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Nocebo in cerebellar ataxia: A systematic review and meta-analysis of placebo-controlled clinical trials

Jawwaria M. Alam[a,b], Marios Hadjivassiliou[a], Panagiotis Zis[a,b,c,*]

[a] Academic Department of Neurosciences, Sheffield Teaching Hospitals NHS Foundation Trust, UK
[b] Sheffield Institute for Translational Neuroscience, Sheffield, UK
[c] Medical School, University of Cyprus, Nicosia, Cyprus

A B S T R A C T

Introduction: Nocebo, the negative counterpart of the placebo phenomenon results in the induction of adverse events (AEs) following the administration of an inert substance. Nocebo has been demonstrated to be associated with low treatment compliance in clinical trials, thus affecting treatment outcomes. This study sought to determine the prevalence of nocebo in cerebellar ataxia.

Methods: A systematic literature search was conducted on Pubmed for randomized controlled trials (RCTs) for cerebellar ataxia treatments. The number of drug-related AEs and the number of withdrawals due to drug intolerance in the placebo group were statistically analysed.

Results: The literature search identified 214 studies, of which 6 studies fulfilled the inclusion criteria. Approximately 1 in 20 (4.8%) placebo-treated patients withdrew treatment due to AEs and approximately 1 in 7 (13.8%) placebo-treated participants reported at least one AE. Participants in cerebellar ataxia trials reported similar AEs across both treatment groups (active and placebo).

Conclusion: Our results demonstrate that the nocebo effect in cerebellar ataxia is amongst the lowest in neurological diseases.

1. Introduction

The nocebo phenomenon, the negative counterpart of the placebo effect refers to the adverse events (AEs) which occur following the administration of an inert substance with no active therapeutic benefit [1,2].

Nocebo occurs in the context of negative patient expectations, whereby the view that treatment will probably harm instead of heal results in AEs [3,4]. Evidence suggests that the nocebo phenomena arises due to the complex interactions between the patient and the surrounding psychosocial context [5], alongside negative pretrial suggestions, previous negative experiences during treatment and psychological factors including anxiety and stress [6,7]. The nocebo phenomena occur in both clinical practice and placebo-controlled randomized clinical trials (RCTs), in which it is typically assessed [2,7]. In RCTs nocebo is associated with difficulty in assessing the efficacy and safety profile of a drug, and if severe enough can lead to discontinuation of the therapeutic intervention and subsequent treatment withdrawal [8,9].

The nocebo effect has been studied in placebo-controlled RCTs for several neurological disorders including chronic inflammatory demyelinating polyneuropathy (CIDP) [10], epilepsy [11], motor neuron disease [12], multiple sclerosis [13], headache [14,15], neuropathic pain [16], fibromyalgia [4], diabetic peripheral neuropathy [17], Meniere's disease [18], restless leg syndrome [19], Parkinson's disease [20], Alzheimer's disease [7] and depression [21]. In these studies, the nocebo response varies greatly with the proportion of placebo patients discontinuing treatment ranging from approximately 2% (in CIDP, multiple sclerosis and restless leg syndrome) up to 9.5% in fibromyalgia. These rates demonstrate that nocebo may be a significant limiting factor in RCTs, and therefore have subsequent implications on treatment outcomes and clinical practice.

The aim of our study was to evaluate the frequency and strength of nocebo in cerebellar ataxia placebo-controlled RCTs, using a meta-analytic approach. The proportion of placebo treated patients who withdrew due to placebo-related AEs was used to estimate the severity of the nocebo effect.

2. Methods

A computer-based literature search was conducted on April 18th, 2018 on Pubmed using the search terms “ataxia”, “placebo” and “treatment”. The limitations applied included text availability to be full text, species to be humans and languages to be English. All relevant studies were then selected for analysis.

* Corresponding author at: Academic Directorate of Neurosciences, Sheffield Teaching Hospitals NHS Trust, Royal Hallamshire Hospital, Glossop Rd, South Yorkshire S10 2JF, Sheffield, UK.

E-mail addresses: jalam1@sheffield.ac.uk (J.M. Alam), m.hadjivassiliou@sheffield.ac.uk (M. Hadjivassiliou), takiszis@gmail.com (P. Zis).

