

Innovative Designs for Chronic Pain Trials



Despite a plethora of information gathered across the fields of neuroimaging, genetics/genomics, proteomics, and neurobiology that has enhanced our basic knowledge of the mechanisms mediating the perception of pain, there has been a relative dearth of approved novel treatments for chronic pain¹. Simply stated, the advances in discovery research have not reliably translated into more effective, affordable, and safer pharmaceutical products, and it is unclear if the major reason for this lack of approved compounds, in spite of a general increase in the number of clinical studies, stems from a genuine lack of compound efficacy or from an inability to detect a positive signal in truly efficacious compounds. This review highlights innovative trials designs that may improve signal detection for novel therapeutics in chronic pain with a predominantly proof of concept emphasis.

It appears that our understanding of the basic sciences in analgesia has outstripped our ability to adequately assess treatment efficacy in an appropriately designed experiential setting. This sentiment is evidenced by the recent increase in “failed” trials, and not just “negative” trials, in which approved active comparators fail to separate from placebo, suggesting that our ability to dissociate signal from noise has been compromised. There are numerous reasons for a lack of assay sensitivity, but one of the biggest culprits appears to be an increase in placebo response – which seems to be steadily growing over the past decade. Much like the clinical trials in depression and anxiety that have long been plagued by an increasing placebo response, recent interventional studies in chronic pain have shown similar vulnerabilities. In an attempt to identify factors associated with positive versus negative trial outcomes, a meta-analysis of 106 chronic pain trials suggested that studies published more recently were associated with higher placebo response². This trend has considerable impact on analgesic drug development in terms of overall cost to the sponsors and increased risk of terminating development programmes prematurely due to early failed studies lacking appropriate sensitivity. Efficient methodologies for increasing within-study assay sensitivity and signal detection are high priorities for analgesic drug development, and are discussed below.

Retrospective analyses of clinical trials with antidepressants provide context, with suggestions for reducing placebo response and increasing assay sensitivity that could be applied to chronic pain trials, particularly those focusing on neuropathic mechanisms³. Recommendations include the exclusion of patients with mild pain severity and shorter episode duration; maximising reliability, validity and responsiveness of outcome measures; minimising extraneous contact with investigative staff and other sources of nonspecific therapeutic effects; and minimising the number of treatment groups and trial duration. Although intuitively attractive, these recommendations remain largely untested, and the resulting operational and analytic implica-

tions are in some cases unknown. However, these analyses also suggested basic changes in study structure, including using placebo run-in periods and flexible-dose versus fixed-dose designs, in which a two-fold greater success rate (and a lower placebo response) has been implied. While the use of a single-blind placebo run-in period for the purposes of enhancing signal detection in a subsequent double-blind study was once considered to be standard in many clinical trials in psychopharmacology, data from recent studies indicate limited utility^{4,5}. In brief, studies utilising a single-blind placebo run-in prior to patient randomisation do not appreciably differ in terms of placebo response or in detecting treatment differences, compared to trials that do not use such a manoeuvre.

In contrast, the use of a double-blind, variable duration, placebo run-in period (in which both the patients and personnel at the investigative site are blinded to the length of the placebo run-in period and start of active treatment) has shown better sensitivity in detecting placebo response⁵ with approximately three times as many patients in these studies meeting criteria for placebo responders compared to single-blind placebo run-in studies. In this design, all patients continue with study procedures as specified by protocol, but the primary efficacy analyses exclude placebo responders as defined a priori. The notion is that once investigators know the point of randomisation, their behaviour towards a subject changes in a non-random manner. In a similar fashion, there may be utility in withholding from investigators the exact pain criteria (e.g., severity) necessary for study entry. This may prevent investigators (and patients) from inadvertently inflating complaints prior to randomisation, and thus control regression to the mean that can affect placebo response and dull effect sizes. Double-blind, variable duration, placebo run-in periods demand a real-time data management system which can support this operationally cumbersome manoeuvre.

