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REVIEW ARTICLE

Personalized treatment of neuropathic pain: Where are we now?

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Abstract

Background: The treatment of neuropathic pain remains a major unmet need that the development of personalized and refined treatment strategies may contribute to address.

Database: In this narrative review, we summarize the various approaches based on objective biomarkers or clinical markers that could be used.

Results: In principle, the validation of objective biomarkers would be the most robust approach. However, although promising results have been reported demonstrating a potential value of genomics, anatomical or functional markers, the clinical validation of these markers has only just begun. Thus, most of the strategies documented to date have been based on the development of clinical markers. In particular, many studies have suggested that the identification of specific subgroups of patients presenting with specific combinations of symptoms and signs would be a relevant approach. Two main approaches have been used to identify relevant sensory profiles: quantitative sensory testing and specific patients reported outcomes based on description of pain qualities.

Conclusion: We discuss here the advantages and limitations of these approaches, which are not mutually exclusive.

Significance: Recent data indicate that various new treatment strategies based on predictive biological and/or clinical markers could be helpful to better personalized and therefore improve the management of neuropathic pain.

1 | INTRODUCTION

Neuropathic pain which affects up to 7%–10% of the general population (Bouhassira, 2019; Bouhassira et al., 2008; Smith & Torrance, 2012; van Hecke et al., 2014) remains a major unmet clinical need. Reviews and meta-analyses have consistently reported that less than 50% of patients respond to the currently recommended treatments and that this response is modest at best (Attal, 2019; Attal & Bouhassira, 2021; Finnerup et al., 2015; Moisset et al., 2020). This poor therapeutic outcome is probably related to multiple factors, including the lack of adequate experimental models and the lack of specificity of the treatments currently recommended (e.g. antidepressants and antiepileptics agents), which may imply that they do not act on the most relevant pathophysiological mechanisms. However, several recently developed drugs with more specific modes of action have also failed to display significant

efficacy in these patients (Attal & Bouhassira, 2015, 2019; Bouhassira & Attal, 2018, 2019). Another plausible explanation for treatment failure in this population may be an insufficient consideration of the clinical heterogeneity of neuropathic pain syndromes in both clinical trials and daily practice. Patients with neuropathic pain present with various combinations of symptoms (e.g. different pain qualities such as 'burning', 'electric shocks-like', etc.) and signs (e.g. sensory deficits and/or allodynia/hyperalgesia). These different sensory profiles may reflect multiple underlying pathophysiological mechanisms, and may, therefore determine the response to treatment. Consequently, a pharmacological agent with a specific mechanism of action may be effective only in a subgroup of patients with signs and symptoms related to this specific mechanism. In support of this hypothesis, a number of studies on various drugs have shown that the effects of these drugs are not uniform in all patients or against all neuropathic pain symptoms, and they instead have preferential action against certain symptoms (e.g. evoked pain or paroxysmal pain) or combinations of symptoms (e.g. spontaneous and evoked pain), even in studies reporting no effect on average pain intensity (e.g. Attal et al., 2002, 2004; Bouhassira et al., 2021b; Hincker et al., 2019; Kalliomäki et al., 2013). Thus, as advocated by many experts in the field (Baron et al., 2012, 2022; Bouhassira & Attal, 2019; Colloca et al., 2017; Edwards et al., 2016, 2022), major improvements in the management of neuropathic pain will probably depend on the development of new approaches facilitating personalized treatment.

In this narrative review, we discuss possible approaches for the personalization of neuropathic pain management. In principle, objective and quantifiable biomarkers should be the most robust way to identify patients likely to respond to particular treatments (Davis et al., 2020). However, as discussed in the first part of this review, despite promising data obtained, it remains premature to envisage the use of such biomarkers in routine practice or in the clinical research settings in the near future. Another well-documented approach, which could be used together with the first, involves the use of simple clinical markers for the identification of specific patient profiles or phenotypes. The phenotypic approach to neuropathic pain management is based on the notion that various combinations of symptoms and signs common to multiple aetiologies of neuropathic pain may reflect different pathophysiological mechanisms and, therefore, different responses to treatment. A number of studies based on quantitative sensory testing (QST) and/or patient-reported outcomes (PROs) have tended to confirm the relevance of this approach and will be discussed in the second part of this review. Finally, other potential clinical markers, including psychological features and other clinical characteristics, will be briefly addressed in the last part of this review.

2 | POTENTIAL BIOLOGICAL BIOMARKERS

A biomarker is an objective and measurable indicator of normal or pathological biological processes or of responses to treatment (pharmacological or otherwise) (https://www.fda.gov). At least four categories of biomarkers can be defined on the basis of their clinical use: diagnosis, prognosis, prediction of treatment response and assessment of treatment target engagement (Davis et al., 2020). A full description of pain biomarkers lies beyond the scope of this review (see Baron et al., 2022; Davis et al., 2020; Tracey et al., 2019), and we provide here only a brief summary of the data for potential predictive biomarkers. In principle, various approaches based on molecular (e.g. genetic, genomic), structural (e.g. histology, anatomical imaging) or functional (e.g. electrophysiology, functional neuroimaging) biomarkers could be used to identify specific subgroups of patients with neuropathic pain for the purpose of personalized pain management.

