의학석사 학위논문

파킨슨병 임상시험에서 위약효과의 예측인자들

– 무작위 배정 비교 임상시험들의 메타분석 –

Predictive Factors of Placebo Effect in Clinical Trials on Parkinson's Disease

- A Meta-Analysis of Randomized Controlled Trials

2015년 2월

서울대학교 대학원

의학과 뇌신경과학 전공

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지도교수 전 범 석

이 논문을 의학석사 학위논문으로 제출함

2014년 10월

서울대학교 대학원
의학과 뇌신경과학 전공

신 채 원

신 채 원의 석사 학위논문을 인준함

2015년 01월

위 원 장 박 병 주 (인)
부 위 원 장 전 범 석 (인)
위 원 김 종 민 (인)

ABSTRACT

Predictive Factors of Placebo Effect in Clinical Trials on Parkinson's Disease

- A Meta-Analysis of Randomized Controlled Trials

Chae Won Shin
Department of Medicine
(Major in Neuroscience)
The Graduate School
Seoul National University

Background Several factors have been reported to be related with the placebo effect in Parkinson's disease (PD). The temporal correlation of nocebo effect (increasing adverse events) in patients on placebo was reported in a meta-analysis in PD. Till now, there have been no studies assessing predictive factors affecting placebo effect and time-placebo effect correlation in PD with a systematic meta-analytic approach.

Objective To examine predictive factors of placebo effect and time-placebo effect correlations using both the year of study publication (YSP) and the year of study initiation (YSI) in randomized double-blind placebo-controlled trials in PD.

Data Sources We searched MEDLINE, EMBASE, and CENTRAL databases (to November 2014). We also reviewed registered studies in the database of www.ClinicalTrials.gov and reference lists of included studies.

Study Selection Eligible studies were randomized double-blind placebo-controlled trials in PD from 4 weeks to 1 year of treatment duration which reported the mean change of the Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor subscale).

Data Extraction and Synthesis Two reviewers extracted data on study characteristics, participants' characteristics in placebo group, and outcomes. The pooled mean change of the UPDRS part III score from baseline to primary end point of placebo treated group in individual studies was calculated using a random effects model. The impacts of predictive factors were assessed using linear meta-regression models. Significant predictors were entered in the multivariate meta-regression model.

Results Thirty eight studies (comprising 4,850 participants on placebo) were included in the meta-analysis. The pooled mean change in the UPDRS part III score from baseline to primary end point was -1.348 (95% confidence

interval [-2.134, -0.563], p = 0.001, I^2 = 93.4%). Duration of treatment (β = 0.09, p = 0.002, N [Number of studies] = 38), use of concomitant levodopa (β = -1.79, p = 0.013, N = 38), and the baseline UPDRS part III score (β = -0.30, p < 0.001, N = 32) were significant predictors in univariate meta-regression analyses. More recently published (β = -0.03, p = 0.566, N = 38) or conducted (β = -0.17, p = 0.120, N = 26) studies showed tendencies to higher placebo effect. Duration of treatment (β = 0.07, p = 0.013) and the baseline UPDRS part III score (β = -0.29, p = 0.001) were statistically significant in the multivariate meta-regression analysis.

Conclusion Duration of treatment and the baseline UPDRS part III score were the independent predictors of the magnitude of placebo effect in randomized controlled trials in PD. Our study implicates that researchers should remind the presence of placebo effect when they design or interpret clinical trials in PD, especially in the short-lasting study enrolled participants with advanced PD.

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keywords: Parkinson's disease, placebo effect, Predictive factors, Meta-analysis, Randomized Controlled Trials

***Student Number*: 2010-21857**

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LIST OF ABBREVIATIONS

CENTRAL = Cochrane Central Register of Controlled Trials;

CI = confidence interval;

DATATOP = Deprenyl and Tochopherol Antioxidative Therapy of Parkinsonism;

ES = effect size;

PD = Parkinson's disease;

PET = positron emission tomography;

RAC = [11C]raclopride;

RCT = randomized clinical trial;

SE = standard error;

STN = subthalamic nucleus;

UPDRS = Unified Parkinson's Disease Rating Scale;

YSP = year of publication;

YSI = year of study initiation;

INTRODUCTION

Placebo treatment is often used in RCTs to prove efficacy of new medications. However, symptomatic improvement on placebo has been reported in various disorders such as pain, depression, anxiety, and PD[1,2]. Placebo effect in PD is distinctive to others because it is an observable movement disorder, not a subjective or psychiatric illness. It has been well documented in the studies using UPDRS[3]. About 21% of participants on placebo experienced clinical improvement in the post-hoc analysis of DATATOP trial[4,5]. Another study using strict placebo associated improvement criteria showed that 17.3% of patients in placebo group improved in DATATOP trial[6]. In a ropinirole study, 16% of patients improved by placebo treatment[7]. A meta-analysis of 11 studies in PD using individual data of patients on placebo showed overall placebo response rate of 16%, with a range of 0 to 55%[8]. Strikingly, only 7% of patients experienced subjective improvement measured by the UPDRS part II subscale[6].

Neuroimaging and neurophysiologic studies have found biologic mechanisms of placebo effect in PD. Dopamine release was enhanced in the dorsal striatum of placebo responders in the PET studies on dopaminergic system using the competition of RAC and endogenous dopamine[9]. Expectation of clinical benefit was associated with endogenous dopamine release[10] and the strength of expectation affected the clinical improvement and dopamine release in patients with PD[11,12]. Patients responded to placebo administration

had reduced discharge and non-bursting activity in single neurons in the STN[13]. Neuronal changes were also found in substantia nigra pars reticulata and thalamus[14]. These results implicate that objective improvement of placebo effect in PD is mediated by neurophysiologic changes in basal ganglia.

Presence of placebo effect could temper the efficacy of study drugs in RCTs by decreasing the drug-placebo difference. Therefore, recognition of factors predicting placebo effect is important for designing clinical trials. Several factors have been found to be related to increase the placebo effect in PD such as higher baseline UPDRS part III scores, PD with motor fluctuation, and surgical intervention[6,8]. Old age (older than 60 years at baseline) was correlated with placebo effect in one study[6], but not in others[7,8]. Placebo assignment rate was also reported as a predictor of placebo effect[8,11]. However, results of previous two studies were controversial. One study[8] reported positive placebo effect was correlated with higher placebo assignment rate (50% vs. <50%), whereas the other[11] reported it was correlated with intermediate placebo assignment rate (25% vs. other probabilities).

A temporal pattern of placebo effect is also an important issue of placebo-controlled trials. The growing number of clinical trials have failed to demonstrate an efficacy of study medications over time especially in psychiatric disorders[15,16]. The temporal increase of placebo effect has been reported in meta-analyses of RCTs in depression[17-20]. Furthermore, the

temporal correlation of nocebo effect (increasing adverse events) in patients on placebo was reported in a meta-analysis in PD[21]. The dropout rate due to adverse events in patients on placebo and the year of study publication were negatively correlated[21]. Based on these evidences, we assumed that the time – placebo effect correlation might exist in RCTs in PD. Up to date, most studies which analyzed time-placebo effect correlation have used the YSP as a time variable. There are some temporal differences between the actual conduction and the publication of the study. The YSI is a more reasonable variable than YSP because it can reflect the impact of placebo effect at the timing of acquisition of clinical data and outcomes. However, only one study used YSI[20].

There have been no studies assessing predictive factors affecting placebo effect in PD with a systematic meta-analytic approach till now. In this meta-analysis, we evaluated predictive factors of placebo effect and time-placebo effect correlations using both YSP and YSI in randomized double-blind placebo-controlled trials in PD.

METHODS

Search Strategy

We searched literatures of MEDLINE, EMBASE, and CENTRAL up to November 2014 for relevant studies. We used generic names of PD medications in evidence based review of treatments for the motor symptoms of PD[22] to build sensitive search strategies. Search strategies for each database are shown in **Appendix 1**. We also reviewed registered studies in the database of www.ClinicalTrials.gov and reference lists of included studies.

Selection of Studies

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

Inclusion Criteria

Studies were required to meet the following criteria for inclusion in this meta-analysis: 1) Randomized double-blind placebo-controlled studies. Studies with two phase design such as delayed-start design studies or double-blind

studies with open-label extension were also included. In this case, we used only outcome data of the double-blind placebo-controlled period. 2) Reported in English. 3) Patients were diagnosed PD. 4) Intervention of the study was medical treatment aimed at improvement of motor symptoms or motor complications such as motor fluctuation or dyskinesia. 5) Duration of treatment from baseline to primary end point lasted at least 4 weeks to 1 year. Upper limit of duration was selected by discussion because natural progression of PD could mask the placebo effect. 6) Signs of PD were measured by the UPDRS. 7) The full-text article could be retrieved and had sufficient data for extraction, especially mean and CI of the change of the UPDRS part III score in patients on placebo from baseline to primary end point.

