of papers and grading of the recommendations have not been presented. Criteria used to evaluate outcome measures in treatment studies included specificity, sensitivity and reliability in neuropathic pain, and availability in different cultures and languages.

## 3. Results

### 3.1. Epidemiology

We evaluated the methods for case identification used in population-based epidemiological studies whose aim(s) included a determination of the incidence or prevalence of neuropathic-type pain, either as a single entity or of specific neuropathic pain condition(s). Inclusion and exclusion criteria are listed in e-Appendix 2. Fifteen original studies were included (e-Table 1). Three of them used screening questionnaires (DN4, S-LANSS, and a combination of these) to identify pain “with neuropathic characteristics” or of

**Table 1**  
Classification of the studies applied to a diagnostic measure.

<i>Evidence classification scheme for a diagnostic measure</i>	
Class I:	A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy
Class II:	A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy
Class III:	Evidence provided by a retrospective study where either persons with the established condition or controls are narrow spectrum, and where the test is applied in a blinded evaluation
Class IV:	Any design where the test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)
<i>Rating of recommendations</i>	
Level A:	(established as useful/predictive or not useful/predictive) at least one convincing class I study or at least two consistent, convincing class II studies
Level B:	(probably useful/predictive or not useful/predictive) at least one convincing class II study or overwhelming class III evidence
Level C:	(possibly useful/predictive or not useful/predictive) at least convincing class III studies

“predominantly neuropathic origin” [52,174,451]. The prevalence ranged from 3.3% to 8.2%. As the screening tools were validated using pain clinic attendants, their ability to detect neuropathic pain in a general population is not fully elucidated. These instruments are likely to show lower sensitivity and specificity in a community setting than in the original validation studies, and these results should therefore be interpreted with caution for epidemiological purposes [37,497]. A review of screening instruments for neuropathic pain highlights their potential value in epidemiological and clinical research and practice, but also some of the limitations [35,36].

The twelve original general population studies of specific neuropathic diagnoses included studies on multiple conditions [100,179,180], postherpetic neuralgia (PHN) [74,189,326,515], neuropathic pain originating in the back [144,517], painful diabetic neuropathy [92,511], and supraorbital neuralgia [421]. Five of these used interview surveys as the method of case ascertainment [174,189,421,511,517], two used standardized questionnaire instruments [421,517], two used standardized instrument [174,511] and another reported no standardization or validity testing of case ascertainment [189]. Two of the interview surveys also included a clinical examination [421,517].

Six studies based their case identification and ascertainment on a review of computer-held primary care medical records, using diagnostic codes [74,100,179,180,326,515], with two of these also reviewing the full-text medical records [74,100]. The accuracy of case ascertainment using diagnostic codes was comprehensiveness of data entry.

One study [92] of painful diabetic neuropathy used a two-stage process: the first stage used one question from a standard, validated postal questionnaire (the Diabetic Neuropathy Symptom Score); the second stage assessed positive respondents by clinical examination using the Toronto Clinical Scoring System, which had previously been found to correlate closely with nerve morphology and electrophysiology. A further study [144] was a two-stage project, the first stage being the development and validation of a screening questionnaire, and the second being the application of this instrument to a population of individuals with low back pain. This screening instrument (PainDETECT) has undergone extensive validation, although it suffers from some of the same limitations as the screening instruments described above.

We also identified two review papers on neuropathic pain epidemiology in general population [387,442]. The case identification methods used and criteria for inclusion in the reviews remained unclear, and hence it is difficult to assess the validity of the estimates presented.

The considerable variability in reported prevalence and incidence (results reported in e-Table 1) of neuropathic pain condi-

tions is likely to be due, in part, to differences in definitions of neuropathic pain, methods of assessment, and patient selection. There is a need for the development and standardization of valid definitions and assessment for the purposes of general population research (as well as for clinical trials of interventions). Good epidemiological studies using these will be informative in understanding the distribution of neuropathic pain and risk factors for its development.

*Recommendation:* We recommend further studies to develop standardized identification and assessment of neuropathic pain for epidemiological research. The methods used should be feasible, valid and acceptable to researchers and participants. They will include both questionnaire-based and clinical assessment methods. Existing screening tools require further validation before they can be completely useful for epidemiological studies in general population samples. To enhance completeness of case identification from medical records in research setting in primary care, we recommend concentrating medical records reviews in networks of “expert practices”, and increased training in the awareness and assessment of neuropathic pain.

### 3.2. Screening tools

In recent years, several screening tools based on verbal pain description with, or without, limited clinical examination, have been developed and validated in neuropathic pain (e-Table 2). We will present here only tools that have been validated in neuropathic pain in general. Tools validated only in a particular subgroup of neuropathic pain patients will not be discussed [401].

*The Leeds assessment of neuropathic symptoms and signs (LANSS)* contains 5 symptom items and 2 clinical examination items [34]. A score of 12 or more (out of a possible 24) suggest neuropathic pain. A self-report tool, the S-LANSS [37], has also been validated. After the initial validation study, the LANSS has been tested and validated in several settings [e.g., 215,352,519] with sensitivity and specificity ranging from 82% to 91% and 80% to 94%, respectively, compared to clinical diagnosis.

*The neuropathic pain questionnaire (NPQ)* consists of 12 items that include 10 related to sensations or sensory responses, and 2 related to affect [240]. The short form of the NPQ maintained similar discriminative properties with only 3 items (numbness, tingling, and pain increase in response to touch) [23]. Research on sub-groups of patients referred to a specialist pain clinic with specific pain diagnoses suggests that it may have power to discriminate between neuropathic pain and non-neuropathic pain [136].

*Douleur neuropathique en 4 questions (DN4)* consists of 7 items related to symptoms and 3 related to clinical examination [50]. The DN4 is easy to score and a total score of 4 out of 10 or higher

suggests neuropathic pain. The 7 sensory descriptors can be used as a self-report questionnaire with similar results [50]. The tool was developed and validated in French and has been translated into 15 languages [467]. It has been fully validated in both Spanish [341] and Thai languages [71]. The DN4 has been used in large epidemiological studies to estimate the prevalence of neuropathic pain both in the general population [52] and specific clinical situations (e.g., diabetic neuropathy) [463].

*painDETECT* was developed and validated in German [144] and incorporates a self-report questionnaire with 9 items that do not require a clinical examination. *painDETECT* has been translated in 22 languages. There are 7 weighted sensory descriptor items and 2 items relating to the spatial (radiating) and temporal characteristics of the individual pain pattern. It is also available in English.

*ID-Pain* consists of 5 sensory descriptor items and 1 item relating to whether pain is located in the joints (used to identify nociceptive pain); it also does not require a clinical examination [351]. It was designed to screen for the likely presence of a neuropathic component to the patient's pain. In the validation study, 22% of the nociceptive group, 39% of the mixed group, and 58% of the neuropathic group scored above 3 points, the recommended cut-off score.

*Recommendation:* Until consensus is reached on a diagnostic approach to neuropathic pain, screening tools will serve to identify patients with possible neuropathic pain, particularly when used by non-specialists and this is probably their chief clinical strength. These screening tools share many features despite being developed by different groups in different contexts [35]. Their ease of use by professionals and patients alike, in clinic or via telephone or internet, makes them attractive because they provide immediately available information. As none of the screening tools has been validated in all major languages, preference should be given to a tool validated in the language in which it will be applied. However, screening tools fail to identify about 10–20% of patients with clinician diagnosed neuropathic pain indicating that they may offer guidance for further diagnostic evaluation and pain management but cannot replace clinical judgment.