2.1 | Genetic and genomic biomarkers

The most promising studies on potentially predictive genetic markers in neuropathic pain syndromes to date are those relating to the identification of variants of genes encoding ion channels, such as *SCN9A*, which encodes Nav1.7 subtype sodium channels, in particular. Specific mutations inducing a gain-of-function for Nav1.7 are associated with rare hereditary painful syndromes, such as erythromelalgia or paroxysmal extreme pain disorders. Conversely, mutations inducing a loss-of-function are associated with congenital analgesia (Dib-Hajj et al., 2013). These findings elegantly demonstrated the major role of Nav 1.7 in nociception and pain, but their clinical significance beyond extremely rare genetic conditions remained unclear. However, more recent studies have shown that gain-of-function variants, not only of *SCN9A*, but also of *SCN10A and SCN11A*, which encode other sodium channel subtypes (Nav 1.8, Nav 1.9), occur in subgroups of patients with more common neuropathic pain conditions, such as small-fibre neuropathy or painful diabetic neuropathy (Bennett et al., 2019; Bennett & Woods, 2014; Blesneac et al., 2018; Sopacua et al., 2019). The presence of these variants has been associated with stronger responses to sodium channel blockers, such as lacosamide or Nav1.7 antagonists (de Greef et al., 2019; Price et al., 2017). These studies have tended to confirm the potential relevance

of genetic testing for the personalized management of neuropathic pain, but they were performed in only small numbers of patients and reported minimal differences in the magnitude of analgesic effects between responders and non-responders. In addition, the predictive value of such monogenic variants is limited to small, highly specific groups of patients. The development of clinically relevant applications of these approaches may depend on the identification of more sophisticated polygenic variants in large populations of patients, but this remains highly challenging. The validation of such genetic biomarkers for the personalization of neuropathic pain management therefore remains in its infancy.

Other potential omics-based biomarkers include microRNAs (miRNAs). These non-coding RNAs involved in the regulation of genes expression are easily quantified by RT-PCR in various body fluids and tissues. Changes in miRNA levels have been reported in several chronic pain conditions (Polli et al., 2020), but do not appear to be stable enough for the reliable stratification of patients. Many other omics-based measurements including analyses of the transcriptome, proteome, metabolome and lipidome, may also provide new clinically relevant biomarkers, as already reported in other medical fields, such as oncology. However, too few studies have been performed in the pain field, particularly for neuropathic pain syndromes, for an assessment of the relevance of these approaches. Nevertheless, it is possible that this situation will change in the near future, due to the rapidity of technological developments in this field.

2.2 | Functional biomarkers

Both electrophysiology and functional neuroimaging have been used to identify potential functional biomarkers in patients with neuropathic pain. Some of these techniques have the theoretical advantage of being directly related to pathophysiological mechanisms (e.g. peripheral sensitization). In addition, analyses of changes in whole-brain activity or in functional connectivity between specific brain areas, not necessarily directly related to pain mechanisms, could also potentially provide useful biomarkers for patients stratification.

2.2.1 | Peripheral functional biomarkers

Peripheral mechanisms can be investigated by microneurography, which can record pathophysiological changes in nerve fibres activity (e.g. ectopic discharges or peripheral sensitization) (Ackerley & Watkins, 2018). However, this powerful, but invasive, electrophysiological approach has been used only in very specific research settings, and there are no data demonstrating its utility for predicting treatment response. The measurement of axonal excitability using threshold tracking techniques (Bostock et al., 1998), allowing the assessment of ion channel function and axonal resting membrane potential directly in patients, is another potentially interesting approach. However, there are no data regarding its potential predictive value and a recent study (Themistocleous et al., 2022) showed that distal axonal excitability does not differ between patients with painful or painless polyneuropathies, which is probably due to the fact that only large fibre function is assessed with these technique. More recently, innovative techniques based on heterologous expression systems and bioassays, and involving the induced differentiation of pluripotent stem cells from patients into neurons or non-neuronal cells have been used to investigate the pathophysiological changes in nociceptors and to predict the effects of treatment in highly selected patients (Geha et al., 2016; Han et al., 2018; Middleton et al., 2021). However, it is likely to prove difficult to implement these sophisticated techniques in large-scale clinical trials.

2.2.2 | Central functional biomarkers

The measurement of brain activity by electroencephalography (EEG) or magnetoencephalography (MEG) has the advantage of being non-invasive and, at least for EEG, readily available in clinical practice. Both evoked (event-related potentials) and spontaneous (i.e. resting-state oscillations) changes in brain activity can be assessed (Ploner & May, 2018). Changes in resting-state EEG spectral power, which are probably more relevant as biomarkers, have been reported in patients with neuropathic pain (Mussigmann et al., 2022). The principal change detected is a significant increase in the power spectral density of the theta band (4–7 Hz), potentially reflecting thalamocortical dysrhythmia, and, to lesser extent, the alpha (8–12 Hz) and beta (13–30 Hz) bands; however, the correlation of these changes with ongoing pain intensity is inconsistent (Mussigmann et al., 2022; Zebhauser et al., 2022). The specificity and potential predictive value of these changes for treatment response remains unknown. It would certainly be of interest to assess the predictive value of these changes for the efficacy of non-invasive brain stimulation techniques (e.g. repetitive transcranial magnetic stimulation, rTMS), which are known to modify brain oscillations.

