The Use of Quantitative Sensory Testing to Phenotype Patients' Sensory Profile in the Multi-Center Clinical Trial Arena

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Abstract

Demonstrating the clinical efficacy of potential analgesics is challenging, as observed by the unfortunate high rate of failed analgesic trials. One contributor is the huge variability in treatment response - even in case of truly efficacious treatment, in most cases only a subgroup of the population respond. Thus, in the entire cohort the study might fail to demonstrate superiority over placebo, resulting in non-approval of treatments that some patients actually benefit from.

One possible contributor to this huge variability in patients' responses to analgesics is that even within the same painful condition, there could be more than one mechanisms generating the pain. Much research has focused on the development and assessment of methods to phenotype patients to reveal underlying pain mechanisms. Evidence from recent years supports the value of phenotyping methods in the prediction of treatment response. Among these methods, Quantitative Sensory Testing (QST) has shown promise.

This white paper discusses the evidence, benefits and challenges of implementing QST methods in the multi-center clinical trial arena, while introducing Medoc's new offerings aimed to seamlessly integrate QST protocols in pharma-sponsored multi-center analgesic trials.

Introduction and Historical Perspective

Demonstrating analgesic efficacy of potential treatments in a randomized control trial is challenging, even for effective analgesics. A major contributor to this low assay sensitivity of analgesic trials is the great variability in subjects' responses to treatment. This variability is especially relevant for neuropathic pain, as reflected in the unfortunately high number needed to treat (NNT) in clinical trials of analgesics prescribed for neuropathic pain indications (NNT is the number of patients needed to treat to observe clinically significant pain relief in one patient). For these clinical trials, the NNT falls in the range of 4–8 patients.[9] With this in mind, the high rate of failed analgesic trials might not be unexpected: even with an effective treatment, only a subgroup of patients might respond. Under these circumstances, the treatment will fail to demonstrate superiority over placebo for the entire cohort. Such results would lead to the non-approval by regulatory agencies of treatments that actually some patients do benefit from.

The reasons for the great variability in responses to a given treatment for the same clinical painful condition remain elusive. One possible contributor is that the same painful condition is often derived by more than one underlying mechanism (or pathology). Max (1990)[15] introduced the notion that pain medications could be tailored to a particular impairment in an underlying pain mechanism, regardless of etiology. He emphasized that to increase the likelihood of observing efficacy, investigators need to carefully select the patients in a

clinical trial according to their underlying physiology of pain. In 1995, Woolf and Max further expanded this idea in a seminal paper in which they discussed mechanism-based analgesic development.[21]

Methods for Phenotyping Patients' Sensory Profile to Reveal Pain Mechanisms

Few methods have been proposed for phenotyping patients, that is, for identifying the mechanisms that generate pain. In their recent comprehensive review, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), have generated recommendations for patients' phenotyping in clinical trials of chronic pain.[8] The recommendations included phenotyping tools that best predicted analgesic treatment response. Among these tools are those to assess pain [4,12] and other related domains (psychological-related [13,20], sleep [19], etc.) and assessment of sensory and pain modulation profiles with Quantitative Sensory Testing (QST). Various other papers discuss the potential benefits and challenges of phenotyping patients for the purpose of personalizing their analgesic treatment.[2,3,7,11]

In this white paper, we focus on the use of QST for phenotyping patients. QST is a method to quantitatively measure pain sensitivity in response to different types of noxious and non-noxious stimuli.[1,5,10,14] Traditional QST measures include thresholds, intensity, and tolerance in response to a given stimulus (i.e., "static QST measures"). The past two decades have seen an increase in the use of advanced QST techniques in which a combination of stimuli is administered simultaneously, allowing researchers to assess distinct pro- and/or anti-nociceptive mechanisms, such as temporal summation (TS) and conditioned pain modulation (CPM)(i.e., "dynamic measures").[18]

Few studies demonstrated the value of utilizing QST to predict treatment response. For example, Demant et al. (2014) [6] studied the effects of a six-week oxcarbasepine (a sodium channel blocker) treatment on peripheral neuropathic pain in a heterogenic cohort of patients suffering from polyneuropathy, peripheral nerve injury, and postherpetic neuralgia. Eighty-three patients completed this randomized, double-blind, placebo-controlled, crossover study. The primary aim was to assess if phenotyping the patients through QST could predict who would respond to the treatment. A wide battery of QST of cold, heat, vibration, and pressure modalities was used (based on the German Research Network on Neuropathic Pain protocol).[17] The results were promising: Demant and coworkers stratified the cohort into two distinct phenotypes ("irritable" and "non-irritable" nociceptors), and this stratification predicted response to treatment, with the irritable nociceptor group demonstrating better analgesic response than the non-irritable group did. Importantly, among all QST modalities, the preservation of thermal sensation (i.e., cold and warm detection thresholds) was the best predictor of response to oxcarbasepine.

