ARTICLE

Measuring mild-to-moderate acute pain – a regulatory perspective

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KEYWORDS

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ABSTRACT

Assessment of pain and pain relief is challenged by the complexity of the medical presentations, the subjective nature of the measurements and the desire to have a single solution to demonstrate efficacy in our evidence-based regulatory environment. In this article we will take a brief look at the available guidance and describe some of the limits of measurement. We conclude that while regulatory guidance exists to direct clinical research, further consideration is needed for mild-to-moderate acute pain. The methods of clinical assessments and interpretation of the outcomes in this area still raise challenges in terms of the interpretation and translation to clinical research and regulatory decision-making, as well as what is clinically meaningful to patients, many of whom are self-medicating.

Introduction

Pain is an unpleasant experience common to everyone. However, all experience pain differently and have varying opinions of their pain's intensity. Chronic pain is generally more often a symptom of deeper underlying issues while acute pain is usually nociceptive and often serves as a warning to protect and cause withdrawal from the trauma, often self-limiting and subject to context. Acute pain, resulting from either trauma or medical procedures, is a challenging outcome to measure due to its multifaceted and subjective nature whereby the level of pain and the intensity is subject to when and how the injury was sustained or the nature of the procedure undertaken.[1] Development and measurement in this area is made even more challenging where the pain is considered to be mild to moderate, an area that, while worthy of treatment, is often treated by self-medication, sometimes even by non-medicated interventions.

With the demands of evidence-based medicine the need for "selecting proper outcome measures is high" and scientifically valid demonstrations of treatment efficacy becomes a priority.[1] This article will review the current regulatory guidance around development of products to treat mild-to-moderate acute pain and will reflect on how regulators have sought to address these challenges in the measurement of efficacy for products that have a long- and well-established history of providing pain relief in this area. Available guidance and literature discusses the various methodologies used in practice. The most employed tools are the unidimensional categorical instruments which use a linear scale. Multidimensional categorical instruments are also used in conjunction with the unidimensional scales to provide greater insight into patient acceptability of pain.[2] From a statistical perspective, pain intensity differences (PID), sum of pain intensity differences (SPID), and area under the time analgesic effect curve for pain relief (total pain relief, TOTPAR) track pain over time and can be used in evaluating clinical effect.[2] Lastly, a relatively new concept for determining the minimally clinical important difference (MCID) is being studied and developed for various pain models.

Regulatory guidance

Available guidance is non-specific to acute, mild-to-moderate pain assessment despite the large number of patients affected. The primary focus of guidance documents is focused more on evaluating the appropriateness of opioid therapy, chronic pain or more-severe acute pain from surgery and traumas. There remains a gap with regard to established non-opioid analgesics and novel delivery formulations designed for patient convenience in the self-medicated acute pain setting for pain relief of muscle and joints associated with sprains, strains, and bruises.