Changes in brain activity have also been assessed with functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), the two main functional neuroimaging techniques developed to date. Magnetic resonance spectroscopy, which quantifies changes in a

large number of brain neurotransmitters, is another interesting functional approach to assessing changes in brain metabolic activity (Teckchandani et al., 2021). These powerful techniques, which have been widely used over the last 30 years, have yielded highly valuable information regarding central pain mechanisms in humans (Garcia-Larrea & Peyron, 2013; Peyron & Fauchon, 2019), but their clinical applications remain very limited. However, new paradigms, shifting from classical brain mapping studies to multivariate brain models of sensory perception, have recently been developed (Kragel et al., 2018; Woo et al., 2017). These models use machine learning and big data approaches to develop specific algorithms based on the assessment of distributed neural activities in large networks extending over many regions of the brain. The neurological pain signature (NPS), an algorithm based on the analysis of individual brain fMRI images, was identified through the application of such approaches. It can be used to discriminate between painful and non-painful sensations with very high sensitivity and specificity (Wager et al., 2013). However, despite the success of the NPS for predicting pain induced by acute experimental stimuli in healthy volunteers, its efficacy for predicting chronic pain remains unclear. Other approaches based on analyses of resting-state activity, including the default mode network (DMN) and/or functional connectivity between different brain regions, have given promising results in patients with chronic pain. A series of studies by the Apkarian group have highlighted the utility of changes in functional connectivity in the mesolimbic system, particularly between the nucleus accumbens and medial prefrontal cortex, for predicting the transition from subacute to chronic low back pain (Baliki et al., 2010, 2012; Baliki & Apkarian, 2015). Interestingly, recent data have suggested that changes in functional connectivity in the mesolimbic system can also predict the effects of treatment (with levodopa and naproxen) in female patients with chronic low back pain, this effect apparently being sex-dependent (Reckziegel et al., 2021). Additional studies in chronic low back pain and fibromyalgia have shown that changes in functional connectivity between other brain areas known to be involved in pain perception and modulation, including the anterior or posterior cingulate cortex, posterior insula, periaqueductal grey (PAG) and dorsolateral prefrontal cortex, can predict response to the antidepressant milnacipran (Ichesco et al., 2021; Schmidt-Wilcke et al., 2014), the antiepileptic drug pregabalin (Ichesco et al., 2021) and placebo (Hashmi et al., 2012; Vachon-Presseau et al., 2018, 2022). Large-scale changes in connectivity between the DMN and specific brain areas (e.g. the insula and the mid frontal cortex) have also been reported to be predictive of the response to pregabalin (Harris et al., 2013) or to rTMS of the motor cortex (Argaman et al., 2022) in patients with fibromyalgia. However, no data have yet been reported for such changes in neuropathic pain patients. Only one small open-label study has suggested that the response to ketamine infusion is related to changes in functional connectivity between the DMN and structures involved in descending pain modulation such as the PAG (Bosma et al., 2018).

2.3 | Structural biomarkers

2.3.1 | Central structural biomarkers

Structural changes in the brain can be assessed with several techniques, including anatomical MRI, volume and grey matter density determinations and diffusion-weighted imaging to assess white matter integrity and pathways. Since the pioneering work by Apkarian and his group showing alterations to prefrontal grey matter density in patients with chronic low back pain (Apkarian et al., 2004), many studies using voxel-based morphometry (VBM) have confirmed structural changes in various brain areas in several chronic pain conditions, although neuropathic pain was considered in only a few of these studies (Cauda et al., 2014; Tatu et al., 2017). However, these studies did not yield consistent results (some showed increases, whereas others found decreases in grey matter volume) and the pathophysiological and clinical significance of these anatomical changes remains uncertain (Kang et al., 2019). They may be of prognostic value for predicting the development of chronic low back pain (Baliki et al., 2012), but their predictive value for treatment response is unknown.

2.3.2 | Peripheral structural biomarkers

Intra-epidermal nerve fibre density (IEFND), which can be measured by skin punch biopsy, is a potential peripheral structural biomarker. Skin biopsy has mostly been used for the diagnosis of small-fibre neuropathy and is considered to be one of the most relevant diagnostic tests for this condition (Devigili et al., 2008, 2020; Sommer & Lauria, 2007). It was suggested years ago that IEFND might be predictive of the response to topical treatment with lidocaine plasters in patients with postherpetic neuralgia, with an enhanced response anticipated in patients with preserved sensory innervation (Rowbotham & Fields, 1996). We recently showed that the preservation of peripheral sensory innervation, as assessed by skin punch biopsy, was predictive of the response to subcutaneous injections of botulinum toxin A (BTXA) in patients with peripheral neuropathic pain (Attal et al., 2016). Thus,

although IENFD is not necessarily directly related to pain, as not all small-fibre neuropathies are painful and no clear relationship has been established between pain intensity and IEFND in patients with pain (Sommer & Lauria, 2007), it may be a relevant biomarker for a few specific treatments.

3 | CLINICAL MARKERS

Most studies on potentially predictive clinical markers in patients with neuropathic pain have focused on identifying sensory profiles or phenotypes consisting of specific combinations of symptoms and signs. However, other clinical markers are also of potential value, as discussed briefly below.

3.1 | Sensory phenotyping

The presence of a neurological lesion confers particular qualities on pain symptoms, justifying the consideration of neuropathic pain as a relevant clinical entity. However, this clinical entity is now known to be heterogeneous and multidimensional, not only in terms of its causes, but also in terms of the variety of its clinical expression. The personalization of neuropathic pain management could therefore be based on the identification of relevant clinical markers better reflecting such heterogeneity. In particular, many experts have suggested that the identification of specific sensory profiles, corresponding to various combinations of symptoms (e.g. spontaneous continuous pain, spontaneous paroxysmal pain) and signs (e.g. sensory deficits, mechanical and/or thermal allodynia/hyperalgesia), potentially reflecting pathophysiological mechanisms, may be a relevant strategy (Attal et al., 2011; Baron et al., 2012, 2022; Bouhassira & Attal, 2016, 2019; Colloca et al., 2017; Edwards et al., 2016, 2022; Forstenpointner et al., 2018). Several approaches have been used to identify these sensory profiles or phenotypes in clinical trials, including standardized sensory bedside examination, QST and questionnaire-based patients reported outcomes (PROs), but there is no clear consensus about the optimal approach as yet.

