Review: Clinical Trial Methodology

CLINICAL INVESTIGATION

Assessment of neuropathic pain in the setting of intervention trials

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Nadine Attal

INSERM U 987, Centre d'Evaluation et de Traitement de la Douleur, Hôpital Ambroise Paré, APHP, Boulogne-Billancourt, France
E-mail: nadine.attal@apr.aphp.fr

Optimal assessment of neuropathic pain is crucial for the design and conduct of clinical trials. In recent years, the assessment of neuropathic pain in clinical trials has evolved from crude evaluations of overall pain intensity to a more specific assessment of pain quality and sensory function. Such specific assessment may be relevant to determine sensory profiles of responders to drug or nondrug treatments. This article outlines the various clinical outcome measures currently used in neuropathic pain therapeutic trials with emphasis on their advantages and limitations, and summarizes current recommendations concerning their use in clinical trials of neuropathic pain.

Keywords: assessment • neuropathic pain • outcome measures • quantitative sensory testing • questionnaires

Neuropathic pain (NP) may result from a lesion or a disease affecting the somatosensory system [1,2] and encompasses a wide variety of conditions involving the brain, spinal cord or peripheral nerves. Examples of common and well-characterized NP conditions include cervical/lumbar radiculopathy, painful diabetic neuropathy, postsurgical/post-traumatic neuropathies, postherpetic neuralgia, chemotherapy-induced painful neuropathy, HIV neuropathy, spinal cord injury pain and multiple sclerosis-related pain. Although more epidemiological studies are needed, the prevalence of pain of neuropathic origin in the general population has been estimated to range between 7 and 8%, suggesting that this is a significant health problem [3,4].

Optimal assessment of NP is crucial for the design and conduct of clinical trials (see [5,6] for reviews). In recent years the assessment of NP in clinical trials has evolved from crude evaluations of overall pain intensity to a more specific assessment of pain quality and sensory function [5]. Such specific assessment may be relevant to determine sensory profiles of responders to drug or nondrug treatments. Here, the forms of assessment of NP currently used in NP therapeutic trials, including intensity scales, specific and nonspecific pain measurement questionnaires and quantitative sensory testing will be discussed, with emphasis on their advantages and limitations. Prior recommendations about the use of these measures in clinical trials will also be summarized and discussed. Although standard clinical examination is a crucial part of the diagnosis workup of NP [1], its relevance in the context of trial interventions will not be discussed because it is generally not used as a measure of efficacy in this context (with the exception of brush-evoked allodynia, which will be discussed in the context of quantitative sensory testing). Finally, although quality of life and comorbidities are also increasingly assessed in clinical trials of NP, emphasis will only be given on measures related to sensation or pain (see [5] for an extensive review).

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Neuropathic pain characteristics

Neuropathic pain patients generally exhibit 'spontaneous' (or stimulus-independent) versus 'evoked' (or stimulus-dependent) components, which may often coexist. Spontaneous NP may be continuous (e.g., foot pain in diabetic neuropathy) or intermittent (e.g., spontaneous pain paroxysms in trigeminal neuralgia). In addition to temporal variations in pain intensity, individuals with NP often also report variable pain qualities such as burning, cold, sharp and squeezing [5–7]. Intermittent NP, often referred to as pain paroxysm, is often described as 'shooting', 'stabbing' or 'electric shock-like' [5–7]. Evoked NP (hyperalgesia or allodynia) is generally defined with reference to the evoking stimulus and may be provoked by brush, pressure, cold or heat [2]. Importantly, these neuropathic characteristics are shared by most NP etiologies, which shows that despite obvious differences in etiology, the clinical entity of NP has strong clinical consistency [7].

Screening for NP

Several screening tools have been developed in recent years for the identification of NP. One feature common to all these tools is a reliance principally on verbal reports of pain qualities (i.e., pain descriptors). Two of the five screening tools – the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and the Douleur Neuropathique en 4 questions (DN4) questionnaires – are clinician-administered questionnaires including items related to the interview (i.e., symptoms) and items related to the sensory examination (i.e., signs) [5,8]. The other three screening tools are self-administered questionnaires including only items related to the symptoms of NP: The Neuropathic Pain Questionnaire (NPQ), ID Pain and PainDetect [5,8]. These tools have not been validated to measure NP symptoms for therapeutic intervention [5]. Their main relevance regarding clinical trials would be to increase diagnostic accuracy of NP for patient selection. Indeed, some of these tools have been included in the diagnostic criteria of NP in several clinical trials [9,10], allowing selection of more homogenous cohorts of patients.

