

Measuring pain in clinical trials: Pain scales, endpoints, and challenges

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Abstract

Measuring pain objectively in clinical trials is a challenging task; deciding upon endpoints, selecting the tools to measure the pain, evaluation, analysis, and interpretation of data further complicates this. Though there are some guidelines available but technical and operational variations and complexities make it difficult. Since pain is a subjective dimension, an objective measurement of pain becomes highly complex. Currently, available tools for pain measurement include both uni- and multi-dimensional tools. While acute pain can be adequately measured using uni-dimensional tools, measurement of chronic pain requires multi-dimensional tool. There are several factors that may bias the measurement, analysis as well as results, and need to be considered while measuring pain in clinical trials. The present article briefly reviews the available pain assessment tools, the recommendations, issues in measurement, accuracy, validity, statistical, and interpretational challenges. We will also discuss about confounding factors while measuring pain, and how to adjust for these while analyzing the data.

Key words: Analysis, challenges, clinical trials, pain measurement

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INTRODUCTION

Pain perception is highly individual and subjective in nature. Measurement of pain objectively remains a colossal challenge in clinical practice as well as in research. Clinically, an increase or decrease in pain intensity may suffice as an endpoint, however, in research it is a marathon task. Furthermore, there is a large variation, both intra-personal as well as inter-personal, in the perception of pain. Of these, intra-personal variation is more complex since the same person may perceive the same amount and type of pain differently at two different occasions.^[1] This high subjective variability complicates the assessment and management of pain, and also brings in the picture, the multi-faceted nature of pain. Two important measures of pain are the intensity of pain, and clinically meaningful reduction in pain following the treatment. To evaluate these aspects, there are several tools that not only quantify pain, but

also measure its functional or qualitative aspect. The standardization of pain measuring tools and techniques is an emergent need that would not only assist in unifying the protocol development, but also allow pooling the data for meta-analysis and comparison purposes.

KEY ISSUES IN PAIN MEASUREMENT

Characterization of pain and choice of trial endpoints

Pain is a multi-dimensional sensation characterized by intensity, quality, location, frequency, etc., besides psychosocial domains. This clearly indicates that defining the trial endpoints is a tedious task and accentuates the need of including these domains in the trial endpoints.^[2] Hence, for

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any treatment to be proved as efficacious, it has to meet certain expectations. This requires a stringent approach while zeroing in on the endpoints of interest strictly in-line with the trial objectives.

Tools: Accuracy, validity, acceptability and reproducibility

Once an endpoint has been decided, the next step is to choose an appropriate pain scale. Ideally, there should be a standard scale that can be used universally. However, variability in human behavior in pain, and clinical course of disease prohibits this “unity in diversity” approach. Therefore, four key considerations while choosing a pain scale are accuracy (with minimal errors and artefacts), validity (in similar indication), acceptability (by regulatory authority and physicians), and reproducibility (in similar population).

PAIN ASSESSMENT IN CLINICAL TRIALS: OUTCOME MEASURES

Quantity of pain

Quantity of pain is the most sought after measuring pain in clinical trials since pain relief is the primary aim. Attaining significance with respect to pain relief is important; however, often statistical significance may not be clinically meaningful. This is because of two reasons. First, statistical significance is a function of size and variability of treatment effect, and the sample size. Second, a statistically significant benefit may not be relevant for treating physician and/or the patient. This challenge can be addressed by defining and measuring a minimal clinically important difference (MCID). The quantitative data obtained for MCID can be further dichotomized to qualitative data, such as responders and non-responders using a defined set of responses.

Frequency of pain

Frequency of pain is an important aspect of pain since having pain on a regular or frequent basis may have a larger effect size. However, the severity of pain should be considered in relation to the frequency of pain. For example, a mild pain that is chronic in nature may have an effect equivalent to that of an acute pain that lasts 1–2 days a month. For chronic pain trials, therefore, bringing down the frequency of pain, e.g., from daily to once a week or so seems clinically relevant. Interestingly, the frequency of pain can be treated as qualitative as well as a quantitative variable. For example, the number of days when patient experienced pain during a time span is quantitative while when measured on Likert scale using daily, once a week, and so on is a qualitative assessment. In our opinion, both should be used to account for the variability and increasing the scope for data comparability.