3.1.1 | Quantitative sensory testing and sensory bedside examination

QST is a psychophysical method complementary to routine bedside sensory examination used for the quantitative assessment of various sensory modalities (Backonja et al., 2013; Haanpää et al., 2011; Hansson et al., 2007; Truini et al., 2023). It is based on the measurements of pain and detection thresholds in response to calibrated, graded mechanical and thermal stimuli and the assessment of responses to suprathreshold stimuli. It can be used to assess the presence and severity of both positive phenomena (i.e. allodynia and hyperalgesia) and negative phenomena (i.e. sensory deficits). The intensity of the stimulus is controlled, but the response is entirely dependent on the patients' reports. QST is, therefore, regarded as a 'semi-objective' approach, and, contrary to statements made in recent recommendations (Edwards et al., 2022; Smith et al., 2017), it should not be considered a biomarker (like those reported above), but should instead be seen as a clinical marker.

The clinical use of QST was initially limited by the lack of reference normative data. Several normative datasets have now been published, the more widely used being that developed by the German Research Network on Neuropathic Pain (DFNS) (Magerl et al., 2010; Rolke, Baron, et al., 2006; Rolke, Magerl, et al., 2006). However, contrasting with detection thresholds, the range of normative data for thermal pain thresholds is very broad both within and between individuals, and reproducibility is also lower than that for detection thresholds. It can, therefore, be difficult to interpret pain thresholds results in individual patients, and QST is probably more appropriate for comparisons of group data (Backonja et al., 2013; Haanpää et al., 2011; Hansson et al., 2007).

QST has mostly been used in research studies, for the diagnosis, assessment or pathophysiological exploration of sensory neuropathies and various pain syndromes, but a few pharmacological studies based on QST in patients with neuropathic pain have been reported (Backonja et al., 2013). These studies conducted in patients with various neuropathic pain conditions, reported selective or preferential effects of multiple drug treatments (infusions of NMDA antagonists, lidocaine or opioids, subcutaneous injections of BTXA, oromucosal cannabinoids and oral gabapentin) on evoked pain (i.e. allodynia, hyperalgesia) (Attal et al., 1998, 2000, 2002, 2004, 2016; Gottrup et al., 2006; Leung et al., 2001; Nurmikko et al., 2007; Ranoux et al., 2008; Wallace et al., 1996, 2002). However, these data, which suggested that these treatments may have preferential anti-hyperalgesic effects, are heterogeneous, and all but a few emanated from small single-centre pilot studies with few exceptions (Attal et al., 2016; Nurmikko et al., 2007). This may account for their lack of impact on therapeutic recommendations to date (Finnerup et al., 2015; Moisset et al., 2020).

QST has also been used to predict treatment response. Several randomized placebo-controlled studies have suggested that sensory (pain or detection) thresholds at baseline may be associated with an enhanced response

to various drug therapies. For example, higher heat pain thresholds in the painful area have been found to predict the response to opioids in postherpetic neuralgia (Edwards et al., 2006). Cold and pinprick hyperalgesia have been found to be associated with a better outcome in patients treated with high-concentration capsaicin patches (Mainka et al., 2016), and mechanical allodynia has been shown to predict the efficacy of the sodium channel blocker lamotrigine and iv lidocaine in some studies (Attal et al., 2004; Finnerup et al., 2002), but not in others (Finnerup et al., 2005; Todorovic et al., 2021). One multicentre study reported that patients with painful HIV polyneuropathy presenting with severe punctate mechanical hyperalgesia had better responses to pregabalin (Simpson et al., 2010). Detection thresholds, which are used to evaluate the presence or severity of sensory deficits, have also been shown to be relevant as potential predictors, as illustrated by studies suggesting that the preservation of thermal sensitivity is associated with a higher efficacy of BTXA in patients with peripheral neuropathic pain (Attal et al., 2016; Ranoux et al., 2008) or of a new oral TRPA1 receptor antagonist in painful diabetic neuropathies (Jain et al., 2022). Conversely, preserved thermal or mechanical sensation has been reported to have no predictive value for the response to topical lidocaine (Herrmann et al., 2006; Wasner et al., 2005), duloxetine (Yarnitsky et al., 2012) or pregabalin (Hincker et al., 2019).

This brief summary highlights the considerable heterogeneity of data for the clinical relevance of detection or pain threshold measurements for the stratification of patients with neuropathic pain. In addition, most of the results described above were obtained in post hoc exploratory analyses. The variability of the results may also reflect the non-optimal nature of single-threshold measurements for the identification of clinically relevant sensory profiles. The use of sensory profiles based on combinations of several QST parameters would probably be more appropriate, as it would better reflect pathophysiological mechanisms and might therefore be more predictive of treatment response. Extensive QST profiling is currently best based on the DFNS protocol consisting of a comprehensive battery of 13 tests, including thermal and mechanical detection and pain thresholds, mechanical suprathreshold stimulation, temporal summation and paradoxical heat sensation (Rolke, Baron, et al., 2006; Rolke, Magerl, et al., 2006).

