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# Can the Placebo Response **Be Predicted in Parkinson's Disease?**

How placebo response technology can de-risk drug development in Parkinson's disease

***When it comes to bringing new drugs to market, high development costs and long timelines have proven to be significant barriers to delivering much-needed therapies to patients; [1,2,3] especially in indications like Parkinson's Disease (PD) that rely on subjective measures of motor function and complications. Despite these challenges, these barriers have pushed the industry towards unique, cost-effective strategies that de-risk the drug development process and improve development success in PD.***

In this eBook, we explore the top challenges clinical trials in Parkinson's disease face — and offer one unique strategy to de-risk the process.

The crux of the problem comes down to the inability to demonstrate clear superiority of the tested therapy versus a placebo. 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. This snowballs into higher development costs, longer timelines and even the premature abandonment of entire development programs.[4,5]

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.

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

PART 1

# The Placebo Problem in Parkinson's Disease

**One of the most common neurodegenerative disorders, Parkinson's Disease affects 1-2 per 1000 of the population at any given time.[6] Although it is primarily a disease of the elderly, individuals can develop PD in their 30s and 40s.[7]**

Our understanding of the neural mechanisms behind the placebo effect has grown significantly due to advances in brain imaging. In the context of Parkinson's Disease, clinicians have long observed placebo effects in their patients. These effects are also evident in clinical trials for medications and invasive procedures like deep-brain stimulation and stem-cell implantation. Neuroimaging studies reveal that placebos trigger dopamine release in the striatum of Parkinson's patients and can influence dopamine neuron activity. Overall, a unified mechanism for the placebo effect in Parkinson's Disease is emerging, combining expectation-induced neurochemical changes with disease-specific dopamine release.[8]

### Determinants of Placebo Response in Parkinson's Disease

- Patient characteristics: expectations, pre-conditioning, personality traits, and demographics
- Study design
- Medication costs

Currently, treatment of PD is only focused on symptomatic management.[9] Though promising disease-modifying therapies are being developed for PD,[10,11,12] the placebo response barrier must be addressed in order to successfully deliver a cure.

But the placebo response has biological roots in patients with Parkinson's. In these patients, the placebo response is mediated by activation of the dopaminergic system, including both neural circuits involved in the reward system (ventral striatum) and the nigrostriatal pathway involved in motor control (dorsal striatum), which ultimately produces objective motor improvements.[13]

It's important to note that the placebo response is unique to each patient, influenced by the patient's personality traits, the investigator-patient relationship,[14] and the patient's expectations of not only drug efficacy and overall well-being but also about receiving a treatment in general.[8] This patient-specific nature of the overall placebo response (which includes the placebo effect) combines with the patient's response to the investigational treatment, clouding the ability to clearly demonstrate efficacy of the study drug.

### Influence of the Investigator-Patient Relationship

The physician-patient relationship is highly relevant to PD more than other areas. In PD, the investigator provides a qualitative and semi-quantitative assessment of the patient. Some outcomes are indeed physician reported (not patient reported).

Moreover, the placebo response has proved stable in PD over time through the progression of the disease. Researchers in Chicago, U.S. – led by Christopher Goetz, MD – conducted a review of 11 placebo-controlled Randomized Clinical Trials (RCTs) with about 900 patients[15] across different stages of the disease and various treatment interventions. In this review, the placebo response rate was about 16 percent, and there was no evidence of reduction over time of the placebo response, even as the disease progressed and patient's disability increased.

As mentioned, there are promising disease-modifying therapies being developed for PD. So, what are these clinical trials doing – or what have they done in the past – to try to manage the ever-present placebo effect?

PART 2

# Historical Approaches to Managing the Placebo Effect in Parkinson's Disease

Historically, interventions in RCTs that neutralize staff and subject expectations have shown the most promise to reduce the placebo response.[16]

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

But because Parkinson's Disease studies largely rely on physician reported outcomes – not those reported directly by the patient – clinical trials have been limited to site training in an attempt to neutralize patient expectations. However, this approach is limited by itself. Training site personnel can become cumbersome, and it's inherently difficult to standardize the way staff behave.

Further, this approach fails to address all components of the placebo response, which consists of both extrinsic and intrinsic factors.

| Sources of Placebo Response | |
|---|---|
| Extrinsic Factors (Can be changed) | Intrinsic Factors (Cannot be changed/reduced) |
| - Study design biases | - Demographics |
| - Patient reporting errors | |
| - Clinical site factors | - Placebo Effect |
| - Regression to the mean | |

Site training to standardize staff interactions with patients addresses one aspect of this complex phenomenon – clinical site factors – and fails to account for the full spectrum of intrinsic and extrinsic factors that contribute to the placebo response.

While this method is not comprehensive of the full phenomena, it has – until recently – been the only option in PD drug development.

Capturing the variability caused by the placebo response – and, in particular, the intrinsic placebo effect – will be critical to account for the full spectrum of the placebo response and decrease clinical trial failure. This can be done with minimal trial burden and absolutely no study risk.

**PART 3**

# The Placebell® Approach in Parkinson's Disease

**Placebell (by Cognivia) offers a straightforward technology to account for placebo response. This solution generates a Placebo prognostic composite covariate, which predicts each patient's placebo responsiveness in clinical trials.[17]**

By using predictive algorithms – trained in specific indications like PD – Placebell calculates a relative placebo response score for each patient at study baseline, based on

The Placebell approach is complementary to other methods that may be used to attempt to minimize the placebo response (e.g., site training) as these address different components of the placebo response.

