

# Minimising Placebo Response in Chronic Pain Trials



Analgesic drug development had been plagued by an increase in the number of negative confirmatory chronic pain trials. Although the reasons for this are manifold, much attention has been focused on the increasingly high and variable placebo response. Various explanations for rising placebo response rates and corresponding decreases in treatment effect sizes in chronic pain trials have been purported, including the nature of subjective pain ratings, poorly defined trial populations, investigator bias in patient recruitment and selection, and the non-specific treatment effects associated with trial conduct<sup>1</sup>. This brief review elucidates some of the factors that contribute to the heightened placebo response in trials of drugs for common chronic pain indications such as osteoarthritic pain, low back pain and neuropathic pain (e.g., from painful diabetic neuropathy and post herpetic neuralgia) and highlights easily implemented manoeuvres to remedy this problem. These manoeuvres can be broken down into five main areas: 1. optimising the allocation of patients to placebo; 2. ensuring adequate levels of disease and pain severity, duration and consistency; 3. using objective outcomes and withholding important trial information from investigators and patients; 4. controlling the permissiveness, type and frequency of rescue medications and; 5. implementing an effective rater training programme to control non-specific treatment effects.

## Optimising Allocation of Patients to Placebo

It is generally thought that studies with fewer treatment arms (and studies with flexible versus fixed dosing) are more likely to show statistically significant differences from placebo. However, as flexible dose studies typically have fewer treatment arms than fixed dose trials this assertion may be confounded<sup>1</sup>. Nonetheless, it has been determined across numerous central nervous system (CNS) trials that increasing the number of treatment groups also increases patients' expectation of receiving treatment. The probability of randomisation to active drug versus placebo influences patients' expectation of improvement, thereby increasing placebo response and reducing drug-placebo differences. However, this can be remedied simply by increasing or optimising the allocation of patients to the placebo arm. This may seem counterintuitive to many triallists who erroneously allocate any extra patients in the highest dose group in an effort to increase statistical significance. However, it is clear that as the number of treatment arms increases, the variance of each treatment contrast is minimised. Therefore, the probability of getting at least one significant contrast is maximised only when the placebo group has greater allocation than any of the treatment arms<sup>2</sup>. If one patient is added to the placebo group, the power for all drug-placebo contrasts is increased, whereas

if one patient is added to an active treatment arm that is the only contrast where power will be increased. For studies with 2, 3, and 4 active treatment arms, maximum or near maximum power would result from allocating 40% of patients to placebo (in a 4:3:3 ratio) or 33.3% on placebo via 3:2:2:2 or 2:1:1:1:1 ratios, respectively<sup>2</sup>.

## Ensuring Adequate Pain Severity, Duration and Consistency

When enrolling patients into chronic pain studies it is essential to ensure that the underlying chronic disease states and the pain levels are of adequate severity and stability. Specifically, it is critical that the patients have a diagnosis of the primary chronic pain indication for greater than six to twelve months and report having moderate to severe pain for greater than 15 days of each month for at least three to six months prior to study entry. Insisting on pain stability is essential given the variable nature of most chronic pain conditions that wax and wane over time and are often characterised by symptomatic flares. In many instances patients seek out clinical trials at times when their pain is relatively worse. And, this peak pain often ameliorates regardless of assignment to drug or placebo, and thus can lead to a heightened placebo response.

It has been shown that an increased variability of baseline diary pain measures has been associated with increased placebo response in chronic pain trials<sup>3</sup>. Consistency of painful symptoms can be ensured by enrolling patients who exhibit low standard deviations on diary measures and/or alternately allowing no greater than a 2-point difference in pain assessments on a pain scale between multiple screening visits or between screening and baseline periods. Separate and multiple screening or baseline measures, or even a brief placebo controlled run-in period that reduces the placebo response, may be helpful in minimising placebo response. In addition to excluding placebo responders, the extra time may also better determine compliance with taking study drug or completing pain diary assessments. Specifically, patients who take less than 90% or more than 110% of study drug or who do not complete pain diaries with greater than 85% accuracy during this run-in period can be excluded.

As placebo response has also been associated with relatively lower pain severity at baseline, it is beneficial to consider inclusion of patients with both screening and baseline pain severity scores of  $\geq 5$  but less than 9 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain)<sup>4</sup>. This will help ensure that the average pain intensity at baseline falls somewhere between 6 and 8 points, avoiding both ceiling

and floor effects and providing a greater chance to see drug-related treatment effects if they truly exist. It may also be useful to utilise an inclusion measure that is not the same as the primary endpoint in order to minimise statistical regression to the mean. Statistical regression to the mean is merely the recognition that higher pain scores are more likely to have positive measurement error, while less severe or lower ones are more likely to have negative measurement error. When utilising a high pain score (positively biased measurement error) for inclusion purposes, a decrease the next time the scale is administered (even with no treatment) would be expected. As measurement error by definition is uncorrelated with the true measurement of the underlying construct, the measurement error of any two independent measures of the same construct should be zero.