Measurement of NP with pain scales or questionnaires in the setting of intervention trials

Pain intensity

Pain intensity, including average pain, pain at its worst and at its best, is the most common primary outcome measure used to assess efficacy of treatments for chronic pain [11–13] and is currently recommended as a primary outcome in NP trials [5]. The 11-point numerical rating scales (NRS) or visual analog scales (VAS) appear similarly sensitive to change in NP. However, the NRS may have fewer failures than the VAS in elderly patients and is currently considered as the most reliable to assess treatment effect [11]. An additional measure of pain intensity using categorical pain scales (in which the patients choose one of the given verbal descriptors of the intensity of pain they feel) is recommended as a secondary outcome [11], because it is sometimes less sensitive to change than numerical scales (e.g., [14,15]). Fluctuations of NP over time can be assessed by measuring average pain, 'pain as its worst' 'pain as its least' and 'pain right now', as in the Brief Pain Inventory [16], which has been validated for NP [17]. Different components of NP should be measured separately (e.g., spontaneous, continuous and evoked pain) [5].

Nonspecific multidimensional questionnaires

The McGill Pain Questionnaire (MPQ [18]), and the 15-item short-form (SF-MPQ [19]), the most frequently used self-rating multidimensional instruments to assess pain quality, have been largely used to evaluate the efficacy of treatments in NP (e.g., [20,21]). These scales are not specific for NP and the SF-MPQ has occasionally been found to be only weakly sensitive to treatments in NP trials (e.g., [22–24]). The main purpose of the original MPQ was to differentiate many qualitative aspects of pain, with the assumption that they represent different mechanisms. The SF scale has also been used to discriminate between the sensory and affective dimensions of pain, the latter not being assessed by other pain questionnaires. It remains to be determined whether such differentiation may be relevant in NP assessment, particularly with regard to therapeutic outcome. In fact, therapeutic trials using this questionnaire in NP have invariably found a similar impact of drugs on both sensory and affective pain components (e.g., see [25]). Recently, a revised version of the SF-MPQ, the SF-MPQ-2 adding symptoms more relevant to NP, has been proposed [26], and was found to be sensitive to changes in diabetic NP. However, the validation of this scale may be regarded as preliminary [27].

Specific NP measurement questionnaires

The lack of specificity of the MPQ and SF-MPQ for NP has led to the development of various NP measurement scales that have been designed to evaluate separately the various symptoms of NP. The advantage of specific NP scales over more conventional assessment is that they may capture distinct dimensions of NP experience that may be differentially sensitive to treatments. They may also be used to determine profiles of patients susceptible to responding to therapeutic interventions based on specific symptoms or their combinations. Two of them have been validated in NP in general and will be discussed here. Other NP scales have been specifically designed to discriminate NP from non-NP (see previous paragraph).

The Neuropathic Pain Scale (NPS) includes ten pain quality items rated on Likert scales and a temporal assessment of pain [28]. Various composite scores have been proposed, although not formally validated, whereas a recent validation study in multiple sclerosis identified three factors for NPS items ('familiar', 'superficial' and 'alien' perception) [29]. The NPS has been used in several NP double-blind trials, most commonly as a secondary outcome measure. Some trials reported differential effects of treatments on specific items [30]. It has been translated into several languages and an Italian version has been published. A derived version aiming to assess NP and non-NP conditions, the Pain Quality Assessment Scale, includes additional NP qualities (e.g., paroxysmal pain) [31], but it has only been validated in carpal tunnel syndrome and its sensitivity to change has not been assessed to date in double-blind trials.

The Neuropathic Pain Symptom Inventory (NPSI) contains ten descriptors grouped into five distinct dimensions (burning, paroxysmal, deep, evoked and paresthesia) and two temporal items that assess pain duration and the number of pain paroxysms [32]. The items used to assess evoked pain have been validated against clinical examination and QST, thus making it suitable for assessment of allodynia and hyperalgesia [7]. The original validated French NPSI has been translated and linguistically validated in 50 other languages; its conceptual adequacy has been confirmed in six languages and it has been revalidated in Italian and in German [5]. Its factorial structure makes it suitable to capture different aspects of NP that may have distinct pathophysiological mechanisms. Thus, it has been found that the various pain qualities of NP as assessed with the NPSI were distinctly correlated to neurophysiological data in patients with carpal tunnel syndrome [33] or with structural investigations of the spinal cord in syringomyelia [34]. The NPSI has been used in several double-blind trials as a secondary outcome measure, with some dimensions being differentially sensitive to treatment effects (e.g., [35,36]).

Temporal aspects of pain

Temporal aspects represent a distinct dimension of NP [8]. However, few trials in NP, except those dealing with trigeminal neuralgia [37], have assessed them specifically, although these aspects may be highly sensitive to change in NP (e.g., time to onset of pain relief, proportion of pain-free days and number of pain paroxysms; see [35,38]).