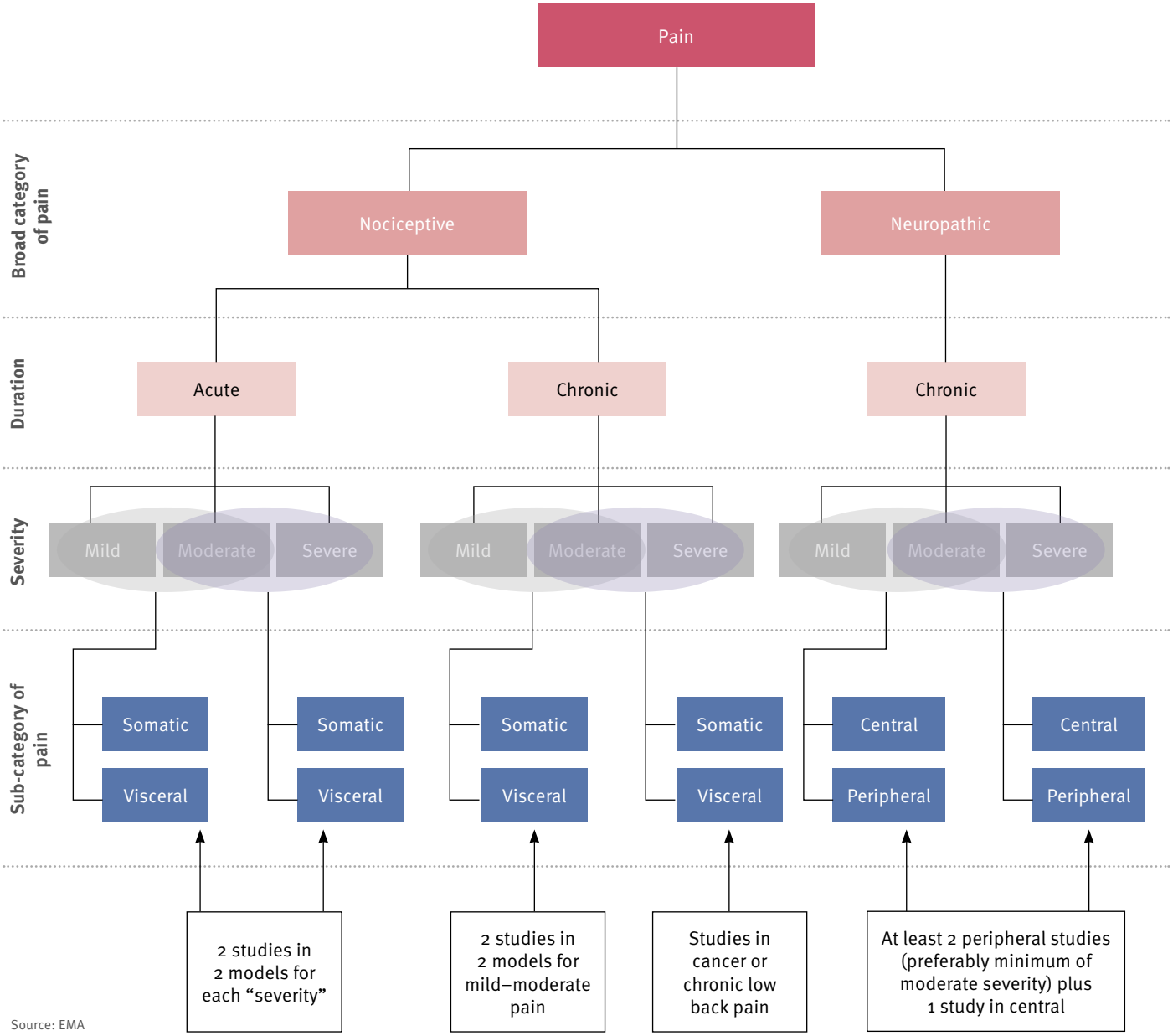
The EU

The European Medicines Agency (EMA) adopted guidance in 2016 on the clinical development of medicinal products intended for the treatment of pain (see Figure 1).[2] This is the most substantial pain development guidance available specific to conducting clinical trials covering a wide array of pain types, study design, considerations for safety and efficacy, and eventual labelling claims based on the combination of studies presented in support of registration.

Most critically for development products in acute pain, whether from trauma or procedural pain, the primary efficacy endpoints rely on specific pain assessment models. The guidance provides some insight describing the subjective nature of pain insisting that "it is difficult or impossible to measure pain severity objectively."[2] Furthermore, the EMA endorses unidimensional categorical assessment tools stating that the self-assessment scales are the most valid instruments and that currently there are "no validated objective measures available that would be feasible in clinical trials".[2] The MCID is not mentioned, but the EMA does support the use of multidimensional assessment tools in addition to pain rating scales especially for chronic pain. This is due to the inability of single-item pain rating scales to capture the complete range of pain qualities such as the "sensory and affective qualities of pain."[2] Only chronic pain is mentioned in the guidance summary of the various multidimensional pain instruments.

FIGURE 1

The EMA guideline on the clinical development of medicinal products intended for the treatment of pain: EMA/CHMP/97005



Source: EMA

The US

The US FDA withdrew its 2014 guidance on drug and biological development for analgesic indications announcing plans to introduce four replacement guidance documents to address concerns with the opioid crisis.[3] Currently, only one has been published and its focus is solely on the benefit–risk profile in opioid therapy.

In the withdrawn guidance, the FDA stressed the importance of using appropriate and established scales or instruments to assess pain effectively over time. The agency emphasised the crafting of well-defined endpoints that provide insight to pain intensity in multiple settings. Assessments that evaluate the "concept of pain relief" were discouraged, as were multidomain scales. In short, the FDA considered "pain intensity, use of rescue and ability to complete the study period" as appropriate outcome measures.[4]

