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Placebo Influences on Dyskinesia in Parkinson's Disease

Christopher G. Goetz, MD^{1,*}, Eugene Laska, PhD^{2,3}, Christine Hicking, Dipl Stat⁴, Philippe Damier, MD, PhD⁵, Thomas Müller, MD⁶, John Nutt, MD⁷, C. Warren Olanow, MD⁸, Olivier Rascol, MD, PhD⁹, and Hermann Russ, MD, PhD⁴

¹Rush University Medical Center, Chicago, Illinois, USA

²New York University School of Medicine, New York, New York, USA

³Nathan Kline Institute, Orangeburg, New York, USA

⁴Merck KGaA, Darmstadt, Germany

⁵Centre Hospitalo-universitaire de Nantes, Centre d'Investigation Clinique, Nantes, France

⁶Ruhr University, Bochum, Germany

⁷Oregon Health Sciences University, Portland, Oregon, USA

⁸Mount Sinai School of Medicine New York, New York, USA

⁹Toulouse University Hospital, INSERM Clinical Investigation Center, Toulouse, France

Abstract

Clinical features that are prognostic indicators of placebo response among dyskinetic Parkinson's disease patients were determined. Placebo-associated improvements occur in Parkinsonism, but responses in dyskinesia have not been studied. Placebo data from two multicenter studies with identical design comparing sarizotan to placebo for treating dyskinesia were accessed. Sarizotan (2 mg/day) failed to improve dyskinesia compared with placebo, but both treatments improved dyskinesia compared with baseline. Stepwise regression identified baseline characteristics that influenced dyskinesia response to placebo, and these factors were entered into a logistic regression model to quantify their influence on placebo-related dyskinesia improvements and worsening. Because placebo-associated improvements in Parkinsonism have been attributed to heightened dopaminergic activity, we also examined the association between changes in Parkinsonism and dyskinesia. Four hundred eighty-four subjects received placebo treatment; 178 met criteria for placebo-associated dyskinesia improvement and 37 for dyskinesia worsening. Older age, lower baseline Parkinsonism score, and lower total daily levodopa doses were associated with placebo-associated improvement, whereas lower baseline dyskinesia score was associated with placebo-associated worsening. Placebo-associated dyskinesia changes were not correlated with Parkinsonism changes, and all effects in the sarizotan group were statistically explained by the placebo-effect regression model. Dyskinesias are affected by placebo treatment. The absence of correlation between placebo-induced changes in dyskinesia and Parkinsonism argues against a dopaminergic activation mechanism to explain placebo-associated improvements in dyskinesia. The magnitude and variance of placebo-related changes and the factors that influence them can be helpful in the design of future clinical trials of antidyskinetic agents.

Keywords

Parkinson's disease; placebo; dyskinesias; sarizotan; randomized clinical trials

Placebo-associated improvements are characteristic of several neurological diseases, but particularly prominent in Parkinson's disease (PD).¹ Using a strict definition of placebo-associated improvement based on objective changes in the Unified Parkinson's Disease Rating Scale (UPDRS) motor scale, investigators have documented placebo response rates averaging ~17% across multiple studies.²⁻⁴ Placebo-related improvements in Parkinsonism have been postulated to relate, at least in part, to heightened dopaminergic activity in pathways influenced by anticipation, novelty response, and motivation.^{5,6} Neuroimaging studies and direct intraoperative cellular recordings demonstrate objective evidence of enhanced dopaminergic activity during placebo treatment among PD patients in the context of anticipated clinical benefit in Parkinsonism.^{7,8} No large study has examined outcomes in dyskinesia with placebo treatment, and how these relate to changes in measures of Parkinsonism. If enhanced dopamine release occurs in response to participation in a clinical trial, then regardless of the targeted outcome, placebo treatment should produce improved PD symptoms, but also potentially exacerbate hyperdopaminergic behaviors such as dyskinesia.⁹ On the other hand, if expectation or anticipation of improvement targeted to the clinical trial-specific endpoint is the driver of placebo response and primary increases in dopamine activity does not occur or occurs to a limited extent, then patients should experience improved dyskinesia uncorrelated to their change in PD symptoms.