The results of a randomized controlled study performed by Demant et al. (2014) have been widely cited to illustrate the success of patients' stratification based on full QST profiling (Baron et al., 2022; Edwards et al., 2022; Forstenpointner et al., 2018). These authors assessed the effects of the sodium channel blocker oxcarbazepine in patients with peripheral neuropathic pain stratified into two different clinical phenotypes on the basis of the DFNS-QST protocol (Rolke, Baron, et al., 2006). One of these phenotypes, the 'irritable nociceptor' (IN) phenotype was characterized principally by a limited thermal deficit in the painful area and the presence of evoked pain, whereas the other phenotype, the 'deafferentation pain' or non-'irritable nociceptor' (NIN) phenotype, was characterized principally by a severe thermal deficit. The study found that the effects of oxcarbazepine were significantly stronger than placebo in patients with the IN phenotype than those with the NIN phenotype. However, the difference in the magnitude of the effects of oxcarbazepine between the two subgroups was very small and this study had several limitations related, in particular, to a very high attrition rate (60%). Furthermore, other studies with a similar stratification of patients were unable to confirm the predictive value of these sensory profiles. In a study by the same group (Demant et al., 2015), which was probably also statistically underpowered, the effects of topical lidocaine were similar in patients with the IN and NIN profile. A more recent study also found no predictive value of IN or NIN sensory profiles for the effects of lacosamide, an antiepileptic with sodium channel blocking properties (Carmland et al., 2019). This new study was also subject to the limitation of a high attrition rate, but its overall negative results for a molecule from the same class and with similar mechanisms to oxcarbazepine tend to refute the hypothesis that IN and NIN profiles reflect neuropathic pain mechanisms and are relevant for the prediction of treatment response. One reason for the lack of pathophysiological or clinical relevance of these profiles may be their definition essentially on the presence/absence and severity of sensory deficits rather than on the basis of specific neuropathic pain components.

It may be better to use QST to stratify patients based on the identification of clusters of patients with various combinations of hyper- and hypophenomena. In one recent study using the DFNS-QST protocol in a large cohort of 902 patients with peripheral neuropathic pain (with a replication in 233 patients for validation), four clusters, characterized by sensory loss, thermal hyperalgesia, mechanical hyperalgesia and a normal sensory profile, respectively, were identified (Baron et al., 2017). A specific algorithm was developed for allocating individual patients to these clusters, which could be used to stratify patients in clinical trials (Vollert et al., 2017). However, the value of these clusters and of this algorithm for predicting treatment response remain to be confirmed.

QST has also been used to assess alterations to endogenous pain modulation, particularly for descending pain modulatory systems, with conditioned pain modulation (CPM) paradigms (Nir & Yarnitsky, 2015). These paradigms, derived from the classical DNIC experiments (Yarnitsky et al., 2015), involve assessing the interactions

between two painful stimuli (a test stimulus and a conditioning stimulus) applied to different areas of the body. In one open study in patients with painful diabetic neuropathy, impaired CPM, which may reflect impaired descending inhibition, was associated with a better response to duloxetine, possibly due to its reinforcing action on descending inhibitory systems (Yarnitsky et al., 2012). These interesting results suggesting a potential predictive role of CPM, require confirmation in large, controlled studies. Further assessments of the potential relevance of testing the temporal summation of noxious stimuli, also included in the DFNS protocol, are also required to improve the assessment of facilitatory processes, such as central sensitization.

In summary, with the exception of a few heterogeneous results concerning the potential relevance of thresholds measurements, particularly concerning the ability of the preservation of sensory fibres to predict therapeutic response, the data concerning the utility of QST for stratifying patients in clinical trials and predicting treatment response have generally been disappointing. Further prospective trials would be merited. Furthermore, QST has several inherent limitations. One major limitation is related to the absence of an assessment of spontaneous pain, which is, by far, the most frequent complaint in patients with neuropathic pain. QST is also time-consuming (at least 45 min for the DFNS protocol) and requires expensive devices and special training. The interpretation of QST results may also be hampered by a lack of concordance between the outcomes of QST and bedside neurological testing (Devigili et al., 2008; Hansson et al., 2007). This situation may arise due to QST measurements being made in a restricted part of the painful area, whereas more qualitative bedside examinations facilitate the testing of a large part of the innervation territory of the injured nervous system structure (Hansson et al., 2007). Finally, and even more problematically, pain thresholds assessed with QST are poorly correlated, if at all, with patient-reported neuropathic pain symptoms (Gierthmühlen et al., 2018, 2019, see however Attal et al., 2008). This suggests that QST is more suitable for the monitoring of sensory deficits and, therefore, more appropriate for the detection of neurological lesion and assessments of their severity, which was, in fact, the initial purpose for which QST was developed. It was not designed for the assessment of neuropathic pain per se. These limitations probably explain why the use of QST has not substantially increased in clinical practice over the last three decades, with this approach remaining restricted to highly specialized research centres.

It has been suggested that some of these limitations could be overcome by developing simplified standardized 'bedside-QST' protocols using less expensive tools. This is an interesting proposal, but somewhat ironic, given that QST was developed as a means of overcoming the limitations of bedside sensory examination! Several such standardized 'bedside-QST' protocols have been developed (Koulouris et al., 2020; Reimer et al., 2020; Sachau et al., 2023a; Wasan et al., 2020), albeit at single centres (usually with a single investigator), and their sensitivity to change (i.e. to treatments) has not been assessed. In addition, although these new protocols are simpler, they are still time-consuming (20–30 min) and the correlation between 'bedside-QST' and 'laboratory-QST' seems to be weak-to-moderate for several parameters (Reimer et al., 2020). The validation of these protocols is at a preliminary stage, and further studies are required to determine whether these simplified protocols would be feasible in large clinical trials and provide relevant clinical information in terms of the prediction of therapeutic effects.

