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Review article

Nocebo response in Parkinson's disease: A systematic review and meta-analysis

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ABSTRACT

Objective: To estimate the magnitude of the nocebo response in Parkinson's disease and explore possible associations with study characteristics.

Methods: Databases were searched up to February 2017. Placebo-controlled, parallel-group randomized controlled trials investigating pharmacological interventions in people with Parkinson's disease were included. Data were derived from the last measured within-group response in the placebo and intervention arms of randomized controlled trials, after independent extraction. A random-effects model was used to pool study data. The main outcome was the nocebo response, measured as the proportion of placebo-treated participants experiencing any adverse events (AEs). We also measured the proportion of patients with serious AEs (SAEs), and the rates of study dropouts (including due to AEs) and death. PROSPERO registration number is CRD42017070471.

Results: We included 236 randomized controlled trials, with a combined population of 17,381 participants allocated to placebo. The nocebo response was 56.0% (95% CI, 51.7%–60.4%; 148 trials; I^2 = 98%). SAEs were reported in 4.0% (95% CI, 3.4%–4.6%, 157 trials; I^2 = 73%) of placebo-treated patients, dropouts in 14.0% (95% CI, 12.5%–15.5%, 225 trials; I^2 = 91%), dropouts due to AEs in 5.7% (95% CI, 5.1%–6.4%, 219 trials; I^2 = 73%). Deaths occurred in 0.6% (95% CI, 0.5%–0.7%, 227 trials; I^2 = 0%). Similar proportions were identified in patients in intervention arms.

Conclusions: The magnitude of the nocebo response in parallel-designed randomized controlled trials in Parkinson's disease is substantial and should be considered in the interpretation of safety results and in the design and interpretation of future clinical trials.

1. Introduction

The placebo effect, a therapeutic benefit secondary to taking a pharmacologically inert substance [1,2], has been well established in Parkinson's disease (PD). A meta-analysis of randomized controlled trials (RCTs) of symptomatic therapies conducted in different stages of PD estimated that 18% of patients had a placebo response [3]. Other studies have shown that this effect is sustained for at least 6 months [4,5] and that there is an increase in dopaminergic neurotransmission in the ventral (reward related processes) and dorsal (motor) striatum [6–8] when giving placebo to a PD patient, thus providing an association between the basal ganglia circuitry and a clinical response [9].

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Both a high baseline Unified Parkinson's Disease Rating Scale (UPDRS) part III score (but not PD disease duration) and the presence of motor fluctuations have been established as predictors of a larger placebo response in PD RCTs [10].

However, the nocebo effect, the emergence of adverse events secondary to the administration of a placebo, [2,11] and related mechanisms remain comparatively elusive. A nocebo response has been observed in PD, mainly through worsening of motor outcomes and lasting up to 6 months [3–5,12]. A strong placebo response might decrease active drug-placebo difference, while a strong nocebo effect can be interpreted as a sign of disease progression [13], thus confounding assessment of both efficacy and safety of a drug. [11,14]

In this systematic review and meta-analysis, we aim to evaluate the nocebo response in PD patients enrolled in placebo-controlled RCTs.

2. Methods

This systematic review is reported according to the PRISMA guidelines [15]. The protocol was registered in PROSPERO (reference: CRD42017070471).

2.1. Eligibility criteria

We included placebo-controlled, parallel-group RCTs investigating any pharmacological intervention in people with PD.

We considered patients with a clinical diagnosis of PD, defined as people enrolled in RCTs studying this condition, regardless of comorbid conditions, concomitant medications, or age. We accepted any non-surgical intervention with placebo or dummy arm regardless of pharmacological class, dosage, mode of administration, or duration of follow-up.

We excluded trials of surgical interventions, non-parallel study designs, and ambiguous study design. We did not exclude cross-over trials if data of the first parallel-groups period of study were explicit and separated from data of subsequent phases, thus extracting data only from the first, carry-over effect free, period. Similarly, studies with subsequent open label phases or non-randomized phases were not excluded if the design study, methodology, and reporting were clear enough to assure an intervention effect free placebo arm. We excluded subgroup analysis and post-hoc analysis of previously reported trials.

Studies had to report quantitative data on at least one of the following outcomes within the placebo arm:

Primary outcome. The nocebo response, defined as the proportion of participants experiencing adverse events (AEs) in the placebo arm.

Secondary outcomes. The proportion of serious AEs (SAEs), the proportion of dropouts, the proportion of dropouts due to AEs, and proportion of deaths in the placebo arm.