Exclusion Criteria

Studies were excluded from the meta-analysis when they met the following criteria: 1) Crossover trials were excluded because experience of active drugs could influence the placebo effect. 2) Recruited patients with PD in order to study non-motor complications such as psychosis, depression, and dementia. 3) Did not control concomitant anti-parkinsonian medications or permitted adding medications more than baseline doses. 4) Intervention of the study was surgical intervention or parenteral medication except a patch. 5) Interim or post-hoc analyses. 6) When studies were included less than 3 in each medication category, we excluded those studies to strengthen the quality of included studies.

Data Extraction

Two authors (C.S and E.P) independently extracted the following information about studies: Study characteristics (authors, study name, YSP, YSI, total number of participants, medication, assignment rate to each group, use of concomitant levodopa, duration of treatment from baseline to primary end point, primary efficacy outcome), participants' characteristics in placebo group (total number of participants on placebo, age, mean duration of PD, percentage of males, baseline UPDRS scores), outcomes (total number of participants on placebo at primary end point, mean and CI 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 clinical trial registries of the U.S (www.clinicaltrials.gov), E.U (www.clinicaltrialsregister.eu), WHO (apps.who.int/trialsearch/), and contacting pharmaceutical companies or corresponding authors of the studies.

Risk of Bias Assessment

Two authors (C.S and E.P) assessed risk of bias of individual studies independently using the Cochrane Collaboration's tool for assessing risk of bias[23]. Six domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blind of outcome assessment, incomplete outcome data, and selective reporting. Disagreement was resolved by discussion and consensus. Levels of agreement for each domain were assessed using the κ statistics.

Factors Examined

We selected 10 variables for each study as possible factors for predicting placebo effect. Study characteristics included YSP, YSI, assignment rate to placebo group (calculated using assign ratio to each treatment group), use of concomitant levodopa, and duration of treatment from baseline to primary end point. Participants' characteristics included age, mean duration of PD, percentage of males, baseline UPDRS scores, and study completion rate (total number of participants on placebo at primary end point divided by total number of participants on placebo at baseline).

Outcomes

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

Statistical Analysis

The pooled mean change of the UPDRS part III score from baseline to primary end point of placebo treated group in individual studies using a random effects model according to inverse-variance weighting (DerSimonian and Laird method)[24]. Heterogeneity was measured by Higgin's I^2statistics[25]. We used random effects model primarily because significant heterogeneity was expected. Publication bias was assessed using the funnel plot and the

Egger test.[26,27]

The primary objective of this meta-analysis was to examine the predictability of pre-defined 10 factors on the mean change of the UPDRS part III score from baseline to primary end point using a linear meta-regression model. The regression coefficients of the intercept and slope were estimated based on the random effects model. The multivariate meta-regression analysis was conducted to adjust possible confounding effects among predictor variables. We selected statistically significant ($p < 0.05$) variables from the univariate meta-regression analysis to be entered for the multivariate meta-regression analysis. Calculation of p-values in the multivariate meta-regression model used a permutation test based on Monte Carlo simulation with 10,000 replications.

Exploratory analysis was performed with limited duration of treatment because natural aggravation of PD could influence mean change of the UPDRS score in participants on placebo. We selected threshold duration of treatment from baseline to primary end point (28 weeks or less) to balance inclusion of adequate studies and reduction of confounding effect.

RESULTS

Study Selection

Initial search identified 5,163 articles (2,123 from PUBMED, 1,367 from EMBASE, and 1,673 from CENTRAL). Two articles from clinicaltrials.gov were added by reviewing registered trials. After removing 1,918 duplicated articles, we screened 3,247 potentially relevant articles by title and abstract review, and excluded 2,954 articles according to eligibility criteria. Remained 293 articles were assessed by detailed full-text review and 195 articles were further excluded. Subsequently, we excluded 62 articles because data of primary outcome (mean change of the UPDRS part III from baseline to primary end point) did not exist or were insufficient for the meta-analysis. Reasons of excluded articles were shown in **Figure 1**. Finally, 36 articles (38 studies) were included in the meta-analysis. Two articles[28,29] encompassed 2 studies in each article.

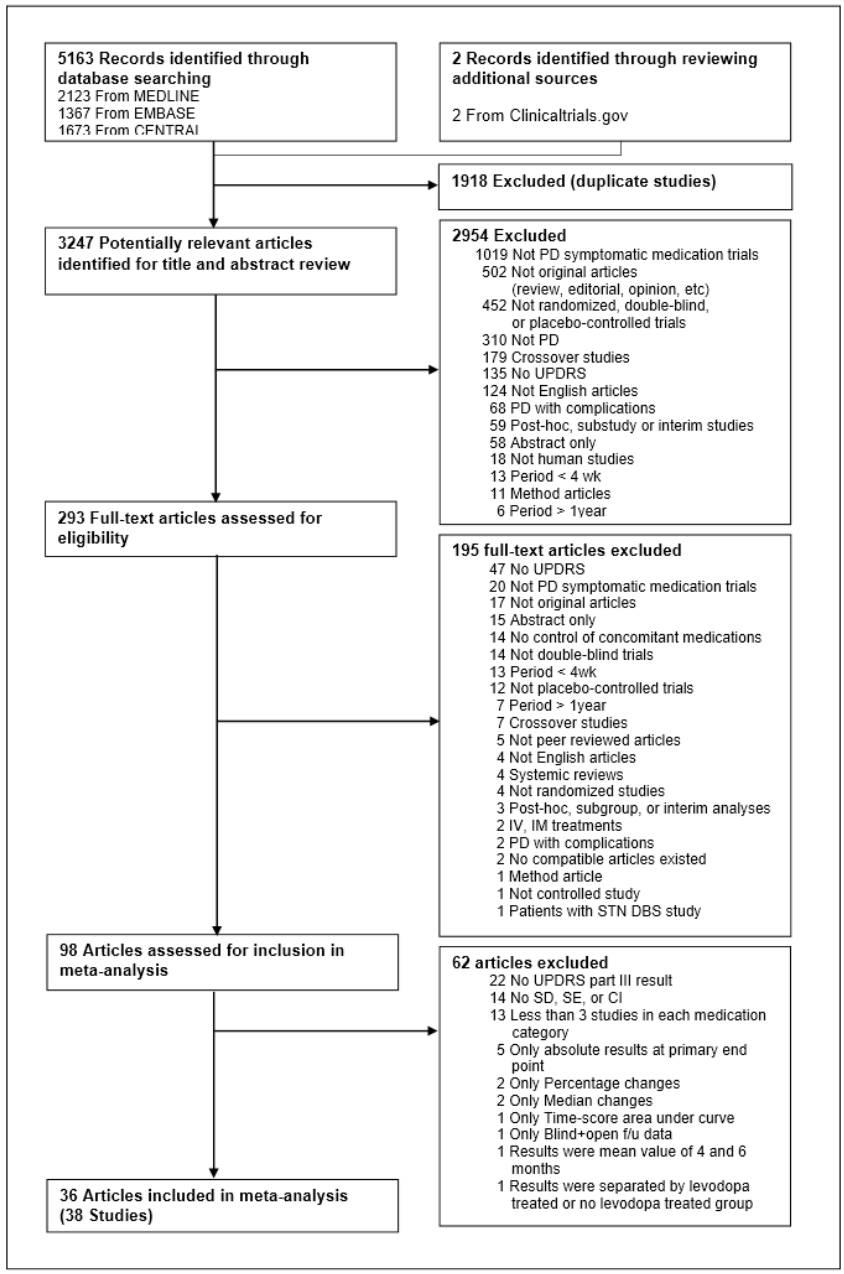

5163 Records identified through database searching
2123 From MEDLINE
1367 From EMBASE
1673 From CENTRAL
2 Records identified through reviewing additional sources
2 From Clinicaltrials.gov
1918 Excluded (duplicate studies)
3247 Potentially relevant articles identified for title and abstract review
2954 Excluded
1019 Not PD symptomatic medication trials
502 Not original articles (review, editorial, opinion, etc)
452 Not randomized, double-blind, or placebo-controlled trials
310 Not PD
179 Crossover studies
135 No UPDRS
124 Not English articles
68 PD with complications
59 Post-hoc, substudy or interim studies
58 Abstract only
18 Not human studies
13 Period < 4 wk
11 Method articles
6 Period > 1year
293 Full-text articles assessed for eligibility
195 full-text articles excluded
47 No UPDRS
20 Not PD symptomatic medication trials
17 Not original articles
15 Abstract only
14 No control of concomitant medications
14 Not double-blind trials
13 Period < 4wk
12 Not placebo-controlled trials
7 Period > 1year
7 Crossover studies
5 Not peer reviewed articles
4 Not English articles
4 Systemic reviews
4 Not randomized studies
3 Post-hoc, subgroup, or interim analyses
2 IV, IM treatments
2 PD with complications
2 No compatible articles existed
1 Method article
1 Not controlled study
1 Patients with STN DBS study
98 Articles assessed for inclusion in meta-analysis
62 articles excluded
22 No UPDRS part III result
14 No SD, SE, or CI
13 Less than 3 studies in each medication category
5 Only absolute results at primary end point
2 Only Percentage changes
2 Only Median changes
1 Only Time-score area under curve
1 Only Blind+open f/u data
1 Results were mean value of 4 and 6 months
1 Results were separated by levodopa treated or no levodopa treated group
36 Articles included in meta-analysis (38 Studies)

Figure 1. Study selection for the meta-analysis

PD indicates Parkinson's disease; CENTRAL, Cochrane Central Register of Controlled Trials; UPDRS, Unified Parkinson's Disease Rating Scale; IV, intravenous; IM, intramuscular; STN, subthalamic nucleus; DBS, deep brain stimulation; SD, standard deviation; SE, standard error; CI, confidence interval.