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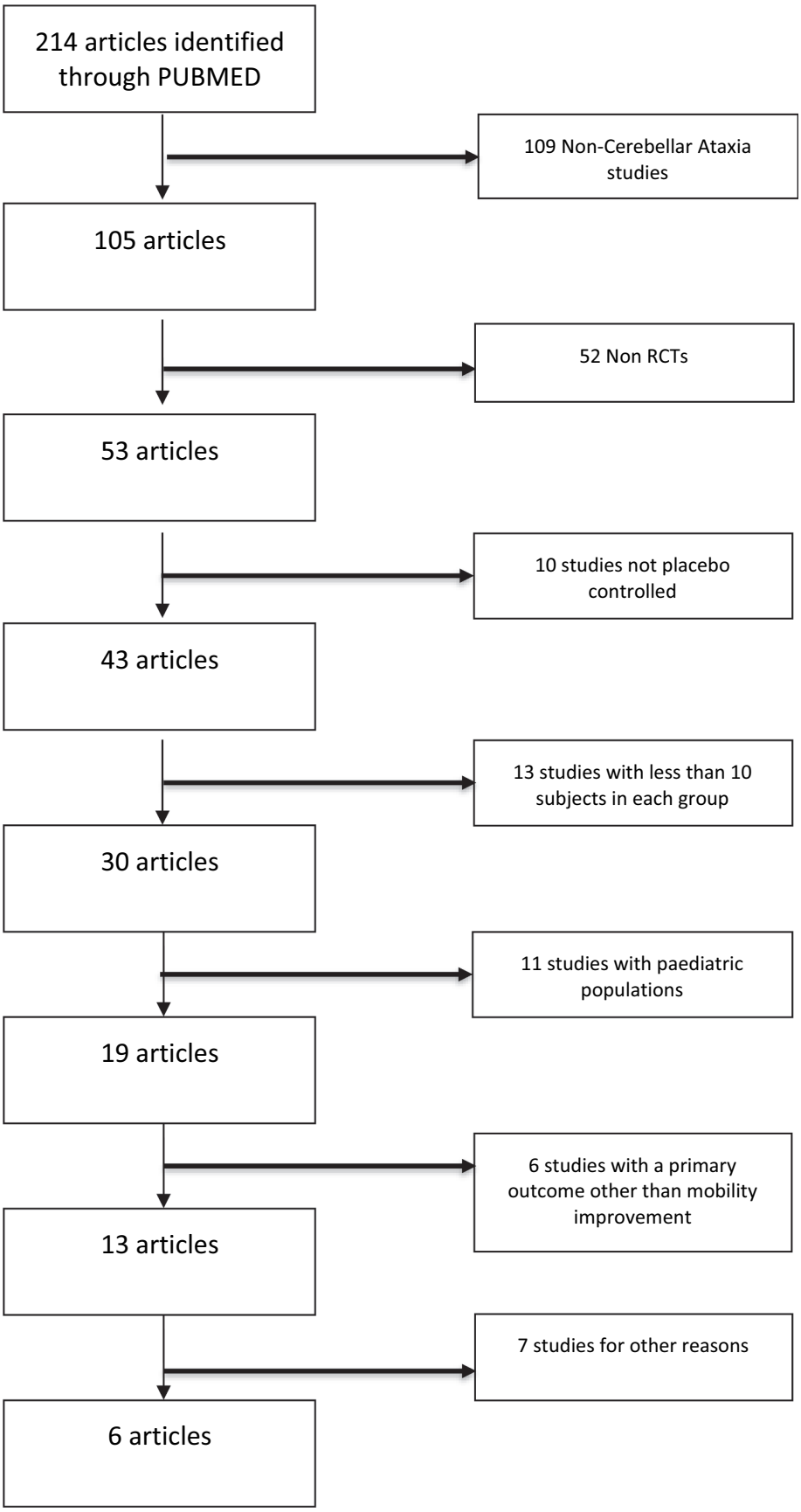


Fig. 1. PRISMA chart.

Table 1
Descriptive of studies included in the analysis.

