INVITED COMMENTARY

Measuring pain and analgesic response

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Pain is a complex phenomenon, defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[1,2] This definition is widely accepted and has led to many advances in pain medicine, but it has shortcomings and has been challenged.[3] The definition of pain underlies the complexity of its measurement. Pain is individual and subjective, modulated by physiological, psychological and environmental factors such as previous events, culture, prognosis, coping strategies, fear and anxiety. Multiple attempts to quantify and analyse the pain experience have been published,[4–6] with most based on self-reporting. Self-report measures have weaknesses and may be influenced by mood, sleep disturbance and medication.[5] Attempting to 'objectify the subjective' can be hazardous because of response biases, situational influences and the context in which pain is reported.

Regrettably, when measuring pain, clinically complex and important parameters are, more often than not, replaced by simpler measures, the most common being unidimensional scales which aim to represent 'subjective' pain intensity[4,7–11]: the 100 mm visual analogue scale (VAS) and the 11-point numerical rating scale (NRS). These measures do not take into account the multidimensional aspects of pain. The VAS and NRS condense what are almost certainly incomplete representations of the pain experience.

Another common metric used in pain studies is analgesic consumption. Pain scores and analgesic consumption are surrogate measures of the pain experience, and although guidelines recommend frequent measurement of pain in order to optimise treatment,[6] a reduction in pain score itself may not equate with a reduction in pain from the patient's perspective.[10–14] It is common for investigators and clinicians to confuse what may be a statistically significant reduction in pain score with a clinically important reduction in pain.

The VAS score has a measurement error of about 15–20 mm,[11,14] and differences less than this should not be interpreted as a clinically meaningful reduction in pain. Other studies have indicated that a reduction in scores of around 30–40% is needed in order to reflect clinically useful improvements in pain.[10,12,14,15] Put simply, the patient is unlikely to notice any improvement in the pain experience with a 10 or 15-mm reduction in a VAS score. Moore et al.[16] have used a 50% change in pain scores to represent a clinically useful effect. This, along with the creation of a dichotomous outcome variable, simplifies interpretation and adds to the clinical relevance of pain scores. Better attempts at condensing clinically important improvements in pain are those studies that focus on pain relief,[17] in which the centre of attention seems to focus back on the patient, that is how patients regard a change in pain status following analgesic therapy and how this change affects their total pain experience.

Similar concerns can be raised about measures of analgesic drug administration. Most patients and their clinicians do not care too much about the dose of analgesic consumed, unless it is matched by increased opioid-related side-effects such as post-operative nausea and vomiting, sedation, respiratory depression or constipation, or, for non-steroidal anti-inflammatory drugs, peptic ulceration, surgical bleeding, or renal injury. Such true end points ought to be an essential component of any pain study, for it is these that ultimately limit analgesic administration.

The present article by Moore et al.[18] considers the distribution of fentanyl consumption in a series of previously conducted trials, pointing out that, because of the skewed distribution of such data, it is unreasonable to use mean estimates to compare groups reliably. In their pooled analysis, they found that fentanyl consumption of less than 750 μg (equivalent to morphine 75 mg) correlated well with a good or excellent pain experience as rated by patients. This dichotomous classification, therefore, discriminated between those who did and those who did not have good pain control, and so they propose this binary outcome as a useful descriptive and predictive outcome variable in acute pain studies.

Moore et al.,[18] consistent with their previous work,[16] aim to provide measures which can be used for simpler

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clinical interpretation. Converting a numerical end point into a dichotomous outcome allows estimation of absolute and relative risk reductions and number needed to treat.[19] These statistics are useful in the clinical setting; they provide practical information for clinicians because they can be used to rank the effectiveness and adverse event profiles of analgesic drugs. They can then provide more reliable information for patients.

The European Agency for the Evaluation of Medicinal Products has published guidelines on the clinical investigation of drugs used for the treatment of nociceptive pain.[20] The guidelines recommend that analgesic drug studies should include end points such as measures of time-specific pain intensity and relief, time to onset and duration of analgesia, time to rescue medication, consumption of rescue medication and decrease in opioid consumption, functional performance and the patient's global assessment of the pain experience. We concur that multiple and relevant end points should be used in clinical trial design. Adverse events, particularly those attributable to the analgesic drugs, should also be reported; despite being uncommon, these data can subsequently be pooled in meta-analyses in order to provide more reliable estimates of benefits and risks.

There are many validated measurement scales representing emotional, disease-specific and overall health status. There are also validated measures of the quality of recovery after surgery.[21–23] In addition, recommendations have been made for core outcome measures for persistent (chronic) pain clinical trials.[24]

Variability in outcome measures across clinical trials hinders evaluations of the efficacy, effectiveness and safety of treatments. It is, therefore, important that, in the design of clinical trials of pain treatments, we consider using multiple and relevant recommended end points which will facilitate meta-analyses and systematic reviews.[25] This will improve our ability to assess pain relief from a variety of perspectives and better represent the multi-dimensional components that make up the 'total' pain experience.

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