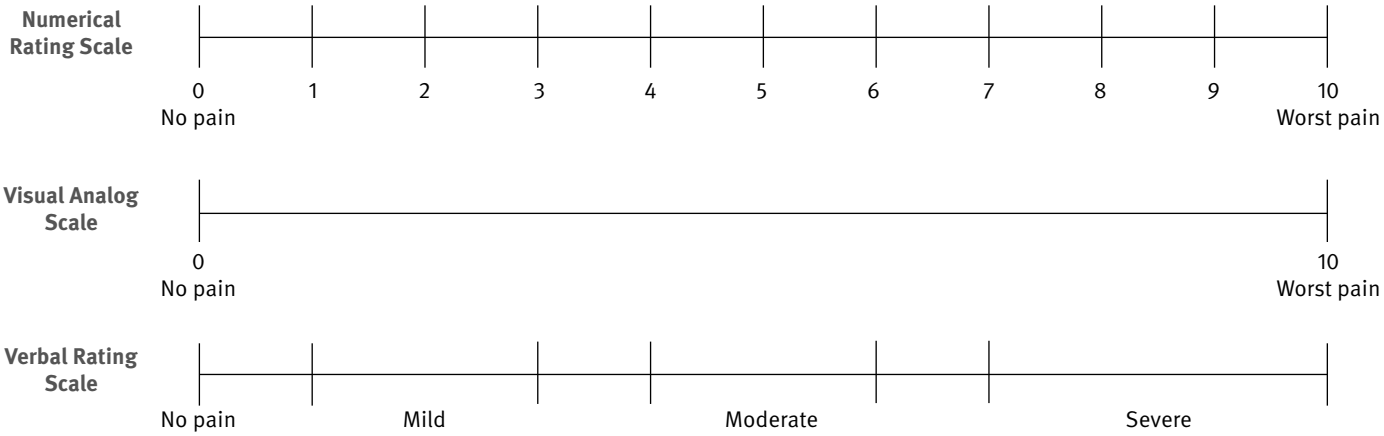
'ACTTION' and 'IMMPACT' initiatives

Analgesic, Anesthetic and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION) is an initiative aimed at partnering with the FDA and other stakeholders to support analgesic development through a streamlined process of "data sharing and innovative thinking."[5]

In an ACTTION-sponsored paper, Gilron *et al*[6] described the current acute pain clinical trial landscape and challenges. Although several improvements have been made in the past 50 years, they claim trial designs should be refined to focus on "patient-related and injury-specific" factors. This includes targeting research toward a subpopulation or using stratification. The authors would also like to see patient-centred outcome measures that more closely align to the acute pain model or treatment being studied. Consistent with this paper's findings, the authors agree that "more robust development of trial designs" are needed that include other

FIGURE 2

Unidimensional categorical instrument scales



types of acute pain aside from post-surgical operations.[6]

Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) is another organisation that collaborates with regulators and other stakeholders to promote clinical research and drug development for treating acute and chronic pain conditions. They have organised conferences to discuss guidelines and key issues in development almost annually since 2002. While they state their recommendations have been implemented in practice and literature, unfortunately it is difficult to access any of their sponsored publications.[7]

The tools for clinical assessment of pain and pain relief

Treatment should be patient-centric with patient reported outcomes (PROs) representing what truly matters to them. These measures must be simple and quick, and the solution often used is a linear scale allowing the patient to indicate the level of pain he or she feels.[1]

Unidimensional instruments

Commonly used tools are unidimensional categorical instruments that are scales used to capture a patient's perceived pain level at a specific point in time. There are essentially three main types of scales used in practice: numerical rating scale (NRS), visual analogue scale (VAS) and verbal rating scale (VRS) (see Figure 2).

NRS. The NRS is typically a left-to-right scale going from zero to 10 or zero to 100 with the left describing "no pain" and the right describing the worst pain imaginable. The NRS can also be administered verbally and does not impact mobility of the patient. This scale is popular due to its practicality.[1,2]

VAS. The VAS may be used where the patient marks anywhere along a 10cm line indicating current pain intensity. The VAS then can be measured to yield a point scale. The VAS provides a "high degree of resolution" and is probably the most sensitive tool used.[1]

VRS. The VRS is "sometimes used for patients who have trouble translating their pain experience into a number value." Instead of number descriptors a four- to six-point scale consisting of adjectives such as no pain, mild pain, moderate pain and severe pain is utilised.[1]

Multidimensional instruments

Although the unidimensional scales are still heavily utilised in practice, it is commonplace for sponsors to complement these with multidimensional categorical pain instruments, such as the brief pain inventory (BPI) or McGill pain questionnaire (MPQ), when developing outcome measures. These multidimensional instruments are thought to be better indicators of patient acceptability of pain levels and an optimal clinical guide for treatment.[2] However, they may be more appropriate for chronic pain.

BPI. Originally developed to assess cancer pain, the BPI directs patients to shade areas on a body diagram indicating pain locales and is used in conjunction with the NRS to describe pain intensity.[8]

MPQ. One of the more popular multidimensional instruments evaluates multiple areas of pain including cognitive and sensory domains in which patients review their pain from a group of word descriptors, each with its own ranking. The overall score is called the pain rating index (PRI) and is a sum of ranked scores allowing for easier statistical analysis.[8]

Clinical significance

Pain is subjective, but some regulators and sponsors are moving toward identifying clinical significance in addition to positive PROs. This is similar to other treatment methodologies such as hypertension. For example, a medicine that lowers blood pressure may show it is more effective than another by 2mm Hg, but that may not be clinically meaningful. It is difficult to rationalise incorporating the same objective methodology for the treatment of something as subjective as pain. This is especially true for acute pain, which by definition has shorter duration and has the potential for self-resolution. An example of finding clinical meaning is the MCID.