3.1.2 | Patients-reported outcomes

Only patients can describe their symptoms and associated disability in an appropriate manner. Thus, in the absence of validated objective biomarkers of pain, PROs, defined as measurements based on reports originating directly from the patient without interpretation of the responses by a caregiver, remain the gold standard for pain assessment. In clinical trials, the assessment of treatment efficacy is based principally on the patient's rating of spontaneous pain intensity as the primary outcome parameter. Various approaches are used, including categorical scales (e.g. mild, moderate and severe), numerical rating scales (NRS) and visual analogue scales (VAS). However, several groups of international experts have recommended the inclusion of other core set outcome domains (refs in Sachau et al., 2023b). In general, these recommendations are consistent as the domains to be assessed in clinical trials. These domains include pain (intensity, quality and temporality), physical functioning (daily activities/well-being, sleep quality), emotional functioning, patient global improvement and satisfaction with treatment. A recent systematic literature review conducted by the European IMI PainCare Consortium showed that only a minority of randomized controlled trials (about 2%) have assessed all the recommended domains (Sachau et al., 2023b). However, the number of domains and PROs used in randomized controlled trials on neuropathic pain has significantly increased over the last two decades. In particular, PROS specific for neuropathic pain, including some assessing neuropathic pain qualities, have increasingly been used in recent studies.

Several simple questionnaires based on the self-assessment and quantification of neuropathic symptoms (i.e. pain descriptors) on numerical scales running from 0

to 10 have been validated. The most frequently used have been the Neuropathic Pain Scale and the Neuropathic Pain Symptom Inventory (Attal et al., 2018; Bouhassira & Attal, 2011; Bouhassira et al., 2004).

Other non-specific questionnaires, including the McGill Short-Form Questionnaire 2 (derived from the widely used McGill Short-Form Questionnaire), the Pain Quality Assessment Scale (derived from the Neuropathic Pain Scale) and, more recently, the PainPredict questionnaire, have been validated for the assessment of both neuropathic and non-neuropathic pain (Attal et al., 2018; Bouhassira & Attal, 2011; Tölle et al., 2019). In addition, the PainDETECT questionnaire was originally validated as a screening questionnaire, but there is some evidence to suggest that it is also reliable as an assessment questionnaire (Attal et al., 2018).

These questionnaires are useful for characterizing the nature of the symptoms (i.e. quality and intensity) reported by patients with neuropathic pain. They may facilitate the monitoring of treatment outcome and can be used to determine which symptoms (e.g. burning pain, electric shock-like pain, pain evoked by brushing) or dimensions (corresponding to combinations of symptoms) are alleviated by the treatment. For example, the NPSI includes 10 items pertaining to five different clinically relevant dimensions: spontaneous burning pain, spontaneous deep pain, paroxysmal pain, evoked pain and paraesthesia/dysesthesia. These dimensions are present in similar proportions in neuropathic pain of many different aetiologies, with a few exceptions such as trigeminal neuralgia and plexus avulsion (Attal et al., 2008). Multiple randomized controlled studies have demonstrated the sensitivity to change (i.e. to treatment) of the NPSI, and the use of this instrument has helped to show that analgesic drugs do not act uniformly on all the neuropathic pain symptoms, but preferentially on specific symptoms or dimensions (Attal et al., 2018). Interestingly, sensitivity to treatment has sometimes been shown to be better for assessment of neuropathic pain symptoms than the overall assessment of average daily pain intensity. Thus, in several RCTs, average pain intensity (generally, the primary outcome) was not significantly improved after treatment, whereas improvements were noted for one or several dimensions assessed with the NPSI as secondary outcomes. These results appear relevant from a clinical or pathophysiological perspective, as illustrated by the following examples, which are all based on placebo-controlled trials. Thus, a 'negative' phase II study of the effects of a new chemokine receptor 2 antagonist (AZD2423) reported no difference between the effects of the active drug and placebo on average pain intensity, but a dose-dependent decrease in paroxysmal pain and dysesthesia/paraesthesia (Kalliomäki et al., 2013). A trial of the somatosensory predictors of the effects of pregabalin in painful chemotherapy-induced neuropathy found no difference in average pain intensity between pregabalin and placebo, whereas the active drug had significant effects on deep pain and evoked pain (Hincker et al., 2019). A trial of a new Nav1.7 sodium channel blocker in patients with painful diabetic neuropathy yielded negative findings for the primary outcome (average pain intensity), but the drug specifically decreased burning pain, suggesting a role for Nav1.7 in this symptom (McDonnell et al., 2018). Interestingly, patients with diabetic neuropathy carrying (rare) Nav1.7 variants report more severe burning pain (Blesneac et al., 2018). In a recent study of the effects of inhaled nitrous oxide in patients with peripheral neuropathic pain, the change in average pain intensity did not differ between the active treatment and placebo, but there was a significant difference in the change in evoked pain score (Bouhassira et al., 2021b). Interestingly, this change was directly correlated with the overall improvement assessed with the PGIC, confirming its clinical relevance. In other studies, the effects on average pain intensity were significant, but stronger effects were reported for specific NPSI items and/or dimensions (Attal et al., 2016; Bouhassira et al., 2014; Ranoux et al., 2008; Wang et al., 2014).