Study Characteristics

Characteristics of included studies were shown in **Table 1**. Total number of participants on placebo in the meta-analysis was 4,850. All studies reported mean change of the UPDRS part III from baseline to primary end point. One study[30] used delayed start design and data of double-blind period were obtained from post-hoc analysis[31].

Quality assessments of included studies were described in **Appendix 2**. The overall inter-rater agreement was 98.7% and agreement for each domain ranged from 97.4% to 100%. Domains with the highest quality were blinding of participants and personnel, blinding of outcome assessment, and incomplete outcome data (low risk: 100%). Domain with the lowest quality was allocation concealment (low risk: 55.3% and unclear risk 44.7%).

Table 1. Characteristics of the included studies

Reference	YSP	YSI	Intervention	Duration of treatment, Weeks	No. of participants on placebo	Baseline age, Mean (SD), Years	duration of PD, Mean (SD), Years	Male, %	Baseline UPDRS part III score, Mean (SD), Years
Pinter et al.[40]	1999	N/A	Pramipexole	11	44	60.7 (8.7)	8.5 (5.2)	70.5	30.5 (12.2)
Pogarell et al.[41]	2002	N/A	Pramipexole	11	40	65.4 (7.1)	6 (3.5)	77	32.1 (11)
PSG[42]	2007	1997	Pramipexole	10	35	65.4 (10.3)	5.82 (4.39)	71.4	N/A
Hauser et al.[43]	2010	2007	Pramipexole	18	50	63.2 (8.7)	0.8 (1.1)	46	22.4 (13.6)
PSG[44]	1997	1994	Pramipexole	10	51	60.4 (12)	1.7 (1.5)	62.7	N/A
Mizuno et al.[45]	2003	1999	Pramipexole	12	108	63.96 (8.64)	5.73 (7.05)	52.3	27.36 (13.53)
Moller et al.[34]	2005	N/A	Pramipexole	31	183	64.7 (N/A)	7.9 (N/A)	67.8	29.8 (N/A)
Schapira et al.[32]	2013	2006	Pramipexole	39	274	62.9 (9.9)	4.5 (5.9)	61	N/A

Poewe et al.[33]	2011	2007	Pramipexole	33	103	62 (9.6)	0.9 (1)	49.5	21.4 (11.7)
Mizuno et al.[46]	2007	2002	Ropinirole	16	122	64.7 (9.31)	5.52 (4.1)	45	24.9 (12.63)
Zhang et al.[47]	2013	2010	Ropinirole	24	170	63.6 (10.5)	7.97 (4.03)	N/A	29.3 (12.39)
Pahwa et al.[48]	2007	2003	Ropinirole	24	191	66 (9.7)	8.6 (5.2)	68	30.7 (14.4)
Bronzova et al.[49]	2010	2003	Pardoprunox	9	70	59.6 (10)	N/A	70	25.8 (8.7)
Rascol et al.[50]	2012	2007	Pardoprunox	22	145	62.1 (9.3)	6.58 (4.67)	67	30.7 (13.5)
Sampaio et al.[28]**(Vermeer study)**	2011	2006	Pardoprunox	31	110	62.8 (8.95)	0.84 (0.94)	62.7	20.6 (7.83)
Sampaio et al.[28]**(Rembrandt study)**	2011	2006	Pardoprunox	31	119	62.8 (9.91)	1.38 (1.68)	61.3	22.4 (9.43)
Hauser et al.[51]	1998	N/A	Tolcapone	4	41	63 (11)	1.1 (1.08)	73	15.5 (8.01)
Dupont et al.[52]	1997	N/A	Tolcapone	6	33	66 (8)	6.6 (3.87)	57.58	23.3 (11.68)

Myllyla et al.[53]	1997	N/A	Tolcapone	6	42	63 (9)	10.1 (4)	57	26.5 (10.8)
Baas et al.[54]	1997	N/A	Tolcapone	13	58	64 (8)	10.5 (5.5)	60	N/A
Rajput et al.[55]	1997	N/A	Tolcapone	13	66	65 (10)	10.5 (5.8)	71	N/A
Adler et al.[56]	1998	N/A	Tolcapone	6	72	64 (8)	10.6 (5.2)	72.22	N/A
Zhang et al.[57]	2013	N/A	Rasagiline	12	125	61.56 (9.5)	5.4 (2.24)	53.6	20.67 (6.83)
PSG[58]	2002	1997	Rasagiline	26	138	60.5 (10.8)	0.94 (1.1)	67.4	17.6 (8.8)
PSG[59]	2005	2000	Rasagiline	26	159	64.5 (9.9)	9.7 (4.9)	65.4	20.7 (10.3)
Rascol et al.[60]	2005	2001	Rasagiline	18	229	64.8 (8.8)	8.8 (4.8)	58	23.7 (13.4)
Olanow et al.[30]	2009	2005	Rasagiline	36	593	62.15 (N/A)	0.37 (N/A)	61.85	13.9 (N/A)
PSG[61]	1994	N/A	Lazabemide	4	32	68.5 (8.7)	4.19 (1.88)	68.8	18.9 (8.8)
PSG[62]	1993	N/A	Lazabemide	4	51	61.7 (11.5)	2.17 (1.51)	66.7	18.7 (7.5)
PSG[35]	1996	1992	Lazabemide	52	66	62.5 (10.8)	1.7 (1.4)	68.2	13.5 (7.5)
Fernandez et al.[63]	2010	2005	Istradefylline	12	82	63.7 (9.7)	1.3 (1.3)	57.3	19.4 (7.9)

LeWitt et al.[64]	2008	2002	Istradefylline	12	66	64 (10)	9.3 (5.1)	60.6	18 (11.2)
Hauser et al.[65]	2008	2004	Istradefylline	12	115	64 (10.2)	8.8 (4.4)	67	22.8 (11.2)
Pourcher et al.[66]	2012	2004	Istradefylline	12	154	63 (8.3)	9.1 (5.1)	64.2	22.7 (11.8)
Rascol et al.[67]	2012	2006	Perampanel	18	247	63.6 (8.82)	6.9 (N/A)	60	22.3 (N/A)
Lees et al.[29] **(study 302)**	2012	2006	Perampanel	20	250	62.2 (9.3)	8.3 (4.3)	66	19.7 (10.8)
Lees et al.[29] **(study 301)**	2012	2006	Perampanel	30	254	64.1 (9)	9.1 (5)	60	23 (11.4)
Hauser et al.[68]	2014	2009	Rasagiline	18	162	62.8 (10.1)	2.1 (1.9)	68.5	20.4 (10)

YSP indicates year of study publication; YSI, year of study initiation; SD, standard deviation; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; N/A, not available; PSG, Parkinson Study Group.

Placebo Effects

The pooled ES of change in the UPDRS part III from baseline to primary end point was -1.348 (95% CI [-2.134, -0.563], p = 0.001). ES of each study was presented in **Figure 2**. Significant heterogeneity across the studies was found in the meta-analysis (I^2=93.4%).Visual inspection of funnel plot (**Figure 3**) showed asymmetry and the Egger's test was significant (bias coefficient = -4.304, SE = 1.263, p = 0.002). Because the primary aim of our study is evaluation of predicting factors which influence the placebo effect, eligibility criteria were not focused on homogeneity of included studies and significant heterogeneity was anticipated.

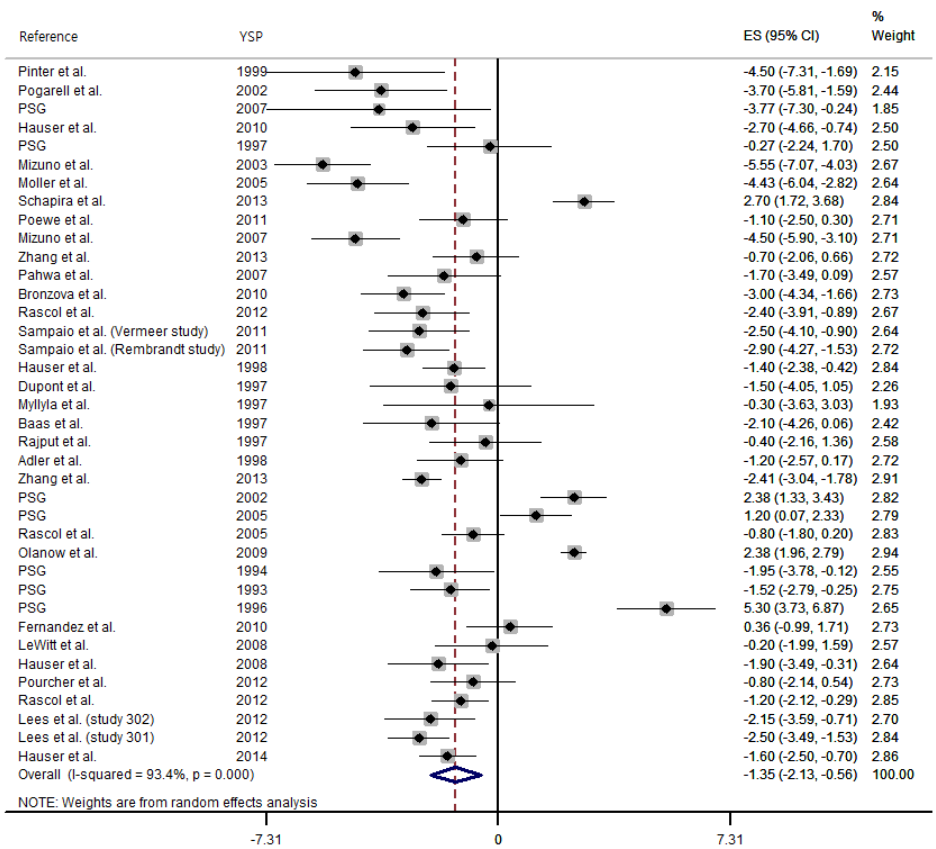


Figure 2. Placebo effect on the mean change of the UPDRS part III score from baseline to primary end point for each study

YSP indicates year of study publication; ES, effect size; CI, confidence interval; PSG, Parkinson Study Group; UPDRS, Unified Parkinson's Disease Rating Scale.