Two large-scale placebo controlled clinical trials of a putative antidyskinetic treatment studied sarizotan, a 5HT_{1A} agonist with high affinity for D₃, D₄, and to a lesser extent, D₂ receptors.^{10,11} These studies failed to show sarizotan-related improvement in dyskinesia in comparison with placebo, although both treatment groups had improved dyskinesia compared with baseline. At a dose of 2 mg/day, sarizotan is not likely to be studied further as an antidyskinetic agent, but data from the placebo-treated groups in these clinical trials offer the opportunity to examine issues related to placebo treatment: first, the rate of placebo response and the demographic/clinical characteristics of patients whose dyskinesia improved or worsened on placebo treatment; second, the relationship between placebo-related changes in dyskinesia and placebo-related changes in Parkinsonism; and third, the degree to which the characteristics predictive of placebo response were predictive of sarizotan response. An analysis of placebo-related issues provides information that can be incorporated into study design, patient recruitment profiles, and power/sample size calculations for future studies.

This analysis tested four hypotheses: first, that baseline demographic/clinical features are predictive of placebo-induced improvements in dyskinesia and differ from those predictive of placebo-induced worsening; second, that placebo-induced changes in dyskinesia and changes in Parkinsonism are not correlated, refuting the simple dopaminergic overactivity concept as an explanation for placebo-related improvements in Parkinsonism; third, that adverse effects experienced during placebo treatment influence response; and finally, that dyskinesia effects in the sarizotan-treatment group could be adequately explained by placebo-related changes.

PATIENTS AND METHODS

Overview

The placebo data from two multicenter placebo-controlled trials of sarizotan involving the same study design were accessed (Paddy-1, Paddy-2).^{10,11} In these studies, PD patients with dyskinesia, having a minimal entry dyskinesia score of >2 on both UPDRS items 32 and 33 [dyskinesia of at least moderate severity (item 33) present for at least 25% of the waking day

(item 32)] were randomly assigned to sarizotan 2 mg/day or an identical placebo and followed without changes in other medications. The master Subject Information Sheet provided by the sponsor for translation and adaptation at each site disclosed that sarizotan was being tested for its safety and efficacy for dyskinesia treatment among PD patients. In that document, aggravation of Parkinsonism was identified as the most frequently reported adverse effect from prior experience, although in placebo-controlled trials no difference was detected in comparison to placebo. Prior to randomization, the protocol included a 4-week single-blind placebo phase specifically designed to exclude placebo responders who improved on placebo, based on home diaries, to the point of having less than 4 hours of ON time with dyskinesia daily on two occasions. The primary outcome in the original studies was improvement of >25% in the composite score of UPDRS items 32 + 33 at 12 weeks. To be consistent with the primary outcome for the efficacy study, in this analysis, improvement by >25% over baseline was termed placebo-associated improvement; in parallel, worsening by >25% over baseline on the same measure was termed placebo-associated worsening. Including placebo-associated worsening of dyskinesia in the analysis was important for testing the “placebo-induced dopaminergic activation” concept in Parkinsonism, because this mechanism would predict that such an activation would aggravate dyskinesia.¹² The UPDRS-based ratings of dyskinesia considered all forms of dyskinesia together and did not distinguish between peak-dose and diphasic forms.