Number of studies	6
Total number of all patients	223
Mean number of patients per study (SD)	37.2 (22.3)
Mean age of patients, in years	50.2
Male gender	48.2%
Total number of placebo treated patients	160
Mean number of placebo treated patients per study (SD)	26.7 (9.3)
Total number of active drug treated patients	159
Mean number of active drug treated patients per study (SD)	26.5 (9.0)
Origin of population (Number of studies)	
Canada	1 (16.7%)
Germany	3 (50.0%)
Japan	1 (16.7%)
United States of America	1 (16.7%)
Drug studied (Number of studies)	
Amantadine hydrochloride	1 (16.7%)
Branched-chain amino acids	1 (16.7%)
Hydroxytryptophan (levorotatory form)	1 (16.7%)
Memantine	1 (16.7%)
Physostigmine	1 (16.7%)
Trimethoprim – Sulfamethoxazole	1 (16.7%)
Route of drug administration (Number of studies)	
Oral	5 (83.3%)
Transdermal	1 (16.7%)

SD, standard deviation.

2.1. Selection criteria

To be included in the statistical analysis the studies had to fulfil the following criteria; (i) they were RCTs, (ii) they referred specifically to cerebellar ataxia which was either idiopathic or genetic, (iii) there was a purely placebo arm whereby no concomitant ataxia medication was continued, (iv) there were 10 or more participants in each treatment arm, (v) there was a washout period where applicable, (vi) they contained only adult populations, (vii) the studies contained a primary outcome related to mobility improvement, (viii) withdrawals and dropouts were reported in adequate detail in each treatment arm, (ix) the full text was available, (x) the text was in English, (xi) the studies contained only human subjects, (xii) and they scored a JADAD score of 3 or above. The Jadad scale is a five-item scale which evaluates the methodological quality of clinical trials depending on the study randomization, blindness of participants and investigators, and reports of withdrawals and dropouts [22,23].

Studies referring to acquired cerebellar ataxia (i.e. due to multiple sclerosis) were excluded from the analysis.

2.2. Data extraction

Data were extracted from each of the relevant studies in a structured coding scene using Excel and included information regarding: (i) article identification, (ii) year of publication, (iii) geographical location, (iv) JADAD score, (v) ataxia type, (vi) duration of the placebo and active drug treatment, (vii) total number of patients, (viii) total number of placebo-treated patients, (ix) number of male placebo-treated patients, (x) number of placebo-treated patients who experienced AEs, (xi) total number of placebo-treated patients who dropped out, (xii) number of placebo-treated patients who dropped out due to AEs, (xiii) mean age of placebo-treated subjects, (xiv) total number of active-drug treated patients, (xv) number of male active drug-treated patients, (xvi) number of active drug- treated patients who experienced AEs, (xvii) total number of active drug treated patients who dropped out, (xviii) number of active drug-treated patients who dropped out due to AEs, (xix) and the mean age of active drug-treated patients.

2.3. Statistical analysis

A database was developed using the IBM SPSS Statistics (version 23.0 for Mac). The two outcomes of interest were the proportion of patients receiving the placebo and the active drug who experienced AEs, and the proportion of patients who withdrew from each treatment arm due to drug-related AEs. Frequencies and descriptive statistics were calculated for each variable.

Meta-analysis of the pooled proportions was conducted in R language [24] using the default settings of the 'metaprop' package. The meta-analysis of odds ratios was conducted using the RevMan programme [25] as suggested by the Cochrane Collaboration Group. Heterogeneity between studies was assessed using the I^2 statistic. Data were analysed using a random effects model.

3. Results

The process of the article selection is presented in Fig. 1. From the 214 articles retrieved, 6 placebo-controlled RCTs were considered in the final analysis. These studies were published between 2014 and 1995 and involved 160 placebo treated patients with cerebellar ataxia. The main characteristics of the studies and their populations are presented in Table 1.