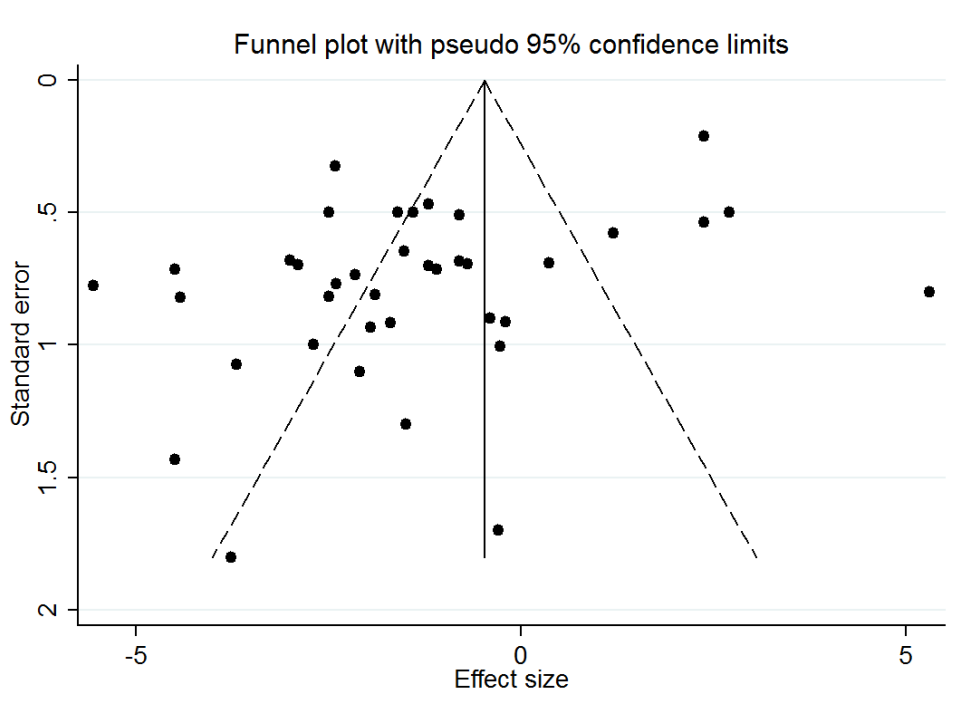


Figure 3. Funnel Plot of the Mean Change of the UPDRS Part III Score

Predictors of Placebo Effects

The univariate meta-regression analyses of predictors were presented in **Table 2.** Longer duration of treatment from baseline to primary end point predicted lower placebo effect, whereas use of concomitant levodopa and the higher baseline UPDRS part III score predicted higher placebo effect. The impacts of duration of treatment and the baseline UPDRS part III score were depicted in **Figure 4**. More recently published (YSP) or conducted (YSI) studies showed tendencies of higher placebo effect (**Figure 5**). However, time – placebo effect correlations were not statistically significant. Study completion rate, assign rate to placebo group, age, duration of PD, and male percentage did not predict the placebo effect.

Significant predictors were entered in the multivariate meta-regression analysis. Duration of treatment from baseline to primary end point (coefficient = 0.07, 95% CI [0.02, 0.13], p = 0.013) and the baseline UPDRS part III (coefficient = -0.29, 95% CI [-0.43, -0.15], p = 0.001) were statistically significant in the multivariate analysis, whereas use of concomitant levodopa was not significant (coefficient = 0.39, 95% CI [-1.01, 1.78], p = 0.880).

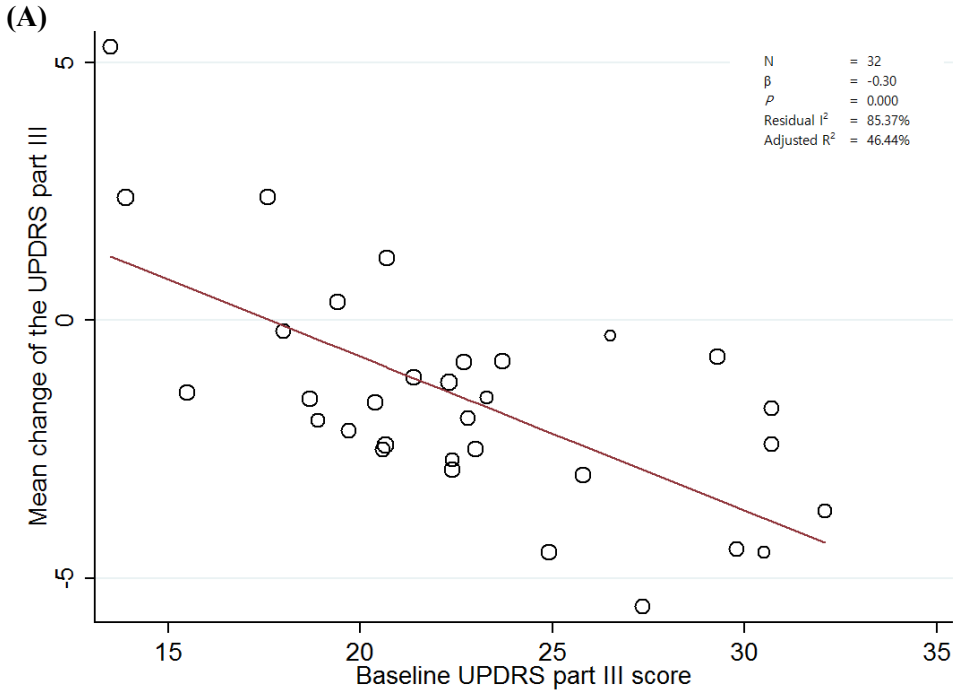
Table 2. Predictors of the mean change in the UPDRS part III score of participants on placebo from baseline to primary end point

Predictors	No. of studies	UPDRS part III score change	
		Univariate meta-regression	
		Coefficient (SE)	*p*-value
Characteristics of Study			
Duration of treatment from baseline to primary end point	38	0.09 (0.03)	**0.002**
Use of concomitant levodopa	38	-1.79 (0.69)	**0.013**
Assignment rate to placebo group	38	-0.04 (0.03)	0.238
YSP	38	-0.03 (0.06)	0.566
YSI	26	-0.17 (0.11)	0.120
Characteristics of Participants			
Initial UPDRS part III score	32	-0.30 (0.06)	**<0.001**
Age	38	-0.24 (0.21)	0.265

Mean duration of PD	37	-0.14 (0.10)	0.175
Male percentage	37	0.04 (0.05)	0.479
Study completion rate	37	-4.69 (2.54)	0.074

YSP indicates year of study publication; YSI, year of study initiation; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; SE, standard error.