## How Placebell Works

**1. Assess Patient Traits**

Using Cognivia's proprietary, validated Multi-Dimensional Participant Questionnaire (MPsQ),[18] each patient's traits are assessed. The questionnaire has a modular design and can be administered at different study visits (prior to first dose) to minimize the patient burden while maximizing the value of the data collected. 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-dose data that is typically collected in the trial (like patient demographics or medical history). These data are then used as inputs to the Placebell model that has already been specifically trained in Parkinson's Disease, resulting in the calculation of the Placebell Score on a per patient basis.

**3. Provide Placebell Prognostic Covariate to Study Statisticians**

The Placebell Prognostic Covariate calculated for each patient in step 2 can be used as a baseline covariate, just as you would for age or other inherent patient characteristics to reduce data variance. This method is consistent with the FDA's final official opinion on the use of covariates to adjust statistical analysis and improve treatment effect size evaluation.[19]

a sophisticated assessment of patient traits, expectations, demographics, baseline disease intensity and other factors.

This score can be used as a covariate in the statistical analysis to "see through" the variability placebo response causes. Just like any other covariate (e.g., age), the Placebell Score can dramatically reduce data variance and subsequently improve the ability to detect true treatment efficacy.[17]

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

Ultimately, the Placebell approach improves study power and increases the precision of the treatment effect size. To understand the impact, let's look at the results from a real study in Parkinson's Disease.

## Model Development in PD

In a clinical study conducted by Cognivia, predictive covariates of the placebo response in Parkinson's Disease were built and trained using data from N=94 patients with mild to moderate Parkinson's Disease receiving placebo orally by blinded administration (TID) for 3 months.

The placebo response in this study was assessed as a change from baseline in the primary endpoint, MDS-UPDRS Part III, as well as:

- MDS-UPDRS Part I, II and IV
- Investigatory Global Assessment of Change (IGAC)
- Patient Global Assessment of Change (PGAC)
- Parkinson's Disease Questionnaire (PDQ-39)
- Epworth Sleep Scale (ESS)
- Fatigue Severity Scale (FSS)

While the placebo response in MDS-UPDRS Part III (primary endpoint) was small in this study, a predictive Placebell model was still able to be trained using these data.

The performance of the model was determined by comparing the Placebell Covariate with the actual placebo response for all study endpoints. A multivariate descriptive analysis was used to estimate the predictivity of the placebo response. This analysis (Table 1) demonstrated that Placebell significantly predicted the placebo response in MDS-UPDRS Part II, Part III and Part IV, PDQ-39, ESS, IGAC and PGAC with adjusted $R^2$ values ranging from 0.16 to 0.33.[20]

| Study Endpoints* | N | Pop.R2 | p-value |
|---|---|---|---|
| MDS-UPDRS-3 | 94 | 33.2% | <0.001 |
| MDS-UPDRS-1 | 93 | 11.0% | 0.084 |
| MDS-UPDRS-2 | 94 | 14.5% | 0.037 |
| MDS-UPDRS-4 | 88 | 22.4% | 0.007 |
| PDQ-39 | 94 | 23.2% | 0.003 |
| FSS | 92 | 11.4% | 0.078 |
| ESS | 93 | 15.7% | 0.029 |
| IGAC | 84 | 43.1% | <0.001 |
| PGAC | 94 | 43.4% | <0,001 |

## Results

Table 1: Variance explained presented as $R^2$

*MDS-UPDRS: Unified Parkinson's Disease Rating Scale; PDQ-39: Parkinson Disease Questionnaire; FSS: Fatigue Severity Scale; IGAC: Investigator Global Assessment of change; PGAC: Patient Global Assessment of change.

The Placebell model can explain between 11% and 44% of data variability related to the placebo response in multiple efficacy endpoints, including explaining 33% of the variability in MDS-UPDRS part III, the primary endpoint of the study.

Significant placebo responses have been reported for quality-of-life endpoints, which are subjective and more difficult to measure.[21] In the PD study, the same Placebell approach was applied to QoL endpoints, including ESS, FSS and PDQ-39.

The model was statistically significant for 8 out of 10 efficacy endpoints, including the MDS-UPDRS Part II, III and IV, and Quality-of-Life (QoL) endpoints PDQ-39 and ESS.

In RCTs, Placebell's pre-defined model may be applied to reduce variance, increase study power and manage the risk of placebo response impact on treatment effect size estimation – reducing the risk of clinical trial failure.[22]

**CONCLUSION**

# De-Risk Drug Development for Parkinson's Disease

The placebo effect is a glaring issue in drug development that leads to inconclusive trials. But the combination of machine learning technology and unique patient traits data positively impacts drug development timelines and costs by reducing the need to repeat trials or, even worse, the need to abandon good compounds.

For trials, this offers a new way to address a complex phenomenon without adding more risk to studies. For patients – and their loved ones – suffering from Parkinson's Disease, this offers hope for the future.

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

# About Cognivia

Every patient is different. These differences make patient unpredictable, data more variable and decisions more difficult. To solve this challenge, Cognivia develops validated technologies that de-risk study conduct and clinical data interpretation. Founded over a decade ago by career drug developers frustrated by the high failure rate in clinical trials, Cognivia helps life science companies address challenges inherent to diverse clinical trials so they can make better portfolio management decisions.

Cognivia's technology combines a unique evaluation of patient traits and characteristic with machine learning. Placebell, Cognivia's flagship technology, calculates a score at baseline that can be used as a covariate to "see through" the noise caused by patient variability. Compl-AI predicts nonadherence and dropout risk, helping clinical trial managers personalize patient engagement strategies. These solutions, coupled with Cognivia's expert data analysis services, will help pharma, biotech, and device companies conduct more successful clinical trials and 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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