3.1. Adverse events in placebo and active drug groups

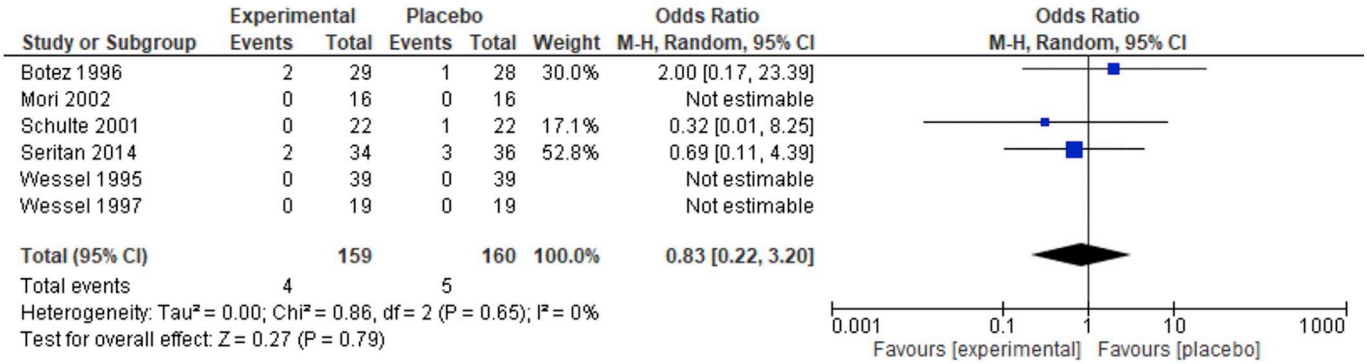
The pooled estimate of the percentage of placebo treated patients who withdrew from treatment was 8.6% (95% CI 3.5–19.7%). The pooled estimate of the percentage of placebo treated patients who withdrew from treatment due to AEs was 4.8% (95% CI 2.2–10.0%). The AEs resulting in the withdrawal of patients included, gastrointestinal (GI) side effects, rash, headache and dizziness.

The pooled estimate of the percentage of active drug treated patients who withdrew from treatment was 6.9% (95% CI 2.9–15.4%). The pooled estimate of the percentage of active drug treated patients who withdrew treatment due to AEs was 4.4% (95% CI 2.0–9.4%). The adverse events resulting in withdrawals included loss of weight, sleep disorders, fatigue and rash.

Table 2
Adverse events as reported in the active drug and placebo arms of the randomized controlled trials that were included in the analysis.

Trial	Placebo arm (%)	Active drug arm (%)	Active drug
Botez et al. (1996)	Gastrointestinal (3.6)	Loss of appetite (6.9) Loss of weight (3.4) Insomnia and nightmares (3.4) Insomnia, concentration difficulties and mood changes (3.4) Sleep disorder (3.4)	Oral Amantadine Hydrochloride
Wessel et al. (1995)	Gastrointestinal (12.8)	Gastrointestinal (20.5)	Oral Levoratory form of Hydroxytryptophan
Wessel et al. (1997)	Diarrhoea, headache, mild itching and redness at patch site (26.3)	Diarrhoea, headache, mild itching and redness at patch site (26.3)	Transdermal Phystogmine

a)



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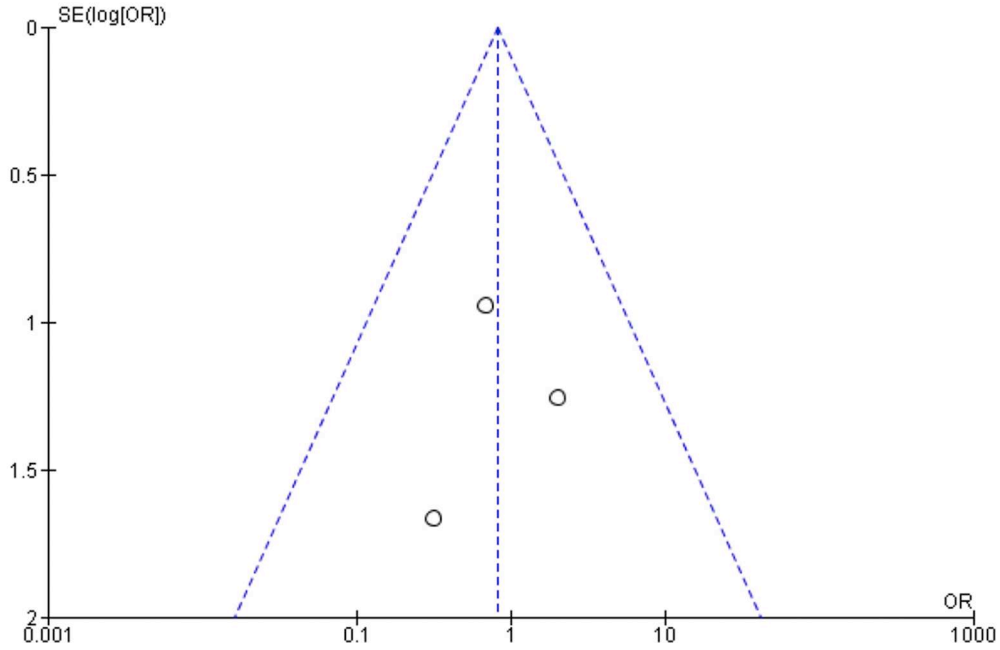