### 3.3. Clinical examination and psychophysiological measures

#### 3.3.1. Clinical examination

The clinical examination of a pain patient with a possible neuropathic pain condition is aimed at verifying or rejecting the hypothesis of a lesion or disease of the somatosensory system, which fits the assumed injured/diseased level of the nervous system as extracted from the history [182,256,452]. Sensory, motor and autonomic signs should be sought [183]. It is important to emphasize that the clinical examination can never prove any pain to be of neuropathic origin, it can only provide supporting evidence for altered function of the nervous system. Bedside examination is the only approach that can address the issue of presence of other types of pathological processes that can also cause the pain (i.e., generates and ranks types of pain as matter of differential diagnosis) and it is the only approach that can answer the question where on the neuraxis is pathology that generates neuropathic pain. Neuropathic pain is usually confined to part of, or the entire, innervation territory of the affected nervous structure [452]. Yet, pain in a region with nerve injury is not necessarily all of neuropathic origin, and a nerve injury may also give rise to, for example, altered muscle tone or movement pattern and a concomitant nociceptive pain.

A careful bedside examination of somatosensory functions is recommended, including touch/vibration, cold, warmth and pain sensibility [182]. Tactile sense is assessed by a piece of cotton wool, pinprick sense by a wooden cocktail-stick, thermal sense by warm and cold objects (e.g., metal thermorollers), and vibration sense by a 128-Hz tuning fork [84]. Patients may find sensory abnormalities

in neuropathic pain conditions unfamiliar and perhaps difficult to communicate. Somatosensory aberrations found in neuropathic pain conditions have some common denominators, i.e., borders fitting the distribution of the affected peripheral nervous structure (nerve, plexus, root) or the topographic representation of a body part in the central nervous system. Hence, surveying the borders of sensory dysfunction is mandatory. Quantitative aberrations such as hypo- and hyperesthesia may be found as well as qualitative dysfunctions such as allodynia and dysesthesia [182]. Also, temporal (e.g., aftersensation, summations) and spatial (dyslocalization, radiation) alterations may be demonstrated [182]. The findings in the painful area should be compared with the findings in the contralateral area in unilateral pain conditions. In polyneuropathy a proximo-distal delineation is sought.

When performing sensory testing and interpreting sensory findings the clinician should be aware of the complexity of sensory aberrations. Positive sensory phenomena (allodynia and hyperalgesia) are common in nociceptive pain states, especially in inflammatory conditions. Negative sensory phenomena (hypoesthesia and hypoalgesia) have also been reported in non-neuropathic pain, e.g., in muscular pain [256]. Bilateral sensory abnormalities are possible in neuropathic pain conditions regarded as unilateral, e.g., postherpetic neuralgia. To avoid erroneous conclusions of the origin and type of pain on the basis of sensory findings, clinical examination of other organ systems should also be performed to identify possible causes of nociceptive pain. It may be coexisting with neuropathic pain or the sole cause of the pain. The plan of further examinations is evaluated case by case. Surveying the borders of sensory dysfunction to differentiate diffusely located non-neuropathic pains from neuroanatomically plausible distribution of neuropathic pain is crucial. In addition, repeated testing may be helpful. The outcome of repeated testing during one session should be reproducible, keeping in mind that degree of variability could be present because of modulation of sensory pain perception is under influence of modulatory pain system. It should be emphasized that lesions of somatosensory fibers/pathways lacking a cutaneous distribution may escape detection with available techniques for somatosensory examination of the skin. Validated methods to test sensibility in deeper tissues are lacking.

Clinical examination alone is less sensitive than several complementary testing to document the presence of a somatosensory lesion [119,120,122]. For example, ENMG has been shown superior to clinical examination alone for the diagnosis of peripheral neuropathy [122]. However, the relevance of clinical examination to differentiate neuropathic pain from non-neuropathic pain has been demonstrated in several studies using large sample sizes [34,50,361,403]. These studies have shown that sensory examination (i.e., pinprick, heat, cold and tactile stimuli) in the painful area could discriminate patients with neuropathic pain from those without neuropathic pain. Furthermore, allodynia, although also found in patients with non-neuropathic pain, has distinctive features in patients with neuropathic pain. The same studies have shown that allodynia to brush, cold and heat and temporal summation to tactile stimuli, although not pathognomonic, was observed with much higher frequency in patients with neuropathic pain. Conversely, allodynia to pressure is not specific and is common in both neuropathic and non-neuropathic pain [50]. In some of these studies, the clinical examination was repeated (test-retest) and was found highly reproducible from one tester to another, when performed blindly of the status of the patient [50]. These studies have therefore confirmed that some items of clinical examination (hypoalgesia to pinprick, hypoesthesia to tactile stimuli, allodynia to brush and cold, and temporal summation) are particularly discriminant. A study comparing clinical examination to skin punch biopsy and QST in patients with painful small fiber neuropathy

showed that clinical examination was even more sensitive than QST [99].

**Recommendation:** Clinical examination is a crucial part of the diagnostic process of neuropathic pain, aiming at finding possible abnormalities relating to a lesion of the somatosensory system. Sensory testing is the most important part of this examination and includes testing of touch, vibration, pinprick, cold and warmth. It is recommended that the examination of somatosensory function should be guided by a tentative diagnosis based on the information collected up to that point. As the patients may find sensory abnormalities in neuropathic pain conditions unfamiliar, the physician must be receptive in order for the psychophysical examination to be complete. Bedside sensory examination using simple utensils should always precede the use of more sophisticated neurophysiological techniques, including quantitative sensory testing. Importantly, no gold standard is available to label a specific pain within an area of sensory abnormalities as neuropathic pain. For the pain diagnosis the physician is advised to use clinical judgement based on the outcome of a comprehensive clinical approach.

### 3.3.2. Quantitative sensory testing

Since the original EFNS guidelines were published [84], 76 new case series have been published that used quantitative sensory testing (QST) with a variety of different protocols (e-Table 3). Of these studies, 43 included assessment of mechanoreception, 57 thermoreception, and 58 nociception. All three aspects were covered in 30 studies. Thus, QST is still biased towards thermal, including nociceptive, testing, which means that it excludes assessment of large fiber function. More studies with complete somatosensory profiles are needed. Only then will it be possible to perform meta-analyses on differential sensitivities of the various QST parameters. Multicenter reference and extensive validation data have been published for the German Research Network on Neuropathic Pain protocol ([www.neuro.med.tu-muenchen.de/dfns/](http://www.neuro.med.tu-muenchen.de/dfns/)) [376,377], but only few clinical studies have reported its use to date.

Assessing diagnostic accuracy to identify neuropathic pain has not been a major topic for QST studies. Instead, they mostly focus on the somatosensory profile of various clinical conditions (34 studies). However, 14 trials compared patients with the same diagnosis with and without pain. Four of these studies reported no difference, the remainder found differences in one or more QST parameters (loss of cold and warm detection, tactile detection or pinprick detection; or hyperalgesia). Loss of cold detection was reported to be predictive most frequently (four studies), but this may reflect a bias of what type of test was performed.

Pharmacological and non-pharmacological treatment trials using QST were reported in 25 papers. Effects were found on dynamic mechanical allodynia (5 trials), pinprick hyperalgesia (1 trial) and sensory loss (4 trials). Treatment efficacy was predicted by thermal detection thresholds (2 trials) vibration detection thresholds (2 trials), heat hyperalgesia (1 trial) and dynamic mechanical allodynia (1 trial). In 15 trials, QST was validated against evoked potentials or skin biopsy, with generally good correlations for small fiber function. Validation for large fiber function has not been reported.

