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QUANTIFY THE POWER OF THE MIND

UNDERSTANDING & TACKLING THE PLACEBO RESPONSE IN PARKINSON'S DISEASE

De-risking the drug development process with a unique, cost-effective strategy

CONTENTS

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INTRODUCTION

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]; 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 PD face – and offer one unique strategy to de-risk the process. But first, why are costs so high and development timelines so long?

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.[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 patient's suffering from PD. Let's examine why – and what can be done about it.

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]

In short, PD is very prevalent in society today. A cure, unfortunately, is not.

Currently, treatment of PD is only focused on symptomatic management.[8] Though promising disease-modifying therapies are being developed for PD,[9] the placebo response barrier must be addressed in order to successfully deliver a cure.

But the placebo response has biological roots in patients with PD. 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.[10]

Determinants of Placebo Response in Parkinson's Disease

- **Patient characteristics**: expectations, pre-conditioning, personality, and demographics
- **Study design**
- **Medication costs**
- **Biological factors**

It's important to note that the placebo response is unique to each patient, influenced by the patient's expectations[11] (in terms of drug efficacy and overall well-being), the patient's personality traits, and even the investigator-patient relationship.[12] This patient-specific nature of the overall placebo response (which includes the placebo effect) combines with patient response to investigational treatment, clouding the ability to clearly demonstrate efficacy of the study drug.

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 RCTs with about 900 patients[13] 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?

Influence of the Investigtor-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).

HISTORICAL APPROACHES TO MANAGING THE PLACEBO EFFECT IN PARKINSON'S DISEASE

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 PD 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.

Site training to standardize staff interactions with patients only 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 "suboptimal", it has – until recently – been the only option in PD drug development.

Historically, interventions in RCTs that neutralize staff and subject expectations have shown the most promise to reduce the placebo response.[14]

Table 1:

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	

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 absolutely no additional study risk.

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THE PLACEBELL©™ APPROACH IN PARKINSON'S DISEASE

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

By using predictive algorithms – trained in specific indications like PD – Placebell defines individual patient placebo responsiveness at study baseline, based on a sophisticated assessment of patient psychology, expectations, demographics, baseline disease intensity and other factors.

This individual patient placebo responsiveness results in the calculation of a single score – the Placebell Covariate – for each patient in the study to be used in the statistical analysis. 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.

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 Psychology

Using Cognivia's proprietary, validated Multi-Dimensional Participant Questionnaire (MPsQ),[15] each patient's psychological traits are assessed. The questionnaire has a modular design and can be administered at different study visits 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.[16,17]

#2.
Predict Patient Placebo Responsiveness

The data from the MPsQ can then be combined with other pre-trial 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 PD, resulting in the calculation of the Placebell Covariate on a per patient basis.

#3.
Provide Placebell Covariate to Study Statisticians

The Placebell score calculated for each patient in step 2 can be used as a covariate, just as you would for age or other inherent patient characteristics to reduce data variance.

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MODEL DEVELOPMENT IN PARKINSON'S DISEASE

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

The placebo response in this study was assessed as a change from base line 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)

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

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 demonstrated that Placebell significantly predicted the placebo response in MDS-UPDRS Part III, Part II and Part IV, PDQ-39, ESS, IGAC and PGAC with adjusted R2 values ranging from 0.14 to 0.33.[18]

Endpoint	Pop· R^2	P-value
MDS-UPDRS-3	**33.2%**	**<0.001**
MDS-UPDRS-1	11%	0.084
MDS-UPDRS-2	14.5%	0.037
MDS-UPDRS-4	22.4%	0.007
data	23.2%	0.003
IGAC	**43.1%**	**<0.001**
PGAG	43.4%	<0.001

Physician-reported outcomes Patient-reported outcomes

Table 2:

Placebell Multivariate Model Prediction in PD.

Performance is measured by the R^2 value comparing the predicted placebo response versus the actual response

This study defines a Placebell model that can be pre-specified in sponsored RCTs to reduce variability and increase study power.

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RESULTS

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.[19] 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 QoL endpoints PDQ-39 and ESS. The score calculated by the model can be used as a covariate in statistical analyses to reduce variability and increase study power, thus reducing the risk of clinical trial failure related to the placebo response.

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 patient psychology 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 PD, this offers hope for the future.

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

ABOUT COGNIVIA

Cognivia is an innovator of analytical tools to optimize and accelerate the clinical development of new medicines. The privately held company was founded in 2013 by longtime colleagues with decades of experience in the pharmaceutical industry who set out to tackle some of the most challenging issues that prevent drugs from reaching the marketplace. Cognivia helps lessen risk and increase clinical trial success. It can help reduce the variability of study data by 30 percent, which directly translates into increased study power and reduced risk of trial failure. This can further lead to fewer patients needed in a study, equating to less cost and time.

The company offers Placebell, a solution that improved clinical trial assay sensitivity by characterizing and managing the individual placebo response in a variety of disease states where the placebo effect masks the true efficacy of potentially important therapies.

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