Use of rescue medications

Rescue medication for immediate relief of pain in the case of test drug being noneffective tends to bias the results on one hand while providing important information with respect to pain relief on the other. Therefore, it may act as a co-primary/secondary endpoint, e.g., time to and/or quantity of rescue medication. Predefined use of rescue medications, dose and class, and especially the indication for use, e.g., if pain is not relieved within 2 h, or not reduced to 50% in a month, and so on can form the basis of such assessment. A composite scoring tool for rescue medication usage and pain intensity is also available.^[3]

Impact on quality of life and physical functioning

Pain can have negligible to severe compromising effect on the quality of life (QoL). It might be quite apparent for acute pain. However, the difference may not be apparent for chronic pain since some patients become accustomed to pain and compromise in QoL becomes independent of pain and pain relief. In contrast, some patients become tolerant even to severe pain and maintain an optimum level of physical activity. Health-related quality of life,^[4] multi-dimensional pain inventory (MPI),^[5] and brief pain inventory (BPI)^[6] are now increasingly being used in clinical trials to assess the composite effect on chronic pain.

Impact on emotional functioning

Chronic pain is inadvertently associated with altered emotional functioning. Guidelines recommend that emotional functioning should be taken into account while measuring the effect on pain, especially when it is chronic in nature. The available reliable and valid tools are the profile of mood states and beck depression inventory.^[7]

Different domains of pain assessment are summarized in Table 1.

MEASURING PAIN: GUIDELINES

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) commenced

Table 1: Domains relevant to measurement of pain

Domain
Pain quantity
Pain quality
QoL
Physician's and patients' assessments
Treatment tolerability
Functioning: Social, emotional and physical
QoL: Quality of life

in November 2002 with an aim to streamline pain assessment in clinical trials. The IMMPACT indicates that six core domains be considered while assessing pain: pain, physical and emotional functioning, patient ratings of improvement and satisfaction with treatment, other symptoms and adverse events during treatment, and patient's disposition and characteristics data.^[8] An 11-point numerical rating scale (numeric rating scale [NRS]; 0–10) is recommended for assessing chronic pain,^[9] along with a scale that uses different categories of pain (none, mild, moderate, and severe).

PAIN SCALES FOR ADULTS AND OLDER CHILDREN

Uni-dimensional pain scales

Visual analog scale

Visual analogue scale (VAS) measures pain intensity, an important aspect of clinical decision making, on a premeasured vertical or horizontal line, where each of the ends of the line represent the extreme (lower and higher) limits of pain intensity. It is easy to use, has wider applicability, acceptability, high resolution, and results are usually reproducible while excluding the effect of language.^[10] It has linear properties for mild to moderate pain, that is if pain score is halved, the pain is also halved, increasing its clinical utility.^[11] VAS also showed more responsiveness over McGill pain scale.^[12] A rating of >70 mm on VAS indicates severe pain while 0–5 mm indicates no pain.^[13] The key disadvantage is that it does not measure other domains of pain and does not control the effect of behavior, gender, age, and location of pain.

Numeric rating scale

The NRS is a 11-point scale that measures pain intensity from 0 (no pain) to 10 (worst possible pain) and qualitatively is as good as VAS. It is easier to administer than VAS since a pen/pencil is not required to mark a response, and can be administered verbally over the phone in patients with limited mobility thereby increasing the compliance.^[14,15]

Likert scale

Likert scale remains one of the oldest methods for pain assessment, and also most widely used scale for pain measurement.^[16] Likert scale is a 4- or 5-, and sometimes 7-point ordinal scale that measures the severity of pain, and 7-point version is more sensitive versus a 4- or 5-point version. Likert scales are easier to use and interpret without using any conversions since pain is rated as worst to no pain; point responses are defined adequately with minimal to no overlapping of response categories.

Multi-dimensional pain scales

The brief pain inventory

The BPI, a 15 items inventory,^[17] assesses pain history, intensity, location, and quality of pain (severity) and the degree of interference with function, using 0–10 NRS and allows a time frame of 24 h to 1-week. It can be self-administered, and administered over the phone, and a short-form can be completed as quickly as 2–3 min.

