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Can the Placebo Response **Be Predicted in Pain?**

How AI-based tools can de-risk drug development in pain indications like osteoarthritis

When it comes to bringing new drugs to market, high development costs and extensive timelines have proved significant barriers to delivering much-needed therapies to patients[1,2,] especially in chronic pain indications like osteoarthritis (OA). The good news is these barriers have pushed the industry towards unique, cost-effective strategies that de-risk the drug development process.

In this eBook, we explore the top challenges clinical trials face – especially prevalent in chronic pain – and offer our perspective to de-risk the process.

In pain, the two very things clinical trials promise to address – safety and efficacy – are so difficult to pinpoint that phase II and III clinical trials often fail. The inability to demonstrate clear superiority of the tested therapy versus a placebo makes pain compound development extremely challenging. This snowballs into higher development costs, longer timelines and even the premature abandonment of entire development programs.[3,4]

The placebo response, in which patients experience a clinical improvement in symptoms after treatment with a "sham" medicine, is one culprit. The placebo response creates a very real challenge that must be understood and managed – regardless of the size or disease being evaluated in a phase II or III trial.[5]

It's especially troubling for patients suffering from chronic pain. Let's examine why – and what can be done about it.

PART 1

The Placebo Problem in Chronic Pain

The first problem with chronic pain is that there are many different types of it – all treated differently with varying levels of response. The second problem is that demonstration of treatment efficacy relies on subjective, patient-reported or physician-reported outcomes.

In peripheral neuropathic pain (PNP), for example, the placebo response alone may account for as much as 60% of the analgesic response.[6]

Another example is osteoarthritis (OA), a common musculoskeletal disease with increased incidence and prevalence associated with aging – and a major cause of disability and impaired quality of life. Even though OA presents a significant burden to patients, most patients do not receive the right therapies or treatments[7] due to high trial failure rates[8].

Why Do OA Trials Fail?

- Disease heterogeneity
- Disconnect between pain and structural improvement
- High variability/inaccuracy in patient reporting
- Strong placebo response

What Influences the Placebo Effect in OA?

- Injection vs. oral vs. topical administration
- Pain variability
- Health professional behavior
- Expectations from enhanced messaging
- Personality traits

In OA, the placebo response has been estimated to comprise of approximately 44-68% of the measured treatment effect,[9,10] jeopardizing the ability to clearly demonstrate a study drug's efficacy.

Due to the vast improvements of perceived pain by patients because of this placebo response prevalence, some experts have even suggested that OA patients may benefit from placebo as a treatment option.[11] But clinical trials should also take steps to overcome the placebo effect and get patients the real treatment and relief they deserve.

PART 2

Historical Approaches to Managing the Placebo Effect in Pain

Across the board, clinical trials have turned to a few methods to try to minimize variance caused by the placebo effect: optimizing study design, patient training and site training.

For example, studies may incorporate a placebo run-in phase design. Also known as a lead-in phase, this design excludes patients who show an improvement after taking a placebo in the lead-in period. A variant of this design is the Sequential Parallel Comparison Design (SPCD), which involves two double blind identical steps[12]. However, these approaches have not proved to positively impact trial sensitivity. Not to mention, the use of a SPCD was cited as a potential reason for regulatory rejection[13].

As an alternative, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consortium examined several additional areas to increase outcome measurement sensitivity in chronic pain studies:

- Patient psychology
- Expectation
- Investigator site training
- Staff-patient interactions

None of these methods – optimizing study design, patient training and site training – incorporate the two other factors put forth by the IMMPACT group: patient psychology and expectations (at least, not a full and comprehensive collection of the sources of expectations). Training addresses the extrinsic factors that contribute to placebo response. The intrinsic factors – like the placebo effect, which is innate to the patient and closely linked to patient traits – are still left unaddressed.

Until recently, there have been no existing methods that fully address the variance attributed to the placebo effect as a true psychobiological phenomenon in patients suffering from chronic pain.

That's why, in the rest of this paper, we offer a unique approach that helps clinical trials account for the full spectrum of the placebo response – with minimal trial burden and no additional study risk.

Patient & Site Training

Patient and investigator site training has been widely employed in pain trials, most of the time to manage expectations or train patients to report symptoms[14]. Unfortunately, expectations are highly complex in nature, and only a portion (30%) results from patient interactions with site personnel[15,16]. Plus, it's more difficult to train patients to more accurately report symptoms that are highly complex and less intuitive than pain (e.g. Quality of Life scales in OA).