The EFNS quality criteria cannot be applied to QST as most studies do not mention blinding required for class I–III evidence except pharmacological studies (QST was performed blindly with regards to the treatment used, see e-Table 4). Researchers should be encouraged to use observer blinding in QST. On the other hand, EFNS should re-evaluate its quality criteria for class III evidence in diagnostic tests: whereas blinding is essential in therapeutic trials, it is arguable what influence the operator can have on a thermotest machine. The American Academy of Neurology

criteria are difficult to apply as well, since they require a diagnostic gold standard ([www.aan.com](http://www.aan.com)). The grading system of definite and probable neuropathic pain as suggested for the NeuPSIG redefinition of neuropathic pain should be used in future studies [452].

As QST abnormalities are also found in non-neuropathic pains, they cannot be taken as a conclusive demonstration of neuropathic pain [84]. QST findings, however, are considered a confirmatory diagnostic test in the neuropathic pain grading system, since QST can provide independent verification of sensory signs.

**Recommendation:** QST can be used in clinic along with bedside testing to document the sensory profile. However, it cannot allow for the estimation of the level of the lesion within the neuraxis. Future QST studies should always assess full somatosensory profiles by blinded observers, and the patients should be clinically characterized as definite or probable neuropathic pain according to the proposed grading system. QST can also be helpful in pharmacological studies to document treatment effects on subtypes of evoked pains. However, the relevance of QST to predict therapeutic outcome has yet to be established in prospective studies.

### 3.4. Pain intensity, quality and assessment of the treatment effect

#### 3.4.1. Pain intensity

Pain intensity may be measured by Likert scales (0 = no pain, 10 = worst possible pain), visual analog scales (VAS) or verbal rating scales (VRS) [207]. A combination of verbal and numerical rating is the Gracely Pain Scale [169], used in several neuropathic pain studies [124,391,415]. The Likert scale and VAS are the most frequently reported measures of pain intensity in neuropathic pain and data may be collected using paper or electronic diaries. These scales have been the most commonly used primary outcome measures in neuropathic pain trials and are sensitive to change (see e-Table 4). The categorical pain scale has been found similarly [359,379,494] or less [54,219] sensitive to change than numerical scales.

Fluctuation of neuropathic pain over time can be assessed by measuring average pain, “pain as its worst” (which has sometimes been found more sensitive than average pain intensity) [228,229,294,441], “pain as its least” and “pain right now” (as in the Brief Pain Inventory) [76]. Different components of neuropathic pain should be measured separately (e.g., spontaneous continuous and evoked pain) [284,324,418,419,493,494,495]. Event dairies may be a more appropriate method for measuring spontaneous paroxysmal pain than pain intensity measures. Separate evaluations of the intensity and unpleasantness of pain have been performed uncommonly in neuropathic pain [242].

#### 3.4.2. Pain quality and temporal aspects of pain

The *McGill pain questionnaire* [292], and the 15-item short form (SF-MPQ) [293] were conceived as generic questionnaires applicable to any type of pain and have not been validated for neuropathic pain assessment, although they have been sometimes used to attempt to discriminate neuropathic from non-neuropathic pains [53,361]. Despite this limitation, the SF-MPQ has been to date the most commonly used quality assessment tool particularly in recent large scale therapeutic studies of neuropathic pain (31 from 2002 to 2009) most commonly as secondary outcome [e.g., 109,161]. However, the total score or subscores of the SF-MPQ are not more sensitive to change [e.g., 109,368] or have occasionally been less sensitive [24,39,415, see however [159]] than intensity scales. Recently a revised version of the SF-MPQ, the SF-MPQ-2 adding symptoms more relevant to neuropathic pain has been proposed [112] and found sensitive to change in diabetic neuropathic pain. However, the validation of this scale should be regarded as preliminary [49].

Specific neuropathic assessment scales have been designed to evaluate separately the various symptoms of neuropathic pain. Two of them have been validated in neuropathic pain in general while others such as the Total symptom score or Neuropathic total score 6 [28] have been exclusively validated and used in trials of painful diabetic neuropathy [6140,516,526].

The neuropathic pain scale (NPS) [147] includes 10 pain quality items rated on Likert scales and a temporal assessment of pain. Various composite scores have been proposed although not formally validated [148] whereas a recent validation study in multiple sclerosis identified 3 factors for NPS items ("familiar", "superficial" and "alien" perception) [374]. The NPS has been used in 12 neuropathic pain double blind trials most commonly as secondary outcome measure [e.g., 58, 148, 206, 222, 315, 363, 373, 412, 478], sometimes as primary outcome [499], some of them reporting differential effects of treatments on specific items [206,259,268,373,499]. It has been translated into several languages and an Italian version has been published [309]. A derived version aiming to assess neuropathic and non-neuropathic pain conditions, the Pain Quality Assessment Scale, includes additional neuropathic pain qualities (e.g., paroxysmal pain) [206,472] but its sensitivity to change has not been assessed to date in double blind trials and it has only been validated to date in carpal tunnel syndrome.

The neuropathic pain symptom inventory (NPSI) contains 10 descriptors grouped into 5 distinct dimensions (burning, paroxysmal, deep, evoked, paresthesia) and 2 temporal items which assess pain duration and the number of pain paroxysms [19,51]. The items used to assess evoked pain have been validated against clinical examination and QST, thus making suitable for assessment of allodynia and hyperalgesia [19]. The originally validated French NPSI has been translated and linguistically validated in 50 other languages; its conceptual adequacy has been confirmed in 6 languages [82] and it has been revalidated in Italian [338] and in German. Its factorial structure makes it suitable to capture different aspects of neuropathic pain that may have distinct pathophysiological mechanisms [17,454]. Thus it has recently been found that the various pain qualities of neuropathic pain as assessed with the NPSI were distinctly correlated to neurophysiological data in patients with carpal tunnel syndrome [454]. The NPSI has been used in 3 double blind trials as secondary outcome [91,31,357] with some dimensions being more sensitive to treatment than the overall assessment of pain intensity [357].

Few neuropathic pain trials, except those dealing with trigeminal neuralgia [18,133], have assessed the temporal aspects of pain [111]. Some of them are assessed in specific neuropathic pain questionnaires (see above). Temporal aspects represent a distinct dimension of pain [207], and have been found sensitive to change in neuropathic pain [160,357,363,416,430].

#### 3.4.3. Measures designed to assess treatment efficacy

One hundred and thirty-seven randomized controlled trials and 3 *post hoc* analyses of outcome measures published since 2002 were included for analysis of treatment outcome (see e-Table 4).

Several additional methods have been conceived for assessing treatment efficacy [111]. The numerical or categorical pain relief scales [98] have been found as sensitive [e.g., 54, 302, 379, 381, 494] or more sensitive than intensity scales [163,227,419]. The *Global impression of change* reported by the patient (PGIC) or evaluated by the physician (CGIC) is recommended in chronic pain trials by IMMPACT [111] (<http://www.immpact.org>). It has been shown more sensitive to treatment effects in neuropathic pain [109,360,407,501] than pain intensity measurement [163,407]. Other global outcome measures of efficacy (e.g., patient's preference for treatment, satisfaction with treatment or pain relief, composite measures of treatment efficacy) have also been shown sensitive to treatment effect in neuropathic pain [9102,143,160,356,359,494].

The proportion of responders has been evaluated in 41 neuropathic pain studies as co-primary or secondary outcome and found sensitive to treatment effects [163,258,368,379]. Responders are generally defined on the basis of a 50% pain relief, which is the "gold standard" criterion in meta-analyses to calculate the "Number Needed to Treat" (NNT) [290]. However, 30% reduction in NRS of pain intensity is also clinically important [129] and may provide important complementary information [2,63,146,163,241,410]. Importantly, the NNT may be very different depending on the method of calculation [163].