Fig. 2. a. Forest plot. Meta-analysis results (all RCTs with available data) as illustrated in the funnel plot regarding the percentage of patients who dropped out because of an adverse event. b. Funnel plot. Meta-analysis results as illustrated in the funnel plot regarding the percentage of patients who dropped out who dropped out because of an adverse event.

The pooled estimate of the percentage of placebo treated patients with at least one AE was 13.8% (95% CI 5.4–31.1%), in comparison to 21.9% (95% CI 14.4–31.9%) for active drug treated patients. The most commonly reported AEs in the placebo treatment group were gastrointestinal effects, followed by rash. Similarly, the most commonly reported AE in the active treatment group were also gastrointestinal effects. Table 2 illustrates the adverse events in all studies across both treatment arms.

As demonstrated in the forest plot (Fig. 2a), the likelihood of dropping out because of an adverse event was reduced by 17% (95% CI -78% to +220%) with administration of the active drug in comparison to the placebo. This was not a statistically significant difference.

Only 3 studies provided information on the exact number of individuals experiencing adverse events. As illustrated in the forest plot (Fig. 3a) the likelihood of experiencing at least one adverse event was 1.80 times greater (95% CI 0.73–4.43) in the active treatment group compared to the placebo treatment group. This was also not a statistically significant finding.

As demonstrated in both funnel plots (Figs. 2b and 3b) there was no significant heterogeneity amongst the studies included in the meta-analysis.

4. Discussion

Research has demonstrated a significant variation in the nocebo effect amongst neurological conditions [26–28]. Although it is difficult to draw comparisons between trials assessing nocebo because of the heterogeneity of trial populations, severity of disease and differing pathophysiological mechanisms, it remains important to determine the magnitude of nocebo in disorders of the nervous system.

The nocebo AE rates and nocebo dropout rates in various neurological disorders are highlighted in Table 3. The results from the table are derived from trials in which the nocebo effect was studied using identical methodology to that used in this meta-analysis. As highlighted in Table 3, the nocebo AE and withdrawal rates in cerebellar ataxia are amongst the lowest in neurological disorders that have been studied up to date. The low nocebo prevalence rates in cerebellar ataxia variation may be partially explained by the fact that cerebellar ataxias are chronic neurodegenerative diseases with currently no established efficacious therapies [29]. Consequently, patients have a considerably reduced health-related quality of life [30] and therefore may display greater willingness to complete trials whereby they may underreport symptoms, resulting in low nocebo AE rates. It has been proposed that comorbidity with somatoform disorders and the pathophysiology of neurological disorders including changes in the dopamine pathway in