We also extracted the same data from the intervention arms, to establish a term of comparison. No language, year of publication, or publication status restrictions were applied.

2.2. Information sources

We searched MEDLINE, EMBASE, and CENTRAL databases, the WHO International Clinical Trials Registry Platform, and clinicaltrials.gov, from inception to February 2017.

2.3. Search

The search strategy developed for all databases combined the terms (placebo OR sham OR dummy) with (Parkinson* OR Parkinsonism), was restricted to randomized trials, and was adapted from previous Cochrane systematic reviews of interventions for this condition. All terms were searched as free-text and MeSH terms. The full search strategy is available in the Supplemental Data.

2.4. Study selection

Three reviewers (ANF, GSD, MLR) independently screened the titles and abstracts yielded by the search against the inclusion criteria. Disagreements were solved by consensus. Two reviewers (ANF, MLR) analyzed full texts for potential inclusion and motives for exclusion were recorded.

2.5. Data collection process

One reviewer (MLR) extracted data onto a previously piloted spreadsheet, and data were confirmed by one of two additional reviewers (GSD, MA).

2.6. Risk of bias

We used the Cochrane risk of bias tool to classify studies as being at low, high, or unclear risk of bias in the following domains: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting [16]. Two researchers (BM, MA) independently assessed risk of bias, and disagreements were solved by a third reviewer (GSD). We rated studies as having a high or low overall risk of bias using previously defined criteria [17].

2.7. Summary measures

Data were derived from the last measured within-group response in the placebo or intervention arms of RCTs. Whenever possible, we retrieved and analyzed intention-to-treat data. We used OpenMetaAnalyst and Review Manager version 5.3 for statistical analysis and to derive forest plots. We used a random-effects model to pool data due to the anticipated heterogeneity among the included trials. We reported pooled dichotomous data using risk ratios (RRs), reporting 95% confidence intervals (95% CIs).

Statistical heterogeneity between trial results was assessed using I^2.

2.8. Additional analyses

The following subgroup analyses, defined after protocol registration, were conducted: nocebo and placebo response according to primary endpoint of trial (motor or non-motor - cognitive, psychiatric, disease progression, global, or other), class of drug being tested (dichotomously as dopaminergic vs. non-dopaminergic), disease stage at baseline (dichotomously as early/mild vs. advanced/late) and duration of follow-up ($\leq$6 months vs. $>$ 6 months). We also conducted a meta-regression for adverse events according to baseline UPDRS scores.

The proportion of symptoms not attributable to the pharmacological action (PSN) of a drug was also established [18,19,20], using the following formula:

$$PSN = \left[1 - \frac{\rho_{intervention} - \rho_{placebo}}{\rho_{intervention}}\right] x\ 100$$

$\rho_{intervention}$: pooled proportion of an event in the intervention arm, $\rho_{placebo}$: pooled proportion of the same event in the placebo arm.

3. Results

3.1. Study selection and characteristics

We included 236 trials (47,189 participants overall) enrolling between five and 1741 participants. Participants had a mean age of 63.9 ± 3.3years and a PD disease duration of 5.5 ± 3.5 years (weighted mean ± SD). There were 28,205 participants allocated to intervention arms and 17,381 to placebo arms. Trials were published