The effect size [79] measures the magnitude of a treatment effect and complements well other measures of efficacy but has been calculated in only few neuropathic pain trials [143,291,363].

The use of rescue medication has shown good sensitivity to change in some trials [54,161,419,501] and poor sensitivity in others [63,241,420,438] probably because neuropathic pain is weakly sensitive to conventional analgesics.

*Recommendation:* We recommend the use of NRS or VAS scales to assess pain intensity in neuropathic pain and effects of treatment on neuropathic pain intensity both in daily practice and in clinical trials (level A). The NRS may be easier to use than the VAS for elderly people [111] and is the most reliable to assess treatment effect in chronic pain [111]. In clinical trials categorical pain intensity measures can be used as secondary outcome [111] but are variably sensitive to change. Validated neuropathic pain quality measures are perhaps useful to discriminate between various pain mechanisms associated with distinct dimensions of neuropathic pain experience. The NPS or NPSI have been validated specifically for neuropathic pain and found sensitive to change in double blind trials; they are recommended to evaluate treatment effects on neuropathic symptoms or their combination (level A), but should also be used in future trials to try and predict treatment outcome and better define responder profiles to treatments (level C). Temporal aspects of neuropathic pain may be considered as an additional measure. Assessment of the sensory and affective dimensions of pain can also be performed with the SF-MPQ (level A) but whether such assessment is more sensitive than measures of pain intensity in neuropathic pain trials remains to be confirmed. For assessing overall change of neuropathic pain under treatment, we recommend to use the PGIC, CGIC and pain relief scales (numerical or categorical) and measure the NNT with regards to 30% and 50% pain relief (level A). Determination of the effect size may help compare treatments across trials and painful conditions.

#### 3.5. Psychological assessment

A longstanding literature documents the influence of psychological factors on the severity and impact of neuropathic pain [187,208] (see e-Table 5). A newer literature demonstrates the predictive utility of psychological factors in identifying patients at risk for chronicity of neuropathic pain [96,188,221], with some conflicting results [327]. Negative emotions (anxiety, depression, and fear), circadian rhythm disturbance (see below), and passive coping, particularly catastrophizing, show the strongest evidence. Fear of movement/(re)injury predicts persistent pain and disability in lumbar radicular syndrome [96] and in non-neuropathic pains such as musculoskeletal pain [253] and CRPS [95].

Measures of sleep interference/disturbance have been used across a variety of neuropathic pain studies [258,334,337,359, 363,368,378,444,457,499] and generally show good responsiveness following successful pain treatment (see e-Table 4). Measures of overall sleep quality have been studied less frequently, with some studies findings no change in overall sleep quality following successful neuropathic pain treatment [181,286,291] and others with

positive results [160,314,315]. The variety of measures and outcomes make it difficult to draw a conclusion as to the quality of the evidence; thus, use of a measure such as the Daily Sleep Interference Scale [469], which uses an 11-point Likert scale to assess sleep interference of pain, is recommended.

Mood and anxiety have generally been evaluated by generic scales as secondary outcomes in a number of recent neuropathic pain trials (see e-Table 4). The Profile of Mood States [289] has been the most extensively used [e.g., 40,258,378] and found responsive to change. The Beck Depression Inventory [31], the Zung depression scale [529] and the Hospital Anxiety and Depression Scale [527] have been somewhat less commonly used and also shown responsiveness to change [e.g., 94,159,384], although not always consistently [e.g., 44,228]. Anxiety has been evaluated much less often than mood in therapeutic trials of neuropathic pain; measures to assess anxiety have included a simple 0–10 NRS or VAS scale [e.g., 143,430], the Hospital Anxiety and Depression Scale [141,373,410], or the Spielberger's State-Trait Anxiety Inventory [222, 429]; only the VAS-anxiety has shown responsiveness to change in one trial [430].

*Recommendation:* The Tampa Scale of Kinesiophobia [480] is the recommended measure of fear of movement (level B). The measurement of passive coping/catastrophizing is recommended using the Pain-Coping Inventory [238] or the Pain Catastrophizing Scale [436] (level A). These measures are suitable for both daily practice and clinical trials.

We recommend that secondary outcomes in intervention studies include the assessment of sleep, mood, functional capacity, and quality of life, consistent with the recommendations of the IMMPACT group [458]. Sleep can be assessed using the MOS-Sleep scale [365] or the Daily Sleep Interference Scale [469] (level A). It is recommended that mood be assessed preferentially using the Profile of Mood States, or the Hospital Anxiety and Depression Scale or Beck Depression Inventory if specific measures of depressive symptoms are indicated (level A).

### 3.6. Assessment of disability (e-Table 6)

Neuropathic pain interferes with physical and psychological functioning and causes disability that matters to patients [164,287,296,459]. The International Classification of Functioning, Disability and Health describes functioning as the complex interplay of body functions, body structures, activities and participation, environmental and personal factors and provides a theoretical framework for evaluating functioning and disability. Disability is defined as a physical or mental condition that limits a person's movements, senses or activities. Subjective assessment of functioning can be measured with validated scales (e-Appendix 3), which are used also for neuropathic pain patients, although only few tests are validated for them [66,104].

Both general disability scales such as Sickness Impact Profile [88,160,325] and the Sheehan Disability Scale [149,364,365] and pain specific scales such as Brief Pain Inventory [160,427,466], its modification for patients with painful diabetic neuropathy (PBI-DPN) [165,523,524] and the Pain Disability Index [116,184,315,385,437,484,494] have been applied. Of the condition-specific disability measures, the Oswestry Disability Index is the most commonly used scale for back pain patients with a neuropathic pain component [8,12,42,186,227,241,288,385,473,503]. For low back pain patients, the Roland-Morris Questionnaire [298], the Dallas Pain Questionnaire [8,473] and the Japanese Orthopaedic Association Scale [186] have also been used. The Roland-Morris Questionnaire and the Oswestry Disability Index are equally responsive in patients with radicular pain in leg [250,411]. Specific scales have been developed for patients with carpal tunnel syndrome (the Carpal Tunnel Treatment Assessment

Questionnaire) [278] and traumatic nerve injury-induced cold allodynia in hand (the Cold Intolerance Severity Score) [384].

Improvement of radicular pain was associated with reduction in the Oswestry Disability Index [12,42,186,241,288,385,473] and Dallas Pain Questionnaire scores [8473] in all the studies reporting significant reduction of radicular pain reflecting their sensitivity to detect pain-induced changes in functioning. Analogously, higher BPI-DPN score was associated with more severe neuropathic pain [523]. In treatment studies, relief of neuropathic pain was differentially associated with improvement in disability which was detectable with the Brief Pain Inventory score [160] and the Pain Disability Index [116,184,315,385,483,494]. In cross-sectional studies, the higher the Brief Pain Inventory [165,424,466], the more severe pain intensity reported by the patients. The Sheehan Disability Scale interacted analogously with neuropathic pain scores [149,365]. Treatment-induced pain relief was associated with significant improvement in all three subscales [325] or minimal improvement (significant change only in one category in the Sickness Impact Profile) [160].

*Recommendation:* We recommend the use of the Oswestry Disability Index to assess disability in low back pain patients with a neuropathic pain component (level A). Alternatively, the Dallas Pain Questionnaire is also useful (level A). The BPI-DPN is recommended to assess disability in patients with painful diabetic neuropathy (level A). The Brief Pain Inventory and the Pain Disability Index are recommended to assess disability in other entities of neuropathic pain (level A). At least in cross-sectional studies, the Sheehan Disability Scale can be used as a measure of functioning and disability (level A).