There are several other innovative designs that have shown success in affective disorder trials, which may also increase signal detection and decrease placebo response in chronic pain clinical trials. One is the Enriched Enrollment Randomized Withdrawal (EERW) design⁶. This design differs from classic analgesic study designs by shifting the point of randomisation from prior to receiving therapy to a time after satisfactory efficacy and worst tolerable adverse event levels are established. This design uses an open-label titration period of the active treatment under investigation, more closely mirroring routine clinical practice. Only responders (e.g., those who have shown 30% response) are then randomised to placebo versus drug. The actual point of randomisation can vary, and a double-blind variable duration run-in period can be used to blind investigators to randomisation time point and baseline entry criteria for pain (although typically the point of randomisation only differs by a few visits). Data gleaned from the pre-randomisation phase can be used to estimate proportions of responders and optimal

dose in subsequent studies, as well as establish the quantity and quality of adverse events.

Researchers have argued that traditional analgesia trial designs developed for testing compounds in the more homogeneous setting of nociceptive postoperative pain may underperform in chronic pain clinical trials, failing to detect efficacy in particular subgroups because it is masked by poor efficacy in other subgroups. The EERW design has particular utility in proof of concept settings, given its ability to detect effects in a subgroup of patients, and has selective advantages when adverse effects may be problematic, or when there is a strong possibility for separate groups of responders and non-responders, or when initial dose titration is complex or lengthy or must mimic clinical practice. Criticism of the design, however, is also noted, including lack of generalisability to larger populations, and limitations inherent in open-label titration as opposed to randomised titration that might establish effective dosages in a formal manner. Despite these criticisms, EERW designs have shown promise in chronic pain studies using both traditional measures such as pain intensity, and non-traditional measures such as time to efficacy failure. Importantly, this design may require fewer patients than classic designs, providing a more sensitive option for conducting proof-of-concept studies with increased signal detection.

Another novel design that has shown utility in increasing signal detection and reducing placebo response across several psychopharmacology studies is the Sequential Parallel Comparison Design (SPCD)⁹. This design has two phases of treatment; the first phase involves an unbalanced randomisation between placebo and active treatment favouring placebo. In the second phase, only the group of placebo non-responders are randomised to either active treatment or placebo. Placebo non-responders can be defined as those patients who failed to achieve a certain (e.g., 50%) decrease in their pain scores at a certain visit. The placebo responders can remain in the study in order to maintain the blind, but only the data from the placebo non-responders is used for analytic purposes in the primary efficacy data set. In this way the SPCD can be considered a type of enrichment design in which the population of placebo non-responders is enriched in the final sample. Since placebo non-responders have already essentially “failed on placebo,” their placebo response in the second phase of the study is theoretically reduced and the drug-placebo difference in Phase 2 should be greater than in Phase 1 if in fact the compound is active. This analysis method pools data from both phases in order to maximise power and reduce the required overall sample size with increased power (10-20%) relative to same size classical designs, or the same approximate power with much fewer subjects (20-25% fewer subjects). The biggest deterrents to the SPCD are the extended length of the trial, increased analytic difficulty due to the creation of multiple data sets, and an overall lack of experience with the operational complexities associated with this design. Although the SPCD is longer than traditional designs in terms of study duration, overall study length expressed as first patient visit to last patient visit may be shorter due to a reduced need for patients and a decreased enrolment period. Modifications to the SPCD involve the use of different test statistics according to equality of treatment effects across the two phases⁸, and keeping investigators blinded to the criteria for response and timing of the initiation of the second phase, as discussed above.

Finally, various adaptive designs that increase the prob-

ability of trial success by providing more flexibility than conventional designs should play a larger role in analgesia trials. Adaptive design trials are particularly relevant in chronic pain studies, which are characterised by highly subjective and variable endpoints, and a lack of accepted biomarkers which can be used as a short-term proxy for clinical outcome. According to the US Food and Drug Administration (FDA) draft Guidance for Industry on Adaptive Design Clinical Trials for Drugs and Biologics⁹, an adaptive design clinical study is defined as a study that includes a prospectively planned modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. The relevance of adaptive study design to drug development has been extensively examined, and adaptive designs may more efficiently provide the same trial

information, increase the likelihood of success on the study objective(s), and yield improved understanding of the treatment's effect¹⁰.