MCID. Despite widespread acceptance of unidimensional single-item scales and multidimensional instruments, there is some growing interest in identifying the MCID for specific pain types and placing a more clinical approach to the subjectivity of pain.

The MCID is a specified reduction in pain typically on the VAS scale that is required to show clinical meaning in the treatment of pain. This reduction is specific to the pain model under evaluation. For example, hip arthroscopy may necessitate a –15mm on the VAS scale to be considered clinically meaningful. Although there are more studies and literature being published on the subject, there are a few issues with this methodology. Aside from the obvious objective nature, researchers have not standardised the MCID for several pain models. Additionally, pain models studied tend to focus on post-surgical pain and do not address other types of acute pain. However, for the purposes of both clinical and regulatory decision-making in each indication, it is vital that MCID scores are robustly defined and stable.

Olsen *et al*[9] conducted a systematic review of the value and validity of MCID in clinical trials for acute pain. They found large heterogeneity between studies and could not identify a single meaningful MCID. There

also was a large MCID range reported among the studies (8mm to 40mm). Moreover, it was stated that the MCID was affected by "baseline pain, definitions of improved patients and study design."[9] Additionally, it is worth noting that heterogeneity in MCID is in no way unique to acute pain, with a review by Wright *et al* reaching a similar conclusion across a number of pain models, including severe and chronic pain.[10] The reviews conclude that caution should be exercised when making clinical and research decisions using MCID, noting that while the tool is useful in terms of providing thresholds to detect change and calculate necessary sample sizes, there are still significant limitations related to methodology in MCID calculation, applicability across pain models, the impact of high variability and risk of misinterpretation.[9,10]

Measures of pain over time

Pain fluctuates and therefore it is recommended to not only record pain intensity at baseline, but also throughout the healing process. The three main pain over time measurements include PID, SPID, and TOTPAR. PID measures the mean difference in pain intensity from baseline to specific time points. SPID is the sum of the difference in pain intensity for all post-treatment assessments as compared to baseline. Lastly, TOTPAR is the area under the pain relief scores for a given time interval. These summary measures are used in conjunction with the unidimensional assessments.[2]

Conclusion

Although regulatory guidance exists to direct clinical research into acute pain, further consideration is needed around mild-to-moderate pain. Methods of clinical assessments and interpretation of the outcomes in this area still raise challenges in terms of the interpretation and translation to clinical, research and regulatory decision-making, as well as what is clinically and practically meaningful to patients, many of whom are self-treating in this category of pain models. Too often, pain guidelines discuss multiple categories of pain without providing the same level of detail for all types. With further guidance anticipated from the US FDA, perhaps regulatory guidance for development of treatment in pain should be further sub-divided to specific areas to best meet patient needs. ■

References

1. Younger J, McCue R, Mackey S. Pain outcomes: a brief review of instruments and techniques. Curr Pain Headache Rep. 2009;13(1):39–43.
2. EMA/CHMP. Guidelines on the clinical development of medicinal products intended for the treatment of pain. 2016;5:7.
3. FDA.gov. FDA: Statement by FDA Commissioner Scott Gottlieb, M.D., on the agency's ongoing work to forcefully address the opioid crisis. Available at: www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-ongoing-work-forcefully-address-opioid-crisis (accessed 12 May 2021).
4. FDA. Analgesic indications: developing drug and biological products. February 2014.
5. acttion.org. Analgesic, anesthetic, and addiction clinical trial translations, innovations, opportunities, and networks. Available at: www.acttion.org/ (accessed 12 May 2021).
6. Gilron I, Carr DB, Desjardins PJ et al. Current methods and challenges for acute pain clinical trials. Pain Reports. 2018;4(3):10.
7. immpact.org. Initiative on methods, measurement, and pain assessment in clinical trials. Available at: www.immpact.org/ (accessed 12 May 2021).
8. Bendinger T, Plunkett N. Measurement in pain medicine. BJA Education. 2016;16(9):311.
9. Olsen MF, Bjerre E, Hansen MD et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Medicine. 2017;15(35):1, 14.
10. Wright A, Hannon J, Hegedus EJ et al. Clinimetrics corner: a closer look at the minimal clinically important difference (MCID). Journal of Manual Manipulative Therap. 2012;20(3):165–6.