Analytic/Statistical Methods

Factors Predictive of Placebo-Associated Improvement and Worsening of Dyskinesia—Using stepwise regression methods, we obtained a linear model for predicting dyskinesia response to placebo based on pretreatment values. The baseline variables considered were gender, age, PD, and dyskinesia durations, severity of PD (UPDRS Part III motor examination score in ON phase), severity of dyskinesia (combined UPDRS items 32 + 33), baseline levodopa (L-dopa) dose as well as geographical site of enrollment, and a study identifier (Paddy I or Paddy 2). Items were entered stepwise in the order that maximally increased the percent of variance explained at each step. The stepwise process for identifying explanatory variables ended when the statistical test of the hypothesis that the regression coefficient of a new candidate was zero was not rejected ($P \geq 0.15$). Otherwise, a new variable was entered, and the regression model was refit. All of the resulting items identified in the stepwise regression as being placebo treatment were utilized as explanatory variables in two logistic regression models to identify factors selectively associated with placebo-related improvement or worsening of 25% or more in the dyskinesia score. To test whether the presence and severity of adverse events were associated with placebo responses, whether improvement or worsening, a similar stepwise regression analysis, followed by logistic regression procedures, was performed. We identified the adverse events that occurred in 3% or more of placebo-treated subjects in at least one of the studies. In the stepwise regression model, we utilized binary variables which of these adverse events a subject experienced. Also, we included in the model a total adverse events severity score, defined as the sum of the individual adverse event severity scores, quantified in the original studies as “not present” = 0, “mild” = 1, “moderate” = 2, and “severe” = 3. As mentioned earlier, items identified in the regression as being associated with changes in dyskinesia during placebo treatment were utilized as explanatory variables in two logistic regression models to detect factors selectively associated with dyskinesia improvement or worsening on placebo. The impact of each factor studied was expressed in terms of the probability (P) of obtaining the response, the odds of obtaining the response ($P/1 - P$), and odds ratios (OR).

Associations of Dyskinesia and Parkinsonism at Baseline and Change in Dyskinesia and Change in Parkinsonism After Receiving Placebo—To evaluate baseline associations between UPDRS scores, age, and dyskinesia scores, Pearson correlation

coefficients were calculated and a test of whether these differed significantly from zero was based on Fisher's Z transformation. Similar calculations were performed to assess the association between dyskinesia change and Parkinsonism change.

Testing the Placebo Model in the Sarizotan Groups: Is There a Component of the Response to Sarizotan That Is Not Accounted for by the Predicted Placebo Response?

—Because the sarizotan and placebo treatment groups improved at the same rate of response in both Paddy-1 and Paddy-2 studies, we tested whether the predicted placebo response accounted for all changes seen in the sarizotan group. Using the regression equation resulting from the model fit of the data from the placebo-treated subjects as outlined earlier, we calculated the predicted placebo response for each sarizotan-treated subject. The predicted placebo response for a patient was obtained by substituting the patient's baseline values into the regression equation. We calculated the difference between each subject's actual sarizotan dyskinesia response and the predicted placebo, calling these differences “residuals.” The usual use of this term occurs in the context of appraising the fit of the model in the data set on which the regression analysis was performed. We reasoned that, even though the study mean sarizotan and mean placebo dyskinesia outcomes did not differ, if the residuals were not close to equal, a component of response to sarizotan would have to be explained by effects specific to sarizotan. If residuals were close to zero, then the observed response to sarizotan would be adequately explained as a placebo response. To test the null hypothesis at $\alpha = 0.05$ that all of the response to sarizotan was accounted for by placebo response, we computed a *t*-test on the residuals, hypothesizing that it would not be significant.

RESULTS

The placebo group included 484 subjects (Paddy-1 = 250, Paddy-2 = 234) with baseline and 12-week assessments. Twenty additional patients who were enrolled in the 4-week single-blind placebo-treatment phase were not randomly assigned because they improved in terms of ON time with dyskinesia and no longer met the minimal entry criteria.

The primary outcome of the study was a change in a composite calculation covering disability and duration of dyskinesia, and very few patients were discordant for the two outcomes (Table 1). In 13 subjects, duration improved, but disability worsened, and in nine subjects disability improved, but dyskinesia was more frequent. Otherwise change patterns were the same for the two domains ($N = 310$) or the change occurred in only one domain without change in the other ($N = 152$). Baseline dyskinesia severity did not correlate with patient age ($r = -0.01$, $P = 0.80$) nor with baseline UPDRS score ($r = 0.06$, $P = 0.18$).