### 3.7. Assessment of health-related quality of life

Health-related quality of life (HRQoL) is an important measure of the impact of disease on the patient's physical, psychological and social functioning. Studies consistently report reduced quality of life in patients with neuropathic pain [205]. No gold standard exists to study HRQoL [470]. The choice of a HRQoL instrument depends upon its ultimate purpose. A condition-specific instrument is appropriate to detect treatment response or changes due to disease progression or remission. A generic HRQoL measure is suitable for evaluating the impact of pain on the common elements of health, well-being and functionality and allows comparison between various conditions. The societal value or utility of a particular health state requires the use of preference-based instruments.

Of the generic instruments, Medical Outcomes Survey Short Form, SF-36 (version 1 and version 2) is extensively used and validated [56] in chronic non-neuropathic pain conditions [128,237,490]. It is comparable or better than other existing instruments, but its usefulness is also restricted by ceiling and floor effects and limited sensitivity to change [142,281,490]. It is the only HRQoL recommended by IMMPACT [111]. A number of other generic HRQoL tools may prove useful when better validated for neuropathic pain [59,75,422].

Two condition-specific tools, NePiQoL for miscellaneous conditions [350] and Neuroqol [475] for painful diabetic neuropathy are available for HRQoL measurement in neuropathic pain. A further neuropathy oriented HRQoL measure for diabetes focuses on the multiple symptoms of neuropathy in general rather than pain [478]. Condition-specific proxy tools for neuropathic pain, many derived from the Brief Pain Inventory, exist for diabetic neuropathy and herpes zoster [80,523] and are useful measures of functionality.

Preference-based tools, EQ-5D, HUI12, HUI13, and SF-6D (derived from SF-36) incorporate patient opinion of the utility value of a particular health state, and are suitable for cost-utility analyses and can be used for comparisons across diseases [470]. Their

mutual correlations are low suggesting they measure somewhat different aspects of HRQoL [267,279].

### 3.7.1. The effect of neuropathic pain on quality of life (e-Table 7)

Neuropathic pain alone without concomitant disease (phantom limb pain, post-mastectomy pain, postherpetic neuralgia) reduces quality of life [65,236,273,332,464,466]. Pain associated with neurological disease or injury (e.g., diabetic neuropathy, spinal cord injury) causes an incremental reduction in HRQoL [33,92,312,439,464,502]. This reduction is comparable or greater than in depression, coronary artery disease or poorly controlled diabetes [97,149,164,186,203,204,287,296,335,424,439]. In patients with both neuropathic pain and non-neuropathic pain the former tends to lead to a greater reduction in HRQoL, although this effect is not consistent [65,92,236]. When patients with predominantly neuropathic pain are compared to those with non-neuropathic chronic pain the former report lower levels of HRQoL [424].

### 3.7.2. Relationship between neuropathic pain and disability

In 9 of 11 studies an inverse correlation between the severity of pain and HRQoL was reported. In patients with severe pain, very low levels were reported [165,287]. In addition, when patients with disability and pain were asked to estimate their HRQoL following hypothetical complete pain relief, they gave a score that was 29–44% higher [164,447]. Correlations between HRQoL and physical or psychological impairment were reported [78,92,97,149,287,424,447].

### 3.7.3. Relationship between improvement of neuropathic pain and quality of life

We identified 39 articles of randomized controlled trials in which change in neuropathic pain and HRQoL were measured (see e-Table 8). Five different types of validated HRQoL instruments (SF-36 in 30, EQ-5D in 6, GHQ-12, NHP and EORTC) were employed in these publications. Whilst three papers were published that used HRQoL as the primary outcome measure [14,97,277], they all reported *post hoc* analyses of previously published data. Of 26 randomized controlled trials in which clinically meaningful reduction in pain (active treatment versus placebo/comparator) was demonstrated a robust improvement in HRQoL was seen 11 (improvement of  $\geq 2$  domains of the SF-36 in addition to bodily pain). Of 11 randomized controlled trials in which the active treatment failed to show a change in the primary outcome measure (pain), 3 studies reported HRQoL improvement. In one such study, the response was so substantial that it is unlikely to be accurate [483]. The use of either SF-36 or EQ-5D in clinical trials has not been standardized [152].

**Recommendation:** No generic HRQoL instrument has been sufficiently validated for use in neuropathic pain, but several of them have been used in various neuropathic pain studies. However, their responsiveness to change is equivocal [111,152]. In trials with large pain relief response on active treatment, or with large sample size, generic HRQoL measures appear robust. There is, however, a general lack of consensus as to what constitute meaningful changes in HRQoL. With these caveats, we recommend that HRQoL be assessed using either SF-36 or EQ-5D, both in research and audit studies. The newly developed method of transforming SF-36 into a preference-based tool (SF-6D) makes it equally useful to EQ-5D for health state assessment. The users should consult guidelines on the use these instruments [152,300]. As neither of the two condition-specific tools (Neuroqol and NePIQoL) has been subject to assessment of responsiveness to change, no recommendation for their usefulness can be made. In cases of severe neurological conditions or in short-lived neuropathic pain conditions (e.g., herpes zoster) the Brief Pain Inventory or its modifications can be used to assess

the degree of interference of pain in social and physical functioning [80,523].

## 3.8. Laboratory tests

### 3.8.1. Reflexes

For facial pains, the recent AAN-EFNS guidelines on trigeminal neuralgia management [86] and a Class I study [85] confirm that the A-beta mediated trigeminal reflexes (early R1 blink reflex and early SP1 masseter inhibitory reflex) are efficient tools to reveal symptomatic forms of trigeminal neuralgia, yielding an overall specificity of 94% and sensitivity of 87% in 628 patients. Six other studies used blink reflexes in facial pains (e-Table 9). One Class I study in patients with ophthalmic PHN yielded a specificity of 100% and sensitivity of 73% for the early R1 blink reflex [455]. One study found that the nociceptive blink reflex (elicited by the concentric electrode) was delayed in patients with atypical odontalgia, thus supporting the view that this condition is neuropathic [22].

For the upper limb, the cutaneous silent period has been applied in one neuropathic pain study, in which the laser-evoked potentials, but not the cutaneous silent period, differentiated patients with and without pain and this measure was strongly correlated with pain [455]. This confirms earlier finding that the cutaneous silent period is not an adequate tool for assessing nociception [84]. The nociception flexion reflex is still being used in physiological and pharmacological studies of modulation of nociception, but not in patients with neuropathic pain.

**Recommendation:** The trigeminal reflexes mediated by A-beta fibers are established as useful for trigeminal pain diagnosis in that they are abnormal in patients with structural damage, such as trigeminal neuropathy, symptomatic trigeminal neuralgia and PHN, and normal in patients with classical trigeminal neuralgia (level A).

### 3.8.2. Evoked potentials

According to the previous EFNS guidelines on neuropathic pain assessment [84] and the Recommendations from the I International Federation of Clinical Neurophysiology [83] laser-evoked potentials have been suggested as an easy and reliable neurophysiological method for assessing function of subcortical nociceptive pathways. Importantly, laser-evoked potentials can be obtained in response to stimulation of virtually all skin territories [456], including glabrous skin [197].

