Parkinsonism and Related Disorders xxx (2016) 1–7

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

# Predictors of the placebo response in clinical trials on Parkinson's disease: A meta-analysis

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ARTICLE INFO

*Article history:*
Received 9 November 2015
Received in revised form
10 May 2016
Accepted 19 May 2016

*Keywords:*
Parkinson's disease
Placebo
Randomized clinical trials
Meta-analysis

ABSTRACT

*Introduction:* Previous studies have assessed the placebo response in clinical trials on PD using the individual data of participants from the placebo-assigned group. The aim of this study was to examine the group predictors of the placebo response in randomized placebo-controlled trials on PD using a meta-analysis with meta-regression models.

*Methods:* The placebo response was defined as the mean change in the UPDRS part III score from baseline to the primary efficacy end point in the placebo group. The impacts of the predictors were assessed with meta-regression analyses, and significant predictors were used in a multivariable analysis. Subgroup analyses were conducted in studies that enrolled PD patients with or without motor fluctuations.

*Results:* Forty-eight studies (consisting of 5618 participants on placebo) were included. Motor fluctuation and baseline UPDRS part III score were significant predictors in the univariable analyses. The high baseline UPDRS part III score ($\beta = -0.21$, 95% CI −0.34, −0.08; $p = 0.005$) significantly increased the magnitude of the positive placebo response in the multivariable analysis. In the subgroup analyses, the positive placebo response was significant only in studies that enrolled patients with motor fluctuations; high baseline UPDRS part III score and low baseline daily levodopa dose increased the positive placebo response independently in the subgroup with motor fluctuations.

*Conclusion:* Researchers should consider the positive placebo response when they design clinical trials in advanced PD patients with motor fluctuations and severe motor symptoms. Baseline daily levodopa dose may be the independent predictor in studies that enrolled fluctuating patients.



## 1. Introduction

Placebo treatment is used in randomized controlled trials (RCTs) to evaluate the efficacy of medications. Theoretically, as inactive pharmacological agents, placebos should not have any effect on subjects; nevertheless, both placebo and nocebo effects have been reported for various neurologic disorders such as pain, depression, anxiety, and Parkinson's disease (PD) [1–4]. The placebo effect in RCTs on PD has been well documented using the Unified Parkinson's Disease Rating Scale (UPDRS) scores [5], and the overall positive placebo response rate has been reported as 16–21% [6–9]. The presence of the placebo effect could temper the efficacy estimates of study drugs in RCTs by decreasing the drug-placebo difference. Therefore, recognizing factors that predict the placebo effect is important in designing RCTs. Several factors have been reported to increase the placebo effect in RCTs on PD such as high baseline UPDRS part III scores, PD with motor fluctuations, and surgical intervention [8,9]. Interestingly, the temporal increase was

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http://dx.doi.org/10.1016/j.parkreldis.2016.05.019
1353-8020/

reported in a meta-analysis of the nocebo effect on PD, and it was also found in meta-analyses of the placebo effect in depression [4,10,11]. The study completion rate was related to the placebo effect in a meta-analysis in depression [11].

Previous studies have used the individual data of patients in the placebo group and rigorous definitions for the placebo response, such as at least 50% improvement in the total UPDRS part III score or a positive change by at least two points on at least two UPDRS part III items compared to baseline, to avoid unwanted influence from the natural variability of PD or the UPDRS scores [6–9]. These efforts have contributed to the evaluation of the true nature and the predictors of placebo effect in RCT on PD. However, it is hard to apply the results of previous studies to the group data of placebo-assigned patients. To determine group predictors of the placebo response, we defined the mean change of the UPDRS part III score from baseline to the end point in the placebo group as the "placebo response" and conducted a meta-analysis in a large number of RCTs on PD with meta-regression models.

## 2. Methods

### 2.1. Search strategy and selection of studies

We searched the databases of PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) up to December 2014 for relevant studies. We used the generic names of PD medications in evidence based review of treatments for the motor symptoms of PD [12] to build sensitive search strategies (Table e-1). We also reviewed registered studies in the database at www.ClinicalTrials.gov and the reference lists of the included studies.