Other measures designed to assess treatment efficacy

Several additional methods have been specifically conceived for assessing treatment efficacy [8]. The numerical (VAS, NRS; 0–100%) or categorical pain-relief scales have been found very sensitive to change in several NP trials. Thus, in a comparative placebo-controlled trial of imipramine and venlafaxine in diabetic polyneuropathy, both active drugs were equally effective on pain intensity, but imipramine had a much better effect on categorical pain relief [39]. In two trials using gabapentin or topiramate with negative or marginal effects on pain intensity, pain relief was significant with the active drugs [40,41].

The Global Impression of Change (GIC; which consists of seven verbal descriptors from 'very much improved' to 'very much worse', either reported by the patient (PGIC) or evaluated by the physician (CGIC) is very sensitive to change. It has occasionally been found more sensitive to NP treatments than pain intensity probably because it may assess various aspects related to quality of life beyond pain [40,42]. Other global outcome measures of efficacy include the patient's preference for treatment, satisfaction with treatment or with pain relief or composite measures of treatment efficacy [6].

The proportion of responders is widely used in NP studies (e.g., [20,40]). Responders are generally defined on the basis of a 50% pain relief. This has been the 'gold standard' criterion used in meta-analyses to calculate the number needed to treat (NNT) [43]. However, it has been shown that a ≥30% reduction in NRS of pain intensity was also clinically important [44] and may provide important complementary information [40,45,46]. Importantly, the NNT may vary depending on the method of calculation. Thus, in a recent trial of gabapentin on traumatic nerve injury pain, the NNT for marked improvement using categorical pain relief was 7.7, whereas the NNT for 50% improvement in average pain intensity from pain diaries was 28 [40].

Several trials of NP have assessed the use of rescue medication (generally with weak analgesics, sometimes with opioids) as a secondary outcome of the efficacy of treatments. Discrepant findings have been observed with the use of this measure in NP with good sensitivity [21,39,47] or no sensitivity to change [46] probably because NP is poorly sensitive to weak analgesics.

Quantitative sensory testing

General principles & normative data of QST

Quantitative sensory testing (QST) allows the analysis of perception in response to external stimuli of controlled intensity [48]. QST is considered as a semi-objective method because the stimulus is controlled whereas the response depends on subjective ratings by the individual being assessed. Thermal and mechanical stimuli may assess the different sensory modalities corresponding to different types of receptors, peripheral nerve fibers or CNS pathways, without allowing the exact level of impairment to be determined. Mechanical sensitivity for tactile stimuli is generally measured using Von Frey

filaments, standardized brush for moving tactile stimulation, pinprick sensation with weighted needles and vibration sensitivity with an electronic vibrameter [48]. Thermal perception and thermal pain are measured using a probe that operates on the Peltier principle. QST allows an assessment of sensory detection thresholds for innocuous stimuli and pain thresholds, generally using the method of limits, less commonly the methods of levels [48]. Such determination allows a more precise assessment of the magnitude of sensory deficits and a quantification of thermal and mechanical allodynia. Generally, the contralateral homologous side is used as control, but normative data for thermal and mechanical detection and pain thresholds for the hand, foot and face have been proposed based on a large group of healthy volunteers [49,50]. However, the range of thermal, particularly cold pain thresholds is very large within individuals and the repeatability is not optimal for cold pain thresholds [51], which illustrates the difficulty for interpreting the results obtained regarding pain thresholds in individual patients and makes QST more appropriate for comparison of group data [48]. QST also includes the assessment of sensations induced by subthreshold [49] or suprathreshold stimuli [52], which may contribute to the identification and quantification of hyperalgesia. However, there is no widely accepted consensus regarding a specific algorithm for the assessment of thermal or mechanical allodynia and hyperalgesia.

QST in the setting of intervention trials

QST has been used in several therapeutic trials to measure the effects of treatments on evoked pains. Whereas most studies failed to detect treatment effects on pain thresholds in response to mechanical or thermal stimuli, treatments did significantly modulate brush-induced allodynia (intensity or area, e.g., [53]), hyperalgesia to static mechanical or cold stimuli [35,54], and other less common components of NP (such as temporal summation, aftersensation and radiating pain, e.g., [55]). Some studies have suggested that drugs such as morphine, lidocaine or NMDA antagonists may not act uniformly on the different components of NP [35,53,55]. In particular, the clinical profile of these agents might relate to their preferential antihyperalgesic and antiallodynic action. However, little is known about the effects of first-line drug treatments (e.g., antiepileptics or antidepressants) on these outcomes.