Since 2003 eight new trials studied the A-delta fiber pathways in patients with neuropathic pain. Four used laser-evoked potentials, 2 the new technique of contact heat evoked potentials, and 2 evoked potentials elicited by a surface concentric electrode that provides a preferential activation of superficial terminals (i.e., small-diameter afferents) (e-Table 10). In general, all techniques revealed significant sensory abnormalities when compared to controls or contralateral side, and several showed significant correlations with pain and other laboratory measures, such as intraepidermal nerve fiber density measurement. A cumulated analysis of the best four studies, considering the responses to be certainly abnormal only when absent, reveals a significant difference compared to controls, with an overall specificity of 83% and sensitivity of 64%, in a total of 142 patients with sensory neuropathy or PHN and 133 controls (see e-Table 10). The sensitivity would probably increase considerably if the recently published normal limits of amplitude were used [83,339]. One study only, in patients with ophthalmic PHN, dealt with C-fiber-related laser-evoked potentials from the trigeminal territory [455]. Probably the recording of C-related laser-evoked potentials after limb stimulations is still technically too difficult to allow routine clinical application. It is worth highlighting that a serious limitation of



the current evoked-potential approaches is that they do not allow definition of the level of the lesion within the nociceptive system.

**Recommendation:** Although expensive, laser-evoked potentials are established as useful for assessing function of the A-delta fiber subcortical pathways in patients with neuropathic pain (level A). The available evidence regarding evoked potentials assessing the C-fiber pathways is insufficient to make recommendations.

### 3.8.3. Microneurography

Microneurography is a technique in which single-fiber recordings from peripheral nerves are made in awake subjects [177,448]. Microneurography provides valuable information on the physiology of all peripheral nerve fiber types [449,462]. The possibility of performing intraneural microstimulation represents an opportunity to provide a direct link between activity in peripheral nerve fibers and pain perception [323], although this is controversial (see [366]).

Unlike conventional nerve conduction studies, which can only record compound nerve action potentials, microneurography can discriminate individual action potentials in single, identified peripheral fibers. Therefore, microneurography is the only technique for detecting and quantifying the pathophysiology of positive sensory phenomena mediated by both large myelinated fibers (tactile paresthesiae and dysesthesiae) and by small thinly myelinated and unmyelinated fibers (spontaneous pains).

Microneurography is regarded as a safe technique if performed by adequately trained hands [but see 366]. There have been no reports of overt or persistent nerve damage, and prospective studies monitoring side effects of the technique have proved it to be safe [113,262]. Microneurography is time-consuming and difficult and requires both an expert investigator and a collaborative patient. For these reasons microneurography has been used on relatively few occasions to study neuropathic pain patients ( $n = 67$  in published data), although recent technical and software developments have resulted in an increase in the number of studies. Nevertheless, there are no normative data available for healthy subjects, and published reports are group comparisons only. Phenomena documented by microneurography include spontaneous nociceptor activity, gain of function changes (erythromelalgia) and loss of function changes in encoding of noxious stimuli.

Patterns of activity-dependent slowing of conduction velocity in response to repetitive stimulation allow classification of different functional types of peripheral C-fibers [404], among them mechano-sensitive and mechano-insensitive C-nociceptors [405,496]. Development in analysis software allows multiple simultaneous recordings of C-fibers, which enhances studying ongoing abnormal activity arising from peripheral nociceptors. In patients with peripheral neuropathies, this is a possible cause for spontaneous neuropathic pain [322,329,331,406, see e-Table 11].

**Recommendation:** Microneurography cannot be recommended as a routine procedure for the assessment of patients with neuropathic pain. However, it is suggested that more recordings are performed in selected groups of neuropathic pain patients by trained researchers to understand the frequency and pathophysiological role of spontaneous ectopic activity in the generation of neuropathic pain symptoms. It would also be important to study if the technique can be used in human pharmacological studies to assess the effectiveness of new compounds in reducing or abolishing ectopic impulse generation in peripheral nociceptors.

### 3.8.4. Functional brain imaging (e-Tables 12 and 13)

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) measure with different methods cerebral blood flow or metabolic changes that reflect local synaptic activity in defined brain regions. The so-called “activation” PET or fMRI studies investigate variations of regional blood flow elic-

ited by a given task or a particular stimulus. Data interpretation is based on statistical comparisons of signal measured in different clinical or experimental situations, often labelled “activated” and “control” conditions. In experimental pain, fMRI and PET studies have disclosed a network of brain regions responding to noxious stimuli. These regions include the secondary somatosensory cortex (SII), the insular cortex, the anterior cingulate cortex (ACC), and less consistently, the contralateral thalamus and the primary somatosensory cortex [347]. Importantly, virtually every brain area activated by noxious stimuli also responds to non-noxious stimuli, and activation patterns similar to those elicited by noxious stimuli can also be observed in non pain-related functional neuroimaging experiments. Thus, PET and fMRI responses to noxious stimuli have to be interpreted with caution.

In patients with chronic spontaneous neuropathic pain, there is converging evidence that (a) unilateral pain is associated with decreased resting blood flow in contralateral thalamus, and (b) that such decrease in resting blood flow may be reverted by different analgesic procedures. This has been described in cancer pain alleviated by cordotomy [101], in peripheral neuropathic pain at baseline [196] and after alleviation by anesthetic blocks [195], as well as in central pain treated with thalamic stimulation [107,220], i.v. lidocaine [60] or with motor cortex stimulation [150,151,346,389]. Increase in thalamic blood flow has also been observed in cases where therapy was ineffective [107,346], thus suggesting that restoration of thalamic blood flow may be a necessary but not sufficient condition of pain relief. Although occasional changes have been described in other areas during ongoing neuropathic pain (including ACC, parietal cortex, anterior insula and cerebellum), consistency is not enough to warrant diagnostic or monitoring use.

In patients with provoked neuropathic pain, allodynia and hyperalgesia stimulation have not yielded conclusive results. While some studies described amplification of the thalamic, insular, primary and secondary somatosensory cortical responses, but not of ACC [25,106,155,344,348], others described a reduction of activity in the sensory-discriminative “pain matrix” (e.g., in SII and insula) [348,507], together with reports of ACC activations in allodynic patients [155,507]. These contrasting results highlight the difficulties in understanding the functional significance of PET and fMRI responses to noxious stimulation in healthy subjects and patients with neuropathic pain, especially considering the heterogeneity of patients and experimental designs.

The combination of administration of drugs with fMRI in order to elucidate pharmacological effects on brain function (pharmacological functional magnetic resonance imaging) has been recently proposed. However, data in patients are still lacking.

**Recommendation:** Functional brain imaging is not currently useful for individual patients in clinic, but is an interesting research tool. There is converging evidence that chronic spontaneous neuropathic pain is associated with decreased activity in contralateral thalamus (level B).

### 3.8.5. Skin biopsy

**Rationale and method of assessment of epidermal innervation by skin biopsy.** Peripheral neuropathic pain may be related to dysfunction of C-fiber and A-delta fiber nociceptors. C-fibers can be visualized by immunostaining in skin biopsies as these neurons exclusively penetrate into the epidermis. C-fiber morphology and pathology can be investigated by immunostaining for nerve fibers in 3-mm punch skin biopsies (including nerve fibers, sweat glands, blood vessels, and resident or infiltrating cells in the epidermis and superficial dermis) from the affected area. Nerve fibers can be visualized with antibodies against PGP 9.5, a panaxonal marker. Bright field immunohistochemistry or immunofluorescence can be used,

standardized methods and strict counting rules for intraepidermal nerve fibers [247,426].

In addition to quantification of intraepidermal nerve fibers, evaluation of the subepidermal nerve plexus may provide evidence of larger fiber involvement in patients with burning feet [482]. Functional tests such as contact heat evoked potentials [15] and pain-related evoked potentials [320] correlate well with intraepidermal nerve fiber density. It also correlated with QST findings, neurophysiology, and neuropathy scales [482,525]. In small fiber neuropathy, the sensitivity of skin biopsy assessment may be higher than that of QST [99,263,395] and of laser-evoked potentials [99].