Identifying Factors That Influence Placebo Responses

The first stepwise regression tested if baseline clinical/demographic variables contributed to changes in end-of-study dyskinesia scores on placebo treatment. Four items were identified with *P* values < 0.15 and were retained for use in the logistic regression: baseline dyskinesia severity ($P < 0.0001$), baseline UPDRS motor score ($P = 0.011$), age ($P = 0.040$), and baseline daily L-dopa dose ($P = 0.13$). Other baseline factors, gender, PD and dyskinesia durations, and geographical site of enrollment, and study (Paddy-1 or Paddy-2) did not improve the model fit. The model based on the four identified influences on placebo response accounted for 7.9% of the variance, an effect that lies between small and medium, according to Cohen's criteria, ¹³ in contexts other than PD.

Factors Associated With Improved Dyskinesia During Placebo Treatment

One hundred seventy-eight placebo-treated patients (36.8%) fulfilled the definition of a $>25\%$ improvement in the composite UPDRS Items 32 + 33. In the logistic regression model, older

age ($P < 0.05$), lower baseline UPDRS scores ($P = 0.012$), and lower daily L-dopa treatment dose ($P = 0.034$) all increased the likelihood of being a positive placebo responder compared with a nonresponder. For positive placebo outcome, the fourth item in the stepwise regression, baseline severity of dyskinesia, had no significant influence on the likelihood of placebo-associated improvement ($P = 0.322$). In a clinical context, for a reference case with the mean values for the four target factors in the entire placebo-treated group (age = 66, UPDRS motor score = 22.4, daily dose of L-dopa = 780 mg, and baseline dyskinesia score = 4.8), the probability of being a positive placebo responder was 0.37 (Table 2).

To exemplify the impact of clinically pertinent shifts in these indices against this reference case, we examined a prototypic clinical case, where all three influences occurred in one patient, being older than the mean by 10 years, having a lower UDPRS motor score by 10 points at baseline, and having a lower baseline L-dopa dose by 300 mg/day. In this situation, the likelihood of being a improved placebo responder was nearly 80% higher than the reference case (OR, 1.8), and the probability of placebo-associated improvement increased from 0.37 to 0.51. Conversely, in comparison to the reference case representing the group mean, if the patient was 10 years younger, with a UPDRS motor score at baseline 10 points higher, and a L-dopa daily baseline dose 300 mg/day higher, the subject's odds ratio of showing placebo-associated improvement shifted to 32% lower than the reference case (OR, 0.54), and the probability of being a responder decreased from 0.37 to 0.25. The probability of being a placebo responder in these two extreme situations doubled from 0.25 in the patient who was younger, with a high baseline UPDRS score and high L-dopa daily dose to 0.51 in the patient who was older with a low baseline UPDRS score and low L-dopa dosage.

Factors Associated With Worsening of Dyskinesia During Placebo Treatment (Negative Placebo Influences)

For negative placebo response calculations, only 37 placebo-treated patients (7.6%) fulfilled the definition of a >25% worsening in the composite UPDRS items 32 + 33 measure of dyskinesia. In contrast to placebo-associated improvements, age ($P = 0.36$), baseline UPDRS scores ($P = 0.79$), and daily L-dopa treatment dose ($P = 0.84$) did not affect the likelihood of placebo-associated worsening. However, a lower baseline severity of dyskinesia had a significant influence on the likelihood of worsening on placebo ($P < 0.0001$). In a clinical context, for a reference case with the mean values for the four target factors in the entire placebo-treated group (age = 66, UPDRS motor score = 22.4, daily dose of L-dopa = 780 mg, and baseline dyskinesia score = 4.8), the probability of being a negative placebo responder was 0.038 (Table 3). When the baseline dyskinesia score was the minimum for study entry (4.0), the likelihood of placebo-associated worsening shifted to over twice as high (OR, 2.57), with the probability of showing placebo-associated worsening increasing from 0.038 to 0.093. Conversely, if the patient's baseline score was 0.8 points higher than the mean for the group, the patient's likelihood of being a negative placebo responder was only 40% of the reference case, with a reduced probability from 0.038 to 0.015.