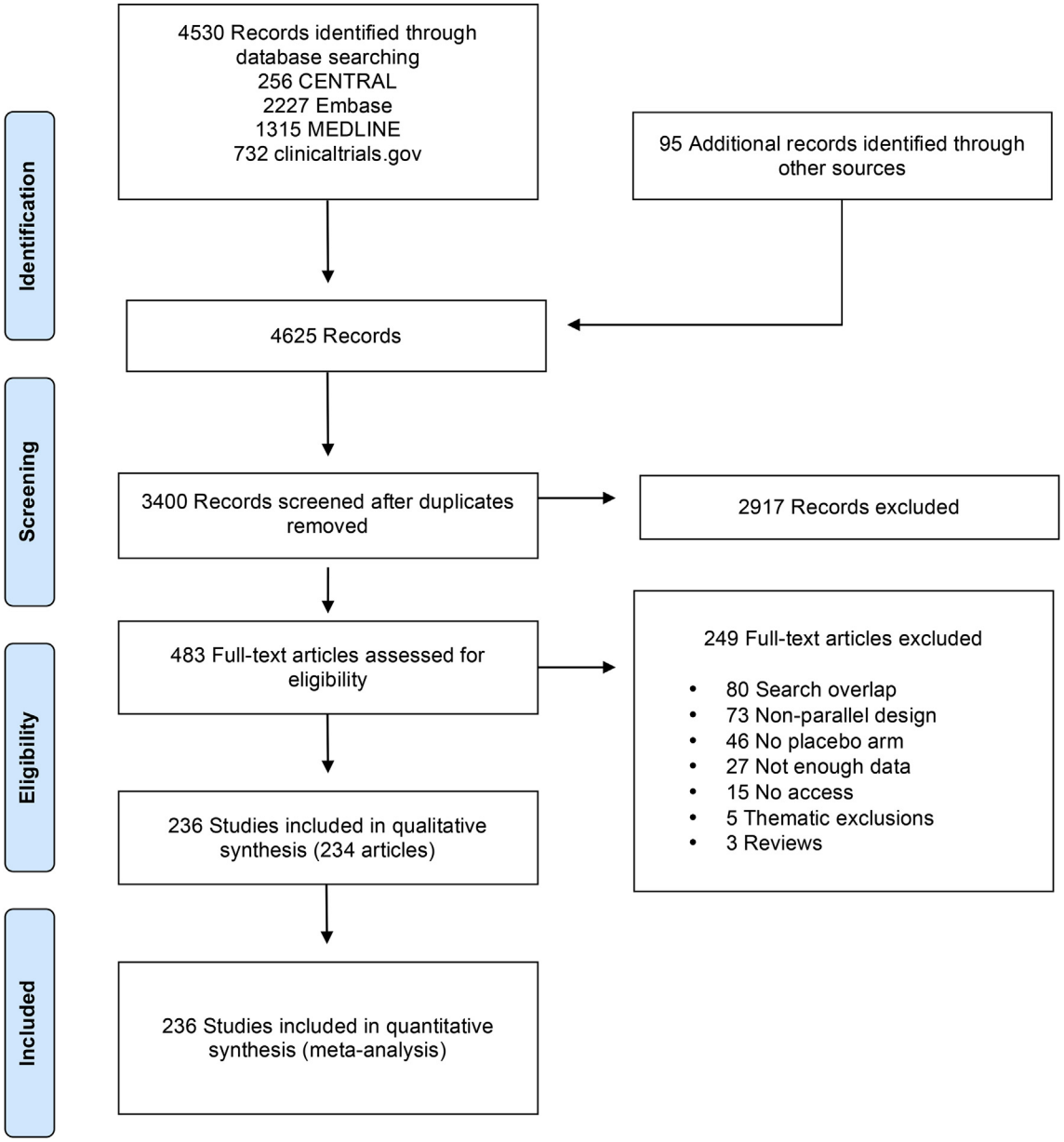

Fig. 1. PRISMA chart.

between October 1974 and February 2017. For the PRISMA flow chart refer to Fig. 1. The list of included trials, with full references, can be found in Supplemental Data.

The most commonly studied drugs were pramipexole (n = 20), rasagiline (n = 14), selegiline (n = 14), rotigotine (n = 12), entacapone (n = 8), istradefylline (n = 8), and ropinirole (n = 8).

Regarding primary study outcomes, 147 studies had a primary motor endpoint, 21 had a "global disease" endpoint, 14 focused on disease progression, 12 on psychiatric symptoms, 11 on cognitive, 10 on safety outcomes, and 3 specifically addressed sleep outcomes.

There were 96 trials that enrolled participants with advanced or late-stage PD (including trials in PD patients with motor fluctuations), while 41 included participants with early or intermediate PD. Overall, 99 trials did not specify disease stage at inclusion or included participants in any stage or in other stage (such as moderate PD). Table 1 summarizes study characteristics.

3.2. Risk of bias across studies

We judged 61 (25,8%) trials to be at a low overall risk of bias. The detailed risk of bias across studies can be found in Fig. 2. The complete summary of bias for all studies can be found in Supplemental Data (Figures e−1 to e−7).

3.3. Synthesis of results and additional analysis

See Table 2 for the main results.

3.3.1. Primary safety outcome: nocebo response

148 trials clearly reported the proportion of placebo-treated patients with AEs. Overall, 56.0% of placebo-treated patients experienced AEs (95% CI, 51.7%–60.4%; I^2 = 98%).

3.3.2. Secondary safety outcomes

SAEs were reported in 4.0% (95% CI, 3.4%–4.6%, 157 trials; I^2 = 73%) of placebo-treated patients, dropouts in 14.0% (95% CI,

Table 1
General characteristics of the included trials.