*Skin biopsy in peripheral neuropathy and PHN.* Quantification of intraepidermal nerve fibers in a skin biopsy can be used to demonstrate the presence of a small fiber neuropathy [67,162,167,283,395,482]. Against a composite gold standard for small fiber neuropathy, the sensitivity and specificity of skin biopsy evaluation is 88% [99], if appropriate techniques are used [247]. Early diabetes [423], hypothyroidism [330], and other diseases [99] may reveal themselves in these neuropathies. Qualitative changes have also been reported [156,249] but their role in diagnostics is uncertain [500].

In patients with PHN, skin biopsy has been used to assess the pathophysiology and to define disease subtypes. No studies of intraepidermal nerve fiber density in acute zoster have been published, although pathological studies confirm acute demyelination [304,113,522]. In PHN, the number of intraepidermal nerve fibers is lower in the pain area than in contralateral mirror-image or distant control skin [317,342,343], and loss of cutaneous innervation was inversely correlated with allodynia, suggesting that allodynia was a function of remaining nociceptors [383]. Nerve fiber loss has also been found contralateral to an affected area [318]. Numbers of Langerhans cells, the primary immune cells of the epidermis, were not related to the severity of pain in PHN [319]. Patients with PHN had greater denervation of the skin than a sample of pain-free post-zoster [317]. In patients with diabetes and HIV neuropathy, intraepidermal nerve fiber density was inversely correlated with pain, i.e., greater fiber loss was correlated with more severe pain [395,427,525]. In an unselected population, intraepidermal nerve fiber density had only a weak inverse correlation with pain [482].

*Skin biopsy and treatment response.* The density of skin innervation does not predict the response to topical lidocaine [190]. Longitudinal skin biopsy assessment is being used in as an outcome measure in several trials on diabetic neuropathy. Limited data to date suggests that intraepidermal re-innervation improves after treatment, but the treatment effect is small [48,423]. In severe length dependent neuropathies, only biopsies from a proximal site may be responsive to change [427].

*Recommendation:* Skin biopsy with appropriate histological processing and image analysis of the specimen should be performed in patients with clinical signs of small fiber dysfunction to determine intraepidermal nerve fiber density (level B). Measurement of intraepidermal nerve fiber density may be used in the follow up and to detect a treatment response in diabetic patients with small fiber neuropathy (level C).

### 3.9. Assessment of the autonomic nervous system functions

Local administration of norepinephrine has been reported to evoke pain in traumatic neuropathy [5,450]. Furthermore, density of efferent sympathetic axons in sural nerve biopsies has been reported to be increased in patients suffering from peripheral neuropathic pain [41]. These observations have led to several theories on how autonomic nervous system is involved in generation of neuropathic pain.

In half of the studies with neuropathic pain patients, laser Doppler flow [264] was the method selected to study autonomic nervous function (e-Table 15). Measuring skin temperature [57] was used in one neuropathic pain study [170]. The mirror side served as the control site in both the temperature and laser Doppler flow studies.

Measurement of sudomotor function was commonly used in both neuropathic pain studies. Quantitative sudomotor axon reflex [265,266,399], thermoregulatory sweat test [175], sympathetic skin response [108,408], and ninhydrine test [299] were the measures used.

*Recommendation:* Several studies suggest that laser doppler flow is a reliable method to study autonomic nervous function both in peripheral neuropathic pain (level B). Analogously, quantitative sudomotor axon reflex was found to be useful (level B). Measurement of skin temperature and sympathetic skin response may also be suitable (level B).

### 3.10. Peripheral nerve blocks and intravenous drug infusion tests

Peripheral nerve blocks and infusions have a long tradition in pain practice. We systematically searched the literature in this area with focus on use of these approaches for diagnosis and assessment of neuropathic pain. Whilst there are a number of reports of the therapeutic use of such techniques in neuropathic pain and reports of their diagnostic use in a broad range of pain conditions, we were unable to locate any reports of systematic evaluation of their utility for diagnostic or assessment purposes in neuropathic pain, which were of sufficient methodological quality on which to base guidelines. We therefore conclude at that, at the present time, there are insufficient data on the use of peripheral nerve blocks or intravenous drug tests to make a recommendation that they be routinely used as diagnostic tools in the assessment of patients with suspected neuropathic pain. However, it is recognised that there is a literature which demonstrates that, for example, intravenous infusions of local anaesthetics or NMDA receptor antagonists acutely modulate pain and/or sensory dysfunction in patients with central or peripheral neuropathic pain. This suggests that such manoeuvres may have diagnostic utility, especially when combined with other methods of neuropathic pain assessment such as quantitative sensory testing, which then further can advance our understanding of underlying mechanisms. More research is required in this area, especially to directly assess the specificity, sensitivity and reliability of such tests for diagnostic use.

## 4. Discussion

### 4.1. Neuroanatomy of neuropathic pain

The somatosensory system comprises mechanoreception, thermoreception, nociception, proprioception and visceroreception [83], providing conscious perception of sensory information from the skin, the musculoskeletal system and the viscera. In addition, somatosensory afferents are involved in numerous motor and autonomic reflex pathways and feedback loops with relay centers in the spinal cord, brainstem and forebrain. Somatosensory afferents also provide an excitatory input to the ascending reticular activating system that regulates sleep and wakefulness. The somatosensory system can be divided into the dorsal column-lemniscal system and the spinothalamic tract system. The former subserves mechanoreception and proprioception, and the latter thermoreception, nociception and visceroreception. The two systems project via the ventrobasal and intralaminar groups of thalamic nuclei into a network of somatosensory cortex areas, which include

primary and secondary somatosensory cortex, posterior parietal cortex, posterior and mid-insula and mid-cingulate cortex. The relative roles of the various parts of this network in the brain for nociception and other somatosensory submodalities are still a matter of ongoing research. Besides these two main systems, other pathways have been suggested to be involved in mediating somatosensory functions, such as the dorsal spino-cerebellar tract (lower limb proprioception), postsynaptic dorsal column pathway (pelvic organ pain), and vagus nerve (non-painful visceral percepts). Descending tracts are also part of the somatosensory system [297]. These tracts originate in the brainstem and the cortex and include the midbrain periaqueductal grey. They are mostly inhibitory, but a facilitatory descending projection from the brainstem has also been described. The variable nature of neuropathic pain is not surprising, considering the complexity of the somatosensory system and in how many ways it may be affected by disease or injury.

The literature on neuropathic pain is mainly concentrated on conscious perception of sensory information from the skin. We lack standardized methodology for assessment of pain from deep tissues (like muscles and joint) and from viscera. However, recent histological evidence from patients with chronic pancreatitis or pancreatic cancer supports the concept of visceral neuropathic pain [68].

#### 4.2. Assessment of neuropathic pain in clinical practice

Examination of a patient presenting with pain starts with interviewing the patient about his or her symptoms (their onset, location, intensity and possible connection to a possible causative event such as trauma). Neuropathic pain screening tools can be used to alert the physician to the possibility of neuropathic pain. The severity of pain and its impact on daily life, including disability and effect on sleep and mood, should be explored. In daily practice this is usually performed by interview, but questionnaires can also be used. General clinical examination and targeted examination guided by the character and localization of the symptoms should be performed to diagnose nociceptive pain. Clinical examination to test the hypothesis of neuropathic pain should be performed as explained in Section 3.3.1. On the basis of information gathered, the physician may reach an obvious clinical diagnosis, identify pain type(s) (nociceptive, neuropathic, combined, or neither), or need further investigation to diagnose the condition or to confirm the clinical diagnosis.