(A)


N = 32
β = -0.30
P = 0.000
Residual I² = 85.37%
Adjusted R² = 46.44%
Mean change of the UPDRS part III
5
0
-5
15
20
25
30
35
Baseline UPDRS part III score

(B)

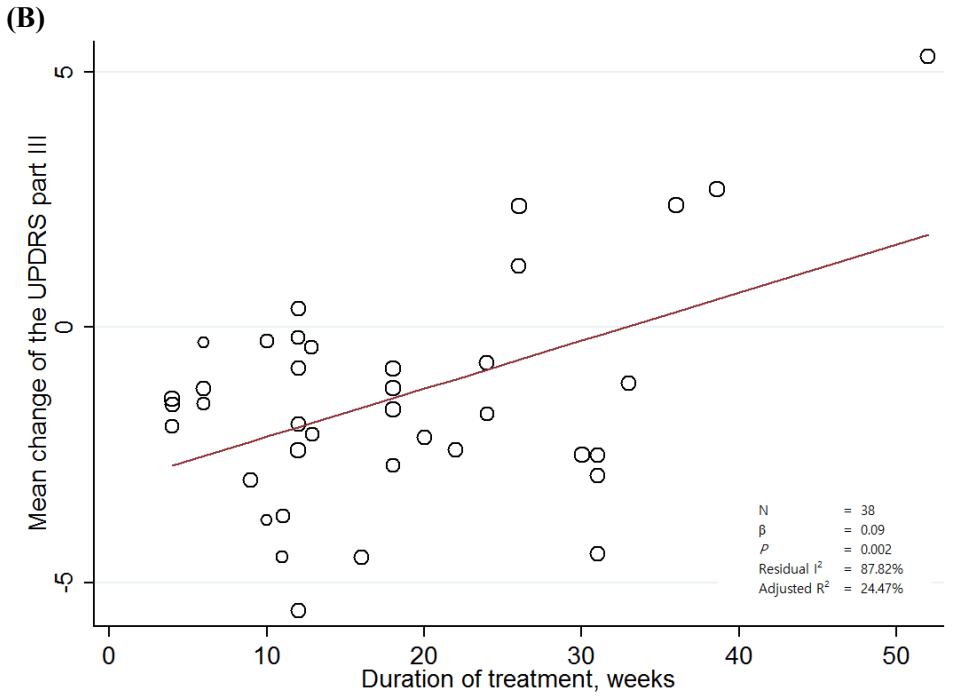
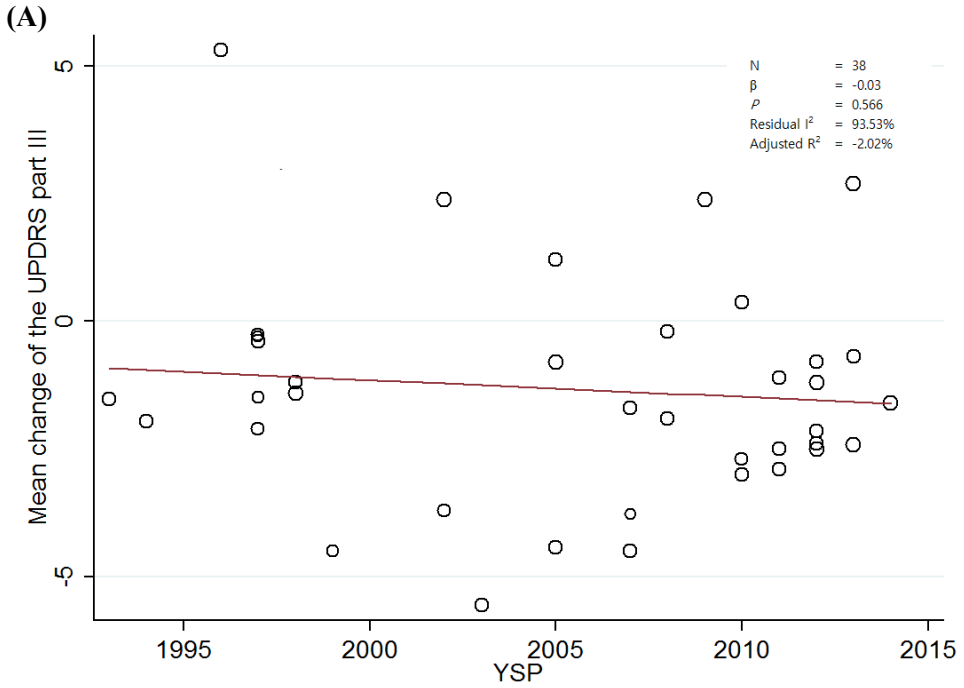

N = 38
β = 0.09
P = 0.002
Residual I² = 87.82%
Adjusted R² = 24.47%
Mean change of the UPDRS part III
5
0
-5
0
10
20
30
40
50
Duration of treatment, weeks

Figure 4. The impacts of duration of treatment and the baseline UPDRS part III score on placebo effect

(A) Relationship between duration of treatment and the change of the UPDRS part III score from baseline to primary end point. (B) Relationship between the baseline UPDRS part III score and the change of the UPDRS part III score from baseline to primary end point. UPDRS indicates Unified Parkinson's Disease Rating Scale; N, number of studies; β, coefficient of the meta-regression model; Residual I^2, percentage of the residual variation that is attributable to between-study heterogeneity; Adjusted R^2, the proportion of between-study variance explained by the predicting factor.

(A)


N = 38
β = -0.03
P = 0.566
Residual I² = 93.53%
Adjusted R² = -2.02%
Mean change of the UPDRS part III
5
0
-5
1995
2000
2005
2010
2015
YSP

(B)

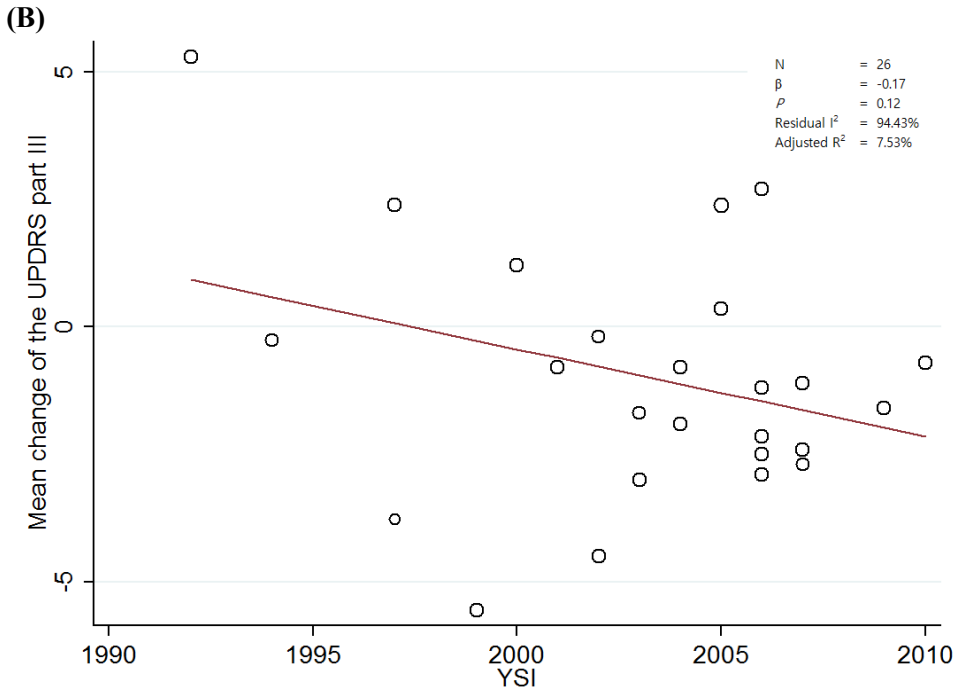

N = 26
β = -0.17
P = 0.12
Residual I² = 94.43%
Adjusted R² = 7.53%
Mean change of the UPDRS part III
5
0
-5
1990
1995
2000
2005
2010
YSI

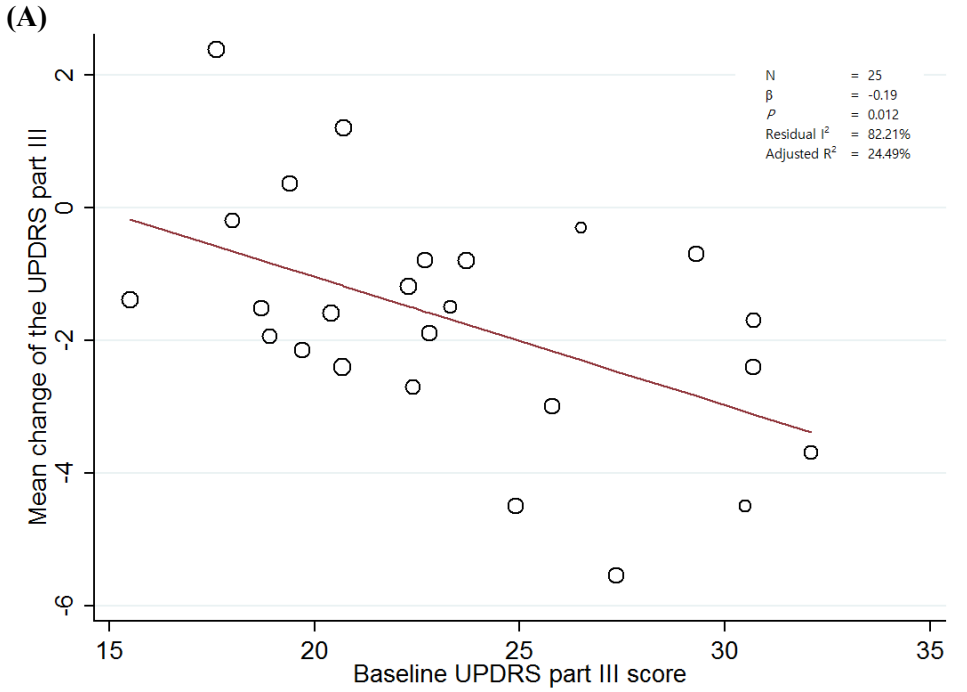
Figure 5. Time – placebo effect correlations on the mean change of the UPDRS part III from baseline to primary end point

More recently published (A) or conducted (B) studies showed tendencies of higher placebo effect. However, time – placebo effect correlations were not statistically significant. YSP indicates year of study publication; YSI, year of study initiation; UPDRS, Unified Parkinson's Disease Rating Scale; N, number of studies; β, coefficient of the meta-regression model; Residual I^2, percentage of the residual variation that is attributable to between-study heterogeneity; Adjusted R^2, the proportion of between-study variance explained by the predicting factor.