Yarnitsky et al. (2012)[22] compared the analgesic effect of duloxetine (a serotonin-noradrenalin reuptake inhibitor) with that of placebo in 30 patients with painful diabetic neuropathy. Again, the aim of this study was to assess the predictive value of a wide battery of phenotyping tools, including questionnaires and static and dynamic QST measures. The researchers hypothesized that patients with a malfunctioning pain modulation pattern would benefit more from duloxetine, since the medication is assumed to augment descending inhibition. QST measures were evaluated at the beginning of the study and their predictive value was assessed. The patient's CPM was found to significantly predict treatment response; patients with less efficient CPM responded better to duloxetine. CPM was the only measure that showed correlation with treatment response, highlighting the importance of choosing the most appropriate QST measure for a given compound and a clinical condition. Results from Niesters et al. (2014)[16] supported Yarnitsky's findings. In the latter study, the effects of tapentadol (a μ-opioid receptor agonist) correlated with CPM.

Challenges in Implementing QST in Pharma-Sponsored Clinical Trials

Although results should be confirmed and additional studies conducted, the emerging evidence that QST successfully predicts treatment response can help address the discouragingly high rate of failed analgesic clinical trials. For this reason, the current recommendation is to phenotype subjects at baseline in an attempt to predict treatment response. The potential benefit of such approach is clear. If QST is implemented in early clinical development phases (phase I or II) and proves beneficial (i.e., predicts who will benefit from the treatment), it could help shape the design (and inclusion criteria) of later pivotal trials (phase III). By facilitating the recruitment of the cohort most likely to benefit from the treatment, QST could dramatically increase the chances of a positive trial and support the approval of new analgesics.

The IMMPACT comprehensive review aptly described the advantages and disadvantages of phenotyping: "Balanced against the benefits of phenotyping are the associated costs of additional assessment, as well as obstacles to the implementation of phenotyping protocols."[8] Such an argument is most probably a major reason for QST's slow adoption into the multicenter drug-development arena. While phenotyping with a questionnaire is straightforward and cost-effective, implementing QST in multicenter trials can be challenging. QST requires costly equipment and experienced staff. Moreover, the QST results are based on subjective reports that can be affected by the exact instructions given to both the staff and the patients, as well as the patients' interactions with study staff. Although QST protocols are not as challenging in a single-center study or a small multicenter study conducted in an academic setting by experienced researchers, the situation is different in large pharma-sponsored trials. The protocols in these large studies are conducted by personnel not as experienced in QST. Further complicating matters, opportunities to train the study staff in the QST procedures are restricted to a short presentation during the investigator meeting conducted before the study begins.

Medoc's new Offerings for the Implementation of QST in Pharma-Sponsored Multi-Center Analgesic Trials

Medoc is the leading manufacture of thermal QST devices for pain assessment. Medoc devices are used in hundreds of research and clinical centers around the world for neurodiagnostic testing of small sensory nerve fibers and pain mechanism function using QST and Contact Heat Evoked Potential (CHEPS) techniques.

In a recent commentary in the prestigious Pain journal, Dworkin and Edwards (2017)[7] concluded, "Assessments of sensory phenotypes that are as brief as possible, require minimal training, and use inexpensive equipment would not only facilitate their implementation in large confirmatory multisite clinical trials, but would also ensure translation to clinical practice, which is, of course, the ultimate objective of all these efforts."

To address this need, and in light of the recent implementation of Medoc QST devices in multicenter trials, Medoc has been developing QST devices and additional offerings that promote seamless integration of QST procedures in multicenter trials. Toward this end, Medoc have designed new portable and less expensive devices alongside with new business models that reduce the cost of using large numbers of devices in a multicenter trial.

In addition, Medoc's current software for the QST procedures was perfected over the years for the single user. As such, it allows for a large range of stimuli intensities and multiple other testing properties. These characteristics, albeit a great advantage for the needs of a single pain-research laboratory, can become limitations in the multicenter arena, since the many options introduce numerous opportunities for the unexperienced operator to do something wrong.

Medoc multi-center version of the software is tailored to specific trial needs, with a single-button approach: operators need only to touch a single button to successfully conduct the QST procedure. In addition to simpler, more intuitive procedures, the software includes automatic data upload to the cloud as well as other features

that ensure data quality and adherence to US FDA and CE regulations. In addition, Medoc now offer tailored trainings materials, including presentations at investigator meetings, workshops, and printed training documents along with onsite personal training and interactive training webinars.

Our hope is that by simplifying QST procedures and reducing the associated cost of phenotyping, the usefulness of QST measures as predictors of analgesic treatment response could be assessed and validated in large number of multi-center clinical trials. Positive results could signal the emergence of a new era of personalized pain medicine.

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