Pain

More Than Just a Number

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In this issue of *Regional Anesthesia and Pain Medicine*, Gilron and Jensen[1] have provided an excellent primer related to the multiple and challenging issues confronted in selecting an appropriate primary outcome measure for use in clinical trials assessing the efficacy of treatments for acute and chronic pain. Beyond making a simple recommendation, the authors describe key methodological concerns such as reliability and validity, review the merits and drawbacks of certain measurement approaches, discuss clinically meaningful differences, and highlight the notion that instruments should be selected to address the specific aims of a given trial. In this context, they conclude that "research on primary outcomes in analgesic trials supports the conclusion that single-dimension measures (eg, visual analog scales, numerical rating scales, and verbal rating scales) of both pain intensity and pain relief are valid and reliable measures of treatment effect." However, they also make it clear that single-dimension measures are not the final destination. Their collective body of work, role as collaborators on the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials), and content of their review emphasize the notion that "pain is a complex, multidimensional, sensory, and emotional experience that is individually perceived and described in many different ways."

Cartesian philosophy, dictating that pain signals traveled from the periphery along dedicated pathways to the brain, where the impulse was experienced as pain, dominated the field until less than 50 years ago. In 1965, the gate-control theory of pain put forward by Melzack and Wall[2] forever changed how pain was conceptualized. Their theory proposed that pain did not travel uninterrupted along a dedicated line from point A to point B, but rather modulation of peripheral sensory input could take place in the dorsal horn of the spinal cord. Such spinal level influences could play a significant role in determining both the presence and severity of pain. Since then, research using functional magnetic resonance imaging suggests that, in addition to this spinal control of pain, supraspinal processes can influence the experience of pain as well. Thus, it seems that pain can be controlled at three or more levels in the central nervous system (ie, peripheral, spinal, supraspinal), and in the spirit of the gate-control theory, three aspects of pain are sensed by cortical regions: (1) "sensory," registering the location of the pain and level of discomfort; (2) "affective," reflective of the emotional valence associated with the pain; and (3) "cognitive/evaluative," processing of thoughts regarding the meaning of the pain. It is now clear that the pain experience (especially in those with chronic pain) is the result of an intricate information processing network that is far more sophisticated than a simple unidirectional signal relayed by specific pain fibers to the brain.[3]

Advances in neuroscience have also made it clear that there are different types of pain including "nociceptive" pain that is generally considered adaptive and protective and "pathological" pain caused by abnormal function of the central nervous system.[4] Nociceptive pain results when noxious stimuli (eg, tissue injury or inflammation) are appropriately detected, in contrast to pathological pain that can be the result of either damage to the central nervous system (eg, neuropathic pain) or augmentation of sensory signals in the central nervous system, as is the case in fibromyalgia.[4–6] Gilron and Jensen note that instruments that account for diverse pain qualities and help distinguish between neuropathic and nociceptive pain are already being used in pain treatment trials. Properly characterizing pain will be pivotal in future studies as data suggest that different types of pain respond to different classes of analgesics. Pain assessment strategies that can help

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untangle the pathophysiological underpinnings include pressure pain and other forms of experimental pain testing, functional magnetic resonance imaging and other neuroimaging techniques, and qualitative pen-and-paper measures such as the McGill Pain Questionnaire and the PainDETECT.[7,8]

In light of these findings, many in the field are reaching the same conclusion: pain is a disease, and, like other diseases, affective and evaluative aspects vary in importance and on an individual basis. It should be remembered that emotions and thinking patterns do not need to be at pathological levels to influence pain perception. According to Melzack and Wall's model,[2] normal levels of affect and cognition are essential for pain to be experienced in the first place. Thus, to fully understand the various components influencing pain, a more comprehensive approach to measurement is often warranted. As Gilron and Jensen suggest,[1] although more multifaceted measures include the limitations of increased missing data and assessment burden, these approaches could result in the more accurate depiction of the full experience of pain. This observation is in agreement with the IMMPACT recommendations that multiple core domains and related measures be considered in pain treatment trials[9,10]; such an approach has been used in clinical trial research by Gilron et al.[11] Electronic data capture that monitors the experience of pain over time and takes advantage of multiple data points, as well as using questionnaire measures that tap into a wider experience of pain over time and its impact on functioning and quality of life, should be considered for studies of analgesia. This process is being made more accessible by efforts to establish "responder indices" composed of multiple measures and associated subscales to be used in clinical trials (eg, see Mease et al[12]).

The research of Jensen et al[13] over the years has shown that psychological variables may be among the most important to assess in clinical pain research. Studies of acute and chronic pain both clearly indicate that anxiety, depression, and catastrophizing have predictive values in the degree of acute pain reported, analgesic consumption, and potential development of chronic pain,[14,15] yet these variables are often not assessed. Whereas it is no longer believed that somatization underlies all chronic pain complaints, psychological factors certainly affect patient responses to questions assessing pain intensity. As such, these variables should be included as covariates for analysis or as measures to ensure equivalent groupings before randomization. If the power of these variables is in doubt, imagine the outrage surrounding a clinical trial where the group receiving the study drug was composed of depression-free subjects, whereas the placebo group consisted of only severely depressed individuals.

There are an overwhelming number of measures and questionnaires that have been developed to assess the various domains of importance for pain, and selecting the correct tools can be intimidating. Many of the measures commonly used have associated fees or require permission to use. The National Institutes of Health–sponsored Patient-Reported Outcomes Measurement Information System (PROMIS) initiative aims to build and validate measures for common illnesses and symptoms.[16,17] These measures are publicly available and allow for easy interpretation, analyses, and comparison of results across studies. The manner in which the PROMIS assessment tools were developed allows for the assessment of multiple domains of importance using the least number of items, thus limiting patient burden while retaining precision in measurement. An exciting goal of PROMIS is to move these measures, which have largely been limited to clinical research, into clinical care. As such, healthcare providers can begin to directly translate findings into clinical practice to improve decision making and overall patient care.

So, what is the future for acute and chronic pain research as it pertains to the anesthesiology community? Gilron and Jensen conclude that single-item measures of pain intensity and pain relief are, at this moment, the most reliable and valid option; however, they also state that "individual variability in the experience and reporting of pain" contributes to the difficulty regarding accurately assessing pain in analgesic trials. Although there are certainly challenges associated with more dense assessments of psychosocial aspects, physical functioning, and comorbid pain symptoms in clinical studies, it is important that we work toward considering pain beyond a 0- to 10-point or 1- to 100-point scale. The anesthesia clinical research community needs to regard these other domains as essential inclusions, rather than "secondary outcomes." At the same time, the community of researchers developing and validating self-report questionnaires should work toward lessening the burden, cost, and time associated with collecting these essential data. Even the "short forms" of longer questionnaires build to an imposing number of questions when the many aspects of pain intensity, pain quality, physical function, psychological status, fatigue, sleep, and demographic data are all assessed. Shortened, publicly available versions of the questionnaires will allow clinical pain researchers to collect more data in the context of clinical research and care. It is true that adding variables may increase the amount of missing data and sample size estimates, but the results of studies without key covariates and relevant secondary outcomes offer little to our current knowledge base and may potentially misguide the field. Pain is more than just a number; it is also a thought and an emotion that together can dictate whether the number is a 2 or a 10.

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