These techniques have also been used to predict the response to treatment interventions. Thus, it has been shown that a selected sensory abnormality, specifically impaired thermal detection in the affected dermatomes, may predict the outcome of motor cortex stimulation in central pain [56] or of epidural steroid injection in patients with sciatica [57]. Similarly, one study showed that higher heat pain thresholds at baseline in the affected area might predict opioid response in postherpetic neuralgia [58]. Conversely, preservation of thermal sensation has been found to be associated with a better response to botulinum toxin type A, which suggests that this treatment may have an impact on preserved sensitized nociceptive fibers to induce its analgesic effect [35]. Finally, it has also been reported that the presence of mechanical allodynia might predict treatment outcome with the sodium-channel blockers lamotrigine or intravenous lidocaine [53,59]. However, one study using intravenous lidocaine in central pain patients stratified on the basis of the presence or absence of mechanical allodynia failed to confirm these results [60]. Similarly, QST was not helpful in predicting which patients with peripheral neuropathy or postherpetic neuralgia would benefit from lidocaine patches [61] and yielded unexpected results with the same treatment in PHN patients classified on the basis of their putative underlying mechanisms (see above) [62].

Thus, the expected role of QST in the definition of a mechanism-based treatment of NP, although promising [63–65], has not yet been fully met [66]. This may be due to several reasons. One is the fact that most therapeutic studies using QST did not use standardized assessment. It should also be noted that the sensory changes measured by QST in these trials were mostly a secondary outcome. Thus, some studies were probably underpowered to detect changes in the sensory profiles. Finally, most studies attempting to find predictors of the response to treatment were based on *post hoc* analyses. Given the heteorogeneity of sensory profiles within the same neuropathic condition, pharmacological trials, including a stratification of the patients according to the sensory profiles, are needed.

Conclusion & recommendations

Recent advancement in the methods used to assess NP has greatly improved research on treatment response to NP. Although assessment of pain intensity and relief remains essential, the characterization of self-reported pain quality descriptors and sensory signs that are frequently associated with NP is relevant for clinical trials because pain associated with a nerve lesion has distinct pain symptomatology and symptoms and signs of NP may provide some indications about underlying mechanisms. Thus, screening tools to identify NP may be helpful in clinical trials of NP to increase diagnostic accuracy of NP for patient selection and should probably be included in the diagnostic criteria of NP in clinical trials. Specific validated measurement scales based on pain descriptors are relevant to characterize the effects of treatments on distinct pain symptoms or dimensions (i.e., combination of symptoms) and should also be used

in future trials to try and predict treatment outcome. Further development of QST to characterize sensory deficits and hyperalgesia, allodynia or other alterations that are commonly encountered in NP conditions may also provide a comprehensive assessment of treatment response on sensory signs. However, although QST has also been found useful to predict response to therapy in some proof-of-concept studies, many disappointing results have been reported. The use of QST combined with other techniques such as functional MRI would also certainly be more valuable to increase therapeutic prediction. Studies using standardized QST methods of assessment on large cohorts and including a stratification of the patients according to the sensory profiles are also warranted (see [52]).

Future perspective

The standardization of sensory testing and the validation of specific NP assessment questionnaires should contribute to better matching patients to specific treatments, thus leading to an optimal therapeutic outcome. It will soon become critical to perform appropriately powered multicenter studies of QST. Since such studies are extremely difficult to implement with a comprehensive range of tests, an optimized range of QST tests suitable for large-scale pharmacological studies should be developed. Future multicenter studies should also use validated NP assessment scales to help predict the response to treatments.

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Executive summary

- This review presents the various forms of assessment of neuropathic pain (NP) currently used in NP therapeutic trials, including intensity scales, specific and nonspecific pain measurement questionnaires, and quantitative sensory testing.
- Pain intensity in NP intervention trials is best measured using numerical rating scales or visual analog scales.
- Screening of NP with specific tools (i.e., DN4, PainDetect and ID Pain) may be helpful to increase diagnostic accuracy for enrolment in clinical trials of NP.
- Temporal aspects of pain, Patients' Global Impression of Change, pain-relief scales and specific measurement questionnaire such as the Neuropathic Pain Scale and the Neuropathic Pain Symptom Inventory, represent relevant additional measures that may capture different dimensions of NP experience and are suitable for use as secondary outcomes in intervention trials of NP. Specific measurement scales may also serve to identify responder profiles to specific treatments.
- Quantitative sensory testing has been used in several therapeutic trials to measure the effects of treatments on detection/pain thresholds or on evoked pains. It has also been used to predict the response to treatment interventions. Studies using standardized assessment on large cohorts with adequate sample sizes are now warranted.

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