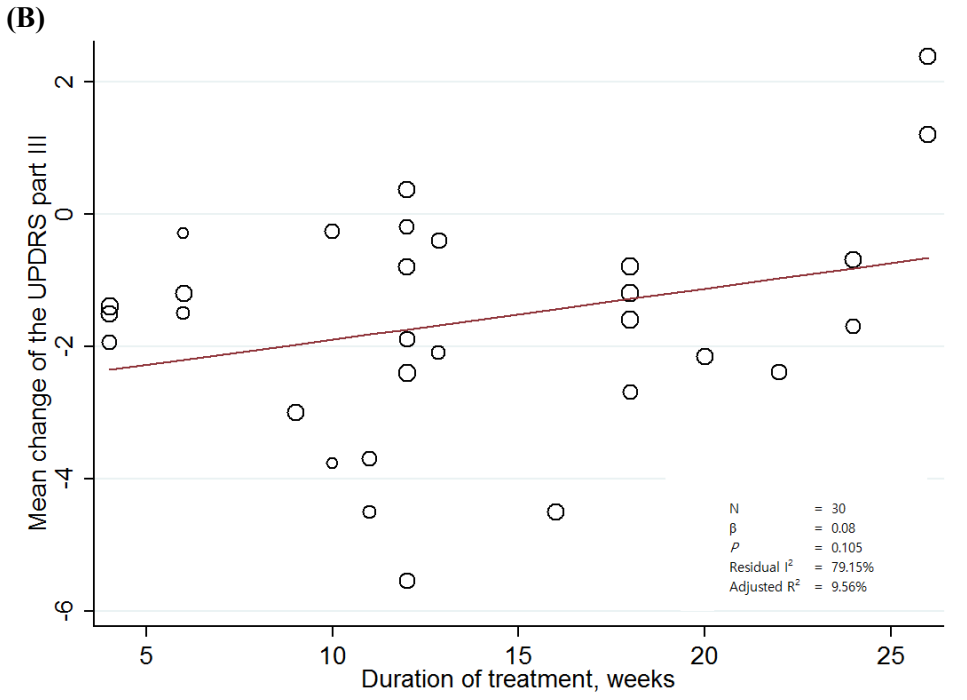
Exploratory Analysis

Eight studies [28-30,32-35] were excluded by limited duration (28 weeks) of treatment from baseline to primary end point. Of 2 studies in the article of Lees et al.[29], only study 302 (20 weeks) was included, but study 301 (30 weeks) was excluded in the exploratory analysis. The pooled ES of change in the UPDRS part III from baseline to primary end point was -1.591 (95% CI [-2.201, -0.981], $p < 0.001$, $I^2 = 82.3\%$). In the univariate meta-regression analyses, only the baseline UPDRS part III score predicted placebo effect with statistical significance (coefficient = -0.19, $p = 0.012$, **Figure 6**).

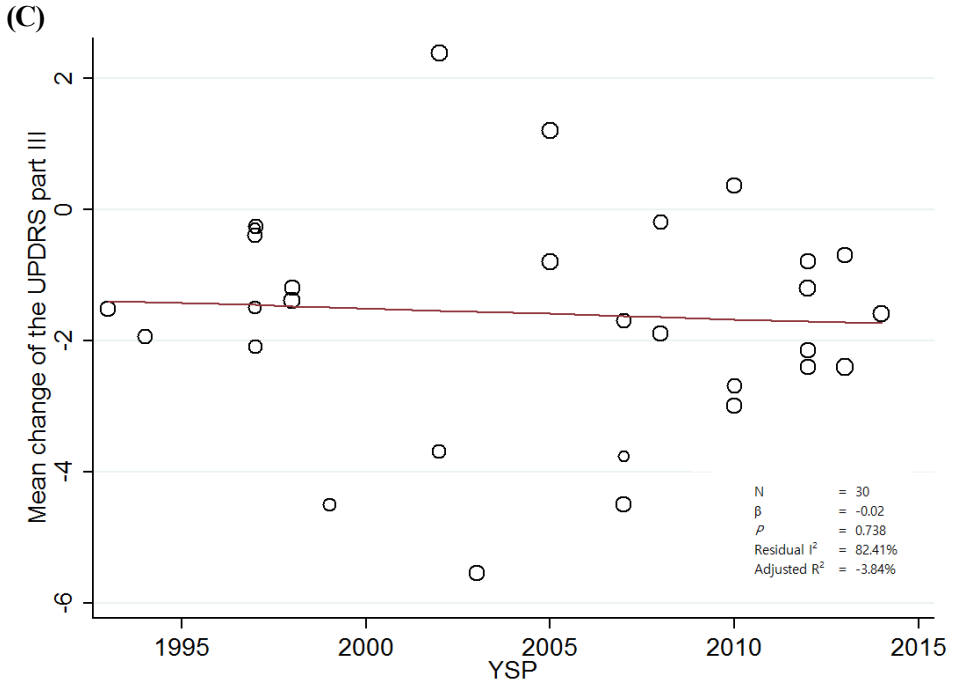
(A)


N = 25
β = -0.19
P = 0.012
Residual I² = 82.21%
Adjusted R² = 24.49%
Mean change of the UPDRS part III
2
0
-2
-4
-6
15
20
25
30
35
Baseline UPDRS part III score

(B)


N = 30
β = 0.08
P = 0.105
Residual I² = 79.15%
Adjusted R² = 9.56%
Mean change of the UPDRS part III
2
0
-2
-4
-6
5
10
15
20
25
Duration of treatment, weeks

(C)


Mean change of the UPDRS part III
2
0
-2
-4
-6
1995
2000
2005
2010
2015
YSP
N = 30
β = -0.02
P = 0.738
Residual I² = 82.41%
Adjusted R² = -3.84%

(D)

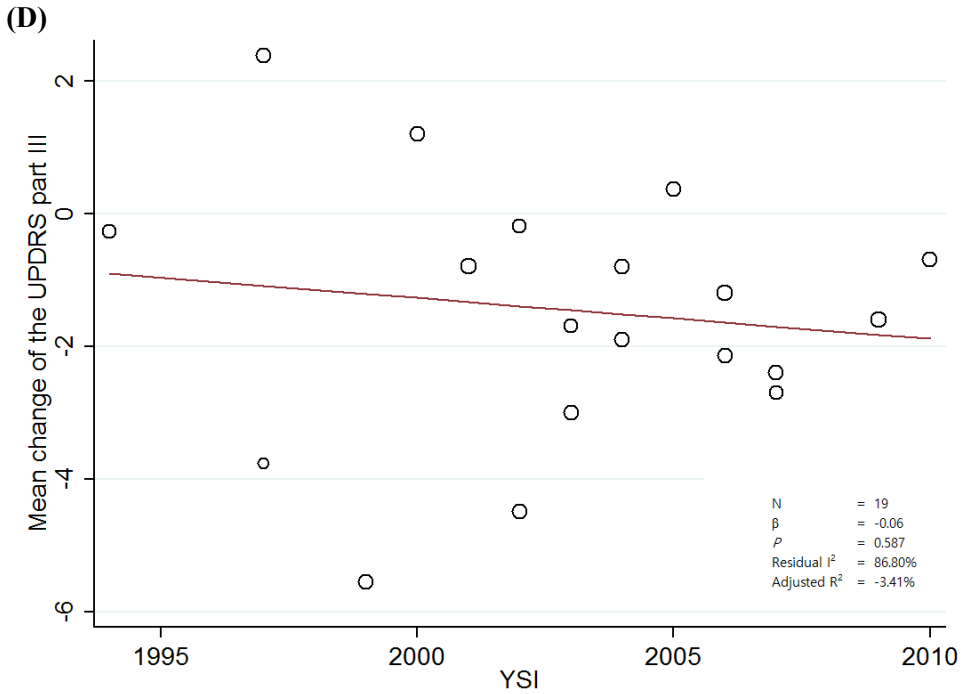

Mean change of the UPDRS part III
2
0
-2
-4
-6
1995
2000
2005
2010
YSI
N = 19
β = -0.06
P = 0.587
Residual I² = 86.80%
Adjusted R² = -3.41%

Figure 6. Meta-regression Analyses in the Exploratory Analysis with Limited Duration of Treatment (≤28weeks)

(A) Relationship between the baseline UPDRS part III score and the change of the UPDRS part III score from baseline to primary end point (coefficient = -0.19, p = 0.012, N = 25). (B) Relationship between duration of treatment and the change of the UPDRS part III score from baseline to primary end point (coefficient = 0.08, p = 0.105, N = 30). (C) Relationship between YSP and the change of the UPDRS part III score from baseline to primary end point (coefficient = -0.02, p = 0.738, N = 30). (D) Relationship between YSI and the change of the UPDRS part III score from baseline to primary end point (coefficient = -0.06, p = 0.587, N = 19). YSP indicates year of study publication; YSI, year of study initiation; UPDRS, Unified Parkinson's Disease Rating Scale; N, number of studies; β, coefficient of the meta-regression model; Residual I^2, percentage of the residual variation that is attributable to between-study heterogeneity; Adjusted R^2, the proportion of between-study variance explained by the predicting factor.