Variable	Value
Number of studies, n	236
Number of total participants, n	47,189
Number of placebo treated patients, n (%)	17,381 (37)
PD stage, n	
Early/Intermediate	41
Late/Advanced	96
Mixed or not-classifiable	99
Follow up duration, weeks (range)	1–261
Follow up duration, n	
≤6 months	175
> 6months	61
Number of drugs studied, n	87
Interventions assessed, n (%)	
Pramipexole	20 (8,5)
Rasagiline	14 (5,9)
Selegiline	14 (5,9)
Rotigotine	12 (5,1)
Entacapone	8 (3,4)
Istradefylline	8 (3,4)
Ropinirole	8 (3,4)
Other	152 (64,4)
Drug class of intervention	
Dopaminergic	112
Non-dopaminergic	124
Main outcomes, n	
Motor	146
Global	21
Disease progression	14
Psychiatric	12
Cognitive	11
Safety	10
Sleep	3
Other	19

Abbreviations: PD, Parkinson's Disease.

12.5%–15.5%, 225 trials; I^2 = 91%), dropouts due to AEs in 5.7% (95% CI, 5.1%–6.4%, 219 trials; I^2 = 73%). Deaths occurred in 0.6% (95% CI, 0.5%–0.7%, 227 trials; I^2 = 0%).

3.3.3. Comparative outcomes

Overall, 63.9% (95% CI, 59.3%–68.4%, 147 trials; I^2 = 99%) of patients in the intervention arm experienced AEs. SAEs were reported in 5.0% (95% CI, 4.2%–5.7%, 158 trials; I^2 = 89%), dropouts in 15.7% (95% CI, 14.0%–17.4%, 225 trials; I^2 = 95%), and dropouts due to AEs in 9.0% (95% CI, 7.8%–10.1%, 217 trials; I^2 = 93%). Death occurred in 0.3% (95% CI, 0.3%–0.4%, 227 trials; I^2 = 0%).

The calculated PSN are 87.6% for AEs, 81.6% for SAEs, 89.2% for dropouts and 63.3% for dropouts due to AEs.

All relevant results, including the subgroup analyses, are available in Supplementary Material (Table e−1).

3.3.4. Additional analysis

We conducted a meta-regression based on baseline UPDRS scores, and did not find a significant relationship (p = 0.13).

4. Discussion

Our meta-analysis demonstrated that most placebo-treated PD patients suffered AEs (56%), constituting evidence of a strong negative effect from a theoretically inert intervention. In the active treatment arms, 64% of participants had AEs.

To our knowledge, this is the broadest systematic review evaluating the nocebo response in PD. A previous systematic review by Stathis et al. [21] used stricter criteria, over a smaller span of time of publication, excluding trials that addressed clinical problems associated to PD (i.e. dementia, psychosis, hallucinations, orthostatic hypotension, sleep disorders, among others) that have been established as major contributors to clinical progression and disease burden [22]. It included 21 studies and reported a higher nocebo response of 64.7% but it also reported a higher proportion of patients with AEs across intervention arms (73.3%). In that study, a quantitative and qualitative correlation between AEs in the active and the placebo groups, independent of study drug, was found. A confounding factor should be noted when reading these results, as crossover trials were included. This means a there may have been a potential carry-on effect of AEs reflected in an increase in apparent nocebo effect cannot be ignored. In a crossover trial, if placebo is given as the first treatment, only suggestion is at play, while if placebo is given as a second treatment both suggestion and expectation [6] can be assumed to contribute to the effect. Another work [23] explored a parallel notion, the lessebo effect, in which the possibility of receiving a placebo lessens the efficacy of an active treatment.

Randomized, placebo-controlled, double blind trials are the gold standard for demonstrating efficacy. In our work, 4.0% of patients in the placebo arms of PD RCTs experienced SAEs, 14.0% dropped out, 5.7% dropped out due to AEs, and 0.6% died during the follow-up period. As indicated by our PSN analysis, up to 88% of the AEs may be attributable to the nocebo response and not due to the intervention being studied. Furthermore, 89% of the dropouts and 63% of dropouts due to AEs across intervention arms may be attributable to nocebo.