#### **Using Objective Outcomes and Keeping Patients and Investigators Blinded to Key Entry Criteria and Design Features**

Issues surrounding investigator bias in patient recruitment and selection in chronic pain trials have also been identified as possible sources of exaggerated placebo response. The randomisation of patients with artificially high pain levels may result in an a specious improvement of symptoms following randomisation, independent of treatment group assignment. Insisting on some objective criteria, such as the time to walk a certain distance for osteoarthritis trials or using quantitative sensory testing measures for neuropathic pain trials, as well as using several of these inclusion

criteria in combination with other inclusion criteria that reflect both patient and investigator ratings, may be beneficial in reducing the chances of enrolling inappropriate patients. Some of these inclusion criteria can be quite complex and drug companies have recently proposed proprietary algorithms consisting of various weighted and unweighted outcome measures taken across several time points for patient inclusion.

Another complementary method is to ensure that both the patient and the investigational staff are unaware of the exact inclusion criteria cutoff scores needed for randomisation and any definitions of treatment response and failure that may be needed for entry into a phase of study, as well as the point at which randomisation occurs<sup>4</sup>. Blinding the actual time of randomisation may be useful as both investigator and patient behaviour tends to change once the patient is administered study drug. This tactic can be challenging as there are typically only a limited number of time points for randomisation to choose from, even when randomisation is not restricted to an office visit.

#### **Permissiveness, Type and Frequency of Rescue Medications**

Allowance and provision of rescue medication may not only affect placebo response but may also impact recruitment/enrolment as well as confound efficacy evaluations. It is not uncommon for patients to report being very satisfied with their trial medication at study conclusion while still reporting moderate levels of pain.



It is possible that the therapeutic milieu of being in a study and interacting with site staff may account for this paradox. However, this paradox, may also be partially explained by the confounding impact of rescue medication on the pain outcome measure. Therefore, it is important to assess rescue in relation to pain, and a composite measure of pain relief along with the number of rescue tablets taken on a daily basis may be helpful in defining the impact of rescue medication on pain<sup>5</sup>. Specifically, the total number of rescue medication doses and amount of dose should be evaluated in a matrix alongside pain relief, with higher scores assigned to those patients with high levels of relief and minimum rescue, and lower scores assigned to patients who have rescued the most and have lower pain relief scores. It is important that sponsors provide rescue medication to all patients at the very beginning of the study wherever possible. Two to three grams of acetaminophen per day is considered standard across most chronic pain trials, but exact requirements for allowance of rescue are variable and often dictated by the site. The provision of a second tier rescue of a stronger analgesic medications of a different class may also be necessary to keep patients in the trial. Attrition is particularly problematic in chronic pain trials as drop-outs can diminish efficacy results by having baseline or worst-observation-carried-forward in classic designs, or by having drop-outs viewed as treatment failures in time-to-event designs, such as those that examine time to efficacy failure in enriched enrollment randomised withdrawal designs.

#### Use of a Rater Training Programme to Control Non-specific Treatment Effects

The therapeutic milieu of simply being in a study and interacting with site staff may heighten placebo response. This can be at least partially mitigated through an effective training programme for site staff and patients. To this end a variety of methods can be used to help build a “research” and not “therapeutic” milieu in order to establish a true sense of clinical equipoise at the site in which site staff do not have predispositions about study drug effects. All rater training programmes should incorporate an assessment of site staff beliefs and expectations regarding clinical practice versus research as well as training on practical methods of limiting and standardising patient interactions that will restrict non-specific treatment effects<sup>6</sup>. Demanding that site staff interactions with patients be controlled, and not inappropriately and unintentionally creating a non-specific supportive treatment environment that heightens placebo response, is imperative. Site staff should be instructed that they are participating in an experiment and, therefore, should have no expectations of drug response (either positive or negative). Reminders should be made that supportive messages to patients can adversely affect the sites’ ability to make accurate clinical assessments. Sites in turn should remind patients they are under no obligation to improve during the blinded trial, and there should be no stated or unstated communication to patients that they will improve during trial<sup>6</sup>. Clearly

defined and easily monitored guidelines should help ensure valid and reliable patient-reported assessments that minimise the impact of placebo response.

In summary, these five relatively easy to implement procedures, including: 1. optimising the allocation of patients to placebo; 2. ensuring adequate levels of disease and pain severity, duration and consistency; 3. using objective outcomes and withholding important trial information from investigators and patients; 4. controlling the permissiveness, type and frequency of rescue medications and; 5. implementing a rater training programme to control non-specific treatment effects, can be effectively used to reduce the heightened placebo response ubiquitous in chronic pain trials and uncover possible treatment effects.

#### References

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**Henry J. Riordan**, Ph.D. is Executive Vice President of Medical and Scientific Affairs and Global Lead for Neuroscience at Worldwide Clinical Trials. Dr Riordan has been involved in the assessment, treatment and investigation of various CNS drugs and disorders in both industry and academia for the past 20 years. Dr Riordan specialises in clinical trials methodology and has advanced training in biostatistics, experimental design, neurophysiology, neuroimaging and clinical neuropsychology. He has over 90 publications, including co-authoring two books focusing on innovative CNS clinical trials methodology. Email: [henry.riordan@wwctrials.com](mailto:henry.riordan@wwctrials.com)