DISCUSSION

In this meta-analysis, significant predictors of the placebo effect in PD were duration of treatment from baseline to primary end point and the baseline UPDRS part III score. Longer duration of treatment predicted lower placebo effect, and the higher baseline UPDRS part III score predicted higher placebo effect. We confirmed these predictors were significant in the multivariate meta-regression model excluding the possibility of confounding effect. We believe that this study is the first meta-analysis using meta-regression models to discriminate predictive factors of placebo effect in PD.

Duration of treatment was one of our major concerns of the meta-analysis design because natural aggravation of PD could lessen the placebo effect. Annual progression rate of PD measured by the UPDRS part III score has been reported from 1.5 (1.5%) to 3.3 (3.1%) points.[36,37] In our study, annual progression rate in the UPDRS part III score calculated with the coefficient of duration of treatment were 4.90 points in the univariate meta-regression model and 3.81 points in the multivariate model. Higher progression rate in our meta-analysis compared with natural progression rate of PD suggests that long duration of treatment would weaken the placebo effect. This finding is in contrast with previous studies[6-8] which reported stationary rates of positive placebo response at early, mid, and late stages of follow up. Two reasons can explain this result. First, previous studies used individual

data of participants in placebo group and strict definition of positive placebo response (≥50% improvement in total UPDRS part III score or ≤2 points reduction on at least two UPDRS part III items)[6-8]. Although the proportion of significantly improved individuals in placebo group are not changed, the group response to placebo may be weakened by long duration of treatment. Second, the longest duration of treatment of previous studies was 23 to 35 weeks[8]. The calculated duration of treatment when the change in the UPDRS part III was zero in the meta-regression model was 32.8 weeks. Moreover, the predictability of duration of treatment was insignificant in our exploratory analysis although negative tendency still existed (**Figure 6**). Placebo effect might influence individuals consistently till 35 weeks and disappear by recognition of objective aggravation of PD signs. Further studies with individual data in more than 35 weeks of treatment duration will be needed to confirm this scenario. Interestingly, shorter duration of treatment (≤ 12 weeks) was correlated with higher lessebo effect (decreasing medication effect because of negative expectation to be assigned in a placebo group) in the active treatment group in the recent meta-analysis[38]. Investigators should remind that both lessebo effect and placebo effect could be prominent in short-lasting clinical trials.

Our meta-analysis reaffirmed the results of previous studies that the higher baseline UPDRS part III score predicted higher placebo effect[6,8]. Consistent results in the multivariate meta-regression model and the exploratory analysis increased the power of its predictability. Neuroimaging studies have supported physiologic mechanism of this phenomenon. Placebo induced

changes in RAC binding potential tended to be greater in the contralateral striatum of the more affected body side[9,10]. Because placebo effect is a complex psychobiological phenomenon, the definition of placebo effect encompasses various confounding factors such as spontaneous remission, regression to the mean, and judgment errors[2]. The large number of participants on placebo in our meta-analysis assured that the objective change in the UPDRS part III in patients on placebo was not the result of confounding factors, but well performed observations.

The use of concomitant levodopa in the study predicted placebo effect significantly in the univariate meta-regression model, but not in the multivariate model. Studies evaluating the adjunct therapeutic efficacy of anti-parkinsonian medications enroll more advanced patients than studies evaluating monotherapy. In our meta-analysis, studies using concomitant levodopa had higher baseline UPDRS part III scores (mean 24.9 vs 19.0). Several characteristics are closely related to severity of PD such as duration of PD, presence of motor fluctuation, use of concomitant levodopa, and baseline UPDRS scores. It is not surprising that the predictability of use of concomitant levodopa was not significant in the multivariate meta-regression model.

In 2011, the randomized double-blind placebo-controlled trial that evaluated efficacy of rasagiline was conducted in Korean population. Although efficacy of rasagiline in PD had been already evident, the study failed to show positive results mainly due to the increased placebo effect compared with

previous studies. We interpreted this result as growing confidence and expectation of participants over time could explain this temporal increase in placebo effect. To confirm it, we evaluated time – placebo effect correlations advertently in this meta-analysis. The tendency to higher placebo effect was observed in more recently conducted studies. The tendency was more prominent in YSI than YSP (**Figure 5**). Mean and standard deviation of difference between YSI and YSP were 5.12 ± 1.61 years with the range of 3 to 10 years. Presence of various duration for publication after conduction of the study indicates that YSI is a more appropriate time variable than YSP for evaluation of time – placebo effect correlation. However, no statistical significances were found between time variables and placebo effects. Several reasons can be attributed to this negative results. First, PD is a neurodegenerative movement disorder unlikely to depression. The magnitude of improvement is limited by the pathologic changes of brain. Therefore, the small size of placebo effect could contribute to the lack of statistical significance. Second, predictability of the change in the UPDRS part III was governed by other potent predictors such as duration of treatment and the baseline UPDRS part III score. The correlations of time variables could be tempered by these predictors. Because placebo effect disappeared in studies with long duration of treatment, time – placebo effect correlations in our exploratory analysis would reflect the real change more properly than in whole group. However, tendencies were not significant and even decreased (**Figure 6**). Finally, the small number of included studies could result in paucity of statistical power in our meta-analysis. We intensively searched registries of clinical trials, contacted corresponding

authors, and requested the pharmaceutical companies for acquisition of missing data. However, data of YSI were available in only 26 studies.

Previous studies showed controversial results about the predictability of assignment rate to placebo group[8,11,38]. In our meta-analysis, different assignment rates (50%, 33.3%, 25%, 20%) did not predict the size of placebo effect. Dichotomized comparison (50% vs <50%) showed the similar negative result (coefficient = 0.057, p = 0.446). A study of the impact of placebo assignment in studies in PD revealed that only half of the subjects accurately identified the placebo:active drug ratio assignment of their study[39]. The size of expectation of participants would be not influenced by the assign rate because of inattention of participants. This negative finding is supported by the result of the meta-analysis on lessebo effect in PD[38]. However, one study using individual data of participants on placebo reported that higher assignment rate to placebo group was correlated with higher positive placebo response rate[8]. In contrast, another study using RAC PET showed that significant clinical improvement and dopamine release occurred when the declared probability of receiving active medication was 75%[11]. More studies using both group and individual data of patients on placebo are necessary to conclude this controversial issue.

Study completion rate was not a significant predictor in our meta-analysis. However, higher completion rate showed a tendency to higher placebo effect. It was similar to the result of the meta-analysis in depression which showed higher completion rates predicted smaller drug-placebo differences[20].

Higher completion rate in participants on placebo could reflect higher responsiveness to placebo because the primary reason for early termination of participants in placebo group is inadequate improvement. We expect that study completion rate could be a possible predictor in the future meta-analyses on placebo effect in PD.

Our meta-analysis has some limitations. First, large number of studies were excluded because of inadequate data, which would have given us more valuable information about predictors and time − placebo effect correlations in PD. Furthermore, several characteristics which might influence placebo effect were not evaluated in this meta-analysis. Characteristics of environment, investigators, and investigator-patient interaction have not recorded systematically in RCTs[69]. Although we used multivariate meta-regression analysis to reduce confounding effect, risk of presence of unknown factors that could influence the result of this study still exists.

CONCLUSION

This meta-analysis suggests that duration of treatment and the baseline UPDRS part III score are the independent predictive factors of the magnitude of placebo effect in RCTs in PD. The temporal pattern of placebo effect showed a tendency to increase placebo effect over time. Our study implicates that researchers should remind the presence of placebo effect when they design or interpret clinical trials in PD, especially in the short-lasting study enrolled participants with advanced PD. Further studies with data of drug – placebo differences are needed to confirm the influence of placebo effect to clinical trials in PD.