Identified studies were initially reviewed based on title and abstract using the eligibility criteria. When a decision of eligibility was not made during screening, the study was included in the full-text review. Relevant studies for the meta-analysis after the screening were selected by a detailed full-text review.

### 2.2. Eligibility criteria

Studies were required to meet the following criteria for inclusion in this meta-analysis: 1) The studies were randomized double-blind placebo-controlled studies or had a two phase design such as delayed-start design studies or double-blind studies with open-label extension. In the case of a two phase design, we used only the outcome data of the double-blind placebo-controlled period. 2) They were reported in English. 3) Patients were diagnosed as PD. 4) The intervention of the study was medical treatment aimed at improving motor symptoms or motor complications. 5) The duration of treatment from baseline to primary end point lasted from at least four weeks up to one year. The upper limit of the duration was selected by discussion because the natural progression of PD could mask the placebo response. 6) Signs of PD were measured with the UPDRS part III. 7) The full-text article could be retrieved and had sufficient data for extraction, especially the mean and confidence interval (CI) of the change in the UPDRS part III score in patients on placebo from baseline to primary end point.

Studies were excluded from the meta-analysis when they met the following criteria: 1) Crossover trials were excluded because the experience of active drugs could influence the placebo response. 2) Studies recruited patients with PD in order to study non-motor complications such as dementia, hallucination, or depression. 3) Studies did not control for concomitant anti-parkinsonian medications or permitted adding medications more than the baseline doses. 4) Intervention of the study was a surgical intervention or parenteral medication except for a patch. 5) Interim or post-hoc analyses were excluded when the main publication was screened.

### 2.3. Data extraction

Two authors (C.S and E.P) independently extracted the following information from the studies: The study characteristics (authors, study name, year of study publication [YSP], year of study initiation [YSI], diagnosis criteria of PD, group design, single vs. multicenter, total number of participants, medication, assignment ratio to each group, study in patients with or without motor fluctuations, use of concomitant levodopa, and duration of treatment from baseline to primary end point), cohort characteristics of the placebo group (total number of participants on placebo, age, mean duration of PD, percentage of men, baseline daily levodopa dose, and baseline UPDRS scores), and the outcomes (total number of participants on placebo at primary end point, and the mean and confidence interval of the change in the UPDRS part III score from baseline to primary end point). Disagreement was resolved by discussion. Missing information was sought by searching the clinical trial registries of the U.S (www.clinicaltrials.gov), E.U (www.clinicaltrialsregister.eu), and WHO (apps.who.int/trialsearch/), and contacting pharmaceutical companies or the corresponding authors of the studies.

### 2.4. Risk of bias assessment

Two authors (C.S and E.P) assessed the risk of bias from individual studies independently using Cochrane Collaboration's tool for assessing the risk of bias [13]. Six domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Disagreement was resolved by discussion and consensus. Levels of agreement for each domain were assessed with $\kappa$ statistics.

### 2.5. Factors examined

We selected 11 variables for each study as possible predictors of the placebo response. The study characteristics included the YSP, YSI, assignment rate to the placebo group (calculated from the assignment ratio to each treatment group), study in patients with or without motor fluctuations, and duration of treatment from baseline to primary end point. The cohort characteristics included age, mean duration of PD, percentage of men, baseline daily levodopa dose, baseline UPDRS part III score, and study completion rate (total number of participants on placebo at primary end point divided by the total number of participants on placebo at baseline). We used the UPDRS part III 'ON' score from studies conducted in patients with motor fluctuations.

### 2.6. Outcomes

The primary outcome was the mean change in the UPDRS part III score from baseline to primary end point. The primary end point was defined as the primary end point of the efficacy evaluation in each study.

### 2.7. Data synthesis and analyses

The mean change in the UPDRS part III score from baseline to primary end point in the placebo treated group was pooled using a random effects model according to inverse-variance weighting (DerSimonian and Laird method). Heterogeneity was measured by Higgin's $I^2$ statistics. We used a random effects model primarily. Significant heterogeneity was expected because the eligibility criteria did not focus on the homogeneity of the included studies.

Please cite this article in press as: C.W. Shin, et al., Predictors of the placebo response in clinical trials on Parkinson's disease: A meta-analysis, Parkinsonism and Related Disorders (2016), http://dx.doi.org/10.1016/j.parkreldis.2016.05.019