We considered repeating the same analyses with an even stricter definition of placebo response (>50 improvement or decline), but in this case, the numbers of cases was much lower (placebo-associated improvement in 96 and worsening in nine), and we considered these sample sizes too small for analysis, especially for negative placebo responses.

Association Between Dopaminergic Behaviors: Dyskinesia and Parkinsonism

In examining the association between UPDRS and dyskinesia, neither correlation at baseline ($r = 0.06$, $P = 0.18$) nor correlation of change scores from baseline to 12 weeks ($r = -0.02$, $P = 0.66$) was significantly different from zero.

Adverse Events

The third analysis focused on the impact of adverse events on placebo responses. In the stepwise linear regression to identify specific adverse events and the total severity as predictive of placebo responses, insomnia ($P = 0.061$), depression ($P = 0.081$), and nausea ($P = 0.15$) were identified. These combined contributions accounted for a very small amount of the original variance (2%). Further, when these three adverse events were utilized in logistic regression models, none showed a significant impact on predicting placebo-associated improvement or worsening (all P -values >0.05).

Placebo Model Applied to the Sarizotan-Treated Subjects

When the regression equation for predicting placebo response was applied to each sarizotan-treated subject and the residuals (the difference between the predicted placebo response and the observed sarizotan response) were calculated, the mean value was -0.07 (SD, 1.29) (95% CI: $-0.18, 0.04$). The t -test failed to identify any significant effect unexplained by placebo influences in the sarizotan population ($P = 0.23$). The median of the distribution of residuals was estimated to be 0.23; the standard deviation was 1.28; the skewness, a measure of the asymmetry of the distribution, was estimated to be -0.67 ; and the kurtosis, the fourth moment around the mean, was estimated to be 0.33. These values are similar to the corresponding set of parameters found in fitting the data on the placebo only group. The estimates were mean = -0.0002 , median = 0.31, SD = 1.25, skewness = -0.48 , and kurtosis = -0.10 .

DISCUSSION

Treating dyskinesia in PD patients remains a clinical and neuropharmacological challenge. Dose reductions in dopaminergic therapies can decrease dyskinesia, but generally at the expense of Parkinsonism. Among medications, only amantadine is considered efficacious.¹⁴ Surgical procedures, including unilateral pallidotomy and subthalamic nucleus deep brain stimulation, have been reported to have antidyskinesia effects, but carry potentially serious adverse postoperative complications, are not available at all sites, and are expensive. The failure of the sarizotan program underscores the continuing unmet need of antidyskinetic therapies in PD.¹⁴ The experience also illustrates the importance of large, double-blind placebo-controlled studies, because benefits of sarizotan were reported in open-label and double-blind dose-finding studies.^{15,16}

Our findings that specific factors increase the likelihood of placebo-associated improvement or worsening need to be confirmed by analyses of other data sets and by similar analyses using other measures of dyskinesia, including objective in-office ratings or home-based diaries. Study designers, however, may consider the factors we identified as they develop future protocols for testing antidyskinetic effects of new treatments. Possible strategies include restricting the characteristics of subjects through inclusion/exclusion criteria, stratifying at randomization to ensure that there are equal numbers of individuals with the identified traits in the treatment groups, or adjusting for imbalances at the analysis stage.

We caution that the findings reported here should not be misread as implying that placebo responders can be individually identified based on baseline profiles; instead, they should be interpreted as identifying risk factors that increase the likelihood of a response. We cannot rule out that patients with these same features are more likely to respond to an active antidyskinetic agent as well. Our model accounted for only 7.9% of the variance, which we consider modest, and therefore other factors unexplored in this study may also have affected outcome, including genetic, study-related, and nonspecific factors such as added office visits and attention (Hawthorne effects), and possible physician or patient biases. We also cannot exclude normal variability in the rating measure used. Our results, however, are not explained by extreme scores

at baseline that normalized over the course of the study (regression to the mean), because the samples were equivalent at baseline, and further, both exacerbations and improvements were assessed. Our analysis was restricted to the primary outcome variable of the original studies; other secondary measures of dyskinesia, including diary-based data and clinical global impressions, could also be examined for response patterns to placebo treatment.

