Quantitative sensory testing scaled up for multicenter clinical research networks: A promising start

The concept of mechanism-based treatment of chronic pain is based on the belief that specific signs and symptoms reflect the mechanisms underlying pain generation and pain persistence (Woolf et al., 1998). Neuropathic pain syndromes are generally quite distinct in their clinical presentation and the results of diagnostic tests. Diagnostic criteria are widely accepted, making diagnosis-based clinical trials a practical approach for both clinical researchers and government regulatory agencies responsible for approving new therapies. However, the rationale for mechanism-based treatment algorithms becomes stronger as we learn more about the molecular basis for pain and accumulate evidence that different clinical disorders share the same underlying mechanisms.

Most published norms for quantitative sensory testing (QST) have been oriented toward detection of neuropathy in the distal limb rather than toward exploring the function of the pain system (Dyck et al., 1993). The pain-oriented human somatosensory testing studies published to date have used center-specific protocols, often without validated reference values from a healthy pain-free population. Haanpää and her colleagues provide one exception; they studied over 100 healthy volunteers to gather a reference group for their patients with herpes zoster (Haanpää et al., 1999). Testing of pain-related sensation, such as quantification of dynamic allodynia, have used a wide variety of tools, ranging from a simple foam paintbrush to an electrical toothbrush. Few multicenter clinical trials of investigational drugs for chronic pain have used QST as an outcome measure, and have not created normal reference values (Wallace et al., 2002a,b). Developing standardized protocols for clinical somatosensory testing that include all types of primary afferents and multiple body regions is thus extremely valuable. The first steps toward a broader application of quantitative sensory testing in multicenter clinical trials are training investigators at multiple sites and establishing normal values as reference points.

In this issue of PAIN, the German Research Network on Neuropathic Pain (DFNS) provides important and encouraging evidence of progress in the form of reference data from 180 healthy volunteers tested at 10 participating centers (Rolke et al., 2006). The authors should be commended for undertaking such a challenging task. The DFNS project aims to characterize the somatosensory phenotype of patients with neuropathic pain with the goal of testing the hypothesis that symptoms can be reliably linked to mechanisms across different diagnostic groups. The investigators have successfully developed a standardized protocol that includes assessment of both cutaneous and deep pain sensitivity and can be completed in 30 min for a single body region. The protocol can be used to characterize a cohort and additional measures can be added as needed (e.g., imaging, skin biopsy, provocative tests or pain models). The logical next step is to use positive and negative pharmacological challenges with known mechanism of action to further test the hypothesis of mechanism-based treatment.

The report of Rolke and the DFNS group demonstrates some of the challenges to creating a standardized protocol. They demonstrate that the full battery of assessments can be completed for a single body region in 30 min in healthy volunteers. Testing in patients with chronic pain, including multi-region pain, will undoubtedly take longer. The protocols may need to be simplified considerably, with some tests deleted entirely, when testing the effects of analgesic drugs because of the time constraints inherent in clinical trials. Single dose administration studies have to be paced according to the pharmacodynamics of the drug of interest, while longer-term administration studies involve multiple research center visits and few patients can attend lengthy visits on a weekly or monthly basis. Furthermore, even with 180 healthy volunteers, heat and cold hypoalgesia and mechanical hyperesthesia cannot be reliably diagnosed because of the variability in these parameters is so large.
The paper demonstrates how the DFNS group intends to compare patient exams to the healthy volunteers to determine a sensory profile using two patients suffering from longstanding PHN. As pointed out by the authors, reference values for thoracic sensory function are not included in the protocol presented. Hopefully the DFNS group will establish norms for the thorax too as PHN is the condition most carefully studied from a mechanistic subgroup perspective (Rowbotham et al., 1998) and the thoracic region is the site of more than 50% of all PHN cases (Watson et al., 1988). Future studies can also determine how well somatosensory function in a single testing site (9–12.5 cm²) represents the entire painful area. Smaller studies can further validate the testing protocols and establish correlations with objective tests such as microneurography, imaging, and cutaneous innervation assessment, and also provide correlations with functional testing such as capsaicin application (Petersen et al., 2000).

The DFNS group has demonstrated that standardization of protocols and development of academic clinical trial networks can be accomplished in the pain field. These are two crucial goals that were stressed in the recommendations from a recent international meeting of leaders from pain academia and industry (Baron et al., 2006). Clinical trial networks that use standardized validated assessments have long been in place for other diseases. Successful examples include the AIDS Clinical Trials Group, the National Drug Abuse Treatment Clinical Trials Network linked with National Institute on Drug Abuse, the Blood and Marrow Transplant Clinical Trials Network, the National Comprehensive Cancer Network, and the Asthma Clinical Research Network that was established in 1993 by the Division of Lung Diseases of the National Heart, Lung and Blood Institute. Considering the importance of chronic pain in health care utilization, the pain field has been slow in developing large-scale academically oriented clinical trials networks. Hopefully, the work of the DFNS group will foster development of a clinical trial network that includes academic centers in other countries.

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References


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