The multi-dimensional pain inventory

MPI is also a valid self-reporting tool which evaluates the impact of pain on QoL, social support and general activity along with psychosocial aspects.^[18]

The McGill pain questionnaire

The McGill Pain Questionnaire (MPQ) and its short-form MPQ, both are validated for pain assessment, and provide sensory, affective–emotional, evaluative, and temporal aspects of the pain. It includes pain intensity measurement on a 5-point Likert scale and VAS.^[19]

The patient global impression of change scale

Patients have their own perceptions, expectations and experiences with respect to treatment and its effect. This can be evaluated using the patient global impression of change scale (PGIC) as recommended during IMMPACT-II consensus meeting.^[20] PGIC is a single-item 7-point scale and provides a composite measure of improvement, treatment satisfaction, patient's view of risk-benefit ratio, and possibly treatment cost factor. The data collected using this tool is responsive, interpretable, valid, and measures MCID in QoL measures.^[21]

Minimal clinically important differences

The MCID is applicable to not only to pain but also measures of physical and emotional functioning. With respect to pain, MCID has gained relevance versus the statistically significant difference, because of highly subjective nature of pain. This is especially important because the amount of pain relief that is statistically significant may not be perceived by the patients as "relief". For example, following treatment, the pain scores on VAS in a patient change from 100 to 80, which may be statistically significant, however, the patient may still not find it important or meaningful, and vice versa. Furthermore, a change from 0 to 2 might be clinically more relevant as compared to a 3 unit change on the higher side, that is, 4–6. In the first scenario, patient's status is changed from no pain to mild pain while in the second scenario; pain persists though intensity is slightly changed.

The roots of such difference are in the statistical calculations. For example, the *P* value for significance

will tend to decrease with an increase in the sample size. However, it does not mean that the pain relief also starts increasing. This clearly indicates that the statistical significance does not measure the actual effect but only the chance or probability. This brings in the picture “effect size”, which provides the meaning to “pain relief”. For example, one may decide that a 50% reduction (effect size) in pain will be treated as clinically meaningful while comparing the two treatments.

The IMMPACT II consensus recommended that a 30% reduction in pain from baseline can be considered significant using an NRS (or VAS) in chronic pain clinical trial. Similarly, reduction by 30–35% in pain intensity was rated as MCID in postoperative pain,^[22,23] acute and chronic pain,^[24] as well as breakthrough cancer pain.^[25] In general, effect sizes ranging from 30% to 50%, especially when pain is halved (50%), are considered as substantial pain relief are used in clinical trials.^[26,27] It should be noted that data may be skewed due to large pain relief in few patients despite moderate relief in most of the patients.

FACTORS GOVERNING THE CHOICE

Administration feasibility

The feasibility of administration is the first and foremost criteria as it largely determines the compliance to response recording. Missing or incorrect responses might be noted if patients find it difficult to answer. A retrospective data collection is not advised as patients may not be able to memorize the data correctly. To facilitate data collection and improve compliance, newer gadgets such as patient digital assistants may be used. These can be internet enabled allowing the real data transfer to the database.

Validity, reproducibility, and sensitivity

The validity, reproducibility, and sensitivity of pain assessment tool is critical because in clinical trial scenarios, it is mandate that data has to be accepted and approved by the regulatory authority. Furthermore, it is recommended that the investigators/sponsors should reach out to regulatory authorities while deciding upon tools and endpoints.

CONFOUNDING FACTORS AND BIAS

High pain scores at baseline

It has been widely accepted that high pain scores at baseline will result in a large difference in pain, that is, more is the pain at baseline, higher is the benefit achieved after treatment. This also impacts the power of the trial because the large difference of change after treatment will yield more power versus a trial where pain difference

is small. For example, trial with majority of the patients with high pain scores at baseline will have higher power versus the trial where majority of patients have low baseline pain scores since the differences will be high, and low, respectively. Further, patients with severe pain may rate even a minimal benefit as important while patients with mild pain may rate even a larger difference as not relevant.^[28]

Addiction

Addiction is one of the most notorious challenges posed in trials as it confounds the treatment efficacy. Some patients may experience addiction while on treatment in the trial while some patients might be already addicted even before entering the trial. In general, addiction should be treated as exclusion criteria. However, if this is seen as a limitation to patient accrual in the trial, it should be built as a confounder or bias variable in the statistical analysis.