The frequency of placebo-associated improvements in clinical trials of new treatments for Parkinsonism has been noted in several reports.²⁻⁴ In one study examining demographic factors associated with placebo-associated improvements, age and severity of Parkinsonism impacted placebo-related improvements in Parkinsonism.³ In an analysis of 11 clinical trials representing over 700 placebo-treated PD subjects and based on a very strict definition of placebo response (change in UPDRS motor score by 50% or reduction by at least two points on two different UPDRS items at one visit), the mean prevalence of placebo-associated improvement was 17%.⁴ Study design issues influenced placebo prevalence, and in surgical studies, placebo response rates were as high as 55%. Two different theories have dominated pathophysiological arguments related to placebo-associated improvements in Parkinsonism: first, a general “mind over matter” concept that is not specific to PD or dopamine, and second, a specific dopaminergic theory that proposes enhanced dopaminergic activity in pathways influenced by enhanced motivation, anticipation, and novelty.¹ In the latter case, heightened dopaminergic activity related to study participation would conceivably improve Parkinsonism, but because dyskinesia itself is considered a hyperdopaminergic behavior, the same effect should exacerbate dyskinesia. Two observations from this study challenge the dopaminergic activation theory of placebo-induced changes in PD patients: first, many fewer patients demonstrated placebo-related dyskinesia worsening compared with improvement; second, changes in Parkinsonism were not correlated with changes in dyskinesia. These observations occurred in the context of the findings from the earlier study of sarizotan, where improvements in dyskinesia by sarizotan were often associated with exacerbation of Parkinsonism, so that investigators were sensitized to this possibility.¹⁵ We had hypothesized, however, a lack of correlation between changes in Parkinsonism and dyskinesia based on the complexity of biochemical mechanisms, including receptor sensitization and pulsatile dopaminergic activity related to dyskinesia⁷ and do not consider dyskinesias as a behavior simply indicative of “too much dopamine.” With these two contrasting perspectives, we felt we could test our hypothesis in the context of equipoise without bias. From a clinical perspective, these findings argue in favor of concepts that placebo-induced effects in PD are largely related to expectation principally directed to the primary behavior under consideration, in this case dyskinesia. As such, we suggest that observed placebo-associated changes are largely due to study participation and its attending effects without a specific or exclusive neurochemical relationship to dopaminergic systems.

Regarding alternative nondopaminergic neurochemical mechanisms mediating expectation- or reward-related placebo-associated improvements, experimental work links dyskinesia to glutamatergic, GABAergic, α_2 adrenergic, serotonergic (5HT_{1A}, 5HT_{2A}), opioid, histamine H₃, adenosine A_{2A} receptors, the monoamine transport, and cannabinoid CB1 receptors systems.^{17,18} Of particular interest, alterations of the NMDA receptor complex occur both in PD as well as in L-dopa-induced dyskinesia.¹⁹ Of pertinence to placebo-related issues, the NMDA receptor appears to play a critical role in the mechanisms underlying expectation, anticipation, and reward.²⁰ Because amantadine is the one available agent with demonstrable antidyskinetic effects and is thought to work through the NMDA-glutamate system, we believe that this system is worthy of future study.^{14,21} Clearly, our dataset cannot provide direct insights into these putative biochemical mechanisms as they relate to placebos and dyskinesia, but as drugs affecting these systems are studied in dyskinesia, it will be pertinent to monitor placebo-response profiles.

We examined adverse events, because subjects who experienced new symptoms might be psychologically primed to think they were receiving active drug and thereby demonstrate changes in the target behavior, in this case, dyskinesia. In fact, we did not find a significant impact of any adverse event.