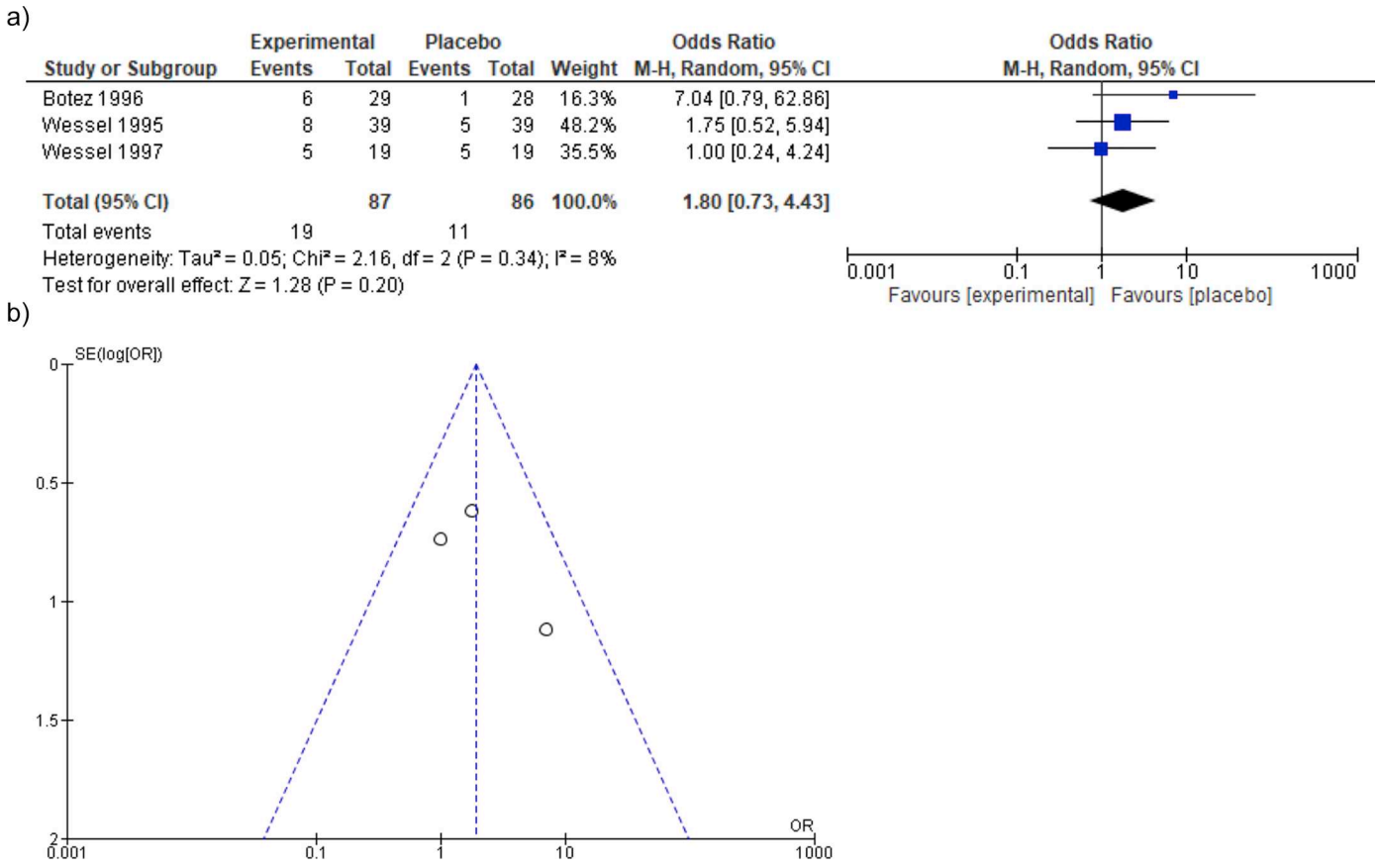

Fig. 3. a. Forest plot. Meta-analysis results (all RCTs with available data) as illustrated in the funnel plot regarding the percentage of patients who experienced an adverse event. b. Funnel plot. Meta-analysis results as illustrated in the funnel plot regarding the percentage of patients who experienced an adverse event.

Table 3
Nocebo AE rates and nocebo dropout rates in all neurological disorders where the nocebo effect was studied.