PART 3

The Placebell® Approach in Pain

Placebell (by Cognivia) is an AI-based method to predict and account for individual patients' placebo responsiveness in clinical trials.

By combining behavioral science with predictive algorithms (trained to specific indications like osteoarthritis), Placebell quantifies individual patient placebo responsiveness at baseline, based on a sophisticated assessment of patient traits, expectations, demographics, baseline disease intensity and other factors.

This individual patient placebo responsiveness translates to a score – the Placebell Covariate – for each patient in the study to be used in the statistical analysis. Use of covariates to adjust statistical analysis is regulated[17] and just like any other covariate (e.g. age), the Placebell Covariate can dramatically reduce data variance and subsequently improve the ability to detect true treatment efficacy.

Placebell may be implemented with a significant added value even if other mitigation strategies are used to minimize the placebo response (e.g. patient and site training) as these address different components of the placebo response.

How Placebell Works

1. Assess Patient Psychology
Using Cognivia's proprietary, validated Multi-Dimensional Participant Questionnaire (MPsQ)[16], clinical trial investigators can assess each patient's characteristics and traits. The questionnaire is designed to minimize the patient burden during any specific visit. The only requirement is that all components must be completed before the first drug administration, ensuring that Placebell meets the regulatory requirements for a baseline covariate.

2. Predict Patient Placebo Responsiveness
The data from the MPsQ can then be combined with other pre-trial data that is typically already collected in the trial (like demographics or medical history). These data are then used as inputs to the Placebell model[19].

3. Provide Placebell Covariate to Study Statisticians
The Placebell scores calculated for each patient in step 2 can be used as covariates, just as you would for age or other inherent patient characteristics to reduce data variance.

Ultimately, the Placebell approach improves the ability to detect statistically significant differences between drug treatment and placebo treatment. To see the impact, let's look at the results from real studies in chronic pain.

Model Development in Chronic Pain

The Placebell chronic pain model was trained using data patients from several clinical studies conducted by Cognivia. The studies evaluated pain outcomes in chronic pain patients with either PNP or painful OA of the hip and/or knee receiving oral placebo twice a day.

In the following case study example, the chronic pain model was fully pre-specified in the statistical analysis plan of a sponsored phase II randomized clinical trial[19]. The RCT evaluated a single dose of an experimental therapy administered by intra-articular injection in patients with moderate to severe painful knee OA (NCT04129944) and was used to calculate the Placebell Covariate score for both placebo-treated and drug-treated patients.

The performance of the model was determined by comparing the Placebell Covariate score (predicted placebo response) with the actual placebo response in placebo-treated patients for multiple study endpoints:

- Average pain score (APS)
- WOMAC-Pain
- WOMAC-physical function
- WOMAC-stiffness
- Patient global assessment (PGA)

A baseline covariate approach is a low-risk, conservative method to reducing the impact of the placebo response on clinical data.

Results

The Placebell prediction of placebo response was significant, with a Pearson's correlation ranging from 55.2% to 59.7% for the three components of the WOMAC battery (R2 ranging from 30.4% to 35.6%, $p<0.001$)[17]. The Placebell model was further predictive for all patients in the trial (R2 ranging from 15.9% to 30.7%, $p<0.001$). The R^2 value relates to the magnitude of variance that can be reduced when this score is used as a baseline covariate in the ANCOVA.

As such, using Placebell as a covariate resulted in a substantial decrease in data variability that translates into a 37.2% improvement in the precision of the treatment effect estimation. These results demonstrate the effectiveness of this tool in increasing clinical trial assay sensitivity.