We still lack gold standard of diagnosing neuropathic pain, i.e., there are no clinically feasible means, in the clinic or laboratory, to differentiate neuropathy with pain from a neuropathy without pain. Thus, when examining pain patients with suspected peripheral nerve lesion, we can only aim to confirm the diagnosis of an underlying neuropathy (that can be rationally connected to the clinical pain condition), and this can be done according to the previously published guidelines for the diagnoses of peripheral neuropathy or small fiber neuropathy in general.

Electroneuromyography (ENMG) is the best and a widely available method to verify a lesion of peripheral large nerve fibers. It can locate and classify the lesion (axonal or demyelinating) and gives an opportunity to follow up the recovery of the nerve by repeated examinations. In some conditions (e.g., nerve entrapment with normal sensory examination results, or old peripheral nerve trauma with well recovered sensory function) it is the method of choice to make the diagnosis. Its early use is recommended in cases with a possible traumatic or iatrogenic nerve lesion [200,371]; an early objective documentation of a lesion helps to verify causality. However, according to a carefully performed prospective study, only 5% of patients who had a peripheral nerve lesion verified by intraoperative ENG developed neuropathic pain [202]. If ENMG re-

mains normal and the clinical picture refers to a possibility of peripheral nerve damage, QST and IENF may demonstrate small fiber alterations. In addition to showing the presence of a nerve lesion, its etiology needs to be clarified (see [119]). It is important to diagnose the disease, as causative or disease-modifying treatment may be available.

If a central lesion is suspected, the first diagnostic tool is usually MRI, although it must be kept in mind that areas of abnormal MRI signal do not necessarily imply tissue damage or dysfunction. The function of the somatosensory pathway can be examined with evoked potentials or QST, which show abnormal function but cannot locate the lesion. Further tests (e.g., cerebrospinal fluid analysis) may also be needed; as described in neurology literature. Illustrative examples of the use of diagnostic procedures are presented in a recent article [153].

The effect of treatment should be assessed by repeated evaluation of the intensity, quality and temporal aspects of pain and possible side effects of the treatment. In addition, sleep, mood, disability and quality of life should be evaluated, usually by interview. Structured questionnaires (e.g., Oswestry Disability Index to assess patients with low back pain) can also be used. All questionnaires presented in this manuscript can be used in the clinic, but the efforts needed from the patient to complete them and the time of the clinician to interpret their results limit their routine use.

#### 4.3. Methods used mainly for research

Some methods presented in this manuscript are used only in research and are not suitable for routine clinical work. Microneurography is time-consuming and hence not feasible in clinical practice. Functional brain imaging is not useful for individual patients in the clinic either. Only a few centers have equipment for A-delta LEPs, limiting its use. Autonomic nervous system assessment methods and QST are not available in all centers either.

#### 4.4. Suggestion for further development

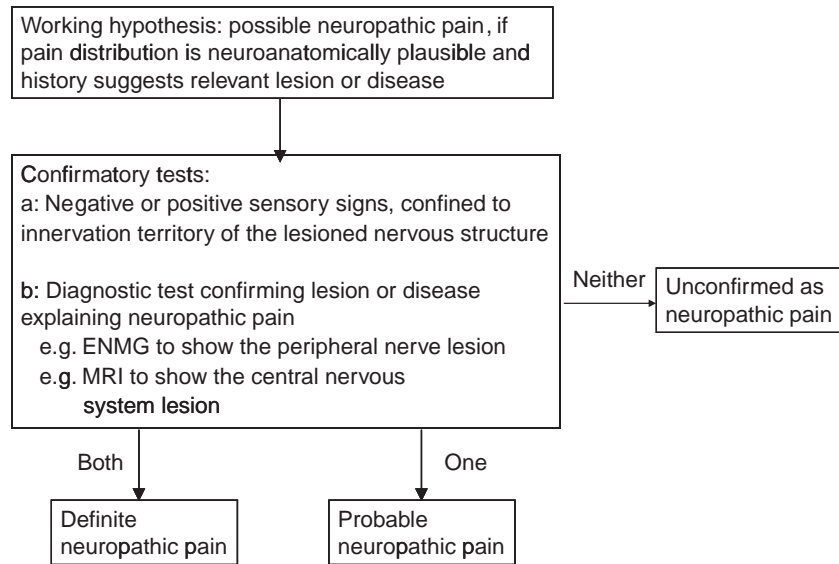
##### 4.4.1. Guidance for preparing guidelines

We prepared our guidelines according to the ENFS guidance [55]. However, we had problems in applying these guidelines to all aspects of this review. The definition for narrow or broad spectrum of persons (see Table 1) is inaccurate and varies from discipline to discipline (e.g., epidemiology vs. neurophysiology). The criterion of blinding is problematic e.g., in QST (see Section 3.3.2) and impossible in microneurography. Instead of arbitrary interpretation of the guidance we preferred to show the evidence in the e-Tables and formulated recommendations without classification in ambiguous areas. More detailed guidance for evaluation of different methods is needed.

##### 4.4.2. Areas needing further research

As mentioned in Section 4.1., we lack methodology for assessment of pain from deep tissues and from viscera. Lesions in somatosensory pathways from these structures can give rise to neuropathic pain, but currently assessment methodology for this group of patients is sparse. As deep structures commonly have innervation independent of cutaneous representation, methods other than cutaneous sensory testing are needed.

For the epidemiological studies, further research is needed for case identification. Validation of screening tools for this purpose is suggested as the next step. In addition, reliable case identification from medical records should be developed. The screening tools are validated in pain clinic samples with clear clinical conditions. However, their validity and reliability in a general population sample needs to be clarified.



**Fig. 1.** Flow chart of grading system for neuropathic pain (modified from [452]). This flow chart was developed bearing in mind that diagnosis should be possible in simple cases from history and clinical examination alone without the need for laboratory tests. It remains to be tested empirically if patients within a given diagnostic category (e.g., polyneuropathy or poststroke pain) that reach the grade 'probable' based on one positive sensory sign in the pain distribution area differ from those reaching the grade 'probable' based on quantitative and objective diagnosis by EMG or MRI.

The sensitivity of clinical examination has not been systematically studied in neuropathic pain patients, e.g., how accurate the diagnosis achieved by pure bedside examination is compared with information retrieved from additional tests. However, the diagnostic procedure is a stepwise process, as shown in Fig. 1. In clinics, clinical examination is the basis of diagnosis (the first step). It may show obvious need to seek and verify a disease causing nerve lesion (e.g., peripheral nerve entrapment verified with ENMG or intracranial tumor or multiple sclerosis lesion explaining facial pain and sensory deficit). If the history and symptoms are compatible with neuropathic pain but findings in clinical examination remain normal or equivocal, further investigations with laboratory tests are mandatory.

QST is widely used in neuropathic pain field. The sub-classification of the clinical condition to "definite" or "probable" neuropathic pain is needed in further studies. Use of a validated protocol with full sensory profile should be used more widely in efforts to try to clarify mechanisms of neuropathic pain.

The feasibility of the NePiQoL, a new condition-specific HRQoL measure for neuropathic pain, should be clarified in clinical studies and compared with the general HRQoL measures.

From among the laboratory studies, microneurography and functional brain imaging should be studied further due to the limited number of patients studied so far, and the attractive potential for their possible use in evaluating the effectiveness of pharmacological agents.

As there is lack of high-quality studies on the use of peripheral nerve blocks and drug infusion tests in neuropathic pain, further studies in these areas are required.

## 5. Conflict of interest statement

J.H., G.I. and M.R. have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2010.07.031.

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The complete reference list for this paper is published online only. Please see Supplementary data.

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