Concomitant and rescue therapies

The use of concomitant pain medications should be adequately tracked, reported and taken into consideration during analysis. In short-term trials, the tracking and recording is less challenging, however, in trials assessing chronic pain in long-term trials is perplexing as complete data recall is not possible, and pain diaries cannot be fully validated. Another challenge with concomitant medications is that these mar the actual effect of the treatment in question. Since rescue medications are unavoidable due to ethical reasons, they should be treated as confounders. For adequately monitored trials, these can be an outcome variable.

Patients lost to follow-up

It has been noted that patients who do not benefit from the treatment may simply discontinue the treatment, and at times lost to follow-up without notifying the treating physician about treatment dissatisfaction. Though patients may be taken as lost to follow-up but are actually the subset of patients who did not benefit from the treatment or showed treatment inefficacy or dissatisfaction.

Statistical analyses

One of the most common challenges is multiple testing, which may give rise to Type I error. This means that null hypothesis (test drug is no better than comparator or placebo) is being rejected while it was true. In multiple testing, the probability of one or more factors/variables yielding a significant result increases with the increasing number of variables resulting in false positive results. In this case, an investigator may be tempted to choose the best results. Therefore, it is recommended that while analyzing the data, appropriate adjustments be made to control the probability of Type I error.^[29,30] Pain trials where primary endpoint is quantitative pain relief

may not require adjustments for multiple testing. When there is two or more co-primary outcomes, either all of these have to be significant or only one or more have to be significant for favorable clinical decision. In first scenario, no adjustment for multiplicity is needed while in latter scenario there is a risk of reduced power of the trial due to multiple testing and hence each endpoint must be tested with a significance level corrected for multiplicity.

CLINICAL TRIALS

According to European Medicines Agency, it is recommended to show superiority of the drug over placebo due to high and variable placebo response in pain trials; however, in trials for chronic severe pain superiority to placebo does not suffice. In order to address the placebo response, the patients enrolled should have at least moderate to severe pain. Another important criteria could be a persistent pain since last 3 months, with consistent severity, and having a notable effect on the QoL.

A MODEL FOR OBJECTIVE PAIN ASSESSMENT

Having discussed the available pain assessment tools, challenges, and advantages, it is worth to bring forth the solutions and emerging needs in pain research. A lot of research is being focused on physiological measurement of pain, namely heart rate, skin conductance, and even neuroimaging. However, there are still several limitations which need to be adequately addressed. We hereby propose a model that can be developed further, and provide better methods of pain assessment as we used in our previous studies.^[27,31,32] In a randomized controlled trial, where we studied the effect of antioxidants on pain in patients with chronic pancreatitis, we used number of painful days per month, number of analgesics used (both oral and injectable), number of days when patient was hospitalized due to pain, and number of man-days missed. The MCID was defined as 50% reduction in a number of painful days per month from baseline, the primary outcome of the study. The type of analgesics and hospitalization provided an idea about the severity of the pain while social and professional aspects were partly covered by the man-days lost at work/social circle. A few measures for pain assessment are suggested in Table 2.

CONCLUSION

Scientific assessment of pain is difficult and poses a huge challenge while drugs or procedures are being tested for pain relieving efficacy in clinical trials

Table 2: Measures for pain assessment

Measures
Unit change on pain scale/variation
Time to onset of meaningful pain relief and mean time to maximum reduction in pain intensity or to peak relief
Duration of pain relief e.g., time for pain to return to at least 50% of baseline, time for pain intensity to return to baseline or for pain relief to fall to zero; time to re-medication/rescue medication
Frequency, duration and intensity of pain episodes
Use of rescue medications (time and quantity)
Hospitalization due to pain
Usage of oral or intravenous analgesic or narcotics
Frequency of breakthrough pain episodes
Total pain relief by area under the time-analgesic effect curve for a given time

due to the high subjective variability of pain, and its measurement. The overall aim shall be an accurate and precise measure of pain, and pain relief taking into consideration the fact that the data available across for a particular indication should be as homogeneous as possible so as to allow the cross-comparisons and meta-analysis.

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Conflicts of interest

There are no conflicts of interest.

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