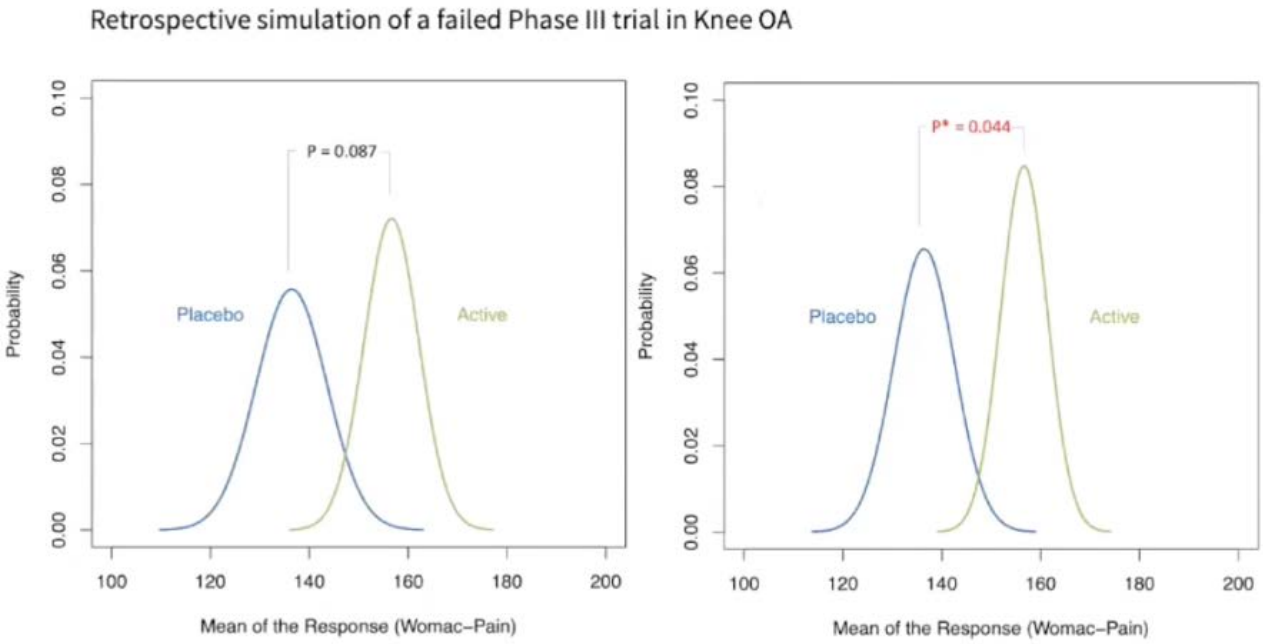
Similar results have been obtained in hand OA[19], confirming that this approach may be generalized to other OA etiologies and beyond.

Since then, Placebell has been implemented in multiple Sponsor RCTs (randomized controlled trials) in variety pain indications with similar outcomes.

Reducing the Risk of Failed Trials

In another example, we worked with an OA clinical trial sponsor to retrospectively evaluate a failed Phase III trial.

Below, we have two graphs comparing the active group with the placebo group. The graph on the left represents the original statistical analysis; the graph on the right represents the statistical analysis after incorporating a covariate calculated based on Placebell methodology.



In the graph on the left, there is not a statistical difference between the two groups – causing the clinical trial to fail.

However, when you apply a correction of variance – the Placebell Covariate – there is now a clinical and statistical difference between the placebo and treated group.

The purpose of this technology and approach is to consider other components of a patient to predict if a patient will be a placebo responder or not. The use of this information allows for a more powerful statistical analysis.

CONCLUSION

De-Risk Drug Development for Chronic Pain

The placebo effect is a glaring issue in drug development that often leads to inconclusive trials. But the combination of behavioral science with machine learning technology, positively impacts drug development timelines and costs. Sponsors can use this new approach avoiding to repeat trials or, even worse, to abandon good compounds.

For drug developers this offers a new way to address a complex phenomenon without adding more risk to studies. For patients suffering from chronic pain, this offers hope for the future.

Reduce data variability and accelerate the launch of new therapeutics with Placebell by Cognivia.

About Cognivia

Cognivia quantifies patient behavioral insights to de-risk clinical trials. Founded over a decade ago by career drug developers frustrated by the state of clinical trials, Cognivia assists sponsors and Clinical Research Organization (CROs) in addressing key sources of variability and noise in their data by combining a sophisticated evaluation of patient characteristics with machine learning.

Cognivia offers digital solutions through its platform, including its flagship AI tool, Placebell. Placebell calculates baseline score that can be used as a covariate to account for the noise caused by the placebo response. The second tool, Compl-AI, predicts nonadherence and dropout risk, helping clinical trial managers in personalizing patient engagement strategies. Coupled with Cognivia's expert data analysis services, these solutions enable pharmaceutical and biotech companies to conduct more successful clinical trials and effectively address unmet patient needs.

Cognivia is headquartered in Belgium. To learn more, please visit cognivia.com or follow @cognivia on LinkedIn.

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