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Nocebo in Alzheimer's disease; meta-analysis of placebo-controlled clinical trials

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ABSTRACT

Background and purpose: Nocebo is very prevalent among neurological diseases resulting in low adherence and treatment outcome. We sought to examine the AEs following placebo administration in Randomized Controlled Studies (RCTs) for Alzheimer's Disease (AD).
Methods: After a systematic Medline search for RCTs for AD pharmacological treatments, we assessed the number of placebo-treated patients reporting at least one AE and the number of discontinuations because of placebo intolerance and searched for factors correlating to nocebo's extent.
Results: Data were extracted from 20 RCTs fulfilling our search criteria. Of 3049 placebo-treated patients, 57.8% (95% CI: 50.1%–66.7%) reported at least one AE and 6.6% (95% CI: 5.3%–8.4%) discontinued placebo treatment because of AEs. All patients participating in these RCTs reported similar AEs independently of the study arm they belonged. Nocebo AE rate and dropout rate were positively related to study population size. The rates of AEs and dropouts because of AEs were parallel between placebo and active arms of RCTs ($r = 0.812$, $p < 0.001$ and $r = 0.787$, $p < 0.001$, respectively). Effectiveness rates correlated significantly to AEs rate and dropout rate because of AEs in placebo treated patients ($r = 0.787$, $p < 0.001$ and $r = 0.812$, $p < 0.001$, respectively).
Conclusion: In RCTs for AD one out of fifteen patients treated with placebo dropped out because of AEs and three out of five experienced AEs indicating that adherence and effectiveness may be adversely affected with additional implications for clinical practice. The principal implications of this paper are that nocebo deserves much.

1. Introduction

Nocebo refers to adverse events (AEs) related to negative expectations that medical treatment will probably harm instead of heal and can be assessed in placebo-controlled randomized clinical trials (RCTs) [1,2]. Nocebo is related to lower adherence in therapy, high rates of dropouts, as well as significant difficulty in assessing the effectiveness and the safety profile (adverse events experienced) of a drug in clinical trials [3,4]. There is evidence that nocebo is related to negative pretrial suggestions and previous negative experiences during treatment [5] along with several psychological factors including stress and anxiety [6–8].

Nocebo has been studied in RCTs for several neurological conditions, including multiple sclerosis [9], headache [10,11], neuropathic pain [12], fibromyalgia [1], diabetic peripheral neuropathy [13], Parkinson's disease [14] and depression [2,15]. In these studies dropouts because of AEs in placebo treated patients varied from 2% (in multiple sclerosis) to almost 10% (in Parksinson's disease and fibromyalgia). These rates indicate significant implications for clinical practice related to adherence and treatment outcome.

The aim of our study was to estimate the frequency and strength of nocebo effects in Alzheimer's disease (AD) trials using a metaanalytic approach. The incidence of drug-related AE in placebo-treated AD patients was used as a measure of the frequency of the nocebo effect. The dropout rate of placebo-treated neuropathic pain sufferers due to drug-related AE was used as a measure of severity of the nocebo effect. In addition, meta-regression analysis was employed in order to examine the association of the above measures of nocebo responses with trial and study population related parameters.

2. Methods

A computer-based literature search was conducted on October 29th, 2013 on PubMed using "Alzheimer'", "treatment" and "placebo" as search words. Limitations included publication date to be during the last 10 years, article type to be Clinical Trial, text availability to be Full text, Species to be Humans and Language to be English. We further filtered the search for pharmacotherapy and RCTs. All selected studies that were relevant were selected for analysis [16] (Table 1).

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Table 1
Descriptive of studies included in the analysis.

Parameter	Value
No. of studies	20
Total no. of patients participated in all studies	8977
Mean no. of patients per study (±SD)	448.9 ± 264.8
Total no. of placebo treated patients	3049
Mean number of placebo treated patients per study (±SD)	152.5 ± 71.9
Mean age of placebo treated patients (years, weighted) (±SD)	75.4 ± 3.9
Males weighted (SE)	33.9% (0.002)
Treatment duration in weeks (±SD)	22.6 ± 9.7
Mean Jadad score (±SD)	4.4 ± 0.6
Mean time since disease onset (years weighted, ±SD)	2.5 ± 1.5
Route of administration (no. of studies. %)	
IV	1 (5%)
Oral	18 (90%)
Oral and Patch	1 (5%)
Origin of population (no. of studies)	
Japan	1 (5%)
Europe	2 (10%)
Russia	1 (5%)
North America	4 (20%)
Multinational	12 (60%)
Drug studied (no. of studies)	
AMPA potentiator	1 (5%)
AZD3480 & donepezil	1 (5%)
Celecoxib	1 (5%)
Cerebrolysin	1 (5%)
Dimebon	1 (5%)
Donepezil	4 (20%)
Galatamine	2 (10%)
Ginkgo Biloba	1 (5%)
Memantine	2 (10%)
Rivastigmine	2 (10%)
Rosiglitazone	2 (10%)
SB-742457	1 (5%)
SB-742457 & donepezil	1 (5%)