These questionnaires have been used not only as outcome parameters, but also at baseline to identify patients' subgroups to predict treatment outcome (Attal et al., 2018). For example, exploratory analyses in a placebo-controlled study using the NGF antagonist fulranumab showed that the presence of severe burning pain or deep pain at baseline was associated with a better overall treatment efficacy (Wang et al., 2014). Similarly, patients with peripheral neuropathic pain reporting burning and paroxysmal pain seem to respond better to oxcarbazepine (Demant et al., 2014). Interestingly, recent data have suggested that refined sensory profiles consisting of combinations of several NPSI items (not necessarily related to the dimensions described above) could also be clinically relevant. The value of this stratification lies in its being based on the identification of clusters corresponding to a more detailed sensory phenotype than the simple presence or absence of a single symptom (e.g. evoked pain). It may, therefore, lead to the more accurate identification of patients likely to respond to different drugs. In particular, the use of an approach similar to that used for QST (see above), in a large cohort of patients revealed that three clusters corresponding to different combinations of NPSI items could be identified and that the response to pregabalin differed between these three subgroups of patients (Freeman et al., 2014). These subgroups were recently confirmed in another large cohort of patients from our internal database with various aetiologies of neuropathic pain (Bouhassira et al., 2021a) (Figure 1). One subgroup,

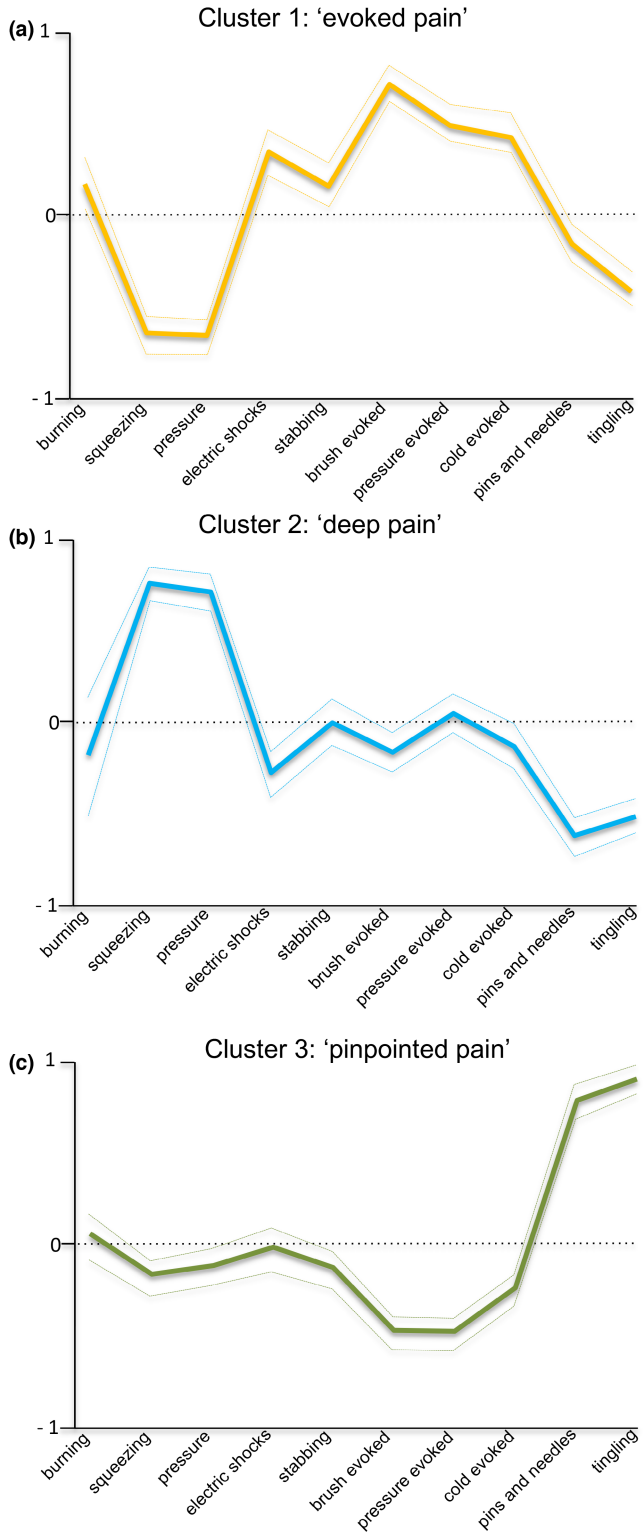

FIGURE 1 Description of the three clusters of patients with distinct sensory profiles consisting of different combinations of symptoms assessed with the 10 neuropathic pain descriptors included in the NPSI. (a) Cluster 1—'evoked pain', was characterized by higher scores for brush-, pressure- and cold-evoked pain and low levels of deep pain. (b) Cluster 2—'deep pain', was characterized by higher levels of pressure and squeezing pain, moderate levels of evoked pain and low levels of paraesthesia/dysesthesia. (c) Cluster 3—'pinpointed pain', was characterized by higher scores for items relating to paraesthesia dysesthesia (i.e. tingling, pins and needles), moderate levels of paroxysmal pain (electric shocks and stabbing pain) and burning and low levels of evoked pain. We developed a specific algorithm and an electronic version of the NPSI facilitating the allocation of individual patients (https://juliocesar9999apps.shinyapps.io/npsi_mobile/) or groups of patients (https://npsi.shinyapps.io/NPSIclustering/) to a specific cluster.