Disorder	AE rate (%)	Dropout rate (%)
Motor neuron disease	78.3	8.4
Multiple sclerosis		
Disease modifying trials	74.4	2.1
Symptomatic therapy trials	25.3	2.3
Fibromyalgia	67.2	9.5
Parkinson's disease	64.7	8.8
Refractory partial epilepsy	60.8	4.0
Alzheimer's disease	57.8	6.6
Neuropathic pain	52.0	6.0
Diabetic peripheral neuropathy	46.2	5.8
Restless leg syndrome	45.4	2.1
Depression	44.7	4.5
Migraine		
Preventative treatment	42.8	4.8
Symptomatic treatment	18.5	0.3
Tension-type headache		
Preventative treatment	24.0	5.4
Cluster headache		
Symptomatic treatment	18.7	NR
Meniere's disease	42.3	3.8
CIDP	42.0	2.1

AE, adverse events; NR, not reported.

the brain may account for differences observed in the nocebo effect across neurological disorders [4,20]. Other factors such as the route of drug administration [14] have also been suggested to be associated with nocebo, however evidence on this is conflicting.

4.1. Limitations

The results of this meta-analysis should be interpreted with caution due to the limitations of our study design. Firstly, although our measures of nocebo were calculated from both trial dropouts designated as drug toxicity-related, and AEs classified as drug related: it is difficult to attribute the symptoms observed in the placebo group to the nocebo effect. In this meta- analysis the most commonly reported AEs were gastrointestinal effects. It is plausible that such symptoms may reflect disease fluctuations or may have occurred secondary to comorbid conditions. However, like other meta-analyses the AEs found in both treatment arms mirror one another thus implying that pre-trial safety information and patient expectations are strongly correlated with the development of nocebo [31]. Nevertheless, despite this cerebellar ataxia nocebo rates are the amongst some of the lowest in neurological disorders, which is an important finding.

Secondly, nocebo severity is indirectly estimated using dropout rate as a proxy measure. Thirdly, the heterogeneity in the incidence of dropout rates and AEs across trials reduces the applicability of the pooled estimates of the nocebo response. Moreover, not all studies provided detail about the timing of the development of AEs and the methods used to record AEs, and therefore only 3 studies were included in the nocebo AE rate analysis.

Finally, only 6 studies of adequate quality were included in this meta-analysis. Therefore, our estimates may not represent the magnitude of the nocebo effect in patients with cerebellar ataxia. However, only a limited number of studies met our inclusion criteria, thereby reflecting the number of well-designed RCTs in cerebellar ataxia.

4.2. Implications for trial design

Prospective, randomized, placebo-controlled, double blind studies are the gold standard for cerebellar ataxia trials. The results of this meta-analysis show that investigators should expect approximately 1 in 7 participants to withdraw from treatment because of nocebo (nocebo AE rate 13.8%), and 1 of 20 placebo-treated patients to withdraw from treatment due to AEs (nocebo dropout rate 4.8%). The close correlation between the nocebo rates and percentages of the active treatment arm and placebo arm, highlight the importance of a nocebo as a confounding factor of reported AEs in cerebellar ataxia trials. It also suggests the presence of idiosyncratic and psychological factors regarding patient expectations of treatments [20].

The lower percentages and rates of AEs in the placebo arm compared to the active arm are in line with our expectations that a chemically inactive drug should not elicit as many issues with patient compliance compared to an active substance [20].

4.3. Implications for clinical practice

The consequences of nocebo in clinical practice are an important concern to consider, given that current treatment for cerebellar ataxia is based upon evidence possibly confounded by nocebo. Though this meta-analysis does not provide any direct evidence for nocebo in clinical practice, RCT findings predict the effectiveness and safety and tolerability of interventions in clinical practice. Therefore, this meta-analysis may provide important considerations relevant to daily clinical practice. Clinicians should be aware of the possibility that the development of AEs in cerebellar ataxia patients such as gastrointestinal side effects and treatment failure may be due to the nocebo effect rather than the active drug. Hence, it is important to employ individualized strategies to reduce the occurrence of this. A genetic predisposition to the placebo effect has been demonstrated in depression and anxiety [1], and although nocebo arises due to patient expectations and pre-trial experiences [6] it is possible that there may also be a genetic predisposition to the nocebo effect.

5. Conclusion

Our meta-analysis showed that in placebo-controlled RCTs for cerebellar ataxia, 13.8% of study participants reported AEs related to nocebo, whereby only 4.8% of participants withdrew due to the occurrence of these AEs. In comparison to other neurological disorders, the nocebo effect in cerebellar ataxia is amongst one of the lowest.

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