This result raises not only issues of clinical trial design, but ethical concerns, as patients not receiving active treatment nonetheless experience considerable negative effects. Up to 19% of healthy volunteers taking placebo in RCTs report AEs [24]. Nonspecific symptoms attributed to the intervention may simply arise from disease symptoms reported as AEs and this is more likely to happen to participants who expect to suffer or have previously experienced AEs [11]. Trial enrichment by excluding placebo-responsive patients is frequently conducted in psychiatric trials [25], and the transposition of this principle to safety outcomes may be considered in future trial design This approach is controversial, as it reduces the representativeness and generalizability of RCTs [26].

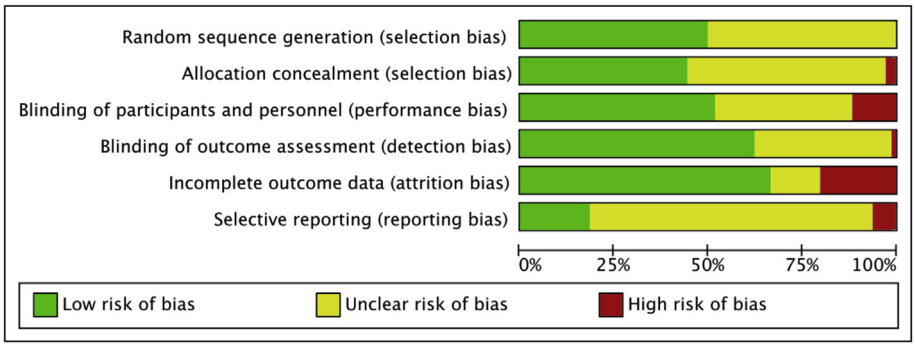

Fig. 2. Risk of bias across domains graph.

Table 2
Summary of main results.

Outcome	Overall estimate (%)	95% CI	Number of trials	I^2	PSN (%)
AE	56.0	51.7 to 60.4	148	98	87.6
Serious AE	4.0	3.4 to 4.6	157	73	81.6
Dropouts	14.0	12.5 to 15.5	225	91	89.2
Dropouts due to AE	5.7	5.1 to 6.4	219	73	63.3
Deaths	0.6	0.5 to 0.7	227	0	NA

Abbreviations: AE, Adverse events, CI, confidence interval; NA, not applicable; PSN, Proportion of symptoms nonpharmacological.

Regarding our subgroup analyses, and although all of the analyzed subgroups have overlapping confidence intervals in the primary safety outcome, there might be a stronger nocebo effect in trials studying dopaminergic drugs, focusing on motor outcomes, including patients with early/intermediate disease, with a follow up period of more than 6 months, and with a lower risk of bias. Levodopa and other dopaminergic drugs are the mainstay of treatment for PD, and their AEs are widely recognized as both common and relevant for the clinical course and patient management [22,27–30].

4.1. Comparison with other neurological disorders

The nocebo effect has been studied in various neurological disorders. Using similar methodology, the nocebo effect was found to differ considerably among different neurological and neuropsychiatric disorders. The nocebo response ranged from 25% in symptomatic treatment trials of multiple sclerosis (MS) [31], to 52% in neuropathic pain trials [32] and 74% in disease-modifying MS trials [31]. In these systematic reviews, only treatment-emergent AEs, as opposed to any reported AE, were considered and authors acknowledged this limitation in their studies. In fibromyalgia [33], 67% of placebo-treated patients reported at least one AE, and dropouts due to intolerance occurred in 10% of participants. The same group of investigators studied migraine [34], and reported a nocebo frequency of 18% in studies of symptomatic treatment and of 43% in preventive treatment studies. In trials for prevention of tension-type headaches, 24% of patients reported at least one AE. For symptomatic treatment of cluster headache, the nocebo frequency was 19%. Epilepsy lacks a comparable assessment of nocebo response, but up to 60% of participants in the placebo arm have AEs in some trials [35]. Recently, an all-inclusive systematic review and meta-analysis of the placebo and nocebo responses in restless legs syndrome documented that 45% of placebo-treated patients had AEs, and that this nocebo response changed proportionally with the placebo response [36].

As for other neurodegenerative diseases, there is a surprising lack of data on the nocebo response. In Alzheimer disease, a meta-analysis addressed this issue [37]. Twenty studies including 8977 patients were included, and the pooled nocebo response was 57.8% (95% CI, 50.1%–66.7%; I^2 = 97%). This study only considered studies with at least 40 participants in each arm, excluding studies with non-cognitive primary outcomes. In amyotrophic lateral sclerosis, the number of AEs reported and patients with at least one AE in trials concerning riluzole and edaravone are concerningly high [38,39]. In a recent trial studying rasagiline as an add-on therapy to riluzole [40], there was no difference between reported AEs in the placebo and intervention arms. This might be suggestive of a significant nocebo effect [41]. The patients' negative expectations regarding the occurrence of AEs were also probably enough to overlap the report of AEs directly attributable to rasagiline.