'deep pain', was characterized principally by higher scores for the deep pain-related NPSI items (i.e. squeezing and pressure pain) and moderate evoked pain scores (brushing-, cold- or pressure-evoked pain). Another subgroup, 'evoked pain', was characterized by higher evoked pain scores and scores for paroxysmal pain and low deep pain scores, and the last subgroup, 'pinpointed pain', was characterized by higher scores for paraesthesia (pins and needles and tingling). Interestingly, consistent with the hypothesis underlying the phenotype-based approach, these two studies confirmed that these clusters were not associated with the aetiology of neuropathic pain (Bouhassira et al., 2021a; Freeman et al., 2014). Instead, they encompassed diverse aetiologies and may, therefore, be regarded as trans-aetiological. For further assessment of the clinical relevance of these clusters, we investigated their association with different responses to treatment. In our two previous studies on the effects of subcutaneous injections of BTXA on peripheral neuropathic pain, we showed that BTXA induces long-lasting analgesic effects and that one of the predictors of the response to this treatment is the presence of evoked pain (Attal et al., 2016; Ranoux et al., 2008). We hypothesized that BTX-A might be more effective in the NPSI clusters with characteristics including evoked pain. For the testing of this hypothesis, we first developed a specific algorithm and an electronic version of the NPSI facilitating the allocation of individual patients (https://juliocesar9999apps.shinyapps.io/npsi_mobile/) or groups of patients (https://npsi.shinyapps.io/NPSIclustering/) to a specific cluster. This algorithm was used to classify our cohort of patients on the basis of their NPSI responses at baseline. We confirmed that the effects of BTX-A differed significantly from those of placebo in the 'evoked pain' and 'deep pain' clusters, but not in the 'pinpointed pain' cluster. Interestingly, BTX-A was found to be more effective in the two clusters characterized by high or moderate scores for the three NPSI items relating to evoked pain. By contrast, BTX-A was no better than placebo in the 'pinpointed pain' cluster, characterized by the lowest level of evoked pain. These results are, therefore, consistent with those of our previous studies showing BTX-A to be more effective in patients with evoked pain. They require confirmation in large prospective studies,

but tend to confirm the utility and feasibility of a trans-aetiological, phenotype-based approach for improving the personalized management of neuropathic pain.

The above data, based on these PROs for predicting outcome in clinical trials, are not exempt from limitations. The major limitation is that they are all based on exploratory analyses. Contrary to the three studies by the Danish group detailed above which used a QST-based phenotypic stratification of patients (Carmland et al., 2019; Demant et al., 2014, 2015), no evidence of the relevance of a pre-planned stratification based on these PROs has yet been obtained in clinical trials of neuropathic pain. Another potential limitation of the above studies is that they did not assess the possible variability of these PROs at baseline. As the baseline variability of average pain scores may be associated with an enhanced placebo effect (see below), we cannot rule out the possibility of a similar effect with these PROs. This approach, based on a self-administered questionnaire, is simpler than that based on QST. However, these two stratification methods are not mutually exclusive and could be combined in future research studies to determine whether their use is complementary and improves patient stratification. Both neuropathic pain-specific PROs and QST are recommended by the EMA for use in clinical trials of neuropathic pain, to characterize the neuropathic phenotype in more details (https://www.ema.europa.eu).

3.1.3 | Other potential clinical markers

Other clinical characteristics of the patients may be predictive of treatment response. In particular, some studies have suggested that the severity of sleep disturbances, depression, anxiety or catastrophizing at baseline may predict treatment responses in patients with neuropathic pain (Edwards et al., 2022). For example, post hoc analyses of pooled data from several studies of pregabalin showed that sleep disturbances were among the best predictors of its analgesic effects (Vinik et al., 2013, 2014). Conversely, other post hoc analyses found that the response to duloxetine was enhanced in patients with an absence of significant mood symptoms according to the Hospital Anxiety and Depression Scale in patients with painful diabetic neuropathies (Marchettini et al., 2016). Most of these data were based on post hoc analyses, but they nevertheless suggest that, in addition to neuropathic pain intensity and qualities, other parameters such as sleep disturbances and mood, should be assessed more systematically in future clinical trials. Another way of indirectly improving treatment outcome would be to improve the prediction of the response to placebo. Several studies have suggested that high variability of reported pain levels at baseline are correlated with a greater response to placebo in various chronic pain conditions, including neuropathic pain (Farrar et al., 2014). This finding has potential implications for future clinical trials, although more recent data have tended to contradict these results (Tiwari et al., 2022).

4 | CONCLUSIONS

Despite the large number of studies performed with multiple techniques and approaches, the quest for reliable and validated objective biomarkers in neuropathic pain syndromes (and in chronic pain in general) has remained fruitless. However, the growing number and availability of new and increasingly sophisticated and powerful techniques could radically change things in the coming years. In particular, promising results have already been reported for electrophysiological and neuroimaging techniques providing information about large-scale changes in brain functional activity and connectivity. Unfortunately, most of the studies performed to date concerned relatively small cohorts of patients (generally not with neuropathic pain) managed at a single centre, and the results obtained have been variable. It, therefore, remains unclear whether some functional changes are common to all chronic pain conditions, or whether each condition is associated with specific changes, and whether the prediction of treatment response is specific for each treatment. In any case, even new biomarkers considered 'objective' will have to be validated against subjective pain measurements (i.e. PROs), which remain the 'gold standard' for clinical pain assessment, to assess their clinical relevance. Thus, biomarkers should not be regarded as surrogates for subjective pain assessment, but could be combined with clinical markers, which are best documented to date. Most of the available data suggest that the definition of such clinical markers will depend on the identification of relevant clinical sensory profiles on the basis of specific PROs and/or QST. There is currently no consensus about which sensory profiles are predictive, but many studies have confirmed that neuropathic pain treatments do not act uniformly, instead acting preferentially on certain symptoms or combinations of symptoms expressed in specific subgroups of patients. More prospective studies are needed to confirm these results and to provide formal validation of this approach. In particular, it would be interesting to combine PROs, which assess symptoms, and QST, which assess signs to improve the definition of new sensory profiles. It would also be possible to develop even more 'composite markers' combining one or several clinical markers (PROs, QST) with biological markers (genetic, anatomical and functional) to provide a more accurate reflection of the clinical heterogeneity of neuropathic pain syndromes.

However, the rigorous validation of such 'composite biomarkers' for clinical use would be a very long and challenging process.

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