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APPENDICES

Appendix 1. Search Strategies for Each Database

MEDLINE

(piribedil OR pramipexole OR ropinirole OR rotigotine OR dihydroergocryptine OR lisuride OR pergolide OR dopamine agonist OR levodopa OR l-dopa OR entacapone OR tolcapone OR catechol-o-methyltransferase inhibitor OR comt inhibitor OR selegiline OR rasagiline OR monoamine oxidase-b inhibitor OR mao-b inhibitor OR benztropine OR trihexyphenidyl OR anticholinergics OR amantadine OR clozapine OR zonisamide) AND (parkinson OR parkinson's) AND (Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp]))

EMBASE

ID	Search
1	'piribedil'/exp OR piribedil
2	‘pramipexole'/exp OR pramipexole
3	‘ropinirole'/exp OR ropinirole
4	‘rotigotine'/exp OR rotigotine

5	‘dihydroergocryptine'/exp OR dihydroergocryptine
6	‘lisuride'/exp OR lisuride
7	‘pergolide'/exp OR pergolide
8	‘dopamine agonist'/exp OR dopamine AND agonist
9	‘levodopa'/exp OR 'l dopa'/exp OR levodopa OR 'l dopa'
10	‘entacapone'/exp OR entacapone
11	‘tolcapone'/exp OR tolcapone
12	‘catechol o methyltransferase inhibitor'/exp OR 'comt inhibitor'/exp OR 'catechol o methyltransferase' AND inhibitor OR comt AND inhibitor
13	‘selegiline'/exp OR selegiline
14	‘rasagiline'/exp OR rasagiline
15	‘monoamine oxidase b inhibitor'/exp OR 'mao b inhibitor'/exp OR monoamine AND 'oxidase b' AND inhibitor OR 'mao b' AND inhibitor
16	‘benztropine'/exp OR benztropine
17	‘trihexyphenidyl'/exp OR trihexyphenidyl
18	‘anticholinergics'/exp OR anticholinergics
19	‘amantadine'/exp OR amantadine
20	‘clozapine'/exp OR clozapine
21	‘zonisamide'/exp OR zonisamide
22	‘parkinson disease'/exp OR parkinson

23	‘randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomised controlled trial'/exp OR 'randomised'
24	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
25	#10 or #11 or #12
26	#13 or #14 or #15
27	#16 or #17 or #18
28	#9 or #19 or #20 or #21 or #24 or #25 or #26 or #27
29	#22 AND #23 AND #28

Cochrane Central Register of Controlled Trials (CENTRAL)

ID	Search
#1	piribedil
#2	pramipexole
#3	ropinirole
#4	rotigotine
#5	dihydroergocryptine
#6	lisuride
#7	pergolide
#8	dopamine agonist
#9	levodopa or l-dopa

#10	entacapone
#11	tolcapone
#12	catechol o methyltransferase inhibitor or comt inhibitor or comt or catechol o methyltransferase
#13	selegiline
#14	rasagiline
#15	monoamine oxidase b inhibitor or maob inhibitor or monoamine oxidase or maob
#16	benztropine
#17	trihexyphenidyl
#18	anticholinergics
#19	amantadine
#20	clozapine
#21	zonisamide
#22	parkinson disease or parkinson or parkinson's
#23	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#24	#10 or #11 or #12
#25	#13 or #14 or #15
#26	#16 or #17 or #18
#27	#9 or #19 or #20 or #21 or #23 or #24 or #25 or #26
#28	#22 and #27

Appendix 2. Table of Risk of Bias Assessment

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Addler et al., 1998[56]	low	low	low	low	low	low
Baas et al., 1997[54]	unclear	unclear	low	low	low	low
Bronzova et al., 2010[49]	low	low	low	low	low	low
Dupont et al., 1997[52]	unclear	low	low	low	low	low
Fernandez et al., 2010[63]	low	low	low	low	low	low
Hauser et al., 1998[51]	unclear	low	low	low	low	low
Hauser et al., 2008[65]	low	low	low	low	low	low
Hauser et al., 2010[43]	low	low	low	low	low	low
Hauser et al., 2014[68]	low	low	low	low	low	low
Lee et al., 2012[29]	unclear	unclear	low	low	low	low

(Study 301)						
Lee et al., 2012[29] (Study 302)	unclear	unclear	low	low	low	low
LeWitt et al., 2008[64]	low	low	low	low	low	low
Mizuno et al., 2003[45]	low	unclear	low	low	low	low
Mizuno et al., 2007[46]	unclear	unclear	low	low	low	low
Moller et al., 2005[34]	unclear	unclear	low	low	low	low
Myllyla et al., 1997[53]	unclear	low	low	low	low	low
Olanow et al., 2009[30]	low	low	low	low	low	low
Pahwa et al., 2007[48]	low	low	low	low	low	low
Pinter et al., 1999[40]	unclear	unclear	low	low	low	low
Poewe et al., 2011[33]	low	low	low	low	low	low
Pogarell et al., 2002[41]	low	low	low	low	low	low
Pourcher et al., 2012[66]	low	unclear	low	low	low	low
Parkinson Study Group 1993[62]	unclear	unclear	low	low	low	low
Parkinson Study Group 1994[61]	unclear	unclear	low	low	low	low

Parkinson Study Group 1996[35]	unclear	unclear	low	low	low	low
Parkinson Study Group 1997[44]	low	unclear	low	low	low	low
Parkinson Study Group 2002[58]	unclear	unclear	low	low	low	low
Parkinson Study Group 2005[59]	low	unclear	low	low	low	low
Parkinson Study Group 2007[42]	low	low	low	low	low	low
Rajput et al., 1997[55]	unclear	unclear	low	low	low	low
Rascol et al., 2005[60]	low	low	low	low	low	low
Rascol et al., 2012[67]	unclear	unclear	low	low	low	low
Rascol et al., 2012[50]	low	low	low	low	low	low
Sampaio et al., 2011[28] **(Rambrandt study)**	low	low	low	low	low	low
Sampaio et al., 2011[28] **(Vermeer study)**	low	low	low	low	low	low
Schapira et al., 2013[32]	low	low	low	low	low	low
Zhang et al., 2013[57]	low	low	low	low	low	high
Zhang et al., 2013[47]	unclear	unclear	low	low	low	low

국문 초록

배경: 파킨슨병에서 위약 효과와 관련하여 지금까지 몇몇 인자들이 연관이 있다고 알려져 왔다. 또한 파킨슨병에서 노세보 효과(nocebo effect)에 대한 메타분석에서 연구 발표 년도와 노세보 효과 간의 상관 관계가 확인되었다. 하지만 지금까지 파킨슨병에서 위약 효과와 연관이 있는 예측 인자에 대하여 체계적인 메타분석적인 방법으로 접근을 한 연구는 없었다.

목적: 이 연구에서는 파킨슨병의 무작위배정, 이중맹검, 위약대조 임상시험에서 연구 발표 년도와 연구 시작 년도를 비롯한 예측 인자들와 위약 효과 간의 연관성을 조사하고자 한다.

자료출처: 2014년 11월까지 발표된 PUBMED, EMBASE 및 the Cochrane Central Register of Controlled Trials (CENTRAL)의 데이터베이스와 www.ClinitcalTrials.gov 사이트에 등록된 임상 시험들 목록, 최종 메타분석에 참여한 연구들의 참고문헌 목록을 검색하였다.

연구선택: 대상이 되는 연구들은 파킨슨병에서 실시한 4주 이상 1년 이내의 치료 기간을 가지는 무작위배정, 이중맹검, 위약대조 임상시험들 중에 통합파킨슨병평가척도 3번째 부분 (Unified Parkinson's Disease Rating Scale part III motor subscale)의 평균 변화를 결과로 보고한 연구들이었다.

자료추출과 통합: 두 명의 연구자가 독립적으로 연구들의 특성, 위약군의 환자들의 특성과 결과들을 추출하였다. 개별 연구들의 위약군에서 연구 시작부터 종료 시점 간의 평균 통합파킨슨병평가척도 3번째 부분 점수 차이 결과들은 무작위 영향 모델을 사용하여 메타분석을 실시하여 통합하였다. 예측 인자들의 결과와의 연관성은 선형 메타-회귀 분석을 실시하여 분석하였다. 선형 메타-회귀 분석에서 유의미한 예측 인자들은 다변량 선형 메타-회귀 모델에 넣어 분석하였다.

결과: 메타분석은 4,850명의 위약군 환자들로 구성된 총 38개의 연구들로 진행하였다. 합쳐진 평균 통합파킨슨병평가척도 3번째 부분 점수 차이는 −1.348 (95% 신뢰구간 [-2.134, -0.563], p = 0.001, I^2 = 93.4%)이었다. 치료 기간 (β = 0.09, p = 0.002, N [분석한 연구 숫자] = 38), 부수적인 레보도파 사용 (β = -1.79, p = 0.013, N = 38)과 연구 시작 시 통합파킨슨병평가척도 3번째 부분 점수 (β = -0.30, p < 0.001, N = 32)가 단변량 메타-회귀 분석에서 유의미하였다. 더 최근에 발표하였거나 (β = -0.03, p = 0.566, N = 38) 시행한 연구들은 (β = -0.17, p = 0.120, N = 26) 위약 효과를 늘리는 경향이 있었으나 통계적으로 유의미하진 않았다. 다변량 메타-회귀 분석에서 치료 기간 (β = 0.07, p = 0.013)과 연구 시작 시 통합파킨슨병평가척도 3번째 부분 점수 (β = -0.29, p = 0.001)가 통계적으로 유의미하였다.

결론: 치료 기간과 통합파킨슨병평가척도 3번째 부분 점수는 파킨슨병에서 실시하는 무작위 배정 비교 임상시험에서 위약 효과의 정도를 예측할 수 있는 독립적인 예측 인자들이다. 파킨슨병에서 임상 시험을 계획하거나 분석하는 연구자들은 특히 진행한 파킨슨병 환자들을 대상으로 한 짧

은 기간의 임상 시험일 때 위약 효과가 크게 나타날 수 있음을 염두에 두어야 할 것이다.

주요어: 파킨슨병, 위약 효과, 예측 인자, 메타분석, 무작위 배정 비교 임상시험

학 번: 2010-21857