The nocebo response in PD that we describe is similar to the nocebo response in other neurological diseases. As such, it is unlikely that the nocebo response is specific of a disease or of a single pathophysiologic process, although we expect that it might be influenced by it. The increasingly recognized non-motor manifestations of PD, whose contribution to disease burden and health-related quality of life is becoming more established [22], may explain this apparent detachment from dopaminergic pathophysiology and nocebo response magnitude, as these non-motor manifestations are not exclusively due to a dopaminergic deficit.

4.2. Study limitations

Our main limitation is that as trials do not normally have a "no treatment arm", we cannot clearly state that the observed AEs result from administration of placebo or merely from a shared context with the intervention group. Direct association is therefore difficult to ascertain. Furthermore, we included trials in which placebo-treated patients were being treated with other medications, either PD-directed or not, and we did not control for disease progression, which may be responsible for some of the reported AEs. PD is a chronic and progressive disease so at least some of the AEs and SAEs noted in the placebo arms can be just a consequence of its natural history and are thus disease-related symptoms and not drug-related AEs. Nevertheless, as patients were randomized, and because no drug developed so far has demonstrated a disease modifying effect, this effect should be equally present in intervention arms.

The large number of included trials, multiple drugs and modes of administration in all stages of disease with no regard for concomitant therapy, and aimed at different endpoints across a considerable time span resulted in a significant heterogeneity. This heterogeneity of studies comprises the great disparity of methods for detecting, evaluating, characterizing, and reporting AEs across studies. We did not have access to the raw data of most trials. Many papers did not report all AEs, usually reporting only the AEs that occurred above a certain threshold. Thus, we expect our estimated nocebo response to be an underestimation.

4.3. Suggestions for future trials

The nocebo response is important for the interpretation safety data. In order to avoid potentially biased interpretations, some measures can be taken into consideration while designing and reporting clinical trials for PD.

Firstly, we know that patient-assessed outcomes differ significantly from researcher-assessed outcomes in terms of nocebo [42]. We also expect that AEs that are spontaneously reported might be less influenced by suggestion than AEs that are identified from a checklist, for example. As such, a detailed description of how the safety data was collected and evaluated may be of importance in balancing how much relevance a given AE has.

Secondly, proof of causality is crucial. In the included trials there were four deaths that were considered related to the drug in patients randomized to receive placebo. This raises questions about how accurate are investigators in establishing a causal relationship between an AE and a studied drug.

Finally, we encourage trialists to publish raw safety data, namely number AEs and number of patients with AEs, separately, for both the intervention and placebo groups. This practice might have two main advantages, in addition to increasing transparency: 1) It becomes possible to account for a "nocebo responder" effect, by signaling the presence of a group of patients that report many AEs with placebo

(indirectly by measuring the difference between number of reported AEs and the number of patients reporting AEs); 2) It becomes feasible to calculate the PSN, and hence to have a rough estimate of how much of the safety concerns may be the mere result of a nocebo effect and/or of natural history of the disease, as explained above.

5. Conclusions

Placebos are not inert interventions, having not only beneficial but also potentially detrimental effects. The high risk of AEs among placebo-treated patients suggests that current interpretation of safety data may be confounded by the nocebo response. Our data corroborates even further the power of expectation in the management of PD patients, be it positive or negative. PD medication is associated with a more complicated clinical course in PD [22], and safety characterization of a drug in PD is increasingly more important.

Author roles

1. Research project:
   A. Conception: JJF
   B. Organization: GSD, JJF, MLR
   C. Execution: ANF, BM, GSD, MA, MLR
2. Statistical Analysis:
   A. Design: GSD
   B. Execution: GSD, MLR
   C. Review and Critique: GSD, JC, JJF, MLR
3. Manuscript Preparation:
   A. Writing of the first draft: MLR
   B. Review and Critique: ANF, BM, GSD, JC, JJF, MA, TM, TT

All authors have approved the final article.

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Declaration of interests

JJF received speaker and consultant fees from Novartis, AbbVie, BIAL, Merck Sharp and Dohme, Biogen, Sunovion Pharmaceuticals, Medtronic.

The remaining authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.04.015.

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