Finally, we considered the possibility that a small, but potentially clinically pertinent, antidyskinetic effect related to sarizotan could have been obscured by the more prominent placebo impact in the study. Also, even with the randomization design, possible differences in the distribution of influential covariates between the treatment and placebo groups could have produced an erroneous outcome. To investigate these possibilities, we utilized the technique of residual estimates in order to identify a “pure sarizotan effect.” This calculation confirmed that all effects seen with sarizotan were explained by the placebo-related outcome without any residual efficacy attributable to sarizotan. We are not aware of prior applications of this statistical technique in PD and consider it a potential model applicable to clinical trials, not only placebo-controlled, but also those with an active comparator control group. The approach may have particular applicability to the concept of causal inference that relies on two principles, “potential outcomes” and “counterfactuals”; the former term considers the result that would have been observed for each treatment had the subject received it, and the latter considers the outcome for the treatment the subject did not receive. In our statistical approach, data from the placebo group was used to predict the counterfactual placebo response of a subject who received sarizotan. Had the residuals differed from zero, causal inference on the effectiveness of the new treatment would have been valid.

The original efficacy studies included an initial single-blind period prior to randomization in which all patients received placebo. A small number of patients were excluded from the randomized placebo-controlled clinical trial of sarizotan because they responded to placebo treatment. We were not comfortable, including these patients in our analysis, because they were considered to be placebo-responders based on a different criterion than the one used as the primary outcome of the study and the raters were not blind. We cannot rule out the possibility that the exclusion of the 20 prerandomization placebo responders altered the estimates of correlation particularly at baseline, but in our view, prerandomization data cannot be merged with this analysis. In approaching the study of placebo-associated changes in dyskinesia, we consider it best to present a conservative analysis anchored in a uniform methodology. Further, our aim was to study the influence of placebo within randomized clinical trials in order to provide insights useful to future trialists. This goal could not be met by examining patients prior to randomization. The results of these trials established that even after a prespecified plan to minimize enrollment of placebo responders, many patients still met the criterion for placebo response, demonstrating that a traditional wash-in placebo phase is entirely insufficient to remove placebo influences from clinical trial designs.

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TABLE 1

Distribution (number, percent) of responses to placebo treatment, based on changes from baseline in UPDRS item ratings 32 (dyskinesia disability) and 33 (dyskinesia duration)

Dyskinesia disability	Dyskinesia duration		
	Improved	No change	Worsened
Improved	117 (24.2)	48 (9.9)	9 (1.9)
No change	63 (13.0)	183 (37.8)	18 (3.7)
Worsened	13 (2.7)	23 (4.8)	10 (2.1)

TABLE 2
Odds ratios for placebo-associated improvement in dyskinesia, showing influences of shifts in the three prognostic baseline factors

Age (yr)	Baseline UPDRS motor score	Baseline daily L-dopa (mg)	Probability	Odds	Odds ratio relative to first row
66	22.4	780	0.37	0.59	1.00
66 + 10	22.4	780	0.42	0.72	1.24
66 - 10	22.4	780	0.32	0.47	0.81
66	22.4 + 10 pts	780	0.32	0.47	0.80
66	22.4 - 10 pts	780	0.42	0.72	1.25
66	22.4	780 + 300	0.33	0.52	0.86
66	22.4	780 - 300	0.40	0.69	1.17
66 + 10	22.4 - 10 pts	780 - 300	0.51	1.07	1.80
66 - 10	22.4 + 10 pts	780 + 300	0.25	0.33	0.55

Bold markings highlight the influence of shifting the identified factor upwards or downwards, and the final two rows show the probability of showing placebo-associated improvement with all three factors shifted in the direction of maximally enhancing (second from the bottom row) or maximally diminishing (the bottom row) placebo response. Probability (*P*) of obtaining the response and the odds of obtaining the response ($P/1 - P$) are mathematically related, but shown separately.

TABLE 3

Odds ratios for placebo-associated worsening of dyskinesia, showing influences of shifts in baseline dyskinesia score

UPDRS items [32+33]	Probability	Odds	Odds ratio relative to first row
4.8	0.038	0.307	1.00
4.8 + 0.8	0.015	0.390	1.08
4.0 ^a	0.093	0.120	2.57

^aMinimal permissible score to enter study.