2.1. Selection criteria

Both authors independently screened all available references. At the last phase of filtering, all articles meeting the selected criteria (pharmacotherapy and RCTs) were fully reviewed and further processed for statistical analysis when (i) they included equal to or more than 40 individuals per arm (ii) there was a purely placebo arm, (iii) they referred specifically to Alzheimer's disease and not any other form of dementia or mild cognitive impairment, (iv) primary outcome was cognitive status, (v) they reported sufficient CONSORT flow diagrams or clearly were reporting adverse events (AEs) and (vi) they scored a Jadad score of higher than or equal to 3. The Jadad scale classifies the quality of reports and includes only five items depending on the study randomization, blindness of participants and investigators, blindness in outcome assessment, report of withdrawals, and dropouts [17,18]. Both investigators determined the suitability of each study for inclusion in this meta-analysis. Their results were compared and disagreements were resolved by consensus.

2.2. Data extraction

Data were extracted from each study in a structured coding scene using excel and included information on the article identification, year of publication, treatment duration, Jadad score, total number of subjects, number of placebo-treated subjects, number of placebo-treated subjects who dropped out because of AEs, number of subjects presenting any AE, number of episodes of AEs, number of male subjects treated with placebo, mean age of placebo-treated subjects, the mean years since AD onset in them, drug, way of administration, number of daily doses, country, body mass index (BMI), mini mental state examination (MMSE) score and Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog) score change. We calculated the nocebo AE rates or dropout rates by pooling the percentage of placebo-treated patients who had at least one AE or dropped out because of AE. Our measures of nocebo were calculated from the trial drop-outs designated as drug toxicity-related and the adverse events that were classified as drug-related.

2.3. Statistical analyses

The meta-analysis was conducted in R language using the 'metafor' package as downloaded from Comprehensive R Archive Network repository (http://cran.r-project.org) [19]. The outcomes of interest were the proportion of patients receiving placebo who experienced AEs and the proportion of patients receiving placebo (safety population) and dropped out of the study because of any AE. The safety population of each study was considered. The estimation of the proportions was based on the logit transformation. Data were analyzed using a random effects model, because of heterogeneity between studies, which was assessed by I^2 and Cochran Q tests [20–22]. The Egger's test was considered to assess the presence of asymmetry in the funnel plots [23]. Mixed model analysis as in meta-regression models using the REML method was used [24] to evaluate the effect of multiple factors (year of publication, percentage of male subjects treated with placebo, age of placebo-treated subjects, Jadad score, years since AD onset, BMI, treatment duration, MMSE score, ADAS-cog change) on the presence of AEs and on dropout because of AEs. Only variables that had statistical significant of $\alpha = 0.1$ at the initital analysis were considered for the meta-regression models. The Pearson product–moment correlation weighted by the population size of each study was employed to assess the association between placebo and active treatment in terms of the presence of AEs and dropouts because of AEs.

3. Results

The process of the article selection is presented in Fig. 1. From the 379 articles retrieved, 20 were considered in the final analysis (Appendix A). These studies were published between 2004 and 2011 and they involved 3049 placebo-treated AD patients. The main characteristics of the placebo-treated patients are presented in Table 1.

3.1. Adverse events in placebo and active drug groups

The five most common AEs reported by placebo-treated and active drug-treated patients are presented in Table 2. The pooled estimate of the percentage of placebo treated patients with at least one AE (nocebo AE rate) and the dropout because of nocebo (nocebo dropout rate) was 57.8% (95% CI: 50.1%–66.7%; I^2: 97.0%; $Q = 328.72$, $p < 0.0001$; Egger bias: −7.50, $p < 0.001$) and 6.6% (95% CI: 5.3%–8.4%]; I^2: 60.4%; $Q = 51.66$, $p < 0.001$; Egger bias: −4.15, $p < 0.001$), respectively (Fig. 2). The pooled estimate of the percentage of active drug treated patients with at least one AE and the dropout percentage because of AE was 61.6% (95% CI: 53.8%–70.6%) and 8.8% (95% CI: 7.1%–11.1%). The rates of AEs and dropouts because of AEs in placebo arms in different studies correlated significantly to the rates of the active arms (weighted Pearson correlation, $r = 0.812$, $p < 0.001$ and $r = 0.787$, $p < 0.001$, respectively).

3.2. Factors correlating to nocebo

The univariate analysis of factors potentially correlating to AEs among the placebo treated population showed that sample size, year of publication, BMI and MMSE score are negatively correlated with nocebo AE when age and disease duration are positively correlated. The tested pharmaceutical treatment did not correlate to nocebos. Meta-regression model indicated that the nocebo AE incidence was negatively correlated only with the sample size ($p = 0.0011$). The