Adaptive designs are generally considered to be either exploratory or confirmatory in nature. Two of the most common exploratory adaptive designs are the adaptive exploratory dose-response and the adaptive randomisation based upon treatment response designs. The most common confirmatory adaptive design involves sample size re-estimation. Despite widespread interest in adaptive designs, there have been very few regulatory submissions based on confirmatory adaptive trials, and the majority of adaptive design studies have been in the exploratory realm. Two examples of exploratory adaptive designs are reviewed here.

An adaptive exploratory dose-response design is a common exploratory adaptive design that begins by examining multiple doses across a fairly broad range with the goal of reducing the number of dose groups as the study progresses by utilising unblinded efficacy or safety data in a predefined manner during one or more unblinded interim analyses⁹. Such designs are capable of eliminating ineffective or intolerable doses with minimal patient exposure, and can also suggest additional doses not originally envisioned, as doses for later confirmatory trials need not be limited to the doses studied in the exploratory adaptive trial. Of particular utility are exploratory designs using five to seven doses to ascertain the shape of the dose-response curve, allowing for optimised selection of doses in confirmatory studies for innovative compounds in which dose response relationships are unknown, and where linearity in response may not be appropriately assumed. It is also possible to utilise a biomarker for the interim analysis to determine the adaptive modification.

Adaptive randomisation based upon treatment response is another more frequently used exploratory adaptive design, requiring subjects to be assigned to a specific treatment group based on a comparative analysis of the accumulated outcome generated in the trial⁹. This design is often referred to as a “play the winner” design, with the randomisation schema changing numerous times (if not continually) over the course of a study, necessitating electronic randomisation via Interactive Voice Response (IVR) or Interactive Web Response (IWR), linked to a drug supply that permits different allocation ratios across treatment groups, and clinical trial management systems that facilitate tracking of adaptations. This type of design has been used in dose response studies to steer subjects towards doses that have a higher likelihood of efficacy and away

from drugs that have a higher likelihood of intolerability due to adverse events. A potential problem with adaptive designs such as this is that they can produce changing randomisation probabilities that may violate the balance among treatment groups with regard to important baseline characteristics. To address this concern, the FDA recommends that sufficient patients are enrolled into the placebo group over the duration of the study to ensure that any analysis of response over time (or by study period) can be evaluated fairly. Loading the placebo group with enough patients also helps the study show a treatment effect⁹. Additionally, adaptive clinical trials present qualitatively different considerations regarding the informed consent process, and the ethics of clinical research given that treatment group allocation depends upon accumulated information, as the first patient versus last patient enrolled can have different probabilities for receiving effective treatment¹¹.

In addition to helping show treatment effects, the importance of allocating the appropriate number of patients to placebo is a key factor in minimising placebo response as patients' expectations of receiving drug influences their response, and imbalance in allocation favouring active medication can be a contributory factor to more favourable placebo responses¹². Results from a recent meta-analysis of 182 clinical trials in depression have shown that the greatest influence on drug-placebo differences was the percentage of patients randomised to placebo⁹. As the proportion randomised to placebo increased, drug-placebo differences increased. For example, with 50% of patients randomised to placebo, the advantage of drug over placebo

is 50% larger than when 25% of patients are randomised to placebo. The logic behind this is evident when considering that adding one patient to the placebo group increases the power for all drug-placebo contrasts, whereas adding one patient to an active treatment arm only increases contrast power for that arm. Appropriate placebo allocation is especially important in analgesia clinical trials where subjective, patient-reported outcomes are prone to moderating variables that lead to heightened placebo responses.

In summary, there are several innovative clinical trial designs and design modifications that may be useful for addressing important issues in chronic pain trials, including heightened placebo response, an increasing number of failed (not just negative) trials, highly subjective and variable endpoints, and a lack of accepted biomarkers. The appropriate application of the above-mentioned designs in chronic pain trials should result in better assay sensitivity, larger effect sizes, and overall increased trial efficiency, ultimately leading to more effective, affordable, and safer pharmaceutical products for patients suffering from chronic pain.

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